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Original Article

Clinical outcomes of dabrafenib plus trametinib in locally advanced or metastatic BRAF V600E-mutant papillary thyroid cancer

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Abstract: BRAF V600E is the most common oncogenic mutation in papillary thyroid carcinoma (PTC). This study aimed to assess the clinical outcomes of combining dabrafenib and trametinib in patients with BRAF V600E-mutant PTC. Patients with BRAF V600E-mutant PTC treated with dabrafenib and trametinib in either first-line or second-line settings were included. Dabrafenib was administered orally at 150 mg twice daily, alongside trametinib at 2 mg once daily. Response was determined using Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1. A total of 71 PTC patients who received systemic therapy were identified, including 21 patients who experienced dabrafenib plus trametinib. For these 21 patients, the objective response rate (ORR) was 66.7%, with a disease control rate (DCR) of 85.7%. In the first-line setting, the ORR and DCR were higher at 75.0% and 91.7%, respectively. The median progression-free survival (PFS) was 40.7 months, and the overall survival (OS) was 47.7 months. While patients treated in the first-line setting (n=12) showed better PFS (40.7 months vs. 18.9 months) and OS (47.7 months vs. 39.4 months) compared to those treated in the second-line setting (n=9), the differences were not statistically significant. Moreover, in the first-line treatment, 12 patients received dabrafenib plus trametinib, while 59 patients were treated with lenvatinib; no significant differences in PFS or OS were observed between the two groups. Most adverse events related to the combination therapy were grade 1-2, with no grade 3-4 toxicities reported. Additionally, most patients (75.0%) were able to receive subsequent treatments following disease progression to this combination therapy. The findings of current study highlight the efficacy and safety of dabrafenib combined with trametinib in patients with BRAF V600E-mutant PTC, particularly as a first-line treatment. These findings suggest a promising therapeutic option for this patient population.

Keywords: BRAF, dabrafenib, trametinib, papillary thyroid cancer

Introduction

Thyroid cancer is the most common malignancy of the endocrine system and ranks as the seventh highest incidence of cancer in Taiwan [1]. Among its various histological subtypes, papillary thyroid cancer (PTC) is the most prevalent, representing around 90% of cases [2]. Systemic therapies such as sorafenib and lenvatinib have been approved for patients with radioiodine-refractory differentiated thyroid cancer (DTC), showing improved progression-free survival (PFS) compared to placebo [3, 4]. However, these treatments are often associated with adverse events (AEs) like hypertension, proteinuria, and hand-foot skin reaction. Advances in understanding molecular pathways have driven the development of novel targeted therapies, significantly changing treatment strategies [5]. Activation of the mitogen-activated protein

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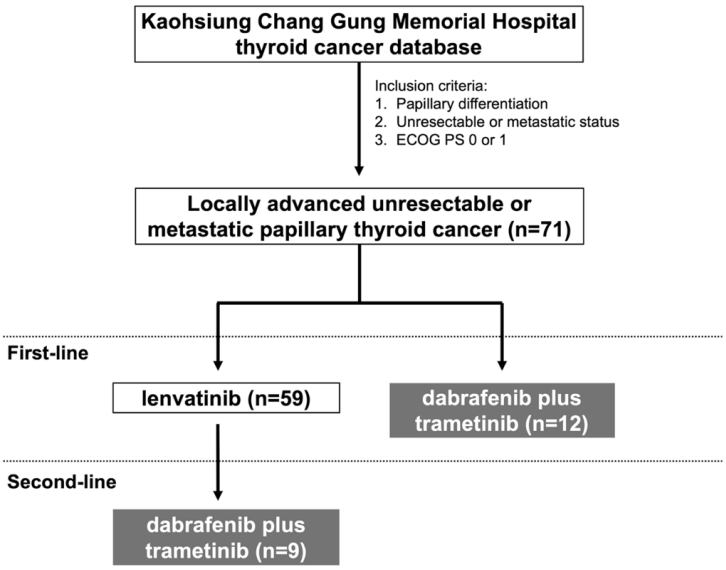

Figure 1. Flow Diagram of patients with papillary thyroid cancer who received dabrafenib plus trametinib.

kinase (MAPK) pathway, which promotes tumor cell proliferation, migration, metastasis, and inhibits apoptosis, plays a key role in tumor progression [6]. This includes mutations in genes such as RAS or BRAF, with BRAF V600E being the most common oncogenic mutation in PTC, found in 49-76% of cases [7].

The clinical impact of the BRAF V600E mutation on PTC outcomes remains controversial [8]. Many studies have linked the BRAF V600E mutation to lymph node metastasis, larger tumor size, advanced tumor stage, extrathyroid extension, and higher recurrence rates compared to wild-type BRAF. However, a large cohort study did not find a correlation between mortality and the BRAF V600E mutation [8-11]. Preclinical research has shown that BRAF and MEK inhibitors can reduce MAPK pathway activation and inhibit tumor cell growth [12-15]. Combining BRAF and MEK inhibitors appears to enhance antitumor activity, improve treatment response, extend survival, and prevent reactivation of the MAPK pathway, a known resistance mechanism, more effectively than BRAF inhibitor monotherapy [16-18]. As a result, the combination of dabrafenib (a BRAF V600 inhibitor) and trametinib (a MEK inhibitor) has been approved for treating BRAF V600-mutant melanoma and non-small cell lung cancer [16, 17, 19, 20].

Recently, the dabrafenib and trametinib combination has been approved for unresectable or metastatic solid tumors with the BRAF V600E mutation. Subbiah et al. reported that this combination showed strong clinical activity in anaplastic thyroid cancer (ATC) with the BRAF V600E mutation [18, 21]. An open-label phase 2 trial indicated that dabrafenib combined with trametinib did not surpass dabrafenib monotherapy in objective response rate (ORR) for patients with BRAF-mutant radioiodine-refractory progressive DTC [22]. However, data on BRAF V600E-mutant PTC remains limited. This study aims to evaluate the clinical outcomes of dabrafenib plus trametinib in patients with BRAF V600E-mutant PTC.

Methods

Patient selection

This retrospective study reviewed the medical records of patients diagnosed with thyroid cancer and treated at Kaohsiung Chang Gung Memorial Hospital between January 2018 and December 2024. Patients with a history of a second primary malignancy or histological subtypes such as follicular, medullary, or anaplastic thyroid cancer were excluded. Patients undergoing concurrent treatments, including other targeted therapies, chemotherapy, immunotherapy, or radiotherapy, were not eligible. Ultimately, 71 patients with locally advanced or metastatic PTC met the strict eligibility criteria for this study, including 21 who received dabrafenib plus trametinib. **Figure 1** presents a flowchart illustrating the selection process of PTC patients according to the inclusion and exclusion criteria.

Test of BRAF V600E mutation

The BRAF V600E mutation was identified through immunohistochemical (IHC) staining using a mutation-specific antibody. This technique provided a sensitive and specific method to detect the mutation in tissue samples. The IHC results were subsequently reviewed and confirmed by experienced endocrine patholo-

gists to ensure diagnostic accuracy and reliability.

BRAF inhibitors and lenvatinib

Patients were treated with dabrafenib at a dose of 150 mg twice daily in combination with trametinib at 2 mg once daily. Lenvatinib was prescribed at a dose of 10 mg daily [23]. These treatments continued until either disease progression or intolerable AEs occurred, with dose adjustments made as necessary to manage AEs according to protocol.

Evaluation of response and safety assessment

Each patient was required to have at least one measurable target lesion to evaluate the treatment response, assessed by computed tomography (CT) scans every 12 weeks post-treatment initiation. Responses were independently evaluated by two radiologists, blinded to patient clinical details, and were assessed using the Response Evaluation Criteria in Solid Tumors (RECIST version 1.1) [24]. AEs were graded and recorded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (version 5.0) [25].

Statistical analysis

Statistical analyses were performed using SPSS version 29 (IBM, Armonk, NY). Differences in clinical characteristics between the two groups were assessed using the chi-square test for categorical variables. PFS was defined as the time from the initiation of targeted therapy to disease progression or death, while overall survival (OS) was calculated from the start of targeted therapy to death or the last follow-up. The Kaplan-Meier method was employed to estimate PFS and OS, with group differences evaluated using the log-rank test. All statistical tests were two-sided, and a *P*-value of <0.05 was considered statistically significant.

Ethics statement

The retrospective study was approved by the Chang Gung Medical Foundation Institutional Review Board (202400912B0) and adhered to ethical guidelines outlined by the Institutional Research Committee and the World Medical Association Declaration of Helsinki. Due to the retrospective nature of the study, the Institutional Review Board waived the need for written informed consent from patients or their families.

Results

Patient characteristics

This study included 21 patients diagnosed with PTC, comprising 7 males and 14 females, with a mean age of 57 years (range: 23-83). The majority of patients (81.0%) underwent thyroidectomy prior to starting targeted therapy. All participants were classified as having a European Cooperative Oncology Group (ECOG) Performance Status of 0 or 1. Regional lymph node involvement was detected in 95.2% of the cases, and 85.7% presented with distant metastases. The most common metastatic sites were the lungs (61.9%), bones (47.6%), and soft tissues (19.0%). Radioactive iodine therapy had been administered to 13 patients (61.9%) before the study. Among the participants, 12 received dabrafenib combined with trametinib as their first-line therapy, while 9 were treated with this combination as a second-line treatment, following prior use of lenvatinib. Additional clinicopathological details are summarized in **Table 1**.

Clinical outcomes of patients receiving dabrafenib and trametinib

In this study, the ORR comprised a partial response (PR) in 14 patients (66.7%), stable disease (SD) in 4 patients (19.0%), and progressive disease (PD) in 3 patients (14.3%), yielding an overall disease control rate (DCR) of 85.7%. Among the 12 patients treated with this combination as a first-line therapy, the ORR reached 75.0%, with a DCR of 91.7%. For those receiving it as second-line therapy, the ORR and DCR were 55.6% and 77.8%, respectively, with no significant difference observed between the two groups (**Table 2**).

The study also reported a median PFS of 40.7 months and an OS of 47.7 months (**Figure 2**). Patients who received the combination as first-line therapy demonstrated better PFS (40.7 months vs. 18.9 months, **Figure 3A**) and OS (47.7 months vs. 39.4 months, **Figure 3B**) compared to those treated in the second-line set-

Table 1. Baseline characteristics of 21 patients with papillary thyroid cancer who received dabrafenib plus trametinib

Variable	
Age (median)	57 years (23-83)
Sex	
Male	7 (33.3%)
Female	14 (66.7%)
ECOG PS	
1	21 (100%)
Surgical resection of thyroid	
Yes	17 (81.0%)
No	4 (19.0%)
Regional lymph nodes metastasis	
Yes	20 (95.2%)
No	1 (4.8%)
Distant metastasis	
Yes	18 (85.7%)
No	3 (14.3%)
Site of metastasis	
Lung	13 (61.9%)
Bone	10 (47.6%)
Soft tissue	4 (19.0%)
Others	7 (33.3%)
Radioactive iodine	
Yes	13 (61.9%)
No	8 (38.1%)
Lines of systemic therapy	
First-line	12 (57.1%)
Second-line	9 (42.9%)
Prior systemic therapy	
Lenvatinib	9 (42.9%)
No	12 (57.1%)

ECOG PS: European Cooperative Oncology Group Performance Status.

ting. However, the differences between these groups did not reach statistical significance.

When comparing dabrafenib plus trametinib with lenvatinib as first-line treatments, the dabrafenib plus trametinib group showed a longer PFS than the lenvatinib group (40.7 months vs. 20.7 months). However, this difference was not statistically significant (P=0.20, **Figure 4A**). Similarly, OS did not differ significantly between the two groups, with a median OS of 47.7 months in the dabrafenib plus trametinib group, while the median OS in the lenvatinib group was not reached (P=0.59, **Figure 4B**).

A total of 13 patients received both first-line and second-line therapies. Among them, 4 patients were treated initially with dabrafenib/trametinib followed by lenvatinib, while the remaining 9 received lenvatinib first, followed by dabrafenib/trametinib. The median OS was 47.7 months and 39.4 months, respectively, with no statistically significant difference between the two treatment sequences.

Safety

The most common treatment-related AEs were fever (47.6%), chills (42.8%), fatigue (33.3%), nausea (23.8%), myalgia (14.3%), diarrhea (14.3%), increased alanine transaminase (14.3%), anorexia (9.5%), increased aspartate transaminase (9.5%), hyperglycemia (9.5%), and vomiting (4.8%). Most AEs were grade 1-2, with no grade 3-4 toxicities or drug-related grade 5 AEs reported. The detailed safety profile is available in **Table 3**.

Patient disposition

A total of eight patients experienced disease progression while on dabrafenib plus trametinib treatment. Among these, six patients (75.0%) received additional therapies after progression, which included multi-kinase inhibitors, BRAF inhibitors, and immune checkpoint inhibitors (ICI). Lenvatinib was the most frequently administered multi-kinase inhibitor (66.7%), followed by sorafenib (33.3%) and cabozantinib (16.7%). Rechallenge with dabrafenib plus trametinib occurred in two patient (33.3%). Additionally, one patient (16.7%) received pembrolizumab following progression on the combination therapy. Details of the subsequent treatment strategies are summarized in **Table 4**.

Discussion

Current real-world data on the combination of dabrafenib and trametinib for patients with BRAF V600E-mutant PTC remains insufficient. Our research provides insights into the ORR, PFS, and OS for such patients. We observed an ORR of 66.7% in our study group, which surpasses previous reports but aligns with the ORR found in the SELECT trial for lenvatinib [4, 22]. Specifically, our cohort of 21 patients treated with dabrafenib and trametinib showed median PFS and OS of 40.7 months and 47.7 months, respectively. These findings were not

Table 2. Treatment response to dabrafenib plus trametinib

	All patients (n=21)	First-line (n=12)	Second-line (n=9)	*P* value
Partial response	14 (66.7%)	9 (75.0%)	5 (55.6%)	0.59
Stable disease	4 (19.0%)	2 (16.7%)	2 (22.2%)	
Progressive disease	3 (14.3%)	1 (8.3%)	2 (22.2%)	
Disease control rate	18 (85.7%)	11 (91.7%)	7 (77.8%)	

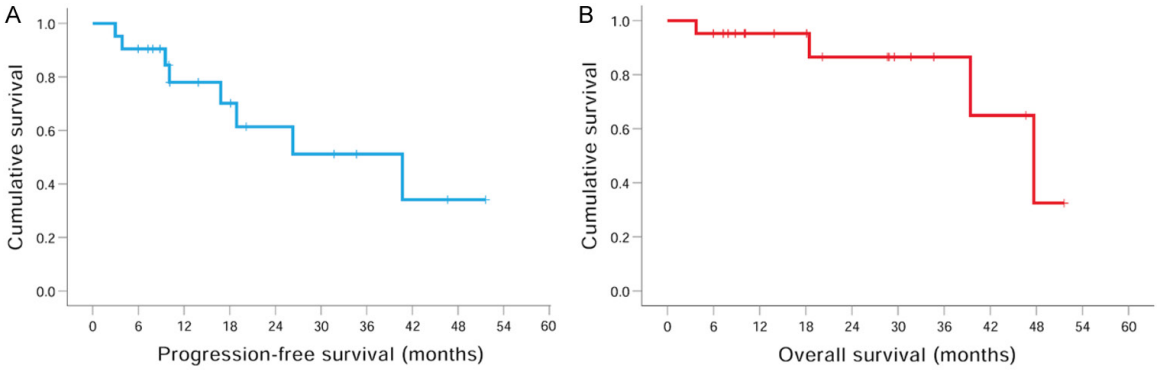

Figure 2. Kaplan-Meier survival curves demonstrating progression-free survival (A) and overall survival (B) in patients with papillary thyroid cancer who received dabrafenib plus trametinib.

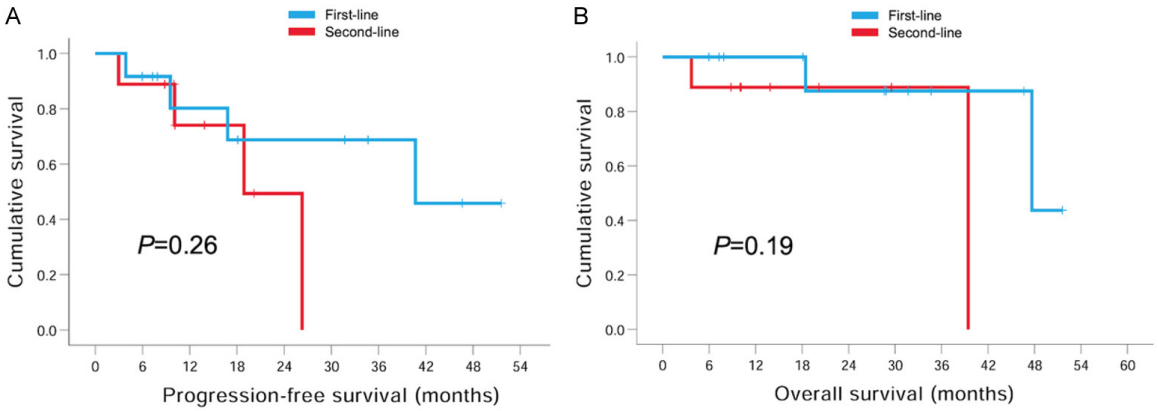

Figure 3. Comparison of Kaplan-Meier curves among patients with papillary thyroid cancer who received dabrafenib plus trametinib as first-line or second-line systemic therapy. (A) progression-free survival and (B) overall survival.

inferior to outcomes from phase 3 randomized trials [3, 4]. Additionally, we found no significant difference in PFS and OS between BRAF inhibitors as a first-line or second-line setting. Most AEs were tolerated and most patients could receive subsequent treatment after disease progression on dabrafenib plus trametinib.

Advancements in precision oncology, particularly through genomic profiling, have shifted cancer treatments towards more molecular-based strategies. Recent research in translational medicine has revealed new insights into systemic cancer therapies, enabling the discovery of novel oncogenic targets and the creation of innovative targeted treatments. Tumor-agnostic therapies, which show efficacy across multiple cancer types, represent a key breakthrough in precision oncology [26, 27]. Several such drugs, targeting BRAF mutations among others, have already received treatment approvals [28]. Subbiah's research on vemurafenib, involving 172 patients across 26 cancer types with BRAF V600 mutations, reported an ORR of 33% and a median DOR of 13 months [29]. Positive responses spanned 13 different

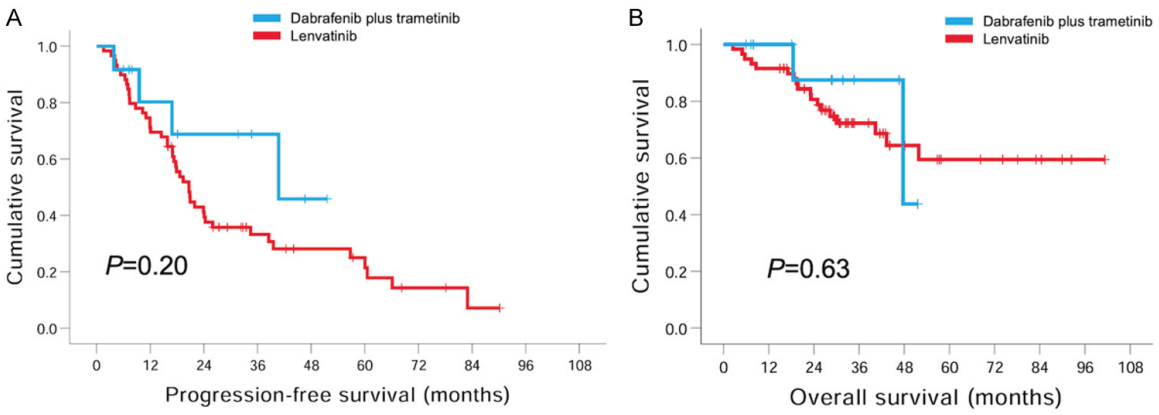

Figure 4. Kaplan-Meier curve analysis comparing patients with papillary thyroid cancer who underwent either dabrafenib plus trametinib or lenvatinib as first-line therapy. (A) progression-free survival and (B) overall survival.

Table 3. Adverse events of dabrafenib plus trametinib in 21 patients with papillary thyroid cancer

Effect	Any grade	Grade 3-4
Fever	10 (47.6%)	0 (0%)
Chills	9 (42.8%)	0 (0%)
Myalgia	3 (14.3%)	0 (0%)
Fatigue	7 (33.3%)	0 (0%)
Nausea	5 (23.8%)	0 (0%)
Vomiting	1 (4.8%)	0 (0%)
Anorexia	2 (9.5%)	0 (0%)
Diarrhea	3 (14.3%)	0 (0%)
AST increase	2 (9.5%)	0 (0%)
ALT increase	3 (14.3%)	0 (0%)
Hyperglycemia	2 (9.5%)	0 (0%)

AST: aspartate transaminase; ALT: alanine transaminase.

Table 4. Subsequent therapy in eight patients with progression to dabrafenib plus trametinib

Category	Number of patients
Any anti-cancer treatment	6 (75.0%)
Multi-kinase inhibitors	
Lenvatinib	4 (66.7%)
Sorafenib	2 (33.3%)
Cabozantinib	1 (16.7%)
BRAF inhibitor	
Dabrafenib plus trametinib rechallenge	2 (33.3%)
Immune checkpoint inhibitors	
Pembrolizumab	1 (16.7%)

cancer types, indicating the potential effectiveness of targeting BRAF V600 mutations beyond melanoma. The phase 2 ROAR trial further supported these findings, with ORR rates between 33% and 89% across various BRAF V600E-mutant cancers [30]. Specifically, the ATC cohort of ROAR trial enrolled 36 patients with either unresectable or metastatic ATC who were treated with a combination of dabrafenib and trametinib, and demonstrated an ORR of 56% with a 12-month DOR rate of 50%. The median PFS was 6.7 months, and the median OS was 14.5 months; the 1-year PFS and OS rates were 43.2% and 51.7%, respectively [21].

Emerging evidence suggests that combining BRAF and MEK inhibitors may enhance antitumor activity, improve treatment responses, extend survival, and reduce MAPK pathway reactivation compared to BRAF inhibitor monotherapy [16-18]. Dabrafenib plus trametinib is currently approved for BRAF V600-mutant melanoma, non-small cell lung cancer, and ATC [16-21]. The SELECT trial reported a median PFS of 18.3 months and an ORR of 64.5% for lenvatinib in radioiodine-refractory DTC [4]. A phase 2 trial including 53 patients with BRAF-mutated radioiodine-refractory DTC showed an ORR of 35% for dabrafenib monotherapy and 30% for the combination with trametinib, suggesting no significant improvement with the addition of trametinib [22]. In our study, among 21 patients treated with dabrafenib and trametinib, the

ORR was 66.7% and the DCR was 85.7%. For those receiving this combination as first-line treatment, the ORR and DCR were 75.0% and 91.7%, respectively. The AEs observed were consistent with previous trials, and no grade 3-4 toxicities were reported in our cohort [22]. This study provides new data on the efficacy and safety of BRAF inhibitors in treatment-naïve BRAF V600E-mutant PTC patients.

In the SELECT trial, lenvatinib demonstrated a DCR of 87.7% and a median PFS of 18.3 months in patients with radioiodine-refractory DTC [4]. Although the initial dosage was 24 mg per day, the median dose administered was 16.8 mg, indicating that dose reductions were frequently required due to intolerance. In clinical settings in Taiwan, most patients are unable to tolerate the full 24 mg daily dose, making dose adjustments a common practice. Our previously published study revealed that a lower maintenance dose of lenvatinib (10 mg/day) was well tolerated in this patient population, resulting in fewer dose reductions, treatment interruptions, drug discontinuations, and only mild AEs [23]. Moreover, this reduced dose still achieved a DCR of 89.2% and a median PFS of 26.1 months, which is comparable to the outcomes reported in the SELECT trial. Additionally, a retrospective study conducted in a real-world setting evaluated various starting doses of lenvatinib (10 mg, 14 mg, 18 mg, 20 mg, and 24 mg) in patients with radioiodine-refractory DTC. The findings indicated that the initial dose had no significant effect on PFS or OS [31]. Despite the variability in starting doses, the observed ORR and OS were comparable to those reported in the pivotal clinical trial [4, 31]. Based on these findings, we initiated treatment with lenvatinib at a starting dose of 10 mg per day in our study.

Our study indicated that both PFS and OS were numerically higher when the treatment was administered in the first-line setting compared to second-line therapy, although the difference did not reach statistical significance. Currently, no clinical trials have directly compared the OS outcomes between first-line use of dabrafenib plus trametinib and lenvatinib, leaving the optimal initial treatment strategy uncertain. Furthermore, data regarding the most effective treatment sequence remain lacking, despite its clinical relevance. In our cohort, 13 patients received both first- and second-line therapies involving dabrafenib/trametinib and lenvatinib. Our findings suggested a trend toward improved OS in patients who received dabrafenib/trametinib followed by lenvatinib (47.7 months) compared to those treated in the reverse order (39.4 months), although the difference was not statistically significant. While the sample size was limited, this study contributes to the scarce real-world evidence on treatment sequencing and may offer insights for clinical decision-making. Further large-scale studies are warranted to validate these observations.

However, our study has limitations, including its retrospective nature and single-institution data, which may limit the generalizability of the results. In addition, the sample size was also relatively small, and the relatively small sample size may have limited the ability to demonstrate statistically significant differences in subgroup analyses. Despite these limitations, our study presents one of the largest real-world cohorts analyzing the efficacy and safety of dabrafenib and trametinib in this population, providing valuable insights for clinical practice. In conclusion, our findings offer a deeper understanding of the clinical outcomes and safety profiles for patients with BRAF V600E-mutant PTC treated with dabrafenib plus trametinib.

Conclusions

Our study illustrates the efficacy and safety of dabrafenib combined with trametinib in patients with BRAF V600E-mutant PTC, including its use as a first-line treatment. These results could signify a significant therapeutic advancement for this population.

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Disclosure of conflict of interest

None.

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