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

Tahara, Makoto ; Kiyota, Naomi ; Imai, Hiroo ; Takahashi, Shunji ; Nishiyama, Akihiro ; Tamura, Shingo ; Shimizu, Yasushi ; Kadowaki,…

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Table S1. Tumor response per investigators' assessment

	Overall (n = 22)	DTC (n = 17)	ATC (n = 5)
ORR, n (%)	13 (59.1)	9 (52.9)	4 (80.0)
95% CI	36.4–79.3	27.8–77.0	28.4–99.5
BOR			
CR	1 (4.5)	0	1 (20.0)
PR	12 (54.5)	9 (52.9)	3 (60.0)
SD	9 (40.9)	8 (47.1)	1 (20.0)
PD	0	0	0

ATC, anaplastic thyroid cancer; BOR, best overall response; CI, confidence interval; CR, complete response; DTC, differential thyroid cancer; ORR, objective response rate; PR, partial response; SD, stable disease; PD, progressive disease.

Table S2. Duration of response per central assessment

	Overall (n = 22)	DTC (n = 17)	ATC (n = 5)
Number of responders	12	8	4
Median DOR, month Min–max	NR 1.9^{+}–16.2^{+}	NR 1.9^{+}–16.2^{+}	NR 3.7^{+}–10.2^{+}
Ongoing response at 6 months (%)	90.9	85.7	100.0
Ongoing response at 12 months (%)	90.9	85.7	N.A.

The symbol "+" indicated a censored value. ATC, anaplastic thyroid cancer; DTC, differential thyroid cancer; DOR, duration of response; NR, not reached; N.A., not applicable.

Table S3. Summary of safety

	Overall (n = 22)		DTC (n = 17)		ATC (n = 5)	
	Any grade	**Grade 3**	**Any grade**	**Grade 3**	**Any grade**	**Grade 3**
AEs	**22 (100)**	**6 (27.3)**	**17 (100)**	**4 (23.5)**	**5 (100)**	**2 (40.0)**
Serious AEs	1 (4.5)	1 (4.5)	0	0	1 (20.0)	1 (20.0)
Treatment-related AEs (TRAEs)	**20 (90.9)**	**6 (27.3)**	**15 (88.2)**	**4 (23.5)**	**5 (100)**	**2 (40.0)**
Serious TRAEs	1 (4.5)	1 (4.5)	0	0	1 (20.0)	1 (20.0)
TRAEs dose interruption of any study treatment	16 (72.7)	3 (13.6)	11 (64.7)	2 (11.8)	5 (100)	1 (20.0)
TRAEs dose reduction of any study treatment	3 (13.6)	0	2 (11.8)	0	1 (20.0)	0
TRAEs discontinuation of any study treatment	4 (18.2)	2 (9.1)	4 (23.5)	2 (11.8)	0	0
TRAEs leading to death	0	0	0	0	0	0

AEs, adverse events; ATC, anaplastic thyroid cancer; DTC, differential thyroid cancer.

Table S4. Treatment-related 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	**20 (90.9)**	**6 (27.3)**	**15 (88.2)**	**4 (23.5)**	**5 (100)**	**2 (40.0)**
Skin and subcutaneous tissue disorders	**14 (63.6)**	**2 (9.1)**	**12 (70.6)**	**1 (5.9)**	**2 (40.0)**	**1 (20.0)**
Palmar-plantar erythrodysesthesia syndrome	6 (27.3)	1 (4.5)	6 (35.3)	1 (5.9)	0	0
Pruritus	3 (13.6)	1 (4.5)	2 (11.8)	0	1 (20.0)	1 (20.0)
Rash	3 (13.6)	0	3 (17.6)	0	0	0
Rash maculo-papular	3 (13.6)	0	2 (11.8)	0	1 (20.0)	0
Gastrointestinal disorders	**12 (54.5)**	**1 (4.5)**	**8 (47.1)**	**0**	**4 (80.0)**	**1 (20.0)**
Nausea	10 (45.5)	0	6 (35.3)	0	4 (80.0)	0
Diarrhea	4 (18.2)	0	2 (11.8)	0	2 (40.0)	0
Vomiting	4 (18.2)	0	3 (17.6)	0	1 (20.0)	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	3 (13.6)	0	3 (17.6)	0	0	0
Visual field defect	3 (13.6)	0	3 (17.6)	0	0	0
General disorders and administration site conditions	**8 (36.4)**	**0**	**7 (41.2)**	**0**	**1 (20.0)**	**0**
Fatigue	5 (22.7)	0	5 (29.4)	0	0	0
Musculoskeletal and connective tissue disorders	**7 (31.8)**	**0**	**6 (35.3)**	**0**	**1 (20.0)**	**0**
Arthralgia	4 (18.2)	0	3 (17.6)	0	1 (20.0)	0
Myalgia	3 (13.6)	0	3 (17.6)	0	0	0
Metabolism and nutrition disorders	**6 (27.3)**	**0**	**4 (23.5)**	**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)**
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
Lipase increased	4 (18.2)	4 (18.2)	3 (17.6)	3 (17.6)	1 (20.0)	1 (20.0)
Ejection fraction decreased	3 (13.6)	0	3 (17.6)	0	0	0
γ-glutamyl transferase increased	3 (13.6)	1 (4.5)	1 (5.9)	1 (5.9)	2 (40.0)	0

Table S5. Outcome of major treatment-related adverse events

	Patients, n	Outcome, n (%)					
		Recovered	recovering	Unrecovered	Recovered with sequelae	Death	Unknown
Gastrointestinal disorders	**12**	**8 (66.7)**	**0**	**4 (33.3)**	**0**	**0**	**0**
Nausea	10	9 (90.0)	0	1 (10.0)	0	0	0
Diarrhea	4	2 (50.0)	0	2 (50.0)	0	0	0
Vomiting	4	4 (100)	0	0	0	0	0
Skin and subcutaneous tissue disorders	**14**	**2 (14.3)**	**1 (7.1)**	**11 (78.6)**	**0**	**0**	**0**
Palmar-plantar erythrodysesthesia syndrome	6	2 (33.3)	2 (33.3)	2 (33.3)	0	0	0
Eye disorders	**15**	**12 (80.0)**	**1 (6.7)**	**2 (13.3)**	**0**	**0**	**0**
Serous retinal detachment	5	5 (100)	0	0	0	0	0
Macular edema	3	2 (66.7)	1 (33.3)	0	0	0	0
Visual field defect	3	2 (66.7)	0	1 (33.3)	0	0	0
Laboratory	**14**	**8 (57.1)**	**2 (14.3)**	**4 (28.6)**	**0**	**0**	**0**
Blood creatine phosphokinase increased	4	4 (100)	0	0	0	0	0
Blood creatinine increased	4	3 (75.0)	0	1 (25.0)	0	0	0
Lipase increased	4	2 (50.0)	1 (25.0)	1 (25.0)	0	0	0
γ-glutamyl transferase increased	3	2 (66.7)	0	1 (33.3)	0	0	0
Ejection fraction decreased	3	1 (33.3)	2 (66.7)	0	0	0	0

Table S6. Outcome of eye disorders (≥10%) by action for encorafenib plus binimetinib treatment

Events	Action of encorafenib or binimetinib	Events, n	Outcome, n (%)					
			Recovered	Recovering	Unrecovered	Recovered with sequelae	Death	Unknown
Eye disorders		**25**	**22 (88.0)**	**1 (4.0)**	**2 (8.0)**	**0**	**0**	0
	Discontinuation	0	0	0	0	0	0	0
	Interruption	7	6 (85.7)	1 (14.3)	0	0	0	0
	Reduction	1	1 (100)	0	0	0	0	0
	Continuation	17	15 (88.2)	0	2 (11.8)	0	0	0
Serous retinal detachment		**7**	**7 (100)**	**0**	**0**	**0**	**0**	**0**
	Discontinuation	0	0	0	0	0	0	0
	Interruption	3	3 (100)	0	0	0	0	0
	Reduction	0	0	0	0	0	0	0
	Continuation	4	4 (100)	0	0	0	0	0
Macular edema		**3**	**2 (66.7)**	**1 (33.3)**	**0**	**0**	**0**	**0**
	Discontinuation	0	0	0	0	0	0	0
	Interruption	2	1 (50.0)	1 (50.0)	0	0	0	0
	Reduction	1	1 (100)	0	0	0	0	0
	Continuation	0	0	0	0	0	0	0
Visual field defect		**3**	**2 (66.7)**	**0**	**1 (33.3)**	**0**	**0**	**0**
	Discontinuation	0	0	0	0	0	0	0
	Interruption	0	0	0	0	0	0	0
	Reduction	0	0	0	0	0	0	0
	Continuation	3	2 (66.7)	0	1 (33.3)	0	0	0

No specific treatment was performed for all eye disorders.

Table S7. Exposure to study treatment

	Overall (n = 22)		DTC (n = 17)		ATC (n = 5)	
	Encorafenib	**Binimetinib**	**Encorafenib**	**Binimetinib**	**Encorafenib**	**Binimetinib**
Median duration of exposure, month	**6.70**	**6.70**	**6.67**	**6.67**	**6.90**	**6.90**
Range*	2.0–19.0	0.9–18.5	2.0–19.0	0.9–18.5	5.6–12.9	5.6–12.9

*The time on study drug includes period of dose interruption. ATC, anaplastic thyroid cancer; DTC, differential thyroid cancer.