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ORIGINAL ARTICLE

Phase 1/2 study assessing the safety and efficacy of dabrafenib and trametinib combination therapy in Japanese patients with *BRAF* V600 mutation-positive advanced cutaneous melanoma

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ABSTRACT

The combination of dabrafenib and trametinib demonstrated encouraging antitumor activity and tolerability, at initial analysis, in Japanese patients with *BRAF* V600 mutant advanced melanoma warranting further investigation. This study evaluated the safety and tolerability, pharmacokinetics (PK) and preliminary efficacy of dabrafenib 150 mg b.i.d. plus trametinib 2 mg q.d. in Japanese patients with *BRAF* V600E/K mutant solid tumors (phase 1) and melanoma (phase 2). Phase 1 was primarily intended to assess safety and tolerability as assessed by adverse events (AE), and the primary end-point in phase 2 was to assess confirmed overall response rate (ORR). The secondary end-points in phase 1 included PK, confirmed/unconfirmed ORR and duration of response (DOR). The secondary end-points in phase 2 were PK, unconfirmed ORR, DOR, safety and tolerability. A total of 12 cutaneous melanoma patients were enrolled in the study (six in phase 1 and six in phase 2) and received the combination therapy of dabrafenib and trametinib. Common AE (≥50.0%) included pyrexia (75%), increased aspartate aminotransferase (67%), peripheral edema (50%) and nasopharyngitis (50%). The investigator-assessed ORR was reported in five patients (83%) in phase 1 and was also reported in five patients (83%; 95% confidence interval, 35.9–99.6; $P < 0.0001$) in phase 2. Plasma concentrations of both dabrafenib and trametinib seemed to a reach steady state by week 3. Overall, efficacy and PK properties for the dabrafenib plus trametinib combination in Japanese patients were comparable with those seen in global studies.

Key words: **dabrafenib, Japanese, malignant melanoma, solid tumor, trametinib.**

INTRODUCTION

Melanomas are the most aggressive form of skin cancers which account for 80% of skin cancer-induced deaths.[1] The origin and progression of melanoma has been associated with genetic mutations in several genes, including *BRAF*, *NRAS*, *MITF* and *KIT*, that are involved in different signaling pathways regulating survival, growth and proliferation in cells. The recent discovery of these mutations not only resulted in better understanding of melanoma and its progression but also resulted in advancement of targeted therapies.[2] *BRAF* mutation, occurring in approximately 50% of patients with melanoma, constitutively activates the mitogen-activated protein kinase (MAPK; RAS→RAF→MEK→ERK) signaling pathway, which plays a vital role in regulating the cell proliferation and survival in human tumors including cutaneous melanoma.[2–4]

Melanoma is relatively more common in Caucasian populations and hence analyses of characteristics of patients with *BRAF* mutations in detail have been restricted to these patients.[5,6] Studies involving China, Korea and Japan revealed that there may be some differences in incidence of melanoma compared with the findings in Caucasians, including frequency and an age association with *BRAF* mutation.[7–10] In a recent study conducted in Japan, the detection rates of *BRAF*, *NRAS* and *KIT* mutations were 30.4%, 12.3% and 12.9%, respectively.[11]

Dabrafenib, a potent and selective inhibitor of BRAF kinase activity, was approved based on the results of a phase 3 trial

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which demonstrated significant improvement in progression-free survival (PFS) in patients with *BRAF* V600E mutation-positive unresectable or metastatic melanoma.[12,13] Trametinib, a reversible, highly selective allosteric inhibitor of MEK1/MEK2 activation and kinase activity was approved for use in the treatment of adult patients with unresectable or metastatic melanoma containing *BRAF* V600E/K mutations based on the results demonstrated in a phase 3 trial.[14,15] Owing to the modest improvement in PFS with BRAF- and MEK-inhibitor monotherapies, development of resistance to BRAF inhibition, poor outcome in patients with *BRAF*-mutant melanoma after development of resistance to BRAF-inhibitor monotherapy, and the associated severe cutaneous toxicity, there was an interest in combining oncogenic BRAF inhibition with downstream MEK inhibition in the MAPK pathway to help in improving the patient outcomes. A synergistic effect of the combination of dabrafenib and trametinib, via concomitant inhibition of the ERK, was observed in *BRAF* V600-mutant melanoma cell lines, and delayed emergence of resistance was observed in *BRAF* V600-mutant melanoma xenografts *in vivo* along with a decrease in skin toxicities compared with monotherapy.[16] In a phase 2 study, the dabrafenib and trametinib combination significantly improved PFS and decreased the frequency of known BRAF inhibitor-induced hyperproliferative skin lesions such as cutaneous squamous cell carcinoma, papilloma and hyperkeratosis, compared with dabrafenib monotherapy in patients with BRAF inhibitor-naïve metastatic melanoma.[17]

The combination of dabrafenib and trametinib in the pivotal phase 3 studies revealed statistically significant and clinically relevant improvements in PFS, overall survival (OS) in patients with *BRAF* V600 mutation-positive melanoma.[18–21] As the data in Asian patients are very limited, this study was conducted to determine the safety and preliminary efficacy of dabrafenib plus trametinib in Japanese patients with *BRAF* V600E/K mutation-positive solid tumors, including melanoma.

METHODS

Study design

In this Japanese, phase 1/2, open-label, non-controlled study, the safety, tolerability, pharmacokinetics (PK) profile and efficacy of the dabrafenib 150 mg b.i.d. and trametinib 2 mg q.d. combination in patients with *BRAF* V600E/K mutation-positive advanced solid tumors (phase 1) and *BRAF* V600E/K mutation-positive cutaneous melanoma (phase 2) were evaluated (Fig. 1).

All patients provided written informed consent before participating in any study procedures. The study was conducted in accordance with the International Conference on Harmonization (ICH) Guidelines for Good Clinical Practice and the Declaration of Helsinki. All protocols and amendments were approved by the independent ethics committee or institutional review board for each study center. This trial was registered with ClinicalTrials.gov (NCT01928940).

Key eligibility criteria

Inclusion criteria

In phase 1, patients aged 20 years or more with histologically confirmed *BRAF* V600E/K mutation-positive advanced solid tumors, which are not responsive to standard therapies or for which there was no approved or curative therapy, were included. In phase 2, patients aged 20 years or more with histologically confirmed *BRAF* V600E/K mutation-positive unresectable (stage IIIC) or metastatic (stage IV) cutaneous

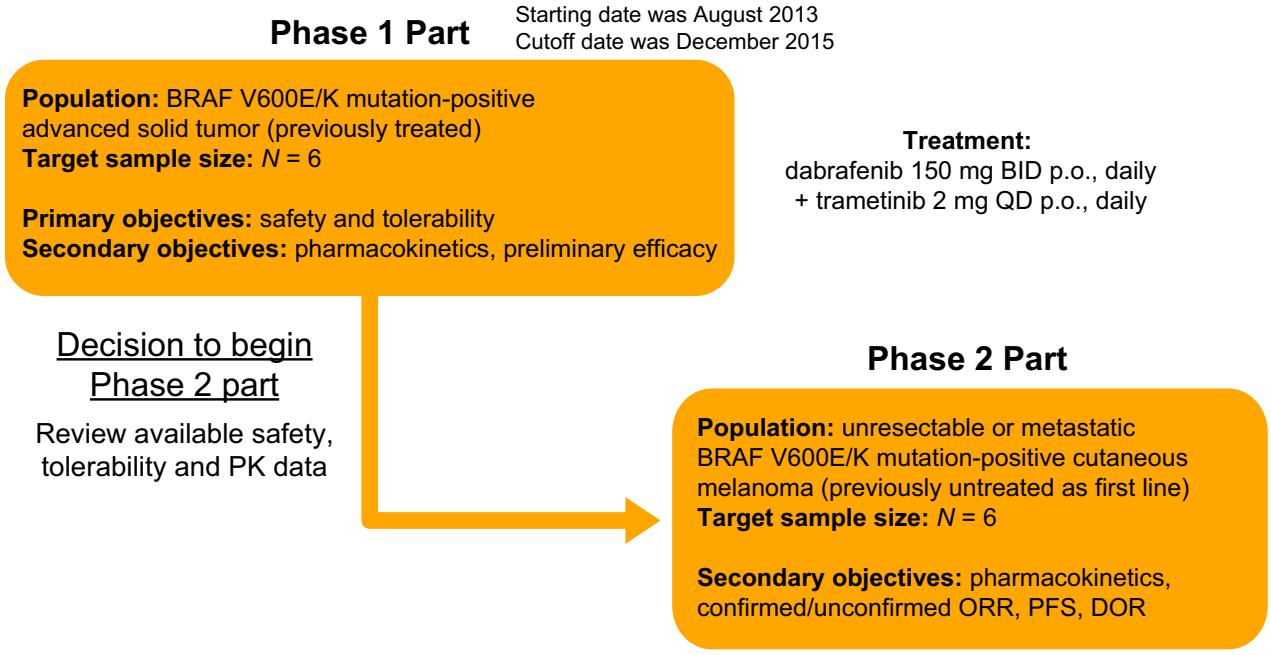


Figure 1. Study design and objectives. DOR, duration of response; ORR, overall response rate; PR, progression-free survival.

melanoma were included. Patients had to have measurable disease (i.e. ≥1 measurable lesion) as per Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST v1.1). For both phase 1 and 2, patients had to have an Eastern Cooperative Oncology Group performance status of 0 or 1.

Exclusion criteria

Patients were excluded from both phase 1 and 2 if they received prior BRAF inhibitor or MEK inhibitor therapy; however, patients treated with prior BRAF or MEK inhibitor who experienced no significant toxicity due to the prior treatment were eligible for phase 1. Patients were also excluded if they received any prior anticancer investigational product within 28 days or five half-lives (minimum 14 days), whichever was shorter, if they had any unresolved toxicity (except alopecia) from previous anticancer therapy of grade 2 or higher according to Common Terminology Criteria for Adverse Events version 4.0 (CTCAE v4.0), or if they had past or current history of cardiovascular risk and retinal vein occlusion.

Patients were excluded only from phase 2 if they had received a prior systemic anticancer treatment (chemotherapy, immunotherapy, biologic therapy, vaccine therapy or investigational treatment) for stage IIIC (unresectable) or stage IV (metastatic) melanoma except if it was received in the adjuvant setting.

Treatment administration

Dabrafenib and trametinib were administrated in the morning at approximately the same time every day, and the second dose of dabrafenib was administrated approximately 12 h after the morning dose. Patients received study treatment until disease progression, death or an unacceptable adverse event (AE). The cycle for safety assessment was defined as 28 calendar days of continuous dosing regardless of dose interruption.

Assessments

In phase 1, the primary end-point was to assess safety and tolerability as assessed by AE. Secondary end-points were PK, confirmed/unconfirmed overall response rate (ORR), PFS, and duration of response (DOR) of dabrafenib and trametinib. In phase 2, the primary end-point was to assess confirmed ORR. Secondary end-points included PK, unconfirmed ORR, PFS, DOR, safety and tolerability.

Overall response rate was evaluated by lesion assessments (by RECIST v1.1) performed every 8 weeks. Confirmed ORR is defined as the percentage of patients with a confirmed complete response (CR) or partial response (PR) as per RECIST 1.1. The unconfirmed ORR was defined as the percentage of subjects who had an unconfirmed CR or PR according to RECIST 1.1. PFS was defined as the time from the first dose of study treatment to the earliest of death or progression. DOR was defined as the time from first documented evidence of CR or PR until disease progression or death due to any cause among patients who achieved a confirmed response. Safety and tolerability were evaluated by routine physical examination findings, vital signs, clinical laboratory tests, clinical monitoring and observations, and AE reporting.

Pharmacokinetics

Blood samples for PK analysis were collected in subjects who participated in phase 1 only (PK population) on day 1 (pre-dose, and at 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12 and 24 h post-dose) and day 21 (pre-dose, and at 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10 and 12 h post-dose). A trough PK sample was collected at pre-morning dose on day 8, day 15, week 8, week 16 and week 24, and at progressive disease (PD) observation. The following PK parameters were calculated by non-compartmental analysis for dabrafenib and its metabolites (e.g. GSK2285403 [hydroxylated form], GSK2298683 [carboxylate form] and GSK2167542 [demethylated form]), and trametinib, following single- and repeat-dose administration of dabrafenib and trametinib: area under the plasma concentration–time curve (AUC0-t), the area under the plasma concentration versus time curve, from time zero to the end of the dosing period (AUC0-tau [repeat dose]), the area under the plasma concentration versus time curve, from time zero to infinity (AUC0-inf [single dose]), maximum measured plasma concentration (Cmax), time of maximum measured plasma concentration (Tmax), terminal elimination half-life (t1/2 [single dose]) and Ctau (repeat dose).

Statistical analysis

The primary focus of phase 1 was to assess the safety and tolerability of dabrafenib and trametinib combination therapy. In phase 1, the sample size was not driven by statistical considerations. The total number of patients depended on the number of dose levels needed. If only the combination of dabrafenib (150 mg b.i.d.) and trametinib (2 mg q.d.) was studied, the sample size of phase 1 was estimated to be six. In phase 2, the primary end-point was confirmed ORR (based on the investigator's assessment). In phase 2, with a threshold ORR of 10% and an expected ORR of 70% (based on phase 3 studies with dacarbazine, vemurafenib and dabrafenib therapies),[13,22] the sample size of six was estimated to provide 90% or more of power, given a one-sided alpha error of less than 0.05. Patients who were not evaluable were treated as non-responders, that is, they were included in the denominator when calculating the percentage. Exact 90% and 95% confidence intervals (CI) were calculated for this estimate, and the exact *P*-values for one-sided binomial test were calculated to allow rejection of the null hypothesis, of which ORR is 10%. An independent central review (ICR) was performed to serve as a sensitivity analysis of tumor assessment. The ICR assessment was used to analyze confirmed ORR. Only the subset of patients who showed a CR or PR was included in the analysis of duration of response.

Progression-free survival and duration of response were summarized descriptively using the Kaplan–Meier method. If a patient received subsequent anticancer treatment prior to the date of documented progression or death, PFS in the patient was to be censored at the last adequate assessment prior to the initiation of the subsequent therapy. Otherwise, if a patient did not have a documented date of progression or death, PFS in the patient was to be censored at the last adequate assessment. PK parameters were listed and summarized for phase 1.

Table 1. Patient demographics and baseline characteristics

	Phase 1 (n = 6)	Phase 2 (n = 6)	Total (n = 12)
Age, years			
Median	52.5	54.0	54.0
Range	21–76	49–77	21–77
Sex, *n* (%)			
Female	5 (83)	2 (33)	7 (58)
Male	1 (17)	4 (67)	5 (42)
Tumor type, *n* (%)			
Melanoma	6 (100)	6 (100)	12 (100)
Bodyweight, kg			
Median	61.65	65.1	63.55
Range	52.8–71.0	55.9–69.3	52.8–71.0
Melanoma histological type, *n* (%)			
Melanoma, NOS	1 (17)	5 (83)	6 (50)
Superficial spreading melanoma	1 (17)	1 (17)	2 (17)
Nodular melanoma	1 (17)	0	1 (8)
Others	1 (17)	0	1 (8)
Unknown	2 (33)	0	2 (17)
Stage at screening, *n* (%)			
IIIC	1 (17)	0	1 (8)
IV	5 (83)	6 (100)	11 (92)
BRAF mutation status, *n* (%)[†]			
V600E	6 (100)	6 (100)	12 (100)
V600K	0	0	0
Baseline LDH, *n* (%)			
>Upper limit of normal	3 (50)	1 (17)	4 (33)
≤Upper limit of normal	3 (50)	5 (83)	8 (67)
No. of organs involved			
1	1 (17)	0	1 (8)
2	2 (33)	4 (67)	6 (50)
≥3	3 (50)	2 (33)	5 (42)
Prior therapy, *n* (%)	6 (100)	6 (100)	12 (100)
Surgery	6 (100)	6 (100)	12 (100)
Chemotherapy (cytotoxics, non-cytotoxics)	6 (100)	0	6 (50)
0	0	6 (100)	6 (50)
1	5 (83)	0	5 (42)
2	1 (17)	0	1 (8)
Immunotherapy	6 (100)	1 (17)	7 (58)
0	0	5 (83)	5 (42)
1	2 (33)	1 (17)	3 (25)
2	4 (67)	0	4 (33)
Biological treatment	2 (33)	0	2 (17)
0	4 (67)	6 (100)	10 (83)
1	2 (33)	0	2 (17)
2	0	0	0
Small molecule targeted treatment	2 (33)	0	2 (17)[‡]
0	4 (67)	6 (100)	10 (83)
1	2 (33)	0	2 (17)
2	0	0	0

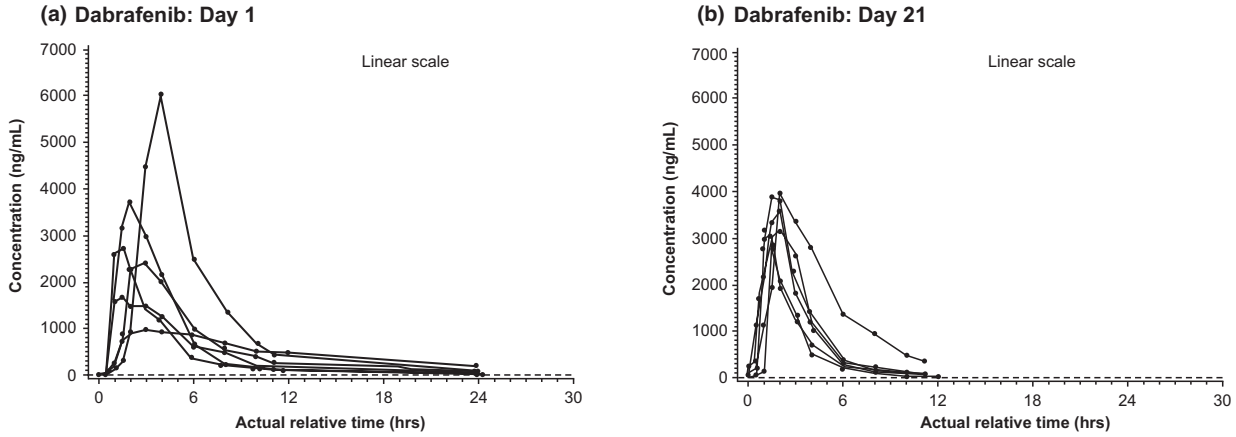
[†]*BRAF* V600E/K mutation was detected by direct sequencing in phase 1 and by ThxID-*BRAF* gene mutation assay, a companion diagnostic assay in phase 2. [‡]Both patients received prior BRAF inhibitors (dabrafenib, n = 1; vemurafenib, n = 1). NOS, not otherwise specified.

AE were coded using the ICH Medical Dictionary for Regulatory Activities (MedDRA) version 19.0 and grouped by system organ class and preferred term. AE were graded by the investigator according to CTCAE v4.0 and were summarized by frequency and proportion of total patients, by system organ class and preferred term.

RESULTS

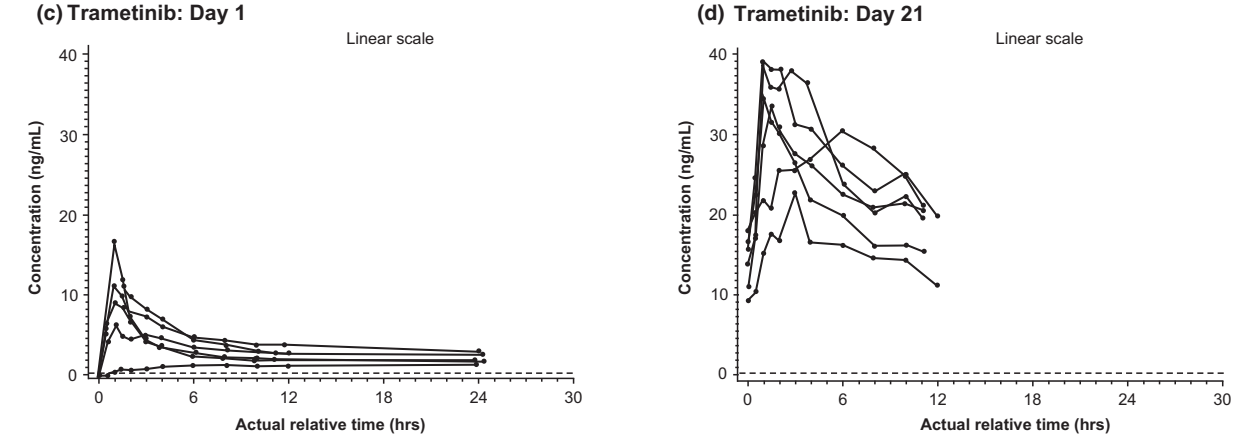
Patient disposition

A total of 12 patients were enrolled in the study (six in phase 1 and six in phase 2) and received the combination therapy of dabrafenib (150 mg b.i.d.) and trametinib (2 mg q.d.). First, six



	AUC0-∞ h·ng/mL	AUC0-12 h·ng/mL	C_{max} ng/mL	T_{max} hr	T1/2 hr
n	6	6	6	6	6
Geomean	13485.6	11414.9	2497.4	2.4	4.9
CV%	36.9	41.3	69.7	43.1	45.2
95% CI	9265-19629	7524-17317	1290-4834	1.5-3.5	3.1-7.7
Min-max	9307-24777	8153-23319	986-6040	1.4-3.9	2.8-9.6

	AUC0-12 h·ng/mL	C_{max} ng/mL	T_{max} hr
n	6	6	6
Geomean	10138.1	3431.3	1.7
CV%	33.1	12.0	34.9
95% CI	7230-14216	3028-3888	1.0-2.1
Min-max	7300-17859	2980-3950	1.0-2.0



	AUC0-∞ h·ng/mL	AUC0-24 h·ng/mL[a]	C_{max} ng/mL	T_{max} hr	T1/2 hr
n	5	5	6	6	5
Geomean	375.5	82.5	7.8	1.0	82.9
CV%	23.1	23.1	112.1	214.1	46.8
95% CI	283-499	62-110	3.0-20.2	0.4-6.5	47.7-144.0
Min-max	278-494	66-107	1.4-16.7	0.9-23.8	39.0-126.3

	AUC0-24 h·ng/mL[a]	C_{max} ng/mL	T_{max} hr
n	6	6	6
Geomean	447.9	32.5	1.2
CV%	25.5	20.2	89.0
95% CI	344-583	26.4-40.1	0.7-3.7
Min-max	282-555	22.7-38.8	0.9-5.9

Figure 2. Pharmacokinetics. (a) Dabrafenib, day 1. (b) Dabrafenib, day 21. (c) Trametinib, day 1. (d) Trametinib, day 21. AUC, area under the concentration curve; CI, confidence interval; Cmax, maximum concentration; CV, coefficient of variation; t1/2, half-life; Tmax, time to maximum concentration. [a]Calculated from extrapolated C24 h.

patients were enrolled in phase 1, who received the study treatment and completed the observation period for dose-limiting toxicities (DLT). All six patients were evaluable for safety and tolerability, and no additional patient was enrolled. This decision of the sponsor was supported by the Safety and Efficacy Review Committee. A case review meeting for discussing the start of phase 2 was held when the first three patients enrolled in phase 1 completed the DLT observation period. No DLT was observed in these three patients, and it was considered possible to start phase 2. A total of six patients were enrolled in phase 2 of the study and received the study treatment. Patient disposition in phase 1 and phase 2 is summarized in Table S1.

Treatment exposure

The mean daily dose of dabrafenib was 269.4 mg (standard deviation [SD], 45.54 mg) in phase 1 and 295.6 mg (SD, 4.04 mg) in phase 2, which was close to the planned daily dose (300 mg) in both periods. The mean daily dose of trametinib was 1.85 mg (SD, 0.235 mg) in phase 1 and 2.00 mg (SD, 0.003 mg) in phase 2, which was the same as or close to the planned daily dose (2 mg).

Demographic baseline characteristics and prior therapies

All of the patients were Japanese and included seven men (58%) and five women (42%). The primary disease was melanoma in all 12 patients. In phase 1, the disease was stage IIIC in one patient (17%) and stage IV in five patients (83%), whereas in phase 2 all six patients were in stage IV. All 12 patients had *BRAF* V600E mutation-positive tumors. Baseline characteristics of the patients enrolled in the study are summarized in Table 1. Patients received chemotherapy, immunotherapy, biologic treatment and small molecule treatment as prior therapies (Table 1).

Pharmacokinetics

Following repeat dosing of 150 mg dabrafenib b.i.d. and 2 mg trametinib q.d. in patients with *BRAF* V600E/K mutation-positive advanced solid tumors, dabrafenib seemed to be rapidly absorbed with the median plasma Tmax of approximately 2 h. Plasma AUC0-12 h on day 21 was lower than that after a single dose on day 1 (Fig. 2). Plasma trough concentrations of dabrafenib and its metabolites seemed to reach a steady state by week 3 (percent coefficient of variation [%CV] of 149% [dabrafenib], 82% [GSK2285403, hydroxylated form], 52% [GSK2298683, carboxylate form] and 84% [GSK2167542, demethylated form]). However, the variability in plasma trough concentrations of dabrafenib and its metabolites was large at week 8 and later (%CV of 184–591% [dabrafenib], 121–239% [hydroxylated form], 39–65% [carboxylate form] and 52–108% [demethylated form]) (Table 2). Trametinib seemed to be rapidly absorbed with the median plasma Tmax of approximately 1 h (Fig. 2). Plasma trough concentrations of trametinib seemed to reach steady state by week 3 (%CV of 26%) (Table 2).

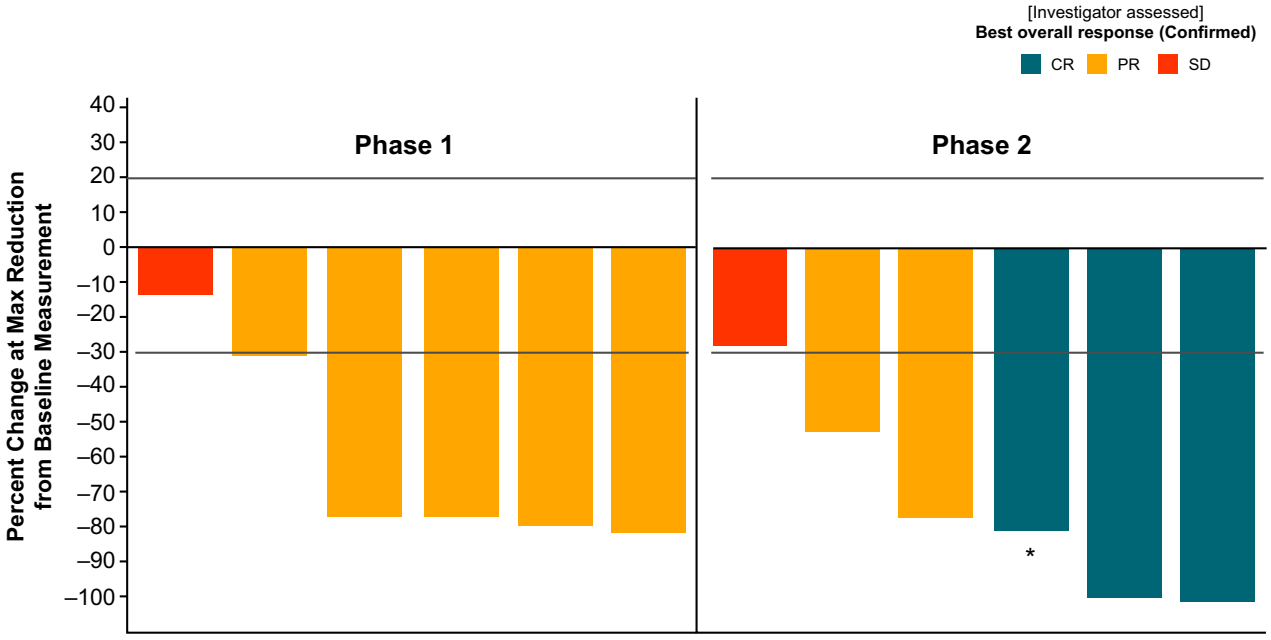
Overall response rate

The investigator-assessed confirmed ORR was observed in five patients (83%) in phase 1 and in five patients (83%; 95% CI, 35.9–99.6) in phase 2. One-sided exact binomial test rejected the null hypothesis of ORR as 10% ($P < 0.0001$) for phase 2. The ICR-assessed confirmed ORR was observed in three patients (50%) in phase 1 and in five patients (83%; 95% CI, 35.9–99.6; $P < 0.0001$) in phase 2 (Fig. 3). The investigator-assessed percentage change at maximum reduction in tumor size from baseline measurement in phase 1 and phase 2 trials are summarized in Figure 3 and the investigator-assessed percentage change in tumor size from baseline over time is summarized in Figure 4.

Table 2. Plasma trough concentrations (ng/mL) of dabrafenib (150 mg), its metabolites and trametinib (2 mg) at different time points (PK population [phase 1])

		Day 8 (n = 6)	Day 15 (n = 6)	Week 3 (n = 6)	Week 8 (n = 6)	Week 16 (n = 6)	Week 24 (n = 5)
Dabrafenib 150 mg (n = 6)	Ctau (ng/mL)	118.36 [188.3] (29.1–728.0)	84.25 [136.2] (25.2–403.0)	78.14 [149.3] (25.5–278.0)	78.29 [591.4] (10.2–1880.0)	105.05 [206.4] (16.8–735.0)	121.85 [183.9] (35.3–830.0)
GSK2285403 (hydroxylated metabolite)		149.61 [111.9] (66.1–605.0)	106.09 [72.8] (46.1–288.0)	93.87 [82.0] (38.9–290.0)	89.12 [239.4] (16.4–933.0)	100.10 [121.8] (24.2–364.0)	117.93 [121.4] (31.0–390.0)
GSK2298683 (carboxylated metabolite)		6011.00 [39.8] (3240.0–8210.0)	5141.38 [39.5] (3210.0–8260.0)	6210.90 [51.8] (3370.0–11400.0)	4408.24 [65.0] (2390.0–9460.0)	4022.93 [39.4] (2680.0–7580.0)	4294.86 [51.9] (2310.0–8700.0)
GSK2167542 (demethylated metabolite		217.73 [46.7] (122.0–384.0)	161.11 [107.5] (27.8–278.0)	224.32 [83.6] (113.0–620.0)	220.93 [52.2] (102.0–447.0)	270.15 [107.5] (61.5–496.0)	227.75 [101.5] (85.3–470.0)
Trametinib 2 mg (n = 6)		11.36 [43.0] (5.3–16.1)	12.47 [22.4] (9.4–15.7)	13.80 [25.6] (9.4–18.1)	14.52 [65.0] (7.7–42.9)	13.47 [39.4] (7.0–22.1)	13.72 [41.3] (8.3–23.7)

Values are presented as geometric mean [%CV] (min–max). CV, coefficient of variance; max, maximum; min, minimum.



Best overall response[a]

	Phase 1 part		Phase 2 part	
	Investigator-assessed (*N* = 6)	**ICR-assessed (*N* = 6)**	**Investigator-assessed (*N* = 6)**	**ICR-assessed (*N* = 6)**
Best overall response (confirmed), *n* (%)				
CR	0	0	3 (50)	2 (33)
PR	5 (83)	3 (50)	2 (33)	3 (50)
SD	1 (17)	0	1 (17)	1 (17)
Non-CR/Non-PD	0	2 (33)	0	0
PD	0	1 (17)	0	0
Confirmed ORR				
CR+PR, *n* (%)	5 (83)	3 (50)	5 (83)	5 (83)
95% CI[b]	N/A	N/A	35.9-99.6	35.9-99.6
P value[c]	N/A	N/A	< 0.0001	< 0.0001

Figure 3. Investigator-assessed maximum reduction (percent change). CR, complete response; ICR, independent central review; N/A, not applicable; ORR, overall response rate; PD, progressive disease; PR, partial response; SD, stable disease. [a]Data cut-off, 18 September 2014. [b]Exact 95% confidence interval (two-sided). [c]One-sided exact binomial test to reject null hypothesis; ORR ≤ 10%. *The malignant lymph nodes were included in the evaluation of target lesions.

Progression-free survival

An event (PD or death) was observed in all six patients in both the investigator-assessed PFS and independently assessed PFS in phase 1. The investigator-assessed PFS ranged 16–65.1 weeks, with PFS exceeding 24 weeks in four patients. The independently assessed PFS ranged 9–65.1 weeks, with PFS exceeding 24 weeks in three patients. The independently assessed and investigator-assessed evaluations of PFS agreed with each other in three patients.

An event (PD or death) was observed in three of six patients in both the investigator-assessed PFS and independently assessed PFS in phase 2. The investigator-assessed PFS ranged 19–47.9 weeks in the three patients. The remaining three patients were censored as no event was observed. Therefore, mature data have not been obtained with respect to independently assessed PFS. The independently assessed and investigator-assessed evaluations of PFS agreed with each other in five of six patients, including the censored patients.

Duration of study treatment

The median duration of treatment with dabrafenib was 323.0 days (range, 132–931) in phase 1 and 569.0 days (range, 104–925) in phase 2. Similarly, the median duration of treatment with trametinib was 311.0 days (range, 131–931) in phase 1 and 567.0 days (range, 101–914) in phase 2.

Adverse events

All 12 patients included in the study experienced AE and treatment-related AE. Common AE (reported in ≥33.0%) included pyrexia (75%), increased aspartate aminotransferase (67%),

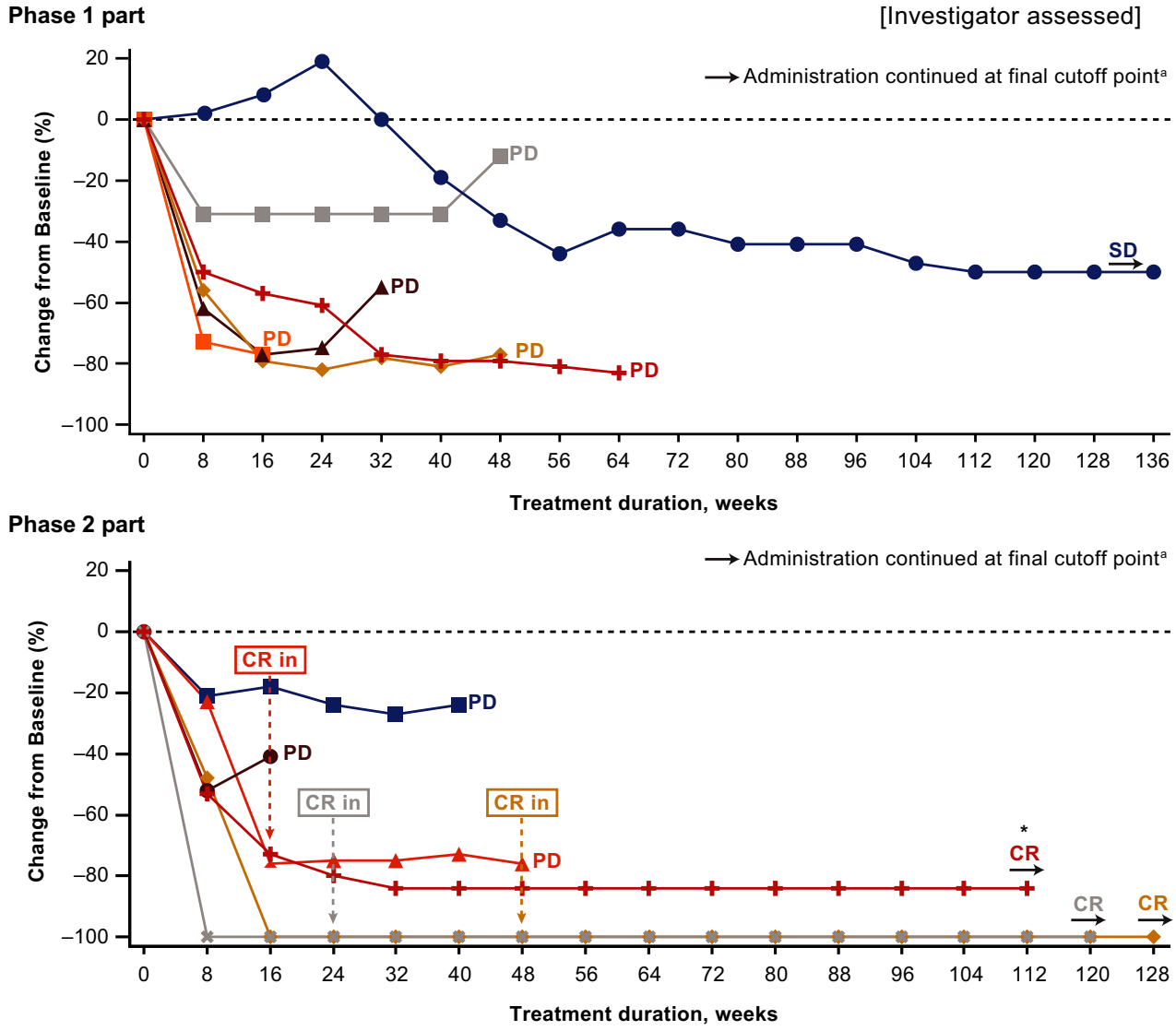


Figure 4. Change from baseline (investigator assessed), spider plot. [a]As of cut-off date, allowed to continue the treatment. *The malignant lymph nodes were included in the evaluation of target lesions.

peripheral edema (50%), nasopharyngitis (50%), blood alkaline phosphatase (42%), stomatitis (42%), erythema (42%), headache (42%), acneiform dermatitis (33%) and maculopapular rash (33%) (Tables 3 and 4). Two patients discontinued due to AE (one patient in phase 1 [patient 1] and one patient in phase 2 [patient 11]). Patient 1 discontinued dabrafenib due to grade 3 increased blood alkaline phosphatase, and patient 11 discontinued both dabrafenib and trametinib due to grade 3 uveitis. Both these AE were considered related to dabrafenib and/or trametinib by the investigator. There were two deaths reported in phase 1 and one death in phase 2 due to progression of the underlying disease, but no serious AE leading to death were found (Table 3).

There were 12 AE (eight in three subjects in phase 1 and four in three subjects in phase 2) leading to treatment interruption in six subjects. They were two instances each of increased alanine aminotransferase, pyrexia and neutropenia, and one instance each of increased blood alkaline phosphatase, pneumonitis, increased aspartate aminotransferase, decreased blood phosphorus, pharyngitis and decreased ejection fraction. With the exception of increased alanine aminotransferase and pharyngitis, all of the AE leading to treatment interruption were considered related to dabrafenib and trametinib by the investigator.

There were three AE (increased blood alkaline phosphatase, pneumonitis, increased alanine aminotransferase) in two subjects in phase 1 that led to dose reduction and all of these AE except one (increased alanine aminotransferase) were considered related to dabrafenib and trametinib by the investigator.

Table 3. Summary of adverse events by phase

Preferred term	Patients, *n* (%)		
	Phase 1 (*n* = 6)	Phase 2 (*n* = 6)	Total (*n* = 12)
Pyrexia	5 (83)	4 (67)	9 (75)
Increased aspartate aminotransferase	4 (67)	4 (67)	8 (67)
Peripheral edema	2 (33)	4 (67)	6 (50)
Nasopharyngitis	4 (67)	2 (33)	6 (50)
Headaches	3 (50)	2 (33)	5 (42)
Increased blood alkaline phosphatase	3 (50)	2 (33)	5 (42)
Stomatitis	2 (33)	3 (50)	5 (42)
Erythemas	4 (67)	1 (17)	5 (42)
Acneiform dermatitis	3 (50)	1 (17)	4 (33)
Maculopapular rash	4 (67)	0	4 (33)
Increased alanine aminotransferase	2 (33)	1 (17)	3 (25)
Constipation	1 (17)	2 (33)	3 (25)
Nausea	2 (33)	1 (17)	3 (25)
Vomiting	2 (33)	1 (17)	3 (25)
Arthralgia	1 (17)	2 (33)	3 (25)
Muscle pains	2 (33)	1 (17)	3 (25)
Alopecias	3 (50)	0	3 (25)
Decreased appetite	3 (50)	0	3 (25)
Adverse event summary			
Adverse events	6 (100)	6 (100)	12 (100)
Adverse events related to study drug	6 (100)	6 (100)	12 (100)
Adverse events leading to study discontinuation	1 (17)	1 (17)	2 (17)
Adverse events leading to dose reduction	2 (33)	0	2 (17)
Adverse events leading to interruption of study drug	3 (50)	3 (50)	6 (50)
Severe adverse events	1 (17)	0	1 (8)
Severe adverse events related to study drug	1 (17)	0	1 (8)
Deaths	0	0	0

DISCUSSION

The advancement of BRAF-targeted therapies has transformed the treatment of *BRAF*-mutant metastatic melanoma by improving outcomes for the treated patients.[23] The purpose of this Japanese phase 1/2 study was to assess the safety and preliminary efficacy of dabrafenib and trametinib combination in 12 Japanese patients with *BRAF* V600E/K mutation-positive advanced solid tumors (phase 1) and *BRAF* V600E/K mutation-positive cutaneous melanoma (phase 2). The target population in phase 1 was patients with advanced solid tumor, but the six patients who were actually enrolled were patients with cutaneous malignant melanoma. In phase 2, six patients with cutaneous malignant melanoma were enrolled, so all of the patients who participated in this study were patients with cutaneous malignant melanoma. The relatively common AE in the six patients (≥50%) in phase 1 were pyrexia, increased aspartate aminotransferase, nasopharyngitis, erythema, maculopapular rash, increased blood alkaline phosphatase, headache, acneiform dermatitis, alopecia and decreased appetite. Relatively common AE (≥50%) in the six patients in phase 2 were pyrexia, peripheral edema, increased aspartate aminotransferase and stomatitis. Most of the AE observed in phase 1 were also observed in phase 2 indicating no major differences in the types and incidences of AE in patients with cutaneous malignant melanoma despite differences in history of prior therapy. The most common AE in the 12 patients in phase 1 and phase 2 combined were pyrexia, increased aspartate aminotransferase, peripheral edema, nasopharyngitis, increased blood alkaline phosphatase, stomatitis, erythema and headache. The relatively common AE in this Japanese study were also relatively common in clinical studies of dabrafenib and trametinib combination conducted in global studies.[18,24,25] Similarly, the majority of AE observed in this Japanese study belong to grade 1 or 2, and it has been reported that the majority of AE were grade 1 or 2 in global clinical studies as well.[18,24,25]

Pyrexia was the most common AE in our study and was also the most common AE in the global combination studies.[18,24,25] Incidentally, pyrexia has been reported as a common AE with BRAF-inhibitor monotherapy in the range of 16–26% when given as monotherapy.[18,19,26,27] In the current study, the first fever was observed within 8 weeks of initiation of therapy in all nine patients in whom pyrexia was observed, while the median time to onset of the first fever in a global clinical study conducted was reported to be 4.3 weeks after treatment initiation.[27] Thus, there seemed to be little difference between Japanese and other ethnicities in terms of pyrexia during dabrafenib and trametinib combination. Based on these findings, the combination of dabrafenib and trametinib in Japanese patients seemed to differ little from that in patients who participated in the global clinical studies.

The AE leading to discontinuation of the therapy were confirmed in two of 12 patients, and dose reduction due to an AE was necessary in two of 12 patients (one patient experienced both). However, no AE were reported in nine patients leading to either dose reduction or discontinuation. AE could be managed with symptomatic therapy or dose interruption of the investigational products. Evaluation of safety data revealed that dabrafenib (150 mg b.i.d.) and trametinib (2 mg q.d.) combination therapy was generally well tolerated in Japanese patients, confirming the manageable safety profile of combination therapy.

In the phase 2 study, the efficacy of dabrafenib and trametinib combination as first-line therapy for unresectable or metastatic disease showed a robust response rate (83%), with agreement between investigator assessment and independent assessment (in terms of confirmed ORR), in Japanese patients, which is sufficient enough to justify further clinical development. Moreover, there seemed to be no major difference in the response rate to dabrafenib and trametinib combination therapy between Japanese patients and patients in global studies.[18,24,25] In the PFS evaluation in phase 1, PFS of 40 weeks or more (65.1 weeks maximum) was confirmed in three of six patients regardless of whether it was the investigator's assessment or the independent assessment. In phase 2 of this study,

Table 4. Summary of adverse events by grade (combined from phase 1 and phase 2, ATS population; ≥25% in total population)

Preferred term, *n* (%)	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Grade ≥3
Pyrexia	4 (33)	5 (42)	0	0	0	0
Increased aspartate aminotransferase	6 (50)	2 (17)	1 (8)	0	0	1 (8)
Edema peripheral	5 (42)	1 (8)	0	0	0	0
Nasopharyngitis	6 (50)	0	0	0	0	0
Headaches	5 (42)	0	0	0	0	0
Increased blood alkaline phosphatase	2 (17)	2 (17)	1 (8)	0	0	1 (8)
Stomatitis	5 (42)	0	0	0	0	0
Erythemas	4 (33)	1 (8)	0	0	0	0
Acneiform dermatitis	3 (25)	1 (8)	0	0	0	0
Maculopapular rash	3 (25)	1 (8)	0	0	0	0
Increased alanine aminotransferase	1 (8)	1 (8)	1 (8)	0	0	1 (8)
Constipation	3 (25)	0	0	0	0	0
Nausea	3 (25)	0	0	0	0	0
Vomiting	3 (25)	0	0	0	0	0
Arthralgia	3 (25)	0	0	0	0	0
Muscle pains	3 (25)	0	0	0	0	0
Alopecias	3 (25)	0	0	0	0	0
Decreased appetite	3 (25)	0	0	0	0	0

ATS, all treated subject.

PD was confirmed in three of six patients. The investigator-assessed PFS in these three patients ranged 19.1–47.9 weeks, which roughly agreed with the independent assessment. The median duration of response was 32.1 weeks according to the investigator's assessment and 45 weeks according to the independent assessment. The median PFS has been reported to be 9.3–11.4 months and the median duration of response has been reported to be 9.2–13.8 months in clinical studies conducted to date.[18,24,25] Thus, the median PFS and the duration of response in phase 1 were similar to the results of clinical studies conducted to date. All of the patients enrolled in this study are patients with V600E mutation-positive malignant melanoma, and clinical data from V600K mutation-positive malignant melanoma patients were not obtained. Therefore, moving forward, clinical data needs to be accumulated to evaluate efficacy in Japanese patients with V600K mutation-positive malignant melanoma.

Following repeat dosing of dabrafenib, 150 mg b.i.d. and trametinib, 2 mg q.d. in patients with V600E or V600K mutation-positive advanced solid cancer, dabrafenib seemed to be rapidly absorbed. It was observed that plasma AUC0-12 h (day 21) of dabrafenib at repeat dosing was lower than that at AUC0-inf (day 1), which may support the result that dabrafenib induces self-induction of metabolism. The results observed in this study are consistent with the results that have been observed in global studies.[28] Similarly rapid absorption of trametinib was also noticed following repeated dosing of trametinib 2 mg q.d. and dabrafenib 150 mg b.i.d. Contrary to the results observed in dabrafenib, absorption plasma AUC0-24 h of trametinib at repeat dosing was higher than that at single dose, which may be attributed to the fact that the half-life of trametinib was long, that is, approximately 3.5 times the dose interval (24 h). Plasma concentrations of both dabrafenib and trametinib seemed to reach steady state by week 3, but the variability in plasma trough concentrations of dabrafenib and its metabolites was large at week 8 and later.

The total number of patients recruited in this study was relatively lower (n = 12) but the results of evaluation of the safety, efficacy and PK of dabrafenib (150 mg b.i.d.) and trametinib (2 mg q.d.) combination therapy differed little from the global clinical study results. In conclusion, the safety, efficacy and PK of this combination therapy in Japanese patients with unresectable or metastatic *BRAF* mutation-positive cutaneous malignant melanoma could be analogically inferred from the global clinical study results.

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SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article:

Table S1. Patient disposition (data cut-off, 4 July 2016).