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A Phase 2 Study of Encorafenib in Combination with Binimetinib in Patients with Metastatic *BRAF*-Mutated Thyroid Cancer in Japan

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Background: Driver mutations at *BRAF* V600 are frequently identified in papillary thyroid cancer and anaplastic thyroid cancer (ATC), in which BRAF inhibitors have shown clinical effectiveness. This Japanese phase 2 study evaluated the efficacy and safety of a BRAF inhibitor, encorafenib, combined with an MEK inhibitor, binimetinib, in patients with *BRAF* V600-mutated thyroid cancer.

Methods: This phase 2, open-label, uncontrolled study was conducted at 10 institutions targeted patients with *BRAF* V600-mutated locally advanced or distant metastatic thyroid cancer not amenable to curative treatment who became refractory/intolerant to ≥1 previous vascular endothelial growth factor receptor-targeted regimen(s) or were considered ineligible for those. The primary endpoint was centrally assessed objective response rate (ORR). The secondary endpoints included duration of response (DOR), progression-free survival (PFS), overall survival (OS), and safety.

Results: We enrolled 22 patients with *BRAF*^V600E^-mutated thyroid cancer: 17 had differentiated thyroid cancer (DTC), and 5 had ATC. At data cutoff (October 26, 2022), the median follow-up was 11.5 (range = 3.4–19.0) months. The primary endpoint of centrally assessed ORR was 54.5% (95% confidence interval [CI] 32.2–75.6; partial response in 12 patients and stable disease in 10). The ORRs in patients with DTC and ATC were 47.1% (8 of 17) and 80.0% (4 of 5), respectively. The medians for DOR and PFS by central assessment and for OS were not reached in the overall population, the DTC subgroup, or the ATC subgroup. At 12 months, the rate of ongoing response was 90.9%, and the PFS and OS rates were 78.8% and 81.8%, respectively. All patients developed ≥1 adverse events (AEs): grade 3 AEs in 6 patients (27.3%). No patients developed grade 4–5 AEs. The most common grade 3 AE was lipase increased (4 patients [18.2%]). Those toxicities were mostly manageable with appropriate monitoring and dose adjustment.

Conclusions: Treatment with encorafenib plus binimetinib met the primary endpoint criteria and demonstrated clinical benefit in patients with *BRAF*^V600E^-mutated thyroid cancer regardless of its histological type, such as

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DTC or ATC, with no new safety concerns identified. Encorafenib plus binimetinib could thus be a new treatment option for *BRAF* V600-mutated thyroid cancer.

Clinical Trial Registration number: Japan Registry of Clinical Trials: jRCT2011200018

Introduction

MUTATIONS IN V600 POSITION OF *BRAF* are driver mutations identified most frequently in thyroid cancer,[1] with *BRAF*[V600E] being the most prevalent variant. According to its pathological type, follicular cell–derived thyroid cancer can be divided into differentiated thyroid cancer (DTC), which includes papillary thyroid cancer (PTC) and follicular thyroid cancer (FTC); oncocytic carcinoma; high-grade follicular-derived carcinomas, which includes poorly differentiated thyroid cancer (PDTC); and anaplastic thyroid cancer (ATC).[2]

The DTC type represents >90% of thyroid cancer. The most common subtype of DTC, PTC, has a particularly high frequency of the *BRAF*[V600E] mutation (27–85%), and such a trend is especially prevalent in East Asia.[3–11] Although less frequent than in DTC, the *BRAF* V600-mutation also occurs in 19–45% of ATC,[12] a subtype with an extremely poor prognosis.[13] In Japan, the standard of care for radioactive iodine (RAI)-resistant DTC that is not amenable to curative treatment has been two vascular endothelial growth factor receptor tyrosine kinase inhibitors (VEGFR-TKIs), lenvatinib and sorafenib. Although these VEGFR-TKIs have shown antitumor activity for RAI-resistant DTC, the treated tumors gradually acquired drug resistance and progressed in most patients.[13,14]

Similarly, a VEGFR-TKI has a modest efficacy in ATC; although in a previous Japanese phase 2 study, lenvatinib (the only approved VEGFR-TKI for ATC in Japan) demonstrated promising antitumor effects in a subgroup of ATC,[15] the recent phase 2 study results showed limited benefit of lenvatinib for patients with ATC.[16,17] Currently in Japan, patients with *BRAF*-mutated ATC or DTC who progressed after treatment with a VEGFR-TKI have no established therapeutic options, thus requiring new treatment strategies.

Preclinical studies have shown that inhibitors for BRAF and its downstream effector, MEK, suppressed the mitogen-activated protein kinase (MAPK) pathway and thereby tumor growth.[18,19] Moreover, in a transgenic mouse model of *BRAF* V600-mutant ATC, a combination of BRAF and MEK inhibitors achieved enhanced tumor response, as compared with treatment with BRAF inhibitor alone.[20] Of note, the combination of BRAF and MEK inhibitors suppressed not only tumor proliferation, but also the re-activation of the MAPK pathway, or emergence of resistance, and hence contributed to the long-term maintenance of the tumor response.

The antitumor effect was confirmed in a phase 2 study, in which a BRAF inhibitor, dabrafenib, plus an MEK inhibitor, trametinib, demonstrated clinical activity in *BRAF*[V600E]-mutated ATC.[21,22] The regimen was approved for *BRAF*[V600E]-mutated ATC in the United States,[23,24] whereas no specific regimens targeting *BRAF*-mutated thyroid cancer are approved in Japan.[25]

Encorafenib is a highly selective BRAF inhibitor with a prolonged pharmacodynamic profile, as compared with other BRAF inhibitors.[26,27] In a previous phase 3 study, encorafenib plus an MEK inhibitor, binimetinib, demonstrated favorable tumor response and survival benefit in patients with *BRAF* V600-mutated melanoma, in which the mutation serves as a driver, the same as in thyroid cancer.[28,29] Since combinatorial BRAF/MEK inhibition has shown clinical benefit in various *BRAF*-mutated cancers, including those of thyroid cancer, encorafenib plus binimetinib could also be effective for patients with *BRAF*-mutated thyroid cancer.

This phase 2 study was conducted to evaluate the efficacy and safety of the BRAF inhibitor encorafenib in combination with the MEK inhibitor binimetinib in patients with *BRAF* V600-mutated thyroid cancer. Here, we report the primary results of the study.

Methods

Study design and patients

This phase 2, open-label, uncontrolled study (Japan Registry of Clinical Trials registration No. jRCT2011200018) was conducted at 10 Japanese institutions. The inclusion criteria were as follows: ≥20 years of age; histological diagnosis of locally advanced or distant metastatic thyroid cancer that was not amenable to curative treatment; *BRAF* V600-mutation in their tumor tissues or blood samples confirmed with central laboratory test; those who became refractory/intolerant with ≥1 oral VEGFR-targeted drugs for thyroid cancer, or were considered medically ineligible for those drugs; ≥1 measurable lesion per response evaluation criteria in solid tumors (RECIST) v1.1, assessed at a local institution; Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0 or 1; a life expectancy of ≥3 months; and those who were able to swallow, ingest, and absorb oral drugs. In addition, the presence or absence of refractoriness or resistance to RAI treatment was confirmed by a local investigator.

For enrollment of a patient with DTC who was ineligible for VEGFR-TKIs, the patient was required to have refractoriness or resistance to RAI treatment. Progressive disease (PD) according to the RECIST guidelines by the independent review committee before study entry was not required.

The presence of a *BRAF* V600 mutation was determined in all patients using PCR-reverse sequence specific oligonucleotide-based assay kits provided by Medical & Biological Laboratories Co., Ltd., Tokyo, Japan (for tumor samples) and next-generation sequencing (NGS) of plasma-derived cell-free DNA with Guardant360 CDx, the Ministry of Health, Labour and Welfare (Japan), and Food and Drug Administration-approved clinical NGS assay system developed by Guardant Health, Inc., Redwood City, California, United States (for blood samples).

Both methods detect the presence of *BRAF* V600E, K, R, D, and M mutations. The exclusion criteria were previous RAF or MEK inhibitor treatment (previous sorafenib was allowed); a history, current evidence, finding, or risk factor of retinal vein occlusion (RVO); a history or current evidence of other retinal degenerative diseases; symptomatic brain metastasis, leptomeningeal disease, or other active central nervous system metastasis; and those who received chemotherapy, small-molecule targeted therapy, radiotherapy, immunotherapy, or hormonal therapy, and others for malignant tumors within 14 days from the first dose of study drugs.

Patients orally received encorafenib (450 mg) once daily and binimetinib (45 mg) twice daily over a 28-day cycle until unacceptable toxicity, disease progression, or consent withdrawal. Dose reduction was allowed if treatment-related adverse events (TRAEs) that met criteria prespecified in the protocol occurred. Radiation therapy and surgery were not allowed during the study treatment. The observational period was defined as the interval between the start of study treatment and either death, last confirmed survival, or data cutoff, whichever occurred first.

The trial protocol was approved by the institutional review board at each site. This study was conducted under the Declaration of Helsinki and local regulations. All patients provided written informed consent.

Assessments

The primary endpoint was centrally assessed objective response rate (ORR). The secondary endpoints included centrally assessed best overall response (BOR) and disease control rate (DCR); investigator-assessed ORR; centrally assessed duration and rate of ongoing response, percent changes in the size of target lesions, and progression-free survival (PFS); and overall survival (OS). As a prespecified exploratory analysis, centrally assessed ORRs by subgroups of background factors were evaluated in patients with ATC and those with DTC.

Safety endpoints included adverse events (AEs) and laboratory tests. Tumor was imaged at screening, cycles 2–4, every 2 cycles for cycle 6–24, and every 3 cycles afterward; and response was assessed according to RECIST v1.1 with categories of complete response (CR), partial response (PR), stable disease (SD), PD, and not evaluable. If a patient discontinued study treatment due to AEs before being confirmed as PD according to RECIST v1.1, the assessments of tumor response were continued until the patient started subsequent treatment or had PD.

The BOR was defined as the best response achieved during the observational period. The ORR and DCR were defined as the proportion of patients who achieved BOR of CR or PR and those who achieved BOR of CR, PR, or SD, respectively. We defined PFS as the interval from the start of treatment to PD or death by any cause, whichever occurred first. For the PFS analysis, if a patient had PD before starting subsequent treatment, the patient was counted as an event; if a patient started subsequent treatment without PD, the patient was censored on the date of final evaluable imaging.

The duration of response (DOR) was defined as the interval between the date on which a confirmed response was first detected as CR or PR and the date of first PD or death by any cause, whichever occurred first. AEs were graded using the National Cancer Institute Common Terminology Criteria for Adverse Events v 5.0.

Statistical analysis

Considering that in Japan there is no standard of care established for patients with *BRAF*-mutated thyroid cancer who are refractory or intolerant for a VEGFR-TKI, we referred to the objective response in patients of natural course to set the threshold response rate. The threshold response rate was set as 5.0% and the expected response rate as 40.0%. With the expected response rate, 19 patients were targeted for enrolment to ensure at least 90% probability of having a lower limit of 95% confidence intervals (CIs) exceeding the threshold response rate.

Patients who received ≥1 dose of study drugs were assessed for safety and efficacy. Both of the efficacy and safety endpoints were analyzed in the overall population, and by histological types. For ORR, DCR, and BOR, their respective CIs were calculated using the Clopper-Pearson method. Medians and CIs of OS, PFS, and DOR; OS rates; and PFS rates were calculated using the Kaplan–Meier method. All statistical analyses were carried out using Statistical Analysis System software, version 9.4.

Results

Patients

After initial screening among 42 Japanese patients, 22 with thyroid cancer that was not amenable to curative treatment were enrolled between March 2021 and May 2022 (Supplementary Fig. S1). All of the enrolled patients were determined to have the $BRAF^{V600E}$ mutation, while not having any of other *BRAF* V600 variants. Baseline characteristics of the entire patient population and those by histological type are shown in Table 1.

The median age was 68 years, 12 patients (54.5%) were male, and 6 (27.3%) and 16 (72.7%) patients had ECOG PS of 0 and 1, respectively. The histological type was DTC in 17 (77.3%) patients, in which all were classified as PTC, and ATC in 5 (22.7%). No patients with FTC or PDTC were enrolled. The most common sites for metastasis were lung (16 patients [72.7%]) and lymph node (16 patients [72.7%]), followed by bone (6 patients [27.3%]). Twenty-one (95.5%) and 20 (90.9%) patients had received surgery and drugs targeting VEGFR, respectively.

Efficacy

At the data cutoff of October 26, 2022, with the median follow-up period of 11.5 (range = 3.4–19.0) months, treatment with encorafenib plus binimetinib was ongoing in 13 (59.1%) patients and had been discontinued in 9 (40.9%). The most common reasons for discontinuation were disease progression, AEs, and consent withdrawal in 6, 2, and 1 patient(s), respectively. The centrally assessed ORR was 54.5% [CI = 32.2–75.6] (Table 2).

Since the lower limit of the CI exceeded the prespecified threshold response rate of 5%, the primary endpoint of the centrally assessed ORR met the prespecified statistical significance. In the central assessment of BOR, we identified no

TABLE 1. BASELINE CHARACTERISTICS OF PATIENTS

Variable	Overall (n = 22)	DTC (n = 17)	ATC (n = 5)
Sex			
Male	12 (54.5)	10 (58.8)	2 (40.0)
Female	10 (45.5)	7 (41.2)	3 (60.0)
Age, year			
Median (range)	68 (50–77)	67 (50–75)	74 (60–77)
<65	9 (40.9)	8 (47.1)	1 (20.0)
≥65	13 (59.1)	9 (52.9)	4 (80.0)
ECOG PS			
0	6 (27.3)	6 (35.3)	0
1	16 (72.7)	11 (64.7)	5 (100)
Initial or recurrent			
Initial	7 (31.8)	5 (29.4)	2 (40.0)
Recurrent	15 (68.2)	12 (70.6)	3 (60.0)
Prior therapy			
Surgery	21 (95.5)	16 (94.1)	5 (100)
Radiotherapy	8 (36.4)	6 (35.3)	2 (40.0)
Radioactive therapy (^{131}I)	15 (68.2)	14 (82.4)	1 (20.0)
Thyrotropin suppression therapy	8 (36.4)	6 (35.3)	2 (40.0)
Number of previous VEGFR-TKIs			
0	2 (9.1)[a]	1 (5.9)[a]	1 (20.0)[a]
1	16 (72.7)	12 (70.6)	4 (80.0)
≥2	4 (18.2)	4 (23.5)	0
Duration of prior VEGFR-TKI therapy,[b] months, median (range)	28.4 (0.3–104.9)	33.4 (1.4–104.9)	10.8 (0.3–52.4)
Metastases sites			
Lung	16 (72.7)	12 (70.6)	4 (80.0)
Lymph nodes	16 (72.7)	13 (76.5)	3 (60.0)
Bone	6 (27.3)	4 (23.5)	2 (40.0)
Pleura	5 (22.7)	4 (23.5)	1 (20.0)
Other	7 (31.8)	5 (29.4)	2 (40.0)
Number of metastases sites			
≤2	12 (54.5)	9 (52.9)	3 (60.0)
≥3	10 (45.5)	8 (47.1)	2 (40.0)
Sum of diameters of target lesions,[c] mm, median (range)	40.1 (10.4–132.4)	43.8 (10.4–132.4)	25.6 (13.9–64.0)

[a]Those patients were considered medically ineligible to VEGFR-TKI.
[b]The treatment period was defined as the interval from the initiation of first-line treatment to the termination of the latest treatment line.
[c]Based on the assessment by independent review committee. Values are shown as *n* (%) unless otherwise indicated.
ATC, anaplastic thyroid cancer; DTC, differentiated thyroid cancer; ECOG PS, Eastern Cooperative Oncology Group Performance Status; VEGFR-TKI, vascular endothelial growth factor receptor tyrosine kinase inhibitor.

TABLE 2. BEST OVERALL RESPONSE PER CENTRAL ASSESSMENT

	Overall (n = 22)	DTC (n = 17)	ATC (n = 5)
ORR, *n* (%)	12 (54.5)	8 (47.1)	4 (80.0)
CI	32.2–75.6	23.0–72.2	28.4–99.5
DCR, *n* (%)	22 (100.0)	17 (100.0)	5 (100.0)
CI	84.6–100.0	80.5–100.0	47.8–100.0
BOR, *n* (%)			
CR	0	0	0
PR	12 (54.5)	8 (47.1)	4 (80.0)
SD	10 (45.5)	9 (52.9)	1 (20.0)
PD	0	0	0

BOR, best overall response; CI, 95% confidence interval; CR, complete response; DCR, disease control rate; ORR, objective response rate; PD, progressive disease; PR, partial response; SD, stable disease.

patients with PD; 12 patients (54.5%) achieved PR and 10 (45.5%) achieved SD, with a DCR of 100%. The investigator-assessed ORR was comparable to but slightly higher than the centrally assessed ORR (Supplementary Table S1).

The centrally assessed ORR by histological type was 47.1% (8 in 17 patients) for DTC and 80.0% (4 in 5 patients) for ATC (Table 2 and Fig. 1A). The median DOR by central assessment was not reached (range = 1.9^{+}–16.2^{+} months) in the entire population or in patients with DTC or ATC. In the entire population, the rates of ongoing response at 6 and 12 months were 90.9% [CI = 50.8–98.7] (Supplementary Table S2) and tumor size reduction was continuously observed irrespective of histological type (Fig. 1B).

The medians of centrally assessed PFS and OS were not reached in the entire population. Both the 6- and 12-month centrally assessed PFS rates were 78.8% and the 6- and 12-month OS rates were 81.8% (Fig. 2). The medians of PFS and
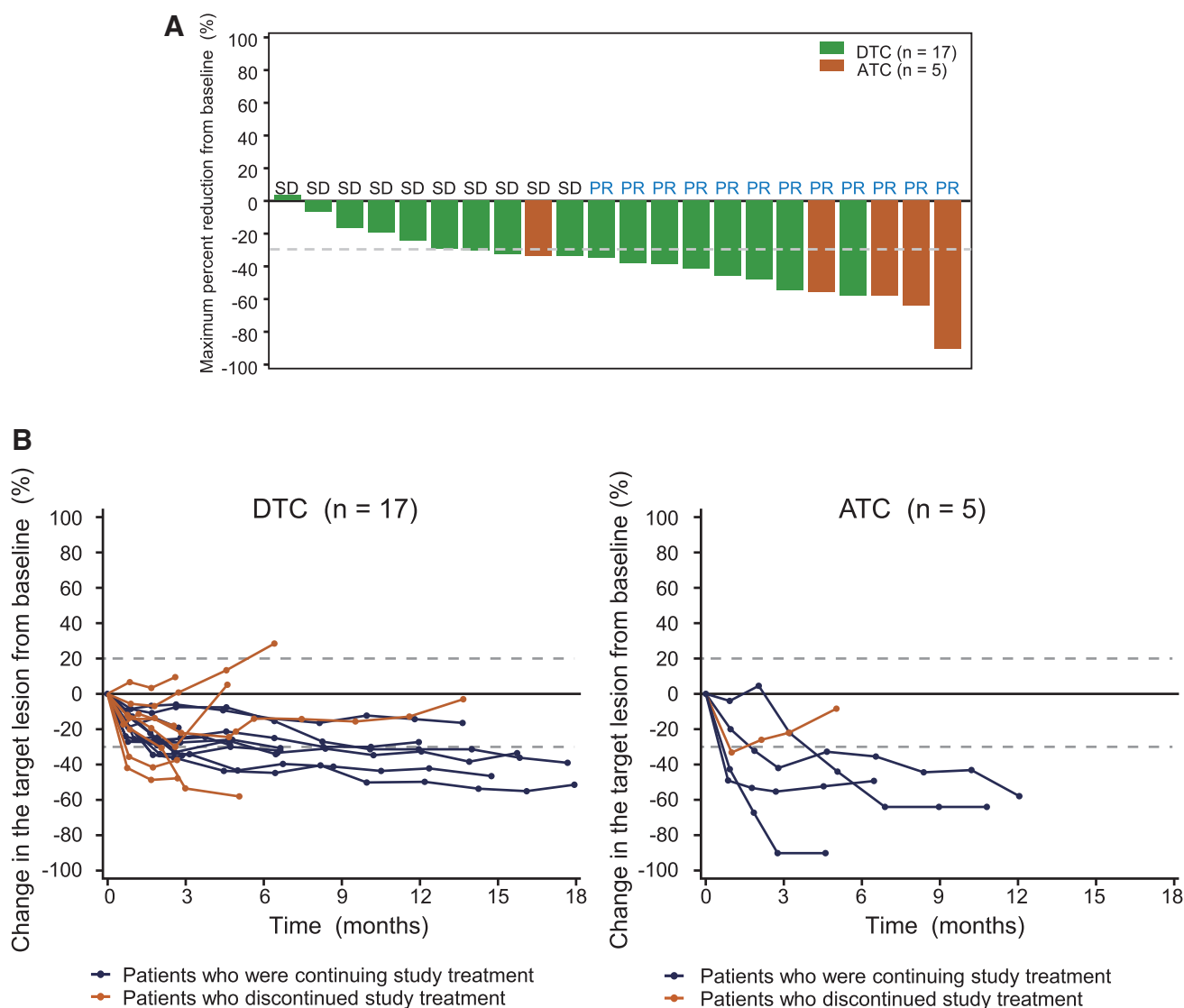
FIG. 1. Changes in tumor size from baseline. (**A**) The maximum percent change in the sum of tumor diameter and (**B**) change in tumor size over time per central assessment. ATC, anaplastic thyroid cancer; DTC, differentiated thyroid cancer; PR, partial response; SD, stable disease.

OS were not reached in patients with DTC or ATC; both of the 6- and 12-month PFS rates were 79.0% for patients with DTC and 75.0% for those with ATC; both of the 6- and 12-month OS rates were 76.5% for patients with DTC and 100% for those with ATC. Results of a prespecified exploratory subgroup analysis on the centrally assessed ORR in patients with DTC and those with ATC are summarized in Supplementary Figures S2 and S3.

Safety

All patients developed at least one AE, and 20 (90.9%) experienced AEs related to treatment with encorafenib or binimetinib (Table 3 and Supplementary Table S3). Grade 3 AEs occurred in 6 patients (27.3%). None of the patients developed AEs of grade 4 or 5. The most common any-grade AE was nausea, which occurred in 10 patients (45.5%); followed by palmar-plantar erythrodysesthesia syndrome, ar-

thralgia, and decreased appetite, each in 6 patients (27.3%); and serous retinal detachment, diarrhea, vomiting, fatigue, and pyrexia, each in 5 patients (22.7%).

The most common grade 3 AE was lipase increased, which occurred in 4 patients (18.2%); followed by neutrophil count decreased in 2 patients (9.1%); and palmar-plantar erythrodysesthesia syndrome, gamma-glutamyl transferase increased, and pruritus, each in 1 patient (4.5%). As a serious AE, 1 patient with ATC developed duodenal ulcer. No apparent difference was observed in AE profiles between patients with DTC and those with ATC.

TRAEs are summarized in Supplementary Table S4. TRAEs leading to discontinuation of encorafenib or binimetinib occurred in 4 patients (18.2%), all of whom were with DTC: ejection fraction decreased in 3, drug hypersensitivity in 1, and palmar-plantar erythrodysesthesia syndrome in 1. TRAEs leading to interruption of encorafenib or binimetinib occurred in 16 patients (72.7%) (Supplementary
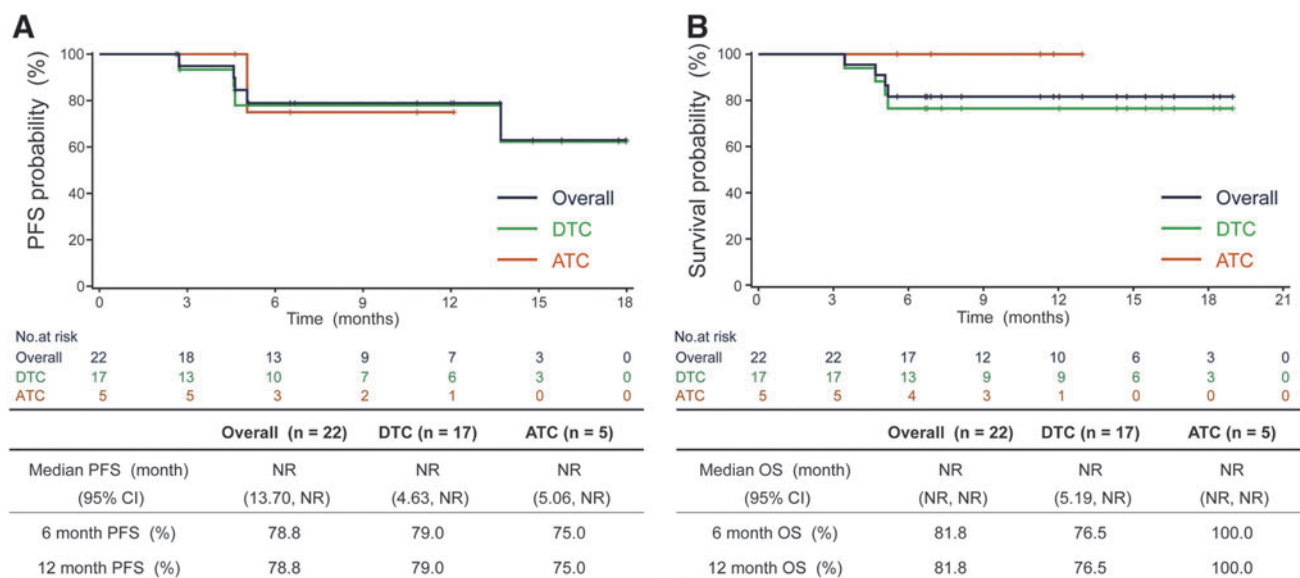
FIG. 2. Progression-free survival and overall survival. (**A**) Progression-free survival per central assessment and (**B**) overall survival. CI, 95% confidence interval; NR, not reached; OS, overall survival; PFS, progression-free survival.

Table S3): palmar-plantar erythrodysesthesia syndrome in 4 (18.2%); and rash, serous retinal detachment, lipase increased, and myalgia, each in 3 (13.6%).

TRAEs leading to dose reduction of encorafenib or binimetinib occurred in 3 patients (13.6%) (Supplementary Table S3): macular edema, electrocardiogram QT prolonged, lipase increased, and muscle spasms. Most of the patients with TRAEs, including those with serous retinal detachment or lipase increased, recovered or were recovering with appropriate intervention such as drug interruption (Supplementary Table S5).

In particular, 86.7% of patients with ocular TRAEs recovered or were recovering under monitoring with or without drug interruption or dose reduction (Supplementary Tables S5 and S6). The median exposure of encorafenib and binimetinib was 6.7 (range = 2.0–19.0) months and 6.7 (range = 0.9–18.5) months, respectively (Supplementary Table S7).

Discussion

Previously, the combination therapy of dabrafenib plus trametinib for $BRAF^{V600E}$-mutated thyroid cancer that was not amenable to curative treatment demonstrated ORRs of 30% (8 of 27) and 56% (20 of 36) for DTC and ATC, respectively, with 20% of enrolled patients having a previous history of VEGFR-TKI treatment.[22,30] In the current study, the combination therapy of encorafenib plus binimetinib for $BRAF^{V600E}$-mutated thyroid cancer who were refractory, intolerant, or ineligible to VEGFR-TKIs achieved ORRs of 47.1% (8 of 17) and 80% (4 of 5) for DTC and ATC, respectively. Of note, ≥70% of the enrolled patients had ECOG PS of 1, about 90% had a previous history of VEGFR-TKI treatment, and 45.5% had ≥3 metastatic sites.

Despite the relatively unfavorable situation, we observed tumor size reduction in most of the patients, with no patients having PD as best response, and the response was maintained in the majority of patients during the observation period.

Taken together, while having limitations of small population size (22 patients) with a follow-up period of only 11.5 months, encorafenib plus binimetinib demonstrated clinically meaningful antitumor activities in those patients.

The BRAF inhibitors, encorafenib, dabrafenib, and vemurafenib, have similar activity for inhibiting BRAF V600E kinase *in vitro*, with different pharmacokinetics[26]: although the half-life of encorafenib concentration in plasma (2.92 hours) is shorter than that of vemurafenib (12.7 hours) or dabrafenib (5.07 hours), the dissociation half-life of encorafenib (>30 hours) was markedly longer than that of vemurafenib (0.5 hours) or dabrafenib (2 hours), suggesting durable activity of encorafenib within tumors.

In addition, the comparison of BRAF/MEK inhibitor combinations (encorafenib plus binimetinib vs. dabrafenib plus trametinib vs. vemurafenib plus cobimetinib) revealed that in *BRAF*-mutant melanoma cell lines, encorafenib plus binimetinib had the longest interval before emergence of resistance, and encorafenib had slightly superior activity for inducing apoptosis as compared with dabrafenib.[31] The superior pharmacological properties of encorafenib may explain the robust and clinically meaningful antitumor activities of encorafenib plus binimetinib in the current results, even with the relatively unfavorable patients' background.

In this study, we administered encorafenib and binimetinib at the dose used in previous studies involving patients with malignant melanoma and found no new safety concerns. Of note, each BRAF/MEK inhibitor combination varies in its safety profile; for instance, pyrexia is frequently observed in combination therapy with dabrafenib plus trametinib, but not in treatment with encorafenib plus binimetinib, which, however, has a relatively high incidence of grade 1–2 ocular toxicities, compared with the dabrafenib plus trametinib.[28,32,33]

Serous retinal detachment is known to be a class effect of MEK inhibitors,[34] and it occurs in patients receiving binimetinib in a dose-dependent manner.[35] In an observational

TABLE 3. ADVERSE EVENTS WITH INCIDENCE ≥10%

Variable	Overall (n = 22)		DTC (n = 17)		ATC (n = 5)	
	Any grade	Grade 3	Any grade	Grade 3	Any grade	Grade 3
Any adverse event	22 (100)	6 (27.3)	17 (100)	4 (23.5)	5 (100)	2 (40.0)
Skin and subcutaneous tissue disorders	16 (72.7)	2 (9.1)	13 (76.5)	1 (5.9)	3 (60.0)	1 (20.0)
Palmar-plantar erythrodysesthesia syndrome	6 (27.3)	1 (4.5)	6 (35.3)	1 (5.9)	0	0
Pruritus	4 (18.2)	1 (4.5)	3 (17.6)	0	1 (20.0)	1 (20.0)
Rash	4 (18.2)	0	3 (17.6)	0	1 (20.0)	0
Rash maculo-papular	4 (18.2)	0	3 (17.6)	0	1 (20.0)	0
Gastrointestinal disorders	16 (72.7)	1 (4.5)	12 (70.6)	0	4 (80.0)	1 (20.0)
Nausea	10 (45.5)	0	6 (35.3)	0	4 (80.0)	0
Diarrhea	5 (22.7)	0	3 (17.6)	0	2 (40.0)	0
Vomiting	5 (22.7)	0	4 (23.5)	0	1 (20.0)	0
Constipation	3 (13.6)	0	1 (5.9)	0	2 (40.0)	0
Stomatitis	3 (13.6)	0	2 (11.8)	0	1 (20.0)	0
Eye disorders	15 (68.2)	0	11 (64.7)	0	4 (80.0)	0
Serous retinal detachment	5 (22.7)	0	2 (11.8)	0	3 (60.0)	0
Macular edema	4 (18.2)	0	3 (17.6)	0	1 (20.0)	0
Visual field defect	3 (13.6)	0	3 (17.6)	0	0	0
Infections and infestations	11 (50.0)	0	9 (52.9)	0	2 (40.0)	0
COVID-19	4 (18.2)	0	3 (17.6)	0	1 (20.0)	0
Musculoskeletal and connective tissue disorders	10 (45.5)	0	8 (47.1)	0	2 (40.0)	0
Arthralgia	6 (27.3)	0	5 (29.4)	0	1 (20.0)	0
Myalgia	3 (13.6)	0	3 (17.6)	0	0	0
General disorders and administration site conditions	10 (45.5)	0	9 (52.9)	0	1 (20.0)	0
Fatigue	5 (22.7)	0	5 (29.4)	0	0	0
Pyrexia	5 (22.7)	0	4 (23.5)	0	1 (20.0)	0
Metabolism and nutrition disorders	7 (31.8)	0	5 (29.4)	0	2 (40.0)	0
Decreased appetite	6 (27.3)	0	4 (23.5)	0	2 (40.0)	0
Endocrine disorders	3 (13.6)	0	1 (5.9)	0	2 (40.0)	0
Hypothyroidism	3 (13.6)	0	1 (5.9)	0	2 (40.0)	0
Laboratory	14 (63.6)	6 (27.3)	9 (52.9)	4 (23.5)	5 (100)	2 (40.0)
Lipase increased	4 (18.2)	4 (18.2)	3 (17.6)	3 (17.6)	1 (20.0)	1 (20.0)
Blood creatine phosphokinase increased	4 (18.2)	0	3 (17.6)	0	1 (20.0)	0
Blood creatinine increased	4 (18.2)	0	2 (11.8)	0	2 (40.0)	0
Neutrophil count decreased	3 (13.6)	2 (9.1)	1 (5.9)	0	2 (40.0)	2 (40.0)
Gamma-glutamyl transferase increased	3 (13.6)	1 (4.5)	1 (5.9)	1 (5.9)	2 (40.0)	0
Ejection fraction decreased	3 (13.6)	0	3 (17.6)	0	0	0

Data are shown in *n* (%). Adverse events are reported according to National Cancer Institute Common Terminology Criteria for Adverse Events Version 5.0.

study of patients with malignant melanoma, ≥90% of patients who received binimetinib developed edema and ≥50% developed bullous lesions, which were frequently accompanied with visual disturbance, and mostly in the early phase of administration.

The patients recovered from those symptoms within 3–6 months while continuously receiving binimetinib.[35–37] In the current study, about 70% of patients experienced interruption, and 20% experienced discontinuation of either encorafenib or binimetinib. Overall, the observed AEs in the current study were mostly manageable with appropriate monitoring and dose adjustment, and were similar to the previous study results in melanoma.[28]

In the current study, patients with DTC, all classified as PTC, had a lower ORR than those with ATC (47.1% vs. 80%). The trend of a higher response rate in ATC as compared with that in DTC was also seen in dabrafenib plus trametinib, which showed a higher ORR for ATC (56%)[22] as compared with ORR for DTC (30%).[30] Studies have suggested that PTC has clonal diversity, including that of $BRAF^{V600E}$-mutant,[38,39] and sub-clonal mutations are associated with a higher risk of relapse.[40]

In addition, the Cancer Genome Atlas project results suggested that *BRAF* V600-mutated PTC exists as a heterogenous population with various differentiation states.[41] The relatively low activity of encorafenib plus binimetinib for PTC may be in part due to the clonal diversity that exists in those tumors.

The high ORR in ATC with $BRAF^{V600E}$ mutation in the previous and current studies may suggest that the MAPK pathway possibly serves a pivotal role in the proliferation of *BRAF*-mutated ATC. During anaplastic transformation, DTC acquires aggressive tumor features through oncogenic mutations such as that in the *TERT* promoter, and it has been suggested that activated MAPK signaling in *BRAF*-mutants promotes the tumor proliferation by enhancing activity of

mutated *TERT* promoter[42,43]; *BRAF*-mutated ATC thus may retain constitutive MAPK pathway activity that contributes to its aggressiveness. Further studies are required to understand the molecular mechanisms in this process.

The current study had two major limitations. First, this was a single-arm, phase 2 study with a limited number of patients, only 17 for DTC and 5 for ATC, which was not histologically confirmed by central review; therefore, confirmation of both efficacy and safety in a larger population will be required. Second, among the 5 patients with ATC, 3 had a record of anaplastic transformation, suggesting the possibility that those 3 patients were of mixed ATC. Third, an inclusion criterion of a life expectancy of ≥3 months may have contributed to the favorable survival results. Last, the median follow-up period was 12.0 and 11.3 months for DTC and ATC, respectively, which might be too short to sufficiently evaluate the duration of antitumor activity, OS, and long-term safety. Thus, longer follow-ups will be required to evaluate those endpoints.

Conclusions

The combination therapy of encorafenib plus binimetinib demonstrated clinically meaningful antitumor activity in patients with *BRAF*[V600E]-mutated thyroid cancer, meeting the primary endpoint criteria. The regimen also showed manageable safety profiles and signs of durable tumor regression activities regardless of histological type, DTC or ATC. Thus, encorafenib plus binimetinib could become a new treatment option for *BRAF* V600-mutated thyroid cancer.

Authors' Contributions

M.Ta. and N.K. contributed to conception and design of the study, and acquisition, analysis, and interpretation of data; H.I., S.Tak., A.N., S.Tam., Y.S., S.K., and K.I. contributed to acquisition of data; M.Y. and Y.H. contributed to conception and design of the study, interpretation of data, and drafting; S.U. contributed to design of the study, analysis and interpretation of data, and drafting; and I.S. contributed to conception and design of the study, and acquisition and interpretation of data. All authors contributed to revision of the article, approved the final version, and had a final responsibility for the decision to submit for publication.

Author Disclosure Statement

M.Ta. has received grants from Ono Pharmaceutical and Bayer; consulting fees from Boehringer Ingelheim, Janssen, Genmab, AbbVie, and Astellas; and payment for lectures from Ono Pharmaceutical, Merck Sharp & Dohme (MSD), Bayer, Rakuten Medical, Bristol-Myers Squibb (BMS), Merck Biopharma, Eisai, and Eli Lilly; and has participated in an advisory board of MSD, Bayer, BMS, Eisai, AstraZeneca, Merck Biopharma, Pfizer, Eli Lilly, and Boehringer Ingelheim. N.K. is an editorial board member of

Thyroid; received a research grant from Bayer; and honoraria for lectures from Bayer, Eli Lilly, and MSD.

S.Tak. has received grants and honoraria from Daiichi-Sankyo, Novartis, Chugai Pharma, BMS, Eisai, MSD, AstraZeneca, and Taiho Pharmaceutical; and an honorarium from Ono Pharmaceutical. S.Tam. has received honoraria for a speaker from Bayer Pharma Japan, Chugai, Eli Lilly Japan, Daiichi-Sankyo, Ono Pharmaceutical, and MSD K.K. Y.S. has received honoraria for lectures from Ono Pharmaceutical. S.K. has received grants from Ono Pharmaceutical, Taiho Pharmaceutical, MSD, Nobelpharma, Janssen Pharmaceutical K.K., BMS, Eli Lilly, Chugai, and Daiichi-Sankyo; honoraria from Ono Pharmaceutical, Taiho Pharmaceutical, MSD, Daiichi-Sankyo, Merck KGaA, BMS, Eli Lilly, Chugai, Bayer, and Eisai. K.I. has received a grant from JSPS KAKENHI Grant Number JP20K08953 and has participated in a joint research with Taiho Pharmaceutical.

M.To., Y.H., and S.U. are employed by Ono Pharmaceutical, and M.To. has ownership of stock in Ono Pharmaceutical.

I.S. has received grants from Bayer and Eisai for his institution; honoraria for lectures and travel expenses to attend a meeting from Eli Lilly; and has participated in an advisory board of Takeda and Eli Lilly. H.I. and A.N. declare no competing interests.

Supplementary Material

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