Comparative efficacy and safety of tyrosine kinase inhibitors for thyroid cancer: a systematic review and meta-analysis

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Abstract. The tyrosine kinase inhibitors (TKIs) sorafenib, lenvatinib, vandetanib, and cabozantinib are currently used for thyroid cancer treatment; however, the differences in their clinical efficacy and toxicity remain unclear. This meta-analysis assessed the efficacy and toxicity of these four TKIs based on 34 studies. The pooled incidence of partial response (PR), stable disease (SD), TKI-related adverse events (AEs), and pooled median progression-free survival (PFS) were calculated with 95% confidence intervals (CI). Complete response to TKIs was extremely rare (0.3%). The highest PR rate and longest PFS were observed for lenvatinib in differentiated thyroid cancer (69%, 95% CI: 57–81 and 19 months, 95% CI: 9–29, respectively) and vandetanib in medullary thyroid cancer (40%, 95% CI: 25–56 and 31 months, 95% CI: 19–43, respectively). Although the discontinuation rate due to AEs was similar for each TKI, there was a difference in the most frequently observed AE for each TKI (hand-foot syndrome for sorafenib, hypertension and proteinuria for lenvatinib, and QTc prolongation for vandetanib). The identified differences in the TKI efficacy and AE profiles may provide a better understanding of thyroid cancer treatment. Although TKIs are promising agents for thyroid cancer treatment, they are unlikely to lead to a cure. Thus, even in the TKI era, a multimodal treatment including surgery, radioiodine therapy, external beam radiotherapy, and TKIs is required to optimize patient chances of improved survival.

Key words: Thyroid cancer, Tyrosine kinase inhibitor, Adverse event, Meta-analysis

THYROID CANCER is the most prevalent endocrine malignancy, which accounts for approximately 4% of all malignancies. Its overall incidence has increased over the years [1, 2]. Differentiated thyroid carcinoma (DTC) is the most prevalent type of thyroid cancer, accounting for 90%–95% of all cases [2]. Although DTC is generally an indolent tumor, distant metastases may occasionally develop [3]. Radioiodine (RAI) therapy is beneficial for the control of metastatic DTC and can lead to tumor remission [4]. However, some metastatic lesions show primary or acquired resistance to RAI therapy. Since the therapeutic options for patients with RAI-refractory DTC (RR-DTC) are limited, a subset of these patients succumb to the disease; thus, the reported 10-year survival rate of patients with RR-DTC was 70% [5]. Anaplastic thyroid carcinoma (ATC) accounts for less than 2% of all

thyroid carcinomas but presents with a very aggressive clinical course [6]. Although surgery has been the most effective treatment to reduce the tumor burden of ATC [7–9], the prognosis remains very poor with mean survival time after diagnosis of 6 months [10]. Furthermore, the survival rate of patients with ATC has not improved over the past 20 years [9]. Medullary thyroid carcinoma (MTC) is also an uncommon type of thyroid cancer, a subset of which is a hereditary form associated with multiple endocrine neoplasia type 2A (MEN 2A), MEN 2B, and familial MTC [11, 12]. Ito *et al.* demonstrated that the prognosis of MTC patients was generally good: the 10- and 20-year cause-specific survival rates were 97.0% and 94.3%, respectively [13]. RAI therapy cannot be applied to MTC, because MTC cells, which originate from thyroid C cells, do not take iodine up. Therefore, if distant metastases develop, the therapeutic options for MTC are limited. The described limited treatment choices for each histological type of thyroid cancer have aroused the need for a novel therapeutic strategy, and tyrosine kinase inhibitors (TKIs) have emerged as promising drugs in the last decade.

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Since positive results were published from two phase III clinical trials (the DECISION and SELECT trials) [14, 15], sorafenib and lenvatinib have been approved and are now available for the treatment of RR-DTC. As for MTC, two TKIs—vandetanib and cabozantinib—have been approved based on two phase III clinical trials (the ZETA and EXAM trials) [16, 17]. Sorafenib and lenvatinib have also been tested in phase II clinical trials and shown to be an effective treatment for advanced MTC [18-23]. Regarding ATC, lenvatinib has shown the potential to improve ATC tumor control and prognosis [23] and has thus been approved for the treatment of ATC in Japan.

Multimodal therapeutic approaches, including surgery, RAI therapy, external beam radiotherapy, and TKIs, will be further developed in the next decade. Specifically, given the increasing evidence of promising results with TKIs in clinical trials, TKIs may play an important role in thyroid cancer treatment. Even though there are currently four TKIs available for the treatment of thyroid cancer, the differences in their clinical efficacy and toxicity are still unclear. Therefore, in this study, we aimed to systematically review the existing literature and meta-analyze the efficacy and safety of the four TKIs (sorafenib, lenvatinib, cabozantinib, and vandetanib) to elucidate the differences among these drugs for the treatment of thyroid cancer.

Materials and Methods

Search strategies

We searched the databases PubMed, Scopus, and ClinicalTrials.gov for relevant studies published up to July 2019 using the search terms “thyroid AND (cancer OR carcinoma) AND (sorafenib, OR lenvatinib, OR vandetanib, OR cabozantinib)”. We performed the analysis according to the Preferred Reporting Items for Systemic Reviews and Meta-Analyses (PRISMA) statement [24]. All studies were assessed individually by two of the authors (TO and MO).

Selection criteria

We selected studies, which fulfilled the following inclusion criteria: (a) clinical trials or observational longitudinal studies, in which the response rate and adverse events (AEs) were reported according to the Response Evaluation Criteria in Solid Tumors (RECIST) and Common Terminology Criteria for Adverse Events (CTCAE), respectively; (b) except for ATC, sorafenib, lenvatinib, vandetanib, and cabozantinib were administered at initial doses of 400 mg twice a day, 24 mg a day, 300 mg a day, and 140 mg a day, respectively; (c) patients were over 18 years of age; and (d) the articles were written in English.

Exclusion criteria were: (a) studies, in which TKIs were combined with other treatments; (b) case reports; (c) literature reviews; and (d) duplicate studies.

Data extraction

The following data were extracted: author name, country, year of publication, study design, and enrolled patient characteristics. Enrolled patient characteristics included age; sex; the Eastern Cooperative Oncology Group performance status; histological type of thyroid cancer; pretreatment; initial dose; response rate [complete response (CR), partial response (PR), and stable disease (SD)]; progression-free survival (PFS); and overall survival (OS). For AEs, we extracted data only from prospective studies, considering the possibility that AEs were overlooked in retrospective observational longitudinal studies (RSs).

Statistical analysis

We performed this meta-analysis using JAMOVI, a software built on the R statistical language. The overall pooled rates for PR, SD, AEs, pooled median PFS, and pooled median OS were calculated with the corresponding 95% confidence intervals (CI) for each drug. The overall pooled discontinuation rate was also evaluated. Heterogeneity was assessed through I^2 statistics. $I^2 > 50\%$ and $I^2 \leq 50\%$ were classified as high and low heterogeneity, respectively. Egger's test was carried out to evaluate the publication bias, and a p value <0.05 was considered statistically significant publication bias.

Results

Study selection

A total of 1,152 potentially relevant articles were identified. Among them, 1,111 articles were eliminated after reading their titles and abstracts. After reading the full texts of the remaining 41 articles, seven articles were excluded due to treatment with a reduced starting dose or inability to extract data for the meta-analysis. Finally, a total of 34 studies with 1,713 patients (14 studies for sorafenib [15, 18-21, 25-33]; 13 studies for lenvatinib [14, 22, 23, 34-43]; five studies for vandetanib [17, 44-47]; and two studies for cabozantinib [48, 49]) were included in this systematic review. Details on the literature search are presented in Supplementary Fig. 1.

The characteristics of the included 34 articles are summarized in Table 1. With regards to sorafenib, eight studies were phase II or III clinical trials [15, 18-21, 25, 29, 30], one study was a prospective observational longitudinal study (PS) [33], and the remaining five studies were RSs [26-28, 31, 32]. Totally, 523 patients (DTC: $n = 381$, MTC: $n = 103$, and ATC: $n = 39$) were enrolled in

Table 1 Descriptive summary of the inclusion studies

Sorafenib	Study type	Countries	Patients	DTC	MTC	ATC	Age	Prior TKIs	ECOG PS
Brose <i>et al.</i> ^[15]	Phase III	Multi country	207	207	0	0	63	–	0–2
Ahmed <i>et al.</i> ^[18]	Phase II	UK	34	19	15	0	55	–	0–1
Gupta <i>et al.</i> ^[19]	Phase II	US	30	27	1	2	63	–	0–1
Kloos <i>et al.</i> ^[25]	Phase II	US	56	52	0	4	N.D	–	N.D
Sneider <i>et al.</i> ^[29]	Phase II	Netherlands	31	31	0	0	64	–	0–2
Cabanillas <i>et al.</i> ^[26]	RS	US	15	15	0	0	61	–	N.D
Ito <i>et al.</i> ^[20]	Phase II	Japan	18	0	8	10	64	–	0–1
Capdevila <i>et al.</i> ^[28]	RS	Spain	34	16	15	3	57.3	–	0–2
Benekli <i>et al.</i> ^[31]	RS	Turkey	30	14	16	0	57	–	0–2
Lam <i>et al.</i> ^[21]	Phase II	US	21	0	21	0	60	–	0–2
Frank-Raue <i>et al.</i> ^[27]	RS	Germany	5	0	5	0	50	+	N.D
Koscic <i>et al.</i> ^[33]	PS	Hungary	10	0	10	0	51.7	–	0–1
de Castroneves <i>et al.</i> ^[32]	RS	Brazil	12	0	12	0	48	+	N.D
Savvides <i>et al.</i> ^[30]	Phase II	US	20	0	0	20	59	–	0–2
Total			523	381	103	39			

Lenvatinib	Study type	Countries	Patients	DTC	MTC	ATC	Age	Prior TKIs	ECOG PS
Schlumberger <i>et al.</i> ^[14]	Phase III	Multi country	261	261	0	0	64	+	0–3
Cabanillas <i>et al.</i> ^[35]	Phase II	Multi country	58	58	0	0	63	+	0–2
Takahashi <i>et al.</i> ^[23]	Phase II	Japan	51	25	9	17	61	+	0–2
Yamazaki <i>et al.</i> ^[43]	RS	Japan	30	30	0	0	68	+	N.D
Suzuki <i>et al.</i> ^[42]	RS	Japan	26	26	0	0	64	+	0–3
Balmelli <i>et al.</i> ^[34]	RS	Switzerland	13	13	0	0	72	+	0–2
Nervo <i>et al.</i> ^[40]	RS	Italy	12	12	0	0	61.1	+	0–2
Schlumberger <i>et al.</i> ^[22]	Phase II	Multi country	59	0	59	0	51.6	+	0–2
Iwasaki <i>et al.</i> ^[37]	RS	Japan	23	0	0	23	77	–	0–2
Iyer <i>et al.</i> ^[38]	RS	US	10	0	0	10	N.D	–	N.D
Koyama <i>et al.</i> ^[39]	RS	Japan	5	0	0	5	58	–	0
Staub <i>et al.</i> ^[41]	RS	Japan	3	0	0	3	66	+	0–3
Iniguez-Ariza <i>et al.</i> ^[36]	RS	US	3	0	0	3	67	–	2–3
Total			554	425	68	61			

Vandetanib	Study type	Countries	Patients	DTC	MTC	ATC	Age	Prior TKIs	ECOG PS
Leboulleux <i>et al.</i> ^[45]	Phase II	Multi country	72	72	0	0	63	+	0–2
Wells <i>et al.</i> ^[17]	Phase III	Multi country	231	0	231	0	50.7	–	0–2
Hu <i>et al.</i> ^[47]	Phase IV	Multi country	41	0	41	0	52.7	+	0–2
Wells <i>et al.</i> ^[44]	Phase II	Multi country	30	0	30	0	49	+	0–2
Werner <i>et al.</i> ^[46]	RS	Germany	18	0	18	0	46.5	+	N.D
Total			392	72	320	0			

Cabozantinib	Study type	Countries	Patients	DTC	MTC	ATC	Age	Prior TKIs	ECOG PS
Cabanillas <i>et al.</i> ^[49]	Phase II	US	25	25	0	0	64	+	0–1
Elisei <i>et al.</i> ^[48]	Phase III	Multi country	219	0	219	0	55	+	0–2
Total			244	25	219	0			

RS, retrospective study; PS, prospective study; DTC, differentiated thyroid carcinoma; MTC, medullary thyroid carcinoma; ATC, anaplastic thyroid carcinoma; TKI, tyrosine kinase inhibitor; ECOG, Eastern Cooperative Oncology Group; PS, performance status; N.D, not described

this meta-analysis. Studies on lenvatinib included four phase II or III clinical trials [14, 22, 23, 35] and nine RSs [34, 36–43], comprising totally 554 patients (DTC: $n = 425$, MTC: $n = 68$, and ATC: $n = 61$). For vandetanib and cabozantinib, all studies except one [46] were clinical trials (Phase II, III, or IV) [17, 44, 45, 47–49], in which 392 (DTC: $n = 72$ and MTC: $n = 320$) and 244 patients (DTC: $n = 25$ and MTC: $n = 219$) were treated, respectively. We could not conduct a meta-analysis for cabozantinib due to the low number of included studies.

Efficacy

Overall, CR was reported with a remarkably low incidence (5 out of 1,713 patients; 0.3%). Among the five patients who showed CR, four were DTC patients treated with lenvatinib [14], whereas one was an MTC patient treated with vandetanib [47].

Next, we meta-analyzed the PR rate, SD rate, and PFS for each pathological type of thyroid cancer (DTC, MTC, and ATC) (Table 2). The meta-analysis for OS could be performed only for ATC, because OS data were lacked in most studies of DTC and MTC.

DTC

In terms of PR, lenvatinib was superior to sorafenib: 15% (95% CI: 5–26, $I^2 = 0\%$, $p = 0.48$) for sorafenib and 69% (95% CI: 57–81, $I^2 = 15.7\%$, $p = 0.29$) for lenvatinib. Contrarily, the pooled SD rate was lower with lenvatinib than with sorafenib treatment: 59% (95% CI: 37–81, $I^2 = 65.2\%$, $p = 0.86$) for sorafenib and 27% (95% CI: 11–43, $I^2 = 36.2\%$, $p = 0.62$) for lenvatinib. The low SD rate with lenvatinib treatment may have

been induced by the high PR rate. Consistent with the higher PR rate for lenvatinib treatment, the pooled PFS was longer for lenvatinib than for sorafenib: 14 months (95% CI: 3–24, $I^2 = 0\%$, $p = 0.66$) for sorafenib and 19 months (95% CI: 9–29, $I^2 = 0\%$, $p = 0.95$) for lenvatinib.

No meta-analysis could be performed for vandetanib and cabozantinib due to the small number of articles. However, the findings of two phase II trials showed that the median PFS was 11.1 months (95% CI: 7.7–14.0) for vandetanib and 12.7 months (95% CI: 10.9–34.7) for cabozantinib [45, 49], which was inferior to the pooled PFS for lenvatinib.

MTC

The pooled PR and SD rates for sorafenib treatment were 23% (95% CI: 1–45, $I^2 = 0\%$, $p = 0.61$) and 77% (95% CI: 45–100, $I^2 = 48.9\%$, $p = 0.42$), respectively, whereas those for vandetanib treatment were 40% (95% CI: 25–56, $I^2 = 21.0\%$, $p = 0.21$) and 59% (95% CI: 37–81, $I^2 = 51.6\%$, $p = 0.32$), respectively. The pooled PFS for vandetanib was longer than that for sorafenib treatment: 16 months (95% CI: 0–45, $I^2 = 0\%$, $p = 0.94$) for sorafenib and 31 months (95% CI: 19–43, $I^2 = 0\%$, $p = 0.81$) for vandetanib.

No meta-analysis could be performed for lenvatinib and cabozantinib due to the limited number of eligible studies. Lenvatinib was tested in a phase II study and showed 9.0 months (95% CI: 7.0–not evaluable) PFS for MTC [22]. Regarding cabozantinib, the median PFS in a phase III trial (EXAM trial) was significantly longer in the cabozantinib arm (11.2 months) than in the placebo arm (4.0 months) (hazard ratio 0.28, 95% CI 0.19–0.40,

Table 2 Pooled incidence of partial response, stable disease, median progression-free survival, and median overall survival

	Sorafenib	95%CI	I^2	p	Lenvatinib	95%CI	I^2	p	Vandetanib	95%CI	I^2	p
DTC												
PR	15%	5–26	0%	0.48	69%	57–81	15.7%	0.29				
SD	59%	37–81	65.2%	0.86	27%	11–43	36.2%	0.62				
PFS	14 months	3–24	0%	0.66	19 months	9–29	0%	0.95				
MTC												
PR	23%	1–45	0%	0.61					40%	25–56	21.0%	0.21
SD	77%	45–100	48.9%	0.42					59%	37–81	51.6%	0.32
PFS	16 months	0–45	0%	0.94					31 months	19–43	0%	0.81
ATC												
PR					24%	0–54	0%	0.46				
SD					50%	14–87	25.0%	0.98				
PFS					5 months	1–9	25.0%	0.98				
OS					11 months	0–22	91.4%	0.65				

DTC, differentiated thyroid carcinoma; MTC, medullary thyroid carcinoma; ATC, anaplastic thyroid carcinoma; PR, partial response; SD, stable disease; PFS, progression-free survival; OS, overall survival; CI, confidence interval; p , p value identified by Egger's regression test

$p < 0.01$) [48]. These reported PFS for lenvatinib and cabozantinib was shorter than the pooled PFS for vandetanib.

ATC

We could perform a meta-analysis only for lenvatinib treatment. The pooled PR and SD rates were 24% (95% CI: 0–54, $I^2 = 0\%$, $p = 0.46$) and 50% (95% CI: 14–87, $I^2 = 25.0\%$, $p = 0.98$). The pooled PFS was 5 months (95% CI: 1–9, $I^2 = 25.0\%$, $p = 0.98$). OS data were available in five articles [23, 36–39], and the pooled OS was 11 months (95% CI: 0–22, $I^2 = 91.4\%$, $p = 0.65$). Although we could not conduct a meta-analysis for sorafenib treatment due to the lack of eligible articles, the reported PFS and OS for ATC were 1.9–4.4 months and 3.9–5.0 months, respectively [20, 28, 30].

Adverse events

Data on dose reduction or drug interruption or discontinuation due to AEs were obtained from 12 [15, 18–21, 25, 27–29, 31–33], eight [14, 22, 23, 34, 35, 40, 42, 43], and four studies [17, 44, 45, 47] for sorafenib, lenvatinib, and vandetanib, respectively. The dose reduction and drug interruption rates were highest for lenvatinib (Supplementary Table 1). However, the pooled discontinuation rate was equivalent for the three TKIs (sorafenib: 16%, 95% CI: 6–26, $I^2 = 0\%$, $p = 0.62$; lenvatinib: 16%, 95% CI: 7–25, $I^2 = 0\%$, $p = 0.71$; and vandetanib: 19%, 95% CI: 6–31, $I^2 = 18.2\%$, $p = 0.57$) (Table 3).

The AEs associated with each TKI and their pooled rates are summarized in Table 4. Diarrhea was a frequent AE in sorafenib, lenvatinib, and vandetanib treatment. With sorafenib treatment, the incidence of skin-related AEs such as hand-foot syndrome (HFS) and rash was extremely high (HFS, all grades: 96%, 95% CI: 86–100, $I^2 = 0.4\%$, $p = 0.49$; Grade 3 or 4: 21%, 95% CI: 11–31, $I^2 = 0\%$, $p = 0.99$; rash, all grades: 79%, 95% CI: 54–100, $I^2 = 77.2\%$, $p = 0.56$; and Grade 3 or 4: 6%, 95% CI: 0–16, $I^2 = 0\%$, $p = 0.89$). Skin-related AEs were not as common with lenvatinib as with sorafenib treatment, but hypertension was reported with a remarkably high incidence (all grades: 96%, 95% CI: 59–100, $I^2 = 90.9\%$, $p = 0.59$ and Grade 3 or 4: 28%, 95% CI: 8–49, $I^2 = 71.1\%$, $p = 0.39$). In addition, proteinuria was documen-

ted with higher incidence for lenvatinib than sorafenib and vandetanib treatment (lenvatinib, all grades: 45%, 95% CI: 9–80, $I^2 = 90.9\%$, $p = 0.33$ and Grade 3 or 4: 3%, 95% CI: 0–13, $I^2 = 0\%$, $p = 0.33$; and sorafenib and vandetanib, not applicable for a meta-analysis due to the lack of data). Vandetanib treatment was associated with higher incidence of QTc prolongation than sorafenib and lenvatinib treatment (sorafenib and lenvatinib, not applicable for a meta-analysis due to the lack of data; vandetanib, all grades: 19%, 95% CI: 8–29, $I^2 = 0\%$, $p = 0.19$; and Grade 3 or 4: 10%, 95% CI: 0–21, $I^2 = 0\%$, $p = 0.48$).

Although we could not conduct a meta-analysis on the reasons for dose reduction or drug interruption or discontinuation due to the lack of available studies, diarrhea was reported as one of the major reasons in phase II or III clinical trials for lenvatinib and vandetanib treatment [14, 44, 45]. Other main causes included hypertension and proteinuria for lenvatinib [14] and QTc prolongation for vandetanib [45]. The most frequently reported AE, which lead to a dose reduction of the sorafenib treatment, was HFS [15, 18–21]. The timing of the dose reduction was within 2 months, 2.2–3.0 months, and 4.9 months for sorafenib [18, 21, 29], lenvatinib [14, 22], and vandetanib [44], respectively.

TKI treatment was associated with fatal AEs such as tumor-related bleeding in various cancer types [50]. Indeed, fatal AEs were also documented with thyroid cancer treatment, although they were rare events [28, 35, 45]. The total incidence of deaths caused by fatal AEs associated with each TKI was 0.7% ($n = 4$ out of 523 patients), 1.9% ($n = 11$ out of 554 patients), and 1.7% ($n = 7$ out of 392 patients) for the treatment with sorafenib, lenvatinib, and vandetanib, respectively. Particularly, tumor-related arterial hemorrhage was documented as a perilous fatal AE associated with lenvatinib treatment [35].

Discussion

In this meta-analysis, several clinically important findings were identified: (1) Regarding the PR rate and PFS, lenvatinib was superior to sorafenib for DTC treatment. (2) Vandetanib treatment showed the most favorable PFS for MTC treatment. (3) The prognosis of ATC remained very poor even with TKI treatment. (4) CR was extremely rare with TKI treatment. (5) Drug discontinuation due to AEs occurred with equivalent incidence for each TKI in approximately 16%–19% of the treated patients. (6) Each TKI was characterized by specific AEs with high incidence (skin-related AEs, hypertension and proteinuria, and QTc prolongation for sorafenib, lenvatinib, and vandetanib, respectively).

Table 3 Pooled discontinuation rate of TKI treatment

	Discontinuation rate	95%CI	I^2	p
Sorafenib	16%	6–26	0%	0.62
Lenvatinib	16%	7–25	0%	0.71
Vandetanib	19%	6–31	18.2%	0.57

TKI, tyrosine kinase inhibitor; CI, confidence interval; p , p value identified by Egger's regression test

Table 4 Adverse events associated with sorafenib, lenvatinib, and vandetanib treatment

Adverse events	Sorafenib				Lenvatinib				Vandetanib			
	Pooled frequency	95%CI	I^2	p	Pooled frequency	95%CI	I^2	p	Pooled frequency	95%CI	I^2	p
All grades												
HFS	96%	86–100	0.4%	0.49	45%	9–80	90.1%	0.61	N.A	N.A	N.A	N.A
Hypertension	41%	31–51	0.0%	0.51	96%	59–100	90.9%	0.59	36%	26–46	0%	0.66
Proteinuria	N.A	N.A	N.A	N.A	45%	9–80	90.9%	0.33	N.A	N.A	N.A	N.A
Mucositis	30%	19–40	3.1%	0.09	38%	24–51	35.5%	0.82	N.A	N.A	N.A	N.A
Diarrhea	81%	69–92	12.5%	0.08	75%	62–88	33.5%	0.55	73%	52–95	67%	0.87
Fatigue	62%	41–84	67.1%	0.42	70%	60–79	0.01%	0.63	31%	12–50	57.2%	0.28
Weight loss	59%	38–79	67.1%	0.30	53%	33–73	67.6%	0.96	N.A	N.A	N.A	N.A
Rash	79%	54–100	77.2%	0.56	14%	4–24	0%	0.44	44%	26–63	57.1%	0.59
Anorexia	35%	17–53	39.2%	0.46	67%	44–90	76.2%	0.45	24%	14–34	0%	0.43
Alopecia	71%	55–87	24.1%	0.21	13%	3–23	0%	0.57	N.A	N.A	N.A	N.A
ECG QT prolonged	N.A	N.A	N.A	N.A	N.A	N.A	N.A	N.A	19%	8–29	0%	0.19
Grade 3, 4												
HFS	21%	11–31	0%	0.99	3%	0–13	0%	0.94	N.A	N.A	N.A	N.A
Hypertension	9%	0–19	0%	0.91	28%	8–49	71.1%	0.39	8%	0–18	0%	0.98
Proteinuria	N.A	N.A	N.A	N.A	3%	0–13	0%	0.33	N.A	N.A	N.A	N.A
Mucositis	2%	0–12	0%	0.86	3%	0–13	0%	0.76	N.A	N.A	N.A	N.A
Diarrhea	5%	0–15	0%	0.84	9%	0–19	0%	0.72	11%	0–21	0%	0.94
Fatigue	7%	0–17	0%	0.82	9%	0–19	0%	0.83	5%	0–15	0%	0.89
Weight loss	5%	0–15	0%	0.83	9%	0–19	0%	0.87	N.A	N.A	N.A	N.A
Rash	6%	0–16	0%	0.89	3%	0–13	0%	0.72	3%	0–14	0%	0.90
Anorexia	2%	0–13	0%	0.98	2%	0–12	0%	0.49	3%	0–14	0%	0.88
Alopecia	N.A	N.A	N.A	N.A	N.A	N.A	N.A	N.A	N.A	N.A	N.A	N.A
ECG QT prolonged	N.A	N.A	N.A	N.A	N.A	N.A	N.A	N.A	10%	0–21	0%	0.48

HFS, hand foot syndrome; ECG, electrocardiogram; CI, confidence interval; p , p value identified by Egger's regression test; N.A, not applicable

Sorafenib and lenvatinib are currently available for RR-DTC treatment. However, no definitive evidence exists on which drug may lead to better patient outcomes, because no clinical trials have compared sorafenib and lenvatinib directly. The result of the current meta-analysis indicates that lenvatinib has higher potential to cause tumor shrinkage and prolong the PFS than sorafenib. Notably, as described in Table 1, all studies on lenvatinib treatment of DTC included patients previously treated with other TKIs (mainly sorafenib). However, no patients previously treated with other TKIs were included in any of the sorafenib studies, because sorafenib was the first drug approved for RR-DTC treatment. Despite the different inclusion criteria, the longer PFS with lenvatinib treatment indicates that lenvatinib has

superior anti-tumor potency to sorafenib and may be effective even for sorafenib-resistant DTC. Notably, lenvatinib has a broader range of target molecules than sorafenib; specifically, lenvatinib blocks signaling *via* the vascular endothelial growth factor receptor (VEGFR) 1 and fibroblast growth factor FGF receptor (FGFR), whereas sorafenib does not; representative target molecules are listed in Table 5. Thus, even after acquired resistance to sorafenib emerges, lenvatinib may delay tumor growth by inhibiting other distinct receptors such as VEGFR1 and FGFR. Altogether, lenvatinib may be a favorable choice for the treatment of RR-DTC in terms of its anti-tumor effect.

However, lenvatinib treatment was associated with a higher rate of dose reduction and treatment interruption

Table 5 Currently available TKIs and their representative target molecules

Drugs	VEGFR1	VEGFR2	VEGFR3	c-KIT	RET	PDGFR	FGFR1-3	Raf
Sorafenib	–	+	+	+	+	+	–	+
Lenvatinib	+	+	+	+	+	+	+	–
Vandetanib	–	+	–	+	+	–	–	–
Cabozantinib	–	+	–	+	+	–	–	–

TKI, tyrosine kinase inhibitor; VEGFR, vascular endothelial growth factor receptor; KIT, v-kit Hardy-Zuckerman 4 feline sarcoma viral oncogene; RET, rearranged during transfection receptor; PDGFR, platelet-derived growth factor receptor; FGFR, fibroblast growth factor receptor; Raf, v-raf murine sarcoma viral oncogene

due to AEs than sorafenib. Besides, the severity of AEs may differ with sorafenib and lenvatinib treatment. For instance, lenvatinib-induced drastic tumor shrinkage may cause tumor-related bleeding, which in certain cases may lead to sudden death [35]. In this regard, the tumor invasion to surrounding tissues or organs such as vessels, esophagus, skin, or trachea has been identified as a risk factor for lenvatinib-induced tumor-related bleeding [41]. Therefore, sorafenib may be a better choice for a patient with a tumor involving those tissues or organs. Another severe AE associated with lenvatinib is tumor fistula formation, including the formation of skin, tracheo-esophageal, and gastrointestinal fistulas [14, 22, 37]. Such fistulas caused by lenvatinib remarkably diminish the patient quality of life and may require long-term drug interruption or discontinuation. In addition, lenvatinib treatment causes renal impairment in some patients despite appropriate drug interruption and supportive care [51, 52]. In cases when lenvatinib is administered before sorafenib, and lenvatinib-induced renal dysfunction cannot be recovered even after drug discontinuation, the patient may lose the chance to be treated by sorafenib. Considering these severe AEs associated with lenvatinib treatment, sorafenib treatment prior to lenvatinib may be a better treatment choice for some DTC patients. In this regard, a biomarker for the prediction of treatment response and severe AEs would facilitate the selection of the initial drug. However, no such predictive marker has been identified up to date, and thus it should be explored in the future. Furthermore, a clinical trial comparing the efficacy and safety of lenvatinib following sorafenib and *vice versa* may provide the solution to this clinical problem.

As for MTC, the median PFS in the cabozantinib phase III trial (EXAM trial) (11.2 months) was considerably shorter than the pooled median PFS for vandetanib (31 months). However, the EXAM trial included patients previously treated with other TKIs, whereas the ZETA trial [17] (a phase III trial that tested the efficacy of vandetanib for MTC) enrolled only TKI-naïve patients. Furthermore, an important inclusion criterion for the

EXAM trial was the requirement for radiographic progression per the RECIST within the prior 14 months. Importantly, the PFS duration for the placebo group in the EXAM trial was also inferior to that in the ZETA trial (19.3 months in the ZETA trial and 4.0 months in the EXAM trial). Therefore, the longer median PFS duration with vandetanib treatment may be explained by the different levels of disease severity. The comparison of vandetanib and sorafenib in this meta-analysis indicates that vandetanib (31 months) shows longer pooled PFS than sorafenib (16 months). Furthermore, the pooled PFS for vandetanib was longer than the PFS for lenvatinib (9.0 months) reported in a phase II study [22]. Therefore, although we cannot draw a definitive conclusion due to the different inclusion criteria for each study, vandetanib may be the most preferred drug for MTC with regards to PFS.

The differences in the TKI AE profiles identified in this study will facilitate the choice of an appropriate TKI for each patient in the clinical practice. These differential profiles of the analyzed TKIs may arise from their different molecular targets (Table 5). VEGFR inhibition, which is the common target for the TKIs investigated in this study, induces hypertension [53]. In addition to VEGFR, lenvatinib inhibits the FGF signaling pathway, which controls vascular function and blood pressure [54], whereas the other TKIs do not. In contrast, Raf is the characteristic target of sorafenib. Raf inhibition by sorafenib induces mast cell degranulation and maturation, which are associated with various types of skin diseases [55]. Therefore, these differences in molecular targets may result in the characterized different highly observed AEs for sorafenib (skin-related) and lenvatinib (hypertension). Early intervention and appropriate management for these common AEs are important to avoid adverse outcomes. For HFS, patient education and proactive management to keep skin well hydrated, remove calluses regularly, and use pain medication are essential to keep sorafenib dose. In addition, topical corticosteroids are effective to prevent worsening [56]. Once hypertension (systolic blood pressure is ≥ 140 mmHg or diastolic

blood pressure is >90 mmHg) has been induced by TKI treatment, antihypertensive drugs including calcium channel blockers, angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers should be administered. These drugs can be used as single therapy or in combination [57].

Given the high rate of dose reduction or drug interruption and the non-negligible drug discontinuation rate due to AEs, an optimal dose that is better tolerated but presents comparable efficacy to the full dose should be explored for each TKI. Indeed, the results of a phase IV study, which evaluated the benefit-risk of two starting doses (150 mg/day or 300 mg/day) of vandetanib in patients with MTC, were published recently [47]. In this trial, the 300 mg dose showed a more favorable overall response rate than the 150 mg dose (150 mg: 20.0%, 95% CI: 10.5–34.8 and 300 mg: 29.3%, 95% CI: 17.6–44.5). However, with regards to safety, a lower discontinuation rate due to AEs was observed with the 150 mg dose (150 mg: 5.0% and 300 mg: 12.2%). These results indicate that the appropriate starting dose is 300 mg; however, a lower initial dose may reduce toxicity. Regarding lenvatinib, a *post hoc* analysis of the SELECT study revealed that patients with shorter dose interruptions showed longer PFS than those with longer interruptions [58]. These results highlight the importance of dose intensity maintenance with appropriate AE management. However, the remarkably high dose reduction and treatment interruption rate with lenvatinib treatment identified in the present study may provide a rationale to explore the optimal starting dose of lenvatinib.

In line with the high incidence of AEs associated with TKIs and the rarity of cure, the timing of TKI initiation is one of the major clinical issues. DTC and MTC generally grow slowly, and patients with metastatic disease may live without any symptoms for long periods. Therefore, the use of TKIs should be limited to the patients with progressive disease or with tumor-related symptoms such as diarrhea caused by MTC [59]. The doubling time of serum markers, thyroglobulin for DTC and calcitonin for MTC, has been investigated to predict disease progression [60, 61]. These markers should be taken into consideration together with the radiographic assessment for the decision when to start TKIs.

Given the rarity of CR with TKI treatment identified in this meta-analysis, the importance of initial surgery as the only treatment to accomplish a cure may stand out. As for DTC, TKI treatment is currently restricted to patients with RR-DTC. Therefore, if complete resection can be accomplished in locally advanced DTC, surgery followed by RAI therapy should be the first choice. In DTC patients with distant metastases or high risk for future relapse, total thyroidectomy should be performed

to remove all normal follicular thyroid cells that take iodine up before the initiation of RAI therapy. Therefore, surgery should preserve its important role in DTC treatment even in the era of TKIs. However, due to the limited number of hospitals providing RAI therapy in Japan, the waiting periods for RAI therapy are long. Another clinical concern is that metastatic disease can progress during the levothyroxine withdrawal before RAI therapy. Additionally, clinicians often encounter a patient with a distant metastasis from DTC who has previously been treated with hemithyroidectomy or subtotal thyroidectomy. Completion total thyroidectomy should be performed before RAI therapy, but a second surgery is associated with higher complication risks than the initial surgery, including the risk of permanent hypoparathyroidism [62]. Considering these unfavorable clinical concerns associated with RAI therapy, the implementation of a treatment strategy where a TKI is administered without RAI therapy (RAI-skip therapy) would be one of the next clinical challenges that may increase the number of patients benefitting from TKIs.

To explore novel therapeutic strategies that further improve the treatment outcomes in the era of TKIs, several phase II/III studies are now ongoing (Table 6). Novel TKIs (anlotinib, apatinib, and donafenib) are currently tested in phase III clinical trials for thyroid cancer (NCT 02586337, NCT3048877, and NCT03602495). In addition to such single TKI therapies, phase II clinical trials are currently ongoing to evaluate the efficacy and safety of combined therapies including TKIs and immune checkpoint inhibitors (pembrolizumab, nivolumab, ipilimumab, and atezolizumab) (NCT02973997, NCT03914300, and NCT03170960). Besides TKI treatment, B-Raf kinase (BRAF) and MEK inhibitors (dabrafenib and trametinib) were recently approved by the FDA for ATC treatment based on the results of a phase II study [63]. For DTC, this combination therapy is currently being tested in phase II studies (NCT03244956 and NCT01723202), and improved outcomes are expected. As another therapeutic option, entrectinib, a potent inhibitor of the tropomyosin receptor kinase (TRK) [64], is currently available for patients with *NTRK*-fusion gene positive thyroid cancer in Japan.

As another potent therapeutic strategy, several studies indicate the feasibility of neoadjuvant molecular targeted therapies including TKIs and BRAF/MEK inhibitors followed by surgery. Milner *et al.* reported an advanced MTC case, in which vandetanib-induced local tumor shrinkage enabled the surgical resection of the primary site [65]. In addition, the results of case studies, which tested the efficacy of neoadjuvant dabrafenib plus trametinib followed by surgery in patients with *BRAF*^{V600E} mutation-positive ATC, have recently been published

Table 6 Currently recruiting and ongoing clinical trials (phase II or III) for thyroid cancer treatment

Drugs	Tumor	Study type	Status	NCT#
Anlotinib	DTC	Phase II/III	Active, not recruiting	NCT02586337
Apatinib	DTC	Phase III	Recruiting	NCT03048877
Donafenib	DTC	Phase III	Recruiting	NCT03602495
Lenvatinib + Pembrolizumab	DTC	Phase II	Recruiting	NCT02973997
Cabozantinib + Nivolumab + Ipilimumab	DTC	Phase II	Recruiting	NCT03914300
Cabozantinib + Atezolizumab	MTC	Phase I/II	Recruiting	NCT03170960
Dabrafenib + Trametinib	DTC	Phase II	Recruiting	NCT03244956
Dabrafenib ± Trametinib	DTC	Phase II	Active, not recruiting	NCT01723202

DTC, differentiated thyroid carcinoma; MTC, medullary thyroid carcinoma

[66]. In this study, six *BRAF*^{V600E} mutation positive ATC patients were enrolled, and a complete resection following neoadjuvant dabrafenib plus trametinib was achieved for all six patients. Furthermore, four patients were free of local, regional, and distant metastases over the course of one year. These results demonstrate the feasibility of surgery after neoadjuvant dabrafenib and trametinib therapy for *BRAF*^{V600E} mutation-positive ATC. In addition, adjuvant external beam radiotherapy following surgery reportedly prolongs the survival of patients with ATC [6, 9, 67, 68]. Therefore, a multimodal treatment including neoadjuvant molecular targeted therapies, surgery, and external beam radiotherapy may be a potent therapeutic strategy for ATC. However, some clinical concerns may be associated with this strategy. One is that ATC may progress rapidly during the drug withdrawal periods before surgery, and the other is that the combined therapy may increase surgery-related AEs such as postoperative wound dehiscence. Therefore, further prospective studies are required to evaluate the benefits from this strategy.

Our study has several limitations. First, no clinical trials have compared each TKI directly for any pathological type of thyroid cancer. Second, a significant heterogeneity was observed in some meta-analyses. Third, this meta-analysis included retrospective studies. These limitations may impair the reliability of the

results. Therefore, future RCTs, which carry out a one-on-one comparison of each TKI with a large number of patients, are needed to verify the findings of this meta-analysis.

In conclusion, the elucidation of the differences in the efficacy and frequently observed AEs of the currently available TKIs would provide a better understanding of thyroid cancer treatment. Future studies should focus on the exploration of the optimal TKI treatment choice for each patient, further improvement of patient outcomes through initial dose optimization, and development of novel therapeutic strategies including new TKIs, combination therapy of TKIs and other anti-cancer drugs such as ICIs, and other molecular targeted therapy including BRAF and MEK inhibitors. Even in the era of TKIs, a multimodal therapeutic approach is required for improved survival.

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