Thyroid Research

RESEARCH

Open Access

BRAF^{V600E} mutation is associated with better prognoses in radioactive iodine refractory thyroid cancer patients treated with multi-kinase inhibitors: a retrospective analysis of registered clinical trials

Di Sun[1,2†], Xin Zhang[1,2†], Xiaona Jin[1,2], Cong Shi[1,2], Yuqing Sun[1,2], Yingqiang Zhang[1,2], Jun Liang[3,4*] and Yansong Lin[1,2*]

Abstract

Background The antiangiogenic multi-kinase inhibitors (MKIs) apatinib, donafenib, and anlotinib have demonstrated satisfactory efficacy in radioactive iodine refractory differentiated thyroid cancer (RAIR-DTC) in their phase II/III trials. However, the potential impact factors on the efficacy of these MKIs remain unclear.

Methods RAIR-DTC patients enrolled in clinical trials of apatinib, donafenib, and anlotinib in our center were retrospectively reviewed. The Kaplan–Meier method was used to examine the relationship between clinicopathological variables and progression-free survival (PFS) and overall survival (OS), followed by a multivariate Cox analysis on PFS.

Results A total of 71 progressive RAIR-DTC patients were reviewed, of which 26.7% were treated by anlotinib, 45.1% by apatinib, and 28.2% by donafenib. The median follow-up time was 44.1 months, the median PFS was 21.1 months, and the estimated median OS was 47.7 months. PFS and OS showed no significant differences in patients treated with apatinib, donafenib, or anlotinib. In the univariate analyses, patients with *BRAF*^{V600E} mutation showed longer PFS (HR 0.345, 95% CI 0.187–0.636, $p < 0.001$) and OS (HR 0.382, 95% CI 0.166–0.878, $p = 0.019$) compared with patients with wild-type *BRAF*. Patients with follicular thyroid cancer and bone metastases had shorter PFS, and patients with worse Eastern Cooperative Oncology Group performance status, bone metastases, and a larger tumor burden had shorter OS. In the multivariate Cox analysis, *BRAF*^{V600E} mutation was the only independent predictor of longer PFS (HR 0.296, 95% CI 0.138–0.638, $p = 0.002$). The overall response rate and disease control rate didn't differ between *BRAF*^{V600E} mutation status. Subgroup analysis of PFS in papillary thyroid cancer patients stratified by *BRAF*^{V600E} mutation status showed that *BRAF*^{V600E} mutation was associated with longer PFS in all clinicopathological subgroups (hazard ratio < 1).

†Di Sun and Xin Zhang have contributed equally to this work and share first authorship.

*Correspondence:
Jun Liang
liangjun1959@aliyun.com
Yansong Lin
linys@pumch.cn; linyansong1968@163.com
Full list of author information is available at the end of the article

Conclusion RAIR-DTC patients with $BRAF^{V600E}$ mutation treated with apatinib, donafenib, or anlotinib achieved better prognoses compared with patients with wild-type *BRAF*, indicating that the genetic background may play a role in predicting the efficacy of MKIs therapies.

Trial registration This retrospective cohort included patients in our center from clinical trials of apatinib (NCT02731352, NCT03048877), donafenib (NCT02870569, NCT03602495), and anlotinib (NCT05007093).

Keywords $BRAF^{V600E}$, Multi-kinase inhibitors, Overall survival, Progression-free survival, Radioactive iodine refractory differentiated thyroid cancer

Background

Patients with differentiated thyroid cancer (DTC) generally have favorable outcomes under the typical regimen of surgery, radioactive iodine (RAI) ablation, and thyroid stimulating hormone (TSH) suppression therapy. However, patients who develop resistance to RAI experience a 10-year survival rate of approximately 10%, contributing to the majority of disease-specific mortality in thyroid cancer [1]. Sorafenib and lenvatinib were the first two multi-kinase inhibitors (MKIs) approved by the United States Food and Drug Administration for patients with progressive or symptomatic RAI refractory DTC (RAIR-DTC) a decade ago, and they are still the first-line-treatment for such patients globally [2–6]. Prior to the approval of sorafenib and lenvatinib by China's National Medical Products Administration in 2017 and 2020, respectively, the lack of effective treatment and the unsatisfactory survival (5-year survival rate of 84.3%, 2012–2015) prompted the development of Chinese domestic MKIs [7]. Apatinib, donafenib, and anlotinib, which primarily target VEGFR-2, are now the most mature Chinese domestic antiangiogenic MKIs for RAIR-DTC patients as a result of their demonstrated progression-free survival (PFS) benefits in placebo-controlled, phase III/II trials [8–11]. Of note, apatinib was the only MKI to show overall survival (OS) benefits worldwide in a phase III trial [10]. While increasing treatment options for RAIR-DTC patients may have contributed to the recent improvement in the 5-year survival rate in China (92.9%, 2019–2021), there is still a significant gap when compared with the United States (98.4%, 2014–2020) [12, 13]. There is considerable space for enhancing the management of Chinese RAIR-DTC patients. One of the challenges is identifying factors that could influence efficacy and timely initiating MKI therapies in patients who are likely to have unfavorable outcomes.

To date, our understanding of the influence of certain factors on the efficacy of MKIs treatments has primarily come from a series of post hoc analyses of the lenvatinib SELECT trial. There were factors in correlation with longer PFS, including a lower baseline Eastern Cooperative Oncology Group performance status (ECOG PS), a neutrophil-to-lymphocyte ratio (NLR) ≤ 3, lower baseline Ang2 levels and dose interruptions of less than 10% [14–16]. Younger age (≤ 65 years), lower baseline VEGF levels, and the aforementioned factors were also associated with a higher overall response rate [14–17]. As the follow-up time extended, the benefit in OS was observed in patients with older age (> 65 years), lower tumor burden (baseline sums of diameters of target lesions ≤ 40 mm), NLR ≤ 3, and ECOG PS of 0 [14, 17, 18]. The presence of tumor-related symptoms was also proven as a negative prognostic factor for PFS and OS in several reports [19, 20].

However, evidence for Chinese patients is limited since they were not included in the SELECT trial. Additionally, the possible correlation between genetic background and the efficacy of MKI therapies was not well addressed, as molecular typing had not been incorporated into clinical practice until recent years. Moreover, there is no information available on factors that may be associated with the efficacy of Chinese domestic MKIs, which are more accessible and widely used in China. China ranked second in the world for the incidence of thyroid cancer with an age-standardized rate of 24.6 per 100,000 and accounted for over half of the new cases worldwide in 2022 (466,118/821,214) [21]. Therefore, there may be a large population of patients with advanced disease, particularly those with RAIR-DTC, who will likely require targeted therapy. In this study, we investigated factors associated with the efficacy of the Chinese domestic antiangiogenic MKIs apatinib, donafenib, and anlotinib in treating RAIR-DTC patients.

Methods

Patients

We retrospectively reviewed patients in our center enrolled in the clinical trials for apatinib (NCT02731352, NCT03048877), donafenib (NCT02870569, NCT03602495), and anlotinib (NCT05007093). For apatinib, the phase II trial enrolled patients from March to November 2016 and the phase III trial enrolled patients from February 2017 to July 2019. For donafenib, the phase II trial enrolled patients from March to September 2017 and the phase III trial enrolled patients from September 2018 to December 2020. For anlotinib, the open-label trial enrolled patients from April 2021 to April 2023. The

study design and results of these trials have been reported previously [8, 10, 22–24]. Briefly, all these trials enrolled patients aged ≥ 18 years old with histologically confirmed locally advanced or metastatic RAIR-DTC, measurable lesions per Response Evaluation Criteria In Solid Tumors version 1.1 (RECIST 1.1) [25], and experienced radiologically confirmed disease progression within 12 (phase III trial of apatinib), 14 (phase II and phase III trials of donafenib and phase II trial of apatinib) or 18 (anlotinib) months. Prior targeted therapies were allowed in all trials except for the phase II trial of donafenib [23]. These trials were approved by the authors' institution's Ethics Committee and were conducted in accordance with the Declaration of Helsinki and the International Conference and Good Clinical Practice guidelines. All patients provided written informed consent before participating in the trials.

Study treatments and assessments

Dosage regimens varied across different trials. In the phase II trial of apatinib, 10 patients started at 750 mg daily and another 10 patients started at 500 mg daily [22]; in phase III trial, 500 mg daily was the standard dose for the treatment group [10]. In the phase II trial of donafenib, patients were randomized at a ratio of 1:1 to either 300 or 200 mg twice daily [23]; in phase III trial, 300 mg twice daily was the standard dose for the treatment group [8]. The trial of anlotinib is open-label, with a standard dose of 12 mg once daily, 2 weeks on, 1 week off, 21 days per cycle [24]. Study drugs were administered orally until disease progression, occurrence of intolerable toxic effects, withdrawal of consent, noncompliance, or the investigators' decision to discontinue treatment.

Efficacy assessments included the PFS, the overall response rate (ORR), and OS. In the current study, PFS was defined as the time from the first day of treatment to death or progression, whichever occurred first. OS was defined as the time from the first day of treatment to death from any cause. Specifically, for patients in the placebo group of the two phase III trials, the starting point for efficacy assessments was the time they crossed over to the treatment group. The data cut-off used to evaluate outcomes was August 1, 2024.

BRAF^{V600E}, *RAS*, and *TERT* promoter mutation analyses

Available formalin-fixed, paraffin-embedded biopsies from the primary tumor or metastatic sites were collected for molecular testing. *BRAF*^{V600E}, *RAS*, and *TERT* promoter mutation status were analyzed by direct Sanger sequencing ($n=19$) and Next-Generation sequencing (NGS) ($n=44$) using the protocols described by Yang et al. and Mu et al., respectively [26, 27].

Other clinical characteristics

Baseline thyroglobulin (Tg) was measured simultaneously by electrochemiluminescence immunoassays (Roche Diagnostics GmbH, Mannheim, Germany). Tg readings with positive Tg antibody (TgAb) or improper TSH suppression level (> 0.1 μIU/mL) were censored. NLR was calculated based on peripheral blood cell counts.

Statistical analyses

Continuous variables are expressed as mean ± standard deviation or median and interquartile range (IQR) as applicable, and categorical variables are expressed as number and percentage. PFS and OS were calculated using the Kaplan–Meier method and compared using the log-rank test. Hazard ratios (HRs) and their 95% confidence intervals (CIs) were calculated using the Cox proportional hazards model. The LASSO Cox model was used to select variables for the multivariate analysis with the glmnet package in R (version 4.3.1) [28].

Results

Patients

Seventy-one patients were retrospectively reviewed from five clinical trials (Fig. 1). The baseline clinical characteristics of patients are presented in Table 1. Most patients had papillary thyroid cancer (78.9%), primary lesions that expanded beyond the thyroid capsule (T3a-4) (64.8%), and pathologically confirmed cervical lymph node metastases (N1) (71.8%). *BRAF*^{V600E} mutation was positive in 55.6% (35/63) of tested patients. Prior to the treatment, approximately one-third of the patients had bone metastases and 26.8% had failed at least one targeted therapy. Sorafenib was the most commonly used regimen among the 26 previous targeted treatment courses (42.3%), followed by donafenib (19.2%). There was no statistically significant difference in baseline characteristics among the patients receiving anlotinib, apatinib and donafenib, except for the number of prior targeted therapy courses ($p=0.002$) (Supplementary Table 1).

At the data cutoff (August 1, 2024), the median follow-up time was 44.1 (95% CI 33.8–54.4) months. Among the 71 patients in the overall cohort, 51 (71.8%) progressed, and the median PFS was 21.1 (95% CI 14.4–27.8) months. Twenty-nine (40.8%) of the patients died, and the estimated median OS was 47.7 (95% CI 18.6–76.8) months.

Factors correlated with PFS

PFS was significantly shorter in patients with follicular thyroid cancer (FTC) than those with papillary thyroid cancer (PTC) (median, 8.7 vs. 23.0 months, HR 1.963, 95% CI 1.018–3.783, $p=0.040$), and those with bone metastases than those without (median, 11.1 vs.

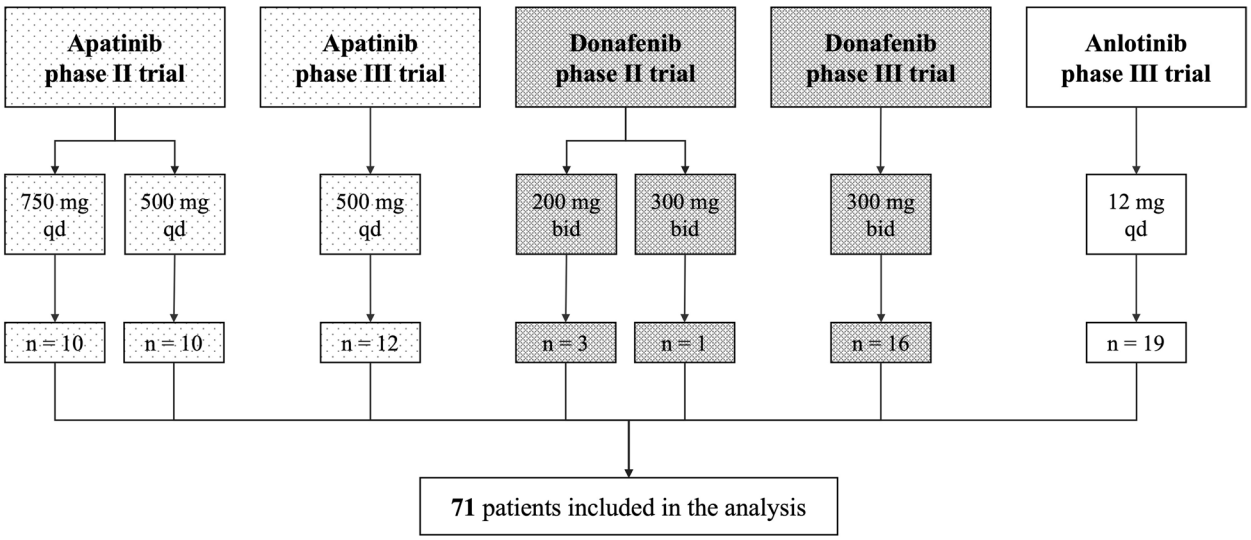

Fig. 1 The study population

25.0 months, HR 2.167, 95% CI 1.174–4.000, $p=0.011$) (Fig. 2, Table 2). Additionally, $BRAF^{V600E}$ mutants had a longer PFS than $BRAF^{V600E}$ wild-type patients (Median, 29.8 vs. 10.3 months, HR 0.345, 95% CI 0.187–0.636, $p<0.001$) (Fig. 2, Table 2). PFS did not differ among different treatment regimens ($p=0.417$, Fig. 2), sex ($p=0.228$), age at initiating MKI treatment ($p=0.165$), *TERT* promoter mutation status ($p=0.088$), *RAS* mutation ($p=0.239$), baseline serum Tg level ($p=0.286$), baseline NLR ($p=0.781$), ECOG PS ($p=0.184$), the sum of target lesion diameters at baseline ($p=0.432$), or prior targeted therapy courses ($p=0.943$) (Table 2).

Given the small sample size and the possibility of multicollinearity among the variables, we first performed a LASSO Cox regression analysis for variable selection (Supplementary Fig. 1). The five selected parameters with non-zero coefficients for the multivariate Cox analysis were sex, histology, $BRAF^{V600E}$ mutant status, regimen, and age at initiating MKI treatment (Supplementary Table 2). Multivariate Cox analysis showed that $BRAF^{V600E}$ status was the only independent predictor of PFS (mutation vs. wild-type, HR 0.296, 95% CI 0.138–0.638, $p=0.002$, Table 3). As $BRAF^{V600E}$ mutation was rare in FTC patients in the current ($n=1$) and many other studies, we further performed a multivariate Cox analysis restricted to PTC patients to avoid the influence of the higher proportion of $BRAF^{V600E}$-negative patients in FTC. $BRAF^{V600E}$ (mutation vs. wild-type, HR 0.267, 95% CI 0.120–0.593, $p=0.001$) remained as the only independent prognostic factor (Table 3). We also performed a Cox regression analysis that included all the significant variables in the univariate analysis of PFS and OS (histology, $BRAF^{V600E}$, bone metastases, ECOG PS, sum of target lesion diameters at baseline). $BRAF^{V600E}$ mutation was still the only independent predictor in both the entire cohort and PTC patients (Supplementary Table 3).

Factors correlated with OS

Shorter OS was observed in patients with larger tumor burden (sum of target lesion diameters at baseline, >40 vs. ≤ 40 mm, median 34.7 vs. 94.0 months, HR 3.738, 95% CI 1.620–8.628, $p<0.001$), higher ECOG PS (2 vs. 0–1, median 34.2 vs. 52.4 months, HR 3.802, 95% CI 1.103–13.108, $p=0.023$) and bone metastases (positive vs. negative, median 34.9 vs. 83.2 months, HR 2.243, 95% CI 1.029–4.891, $p=0.037$) (Fig. 3, Table 2).The benefit of $BRAF^{V600E}$ mutants over wild-type $BRAF^{V600E}$ patients was also observed in OS (median 94.0 vs. 34.7 months, HR 0.382, 95% CI 0.166–0.878, $p=0.019$) (Fig. 3, Table 2). Multivariate Cox analyses was not performed because of the limited number of outcome events.

Baseline characteristics and detailed efficacy stratified by $BRAF^{V600E}$ mutation status

We next evaluated the factors included in the survival analysis in patients stratified by $BRAF^{V600E}$ mutation status (Table 4). $BRAF^{V600E}$ mutation was more prevalent in patients with PTC than those with FTC ($p=0.001$) and frequently co-occurred with *TERT* promoter mutation ($p<0.001$). $BRAF^{V600E}$ wild-type patients were more likely to developed bone metastases ($p=0.034$) and had a higher ECOG PS ($p=0.034$) (Table 3).

$BRAF^{V600E}$ mutants didn't hold superior best overall response ($p=0.135$), objective response rate ($p=0.185$), or disease control rate ($p=0.444$) (Table 5). A longer PFS was observed in $BRAF^{V600E}$ mutated

Table 1 Baseline clinicopathological characteristics of RAIR-DTC patients treated with MKIs

Characteristics	Number/Median	Percentage (%)/IQR
Patient number	71	
Sex		
Female	37	52.1
Male	34	47.9
Age at diagnosis, year	48	42.0–56.0
Histology		
PTC	56	78.9
FTC	15	21.1
T stage		
1-3a	21	29.6
3b-4b	46	64.8
NA	4	5.6
N stage		
0	13	18.3
1a	4	5.6
1b	47	66.2
NA	7	9.9
Number of RAI	2	2–4
Total cumulative activity (mCi)	325	230–611
BRAF^{V600E}		
Mutation	35	49.3
Wild-Type	28	39.4
Untested	8	11.3
TERT promoter		
Mutation	37	52.1
Wild-Type	21	29.6
Untested	13	18.3
RAS		
Mutation	6	8.4
Wild-Type	42	59.2
Untested	23	32.4
Age at initiating MKI treatment (year)	57	49.0–64.0
Age at initiating MKI treatment group		
≥ 55	42	59.2
< 55	29	40.8
Serum Tg, ng/mL ($n = 56$)	502.5	95.9–1982.0
Baseline serum Tg group (ng/mL) ($n = 56$)		
> 500	28	50.0
≤ 500	28	50.0
NLR	2.9	2.13–3.50
Baseline NLR group		
> 3	29	40.8
≤ 3	42	59.2
Sum of target lesion diameters	39.9	29.1–62.2
Sum of target lesion diameters at baseline (mm)		
> 40	35	49.3
≤ 40	36	50.7
Bone metastases		
Negative	47	66.2

Table 1 (continued)

Characteristics	Number/Median	Percentage (%)/IQR
Positive	24	33.8
ECOG PS		
0	32	45.1
1	34	47.9
2	5	7
Regimen		
Anlotinib	19	26.7
Apatinib	32	45.1
Donafenib	20	28.2
Prior targeted therapy courses		
0	52	73.2
1	12	16.9
2	7	9.9
Regimens of prior targeted therapy ($n=26$)		
Sorafenib	11	42.3
Donafenib	5	19.2
Apatinib + Carelizumab	4	15.4
Apatinib	2	7.7
RX208 tablets	2	7.7
Pralsetinib	1	3.8
Vandetanib	1	3.8

Abbreviations: *RAIR-DTC* radioactive iodine refractory differentiated thyroid cancer, *MKI* multi-kinase inhibitor, *PTC* papillary thyroid cancer, *FTC* follicular thyroid cancer, *NA* not available, *RAI* radioactive iodine, *Tg* thyroglobulin, *NLR* neutrophil-to-lymphocyte ratio, *ECOG PS* Eastern Cooperative Oncology Group performance status, *IQR* interquartile range

patients treated with anlotinib (mutation vs. wild-type, median, not reached vs. 10.3 months, HR 0.147, 95% CI 0.030–0.719, $p=0.007$) and apatinib (mutation vs. wild-type, median, 35.3 vs. 11.1 months, HR 0.201, 95% CI 0.064–0.631, $p=0.002$). While the median PFS tended to be longer in the $BRAF^{V600E}$ mutated patients treated with donafenib (Mutation vs. Wild-type, Median, 28.8 vs. 5.5 months) (Table 5), the difference was not statistically significant ($p=0.569$).

We also performed an exploratory subgroup analysis of PFS in PTC patients stratified by $BRAF^{V600E}$ mutation status. Patients with FTC or *RAS* mutation were excluded, as it was rare for FTC patients to exhibit $BRAF^{V600E}$ mutation ($n=1$) or for *RAS* mutations to co-exist with $BRAF^{V600E}$ mutation ($n=0$). $BRAF^{V600E}$ mutants were found to have better PFS in all subgroups (HR < 1) (Fig. 4). Patients with *TERT* promoter mutation appeared to fare better when also harboring with $BRAF^{V600E}$ mutations. Regardless of whether the patients had previously received targeted treatments, $BRAF^{V600E}$ mutation appeared to retain the potential of a longer PFS (Fig. 4).

Discussion

Over the past decade, MKIs have gradually developed a solid position in the treatments of RAIR-DTC. Unlike selective inhibitors, which are only suitable for patients with certain genetic mutations, MKIs are generally applicable to all patients with progressive RAIR-DTC and are often more accessible and affordable [4, 5]. In addition to lenvatinib and sorafenib, more cost-effective options such as anlotinib, apatinib and donafenib are now available for Chinese patients. These MKIs have been demonstrated to prolong PFS and reduce tumor burden [2, 3, 8–10, 29]. However, the varying benefits observed among patients have raised questions regarding the most appropriate candidates and the optimal timing of these drugs.

In this retrospective study, we pooled the participants treated with anlotinib, apatinib, and donafenib into one cohort, as they shared similar baseline characteristics except for the number of prior targeted therapy courses. While the dosing regimens of apatinib and donafenib varied in the trials, ultimately the patients were pooled together because the phase II studies of both drugs showed no statistically significant differences in

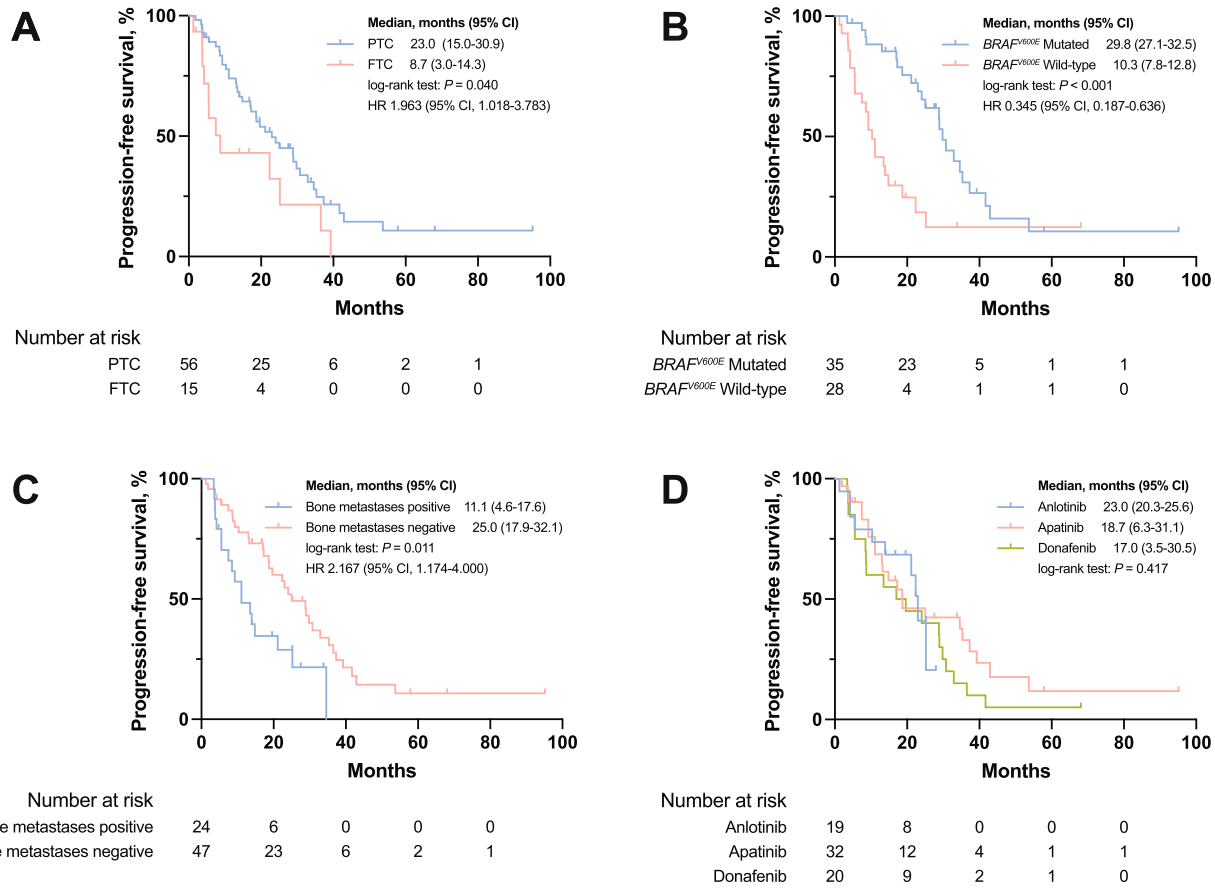

Fig. 2 Kaplan–Meier curves of progression-free survival by clinicopathological factors and regimens. Kaplan–Meier analysis of progression-free survival in patients in the following subgroups. **A** Histology: FTC vs. PTC; **B** *BRAF*^{V600E} status: mutated vs. wild-type; **C** Bone metastases: positive vs. negative; **D** Regimen: anlotinib vs. apatinib vs. donafenib. Abbreviations: PTC, papillary thyroid cancer; FTC, follicular thyroid cancer; HR, hazard ratio

PFS between dosing subgroups [22, 23]. There were no significant differences in PFS and OS among patients treated with anlotinib, apatinib, or donafenib ($p > 0.05$), which allowed us to explore if there were any universal factors that impacted the outcome of the MKI therapies. In addition to conventional clinicopathological factors, genetic alterations including *BRAF*^{V600E} and *TERT* promoter mutations were also taken into consideration in our study, as 85.9% (63/71) of our patients had undergone genetic testing.

The most prominent finding of our study was the favorable outcome of patients with *BRAF*^{V600E} mutation. *BRAF*^{V600E} mutation has been shown to be an indicator of poor clinicopathological outcomes in DTC, including aggressive pathological features, lymph node metastasis, distant metastasis, higher TNM stage, recurrence, persistent disease, and even mortality [30–33]. However, there were studies showed that *BRAF*^{V600E} mutation maybe not an independent predictor of these unfavorable clinical features [34–38]. For example, without the coexistence of additional late molecular events like mutations in *PIK3CA*, *TP53*, or *TERT* promoter (the most frequent co-occurring mutation), *BRAF*^{V600E} mutation alone may not be sufficient to cause poor outcomes [39–43]. In PTC patients with distant metastases, *BRAF*^{V600E} mutation also results in the loss of radioactive iodine avidity, especially when paired with the *TERT* promoter mutation [26, 44–47]. Notably, although over 80% of the *BRAF*^{V600E} mutants in our cohort had accompanying *TERT* promoter mutations, these patients still presented much better PFS and OS than *BRAF*^{V600E} wild-type patients, despite the fact that *TERT* promoter mutation was found to accelerate *BRAF* mutation-induced thyroid cancer dedifferentiation and progression [48]. This finding also supported prior reports of *BRAF*^{V600E} mutants fared better on PFS under the treatment of sorafenib, lenvatinib, and apatinib than wild-type patients [2, 15, 22, 49]. Additionally, our subgroup analysis indicated that previous failed targeted therapies did not hinder the benefit of the *BRAF*^{V600E} mutation in the subsequent MKI treatments in the subgroup analysis. These results bolstered confidence in the efficacy of MKI therapies

Table 2 Univariate analyses of factors associated with PFS and OS of RAIR-DTC patients treated with MKIs

	Progression-free survival					Overall survival				
Characteristics	**Median**	**95% CI**	**Log-rank *P* value**	**Hazard Ratio**	**95% CI**	**Median**	**95% CI**	**Log-rank *P* value**	**Hazard Ratio**	**95% CI**
Overall ($n=71$)	21.1	14.4–27.8				47.7	18.6–76.8			
Sex			0.228					0.553		
Female	22.4	12.9–31.8				83.2	7.5–159.0			
Male	21.1	12.8–29.5				47.7	24.3–71.1			
Age at initiating MKI treatment (year)			0.165					0.168		
≥55	24.0	16.4–31.6				83.2	29.6–136.9			
<55	13.9	2.9–24.9				34.9	33.4–36.4			
Histology			0.040	1.963	1.018–3.783			0.692		
PTC	23.0	15.0–30.9				47.7	17.3–78.1			
FTC	8.7	3.0–14.3				NR	NE			
BRAF^{V600E} ($n=63$)			<0.001	0.345	0.187–0.636			0.019	0.382	0.166–0.878
Mutation	29.8	27.1–32.5				94.0	19.3–168.8			
Wild-Type	10.3	7.8–12.8				34.7	33.8–35.6			
TERT promoter ($n=58$)			0.088					0.835		
Mutation	24.0	12.7–35.3				47.7	40.2–55.2			
Wild-Type	13.9	1.7–26.1				NR	NE			
RAS ($n=48$)			0.239					0.610		
Mutation	25.2	8.4–42.0				NR	NE			
Wild-Type	22.4	14.5–30.3				46.8	36.5–57.1			
Baseline serum Tg (ng/mL) ($n=56$)			0.286					0.241		
>500	21.1	10.4–31.9				46.8	27.1–66.5			
≤500	25.2	7.5–42.9				94.0	19.3–168.8			
Baseline NLR			0.781					0.24		
>3	21.1	4.9–37.4				34.9	NE			
≤3	19.6	12.2–27.1				52.4	23.9–80.8			
ECOG PS			0.184					0.023	3.802	1.103–13.108
0–1	22.4	16.1–28.6				52.4	17.8–86.9			
2	5.5	0.0–15.9				34.2	NE			
Sum of target lesion diameters at baseline (mm)			0.432					<0.001	3.738	1.620–8.628
>40	21.1	15.7–26.6				34.7	33.1–36.3			
≤40	23.0	7.9–38.0				94.0	73.5–114.6			
Bone Metastases			0.011	2.167	1.174–4.000			0.037	2.243	1.029–4.891
Positive	11.1	4.6–17.6				34.9	26.3–43.5			

Table 2 (continued)

Characteristics	Progression-free survival					Overall survival				
	Median	95% CI	Log-rank *P* value	Hazard Ratio	95% CI	Median	95% CI	Log-rank *P* value	Hazard Ratio	95% CI
Negative	25.0	17.9–32.1				83.2	16.6–149.9			
Regimen			0.417					0.425		
Donafenib	17.0	3.5–30.5				83.2	NE			
Apatinib	18.7	6.3–31.1				46.3	29.7–62.9			
Anlotinib	23.0	20.3–25.6				38.9	20.0–57.9			
Prior targeted therapy courses			0.943					0.47		
0	25.0	11.2–38.8				83.2	30.1–136.3			
1	22.4	14.8–29.9				47.7	19.9–75.5			
2	14.8	8.1–21.5				34.2	NE			

Abbreviations: *PFS* progression-free survival, *OS* overall survival, *RAIR-DTC* radioactive iodine refractory differentiated thyroid cancer, *MKI* multi-kinase inhibitor, *PTC* papillary thyroid cancer, *FTC* follicular thyroid cancer, *RAI* radioactive iodine, *Tg* thyroglobulin, *NLR* neutrophil-to-lymphocyte ratio, *ECOG PS* Eastern Cooperative Oncology Group performance status, *CI* confidence interval, *NR* not reached, *NE* not estimable

Table 3 Multivariate Cox analyses of factors for PFS in RAIR-DTC patients treated with MKIs

Characteristics	Category	Full analysis ($n=63$)			PTC patients only ($n=52$)		
		P value	Hazard Ratio	95% CI	*P* value	Hazard Ratio	95% CI
Sex	Male versus Female	0.093	1.953	0.895–4.259	0.088	2.058	0.897–4.720
$BRAF^{V600E}$	Mutation versus Wild-type	0.002	0.296	0.138–0.638	0.001	0.267	0.120–0.593
Age at initiating MKI treatment	≥ 55 versus < 55	0.333	0.713	0.360–1.414	0.281	0.665	0.316–1.397
Regimen	Anlotinib versus Apatinib versus Donafenib	0.434	0.829	0.518–1.326	0.518	0.836	0.485–1.440
Histology	FTC versus PTC	0.167	1.89	0.766–4.663			

Abbreviations: *PFS* progression-free survival, *RAIR-DTC* radioactive iodine refractory differentiated thyroid cancer, *MKI* multi-kinase inhibitor, *PTC* papillary thyroid cancer, *FTC* follicular thyroid cancer, *CI* confidence interval

for RAIR-DTC patients with $BRAF^{V600E}$ and even *TERT* promoter mutations, contradicting previous studies that linked these events to a poor prognosis. Notably, in our study, whereas $BRAF^{V600E}$ mutants exhibited prolonged PFS than $BRAF^{V600E}$ wild-type patients, the ORR did not differ between these patient groups, indicating that $BRAF^{V600E}$ mutated tumors may be able to sustain a more lasting response to MKIs rather than achieving more tumor shrinkage.

The reason why $BRAF^{V600E}$ mutation is an indicator of better prognosis is yet to be elucidated. In the biomarker analysis of the DECISION trial and exploratory post hoc analysis of the SELECT trial, there were no interactions between $BRAF^{V600E}$ mutation and MKIs, and *BRAF* wild-type was found to be prognostic for worse PFS in the placebo arm [2, 15, 50]. The DECISION trial concluded that the better PFS in $BRAF^{V600E}$ mutation patients was attributed to the inner indolent feature of PTC over FTC, as $BRAF^{V600E}$ is prevalent in PTC [2]. The prolonged PFS observed in the placebo-treated patients with PTC harboring $BRAF^{V600E}$ mutation in the SELECT trial strongly suggested that $BRAF^{V600E}$, rather than PTC itself, is responsible for the inherent indolent behavior of tumors. Nowadays cancer is increasingly recognized as a genetic disease, and we agree that the potential influence of $BRAF^{V600E}$ mutation's inherent indolent behavior on the better survival of RAIR-DTC patients receiving MKI therapies should not be overlooked, as $BRAF^{V600E}$ mutation was the only independent predictor for PFS in our study. Aside from its indolent nature, there may be other potential reasons why patients with $BRAF^{V600E}$ mutation may sustain a more lasting response under MKI treatment. $BRAF^{V600E}$ mutation exhibits dual angiogenic effects in promoting both VEGF overexpression and methylation-induced silencing of TIMP3, a tumor suppressor that inhibits angiogenesis by blocking the binding of VEGF to its receptor [51–54]. The more active angiogenesis in tumors harboring $BRAF^{V600E}$ may explain why such patients achieved more prolonged PFS under angiogenesis therapy than wild-type patients. Compared to other driven mutations like *RET/PTC*, *ALK*, *RAS*, etc., $BRAF^{V600E}$ is located in the middle of the mitogen-activated protein kinases pathway, allowing MKIs to block both the primary and the potential bypass signals. This may also explain the relatively limited efficacy in terms of ORR (dabrafenib 35%, dabrafenib + trametinib 30%) and PFS (median, dabrafenib 10.7 months, dabrafenib + trametinib 15.1 months) in the *BRAF*-Mutated RAIR-DTC patients treated with dabrafenib and dabrafenib + trametinib [55].

Notably, no studies have addressed the significance of co-occurring *TERT* promoter mutation in the favorable outcome under MKI therapies. Further studies are needed to determine whether the genetic duet of *BRAF* and *TERT* promoter mutation may act as an Achilles' heel under MKI therapies, resulting in better therapeutic responses as they do under *BRAF* and *MEK* inhibitors [56, 57]. It is also worth mentioning that the insignificant result in the donafenib subgroup was caused by a $BRAF^{V600E}$ wild-type patient who had an impressive PFS of 68.1 months. The data from this patient also led to the intersection of the two curves in the Kaplan–Meier analysis of the entire cohort (Fig. 2B). Sadly, this patient only had Sanger sequencing data for the *BRAF* mutation, and thus more information about other possible mutations were not available. NGS with a larger panel is warranted to provide a more comprehensive look at complex genomic alterations, enabling the investigation of other molecular events that may have an impact on survival outcomes.

Another factor correlated with both shorter PFS and OS was the presence of bone metastases; this was consistent with previous studies in patients receiving sorafenib and lenvatinib [20, 58–60]. The constrained efficacy of MKIs in patients with bone metastases was reflected not only by shorter survival time, but also by less tumor

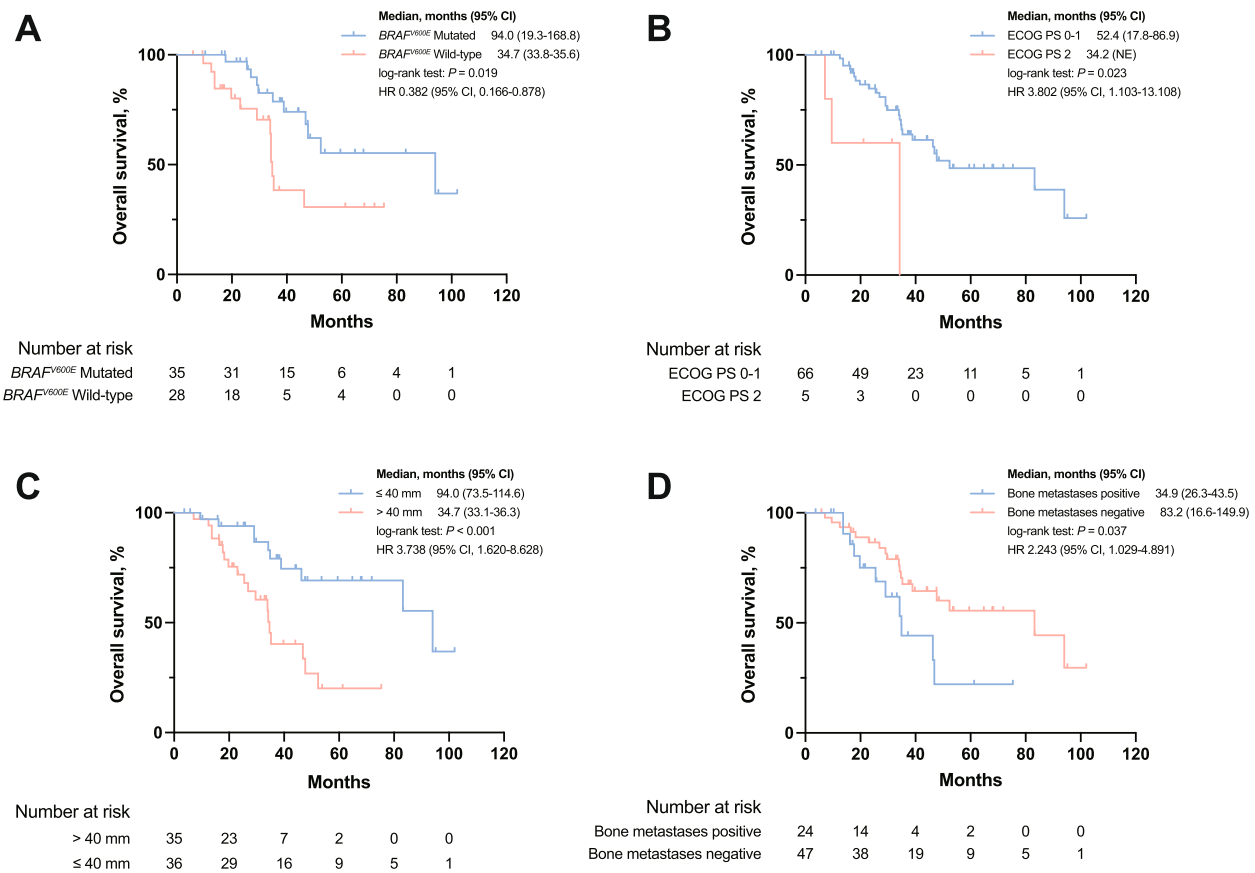

Fig. 3 Kaplan–Meier curves of overall survival based on clinicopathological factors. **A** *BRAF*^{V600E} mutation status: mutated vs. wild-type; **B** ECOG PS: 2 vs. 0–1; **C** Sum of target lesion diameters at baseline: > 40 mm vs. < 40 mm; **D** Bone metastases: positive vs. negative. Abbreviations: ECOG PS, Eastern Cooperative Oncology Group performance status; HR, hazard ratio

shrinkage compared with metastatic lesions in the lung, liver, or lymph nodes [61, 62]. Even if the advantage of MKIs is maintained in other metastatic lesions, bone metastases may grow and result in the sentence of progressive disease [63]. In RAIR-DTC patients with bone metastases, MKI monotherapy appears to be insufficient for disease control, an integrated treatment comprising antiresorptive drugs and local therapies like surgery and radiotherapy is warranted [64].

FTC is more likely to metastasize to distant organs such as the lung and the bone, and therefore its prognosis is worse than that of PTC [65, 66]. In this study, patients with FTC had shorter PFS under MKI therapies than PTC. Other studies reported no significant difference between FTC and PTC, although a real-world study of sorafenib indicated a trend towards a shorter median PFS for FTC (6.07 months) compared with PTC (20.30 months) [19, 58, 67]. In addition, lenvatinib and apatinib prolonged PFS in all histological subgroups, while donafenib, anlotinib, and sorafenib failed to improve PFS in the FTC subgroups [2, 8, 9]. The inconsistent efficacy of different MKIs may explain the shorter PFS in FTC patients of our cohort, as more than half of the patients received donafenib and anlotinib. Additionally, the difference in the prevalence of bone metastases may serve as a confounding factor in the univariate analysis, leading to different outcomes in different cohorts.

In our study, ECOG PS and baseline tumor burden were the other two factors correlated with OS. This was in accordance with several studies of sorafenib and lenvatinib, in which RAIR-DTC patients with better ECOG PS and lower baseline tumor burden showed superior outcomes [14, 18, 20, 58, 67]. In fact, there is a considerable correlation between the two factors. In the SELECT trial, patients with an ECOG PS of 0 had smaller target lesion diameters at baseline compared with patients with an ECOG PS of 1 [14]. Higher ORR and a greater percentage of shrinkage were achieved in patients with better ECOG PS (less tumor burden), while the duration of response was shorter in patients with heavier tumor burden [14, 68]. A worse ECOG PS, which may be caused by

Table 4 Baseline clinicopathological characteristics of the patients stratified by *BRAF*^{V600E} mutation status

	***BRAF*^{V600E}**		
Parameter, n (%)	**Mutation**	**Wild-type**	***P* value**
Sex			0.077
Female	14 (40.0)	18 (64.3)	
Male	21 (60.0)	10 (35.7)	
Histology			0.001
PTC	34 (97.1)	18 (64.3)	
FTC	1 (2.9)	10 (35.7)	
TERT ($n=58$)			< 0.001
Mutation	28 (82.4)	9 (37.5)	
Wild Type	6 (17.6)	15 (62.5)	
RAS ($n=48$)			0.003
Mutation	0 (0.0)	6 (30.0)	
Wild Type	28 (100.0)	14 (70.0)	
Age at initiating MKI treatment group			0.213
≥ 55	22 (62.9)	13 (46.4)	
< 55	13 (37.1)	15 (53.6)	
Baseline serum Tg group (ng/mL) ($n=51$)			0.404
> 500	12 (44.4)	14 (58.3)	
≤ 500	15 (55.6)	10 (41.7)	
Baseline NLR group			0.603
> 3	12 (34.3)	12 (42.9)	
≤ 3	23 (65.7)	16 (57.1)	
Sum of target lesion diameters at baseline (mm)			0.077
> 40	14 (40.0)	18 (64.3)	
≤ 40	21 (60.0)	10 (35.7)	
Bone metastases			0.034
Negative	27 (77.1)	14 (50.0)	
Positive	8 (22.9)	14 (50.0)	
ECOG PS			0.034
0–1	35 (100.0)	24 (85.7)	
2	0 (0.0)	4 (14.3)	
Regimen			0.579
Anlotinib	9 (25.7)	10 (35.7)	
Apatinib	15 (42.9)	12 (42.9)	
Donafenib	11 (31.4)	6 (21.4)	
Prior targeted therapy courses			0.758
0	26 (74.3)	20 (71.4)	
1	6 (17.1)	4 (14.3)	
2	3 (8.6)	4 (14.3)	

Abbreviations: *PTC* papillary thyroid cancer, *FTC* follicular thyroid cancer, *MKI* multi-kinase inhibitor, *Tg* thyroglobulin, *NLR* neutrophil-to-lymphocyte ratio, *ECOG PS* Eastern Cooperative Oncology Group performance status

a larger tumor burden, may impair the patient's tolerance for severe adverse events in MKI therapies [68]. The findings in our and other's studies suggested that it may be better to initiate MKI therapies earlier rather than waiting until the disease progresses.

Our study has several limitations. The retrospective design and the small sample size only allowed us to explore the potential prognostic factors instead of constructing a comprehensive model with more variables to predict efficacy. Additionally, the follow-up period was not long enough to witness half of the OS events, which made multivariate analysis unfeasible. This also explains why the median OS was not reached and the 95% confidence intervals were not estimable in several

Table 5 Detailed efficacy in patients stratified by *BRAF*^{V600E} mutation status

Parameter	*BRAF*^{V600E}		*P* value
	Mutation (*n* = 35)	Wild-type (*n* = 28)	
Best overall response, n (%)			0.135
PR	26 (74.3)	16 (57.1)	
SD	9 (25.7)	11 (39.3)	
PD	0 (0.0)	1 (3.6)	
Objective response rate, % (95% CI)	74.3 (56.7–87.5)	57.1 (37.2–75.5)	0.185
Disease control rate, % (95% CI)	100.0 (90.0–100.0)	96.4 (81.7–99.9)	0.444
Progression-free survival, Median (95% CI), Months			
Anlotinib	NR (NE)	10.3 (0.0–23.4)	0.007
Apatinib	35.3 (30.8–39.9)	11.1 (8.3–13.9)	0.002
Donafenib	28.8 (16.0–41.7)	5.5 (1.8–9.3)	0.569

Abbreviations: *PR* partial response, *SD* stable disease, *PD* progression disease, *CI* confidence interval

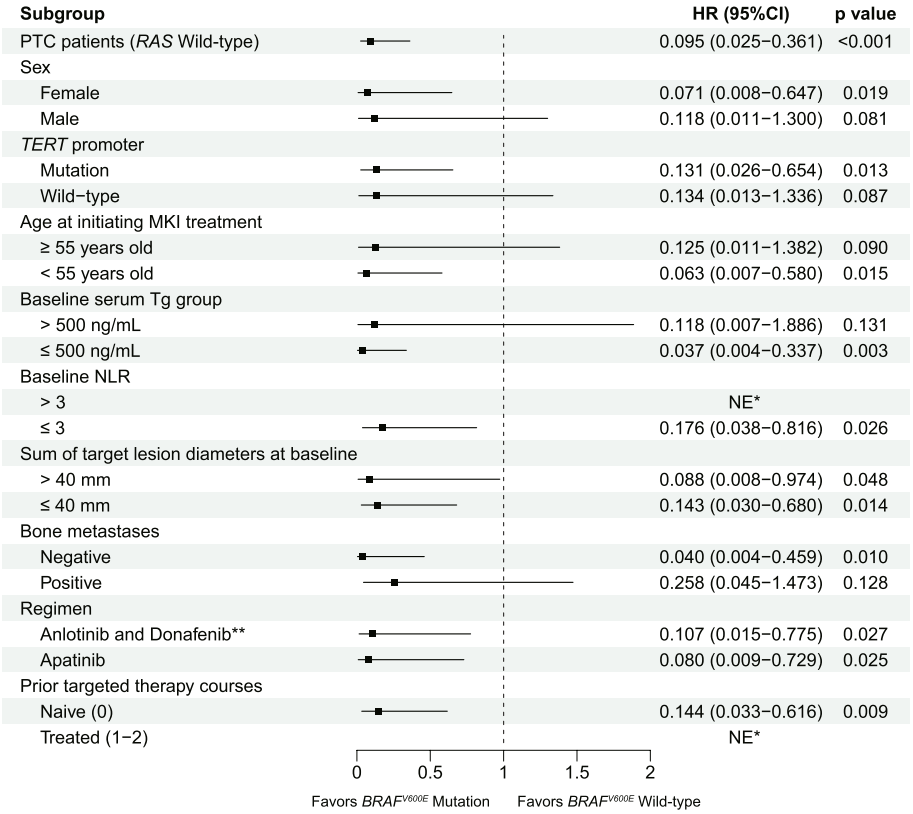

Fig. 4 Forest plot of HR for PFS subgroup analyses in PTC patients stratified by *BRAF*^{V600E} mutation. * Not estimable since the Cox model failed to converge due to the limited number of events. (Baseline NLR > 3: *BRAF*^{V600E} mutation vs. wild-type, median PFS 28.9 vs. 9.3 months, log-rank $p < 0.001$. Treated (1-2): *BRAF*^{V600E} mutation vs. wild-type, median PFS 23.0 vs. 13.9 months, log-rank $p = 0.003$.) ** Patients receiving anlotinib and donafenib were combined because the events were insufficient for a separate analysis. Abbreviations: HR, hazard ratio; PFS, progression-free survival; PTC, papillary thyroid cancer; MKI, multi-kinase inhibitor; NLR, neutrophil-to-lymphocyte ratio; NE, not estimable

subgroups. Nearly one-third of our patients underwent Sanger sequencing for genetic testing. The relatively low sensitivity of Sanger sequencing may not be sufficient for detecting low-frequency variants. Moreover, our Sanger sequencing analysis only focused on *BRAF*^{V600E}, *TERT* promoter, and *RAS* mutation, and thus we were unable

to fully assess the complex genetic background of the patients and the effect on clinical responses to MKIs. Future studies should employ a bigger NGS panel in a much larger cohort to uncover other less frequent mutations that may affect survival outcomes.

Conclusions

Patients with $BRAF^{V600E}$ mutation treated with the MKIs apatinib, anlotinib exhibited a longer PFS and OS under MKIs of apatinib, anlotinib and donafenib. Our findings may support the value of assessing genetic background when considerating MKI therapies. Further investigations are needed to verify the utility of $BRAF^{V600E}$ and other mutations in larger populations.

Abbreviations

CI	Confidence interval
DTC	Differentiated thyroid cancer
ECOG PS	Eastern Cooperative Oncology Group performance status
FTC	Follicular thyroid cancer
HR	Hazard ratio
IQR	Interquartile range
MKI	Multi-kinase inhibitor
NGS	Next-generation sequencing
NLR	Neutrophil-to-lymphocyte ratio
ORR	Overall response rate
OS	Overall survival
PFS	Progression-free survival
PTC	Papillary thyroid cancer
RAI	Radioactive iodine
RAIR-DTC	Radioactive iodine refractory differentiated thyroid cancer
RECIST 1.1	Response Evaluation Criteria In Solid Tumors version 1.1
Tg	Thyroglobulin
TSH	Thyroid stimulating hormone

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s13044-025-00223-0.

Supplementary Material 1.

Supplementary Material 2: Supplementary Figure 1. LASSO-Cox regression for variable selection. (A) The LASSO-Cox regression curve for baseline characteristics; (B) the coefficient plot for variable selection.

Acknowledgements

We thank Gabrielle White Wolf, PhD, from Liwen Bianji (Edanz) (www.liwenbianji.cn) for editing the English text of a draft of this manuscript.

Authors' contributions

D.S and X.Z developed the theory, performed data collection and analytic calculations, and wrote the manuscript. XN.J, C.S and YQ.S provided critical feedback and helped shape the research. YQ.Z helped supervise the project. YS.L and J.L were in charge of overall direction. All authors reviewed the manuscript.

Funding

This work was supported by the National High Level Hospital Clinical Research Funding [grant number 2022-PUMCH-B-072] and the National Natural Science Foundation of China [grant number 82472027].

Data availability

No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate

All the trials were approved by the Ethics Committee of Peking Union Medical College Hospital. All patients provided written informed consent before participating in the trials.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

Author details

[1]Department of Nuclear Medicine, State Key Laboratory of Complex Severe and Rare Diseases, Peking Union Medical College (PUMC) Hospital, Chinese Academy of Medical Sciences & PUMC, No.1 Shuaifuyuan, Wangfujing, Dongcheng District, Beijing 100730, China. [2]Beijing Key Laboratory of Molecular Targeted Diagnosis and Therapy in Nuclear Medicine, Beijing, China. [3]Department of Oncology, Peking University International Hospital, Peking University, No. 1 Life Park Road, Zhongguancun Life Science Park, Changping District, Beijing 102206, China. [4]Department of Medical Oncology, Key Laboratory of Carcinogenesis & Translational Research (Ministry of Education/Beijing), Peking University Cancer Hospital and Institute, Beijing, China.

Received: 27 October 2024 Accepted: 7 January 2025
Published online: 10 February 2025

References

1. Durante C, Haddy N, Baudin E, Leboulleux S, Hartl D, Travagli JP, 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(8):2892–9.
2. Brose MS, Nutting CM, Jarzab B, Elisei R, Siena S, Bastholt L, et al. Sorafenib in radioactive iodine-refractory, locally advanced or metastatic differentiated thyroid cancer: a randomised, double-blind, phase 3 trial. Lancet. 2014;384(9940):319–28.
3. Schlumberger M, Tahara M, Wirth LJ, Robinson B, Brose MS, Elisei R, et al. Lenvatinib versus placebo in radioiodine-refractory thyroid cancer. N Engl J Med. 2015;372(7):621–30.
4. Filetti S, Durante C, Hartl DM, Leboulleux S, Locati LD, Newbold K, et al. ESMO Clinical Practice Guideline update on the use of systemic therapy in advanced thyroid cancer. Ann Oncol. 2022;33(7):674–84.
5. Ge M, Gao M, Cheng R, Chen X, Guan H, Lin Y, et al. CACA guidelines for holistic integrative management of thyroid cancer. Holistic Integrative Oncology. 2022;1(1):17.
6. Health Commission Of The People's Republic Of China N. National guidelines for diagnosis and treatment of thyroid cancer 2022 in China (English version). Chin J Cancer Res. 2022;34(3):131–50.
7. Zeng H, Chen W, Zheng R, Zhang S, Ji JS, Zou X, et al. Changing cancer survival in China during 2003–15: a pooled analysis of 17 population-based cancer registries. Lancet Glob Health. 2018;6(5):e555–67.
8. Lin Y, Qin S, Yang H, Shi F, Yang A, Han X, et al. Multicenter randomized double-blind phase III trial of donafenib in progressive radioactive iodine-refractory differentiated thyroid cancer. Clin Cancer Res. 2023;29(15):2791–9.
9. Chi Y, Zheng X, Zhang Y, Shi F, Cheng Y, Guo Z, et al. Anlotinib in locally advanced or metastatic radioiodine-refractory differentiated thyroid carcinoma: a randomized, double-blind, multicenter phase II trial. Clin Cancer Res. 2023;29(20):4047–56.
10. Lin Y, Qin S, Li Z, Yang H, Fu W, Li S, et al. Apatinib vs placebo in patients with locally advanced or metastatic, radioactive iodine-refractory differentiated thyroid cancer: the REALITY randomized clinical trial. JAMA Oncol. 2022;8(2):242–50.
11. Wang H, Wang J, Wang X, Zhu Y, Sun Y, Zhang X, et al. Comments on National guidelines for diagnosis and treatment of thyroid cancer 2022 in China (English version). Chin J Cancer Res. 2022;34(5):447–50.

12. Zeng H, Zheng R, Sun K, Zhou M, Wang S, Li L, et al. Cancer survival statistics in China 2019–2021: a multicenter, population-based study. J Natl Cancer Cent. 2024;4(3):203–13.
13. Cancer Stat Facts: Thyroid Cancer: National Cancer Institute. Available from: https://seer.cancer.gov/statfacts/html/thyro.html. [cited 2024 5 October].
14. Taylor MH, Takahashi S, Capdevila J, Tahara M, Leboulleux S, Kiyota N, et al. Correlation of performance status and neutrophil-lymphocyte ratio with efficacy in radioiodine-refractory differentiated thyroid cancer treated with lenvatinib. Thyroid. 2021;31(8):1226–34.
15. Tahara M, Schlumberger M, Elisei R, Habra MA, Kiyota N, Paschke R, et al. Exploratory analysis of biomarkers associated with clinical outcomes from the study of lenvatinib in differentiated cancer of the thyroid. Eur J Cancer. 2017;75:213–21.
16. Tahara M, Brose MS, Wirth LJ, Suzuki T, Miyagishi H, Fujino K, et al. Impact of dose interruption on the efficacy of lenvatinib in a phase 3 study in patients with radioiodine-refractory differentiated thyroid cancer. Eur J Cancer. 2019;106:61–8.
17. Brose MS, Worden FP, Newbold KL, Guo M, Hurria A. Effect of age on the efficacy and safety of lenvatinib in radioiodine-refractory differentiated thyroid cancer in the phase III SELECT trial. J Clin Oncol. 2017;35(23):2692–9.
18. Kiyota N, Tahara M, Robinson B, Schlumberger M, Sherman SI, Leboulleux S, et al. Impact of baseline tumor burden on overall survival in patients with radioiodine-refractory differentiated thyroid cancer treated with lenvatinib in the SELECT global phase 3 trial. Cancer. 2022;128(12):2281–7.
19. Sugino K, Nagahama M, Kitagawa W, Ohkuwa K, Uruno T, Matsuzu K, et al. Clinical factors related to the efficacy of tyrosine kinase inhibitor therapy in radioactive iodine refractory recurrent differentiated thyroid cancer patients. Endocr J. 2018;65(3):299–306.
20. Suzuki C, Kiyota N, Imamura Y, Goto H, Suto H, Chayahara N, et al. Exploratory analysis of prognostic factors for lenvatinib in radioiodine-refractory differentiated thyroid cancer. Head Neck. 2019;41(9):3023–32.
21. Bray F, Laversanne M, Sung H, Ferlay J, Siegel RL, Soerjomataram I, Jemal A. Global cancer statistics 2022: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2024;74(3):229–63.
22. Lin YS, Zhang X, Wang C, Liu YQ, Guan WM, Liang J. Long-term results of a phase II trial of apatinib for progressive radioiodine refractory differentiated thyroid cancer. J Clin Endocrinol Metab. 2021;106(8):e3027–36.
23. Lin YS, Yang H, Ding Y, Cheng YZ, Shi F, Tan J, et al. Donafenib in progressive locally advanced or metastatic radioactive iodine-refractory differentiated thyroid cancer: results of a randomized, multicenter phase II trial. Thyroid. 2021;31(4):607–15.
24. Sun D, Zhang X, Sun Y, Mu Z, Wang H, Zhang Y, et al. Early structural, biochemical, and metabolic responses to anlotinib in patients with progressive radioactive iodine refractory differentiated thyroid cancer. Endocr Pract. 2024;30(5):456–64.
25. Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer. 2009;45(2):228–47.
26. Yang X, Li J, Li X, Liang Z, Gao W, Liang J, et al. TERT promoter mutation predicts radioiodine-refractory character in distant metastatic differentiated thyroid cancer. J Nucl Med. 2017;58(2):258–65.
27. Mu Z, Zhang X, Sun D, Sun Y, Shi C, Ju G, et al. Characterizing genetic alterations related to radioiodine avidity in metastatic thyroid cancer. J Clin Endocrinol Metab. 2024;109(5):1231–40.
28. Tibshirani R. The lasso method for variable selection in the Cox model. Stat Med. 1997;16(4):385–95.
29. Zheng X, Xu Z, Ji Q, Ge M, Shi F, Qin J, et al. A randomized, phase III study of lenvatinib in Chinese patients with radioiodine-refractory differentiated thyroid cancer. Clin Cancer Res. 2021;27(20):5502–9.
30. Kebebew E, Weng J, Bauer J, Ranvier G, Clark OH, Duh QY, et al. The prevalence and prognostic value of BRAF mutation in thyroid cancer. Ann Surg. 2007;246(3):466–70 discussion 70-1.
31. Xing M, Alzahrani AS, Carson KA, Viola D, Elisei R, Bendlova B, et al. Association between BRAF V600E mutation and mortality in patients with papillary thyroid cancer. JAMA. 2013;309(14):1493–501.
32. Xing M, Westra WH, Tufano RP, Cohen Y, Rosenbaum E, Rhoden KJ, et al. BRAF mutation predicts a poorer clinical prognosis for papillary thyroid cancer. J Clin Endocrinol Metab. 2005;90(12):6373–9.
33. Xing M. BRAF mutation in thyroid cancer. Endocr Relat Cancer. 2005;12(2):245–62.
34. Ito Y, Yoshida H, Maruo R, Morita S, Takano T, Hirokawa M, et al. BRAF mutation in papillary thyroid carcinoma in a Japanese population: its lack of correlation with high-risk clinicopathological features and disease-free survival of patients. Endocr J. 2009;56(1):89–97.
35. Lai HF, Hang JF, Kuo PC, Kuo CS, Yao SF, Chen JY, Lee CH. BRAF V600E mutation lacks association with poorer clinical prognosis in papillary thyroid carcinoma. Ann Surg Oncol. 2024;31(5):3495–501.
36. Choi SY, Park H, Kang MK, Lee DK, Lee KD, Lee HS, et al. The relationship between the BRAF(V600E) mutation in papillary thyroid microcarcinoma and clinicopathologic factors. World J Surg Oncol. 2013;11:291.
37. Perera D, Ghossein R, Camacho N, Senbabaoglu Y, Seshan V, Li J, et al. Genomic and transcriptomic characterization of papillary microcarcinomas with lateral neck lymph node metastases. J Clin Endocrinol Metab. 2019;104(10):4889–99.
38. Gouveia C, Can NT, Bostrom A, Grenert JP, van Zante A, Orloff LA. Lack of association of BRAF mutation with negative prognostic indicators in papillary thyroid carcinoma: the University of California, San Francisco, experience. JAMA Otolaryngol Head Neck Surg. 2013;139(11):1164–70.
39. Ahmadi S, Landa I. The prognostic power of gene mutations in thyroid cancer. Endocr Connect. 2024;13(2):e230297.
40. Landa I, Cabanillas ME. Genomic alterations in thyroid cancer: biological and clinical insights. Nat Rev Endocrinol. 2024;20(2):93–110.
41. Xing M, Liu R, Liu X, Murugan AK, Zhu G, Zeiger MA, et al. BRAF V600E and TERT promoter mutations cooperatively identify the most aggressive papillary thyroid cancer with highest recurrence. J Clin Oncol. 2014;32(25):2718–26.
42. McFadden DG, Vernon A, Santiago PM, Martinez-McFaline R, Bhutkar A, Crowley DM, et al. p53 constrains progression to anaplastic thyroid carcinoma in a Braf-mutant mouse model of papillary thyroid cancer. Proc Natl Acad Sci U S A. 2014;111(16):E1600-9.
43. Landa I, Ibrahimpasic T, Boucai L, Sinha R, Knauf JA, Shah RH, et al. Genomic and transcriptomic hallmarks of poorly differentiated and anaplastic thyroid cancers. J Clin Invest. 2016;126(3):1052–66.
44. Riesco-Eizaguirre G, Gutierrez-Martinez P, Garcia-Cabezas MA, Nistal M, Santisteban P. The oncogene BRAF V600E is associated with a high risk of recurrence and less differentiated papillary thyroid carcinoma due to the impairment of Na+/I- targeting to the membrane. Endocr Relat Cancer. 2006;13(1):257–69.
45. Yang K, Wang H, Liang Z, Liang J, Li F, Lin Y. BRAFV600E mutation associated with non-radioiodine-avid status in distant metastatic papillary thyroid carcinoma. Clin Nucl Med. 2014;39(8):675–9.
46. Durante C, Puxeddu E, Ferretti E, Morisi R, Moretti S, Bruno R, et al. BRAF mutations in papillary thyroid carcinomas inhibit genes involved in iodine metabolism. J Clin Endocrinol Metab. 2007;92(7):2840–3.
47. Mu Z, Zhang X, Liang D, Fang J, Chen G, Guo W, et al. Risk stratification for radioactive iodine refractoriness using molecular alterations in distant metastatic differentiated thyroid cancer. Chin J Cancer Res. 2024;36(1):25–35.
48. Yu P, Qu N, Zhu R, Hu J, Han P, Wu J, et al. TERT accelerates BRAF mutant-induced thyroid cancer dedifferentiation and progression by regulating ribosome biogenesis. Sci Adv. 2023;9(35):eadg7125.
49. Worden FP, Wirth LJ, Reynolds N, Cooper C, Rajkovic-Hooley O, Milligan G, et al. Patients with radioiodine-refractory differentiated thyroid cancer (RAI-R DTC) with BRAF V600E and/or K601E mutation status: A real-world view of effectiveness of lenvatinib monotherapy. J Clin Oncol. 2024;42(16_suppl):6098.
50. Brose MS, Schlumbeger M, Jeffers M, Kappeler C, Meinhardt G, Pena CEA. Analysis of biomarkers and association with clinical outcomes in patients with differentiated thyroid cancer: subanalysis of the sorafenib phase III DECISION trial. Clin Cancer Res. 2019;25(24):7370–80.
51. Jo YS, Li S, Song JH, Kwon KH, Lee JC, Rha SY, 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(9):3667–70.
52. Xing M. BRAF mutation in papillary thyroid cancer: pathogenic role, molecular bases, and clinical implications. Endocr Rev. 2007;28(7):742–62.
53. Hu S, Liu D, Tufano RP, Carson KA, Rosenbaum E, Cohen Y, et al. Association of aberrant methylation of tumor suppressor genes with tumor aggressiveness and BRAF mutation in papillary thyroid cancer. Int J Cancer. 2006;119(10):2322–9.

54. Qi JH, Ebrahem Q, Moore N, Murphy G, Claesson-Welsh L, Bond M, et al. A novel function for tissue inhibitor of metalloproteinases-3 (TIMP3): inhibition of angiogenesis by blockage of VEGF binding to VEGF receptor-2. Nat Med. 2003;9(4):407–15.
55. Busaidy NL, Konda B, Wei L, Wirth LJ, Devine C, Daniels GA, et al. Dabrafenib versus dabrafenib + trametinib in BRAF-mutated radioactive iodine refractory differentiated thyroid cancer: results of a randomized, Phase 2, open-label multicenter trial. Thyroid. 2022;32(10):1184–92.
56. Tan J, Liu R, Zhu G, Umbricht CB, Xing M. TERT promoter mutation determines apoptotic and therapeutic responses of BRAF-mutant cancers to BRAF and MEK inhibitors: Achilles Heel. Proc Natl Acad Sci U S A. 2020;117(27):15846–51.
57. Thielmann CM, Matull J, Zaremba A, Murali R, Chorti E, Lodde G, et al. TERT promoter mutations are associated with longer progression-free and overall survival in patients with BRAF-mutant melanoma receiving BRAF and MEK inhibitor therapy. Eur J Cancer. 2022;161:99–107.
58. Cheng L, Fu H, Jin Y, Sa R, Chen L. Clinicopathological features predict outcomes in patients with radioiodine-refractory differentiated thyroid cancer treated with sorafenib: a real-world study. Oncologist. 2020;25(4):e668–78.
59. Schneider TC, Abdulrahman RM, Corssmit EP, Morreau H, Smit JW, Kapiteijn E. Long-term analysis of the efficacy and tolerability of sorafenib in advanced radio-iodine refractory differentiated thyroid carcinoma: final results of a phase II trial. Eur J Endocrinol. 2012;167(5):643–50.
60. Hoftijzer H, Heemstra KA, Morreau H, Stokkel MP, Corssmit EP, Gelderblom 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(6):923–31.
61. Robinson B, Schlumberger M, Wirth LJ, Dutcus CE, Song J, Taylor MH, et al. Characterization of tumor size changes over time from the phase 3 study of lenvatinib in thyroid cancer. J Clin Endocrinol Metab. 2016;101(11):4103–9.
62. Massicotte MH, Brassard M, Claude-Desroches M, Borget I, Bonichon F, Giraudet AL, et al. Tyrosine kinase inhibitor treatments in patients with metastatic thyroid carcinomas: a retrospective study of the TUTHYREF network. Eur J Endocrinol. 2014;170(4):575–82.
63. Cabanillas ME, Waguespack SG, Bronstein Y, Williams MD, Feng L, Hernandez M, et al. Treatment with tyrosine kinase inhibitors for patients with differentiated thyroid cancer: the M. D. Anderson experience. J Clin Endocrinol Metab. 2010;95(6):2588–95.
64. Kato S, Demura S, Shinmura K, Yokogawa N, Shimizu T, Tsuchiya H. Current management of bone metastases from differentiated thyroid cancer. Cancers (Basel). 2021;13(17):4429.
65. Shen J, Yan M, Chen L, Ou D, Yao J, Feng N, et al. Prognosis and influencing factors of follicular thyroid cancer. Cancer Med. 2024;13(1):e6727.
66. Hundahl SA, Fleming ID, Fremgen AM, Menck HR. A National Cancer Data Base report on 53,856 cases of thyroid carcinoma treated in the U.S., 1985-1995 [see commetns]. Cancer. 1998;83(12):2638–48.
67. Marotta V, Rocco D, Crocco A, Deiana MG, Martinelli R, Di Gennaro F, et al. Survival predictors of radioiodine-refractory differentiated thyroid cancer treated with lenvatinib in real life. J Clin Endocrinol Metab. 2024;109(10):2541–52.
68. Gianoukakis AG, Dutcus CE, Batty N, Guo M, Baig M. Prolonged duration of response in lenvatinib responders with thyroid cancer. Endocr Relat Cancer. 2018;25(6):699–704.

Publisher's Note