NOVARTIS

Clinical Development

Tafinlar® (dabrafenib)

Dabrafenib Post- Authorization Measure

Secondary Malignancies

Final Report

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List of abbreviations

AE	Adverse event
BCC	Basal cell carcinoma
BID	Twice daily
cuSCC	Cutaneous squamous cell carcinoma
DTIC	Dacarbazine
FDA	Food and Drug Administration
ITT	Intent-to-treat
LDH	Lactate dehydrogenase
MAPK	Mitogen-activated protein kinase
MedDRA	Medical Dictionary for Regulatory Activities
PMR	Post-marketing requirement report
QD	Once daily
SAE	Serious adverse event(s)
SCC	Squamous cell carcinoma
SPM	Second primary malignancy
ULN	Upper limit of normal
US	United States
USPI	US prescribing information

1 Introduction

Treatment-emergent secondary malignancies were identified early on as an adverse event of special interest in the dabrafenib clinical program because of the reported risk of cutaneous squamous cell carcinoma (cuSCC) with vemurafenib treatment (Cichowski and Jänne 2010). Paradoxical activation of MAPK pathway signaling in the presence of mutated, activated RAS is a recognized effect of BRAF inhibitors (Gibney et al 2013). Accelerated growth of cuSCC as a result has been demonstrated and the risk for accelerated growth extends to RAS-driven tumors of non-cutaneous origin (Su et al 2012). RAS-associated malignancies in the presence of BRAF inhibitors have been reported, including chronic myelomonocytic leukemia, oropharyngeal SCC, colorectal cancer, and pancreatic cancer (Gibney et al 2013, Zelboraf SmPC Jan-2020, Tafinlar SmPC Jan-2020, Braftovi SmPC Jun-2020).

A post-marketing requirement following US FDA approval of Tafinlar (dabrafenib) capsules included annual cumulative safety analyses to identify and characterize the risk of new malignancies in randomized controlled clinical trials of dabrafenib alone or in combination with other anticancer drugs. This eighth and Final Report will contain data from BRF113683 (BREAK-3), MEK115306 (COMBI-d), MEK116513 (COMBI-v), and BRF115532 (COMBI-AD).

The tumor type categories analyzed in this report include cuSCC (including keratoacanthoma), basal cell carcinomas (BCCs), new primary melanomas, and "other" treatment-emergent secondary malignancies. The MedDRA terms included in these secondary malignancy categories are listed in Appendix 1.

2 Background

2.1 Study BRF113683 (BREAK-3)

Study BRF113683 (CDRB436A2301) was a 2-arm, open-label, randomized Phase III pivotal study comparing oral dabrafenib with intravenous dacarbazine (DTIC). Subjects either with histologically confirmed unresectable or metastatic melanoma, and BRAF V600E mutation-positive as determined via central testing were enrolled. The study completion date was 16-Sep-2016 (last subject last visit), when either all subjects had died or were lost to follow-up, or all subjects continuing in the study had at least 5 years follow-up.

Eligible subjects were randomized 3:1 to receive oral dabrafenib 150 mg twice daily (bid) or intravenous DTIC 1000 mg/m^2 every 3 weeks. Randomization was stratified according to disease stage at study entry (Stage III/IVM1a/IVM1b vs. IVM1c (AJCC ed. 7)). Subjects continued on treatment until disease progression, death, the occurrence of an unacceptable adverse event (AE), or withdrawal from the study. Subjects randomized to dabrafenib treatment that experienced investigator-reported disease progression but were still benefitting from study treatment with dabrafenib were permitted to continue treatment beyond progression following Amendment 5, effective date 14-Nov-2011. Subjects randomized to DTIC treatment were allowed to cross over to dabrafenib therapy after initial progression was confirmed by independent review.

Skin lesions were monitored by physical examination at Baseline, every 4 weeks for the first 8 weeks, then every 8 weeks until study treatment discontinuation (every 9 weeks following

Amendment 7, effective date 19-Feb-2014). Subjects were also referred to a dermatologist as clinically indicated and events were confirmed by pathology reports from the dermatologist. Follow-up dermatologic skin assessments were performed every 3 months for 6 months until initiation of another anti-neoplastic therapy following discontinuation of dabrafenib, following approval of Amendment 7.

2.2 Study MEK115306 (COMBI-d)

Study MEK115306 (CDRB436B2301) is a 2-arm, double-blinded, randomized, Phase III study comparing dabrafenib and trametinib combination therapy (to be referred to as combination therapy in this report) with dabrafenib administered with a trametinib placebo (dabrafenib monotherapy). Subjects with histologically confirmed unresectable or metastatic melanoma and BRAF V600E or V600K mutation-positive as determined by a central laboratory were screened for eligibility.

Subjects who had prior systemic anti-cancer treatment in the advanced or metastatic setting were not eligible although prior systemic treatment in the adjuvant setting was allowed.

Eligible subjects were randomized 1:1 to receive either oral dabrafenib (150 mg bid) and oral trametinib (2 mg once daily (qd)) combination therapy or oral dabrafenib (150 mg bid) and oral trametinib placebo (qd). Subjects were stratified by lactate dehydrogenase (LDH) level (> the upper limit of normal [ULN] versus ULN) and BRAF mutation (V600E versus V600K). Subjects continued on treatment until disease progression, death, unacceptable toxicity, or withdrawal of consent. Subjects who experienced disease progression but who had received clinical benefit were allowed to continue study treatment after Medical Monitor approval.

Skin lesions were monitored by physical examination at Baseline, Week 8, and every 8 weeks thereafter through Week 56 and then every 12 weeks thereafter until determination of progressive disease. Monitoring guidelines for cuSCC and new primary melanomas after dabrafenib discontinuation were implemented after 14-Oct-2013.

2.3 Study MEK116513 (COMBI-v)

Study MEK116513 (CDRB436B2302) is a 2-arm, randomized, open-label, Phase III study comparing dabrafenib and trametinib combination therapy with vemurafenib monotherapy in BRAF V600 mutation-positive metastatic melanoma. Subjects with histologically confirmed unresectable or metastatic melanoma and BRAF V600E or V600K mutation-positive as determined by a central laboratory were screened for eligibility. Subjects who had prior systemic anti-cancer treatment in the advanced or metastatic setting were not eligible, although prior systemic treatment in the adjuvant setting was allowed. Subjects were stratified by LDH level (> the ULN versus ≤ ULN) and BRAF mutation (V600E versus V600K).

Eligible subjects were randomized 1:1 to receive either oral dabrafenib (150 mg bid) and oral trametinib (2 mg qd) combination therapy or oral vemurafenib (960 mg bid). Subjects continued on treatment until disease progression, death, unacceptable toxicity, or withdrawal of consent. Subjects who experienced disease progression but who had received clinical benefit were allowed to continue study treatment after Medical Monitor approval.

Skin lesions were monitored by physical examination at Baseline, Week 8, and every 8 weeks thereafter through Week 56 and then every 12 weeks thereafter until determination of

progressive disease. Brief skin exams were also conducted at 4 week intervals during brief physical exams. Monitoring guidelines for cuSCC and new primary melanomas were implemented with Amendment 3 of the protocol (October 2013).

2.4 Study BRF115532 (COMBI-AD)

Study BRF115532 (CDRB436F2301) is a 2-arm, randomized, double-blind Phase III study of dabrafenib in combination with trametinib versus two matching placebos in the adjuvant treatment of melanoma after surgical resection. Subjects with completely resected, histologically confirmed, BRAF V600E/K mutation-positive, high-risk (Stage IIIA [>1 mm nodal burden], IIIB, IIIC (AJCC ed. 7)) melanoma were screened for eligibility. Eligible subjects had to be disease-free post-resection ≤ 12 weeks prior to randomization.

Subjects were randomized in a 1:1 ratio, stratified by BRAF mutation status (V600E, V600K) and stage of disease (Stage IIIA, IIIB, IIIC). Subjects in the treatment arm received dabrafenib 150 mg bid and trametinib 2 mg qd. Subjects in the control arm received 2 matching placebos. Subjects in both arms received treatment for 12 months or until disease recurrence, death, unacceptable toxicity, or withdrawal of consent. Subjects were followed for disease recurrence and survival during and after the treatment period.

Dermatologic exams were performed at Screening, Month 2, Month 4, Month 6, Month 8, Month 10 and Month 12 (or discontinuation if subject discontinued prior to Month 12), every three months from Month 12 until Month 24, and every 6 months after Month 24.

2.5 Characterization of treatment-emergent secondary malignancies

In study BRF113683, treatment-emergent secondary malignancies excluding BCC and keratoacanthoma were protocol-specified SAEs.

For both MEK115306 and MEK116513 studies, any new primary cancers and treatment-emergent secondary malignancies with a histology different from the primary tumor, including cuSCC, keratoacanthoma, BCC, and new primary melanoma were protocol-specified SAEs. Non-cutaneous treatment-emergent secondary malignancies diagnosed as malignant following treatment initiation, but which were a pre-existing lesion or mass (not initially diagnosed as malignant), were to be reported as an SAE.

In study BRF115532, any new primary cancers and treatment-emergent secondary malignancies (including cuSCC, keratoacanthoma and second primary melanoma) were protocol-specified SAEs. BCC was reported as an AE or SAE at the discretion of the Investigator.

For any new malignancy, every effort was made to identify the RAS mutation status; the mutation test was performed locally and reported within 12 weeks of diagnosis. Additional genetic analysis might be performed depending on the tumor types, and the results reported at the discretion of the Investigator.

3 Study population

3.1 Study BRF113683 (BREAK-3)

A total of 250 subjects were centrally randomized 3:1 to either dabrafenib or DTIC at 70 centers in 12 countries; 187 subjects were randomized to dabrafenib and 63 subjects were randomized to DTIC.

All 250 randomized subjects were included in the intent-to-treat (ITT) Population. The Safety Population comprised all subjects who had received at least 1 dose of the study drug and was based on the actual treatment received if different from randomized treatment. One subject on the dabrafenib arm and 3 subjects on the DTIC arm were excluded from the Safety Population since they did not receive any study treatment. Additionally, one subject (Subject [redacted]) who was randomized to treatment with DTIC only received dabrafenib and is analyzed in the dabrafenib arm.

Data are presented by treatment group using the safety population, with the data from the dabrafenib arm integrated with that from the dabrafenib monotherapy arm of MEK115306. Data for subjects in the crossover phase and for subjects randomized to the DTIC arm were reported in the 2013 Post-Marketing Requirement report (PMR). As noted in the 2014 PMR, no new events had occurred in either group, but subjects within these populations who experienced events remain in the appendices to this report. Data for subjects randomized to DTIC are included in the in-text tables as the BRF113683 comparator arm, but are generally not described further in the text.

3.2 Study MEK115306 (COMBI-d)

A total of 423 subjects were enrolled at 103 centers in 14 countries; 211 subjects were randomized to dabrafenib plus trametinib combination therapy and 212 subjects were randomized to dabrafenib plus placebo.

All 423 randomized subjects were included in the ITT Population. The Safety Population comprised all subjects who had taken at least 1 dose of the study drug and was based on the actual treatment received if different from randomized treatment. 2 subjects in the combination therapy arm (Subject [redacted] and Subject [redacted]) and 1 subject in the monotherapy arm (Subject [redacted]) were excluded from the Safety Population since they did not receive any study treatment.

Data are presented by treatment group using the safety population, with the data from the combination therapy arm integrated with that from the combination therapy arm of MEK116513 and BRF115532, and the dabrafenib monotherapy arm integrated with that from the dabrafenib arm of BRF113683. This study was completed in 2019 and has been reported.

3.3 Study MEK116513 (COMBI-v)

A total of 704 subjects were enrolled at 193 centers in 28 countries; 352 were randomized to dabrafenib plus trametinib combination therapy and 352 were randomized to and retreated with vemurafenib monotherapy.

All 704 randomized subjects were included in the ITT Population. The Safety Population comprised all subjects who had taken at least 1 dose of the study drug and was based on the actual treatment received if different from randomized treatment. 2 subjects in the combination therapy arm (Subject [redacted] and Subject [redacted]) and 3 subjects in the vemurafenib arm (Subject [redacted], Subject [redacted] and Subject [redacted]) were excluded from the Safety Population.

Data are presented by treatment group using the safety population, with the data from the combination therapy arm integrated with that from the combination therapy arm of studies MEK115306 and BRF115532. This study was completed in 2019 and has been reported.

3.4 Study BRF115532 (COMBI-AD)

The study was conducted in 169 centers across 25 countries. A total of 870 patients were randomized between 31-Jan-2013 to 11-Dec-2014 in the study, 438 patients in the dabrafenib plus trametinib combination arm and 432 patients in the placebo arm. Three patients in the dabrafenib plus trametinib combination arm were not treated. Two of these 3 patients withdrew consent, and one was withdrawn at the discretion of the Investigator as the patient did not comply with study procedures.

Data are presented by treatment group using the safety population, with the data from the treatment arm integrated with that from the combination therapy arm of studies MEK115306 and MEK116513. This study is ongoing; the primary analysis was reported in 2017.

3.5 Integrated data

Integrated data from the safety populations from studies BRF113683, MEK115306, MEK116513, and BRF115532 are presented. The number of subjects included in the treatment arms by study, and discussed in this report is shown in Table 3-1.

Table 3-1 Number of subjects included in the treatment arms in pooled data (Safety Population)

Treatment arms/ Designation in PMR	Number of Subjects in Treatment Arm	Study ID
Dabrafenib + Trametinib Combination	994	MEK115306
		MEK116513
		BRF115532
Dabrafenib Monotherapy	398	BRF113683
		MEK115306[a]
DTIC	59	BRF113683
Vemurafenib Monotherapy	349	MEK116513
Placebo	432	BRF115532

Source: MEK115306 CSR, MEK116513 CSR, BRF115532 CSR, and BRF113683 CSR.

1. Subjects were treated with dabrafenib monotherapy + trametinib placebo

Clinical data from all studies included are mature; each had more than 5 years follow-up. Studies MEK115306 and MEK116513 are completed and have been reported. The Study BRF115532 primary analysis was completed in 2017; follow-up is ongoing.

As of the data cut-off for this final report (22-Jun-2020), 272 (27%) subjects included in the safety set for combination therapy were ongoing in Study BRF115532; none were on treatment.

Subjects in the combination therapy group and subjects in the dabrafenib monotherapy group were on therapy for similar amounts of time (median 11.00 months and 10.80 months). Reasons for study withdrawal are listed in Table 3-2. A summary of safety follow-up over time by time intervals is presented in Table 3-3.

Table 3-2 Summary of subject status and reason for study withdrawal, time on therapy and secondary malignancy follow-up – safety set

	Dabrafenib + Trametinib (MEK115306/ MEK116513/ BRF11532) (N=994)	Dabrafenib Monotherapy (BRF113683/ MEK115306) (N=398)
Subject Status		
Died	446 (45%)	280 (70%)
Ongoing	272 (27%)	0
On study treatment	0	0
In follow-up	272 (27%)	0
In follow-up for sec. malignancies	0	0
On Crossover therapy	0	0
Withdrawn from study	276 (28%)	118 (30%)
Reason for study withdrawal		
Study closed/terminated	143 (14%)	85 (21%)
Lost to follow-up	33 (3%)	17 (4%)
Investigator discretion	17 (2%)	2 (<1%)
Withdrew consent	83 (8%)	14 (4%)
Time on therapy (months)		
Median (min-max)	11.00 (0.0 - 80.1)	10.80 (0.1 – 73.3)
Time in follow-up for secondary malignancies (months) [1]		
Median (min-max)	17.47 (1.5 - 86.6)	13.36 (0.6 – 79.8)

[1] Time in Follow-up for secondary malignancies is calculated for all patients and includes the time on treatment plus the subsequent period in which secondary malignancies are followed up according to the safety follow-up period definition

Data Source: Table 6.1101 modified; EMA PAM-Table 1.1A

Table 3-3 Summary of safety follow-up over time (safety set)

	Dabrafenib + Trametinib (MEK115306/ MEK116513/ BRF11532) N=994		Dabrafenib Monotherapy (BRF113683/ MEK115306) N=398	
	Number of patients followed in period	Number of patients with last follow-up in period	Number of patients followed in period	Number of patients with last follow-up in period
0-12 months	994	297	398	210
>12-24 months	697	507	188	100
>24-36 months	190	57	88	56
>36-48 months	133	33	32	12
>48-60 months	100	24	20	5
>60-72 months	76	13	15	12
>72-84 months	63	61	3	3
>84 months	2	2		

Source: EMA PAM-Table 1.2A

4 Demographic and baseline characteristics

4.1 Demographics

Subject demographics based on age, sex and ethnicity were well-balanced between the treatment groups (Table 6.2001). The median ages were 53 (range 18 to 91 years), 54 (range 22 to 93 years), 54 (range 18 to 88 years) and 51 years (range 20 to 85 years) in the combination therapy, dabrafenib monotherapy, vemurafenib and placebo groups, respectively. The age subgroups (< 65 years and ≥ 65 years) were similar between the treatment arms for combination therapy (< 65 years 78%; ≥ 65 years 22%), dabrafenib monotherapy (< 65 years 75%; ≥ 65 years 25%), vemurafenib (< 65 years 75%; ≥ 65 years 25%) and placebo (< 65 years 83%; ≥ 65 years 17%), with approximately 3-fold more subjects under 65 years old as compared to those 65 years and over. The age subgroup of ≥ 75 years was represented by 4%, 7%, 7% and 3% of subjects in the combination therapy, dabrafenib monotherapy, vemurafenib and placebo groups, respectively. The combination therapy, dabrafenib monotherapy and placebo groups included a higher proportion of male subjects than female subjects (56%, 57% and 55% males, respectively). The vemurafenib group contained approximately equal male and female subjects (51% male).

Among the subjects who experienced any secondary malignancy, the median ages were approximately 10 years higher than for those in the overall safety population, at 61 (range 25 to 81 years), 62 (range 31 to 84 years), 63 (range 23 to 83 years) and 63 years (range 42 to 77 years) in the combination therapy, dabrafenib monotherapy, vemurafenib and placebo groups, respectively. The age subgroups (< 65 years and ≥ 65 years) were similar between the treatment arms for combination therapy (< 65 years 59%; ≥ 65 years 41%), dabrafenib monotherapy (< 65 years 62%; ≥ 65 years 38%), vemurafenib (< 65 years 56%; ≥ 65 years 44%) and placebo (< 65 years 53%; ≥ 65 years 47%), with slightly more subjects under 65 years old as compared to those 65 years and over. All treatment groups had a higher proportion of male subjects than female subjects (55%, 65%, 55% and 69% in the combination

therapy, dabrafenib monotherapy, vemurafenib and placebo groups, respectively) (Table 6.3003).

4.2 Baseline disease characteristics

At screening, 58% of all subjects were diagnosed with Stage IV melanoma and 58% of all subjects had distant metastasis The median time since diagnosis for all subjects was 16.1 months (range: 1 to 456 months), and the majority of subjects had LDH ≤ ULN at Baseline in each treatment arm. All baseline disease characteristics data are unchanged from the 2019 report (Table 4-1).

Table 4-1 Summary of disease characteristics at screening – safety set

	Dabrafenib + Trametinib (N=994)	Dabrafenib Monotherapy (N=398)	DTIC (N=59)	Vemurafenib Monotherapy (N=349)	Placebo (N=432)	Total (N=2232)
Measurable disease at Screening						
No	0	2 (<1%)	0	2 (<1%)	0	4 (<1%)
Yes	559 (56%)	396 (>99%)	59 (100%)	347 (>99%)	0	1361 (61%)
Missing*	435 (44%)	0	0	0	432 (100%)	867 (39%)
Non-target Lesion at Screening						
No	112 (11%)	80 (20%)	14 (24%)	57 (16%)	0	263 (12%)
Yes	447 (45%)	318 (80%)	45 (76%)	292 (84%)	0	1102 (49%)
Missing*	435 (44%)	0	0	0	432 (100%)	867 (39%)
Stage at Screening						
IIIA	82 (8%)	0	0	0	71 (16%)	153 (7%)
IIIB	170 (17%)	1 (<1%)	1 (2%)	0	186 (43%)	358 (16%)
IIIC	197 (20%)	17 (4%)	0	26 (7%)	167 (39%)	407 (18%)
IV	540 (54%)	202 (51%)	1 (2%)	323 (93%)	0	1066 (48%)
IVA (IVM1a)	0	23 (6%)	9 (15%)	0	0	32 (1%)
IVB (IIVM1b)	0	33 (8%)	11 (19%)	0	0	44 (2%)
IVC (IVM1c)	0	122 (31%)	37 (63%)	0	0	159 (7%)
Missing	5 (<1%)	0	0	0	8 (2%)	13 (<1%)
Baseline LDH Categories						
LDH ABOVE ULN	198 (20%)	138 (35%)	18 (31%)	113 (32%)	7 (2%)	474 (21%)
LDH EQUAL TO OR BELOW ULN	784 (79%)	259 (65%)	40 (68%)	236 (68%)	418 (97%)	1737 (78%)

	Dabrafenib + Trametinib (N=994)	Dabrafenib Monotherapy (N=398)	DTIC (N=59)	Vemurafenib Monotherapy (N=349)	Placebo (N=432)	Total (N=2232)
Missing	12 (1%)	1 (<1%)	1 (2%)	0	7 (2%)	21 (<1%)
TNM Staging: Distant Metastasis						
M0	453 (46%)	16 (4%)	0	26 (7%)	432 (100%)	927 (42%)
M1	0	0	0	0	0	0
M1a	75 (8%)	54 (14%)	9 (15%)	49 (14%)	0	187 (8%)
M1b	105 (11%)	66 (17%)	12 (20%)	67 (19%)	0	250 (11%)
M1c	360 (36%)	262 (66%)	38 (64%)	206 (59%)	0	866 (39%)
MX	0	0	0	1 (<1%)	0	1 (<1%)
Missing	1 (<1%)	0	0	0	0	1 (<1%)
TNM Staging: Regional Lymph Nodes						
N0	77 (8%)	62 (16%)	8 (14%)	59 (17%)	0	206 (9%)
N1	82 (8%)	59 (15%)	6 (10%)	43 (12%)	0	190 (9%)
N1a	81 (8%)	0	0	0	95 (22%)	176 (8%)
N1b	88 (9%)	0	0	0	80 (19%)	168 (8%)
N1M	0	0	1 (2%)	0	0	1 (<1%)
N2	91 (9%)	45 (11%)	7 (12%)	55 (16%)	0	198 (9%)
N2a	70 (7%)	4 (1%)	3 (5%)	0	62 (14%)	139 (6%)
N2b	70 (7%)	14 (4%)	4 (7%)	0	80 (19%)	168 (8%)
N2c	18 (2%)	7 (2%)	2 (3%)	0	16 (4%)	43 (2%)
N3	296 (30%)	132 (33%)	13 (22%)	129 (37%)	98 (23%)	668 (30%)
NX	121 (12%)	66 (17%)	12 (20%)	63 (18%)	0	262 (12%)
Missing	0	9 (2%)	3 (5%)	0	1 (<1%)	13 (<1%)
TNM Staging: Primary Tumour						
T0	24 (2%)	19 (5%)	1 (2%)	15 (4%)	0	59 (3%)
T1	57 (6%)	19 (5%)	2 (3%)	35 (10%)	0	113 (5%)
T1a	55 (6%)	16 (4%)	5 (8%)	0	58 (13%)	134 (6%)
T1b	19 (2%)	4 (1%)	0	0	24 (6%)	47 (2%)
T2	75 (8%)	37 (9%)	0	55 (16%)	0	167 (7%)
T2a	79 (8%)	14 (4%)	5 (8%)	0	80 (19%)	178 (8%)
T2b	28 (3%)	7 (2%)	0	0	22 (5%)	57 (3%)
T2c	0	0	0	0	0	0

	Dabrafenib + Trametinib (N=994)	Dabrafenib Monotherapy (N=398)	DTIC (N=59)	Vemurafenib Monotherapy (N=349)	Placebo (N=432)	Total (N=2232)
T3	84 (8%)	52 (13%)	3 (5%)	70 (20%)	0	209 (9%)
T3a	73 (7%)	15 (4%)	9 (15%)	0	54 (13%)	151 (7%)
T3b	67 (7%)	19 (5%)	5 (8%)	0	74 (17%)	165 (7%)
T4	133 (13%)	59 (15%)	5 (8%)	71 (20%)	0	268 (12%)
T4a	28 (3%)	0	0	0	35 (8%)	63 (3%)
T4b	77 (8%)	0	0	0	72 (17%)	149 (7%)
TIS	5 (<1%)	4 (1%)	0	0	0	9 (<1%)
TX	186 (19%)	113 (28%)	20 (34%)	103 (30%)	8 (2%)	430 (19%)
Missing	4 (<1%)	20 (5%)	4 (7%)	0	5 (1%)	33 (1%)
Pathological Dermal Lymphatic Invasion						
ABSENT	88 (9%)	176 (44%)	36 (61%)	23 (7%)	0	323 (14%)
PRESENT	36 (4%)	101 (25%)	21 (36%)	10 (3%)	0	168 (8%)
Missing	870 (88%)	121 (30%)	2 (3%)	316 (91%)	432 (100%)	1741 (78%)
Visceral or Non-visceral Disease						
NON-VISCERAL	118 (12%)	116 (29%)	18 (31%)	79 (23%)	0	331 (15%)
VISCERAL	154 (15%)	52 (13%)	8 (14%)	106 (30%)	0	320 (14%)
VISCERAL AND NON-VISCERAL	287 (29%)	230 (58%)	33 (56%)	164 (47%)	0	714 (32%)
Missing*	435 (44%)	0	0	0	432 (100%)	867 (39%)
Time Since Diagnosis (Months)						
n	992	351	45	346	432	2166
Mean	39.6	44.7	49.9	49.1	24.9	39.2
SD	60.63	51.80	65.80	56.52	45.00	56.40
Median	14.2	26.3	23.9	28.2	6.0	16.1
Min.	1	1	1	1	1	1
Max.	456	358	339	349	351	456

Source: Table 6.2101

*These subjects were from Study BRF115532 (COMBI-AD) where one of the inclusion criteria for the study was that subjects had to be surgically rendered free of disease no more than 12 weeks before randomization.

At screening, 67% of subjects with secondary malignancies were diagnosed with Stage IV melanoma and 67% had distant metastasis. The median time since diagnosis for subjects with

secondary malignancies was 20.0 months (range: 1 to 358 months), and the majority of subjects in each treatment arm had LDH ≤ ULN at Baseline. Disease characteristics data have few changes from the 2019 report (Table 4-2).

Table 4-2 Summary of disease characteristics at screening for subjects with secondary malignancy – safety set

	Trametinib/ Dabrafenib (COMBI-D/V/ AD) (N=91)	Mono Dabrafenib (Break 3/COMBI-D) (N=69)	DTIC (N=2)	Vemurafenib (COMBI-V) (N=77)	Placebo (N=32)	Total (N=271)
Measurable disease at Screening						
No	0	0	0	1 (1%)	0	1 (<1%)
Yes	47 (52%)	69 (100%)	2 (100%)	76 (99%)	0	194 (72%)
Missing*	44 (48%)	0	0	0	32 (100%)	76 (28%)
Non-target Lesion at Screening						
No	13 (14%)	16 (23%)	0	16 (21%)	0	45 (17%)
Yes	34 (37%)	53 (77%)	2 (100%)	61 (79%)	0	150 (55%)
Missing*	44 (48%)	0	0	0	32 (100%)	76 (28%)
Stage at Screening						
IIIA	10 (11%)	0	0	0	4 (13%)	14 (5%)
IIIB	20 (22%)	0	0	0	15 (47%)	35 (13%)
IIIC	16 (18%)	4 (6%)	0	8 (10%)	11 (34%)	39 (14%)
IV	45 (49%)	36 (52%)	0	69 (90%)	0	150 (55%)
IVA (IVM1a)	0	6 (9%)	0	0	0	6 (2%)
IVB (IVM1b)	0	7 (10%)	0	0	0	7 (3%)
IVC (IVM1c)	0	16 (23%)	2 (100%)	0	0	18 (7%)
Missing	0	0	0	0	2 (6%)	2 (<1%)
Baseline LDH Categories						
LDH ABOVE ULN	9 (10%)	17 (25%)	1 (50%)	18 (23%)	0	45 (17%)
LDH ≤ ULN	79 (87%)	52 (75%)	1 (50%)	59 (77%)	31 (97%)	222 (82%)
Missing	3 (3%)	0	0	0	1 (3%)	4 (1%)
TNM Staging: Distant Metastasis						
M0	46 (51%)	4 (6%)	0	8 (10%)	32 (100%)	90 (33%)
M1	0	0	0	0	0	0
M1a	7 (8%)	13 (19%)	0	11 (14%)	0	31 (11%)

	Trametinib/ Dabrafenib (COMBI-D/V/ AD) (N=91)	Mono Dabrafenib (Break 3/COMBI-D) (N=69)	DTIC (N=2)	Vemurafenib (COMBI-V) (N=77)	Placebo (N=32)	Total (N=271)
M1b	12 (13%)	13 (19%)	0	17 (22%)	0	42 (15%)
M1c	26 (29%)	39 (57%)	2 (100%)	41 (53%)	0	108 (40%)
MX	0	0	0	0	0	0
Missing	0	0	0	0	0	0
TNM Staging: Regional Lymph Nodes						
N0	9 (10%)	6 (9%)	0	15 (19%)	0	30 (11%)
N1	13 (14%)	7 (10%)	0	8 (10%)	0	28 (10%)
N1a	11 (12%)	0	0	0	10 (31%)	21 (8%)
N1b	10 (11%)	0	0	0	4 (13%)	14 (5%)
N1M	0	0	0	0	0	0
N2	4 (4%)	6 (9%)	1 (50%)	14 (18%)	0	25 (9%)
N2A	7 (8%)	2 (3%)	0	0	3 (9%)	12 (4%)
N2B	8 (9%)	5 (7%)	1 (50%)	0	6 (19%)	20 (7%)
N2C	2 (2%)	2 (3%)	0	0	3 (9%)	7 (3%)
N3	15 (16%)	25 (36%)	0	31 (40%)	6 (19%)	77 (28%)
NX	12 (13%)	15 (22%)	0	9 (12%)	0	36 (13%)
Missing	0	1 (1%)	0	0	0	1 (<1%)
TNM Staging: Primary Tumour						
T0	2 (2%)	6 (9%)	0	7 (9%)	0	15 (6%)
T1	9 (10%)	2 (3%)	0	8 (10%)	0	19 (7%)
T1a	10 (11%)	2 (3%)	0	0	3 (9%)	15 (6%)
T1b	3 (3%)	0	0	0	2 (6%)	5 (2%)
T2	10 (11%)	7 (10%)	0	6 (8%)	0	23 (8%)
T2a	6 (7%)	1 (1%)	0	0	5 (16%)	12 (4%)
T2b	2 (2%)	1 (1%)	0	0	1 (3%)	4 (1%)
T2c	0	0	0	0	0	0
T3	4 (4%)	9 (13%)	0	17 (22%)	0	30 (11%)
T3a	5 (5%)	2 (3%)	2 (100%)	0	5 (16%)	14 (5%)
T3b	9 (10%)	1 (1%)	0	0	7 (22%)	17 (6%)
T4	7 (8%)	11 (16%)	0	18 (23%)	0	36 (13%)

	Trametinib/ Dabrafenib (COMBI-D/V/ AD) (N=91)	Mono Dabrafenib (Break 3/COMBI-D) (N=69)	DTIC (N=2)	Vemurafenib (COMBI-V) (N=77)	Placebo (N=32)	Total (N=271)
T4a	3 (3%)	0	0	0	0	3 (1%)
T4b	6 (7%)	0	0	0	7 (22%)	13 (5%)
TIS	0	0	0	0	0	0
TX	15 (16%)	20 (29%)	0	21 (27%)	2 (6%)	58 (21%)
Missing	0	7 (10%)	0	0	0	7 (3%)
Pathological Dermal Lymphatic Invasion						
ABSENT	10 (11%)	26 (38%)	2 (100%)	5 (6%)	0	43 (16%)
PRESENT	1 (1%)	19 (28%)	0	2 (3%)	0	22 (8%)
Missing	80 (88%)	24 (35%)	0	70 (91%)	32 (100%)	206 (76%)
Visceral or Non-visceral Disease						
NON-VISCERAL	12 (13%)	27 (39%)	0	18 (23%)	0	57 (21%)
VISCERAL	16 (18%)	7 (10%)	0	24 (31%)	0	47 (17%)
VISCERAL AND NON-VISCERAL	19 (21%)	35 (51%)	2 (100%)	35 (45%)	0	91 (34%)
Missing	44 (48%)	0	0	0	32 (100%)	76 (28%)
Time Since Diagnosis (Months)						
n	91	62	1	76	32	262
Mean	40.3	52.0	69.3	50.8	22.0	44.0
SD	58.21	62.21		56.13	39.38	57.08
Median	17.0	31.6	69.3	31.5	5.8	20.0
Min.	1	2	69	1	2	1
Max.	296	358	69	246	167	358

Source: Table 6.3004

*These subjects were from Study BRF115532 (COMBI-AD) where one of the inclusion criteria for the study was that subjects had to be surgically rendered free of disease no more than 12 weeks before randomization.

5 Summary of treatment-emergent secondary malignancies

Since the 2019 report, the number of subjects with reported secondary malignancy events did not change. However, malignant melanoma previously reported for one subject was removed after the report was queried. Another subject in the same treatment group had a first reported

SPM, malignant melanoma, reported since the 2019 report. Consequently, the overall number of subjects with SPM and in the malignant melanoma category did not change (Section 7.3).

One subject in the placebo group who was previously reported as having BCC had a new report of PT Neoplasm. As a result, the count of subjects in the placebo group with an event in the "Other" category increased from 5 to 6 since the last report.

Consistent with the previous reports, more subjects in the monotherapy groups experienced secondary malignancies (17% and 22%, dabrafenib and vemurafenib, respectively) than those receiving combination therapy (9%) or placebo (7%).

The most common secondary malignancy in the combination therapy and placebo groups was BCC (4% for both groups), and in the dabrafenib monotherapy and vemurafenib groups was cuSCC (11% and 19% respectively). New primary melanomas and other treatment-emergent malignancies occurred at similar frequencies in all 4 treatment groups. Most subjects experienced primarily cutaneous-related events compared to other treatment-emergent malignancies (Table 5-1).

Table 5-1 Overview of secondary malignancies – safety set

Tumor Type Preferred Term	**Dabrafenib + Trametinib (N=994)**	**Dabrafenib Monotherapy (N=398)**	**DTIC (N=59)**	**Vemurafenib Monotherapy (N=349)**	**Placebo (N=432)**
ANY EVENT	91 (9%)	69 (17%)	2 (3%)	77 (22%)	32 (7%)
Cutaneous Squamous Cell Carcinoma (including Keratoacanthoma)					
Any event	31 (3%)	43 (11%)	0	66 (19%)	7 (2%)
Squamous cell carcinoma	11 (1%)	15 (4%)	0	27 (8%)	4 (<1%)
Squamous cell carcinoma of skin	7 (<1%)	23 (6%)	0	31 (9%)	2 (<1%)
Keratoacanthoma	8 (<1%)	10 (3%)	0	34 (10%)	3 (<1%)
Bowen's disease	11 (1%)	3 (<1%)	0	3 (<1%)	2 (<1%)
Lip squamous cell carcinoma	0	1 (<1%)	0	1 (<1%)	0
Basosquamous carcinoma	1 (<1%)	0	0	0	0
Carcinoma in situ of skin	1 (<1%)	0	0	0	0
Basal Cell Carcinoma					
Any event	41 (4%)	26 (7%)	1 (2%)	6 (2%)	16 (4%)
Basal cell carcinoma	41 (4%)	26 (7%)	1 (2%)	6 (2%)	16 (4%)
New Primary Malignant Melanoma					
Any event	17 (2%)	10 (3%)	1 (2%)	10 (3%)	13 (3%)
Malignant melanoma	16 (2%)	5 (1%)	0	7 (2%)	8 (2%)
Malignant melanoma in situ	0	4 (1%)	0	2 (<1%)	4 (<1%)
Lentigo maligna	0	0	0	1 (<1%)	1 (<1%)
Malignant melanoma stage I	0	0	1 (2%)	0	0

Tumor Type Preferred Term	**Dabrafenib + Trametinib (N=994)**	**Dabrafenib Monotherapy (N=398)**	**DTIC (N=59)**	**Vemurafenib Monotherapy (N=349)**	**Placebo (N=432)**
Superficial spreading melanoma stage unspecified	1 (<1%)	1 (<1%)	0	0	0
Other treatment emergent malignancies (excluding Basal Cell Carcinoma)					
Any event	27 (3%)	12 (3%)	0	8 (2%)	6 (1%)
Lung neoplasm malignant	3 (<1%)	0	0	1 (<1%)	0
Breast cancer	1 (<1%)	2 (<1%)	0	0	0
Lung adenocarcinoma	2 (<1%)	0	0	0	1 (<1%)
Neoplasm	1 (<1%)	0	0	1 (<1%)	1 (<1%)
Adenocarcinoma of colon	1 (<1%)	0	0	0	1 (<1%)
Endometrial adenocarcinoma	2 (<1%)	0	0	0	0
Lymphoma	2 (<1%)	0	0	0	0
Papillary thyroid cancer	1 (<1%)	1 (<1%)	0	0	0
Prostate cancer	2 (<1%)	0	0	0	0
Renal cell carcinoma	2 (<1%)	0	0	0	0
Transitional cell carcinoma	0	1 (<1%)	0	1 (<1%)	0
Acute myeloid leukaemia	1 (<1%)	0	0	0	0
Adenocarcinoma	1 (<1%)	0	0	0	0
Adenocarcinoma gastric	0	1 (<1%)	0	0	0
Adenocarcinoma of the cervix	0	1 (<1%)	0	0	0
Astrocytoma	0	0	0	1 (<1%)	0
B-cell lymphoma	1 (<1%)	0	0	0	0
Bile duct adenocarcinoma	0	1 (<1%)	0	0	0
Bladder transitional cell carcinoma	0	0	0	0	1 (<1%)
Carcinoma in situ	0	0	0	1 (<1%)	0
Chronic myeloid leukaemia	1 (<1%)	0	0	0	0
Cutaneous T-cell lymphoma stage I	0	1 (<1%)	0	0	0
Diffuse large B-cell lymphoma	1 (<1%)	0	0	0	0
Dysplastic naevus syndrome	1 (<1%)	0	0	0	0
Hodgkin's disease	0	1 (<1%)	0	0	0
Intraductal papillary-mucinous carcinoma of pancreas	1 (<1%)	0	0	0	0
Intraductal proliferative breast lesion	1 (<1%)	0	0	0	0
Invasive ductal breast carcinoma	0	1 (<1%)	0	0	0

Tumor Type Preferred Term	**Dabrafenib + Trametinib (N=994)**	**Dabrafenib Monotherapy (N=398)**	**DTIC (N=59)**	**Vemurafenib Monotherapy (N=349)**	**Placebo (N=432)**
Neoplasm malignant	0	0	0	1 (<1%)	0
Osteosarcoma	1 (<1%)	0	0	0	0
Pancreatic carcinoma	0	0	0	0	1 (<1%)
Penile neoplasm	1 (<1%)	0	0	0	0
Phaeochromocytoma	1 (<1%)	0	0	0	0
Rectal adenocarcinoma	0	0	0	1 (<1%)	0
Renal cancer	0	0	0	0	1 (<1%)
Salivary gland neoplasm	0	0	0	1 (<1%)	0
Soft tissue sarcoma	0	1 (<1%)	0	0	0
Ulcerated haemangioma	0	1 (<1%)	0	0	0

Source: Table 8.0105
MedDRA terms comprising other treatment-emergent malignancies are listed in Appendix 1.

There were few changes in the data in the summary of characteristics for subjects with secondary malignancy compared to the 2019 report. Among the 271 subjects who experienced any secondary malignancy, the majority experienced events that were grade 3 and serious per protocol definition, except in the DTIC treatment group. For subjects in the dabrafenib monotherapy and vemurafenib groups, the majority experienced events that were considered related to study treatment.

Of the subjects experiencing any secondary malignancy, a single event was reported by 67% (61/91) of subjects in the combination therapy group, 57% (39/69) of subjects in the dabrafenib monotherapy group, 47% (36/77) of subjects in the vemurafenib group and 69% (22/32) of subjects in the placebo group. Most subjects with any secondary malignancy had events that resolved without dose modification or discontinuation of study drug (Table 5-2).

In general, cutaneous secondary malignancies were removed by excision. One subject in the dabrafenib monotherapy group had a fatal event of bile duct adenocarcinoma and one subject in the placebo group had a fatal event of pancreatic carcinoma (from Study BRF115532) (Listing 28.9002).

Four subjects receiving combination therapy discontinued study treatment due to acute myeloid leukemia, osteosarcoma, prostate cancer, and B-cell lymphoma. Three subjects in the placebo group discontinued study treatment due to bladder transitional cell carcinoma and new primary malignant melanoma (Listing 28.9002). Secondary malignancy events leading to discontinuation in the two monotherapy groups were discussed in the 2017 report.

Table 5-2 Summary of characteristics for subjects with secondary malignancy – safety set

	Dabrafenib + Trametinib (N=994)	Dabrafenib Monotherapy (N=398)	DTIC (N=59)	Vemurafenib Monotherapy (N=349)	Placebo (N=432)
Number of Subjects with Event	**91 (9%)**	**69 (17%)**	**2 (3%)**	**77 (22%)**	**32 (7%)**
Number of Events	**182**	**135**	**2**	**180**	**56**
Event Characteristics					
n	91	69	2	77	32
Serious	68 (75%)	56 (81%)	1 (50%)	66 (88%)	25 (78%)
Drug-related	42 (46%)	59 (86%)	0	70 (91%)	14 (44%)
Leading to Withdrawal	0	0	0	0	0
Fatal	0	1 (1%)	0	0	1 (3%)
Number of occurrences					
n	91	69	2	77	32
One	61 (67%)	39 (57%)	2 (100%)	36 (47%)	22 (69%)
Two	14 (15%)	15 (22%)	0	18 (23%)	7 (22%)
Three or more	16 (18%)	15 (22%)	0	23 (30%)	3 (9%)
Outcome					
n	91	69	2	77	32
Recovered/resolved	78 (86%)	62 (90%)	2 (100%)	72 (94%)	31 (97%)
Recovering/resolving	2 (2%)	0	0	0	0
Not recovered/not resolved	16 (18%)	6 (9%)	0	7 (9%)	1 (3%)
Recovered/resolved with sequelae	4 (4%)	3 (4%)	0	1 (1%)	1 (3%)
Fatal	0	1 (1%)	0	0	1 (3%)
Maximum Grade					
n	88	69	2	77	31
Grade 1	10 (11%)	7 (10%)	1 (50%)	1 (1%)	5 (16%)
Grade 2	21 (24%)	5 (7%)	1 (50%)	2 (3%)	8 (26%)
Grade 3	53 (60%)	56 (81%)	0	72 (94%)	16 (52%)
Grade 4	4 (5%)	0	0	2 (3%)	1 (3%)
Grade 5	0	1 (1%)	0	0	1 (3%)
Action(s) Taken					
n	91	69	2	77	32
Investigational product withdrawn	4 (4%)	4 (6%)	0	3 (4%)	3 (9%)

	Dabrafenib + Trametinib (N=994)	Dabrafenib Monotherapy (N=398)	DTIC (N=59)	Vemurafenib Monotherapy (N=349)	Placebo (N=432)
Dose reduced	0	0	0	0	0
Dose increased	0	0	0	0	0
Dose not changed	63 (69%)	64 (93%)	2 (100%)	69 (90%)	17 (53%)
Dose interrupted/delayed	6 (7%)	1 (1%)	0	3 (4%)	1 (3%)
Not applicable*	33 (36%)	1 (1%)	0	8 (10%)	14 (44%)

Source: Table 8.0107

* Not applicable: treatment was already interrupted or discontinued at time of event reported.

MedDRA terms comprising other treatment-emergent malignancies are listed in Appendix 1.

The median time to onset for the first event of secondary malignancy was 48.7 weeks in the combination therapy group, 12.1 weeks in the dabrafenib monotherapy group, 10.0 weeks in the vemurafenib therapy group, and 31.9 weeks in the placebo group (Table 5-3).

Table 5-3 Summary of onset of first occurrence of secondary malignancy – safety set

	Dabrafenib + Trametinib (N=994)	Dabrafenib Monotherapy (N=398)	DTIC (N=59)	Vemurafenib Monotherapy (N=349)	Placebo (N=432)
Number of Subjects Experiencing Any Secondary Malignancy Event	**91 (9%)**	**69 (17%)**	**2 (3%)**	**77 (22%)**	**32 (7%)**
Time of onset of first occurrence, weeks					
n	**91**	**69**	**2**	**77**	**32**
1-<6	5 (5%)	17 (25%)	1 (50%)	13 (17%)	0
6-<12	6 (7%)	16 (23%)	0	31 (40%)	9 (28%)
12-<18	12 (13%)	9 (13%)	0	9 (12%)	4 (13%)
18-<24	4 (4%)	8 (12%)	0	6 (8%)	2 (6%)
24-<30	5 (5%)	2 (3%)	0	6 (8%)	0
30-<36	5 (5%)	2 (3%)	1 (50%)	2 (3%)	3 (9%)
36-<42	3 (3%)	1 (1%)	0	2 (3%)	2 (6%)
42-<48	4 (4%)	1 (1%)	0	1 (1%)	1 (3%)
48-<54	4 (4%)	0	0	1 (1%)	0
54-<60	0	2 (3%)	0	1 (1%)	0
60-<66	4 (4%)	0	0	2 (3%)	2 (6%)
>=66	39 (43%)	11 (16%)	0	3 (4%)	9 (28%)

	Dabrafenib + Trametinib (N=994)	Dabrafenib Monotherapy (N=398)	DTIC (N=59)	Vemurafenib Monotherapy (N=349)	Placebo (N=432)
Mean	**75.7**	**30.8**	**18.6**	**19.2**	**60.8**
SD	**70.03**	**43.60**	**23.13**	**23.24**	**72.88**
Median	**48.7**	**12.1**	**18.6**	**10.0**	**31.9**
Min.	**4**	**1**	**2**	**2**	**7**
Max.	**310**	**193**	**35**	**139**	**264**

Source: Table 8.0108

Overall, a smaller proportion of new secondary malignancy cases per year of follow-up occurred in the combination group than in the monotherapy group (4.4% vs 9.2%, Table 5-4).

Table 5-4 Summary of occurrence of any secondary malignancies over time (safety set)

	Dabrafenib + Trametinib (MEK115306/ MEK116513)/ BRF11532 N=994				Dabrafenib Monotherapy (BRF113683/ MEK115306) N=398			
Period of safety FU[3)]	**N**	**New cases[2)] n (%)**	**Cumulative cases[4)] n (%)**	**% cases per year of FU to period end[1)]**	**N**	**New cases[2)] n (%)**	**Cumulative cases[4)] n (%)**	**% cases per year of FU to period end[1)]**
0−12 months	994	48 (4.8)	48 (4.8)		398	56 (14.1)	56 (14.1)	
>12−24 months	697	17 (2.4)	65 (6.5)		188	6 (3.2)	62 (15.6)	
>24−36 months	190	14 (7.4)	79 (7.9)		88	5 (5.7)	67 (16.8)	
>36−48 months	133	8 (6.0)	87 (8.8)		32	2 (6.3)	69 (17.3)	
>48−60 months	100	2 (2.0)	89 (9.0)		20	0	69 (17.3)	
>60−72 months	76	2 (2.6)	91 (9.2)		15	0	69 (17.3)	
>72-84 months	63	0	91 (9.2)		3	0	69 (17.3)	
>84 months	2	0	91 (9.2)			0	69 (17.3)	
Overall	994	0	91 (9.2)	4.4	398	0	69 (17.3)	9.2

Abbreviations: FU=follow-up

[1)] Calculated by dividing the total cumulative cases by the total safety follow-up in years and multiplying by 100

[2)] Only the first occurrence of each malignancy type for each patient is included in the analysis, even if they are beyond the defined safety follow-up period.

[3)] Follow-up following first incidence of second malignancy type is not included.

[4)] The denominator for the cumulative case % is the total number in the safety population for each treatment (i.e. patients with at least one dose of therapy).

Source: EMA PAM-Table 2.1A

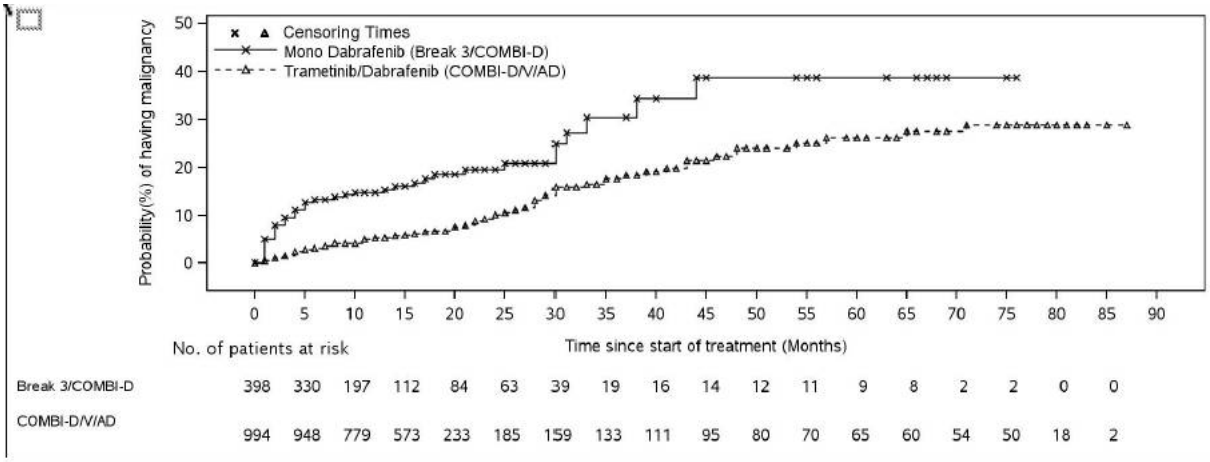
Of all patients enrolled, the probability estimate of having a secondary malignancy was approximately 2-fold lower in subjects in the combination group compared to subjects in the monotherapy group. In the combination group, subjects had a 10.2%, 17.8% and 24.1% probability estimate of having any type of secondary malignancy at 2 years, 3 years and 4 years, respectively, compared with 19.6%, 30.5% and 38.7% in the monotherapy group (Table 5-5, Figure 5-1).

Table 5-5 Summary of time to event of first malignancy – (any secondary malignancy, safety set)

	Dabrafenib + Trametinib (MEK115306/ MEK116513/ BRF115532) N=994	Dabrafenib Monotherapy (BRF113683/ MEK115306) N=398
Secondary malignancy (event), n (%)	91 (9%)	69 (17%)
Censored, FU ended, n (%)	903 (91%)	329 (83%)
Censored, FU ongoing, n (%)	0	0
Probability of malignancy		
1-year estimate (95% CI)	5.2 (3.9, 6.9)	14.8 (11.6, 18.9)
2-year estimate (95% CI)	10.2 (7.7, 13.5)	19.6 (15.1, 25.3)
3-year estimate (95% CI)	17.8 (13.6, 23.0)	30.5 (21.5, 42.0)
4-year estimate (95% CI)	24.1 (18.7, 30.8)	38.7 (26.4, 54.3)
5-year estimate (95% CI)	26.3 (20.4, 33.5)	38.7 (26.4, 54.3)
6-year estimate (95% CI)	28.8 (22.3, 36.8)	38.7 (26.4, 54.3)
7-year estimate (95% CI)	28.8 (22.3, 36.8)	38.7 (26.4, 54.3)
1st quartile	54.0 (41.0, NE)	31.0 (21.0, 44.0)
Median	NE (NE, NE)	NE (44.0, NE)
3rd quartile	NE (NE, NE)	NE (NE, NE)

Abbreviations: CI=confidence interval; FU=follow-up; NE=not estimable
All secondary malignancies are included, even if they are beyond the defined safety follow-up period.
Source: EMA PAM-Table 3.1A

Figure 5-1 Kaplan-Meier plot of time to event of first malignancy – (any secondary malignancy, safety set)



Abbreviations: Break 3 = BRF113683; COMBI-D = MEK115306; COMBI-V = MEK116513
All secondary malignancies are included, even if they are beyond the defined safety follow-up period.
Source: EMA PAM-Figure 1.1A

6 Exposure

The median daily dose of dabrafenib in subjects receiving dabrafenib monotherapy was similar in subjects with no secondary malignancies and in subjects experiencing any secondary malignancy. The median time on study for subjects experiencing any secondary malignancy was at least two times longer as that for subjects who did not have secondary malignancies. Subjects who had cuSCC events had the shortest median time on study amongst subjects experiencing any secondary malignancy (Table 6-1).

Table 6-1 Summary of exposure to dabrafenib in the monotherapy group by tumor type category – safety set

		Tumor Type Category				
		cuSCC (N=43)	**Basal Cell Carcinoma (N=26)**	**New Primary Melanoma (N=10)**	**Other Secondary Malignancies (N=12)**	**No Secondary Malignancies (N=329)**
Average Daily Dose	**n**	**43**	**26**	**10**	**12**	**329**
	Mean	288.81	284.68	292.60	289.76	284.88
	SD	26.239	31.383	21.929	24.927	34.887
	Median	299.83	297.97	300.00	299.60	300.00
	Min.	197.5	182.8	230.3	218.6	104.1
	Max.	300.0	300.0	300.0	300.0	300.0
Cumulative dose (mg)	**n**	**43**	**26**	**10**	**12**	**329**
	Mean	203772.1	210745.2	223405.0	215087.5	101585.3
	SD	164972.4	144329.4	170299.4	170900.7	111807.9
	Median	133050.0	175687.5	169650.0	197175.0	58800.0
	Min.	23800	33750	51000	16800	900
	Max.	669000	569250	551400	471000	631200
Time on study (months)	**n**	**43**	**26**	**10**	**12**	**329**
	Mean	22.893	24.360	25.911	23.778	11.664
	SD	18.5508	16.7925	21.0739	19.1024	12.9451
	Median	15.000	22.310	18.675	21.000	6.900
	Min.	3.00	3.00	5.59	1.00	0.00
	Max.	73.00	62.62	60.68	52.34	69.00
	<3 months	0	0	0	1 (8%)	65 (20%)
	3-6 months	5 (12%)	2 (8%)	1 (10%)	3 (25%)	92 (28%)
	>6-12 months	11 (26%)	5 (19%)	3 (30%)	2 (17%)	76 (23%)
	>12 months	27 (63%)	19 (73%)	6 (60%)	6 (50%)	96 (29%)

Source: Table 8.01011

In subjects receiving combination therapy in whom a new primary melanoma was reported, the median daily dose of dabrafenib was at least 76% of the dose in subjects in whom no secondary malignancies were reported. For the other tumor types, the median daily dose was similar to those in whom no secondary malignancies were reported. The median times on dabrafenib were not decreased for subjects with secondary malignancies compared to those without secondary malignancies (Table 6-2).

Table 6-2 Summary of exposure to dabrafenib in the combination therapy group by tumor type category – safety set

		Tumor Type Category				
		cuSCC (N=31)	**Basal Cell Carcinoma (N=41)**	**New Primary Melanoma (N=17)**	**Other Secondary Malignancies (N=27)**	**No Secondary Malignancies (N=903)**
Average Daily Dose	**n**	**31**	**41**	**17**	**27**	**903**
	Mean	258.98	254.31	232.73	265.12	258.70
	SD	51.494	55.695	54.311	48.884	53.874
	Median	289.96	282.64	222.58	292.62	291.04
	Min.	146.9	96.3	145.6	136.2	88.5
	Max.	300.0	300.0	300.0	300.0	300.0
Cumulative dose (mg)	**n**	**31**	**41**	**17**	**27**	**903**
	Mean	234706.5	194667.1	106158.8	203837.0	122208.2
	SD	188600.5	205842.9	123972.0	180400.5	148674.9
	Median	121550.0	100500.0	76050.0	101100.0	79500.0
	Min.	35300	7950	7900	8700	300
	Max.	654900	654900	562200	647400	696450
Time on study (months)	**n**	**31**	**41**	**17**	**27**	**903**
	Mean	29.968	23.902	14.000	25.222	14.814
	SD	24.4056	23.4898	14.6330	21.5001	17.6309
	Median	17.000	11.000	11.000	11.000	11.000
	Min.	5.00	0.00	1.00	1.00	0.00
	Max.	75.00	71.00	66.00	71.00	80.00
	<3 months	0	1 (2%)	1 (6%)	1 (4%)	117 (13%)
	3-6 months	1 (3%)	5 (12%)	2 (12%)	2 (7%)	171 (19%)
	>6-12 months	13 (42%)	19 (46%)	10 (59%)	12 (44%)	391 (43%)
	>12 months	17 (55%)	16 (39%)	4 (24%)	12 (44%)	224 (25%)

Source: Table 8.01010

In subjects receiving combination therapy in whom a new primary melanoma was reported, the median daily dose of trametinib was at least 93% of the dose in subjects in whom no secondary malignancies were reported. For the other tumor types, the median daily dose was similar to those in whom no secondary malignancies were reported. The median times on trametinib were not decreased for subjects with secondary malignancies compared to those without secondary malignancies (Table 6-3).

Table 6-3 Summary of exposure to trametinib in the combination therapy group by tumor type category – safety set

		Tumor Type Category				
		cuSCC (N=31)	**Basal Cell Carcinoma (N=41)**	**New Primary Melanoma (N=17)**	**Other Secondary Malignancies (N=27)**	**No Secondary Malignancies (N=903)**
Average Daily Dose	**n**	**31**	**41**	**17**	**27**	**903**
	Mean	1.78	1.80	1.65	1.82	1.83
	SD	0.293	0.272	0.340	0.247	0.278
	Median	1.95	1.93	1.80	1.95	1.98
	Min.	1.0	0.9	0.9	1.3	0.6
	Max.	2.0	2.0	2.0	2.0	2.3
Cumulative dose (mg)	**n**	**31**	**41**	**17**	**27**	**903**
	Mean	1527.4	1364.7	728.7	1316.4	847.5
	SD	1262.78	1428.56	808.79	1107.33	1001.05
	Median	788.0	670.0	604.0	674.0	596.0
	Min.	230	54	57	58	2
	Max.	4366	4366	3704	3950	5276
Time on study (months)	**n**	**31**	**41**	**17**	**27**	**903**
	Mean	27.806	23.683	14.000	23.778	14.682
	SD	23.4513	23.4898	14.6629	19.8307	17.3142
	Median	13.000	11.000	11.000	11.000	11.000
	Min.	5.00	0.00	1.00	1.00	0.00
	Max.	75.00	71.00	66.00	71.00	80.00
	<3 months	0	1 (2%)	1 (6%)	1 (4%)	118 (13%)
	3-6 months	1 (3%)	5 (12%)	2 (12%)	2 (7%)	167 (18%)
	>6-12 months	14 (45%)	20 (49%)	10 (59%)	12 (44%)	395 (44%)
	>12 months	16 (52%)	15 (37%)	4 (24%)	12 (44%)	223 (25%)

	Tumor Type Category				
	cuSCC (N=31)	Basal Cell Carcinoma (N=41)	New Primary Melanoma (N=17)	Other Secondary Malignancies (N=27)	No Secondary Malignancies (N=903)

Source: Table 8.0103

Exposures for subjects in the vemurafenib and in the DTIC groups are presented in Table 6-4 and Table 6-5, respectively.

Table 6-4 Summary of exposure to vemurafenib by tumor type category – safety set

		Tumor Type Category				
		cuSCC (N=66)	**Basal Cell Carcinoma (N=6)**	**New Primary Melanoma (N=10)**	**Other Secondary Malignancies (N=8)**	**No Secondary Malignancies (N=272)**
Average Daily Dose	**n**	**66**	**6**	**10**	**8**	**272**
	Mean	1587.74	1403.73	1696.77	1551.34	1620.32
	SD	336.566	479.697	241.491	344.604	367.191
	Median	1649.89	1387.35	1806.37	1566.21	1869.16
	Min.	797.8	869.1	1382.3	938.6	450.4
	Max.	1920.0	1920.0	1920.0	1920.0	1920.0
Cumulative dose (mg)	**n**	**66**	**6**	**10**	**8**	**272**
	Mean	722810.9	1475080	1238784	395010.0	446387.6
	SD	740197.6	1776847	1195844	232837.9	571246.7
	Median	539520.0	515880.0	612480.0	412920.0	267960.0
	Min.	76800	146880	336960	76320	2880
	Max.	3974400	3861120	3974400	740640	4310400
Time on study (months)	**n**	**66**	**6**	**10**	**8**	**272**
	Mean	14.167	28.833	22.500	8.375	8.676
	SD	13.5948	31.8209	20.1839	5.7554	11.3032
	Median	10.000	12.500	13.000	9.000	5.000
	Min.	1.00	4.00	6.00	1.00	0.00
	Max.	68.00	73.00	68.00	16.00	74.00
	<3 months	6 (9%)	0	0	2 (25%)	74 (27%)
	3-6 months	11 (17%)	2 (33%)	1 (10%)	1 (13%)	84 (31%)
	>6-12 months	26 (39%)	1 (17%)	4 (40%)	3 (38%)	58 (21%)
	>12 months	23 (35%)	3 (50%)	5 (50%)	2 (25%)	56 (21%)

Source: Table 8.01012

Table 6-5 Summary of exposure to DTIC by tumor type category –safety set

		Tumor Type Category		
		Basal Cell Carcinoma (N=1)	**New Primary Melanoma (N=1)**	**No Secondary Malignancies (N=57)**
Dose intensity (mg/m2/week)	**n**	**1**	**1**	**57**
	Mean	259.93	333.33	311.64
	SD			33.865
	Median	259.93	333.33	329.41
	Min.	259.9	333.3	205.9
	Max.	259.9	333.3	350.0
Time on study (months)	**n**	**1.0**	**1.0**	**57.0**
	Mean	10.090	1.380	4.518
	SD			4.6212
	Median	10.090	1.380	2.790
	Min.	10.09	1.38	0.69
	Max.	10.09	1.38	19.55
	<3 months	0	1 (100%)	31 (54%)
	3-6 months	0	0	13 (23%)
	>6-12 months	1 (100%)	0	9 (16%)
	>12 months	0	0	4 (7%)

Source: Table 8.0102

7 Incidence of secondary malignancies by tumor type

7.1 Cutaneous Squamous Cell Carcinoma

Paradoxical activation of the MAPK-pathway by RAS mutation has been implicated in the accelerated growth of squamous cell carcinomas in the presence of BRAF inhibitors (Su et al 2012).

The number of subjects with cuSCC events did not increase in any treatment group compared to the 2019 report (Table 7-1). No subjects in the DTIC group experienced cuSCC (Table 8.0105).

Table 7-1 Summary of cutaneous squamous cell carcinoma events including keratoacanthoma – safety set

Tumor Type Preferred Term	Dabrafenib + Trametinib (N=994)	Dabrafenib Monotherapy (N=398)	Vemurafenib Monotherapy (N=349)	Placebo (N=432)
Cutaneous Squamous Cell Carcinoma (including Keratoacanthoma)				
Any event	**31 (3%)**	**43 (11%)**	**66 (19%)**	**7 (2%)**
Squamous cell carcinoma	11 (1%)	15 (4%)	27 (8%)	4 (<1%)
Squamous cell carcinoma of skin	7 (<1%)	23 (6%)	31 (9%)	2 (<1%)
Keratoacanthoma	8 (<1%)	10 (3%)	34 (10%)	3 (<1%)
Bowen's disease	11 (1%)	3 (<1%)	3 (<1%)	2 (<1%)
Lip squamous cell carcinoma	0	1 (<1%)	1 (<1%)	0
Basosquamous carcinoma	1 (<1%)	0	0	0
Carcinoma in situ of skin	1 (<1%)	0	0	0

Source: Table 8.0105

The characteristics of reported cuSSCC (including keratoacanthomas) are unchanged from the 2019 report. The majority of subjects with cuSCC events in all treatment groups had events that were grade 3, serious per protocol definition, and were related to study treatment. The majority of subjects with cuSCC had events that resolved following excision. No subject receiving combination therapy, dabrafenib monotherapy or placebo required dose modification or discontinuation of study drug; 2 subjects receiving vemurafenib interrupted dosing due to cuSCC (Table 7-2).

Most subjects (> 55%) experiencing cuSCC in the combination therapy, dabrafenib monotherapy and placebo groups had a single occurrence as compared to subjects receiving vemurafenib monotherapy, where more than half of subjects experiencing cuSCC had multiple events (Table 7-2).

7 subjects receiving combination therapy experienced an event of cuSCC after treatment discontinuation (Listing 28.9002):

- [redacted] on Study Day 192; 26 days after discontinuation

- [redacted] two events on Study Days 475 and 657; 142 and 324 days, respectively after discontinuation
- [redacted] on Study Day 1627; 1291 days after discontinuation
- [redacted] on Study Day 626; 291 days after discontinuation
- [redacted] two events on Study Days 995 and 1359; 662 and 1026 days, respectively after discontinuation
- [redacted] on Study Day 1004; 672 days after discontinuation
- [redacted] two events on Study Day 600; 268 days after discontinuation

5 subjects receiving vemurafenib experienced events of cuSCC after treatment discontinuation or interruption (Listing 28.9002). These events were discussed in the 2017 report.

4 subjects receiving placebo experienced events of cuSCC after treatment discontinuation (Listing 28.9002).

- [redacted] one event on Study Day 409, 71 days after discontinuation
- [redacted] three events on Study Days 503 (2 events) and 671; 168 and 336 days, respectively after discontinuation
- [redacted] six events on Study Days 835, 911, 926, 1166, 1187 and 1243; 500, 576, 591, 831, 852, 908 days, respectively after discontinuation
- [redacted] on Study Day 453; 98 days after discontinuation

Table 7-2 Summary of characteristics of cutaneous squamous cell carcinoma including keratoacanthomas – safety set

	Dabrafenib + Trametinib (N=994)	Dabrafenib Monotherapy (N=398)	Vemurafenib Monotherapy (N=349)	Placebo (N=432)
Number of Subjects with Event	31 (3%)	43 (11%)	66 (19%)	7 (2%)
Number of Events	64	77	151	19
Event Characteristics				
n	31	43	66	7
Serious	23 (74%)	34 (79%)	58 (88%)	7 (100%)
Drug-related	24 (77%)	41 (95%)	65 (98%)	4 (57%)
Leading to Withdrawal	0	0	0	0
Fatal	0	0	0	0
Number of occurrences				
n	31	43	66	7
One	22 (71%)	27 (63%)	30 (45%)	4 (57%)
Two	4 (13%)	8 (19%)	17 (26%)	1 (14%)
Three or more	5 (16%)	8 (19%)	19 (29%)	2 (29%)

	Dabrafenib + Trametinib (N=994)	Dabrafenib Monotherapy (N=398)	Vemurafenib Monotherapy (N=349)	Placebo (N=432)
Outcome				
n	31	43	66	7
Recovered/resolved	29 (94%)	40 (93%)	64 (97%)	7 (100%)
Recovering/resolving	0	0	0	0
Not recovered/not resolved	2 (6%)	4 (9%)	4 (6%)	0
Recovered/resolved with sequelae	1 (3%)	1 (2%)	1 (2%)	1 (14%)
Fatal	0	0	0	0
Maximum Grade				
n	31	43	66	7
Grade 1	5 (16%)	2 (5%)	1 (2%)	1 (14%)
Grade 2	9 (29%)	3 (7%)	2 (3%)	2 (29%)
Grade 3	17 (55%)	38 (88%)	62 (94%)	4 (57%)
Grade 4	0	0	1 (2%)	0
Grade 5	0	0	0	0
Action(s) Taken				
n	31	43	66	7
Investigational product withdrawn	0	0	1 (2%)	0
Dose reduced	0	0	0	0
Dose increased	0	0	0	0
Dose not changed	27 (87%)	43 (100%)	61 (92%)	6 (86%)
Dose interrupted/delayed	0	0	2 (3%)	0
Not applicable*	7 (23%)	0	5 (8%)	3 (43%)

Source: Table 8.0109
* Not applicable: treatment was already interrupted or discontinued at time of event reported.
Subject may be included in more than 1 category for event characteristics, outcome and action taken

The summary of time to onset of first occurrence of cuSCC is unchanged from the 2019 report. The median time to onset for the first occurrence of cuSCC was longer in the combination therapy group compared to the monotherapy groups or the placebo group: 45% (14/31) of subjects experiencing cuSCC in the combination therapy group had times to onset approximately 15 months (66 weeks) or later following treatment initiation as compared to the monotherapy and placebo groups, where majority of subjects experiencing cuSCC had times to onset of the first occurrence within the first 9 months (36 weeks) of treatment initiation (Table 7-3).

Table 7-3 Summary of onset of first occurrence of cutaneous squamous cell carcinoma including keratoacanthomas – safety set

	Dabrafenib + Trametinib (N=994)	Dabrafenib Monotherapy (N=398)	Vemurafenib Monotherapy (N=349)	Placebo (N=432)
Number of subjects with event	**31 (3%)**	**43 (11%)**	**66 (19%)**	**7 (2%)**
Time of onset of first occurrence, weeks				
n	**31**	**43**	**66**	**7**
1-<6	0	12 (28%)	12 (18%)	0
6-<12	2 (6%)	9 (21%)	26 (39%)	1 (14%)
12-<18	4 (13%)	8 (19%)	8 (12%)	0
18-<24	3 (10%)	6 (14%)	6 (9%)	1 (14%)
24-<30	2 (6%)	1 (2%)	6 (9%)	0
30-<36	2 (6%)	1 (2%)	2 (3%)	2 (29%)
36-<42	1 (3%)	0	2 (3%)	1 (14%)
42-<48	1 (3%)	1 (2%)	0	0
48-<54	1 (3%)	0	1 (2%)	0
54-<60	0	0	1 (2%)	1 (14%)
60-<66	1 (3%)	1 (2%)	1 (2%)	1 (14%)
>=66	14 (45%)	4 (9%)	1 (2%)	0
Mean	**81.7**	**22.4**	**17.0**	**35.9**
SD	**72.24**	**31.29**	**19.85**	**20.40**
Median	**52.0**	**12.0**	**10.1**	**33.6**
Min.	**8**	**1**	**2**	**7**
Max.	**237**	**136**	**139**	**65**

Source: Table 8.0110

Additional information on tumor characteristics from subjects treated with dabrafenib (combination or monotherapy) is provided in Appendix 2 (MEK115306), Appendix 3 (MEK116513), Appendix 4 (BRF113683) and Appendix 5 (BRF115532). Pathology reports were generally not provided for events of keratoacanthoma. Although data on BRAF or RAS mutation status are not available for these tumors, published studies indicate that a significant proportion of keratoacanthoma and SCCs from BRAF inhibitor treated subjects contain activating RAS mutations (Gibney et al 2013).

7.2 Basal Cell Carcinoma

BCC has primary risk factors (age, UV exposure, light coloration) that are very common in patients with melanoma. Genetic mutations associated with BCC (hedgehog pathway) (Epstein 2008) are not known to be impacted by dabrafenib. In contrast to squamous cell

carcinoma, accelerated progression of existing BCC lesions during treatment has not been demonstrated.

In this final analysis, the number of subjects with BCC is unchanged from the 2019 report. One subject in the placebo group ([redacted]) had a second reported BCC, which was previously reported as skin cancer in the Other secondary malignancies category. This event was re-coded to BCC since the 2019 report. The maximum grade was unchanged (Listing 28.9002).

The incidence of BCC was higher in subjects receiving dabrafenib combination therapy than those receiving monotherapy, vemurafenib or placebo. The majority of subjects with BCC events in combination therapy, dabrafenib monotherapy and vemurafenib groups had events that were grade 3, and serious per protocol definition in MEK115306, MEK116513 and BRF115532; BCC was not a protocol specified SAE in BRF113683.

In general, the characteristics of reported BCC are unchanged from the 2019 report. For the majority of subjects in the monotherapy groups and 46% of subjects in combination therapy and 50% of subjects in placebo groups, BCC was drug-related. Most subjects experiencing BCC had a single occurrence and for most, the events resolved following excision. All subjects continued without dose modification or discontinuation of study drug in each treatment groups (Table 7-4).

8 subjects receiving combination therapy experienced an event of BCC after treatment discontinuation (Listing 28.9002):

- [redacted] seven events on Study Days 105, 226, 247, 275, 304, 373 and 443; 79, 200, 221, 249, 278, 347 and 417 days, respectively, after discontinuation
- [redacted] two events on Study Days 1066 and 1703; 730 and 1367 days, respectively, after discontinuation
- [redacted] two events on Study Days 519 and 1184; 183 and 848 days, respectively, after discontinuation
- [redacted] on Study Day 920; 585 days after discontinuation
- [redacted] five events on Study Days 1181 (2 events), 1345, 1510, and 1885; 848, 1012, 1177, and 1552 days, respectively, after discontinuation
- [redacted] on Study Day 341; 4 days after discontinuation
- [redacted] on Study Day 1016; 849 days after discontinuation
- [redacted] on Study Day 845; 476 days after discontinuation

1 subject receiving vemurafenib experienced an event of BCC after treatment discontinuation (Listing 28.9002).

4 subjects receiving placebo experienced an event of BCC after treatment discontinuation (Listing 28.9002):

- [redacted] on Study Day 1187; 852 days after discontinuation
- [redacted] on Study Day 904; 568 days after discontinuation, and on Study Day1352, 1016 days after discontinuation
- [redacted] on Study Day 1618; 1287 days after discontinuation
- [redacted] on Study Day 1176; 842 days after discontinuation

Table 7-4 Summary of characteristics of basal cell carcinoma – safety set

	Dabrafenib + Trametinib (N=994)	Dabrafenib Monotherapy (N=398)	DTIC (N=59)	Vemurafenib Monotherapy (N=349)	Placebo (N=432)
Number of Subjects with Event	41 (4%)	26 (7%)	1 (2%)	6 (2%)	16 (4%)
Number of Events	70	36	1	6	17
Event Characteristics					
n	41	26	1	6	16
Serious	22 (54%)	20 (77%)	0	6 (100%)	5 (31%)
Drug-related	19 (46%)	18 (69%)	0	4 (67%)	8 (50%)
Leading to Withdrawal	0	0	0	0	0
Fatal	0	0	0	0	0
Number of occurrences					
n	41	26	1	6	16
One	28 (68%)	18 (69%)	1 (100%)	6 (100%)	15 (94%)
Two	5 (12%)	6 (23%)	0	0	1 (6%)
Three or more	8 (20%)	2 (8%)	0	0	0
Outcome					
n	41	26	1	6	16
Recovered/resolved	40 (98%)	25 (96%)	1 (100%)	6 (100%)	16 (100%)
Recovering/resolving	1 (2%)	0	0	0	0
Not recovered/not resolved	2 (5%)	0	0	0	1 (6%)
Recovered/resolved with sequelae	1 (2%)	1 (4%)	0	0	0
Fatal	0	0	0	0	0
Maximum Grade					
n	41	26	1	6	16
Grade 1	5 (12%)	4 (15%)	1 (100%)	0	5 (31%)
Grade 2	15 (37%)	1 (4%)	0	0	5 (31%)
Grade 3	20 (49%)	21 (81%)	0	5 (83%)	6 (38%)
Grade 4	1 (2%)	0	0	1 (17%)	0
Grade 5	0	0	0	0	0

	Dabrafenib + Trametinib (N=994)	Dabrafenib Monotherapy (N=398)	DTIC (N=59)	Vemurafenib Monotherapy (N=349)	Placebo (N=432)
Action(s) Taken					
n	41	26	1	6	16
Investigational product withdrawn	0	0	0	0	0
Dose reduced	0	0	0	0	0
Dose increased	0	0	0	0	0
Dose not changed	36 (88%)	26 (100%)	1 (100%)	5 (83%)	12 (75%)
Dose interrupted/delayed	0	0	0	0	0
Not applicable*	8 (20%)	0	0	1 (17%)	4 (25%)

Source: Table 8.0111
* Not applicable: treatment was already interrupted or discontinued at time of event reported.
Subject may be included in more than 1 category for event characteristics, outcome and action taken.

The summary of time to onset of first occurrence of BCC is unchanged from the 2019 report. The median time to onset for the first occurrence of BCC was 29.0 weeks in the combination therapy group, 23.8 weeks in the dabrafenib monotherapy group, 30.6 weeks in the vemurafenib group, and 31.9 weeks in the placebo group (Table 7-5). Approximately 34% of subjects experiencing BCC in the combination therapy group and approximately 27% and 25% of subjects experiencing BCC in the dabrafenib monotherapy and placebo groups, respectively had times to onset for the first occurrence of approximately 15 months (66 weeks) or later following treatment initiation.

Table 7-5 Summary of onset of first occurrence of basal cell carcinoma – safety set

	Dabrafenib + Trametinib (N=994)	Dabrafenib Monotherapy (N=398)	DTIC (N=59)	Vemurafenib Monotherapy (N=349)	Placebo (N=432)
Number of subjects with event	**41 (4%)**	**26 (7%)**	**1 (2%)**	**6 (2%)**	**16 (4%)**
Time of onset of first occurrence, weeks					
n	**41**	**26**	**1**	**6**	**16**
1-<6	2 (5%)	5 (19%)	0	1 (17%)	0
6-<12	5 (12%)	3 (12%)	0	0	4 (25%)
12-<18	8 (20%)	3 (12%)	0	2 (33%)	3 (19%)
18-<24	2 (5%)	2 (8%)	0	0	0
24-<30	4 (10%)	1 (4%)	0	0	0
30-<36	1 (2%)	2 (8%)	1 (100%)	0	2 (13%)
36-<42	1 (2%)	0	0	0	2 (13%)

	Dabrafenib + Trametinib (N=994)	Dabrafenib Monotherapy (N=398)	DTIC (N=59)	Vemurafenib Monotherapy (N=349)	Placebo (N=432)
42-<48	1 (2%)	0	0	1 (17%)	1 (6%)
48-<54	3 (7%)	0	0	0	0
54-<60	0	2 (8%)	0	0	0
60-<66	0	1 (4%)	0	0	0
>=66	14 (34%)	7 (27%)	0	2 (33%)	4 (25%)
Mean	**56.5**	**45.9**	**35.0**	**58.5**	**60.3**
SD	**59.08**	**50.40**		**62.49**	**71.63**
Median	**29.0**	**23.8**	**35.0**	**30.6**	**31.9**
Min.	**4**	**3**	**35**	**3**	**8**
Max.	**281**	**193**	**35**	**156**	**231**

Source: Table 8.0112

Additional information on tumor characteristics from subjects treated with dabrafenib (monotherapy or combination) is provided in Appendix 6 (MEK115306), Appendix 7 (MEK116513), Appendix 8 (BRF113683) and Appendix 9 (BRF115532). Most cases where information was provided, events of BCC were treated by surgical excision. Pathology reports were generally not provided for events of BCC in BRF113683.

7.3 New Primary Melanoma

A possible mechanistic relationship between new primary melanoma and BRAF inhibitor treatment has been identified (Zimmer et al 2012). The authors evaluated 22 melanocytic lesions amongst 19 subjects treated with BRAF inhibitors compared with 22 common nevi of 21 subjects with no BRAF inhibitor treatment. All melanocytic lesions when BRAF mutation status was available were BRAF wild type; expression of cyclin D1 and pAKT was increased in newly developed primary melanomas compared with nevi. The mechanism of action was hypothesized to be paradoxical activation of the MAPK pathway accelerating the development of pre-existing lesions.

One subject in the combination treatment group ([redacted], previously reported here, was removed from the data set after the report was queried. In addition, a first secondary malignancy (malignant melanoma) was reported for another subject ([redacted]) in the same treatment group. Therefore, in this final analysis, the number of subjects with new primary melanoma is unchanged from the 2019 report. New primary melanoma events occurred at a low frequency (1 to 3%) in all treatment groups (Table 7-6).

Table 7-6 Summary of new primary melanoma events – safety set

Tumor Type Preferred Term	Dabrafenib + Trametinib (N=994)	Dabrafenib Monotherapy (N=398)	DTIC (N=59)	Vemurafenib Monotherapy (N=349)	Placebo (N=432)
New Primary Malignant Melanoma					
Any event	**17 (2%)**	**10 (3%)**	**1 (2%)**	**10 (3%)**	**13 (3%)**
Malignant melanoma	16 (2%)	5 (1%)	0	7 (2%)	8 (2%)
Malignant melanoma in situ	0	4 (1%)	0	2 (<1%)	4 (<1%)
Lentigo maligna	0	0	0	1 (<1%)	1 (<1%)
Malignant melanoma stage I	0	0	1 (2%)	0	0
Superficial spreading melanoma stage unspecified	1 (<1%)	1 (<1%)	0	0	0

Source: Table 8.0105

All subjects experienced events that were considered serious except for 1 subject in the dabrafenib monotherapy group (previously reported) and 1 subject in the placebo group. Most subjects in all treatment groups had single events, and most recovered following excision of the melanoma. The maximum grade in all treatment groups was grade 3, compared to maximum grade 4 in the 2019 report. The malignant melanoma previously reported for Subject [redacted] was grade 4; as previously noted, that report was removed from the database . The majority of subjects with new primary melanoma did not require dose modification or discontinuation of study drug. One subject in the vemurafenib arm (previously reported), and two subjects in the placebo arm were withdrawn from treatment due to new primary melanoma (Table 7-7).

12 subjects receiving combination therapy experienced an event of new primary melanoma after treatment discontinuation (the subject first reported in this report in italics; Listing 28.9002):

- [redacted] on Study Day 1163; 291 days after discontinuation
- [redacted] on Study Day 670, 333 days after discontinuation
- [redacted] on Study Day 860; 718 days after discontinuation
- [redacted] on Study Day 744; 410 days after discontinuation
- [redacted] on Study Day 773; 438 days after discontinuation
- [redacted] on Study Day 779; 443 days after discontinuation
- [redacted] on Study Day 499; 164 days after discontinuation
- [redacted] on Study Day 685; 350 days after discontinuation
- [redacted] on Study Day 421; 86 days after discontinuation
- [redacted] on Study Day 1456; 1171 days after discontinuation
- [redacted] on Study Day 500; 166 days after discontinuation
- [redacted] *on Study Day 2169; 2045 days after discontinuation*

7 subjects receiving placebo experienced an event of new primary melanoma after treatment discontinuation (Listing 28.9002):

- [redacted] on Study Day 1650, 1597 days after discontinuation
- [redacted] on Study Day 804; 470 days after discontinuation
- [redacted] on Study Day 525; 189 days after discontinuation
- [redacted] on Study Day 427; 93 days after discontinuation
- [redacted] on Study Day 1352; 1016 days after discontinuation
- [redacted] on Study Day 121; 38 days after discontinuation
- [redacted] on Study Day 1849; 1505 days after discontinuation

Table 7-7 Summary of characteristics of new primary melanoma – safety set

	Dabrafenib + Trametinib (N=994)	Dabrafenib Monotherapy (N=398)	DTIC (N=59)	Vemurafenib Monotherapy (N=349)	Placebo (N=432)
Number of Subjects with Event	**17 (2%)**	**10 (3%)**	**1 (2%)**	**10 (3%)**	**13 (3%)**
Number of Events	**18**	**10**	**1**	**15**	**14**
Event Characteristics					
n	17	10	1	10	13
Serious	17 (100%)	9 (90%)	1 (100%)	10 (100%)	12 (92%)
Drug-related	4 (24%)	8 (80%)	0	9 (90%)	4 (31%)
Leading to Withdrawal	0	0	0	0	0
Fatal	0	0	0	0	0
Number of occurrences					
n	17	10	1	10	13
One	16 (94%)	10 (100%)	1 (100%)	8 (80%)	12 (92%)
Two	1 (6%)	0	0	1 (10%)	1 (8%)
Three or more	0	0	0	1 (10%)	0
Outcome					
n	17	10	1	10	13
Recovered/resolved	14 (82%)	10 (100%)	1 (100%)	10 (100%)	13 (100%)
Recovering/resolving	0	0	0	0	0
Not recovered/not resolved	1 (6%)	0	0	0	0
Recovered/resolved with sequelae	2 (12%)	0	0	0	0
Fatal	0	0	0	0	0
Maximum Grade					
n	16	10	1	10	12
Grade 1	0	2 (20%)	0	0	1 (8%)
Grade 2	3 (19%)	2 (20%)	1 (100%)	0	5 (42%)
Grade 3	13 (81%)	6 (60%)	0	10 (100%)	6 (50%)

	Dabrafenib + Trametinib (N=994)	Dabrafenib Monotherapy (N=398)	DTIC (N=59)	Vemurafenib Monotherapy (N=349)	Placebo (N=432)
Grade 4	0	0	0	0	0
Grade 5	0	0	0	0	0
Action(s) Taken					
n	17	10	1	10	13
Investigational product withdrawn	0	0	0	1 (10%)	2 (15%)
Dose reduced	0	0	0	0	0
Dose increased	0	0	0	0	0
Dose not changed	6 (35%)	10 (100%)	1 (100%)	9 (90%)	4 (31%)
Dose interrupted/delayed	1 (6%)	0	0	1 (10%)	0
Not applicable*	10 (59%)	0	0	0	7 (54%)

Source: Table 8.0113
* Not applicable: treatment was already interrupted or discontinued at time of event reported.
A subject may be included in more than 1 category for event characteristics, outcome and action taken

In this final analysis, there are some changes for time to onset of new primary melanoma in the combination therapy group, compared to the 2019 report. The mean, SD, median and maximum time to onset are higher than in the 2019 report. The median time to onset increased from 95.7 weeks to 97.9 weeks, while the maximum time to onset increased from 208 to 310 weeks. The median time to onset for development of new primary melanoma was longer for the combination therapy group, 97.9 weeks, than for the other groups (Table 7-8).

Table 7-8 Summary of onset of first occurrence of new primary melanoma – safety set

	Dabrafenib + Trametinib (N=994)	Dabrafenib Monotherapy (N=398)	DTIC (N=59)	Vemurafenib Monotherapy (N=349)	Placebo (N=432)
Number of subjects with event	**17 (2%)**	**10 (3%)**	**1 (2%)**	**10 (3%)**	**13 (3%)**
Time of onset of first occurrence, weeks					
n	17	10	1	10	13
1-<6	1 (6%)	1 (10%)	1 (100%)	2 (20%)	0
6-<12	0	4 (40%)	0	4 (40%)	4 (31%)
12-<18	1 (6%)	0	0	1 (10%)	2 (15%)
18-<24	0	1 (10%)	0	0	1 (8%)
24-<30	0	0	0	1 (10%)	0
30-<36	1 (6%)	1 (10%)	0	0	0
36-<42	0	0	0	0	0

	Dabrafenib + Trametinib (N=994)	Dabrafenib Monotherapy (N=398)	DTIC (N=59)	Vemurafenib Monotherapy (N=349)	Placebo (N=432)
42-<48	1 (6%)	1 (10%)	0	0	0
48-<54	0	0	0	0	0
54-<60	0	0	0	0	0
60-<66	1 (6%)	0	0	1 (10%)	1 (8%)
>=66	12 (71%)	2 (20%)	0	1 (10%)	5 (38%)
Mean	**107.1**	**31.8**	**2.3**	**26.8**	**79.6**
SD	**76.87**	**32.93**		**36.27**	**93.19**
Median	**97.9**	**14.9**	**2.3**	**9.6**	**23.7**
Min.	**4**	**5**	**2**	**3**	**7**
Max.	**310**	**95**	**2**	**116**	**264**

Source: Table 8.0114

Additional information on the reported events of new primary melanoma is provided in Appendix 10 (MEK115306), Appendix 11 (MEK116513), Appendix 12 (BRF113683) and Appendix 13 (BRF115532). Most subjects for who treatment information is available were treated by surgical excision.

7.4 Other treatment-emergent secondary malignancies

Secondary malignancies including those with RAS mutation, such as chronic myelomonocytic leukemia and adenocarcinoma of the colon metastatic to the brain, have been described in subjects receiving BRAF inhibitors. The mechanistic basis of these malignancies is believed to be paradoxical activation of the MAPK pathway resulting in accelerated growth of pre-existing RAS mutant cells (Gibney et al 2013 and Su et al 2012).

The overall incidence of "other" treatment-emergent malignancies was low in all treatment arms (Table 7-9). The number of subjects in the placebo group with an event in this category increased from 5 to 6 since the last report. One subject, who previously had a BCC event, had a new event of neoplasm reported since the 2019 report (Listing 28.9002).

The PTs for two events in the Other treatment emergent secondary malignancies category have changed since the last report:

- A PT of mycosis fungoides Stage 1 was reported for a subject in the dabrafenib monotherapy group (Subject [redacted]) in previous reports. The PT for that event has changed to cutaneous T-cell lymphoma, Stage 1 as a result of the update to MedDRA v. 23.0.
- A PT of skin cancer was reported for a subject in the placebo group (Subject [redacted]) in the 2019 report. The skin cancer PT was re-coded to basal cell carcinoma since the 2019 report. Grade 3 lung adenocarcinoma was also reported for this subject; the removal of the skin cancer report did not affect the number of subjects in this summary.

All subjects with "other" treatment-emergent malignancies had a single event each with the exception of 1 subject receiving combination therapy (discussed in the 2017 report).

Table 7-9 Summary of other treatment-emergent malignancies by tumor type excluding cuSCC, BCC and new primary melanoma – safety set

Tumor Type Preferred Term	**Dabrafenib + Trametinib (N=994)**	**Dabrafenib Monotherapy (N=398)**	**Vemurafenib Monotherapy (N=349)**	**Placebo (N=432)**
Any event	**27 (3%)**	**12 (3%)**	**8 (2%)**	**6 (1%)**
Lung neoplasm malignant	3 (<1%)	0	1 (<1%)	0
Breast cancer	1 (<1%)	2 (<1%)	0	0
Lung adenocarcinoma	2 (<1%)	0	0	1 (<1%)
Neoplasm	1 (<1%)	0	1 (<1%)	1 (<1%)
Adenocarcinoma of colon	1 (<1%)	0	0	1 (<1%)
Endometrial adenocarcinoma	2 (<1%)	0	0	0
Lymphoma	2 (<1%)	0	0	0
Papillary thyroid cancer	1 (<1%)	1 (<1%)	0	0
Prostate cancer	2 (<1%)	0	0	0
Renal cell carcinoma	2 (<1%)	0	0	0
Transitional cell carcinoma	0	1 (<1%)	1 (<1%)	0
Acute myeloid leukaemia	1 (<1%)	0	0	0
Adenocarcinoma	1 (<1%)	0	0	0
Adenocarcinoma gastric	0	1 (<1%)	0	0
Adenocarcinoma of the cervix	0	1 (<1%)	0	0
Astrocytoma	0	0	1 (<1%)	
B-cell lymphoma	1 (<1%)	0	0	0
Bile duct adenocarcinoma	0	1 (<1%)	0	0
Bladder transitional cell carcinoma	0	0	0	1 (<1%)
Carcinoma in situ	0	0	1 (<1%)	0
Chronic myeloid leukaemia	1 (<1%)	0	0	0
Cutaneous T-cell lymphoma stage I	0	1 (<1%)	0	0
Diffuse large B-cell lymphoma	1 (<1%)	0	0	0
Dysplastic naevus syndrome	1 (<1%)	0	0	0
Hodgkin's disease	0	1 (<1%)	0	0
Intraductal papillary-mucinous carcinoma of pancreas	1 (<1%)	0	0	0

Tumor Type Preferred Term	**Dabrafenib + Trametinib (N=994)**	**Dabrafenib Monotherapy (N=398)**	**Vemurafenib Monotherapy (N=349)**	**Placebo (N=432)**
Intraductal proliferative breast lesion	1 (<1%)	0	0	0
Invasive ductal breast carcinoma	0	1 (<1%)	0	0
Neoplasm malignant	0	0	1 (<1%)	0
Osteosarcoma	1 (<1%)	0	0	0
Pancreatic carcinoma	0	0	0	1 (<1%)
Penile neoplasm	1 (<1%)	0	0	0
Phaeochromocytoma	1 (<1%)	0	0	0
Rectal adenocarcinoma	0	0	1 (<1%)	0
Renal cancer	0	0	0	1 (<1%)
Salivary gland neoplasm	0	0	1 (<1%)	0
Soft tissue sarcoma	0	1 (<1%)	0	0
Ulcerated haemangioma	0	1 (<1%)	0	0

Source: Table 8.0105

The majority of the subjects experienced "other" treatment-emergent malignancies that were grade 3 or higher. Two subjects: one from dabrafenib monotherapy (previously discussed in 2017 report) and another from placebo experienced AEs that were fatal (bile duct adenocarcinoma and pancreatic carcinoma, respectively). Approximately half of the subjects with events recovered (Table 7-10).

The study drug was withdrawn for:

- 4 subjects receiving combination therapy (acute myeloid leukemia, osteosarcoma, prostate cancer, and B-cell lymphoma)
- 1 subject receiving placebo (bladder transitional cell carcinoma)
- 4 subjects receiving dabrafenib and 1 subject receiving vemurafenib (all events were discussed in 2017 report)

12 subjects receiving combination therapy experienced an event of "other" treatment-emergent malignancies after treatment discontinuation (Listing 28.9002):

- [redacted] (grade 3 lung adenocarcinoma) on Study Day 1712; 1376 days after discontinuation
- [redacted] (grade 3 adenocarcinoma of colon) on Study Day 2032; 450 days after discontinuation
- [redacted] (grade 2 breast cancer) on Study Day 1476; 581 days after discontinuation
- [redacted] (grade 1 endometrial adenocarcinoma) on Study Day 35; 7 days after discontinuation

- [redacted] (grade 3 chronic myeloid leukemia) on Study Day 1295; 961 days after discontinuation
- [redacted] (grade 3 adenocarcinoma) on Study Day 225; 57 days after discontinuation
- [redacted] (grade 3 lung neoplasm malignant) on Study Day 428; 93 days after discontinuation
- [redacted] (grade 3 lymphoma) on Study Day 453; 118 days after discontinuation
- [redacted] (unknown grade diffuse large B-cell lymphoma) on Study Day 893; 559 days after discontinuation
- [redacted] (3 events: grade 1 neoplasm) on Study Day 619; 250 days after discontinuation
- [redacted] (unknown grade renal cell carcinoma) on Study Day 1246; 910 days after discontinuation
- [redacted] (grade 1intraductal proliferative breast lesion) on Study Day 1124; 789 days after discontinuation

1 subject ([redacted]) had grade 4 endometrial adenocarcinoma on Study Day 339, one day after treatment discontinuation

1 subject receiving dabrafenib monotherapy experienced an event of "other" treatment-emergent malignancies after treatment discontinuation (Listing 28.9002). This event was discussed in the 2017 report.

2 subjects receiving vemurafenib experienced an event of "other" treatment-emergent malignancies after treatment discontinuation (Listing 28.9002). These events were discussed in the 2017 report.

4 subjects receiving placebo experienced an event of "other" treatment-emergent malignancies after treatment discontinuation (the subject first reported in this category is in italics; Listing 28.9002):

- [redacted] (grade 4 adenocarcinoma of colon)on Study Day 569; 233 days after discontinuation
- [redacted] (grade 5 pancreatic carcinoma) on Study Day 865; 529 days after discontinuation
- [redacted] (grade 3 lung adenocarcinoma) on Study Day 1869; 1533 days after discontinuation
- [redacted] *(grade 3 neoplasm) on Study Day 1848; 1514 days after discontinuation*

Table 7-10 Summary of characteristics of other treatment-emergent secondary malignancies – safety set

	Dabrafenib + Trametinib (N=994)	Dabrafenib Monotherapy (N=398)	Vemurafenib Monotherapy (N=349)	Placebo (N=432)
Number of Subjects with Event	**27 (3%)**	**12 (3%)**	**8 (2%)**	**6 (1%)**
Number of Events	**30**	**12**	**8**	**6**
Event Characteristics				
n	27	12	8	6
Serious	22 (81%)	10 (83%)	7 (88%)	6 (100%)
Drug-related	7 (26%)	7 (58%)	4 (50%)	1 (17%)
Leading to Withdrawal	0	0	0	0
Fatal	0	1 (8%)	0	1 (17%)
Number of occurrences				
n	27	12	8	6
One	25 (93%)	12 (100%)	8 (100%)	6 (100%)
Two	1 (4%)	0	0	0
Three or more	1 (4%)	0	0	0
Outcome				
n	27	12	8	6
Recovered/resolved	15 (56%)	8 (67%)	5 (63%)	4 (67%)
Recovering/resolving	1 (4%)	0	0	0
Not recovered/not resolved	11 (41%)	2 (17%)	3 (38%)	1 (17%)
Recovered/resolved with sequelae	0	1 (8%)	0	0
Fatal	0	1 (8%)	0	1 (17%)
Maximum Grade				
n	25	12	8	6
Grade 1	5 (20%)	2 (17%)	0	0
Grade 2	2 (8%)	0	0	0
Grade 3	15 (60%)	9 (75%)	7 (88%)	4 (67%)
Grade 4	3 (12%)	0	1 (13%)	1 (17%)
Grade 5	0	1 (8%)	0	1 (17%)

	Dabrafenib + Trametinib (N=994)	Dabrafenib Monotherapy (N=398)	Vemurafenib Monotherapy (N=349)	Placebo (N=432)
Action(s) Taken				
n	27	12	8	6
Investigational product withdrawn	4 (15%)	4 (33%)	1 (13%)	1 (17%)
Dose reduced	0	0	0	0
Dose increased	0	0	0	0
Dose not changed	6 (22%)	6 (50%)	5 (63%)	0
Dose interrupted/delayed	5 (19%)	1 (8%)	0	1 (17%)
Not applicable*	13 (48%)	1 (8%)	2 (25%)	4 (67%)

Source: Table 8.0115
* Not applicable: treatment was already interrupted or discontinued at time of event reported.
The denominator for each category is the number of subjects with an event.
A subject may be included in more than 1 category for event characteristics, outcome and action taken

The median time to onset for development of "other" treatment-emergent malignancies was longer in the combination therapy group than in the other monotherapy treatment groups. The time to onset values in the placebo group changed due to the addition of one additional subject. The median time to onset in the combination group is 88.4 weeks compared to 102.4 weeks in the placebo group (81.3 weeks in 2019 report; Table 7-11).

Table 7-11 Summary of onset of first occurrence of other treatment-emergent secondary malignancies – safety set

	Dabrafenib + Trametinib (N=994)	Dabrafenib Monotherapy (N=398)	Vemurafenib Monotherapy (N=349)	Placebo (N=432)
Number of subjects with event	**27 (3%)**	**12 (3%)**	**8 (2%)**	**6 (1%)**
Time of onset of first occurrence, weeks				
n	27	12	8	6
1-<6	2 (7%)	0	0	0
6-<12	0	3 (25%)	4 (50%)	0
12-<18	0	0	1 (13%)	1 (17%)
18-<24	1 (4%)	2 (17%)	0	0
24-<30	1 (4%)	1 (8%)	1 (13%)	0
30-<36	2 (7%)	0	0	0
36-<42	1 (4%)	1 (8%)	1 (13%)	1 (17%)
42-<48	2 (7%)	0	0	0
48-<54	1 (4%)	1 (8%)	0	0
54-<60	0	0	0	0

	Dabrafenib + Trametinib (N=994)	Dabrafenib Monotherapy (N=398)	Vemurafenib Monotherapy (N=349)	Placebo (N=432)
60-<66	2 (7%)	0	0	0
>=66	15 (56%)	4 (33%)	1 (13%)	4 (67%)
Mean	**114.3**	**60.0**	**23.0**	**130.9**
SD	**88.48**	**63.76**	**21.37**	**111.01**
Median	**88.4**	**32.4**	**13.2**	**102.4**
Min.	**4**	**6**	**8**	**12**
Max.	**290**	**193**	**69**	**267**

Source: Table 8.0116

Additional characterization for the reported events of "other" treatment-emergent malignancies is shown in Appendix 14 (MEK115306), Appendix 15 (MEK116513), Appendix 16 (BRF113683) and Appendix 17 (BRF115532).

8 Summary and conclusions

In this 8th and final report, no new risk was identified with regards to treatment-emergent secondary malignancies in subjects receiving dabrafenib monotherapy or in combination with trametinib. Subjects with treatment-emergent malignancies received approximately the full treatment dose and the median duration of treatment was generally longer as compared to subjects who did not experience secondary malignancies.

Clinical data from all studies included are mature; each had more than 5 years follow-up. Studies MEK115306 and MEK116513 are completed and have been reported. Study BRF115532 began enrollment in 2013, and its primary analysis was completed in 2017; follow-up is ongoing.

Events of secondary malignancies generally occurred later in the combination therapy group (median time to onset from 29 weeks for BCC and 98 weeks for melanoma, post-treatment initiation) as compared to the monotherapy groups (median time to onset from 10 weeks to 32 weeks post-treatment initiation). In general, subjects experiencing cuSCC, BCC or new primary melanoma continued on treatment without dose modification and most cutaneous events resolved with surgical excision. One patient with a bile duct adenocarcinoma in the dabrafenib monotherapy group died.

In conclusion, treatment-emergent secondary malignancies have been reported in subjects with unresectable or metastatic melanoma receiving dabrafenib plus trametinib combination therapy or dabrafenib monotherapy in studies MEK115306, MEK116513, BRF113683 and BRF115532. From this analysis, the following have been noted:

- The incidences of cuSCC (including keratoacanthoma), BCC, new primary melanoma and "other" treatment-emergent malignancies described in this report have remained generally consistent with those reported previously for subjects receiving dabrafenib as monotherapy or in combination with trametinib.

- The frequency of each type of secondary malignancy described in this report, particularly cuSCC, is lower in subjects receiving combination therapy than in those receiving BRAF inhibitor monotherapy.
- The median time to onset for the first occurrence of cuSCC, BCC, new primary melanoma or "other" treatment-emergent secondary malignancies is later for subjects receiving combination therapy than for those receiving dabrafenib monotherapy.
- The occurrence of "other" treatment-emergent secondary malignancies and new primary melanomas remained low in both treatment groups. No specific pattern was identified in "other" treatment-emergent secondary malignancies in either treatment group in terms of affected organ or site.
- No new risk factors for secondary malignancies have been identified for this patient population.
- No changes to monitoring guidelines or dose modifications for secondary malignancies are required based on the data in this final report.

Skin cancers occur with BRAF inhibitor monotherapy because of paradoxical activation of the MAPK pathway in keratinocytes. This can be blocked by the addition of a MEK inhibitor. The skin cancers and "other" treatment-emergent malignancies described in this report are unlikely to affect the overall prognosis for the patient population under study, and most did not require interruption of treatment. Thus, the benefit-risk of dabrafenib combination or dabrafenib monotherapy for the treatment of subjects with metastatic melanoma remains positive.

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