26 July 2018
EMA/550929/2019
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Mekinist

International non-proprietary name: trametinib

Tafinlar

International non-proprietary name: dabrafenib

Procedure No. EMEA/H/C/WS1274

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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List of abbreviations

AE	Adverse Event
AESI	Adverse Event of Special Interest
AJCC	American Joint Committee on Cancer
ALT	Alanine Aminotransferase
ANC	Absolute Neutrophil Count
AST	Aspartate Aminotransferase
BCC	Basal Cell Carcinoma
BID	Twice a day
cfDNA	Cell-free DNA
CI	Confidence Interval
CR	Complete Response
CRO	Clinical Research Organization
CSR	Central Serous Retinopathy
CT	Computed Tomography
CTCAE	Common Terminology Criteria for Adverse Events
cuSCC	Cutaneous Squamous Cell Carcinoma
DMFS	Distant Metastasis-Free Survival
D+T	Dabrafenib plus Trametinib combination therapy
ECG	Electrocardiography
ECHO	Echocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
EMA	European Medicines Agency
EQ-5D	EuroQol-5D
ERK	Extracellular Signaling-Regulated Kinase
EU	European Union
FDA	Food and Drug Administration
FFR	Freedom From Relapse
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
HR	Hazard Ratio
HRQoL	Health Related Quality of Life
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
INR	International Normalized Ratio
IRB	Institutional Review Board
ITT	Intent to Treat
IVRS	Interactive Voice Response System
LDH	Lactate Dehydrogenase
LLN	Lower Limit of Normal
LTFU	Lost to Follow-Up
LVEF	Left Ventricular Ejection Fraction
MAH	Marketing Authorisation Holder
MAPK	Mitogen-Activated Protein Kinase
MedDRA	Medical Dictionary for Regulatory Activities
MRI	Magnetic Resonance Imaging
NCI	National Cancer Institute
NE	Not Estimable
ORR	Overall Response Rate
OS	Overall Survival
PD	Progressive Disease or Pharmacodynamics
PFS	Progression-Free Survival
PK	Pharmacokinetics
PT	Preferred Term
QD	Once Daily
QTcB	QT Duration Corrected for Heart Rate by Bazett's Formula
RAMOS	Registration and Medication Ordering System
RAP	Reporting and Analysis Plan
RFS	Relapse-Free Survival
RR	Response Rate

RVO	Retinal Vein Occlusion
SA	Scientific Advice
SAE	Serious Adverse Event
SOC	System Organ Class
ULN	Upper Limit of Normal
WBC	White Blood Cell

1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Novartis Europharm Limited submitted to the European Medicines Agency on 7 November 2017 an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.

The following variation was requested:

Variation requested		Type	Annexes affected
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB

Extension of indication to include the combination adjuvant treatment with trametinib and dabrafenib of adult patients with stage III melanoma with a BRAF V600 mutation, following complete resection. As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1 of the Mekinist and Tafinlar SmPCs are updated. The Package Leaflet and the Risk Management plan (version 14.0 for Mekinist and version 9.0 for Tafinlar, according to GVP module V revision 2) are updated in accordance. In addition, the Worksharing applicant (WSA) took the opportunity to correct some typos throughout the Mekinist and Tafinlar product information, to include a cross reference to the Mekinist SmPC in section 4.6 of the Tafinlar SmPC regarding fertility, to update the list of local representatives for Bulgaria, Hungary, Estonia, Latvia and Lithuania in the Package Leaflet of both products.

The requested worksharing procedure proposed amendments to the Summary of Product Characteristics and Package Leaflet and to the Risk Management Plan (RMP).

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included EMA Decisions P/0259/2017 for Mekinist and P/0206/2017 for Tafinlar on the agreement of a paediatric investigation plan (PIP) and CW/1/2011 on the granting of a class waiver.

At the time of submission of the application, the PIP P/0259/2017 for Mekinist and P/0206/2017 for Tafinlar were not yet completed as some measures were deferred.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

Scientific advice

The applicant did seek Scientific Advice at the CHMP on the non-clinical and clinical development on 21 June 2012 and 18 May 2017.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP for the WS procedure were:
Rapporteur: Paula Boudewina van Hennik Co Rapporteur: Filip Josephson

Timetable	Actual dates
Submission date	7 November 2017
Start of procedure	25 November 2017
CHMP Lead WS Co-Rapporteur Assessment Report	19 January 2018
CHMP Lead WS Rapporteur Assessment Report	17 January 2018
PRAC Lead WS Rapporteur Assessment Report	19 January 2018
PRAC members comments	31 January 2018
Updated PRAC Rapporteur Assessment Report	1 February 2018
PRAC Outcome	8 February 2018
CHMP members comments	12 February 2018
Updated CHMP Lead WS Rapporteurs Joint Assessment Report	15 February 2018
Request for supplementary information (RSI)	22 February 2018
WSA's responses submitted to the CHMP on	27 March 2018
Re-start	2 April 2018
CHMP/PRAC Rapporteurs Joint Assessment Report on the WSA's responses	2 May 2018
PRAC members comments	7 May 2018
Updated PRAC Rapporteur Assessment Report	N/A
PRAC Outcome	17 May 2018
CHMP members comments	22 May 2018
Updated CHMP Lead WS Rapporteurs Joint Assessment Report on the WSA's responses	24 May 2018
Revised 2nd Request for supplementary information	8 June 2018
SAG meeting to address questions raised by the CHMP	18 June 2018
WSA's responses submitted to the CHMP on	26 June 2018
Re-start	27 June 2018
CHMP Rapporteurs Joint Assessment Report on the WSA's responses	11 July 2018
CHMP members comments	16 July 2018
Updated CHMP Lead WS Rapporteurs Assessment Report on the WSA's responses	19 July 2018
Opinion	26 July 2018

2. Scientific discussion

2.1. Introduction

Melanoma

Melanoma is a malignant tumour that originates from melanocytic cells and primarily involves the skin. Melanoma is potentially the most dangerous form of skin tumour and causes 90% of skin cancer mortality[1].

The incidence of malignant melanoma in the EU varies from 3 to 5/100,000/year in Mediterranean countries to 12-12 in Nordic countries[2]. The incidence of melanoma is increasing worldwide in white populations, [3] .

About 90% of melanomas are diagnosed as primary tumours without any evidence of metastasis. The 10-year survival for early stage melanoma is 75-85%. The most important histological prognostic factors for primary melanoma without metastases are vertical tumour thickness (Breslow's depth), presence of ulceration, mitotic rate and level of invasion (Clark's level). Moreover, prognosis is poorer when patients are older or male and when the tumour is located on the trunk, head and neck tumours compared to melanomas on the limbs.

Melanomas can metastasise either by the lymphatic or the haematogenous route. About two-thirds of metastases are originally confined to the drainage area of regional lymph nodes. A regional metastasis can appear as satellite metastases (up to 2 cm from the primary tumour), in-transit metastases (located in the skin between 2 cm from the site of the primary tumour and the first draining lymph node), micrometastasis in the regional lymph nodes (identified via sentinel lymph node biopsy) and clinically recognisable regional lymph node metastases.

The 10-year survival is 30-50% for patients with satellite and in-transit metastases, 30-70% for patients with lymph node micrometastases and 20-40% for those with clinically apparent regional lymph node metastases. With distant metastases, prognosis is poor with a median survival in untreated patients of 6-9 months.

Staging is based upon the American Joint Committee on Cancer (AJCC) system, which was recently updated to the eighth edition. Key changes in the eighth edition AJCC Cancer Staging Manual include:

- Tumor thickness measurements to be recorded to the nearest 0.1 mm, not 0.01 mm;
- Definitions of T1a and T1b are revised (T1a, <0.8 mm without ulceration; T1b, 0.8-1.0 mm with or without ulceration or <0.8 mm with ulceration), with mitotic rate no longer a T category criterion;
- Pathological (but not clinical) stage IA is revised to include T1b N0 M0 (formerly pathologic stage IB);
- The N category descriptors "microscopic" and "macroscopic" for regional node metastasis are redefined as "clinically occult" and "clinically apparent";

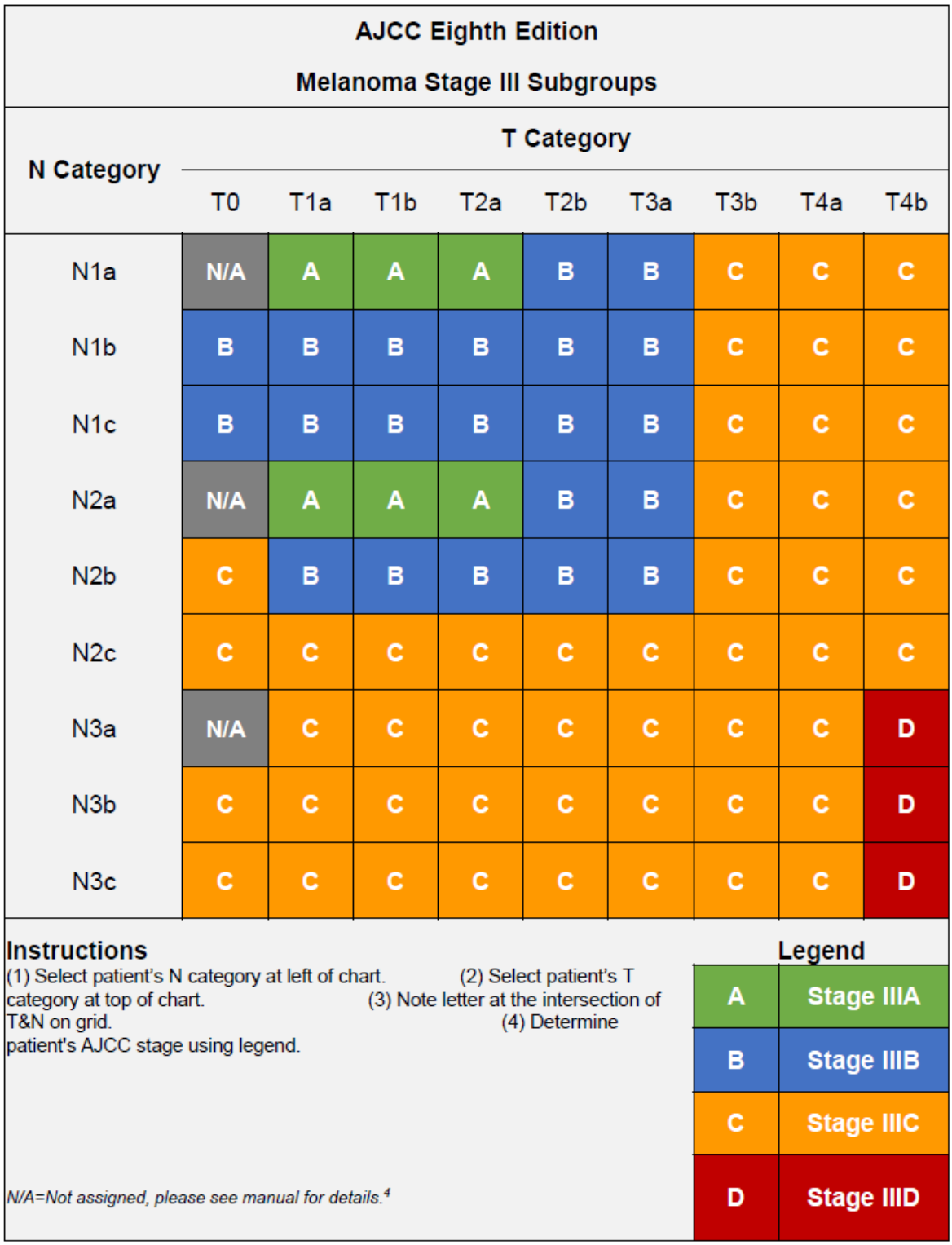
[1] Garbe C, Peris K, Hauschild A, Saiag P, Middleton M, Bastholt L, Grob JJ, Malvehy J, Newton-Bishop J, Stratigos AJ, Pehamberger H, Eggermont AM; European Dermatology Forum (EDF); European Association of Dermato-Oncology (EADO); European Organisation for Research and Treatment of Cancer (EORTC). Diagnosis and treatment of melanoma. European consensus-based interdisciplinary guideline - Update 2016. Eur J Cancer. 2016 Aug;63:201-17.
[2] Dummer R, Hauschild A, Lindenblatt N, Pentheroudakis G, Keilholz U; ESMO Guidelines Committee. Cutaneous melanoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2015 Sep;26 Suppl 5:v126-32
[3] van Zeijl MC, van den Eertwegh AJ, Haanen JB, Wouters MW. (Neo)adjuvant systemic therapy for melanoma. Eur J Surg Oncol. 2017 Mar;43(3):534-543

- Prognostic stage III groupings are based on N category criteria and T category criteria (i.e., primary tumor thickness and ulceration) and increased from 3 to 4 subgroups (stages IIIA-IIID; see also Figure 1);
- Definitions of N subcategories are revised, with the presence of microsatellites, satellites, or in-transit metastases now categorized as N1c, N2c, or N3c based on the number of tumor-involved regional lymph nodes, if any;
- Descriptors are added to each M1 subcategory designation for lactate dehydrogenase (LDH) level (LDH elevation no longer upstages to M1c);
- A new M1d designation is added for central nervous system metastases[4].

With the new prognostic staging in stage 3 (Figure 1), the 5-year melanoma-specific survival rate ranges from 93% in stage IIIA to 32% in stage IIID. In the 7th edition, the 5-year melanoma-specific survival rates for patients with stage IIIA, IIIB, and IIIC were 78%, 59%, and 40%, respectively.

[4] Gershenwald JE, Scolyer RA, Hess KR, Sondak VK, Long GV, Ross MI, Lazar AJ, Faries MB, Kirkwood JM, McArthur GA, Haydu LE, Eggermont AMM, Flaherty KT, Balch CM, Thompson JF; for members of the American Joint Committee on Cancer Melanoma Expert Panel and the International Melanoma Database and Discovery Platform. Melanoma staging: Evidence-based changes in the American Joint Committee on Cancer eighth edition cancer staging manual. CA Cancer J Clin. 2017 Nov;67(6):472-492

Figure 1 AJCC 8th edition stage III subgroups based on T and N categories[4]



AJCC Eighth Edition

Melanoma Stage III Subgroups

N Category	T Category								
	T0	T1a	T1b	T2a	T2b	T3a	T3b	T4a	T4b
N1a	N/A	A	A	A	B	B	C	C	C
N1b	B	B	B	B	B	B	C	C	C
N1c	B	B	B	B	B	B	C	C	C
N2a	N/A	A	A	A	B	B	C	C	C
N2b	C	B	B	B	B	B	C	C	C
N2c	C	C	C	C	C	C	C	C	C
N3a	N/A	C	C	C	C	C	C	C	D
N3b	C	C	C	C	C	C	C	C	D
N3c	C	C	C	C	C	C	C	C	D

Instructions

(1) Select patient's N category at left of chart. (2) Select patient's T category at top of chart. (3) Note letter at the intersection of T&N on grid. (4) Determine patient's AJCC stage using legend.

N/A=Not assigned, please see manual for details.[4]

Legend

A	Stage IIIA
B	Stage IIIB
C	Stage IIIC
D	Stage IIID

BRAF pathway in melanoma

In melanoma, different activating mutations have been described, mainly resulting in an increased signalling of the Mitogen-Activated Protein Kinase (MAPK)-pathway leading to cell proliferation. About 45% of patients with cutaneous melanoma carry an activating BRAF V600 mutation, for which several highly selective inhibitors have been developed in the metastatic setting. Development of secondary resistance to BRAF-inhibitors is a frequent event and hence, the combination with MEK inhibitors significantly increase objective response rate, progression-free and OS compared to single agent BRAF-inhibitory monotherapy. Therefore, the combination of BRAF and MEK-inhibition is the current standard in the treatment of patients with BRAF mutations[5].

Dabrafenib and trametinib are BRAF and MEK-inhibitors currently used to treat cutaneous metastatic melanoma. Dabrafenib is a potent reversible ATP-competitor and selective inhibitor of BRAF kinase activity. Trametinib is a reversible and highly selective allosteric inhibitor of mitogen-activated extracellular signal-regulated kinase (MEK1 and MEK2) activation and kinase activity. Recent 3-year efficacy data in the metastatic setting were published of the double-blind, phase 3 study enrolling previously untreated patients with BRAF V600E/K-mutant unresectable stage IIIC or IV melanoma. Patients were randomised to receive dabrafenib and trametinib or dabrafenib plus placebo. At 3 years PFS was 22% in the combination and 12% in the monotherapy arm. 3-year OS rates were 44% versus 32%, respectively[5].

Current adjuvant treatments for localised Stage III and Stage IV resectable melanoma

Surgery is still the cornerstone of treatment for patients with stage I-IIIB melanoma. Also for locoregional advanced melanomas, surgery alone is standard of care, including resection of satellite or in-transit metastases and regional lymph node dissections once tumour-positive nodes have been detected. However, prognosis for patients with high risk melanoma remains poor with 5-year survival rates of 40 to 80%[3] . Therefore, there is a need for additional adjuvant therapy. Adjuvant therapy can be offered to patients without evidence of macroscopic metastases but at high risk of having microscopic metastases[1].

Chemotherapy

A number of controlled trials with adjuvant chemotherapy in stage II and III patients did not demonstrate any therapeutic advantage. There is as yet no indication for adjuvant systemic chemotherapy for melanoma outside the context of controlled studies[1].

Interferon alpha

Interferon alpha is currently approved in both US and EU for the treatment of stage III melanoma after surgery. It is however not universally used. High-dose interferon alfa-2b was approved more than 20 years ago and has been extensively studied. Overall, high-dose interferon has shown a consistent benefit with respect to relapse (hazard ratios, 0.61 to 0.78). Patients who received pegylated interferon alfa had an improvement in recurrence-free survival versus observation, but no benefit in overall survival. High-dose interferon has been associated with substantial toxic effects, including fatigue, depression, and flulike symptoms. The majority of patients who have received high-dose interferon have not completed 1 year of therapy, and the frequency of grade 3 or 4 adverse events has been more than 65%[6] .

[5] Long GV, Flaherty KT, Stroyakovskiy D, Gogas H, Levchenko E, de Braud F, Larkin J, Garbe C, Jouary T, Hauschild A, Chiarion-Sileni V, Lebbe C, Mandalà M, Millward M, Arance A, Bondarenko I, Haanen JBAG, Hansson J, Utikal J, Ferraresi V, Mohr P, Probachai V, Schadendorf D, Nathan P, Robert C, Ribas A, Davies MA, Lane SR, Legos JJ, Mookerjee B, Grob JJ. Dabrafenib plus trametinib versus dabrafenib monotherapy in patients with metastatic BRAF V600E/K-mutant melanoma: long-term survival and safety analysis of a phase 3 study. Ann Oncol. 2017 Jul 1;28(7):1631-1639

[6] Schuchter LM. Adjuvant Melanoma Therapy - Head-Spinning Progress. N Engl J Med. 2017 Nov 9;377(19):1888-1890

Efficacy of interferon alfa in BRAF-mutated melanoma is unclear. There is preclinical evidence that BRAF mutant melanoma is associated with interferon alpha receptor 1 (IFNAR1) downregulation leading to decreased sensitivity to antitumor effects of IFN alpha[7].

Ipilimumab

In the US adjuvant treatment with ipilimumab is registered based on the results of the EORTC 18071 trial. This was a double-blind, phase 3 trial in patients with stage III cutaneous melanoma (excluding lymph node metastasis ≤ 1 mm or in-transit metastasis) with adequate resection of lymph nodes who had not received previous systemic therapy for melanoma. Patients were randomised between 10 mg/kg ipilimumab (n=475) or placebo (n=476) up to 3 years. The primary endpoint was recurrence-free survival (RFS). At a median follow-up of 5.3 years, RFS was 27.6 months in the ipilimumab group versus 17.1 months in the placebo group (hazard ratio (HR) 0.76; 95%CI 0.64-0.89; p<0.001). The rate of overall survival at 5 years was 65.4% and 54.4% in ipilimumab and the placebo group, respectively (median OS unreliable or not reached; HR 0.72; 95%CI 0.58-0.88; p=0.001). Adverse events of grade 3 or 4 occurred in 54.1% of the patients treated with ipilimumab group and in 26.2% of those in the placebo group. The most common grade 3–4 immune-related adverse events in the ipilimumab group were gastrointestinal (16%), hepatic (11%), and endocrine (8%). Adverse events led to discontinuation of treatment in 52% of the patients treated with ipilimumab and treatment-related deaths were observed (Eggermont Lancet Oncol 2015; Eggermont NEJM 2016). Summarising, although ipilimumab significantly increased RFS, this was accompanied by serious toxicities. In the EU ipilimumab is not approved for adjuvant melanoma.

Nivolumab

Nivolumab is a human immunoglobulin G4 (IgG4) monoclonal antibody (HuMAb), which binds to the programmed death-1 (PD-1) receptor and blocks its interaction with PD-L1 and PD-L2. It has been recently approved for the treatment of adjuvant melanoma in the EU and its approval was based on a randomised phase III study comparing nivolumab vs ipilimumab. The median recurrence-free survival (RFS) was 37.7% in the nivolumab arm compared to 48.8 in the ipilimumab arm, with a HR=0.66 (95%CI 0.54, 0.81, p-value <0.0001). The RFS rate at 24 months was 62.6% (95%CI 57.9, 67.0) compared to 50.2% (95%CI 45.3, 54.8) for nivolumab and ipilimumab, respectively. Also, DMFS was found to be improved in the nivolumab arm with an unstratified HR of 0.76 (96%CI 0.59, 0.98; stratified log-rank p-value = 0.0340). The median OS was not reached but a descriptive OS analysis showed a 12-month OS rate of 96% and a 24-month OS rate of 89% for both nivolumab and ipilimumab.

Developments in adjuvant treatment landscape for melanoma

Currently, many studies are ongoing investigating adjuvant therapy and melanoma. In the previously described ipilimumab trial, the higher 10 mg/kg dose was used. In the ongoing ECOG 1609/NCT 01274338 high-dose interferon treatment is compared with 1 year of treatment with ipilimumab at either 10 mg/kg or 3 mg/kg. Preliminary results show that 10 mg/kg ipilimumab leads to more toxicity than 3 mg/kg, but an unplanned RFS analysis showed no difference in RFS[8] .

Also other immunotherapies are being studies, such as pembrolizumab versus placebo in KEYNOTE-054 and versus adjuvant high dose interferon-alpha in NCT02506153.

[7] Sabbatino F, Wang Y, Scognamiglio G, Favoino E, Feldman SA, Villani V, Flaherty KT, Nota S, Giannarelli D, Simeone E, Anniciello AM, Palmieri G, Pepe S, Botti G, Ascierto PA, Ferrone CR, Ferrone S. Antitumor Activity of BRAF Inhibitor and IFNα Combination in BRAF-Mutant Melanoma. J Natl Cancer Inst. 2016 Feb 5;108(7)

[8] Tarhini AA, Lee SJ, Hodi FS. A phase III randomized study of adjuvant ipilimumab(3 or 10 mg/kg) versus high-dose interferon alfa-2b for resected high-risk melanoma (U.S. Intergroup E1609): Preliminary safety and efficacy of the ipilimumab arms. Abstract ASCO 2017 J Clin Oncol 35; 9500-9500.

Lastly, vemurafenib alone, a BRAF-inhibitor, is studied in the BRIM8 trial. An abstract at ESMO showed an advantage of adjuvant vemurafenib compared to placebo at the primary endpoint DFS in stage IIIC disease. Overall survival could not be determined yet, and further follow-up will follow[9].

About the product

The MAH applied for the following indication:

- Trametinib in combination with dabrafenib is indicated for the adjuvant treatment of adult patients with Stage III melanoma with a BRAF V600 mutation, following complete resection.
- Dabrafenib in combination with trametinib is indicated for the adjuvant treatment of adult patients with Stage III melanoma with a BRAF V600 mutation, following complete resection.

The agreed indication is as follows:

- Trametinib in combination with dabrafenib is indicated for the adjuvant treatment of adult patients with Stage III melanoma with a BRAF V600 mutation, following complete resection.
- Dabrafenib in combination with trametinib is indicated for the adjuvant treatment of adult patients with Stage III melanoma with a BRAF V600 mutation, following complete resection.

Regulatory background dabrafenib and trametinib

The current application concerns the combination adjuvant treatment with trametinib and dabrafenib of adult patients with stage III melanoma with a BRAF V600 mutation, following complete resection. Dabrafenib and trametinb are approved in the European Union (EU) and other countries under the brand names of Tafinlar and Mekinist, respectively, as monotherapies and in combination for the treatment of adult patients with unresectable or metastatic melanoma with a BRAF V600 mutation and for the treatment of adults patients with advanced non-small cell lung cancer with a BRAF V600 mutation.

2.1.1. Non-clinical aspects

No new non-clinical data have been submitted in this application, which was considered acceptable by the CHMP.

2.1.2. Ecotoxicity / environmental risk assessment

Dabrafenib is an orally bioavailable inhibitor of B-Raf (BRAF) protein with potential antineoplastic activity. Trametinib is an orally bioavailable, reversible, highly selective, allosteric inhibitor of mitogen-activated extracellular signal regulated kinase 1 (MEK1) and MEK2. Regarding ERA, the data submitted was in general the same as assessed during the initial MAA for both products. With the extended indication it is the view of the CHMP that neither dabrafenib nor trametinib are expected to pose a risk to the environment.

In the case of trametinib, the PEC was below the trigger value of 0. 01 μg/L and a Phase II assessment was not required. Moreover, trametinib has an octanol-water partition coefficient of 4.04, remaining below the trigger value of 4.5 for a PBT screening. In spite of remaining below the trigger value for a Phase II assessment, a chronic toxicity dataset was submitted. For dabrafenib the

[9] Lewis K, . BRIM8: a randomized, double-blind, placebo-controlled study of adjuvant vemurafenib in patients (pts) with completely resected, BRAFV600+ melanoma at high risk for recurrence. Annals of Oncology 28 (suppl_5): v605-v649.

PECsurface water exceeded the trigger value of 0.01 μg/L and the assessment therefore proceeded to Phase II – Tier A.

Dabrafenib Physico-chemical, fate and effect studies

Study	Findings
Water solubility	6.3 µg/ml (at pH 6.3; 37°C)
n-Octanol-water partition coefficient	log D (pH 5) = 3.229 log D (pH 7) = 3.384 log D (pH 9) = -0.168
Sludge Sorption (OPPTS 835.1110)	Freundlich Sorption Coefficients: Kf = 858 L/kg; Kfoc = 2460 L/kg
Adsorption/Desorption using a batch equilibrium method (OECD 106)	Soil Koc = 1445 – 10615 L/Kg Sediment Koc = 2345 L/Kg
Inherent Biodegradability (OECD 301B/OECD 302C)	Not inherently biodegradable Ultimate biodegradation = 0% Primary degradation = 81%
Transformation in Aquatic Sediment Systems (OECD 308)	DT50 = 162-307 days DT90 = 537 - >1'000 days
Algae Growth Inhibition Test (OECD 201)	72h-NOEC = 0.22 mg/L
Daphnia Reproduction test (OECD 211)	21d-NOEC = 0.0583 mg/L; parental mortality
Fish Early Life Stage Toxicity Test (OECD 210)	28d-NOEC = 1.47 mg/L
Activated Sludge Respiration Inhibition Test (OECD 209)	3h-NOEC = 312.5 mg/L

The Phase II Tier A risk assessment suggests no risk for surface waters, groundwater and microorganisms in sewage treatment plant activated sludge, with the highest risk ratio of 0.00054 found for surface water. Adsorption potential of dabrafenib observed in batch equilibrium studies with sludge remained well below the trigger level for a terrestrial assessment. The study on transformation in a water-sediment study showed significant shifting of dabrafenib into sediment compartments therefore leading to a Tier B risk assessment for sediments. Moreover, the octanol-water partition coefficients for dabrafenib of 3.384 and 3.229 at pH 7 and pH 5, respectively, trigger a bioaccumulation study in Phase II-Tier B of the current risk assessment.

The measured octanol-water partition coefficient (log Dow @pH 7 = 3.384) of dabrafenib is above 3.0 indicating that dabrafenib could have a tendency to sorb to lipid surfaces and therefore could bioaccumulate in the tissues of aquatic organisms. The steady state bioconcentration factors (BCFss) at the end of the uptake phase for the 0.01 mg/L concentrations were 0.836, 9.90 and 4.38, respectively, for edible, non-edible and whole fish tissue and for the 0.1 mg/L concentration 0.779, 8.89 and 3.98, respectively, for edible, non-edible and whole fish tissue. A depuration phase was conducted and the results demonstrate that the radioactivity was rapidly cleared from the fish tissues when the fish were transferred to clean water.

2.1.3. Discussion on non-clinical aspects

In general, the data submitted for the ERA is acceptable. It can be concluded that dabrafenib has limited bioaccumulation potential (BCF < 10).

2.1.4. Conclusion on the non-clinical aspects

The lack on non-clinical data is acceptable as the indication relates to the same disease as the approved indication. In general, the data submitted for the ERA is acceptable. The updated data submitted in this application do not lead to a significant increase in environmental exposure further to the use of dabrafenib and trametinib. Considering the above data, dabrafenib and trametinib should be used according to the precautions stated in the SmPC in order to minimise any potential risks to the environment.

2.2. Clinical aspects

2.2.1. Introduction

To support the extension the company conducted one additional study BRF115532. In this study patients have been treated with dabrafenib 150 mg twice daily in combination with trametinib 2 mg once daily for a duration of 12 months. The clinical dose and schedule for adjuvant treatment of melanoma were based on the currently approved regimen for unresectable or metastatic melanoma with BRAF V600 mutation. The commercial formulations are 50 mg and 75 mg strength dabrafenib capsules and 0.5 mg and 2 mg strength trametinib tablets have been used in Study BRF115532.

GCP

The Clinical trials were performed in accordance with GCP as claimed by the applicant.

The applicant has provided a statement to the effect that clinical trials conducted outside the community were carried **out in accordance with the ethical standards of Directive 2001/20/EC.**

- **Tabular overview of clinical studies**

Table 1: Summary of Study BRF115532

Study type	Population	Primary endpoint	Key secondary endpoint	Treatments	Patients included in analysis
Randomized, placebo-controlled, double-blind, Phase III	Patients with completely resected, histologically confirmed, BRAF V600E/K mutation-positive, Stage III melanoma	Relapse-free survival (RFS)	Overall survival (OS)	Dabrafenib (150 mg bid) and trametinib (2 mg daily) vs 2 placebos	870 patients. randomized in 1:1 ratio

2.2.2. Pharmacokinetics

The clinical pharmacology characteristics of dabrafenib and trametinib when administered as monotherapy, as well as the clinical pharmacology characteristics of dabrafenib and trametinib administered in combination have been well characterized and have been described previously in the monotherapy applications for the two products (EMEA/H/C/2604 and EMEA/H/C/2643).

Pharmacokinetics of concomitant dabrafenib and trametinib

In Study BRF115532 a total of 870 subjects were to be randomized in a 1:1 ratio to receive either dabrafenib 150 mg bid plus trametinib 2 mg once daily or two matching placebos for 12 months. Blood samples for PK analyses of dabrafenib, its metabolites hydroxy-dabrafenib (GSK2285403, M7) and desmethyl-dabrafenib (GSK2167542, M8), and trametinib. Samples were to be collected in a subset of approximately 100 subjects while on treatment using a sparse sampling approach and analysed using previously validated bioanalytical methods.

PK samples (n=316, to be used both for dabrafenib and trametinib analysis) were originally available from 100 subjects treated with dabrafenib and trametinib in study BRF115532.

Finally evaluable dabrafenib PK concentrations (n=73) were available from 40 subjects, and evaluable trametinib PK concentrations (n=81) were available from 42 subjects, after exclusion of samples that exceeded the stability period of 657 days and the samples without complete corresponding dosing and PK collection dates and times.

For these PK samples the collection time windows to distinguish the pre-dose concentrations were then applied and these concentrations (yielding n=45 for dabrafenib, n=68 for trametinib) are summarized (Table 2 and Table 4).

Dabrafenib

Compared to the other PK visits, the most evaluable PK data were available for month 12. Median pre-dose concentration of dabrafenib at this time point was 76.3 ng/mL (Table 2).

Table 2: Summary of dabrafenib plasma concentration-time data for subjects who received adjuvant treatment of melanoma

Visit	Collection time	n	m	Dabrafenib (ng/mL) [1]
Month 1	Pre-dose	3	3	74 (60.8 - 1310)
Month 3	Pre-dose	2	2	104 (75.9 - 132)
Month 6	Pre-dose	5	5	23 (8.84 - 154)
Month 9	Pre-dose	7	7	60.7 (15.5 - 314)
Month 12	Pre-dose	11	11	76.3 (5.18 - 611)

Source: [Study BRF115532 Table 11-7]
n: number of subjects with evaluable values, m: number of non-zero concentrations
[1] Data are expressed as median [n] (minimum-maximum).

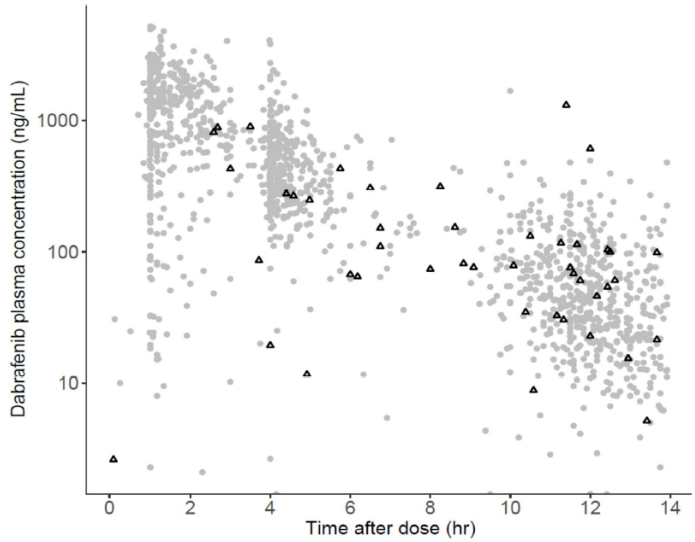
Dabrafenib median PK parameters obtained in combination with trametinib in melanoma subjects treated in the adjuvant setting (study BRF115532) were generally consistent with parameters obtained in subjects with metastatic melanoma as summarised in Table 3 and Figure 2.

Table 3: Summary of dabrafenib pharmacokinetic parameters after repeat-dose administration of dabrafenib 150 mg bid in combination with trametinib 2 mg once daily

Study	Indication	PK Day	Pre-dose concentration (ng/mL)
Combination with trametinib 2 mg once daily			
MEK115306	Metastatic melanoma	Week 8	33.8 [176] (0.0, 2100)
BRF113220 (Part D)	Metastatic melanoma	Week 3	60.2 [12] (29.4, 634)
BRF113928	NSCLC	Week 3	70.2 [19] (15, 3340)
BRF115532	Adjuvant treatment of melanoma	Month 12	76.3 [11] [5.18, 611]

Data reported as median [n] (min, max)

Figure 2: Plasma concentration of dabrafenib in BRF115532 overlaid on historical data from MEK115306



Source script: /vob/CDRB436F/mas/mas_1/model/pgm_001/poppk/r.dataprep/inspect.pk.data.f2301.R

Dose regimen: dabrafenib 150 mg bid and trametinib 2 mg once daily
Note: Dabrafenib concentrations (n = 45) up to 14 hours after the previous dose from 28 subjects in BRF115532 (black triangles) overlaid on historical data from metastatic melanoma subjects in MEK115306 (gray solid circles).

Trametinib

Most evaluable PK data were available for month 12. Median pre-dose concentration of trametinib at this timepoint was 8.77 ng/mL (Table 4).

Table 4: Summary of trametinib plasma concentration-time data for subjects who received adjuvant treatment of melanoma

Visit	Collection time	n	m	Trametinib (ng/mL) [1]
Month 1	Pre-dose	7	7	17.8 (9.07, 29.00)
Month 3	Pre-dose	4	4	11.9 (7.24, 16.20)
Month 6	Pre-dose	7	7	9.31 (7.23, 17.70)
Month 9	Pre-dose	15	14	10.4 (0.00, 24.60)
Month 12	Pre-dose	18	17	8.77 (0.00, 18.10)

Source: [Study BRF115532 Table 11-7]
n: number of subjects with evaluable values, m: number of non-zero concentrations
[1] Data are expressed as median [n] (minimum-maximum).

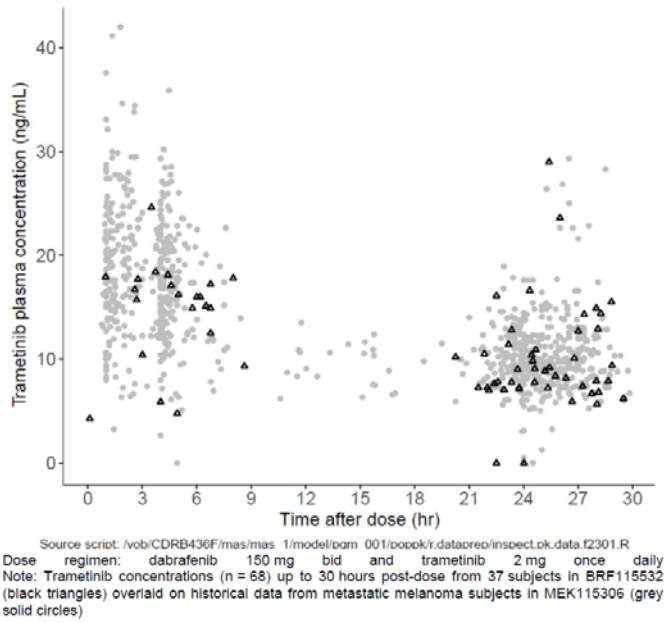
Trametinib median PK parameters obtained in combination with dabrafenib in melanoma subjects treated in the adjuvant setting (study BRF115532) were generally consistent with parameters obtained in subjects with metastatic melanoma as summarised in Table 5 and Figure 3.

Table 5: Summary of trametinib pharmacokinetic parameters after repeat-dose administration of trametinib 2 mg once daily in combination with dabrafenib 150 mg bid

Study	Indication	PK Day	Pre-dose concentration (ng/mL)
Combination with dabrafenib 150 mg bid			
MEK115306	Metastatic melanoma	Week 8	9.5 [176] (0, 26.8)
BRF113220 (Part D)	Metastatic melanoma	Week 3	10.8 [13] (8.1, 17.6)
BRF113928	NSCLC	Week 3	12.9 [26] (9, 25)
BRF115532	Adjuvant treatment of melanoma	Month 12	8.77 [18] [0.00, 18.10]

Data reported as median [n] (min, max)

Figure 3: Plasma concentration of trametinib in BRF115532 overlaid on historical data from MEK115306



Dose regimen: dabrafenib 150 mg bid and trametinib 2 mg once daily
Note: Trametinib concentrations (n = 68) up to 30 hours post-dose from 37 subjects in BRF115532 (black triangles) overlaid on historical data from metastatic melanoma subjects in MEK115306 (grey solid circles)

2.2.3. Pharmacodynamics and PK/PD relationship

No new pharmacodynamic data for dabrafenib and trametinib have been collected in Study BRF115532. Due to limited evaluable PK data, exposure-response analyses were also not conducted.

2.2.4. Discussion on clinical pharmacology

The clinical pharmacology characteristics of dabrafenib and trametinib when administered as monotherapy, as well as when administered in combination have been well characterized and have been described previously in the monotherapy applications for the two drugs (EMEA/H/C/2604 and EMEA/H/C/2643).

When given in combination in Study BRF115532, the applied dose of the combination is 150 mg twice-daily (BID) of dabrafenib with 2 mg once-daily of trametinib, administered under fasting conditions. These doses in combination are equal to the doses applied for the individual drugs dabrafenib and trametinib when given as monotherapy and have been used in other studies applying combination treatment.

Dabrafenib as well as trametinib median PK parameters obtained in combination with trametinib in melanoma subjects treated in the adjuvant setting were generally consistent with parameters obtained

in subjects with metastatic melanoma. The provided analysis, comparing exposure in the adjuvant setting with those in metastatic melanoma setting, is considered sufficient.

2.2.5. Conclusions on clinical pharmacology

Overall, the PK data submitted on dabrafenib and trametinib are considered adequate to characterise the clinical pharmacology in patients with adjuvant melanoma. The exposure of dabrafenib and trametinib in the adjuvant melanoma setting, with dabrafenib given at a dose of 150 mg twice daily and trametinib as 2 mg once daily, is considered comparable to that in the metastatic melanoma setting. Therefore, no changes to section 5.2 of the SmPC are considered necessary.

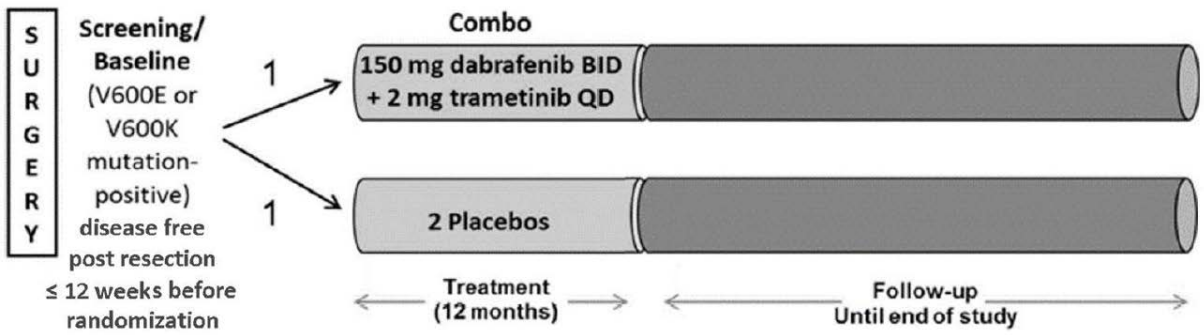
2.3. Clinical efficacy

2.3.1. Main study

Title of Study BRF115532 - COMBI-AD: phase III randomized double blind study of dabrafenib (GSK2118436) in COMBInation with trametinib (GSK1120212) versus two placebos in the ADjuvant treatment of high-risk BRAF V600 mutation-positive melanoma after surgical resection

Methods

Figure 4: Study design



Study participants

Patients with completely resected, histologically confirmed, BRAF V600E/K mutation-positive, high-risk (stage IIIA [lymph node metastasis >1 mm], IIIB, or IIIC based on the 7th edition of AJCC staging) cutaneous melanoma were screened for eligibility.

Inclusion criteria

- At least 18 years of age.
- Had signed written informed consent.
- Completely resected histologically confirmed high-risk (stage IIIA [lymph node metastasis >1 mm], IIIB, or IIIC) cutaneous melanoma determined to be V600E/K mutation positive using the bioMerieux (bMX) THxID BRAF Assay. The testing was conducted by a central reference laboratory. Patients presenting with initial resectable lymph node recurrence after a diagnosis

of stage I or II melanoma were eligible. Patients with an unknown primary melanoma were not eligible.

- Must be surgically rendered free of disease (defined as the date of the most recent surgery) no more than 12 weeks before randomization.
- Recovered from definitive surgery (e.g., no uncontrolled wound infections or indwelling drains).
- Able to swallow and retain oral medication and without any clinically significant gastrointestinal abnormalities that could alter absorption, such as malabsorption syndrome or major resection of the stomach or bowels.
- ECOG Performance Status (PS) of 0-1.
- Had adequate organ function as defined in the table below:

System	Laboratory Values
Hematologic	
ANC	≥ 1.2 × 10^9/L
Hemoglobin	≥ 9 g/dL
Platelet count	≥ 100 x 10^9/L
PT/INR[a] and PTT	≤ 1.5 x ULN
Hepatic	
Albumin	≥ 2.5 g/dL
Total bilirubin	≤ 1.5 x ULN
AST and ALT	≤ 2.5 x ULN
Renal	
Serum creatinine[b]	≤ 1.5 mg/dL
Cardiac	
Left Ventricular Ejection fraction (LVEF)[c]	≥ LLN by ECHO

Abbreviations: ALT = alanine transaminase; ANC = absolute neutrophil count; AST = aspartate aminotransferase; INR = international normalized ratio; LLN = lower limit of normal; PT = prothrombin time; PTT = partial thromboplastin time; ULN = upper limit of normal.

a. Subjects receiving anticoagulation treatment may be allowed to participate with INR established within the therapeutic range prior to randomization.
b. If serum creatinine is > 1.5 mg/dL, calculate creatinine clearance using standard Cockcroft-Gault formula (Appendix 4). Creatinine clearance must be ≥ 50 mL/min to be eligible.
c. ECHO scans must be used throughout the study

- Women of childbearing potential had a negative serum pregnancy test within 7 days of first dose of study treatment and agreed to use effective contraception from 14 days prior to randomization throughout the treatment period, and for 4 months after the last dose of study treatment.

Exclusion criteria

The main exclusion criteria were:

- Known mucosal or ocular melanoma or the presence of an unresectable in-transit metastases.
- Evidence of distant metastatic disease on screening evaluation.
- Prior anti-cancer treatment (chemotherapy, immunotherapy, biologic therapy, vaccine therapy, or investigational treatment) including radiotherapy for melanoma. Prior surgery for melanoma was allowed.

- Taken an investigational drug within 28 days or 5 half-lives, whichever is longer, prior to randomisation.
- Current or expected use of a prohibited medication.
- Known immediate or delayed hypersensitivity reaction or idiosyncrasy to drugs chemically related to the study treatments, their excipients, and/or dimethyl sulfoxide.
- Known human immunodeficiency virus (HIV) infection.
- History of another malignancy, including melanoma or a concurrent malignancy except as noted below. Patients who previously had stage III melanoma or any malignancy with confirmed activating RAS mutation at any time were not eligible.

  Note: Prospective RAS testing was not required. However, if the results of previous RAS testing were known, they were used in assessing eligibility.
- A history or evidence of cardiovascular risk
- A history or current evidence/risk of retinal vein occlusion (RVO) or central serous retinopathy (CSR)
- History of clinically significant or active interstitial lung disease or pneumonitis.
- Pregnant or nursing females.

Treatments

Dabrafenib

Dabrafenib was provided as 50 mg and 75 mg capsules to sites by the sponsor. Each capsule contained 50 mg or 75 mg of free base (present as the mesylate salt).

Trametinib

Trametinib study treatment was provided as 0.5 mg and 2 mg tablets to sites by the sponsor. Each tablet contained 0.5 mg or 2 mg of trametinib parent (present as the dimethyl sulfoxide solvate).

Placebos

Matching placebo capsules for dabrafenib (50 mg and 75 mg) and placebo tablets for trametinib (0.5 mg and 2 mg) were provided to sites by the sponsor. The placebo capsules/tablets contained the same inactive ingredients and film coatings as the dabrafenib and trametinib study treatment.

Permitted dose adjustments and interruptions of study treatment

For patients who were unable to tolerate the protocol-specified dosing scheme, dose adjustments and interruptions were permitted in order to keep the patient on study drug. Permitted dose levels are provided in Table 6.

Table 6: Permitted dose levels

	Dabrafenib/placebo	Trametinib/placebo
Starting dose	150 mg bid	2 mg once daily
L-1 (1st level dose reduction)	100 mg bid	1.5 mg once daily
L-2 (2nd level dose reduction)	75 mg bid	1 mg once daily

Objectives

Primary objective

To evaluate the efficacy of dabrafenib and trametinib combination therapy compared with two placebos with respect to RFS in patients with completely resected, histologically confirmed, BRAF V600E/K mutant, high-risk, stage III cutaneous melanoma.

Secondary objectives

- To compare OS of dabrafenib and trametinib as a combination therapy versus two placebos
- To compare distant metastasis-free survival (DMFS) of dabrafenib and trametinib as a combination therapy versus two placebos
- To compare freedom from relapse (FFR) of dabrafenib and trametinib as a combination therapy versus two placebos
- To evaluate the safety of dabrafenib and trametinib as a combination therapy in the overall study population including incidences of squamous cell carcinoma (SCC), new cancers in other sites, and other proliferative cutaneous lesions

Exploratory objectives

- To evaluate and compare health-related quality of life (HRQOL) of patients in the combination therapy arm with those in the placebo arm
- To further characterize the population pharmacokinetics (PK) in a subset of patients during the treatment phase and to explore the exposure-response relationship of dabrafenib, dabrafenib metabolites and trametinib on clinical endpoints
- Translational research, including the molecular characterization of relapses, analysis of predictive prognostic markers, assessment of immune function, characterization of mechanisms underlying adverse events of special interest, and molecular characterization of treatment-emergent malignancies
- Analysis of levels of circulating cell-free DNA (cfDNA) in plasma as an early predictor of disease recurrence or metastasis. Additionally, cfDNA may be evaluated for BRAF and other mutations associated with response in each therapeutic treatment at baseline, on-treatment and at disease relapse
- As part of pharmacogenetic research, this study will investigate the relationship between genetic variants in host DNA and the PK, safety, tolerability, and efficacy of each therapeutic treatment

Study assessments

Confirmation of BRAF mutation-positive melanoma at baseline

Patients were enrolled based on BRAF V600E or V600K mutation detected by a central laboratory using the bioMerieux BRAF THxID IUO assay (IDE: G120011).

Outcomes / endpoints

Primary efficacy endpoint

The primary efficacy endpoint of this study was RFS, which was defined as the time from randomisation to disease recurrence or death from any cause. The following were considered as RFS events:

- Types of recurrence considered as an event included loco-regional, distant metastases, and new primary melanoma;
- Any death occurring without prior documentation of tumor recurrence was considered as an event (and not censored in the statistical analysis).

The following efficacy assessments were performed:

- Diagnostic quality, contrast-enhanced computer tomography (CT) scans of the chest, abdomen and pelvis was performed at baseline and every 3 months during the treatment period. During the follow-up period a CT scan was performed every 3 months up to month 24 and every 6 months thereafter. Intravenous contrast was used for the CT scans; preferably with oral contrast as well. Magnetic resonance imaging (MRI) could be used instead of a chest CT scan under specific circumstances. The method of imaging was to be consistent throughout the study.
- A baseline MRI of the brain was required for all patients. CT could be performed only if MRI was contraindicated or unavailable. Subsequent brain scans were performed as clinically indicated.
- Biopsy of suspected recurrences could be performed, both to confirm the diagnosis and to obtain tissue for exploratory analyses.

Patients with no event by the time of the analysis cut -off were censored at the date of the last efficacy assessment (i.e., either radiological or non-radiological) prior to the analysis cut-off. Patients lost to follow-up prior to disease recurrence were censored.

Patients who started subsequent anti-cancer therapy prior to disease recurrence were censored at the date of last efficacy assessment (either radiological or non-radiological) before the initiation of subsequent anti-cancer therapy. Patients for whom an event occurred after a period of extended lost-to-follow-up were censored as per the rules described in the analysis plan.

Malignancies (including any new primary cancer from another histology, non-melanoma skin cancers including squamous cell carcinoma, or keratoacanthoma or basal cell carcinoma), excluding new primary melanomas, were not considered as melanoma recurrence events. Instead, these treatment-emergent malignancies, with the exception of basal cell carcinoma, were required to be reported as an SAE. Tumour tissue samples of any new primary cancers (including melanoma) were submitted for biomarker characterization. The analysis of RFS was based on the ITT population.

Secondary efficacy endpoints

- **OS**, the key secondary endpoint, was defined as the interval from randomization to the date of death, irrespective of the cause of death.
- **DMFS** was defined as the interval from randomization to the date of first distant metastasis or date of death, whichever occurred first.

- **FFR** was defined as the interval from randomization to local or distant recurrence with censoring of patients dying from causes other than melanoma or treatment-related toxicity at the date of death.

Safety assessments

Safety was assessed by monitoring and recording potential adverse effects of the treatment using the CTCAE version 4.0, including the relationship to the study treatment, at each study visit.

Assessment of health outcomes

Patients in both treatment groups completed the EQ-5D at baseline and at various time points throughout the study. Changes in HRQOL from baseline were assessed and compared between treatment groups using the EuroQol-5D (EQ-5D) questionnaire.

Sample size

As per the initial protocol design (i.e., before protocol amendment 7), the following assumptions were made in the estimation of the required sample size:

- Exponential survival distributions
- An HR of 0.7143 (median RFS times of 15 and 21 months in the placebo arm and the combination therapy arm, respectively)
- A 1:1 randomization scheme
- An overall 5%, two-sided risk of erroneously claiming superiority of the combination therapy in the presence of no true underlying difference (i.e., overall type I error);
- A 95% chance of successfully claiming superiority of the combination therapy in the presence of a true underlying difference (i.e., power or 1-type II error)
- An accrual rate of 42 patients per month over 20.3 months; and
- A dropout rate of 5% for the placebo group and 15% for the combination group.

To enable the observation of 467 total events, an estimated total of 852 patients (i.e., approximately 426 patients in each of the arms) would need to be enrolled, leading to implementation of final analyses at approximately 32 months after the start of the study (Table 7).

Table 7: Statistical power scenario for RFS analysis

Median RFS		Hazard Ratio	Power
Placebo	Combination Therapy		
14 months	20 months	0.7	94.7%
15 months	21 months	0.714	92.2%
16 months	21 months	0.762	78.4%
16 months	22 months	0.727	89.3%
Note: Power scenarios were based on 410 RFS events. RFS = relapse-free survival			

As per protocol amendment 7, the final primary RFS analysis was to be performed at the predefined cut-off date of 30-Jun-2017, by which time it was expected that approximately 410 RFS events would have accrued, which would provide more than 90% power to detect the originally targeted HR.

The final OS analysis was to be performed when approximately 597 deaths are observed which would provide 80% power to detect a hazard ratio of 0.793 (corresponding to median OS times of 48 and 60.5 months in the placebo and the combination arm, respectively).

Randomisation

Randomisation was done centrally using a randomisation schedule which assigned patients in a 1:1 ratio to dabrafenib (150 mg bid) and trametinib (2 mg once daily) combination therapy or two matched placebos. The following information for stratification was entered into the interactive voice response system (IVRS) system in order to obtain stratified, random, blinded, treatment assignment:

- Mutation type (V600E or V600K)
- Disease stage (IIIA, IIIB, IIIC)

Blinding (masking)

Study treatment was double-blinded.

Statistical methods

Data analysis

Before protocol amendment 7 was issued, the original study design had 95.3% power to detect an RFS HR of 0.71 (corresponding to a median RFS of 15 and 21 months in the placebo arm and the combination therapy arm, respectively) requiring a total of 467 RFS events (relapses or deaths) with an overall two-sided Type I error at 5%. The study was intentionally overpowered for RFS to provide adequate sample size to support the statistical assumptions on OS as the key secondary endpoint. Due to a lower than projected rate of RFS events and a duration of median follow-up considered adequate in this indication, in agreement with the FDA and EMA, the protocol was amended (version 7) in May 2017. With this amendment, a new data cut-off of 30-Jun-2017 for the primary analysis of RFS was planned; approximately 410 RFS events were expected to occur which would still provide sufficient power (92%) to detect the originally targeted HR=0.71. This cut-off (30-Jun-2017) corresponds to approximately 2.5 years after Last patient First dose, with a median study follow up time of approximately 3.3 years.

Analysis sets

- The **Intent-to-Treat Population** (ITT) consisted of all randomized patients whether or not randomized treatment was administered. This population was based on the treatment to which the patient was randomised and was the primary population for the analysis of efficacy data. Any patient who received a treatment randomisation number was considered to have been randomised.
- The **Safety Population** consisted of all patients who received at least one dose of randomised treatment and was based on the actual treatment received. This population was used for the analysis of clinical safety data.
- The **Pharmacokinetics (PK) Population** consisted of all patients included in the Safety population for whom a PK sample was obtained and analysed.

Examination of subgroups

The following subgroups were explored in the analysis of RFS and OS:

- Mutation status: BRAF V600K/E positive
- Disease stage: IIIA/IIIB/IIIC
- Gender: Male/Female
- Age at screening: < 65 years/≥ 65 years
- Race: White/Asian/Other
- Region: North America: USA and Canada/Europe and Israel/Asia/Pac excluding Australia and New Zealand/South America/Australia and New Zealand
- Nodal metastatic mass (micrometastasis/macrometastasis)
- Nodal metastatic mass and primary tumor ulceration (micrometastasis and ulceration/micrometastasis and no ulceration/macrometastasis and ulceration/macrometastasis and no ulceration)

Pike hazard ratios with corresponding 95%CI were calculated within each of the above defined subgroups and results were presented in a forest plot. The analyses performed within subgroups were non-stratified.

In addition, the treatment effect was investigated in the subgroup of patients with stage IIIB/IIIC, which has been a priori identified as a subgroup of primary interest. The RFS analysis within this subgroup included the Pike estimator as well as a multivariate Cox regression analysis to adjust for important prognostic factors.

Analysis of the primary efficacy variable

The study was designed to provide evidence with respect to RFS to either support the null hypothesis, H0: $\lambda = 1$ or reject it in favour of the alternative hypothesis, HA: $\lambda \neq 1$, where λ is the hazard ratio (HR) of combination therapy relative to placebo.

Primary analysis for RFS

RFS was summarised using Kaplan-Meier (K-M) estimates and compared between treatment arms using a stratified log-rank test (using randomization stratification factors). The Pike estimator (Berry et al, 1991) HR was provided, together with a 95%CI.

Median times to RFS with first and third quartiles were presented, along with 95%CI, based on the Brookmeyer-Crowley method with linear transformation function.

The primary analysis was stratified based on the classification reported at the time of randomisation (IVRS system) using the following two stratification factors:

- Mutation type (V600E, V600K)
- Disease stage (IIIA, IIIB, IIIC)

This represents a total of six sub-strata. Patients in each sub-stratum were centrally randomized in a 1:1 ratio to receive either 150 mg twice daily of dabrafenib + 2.0 mg daily of trametinib or matching placebos.

Table 8: Assignment of events and censoring dates for RFS analysis

Situation	Date of Event or Censoring	Outcome
evidence of unresected melanoma or distant metastatic disease on screening evaluation	Randomization	Censored
Recurrence documented between scheduled visits	Date of assessment of Recurrence	Event
No recurrence (or death)	Date of last efficacy assessment	Censored
New anti-cancer therapy (including surgery for melanoma) started prior to documented disease recurrence[1]	Date of last efficacy assessment on or prior to starting anti-cancer therapy	Censored
Death before recurrence assessment	Date of death	Event
Death between adequate assessment visits	Date of death	Event
Death or recurrence after three or more missed scheduled efficacy assessments during study treatment period or after two or more missing during the every 3 months follow up period or one or more missing during the every 6 months follow-up period	Date of last adequate assessment prior to missed assessments	Censored

1. If relapse and New anti-cancer therapy occur on the same day then the relapse will be counted as event. If anti-cancer therapy is started prior to any adequate assessments, censoring date should be the date of randomization.

Sensitivity and supportive analysis for RFS

The following sensitivity and supportive analyses using the ITT population were conducted in order to assess the robustness of the primary analysis:

- RFS regardless of start of new anticancer therapy and extended lost to follow-up: Patients who relapsed or died any time during treatment or follow up were considered as an event regardless of whether the event occurred after extended loss to follow up or after initiation of a new anti-cancer therapy.
- RFS analysis ignoring new melanoma as an event: RFS was analysed as for the primary analysis with the exception that relapse due to new melanoma were not considered as events.
- Cox regression analysis of RFS: A stratified Cox regression model was used to estimate the HR of RFS, along with 95%CI based on the Wald test. The exact method was used to handle the situation where there were ties in the event times.
- Cox regression with prognostic factors as covariates: Multivariate cox regression model stratified by randomization stratification and adjusted for the key baseline prognostic factors was fitted with treatment and the following baseline factors as covariates:
    - Gender
    - T stage (1, 2, 3, 4)
    - Tumour ulceration (Y, N)
    - N stage (N1, N2, N3)
    - In-transit disease (Y, N)
    - Melanoma subtype (superficial spreading, nodular, other)

- Analysis using stratification from the eCRF: In this sensitivity analysis the primary efficacy analysis was repeated using strata from the electronic eCRF rather than the classification from the IVRS system. Actual disease stage (IIIA, IIIB, IIIC) was derived based on the primary tumour (T) stage, regional lymph nodes (N) stage and distant metastasis (M) stage using data from the eCRF.

Percentages of disease free patients: Time point estimates

The percentage of surviving patients who were disease free at 1-year intervals from the time of randomization were estimated from the Kaplan-Meier curves for the primary analysis of RFS. This included the following time points: 1 year, 2 years, and 3 years. Approximate 95%CI were calculated, based on Greenwood's formula for the standard error of the Kaplan-Meier estimate.

Analysis of secondary efficacy variables

Overall survival

OS was estimated using the Kaplan Meier method and treatment comparisons, when performed, were made using a stratified log-rank test (based on the randomization stratification factors). Censoring was performed using the date of last known contact for those who were alive at the time of analysis. The Pike-based HR along with 95%CI were provided.

The assessment of OS was based on a 3-look Lan-DeMets group sequential design with two interim analyses and a final analysis. The first interim analysis of OS was to be performed at the time of the primary analysis of RFS. Per Protocol Amendment 7, an additional OS interim analysis is planned for when approximately 299 death events have occurred ; i.e., at 50% information fraction of the originally targeted 597 OS events in order to provide early efficacy information on survival, since the final OS analysis will occur much later. The final OS analysis is planned to be performed when 70% of the total number of randomized patients have died (i.e. at approximately 597 deaths). The thresholds for statistical significance were to be determined based on the observed information fraction and pre-defined O'Brien-Fleming type of stopping boundary.

A hierarchical approach was chosen to control for the overall type-I error rate for testing of multiple endpoints. Therefore, OS was to be formally statistically tested only if the primary efficacy endpoint RFS was statistically significant.

The first potential time point for OS analysis would be at the time of the primary RFS analysis:

- If RFS is significant, the first interim analysis for OS would be performed:
    1. If OS is not significant at this stage, based on O'Brien-Fleming, a second interim OS analysis will be performed when approximately 299 randomized patients have died (50% information fraction of final OS analysis), and the final OS analysis would be performed when 70% of the total number of randomized patients have died (i.e. 597deaths).
    2. If OS is significant at the first interim analysis, no further formal OS analysis would be performed.
- If RFS is not significant, OS would not be formally statistically tested.

The percentage of surviving patients at 1-year intervals from the time of randomization was estimated from the Kaplan-Meier curves for OS for the ITT population. This included the following time points: 1 year, 2 years, and 3 years. Approximate 95%CI were calculated, based on Greenwood's formula for the standard error of the Kaplan-Meier estimate.

The multivariate Cox regression analysis described above for the RFS analysis was repeated for the OS analysis.

Distant metastasis-free survival (DMFS)

DMFS was estimated using the Kaplan Meier method and treatment comparisons were made using a stratified log-rank test. The first appearance of distant metastasis or all-cause mortality were used as events. Censoring was performed using the date of the last assessment for those who were alive without distant metastasis at the time of analysis. The Pike HR with 95%CI was provided.

Freedom from relapse (FFR)

FFR was estimated using the Kaplan Meier method and treatment comparisons were made using a stratified log-rank test. The first appearance of local/distant metastasis or mortality due to disease recurrence or toxicity were used as events. Censoring was performed using the date of last assessment for those who were alive without local/distant metastasis or new primary melanoma at the time of analysis. FFR was censored if patients died from causes other than melanoma or treatment-related toxicity at the date of death. The Pike HR with 95%CI was provided.

Time to assessment

For the RFS analysis described above, a box-and-whisker plot of the assessment intervals was provided to compare the timing of disease assessments between arms to assess potential imbalance between treatment arms.

Analysis of safety

The Safety set was used for presentation of safety data. Adverse events, SAEs, deaths, laboratory data, vital signs, ECG, and questionnaire data (EQ-5D) were assigned to assessment windows as defined below:

- **Pre-therapy** is defined as the time prior to the patient's first dose of study treatment.
- **On-therapy** is defined as the time from first dose of study treatment to the date of the last dose of study treatment + 30 days.
- **Post-therapy** is defined as any time beyond the on-therapy period.

Analysis of exploratory variables

Health outcomes

Analyses were based on the ITT population. Results for the EQ 5D were summarized using descriptive statistics at each assessment time for which there are adequate data. Summary statistics on change from baseline were also provided. Changes of mean scores over time were analysed with a repeated measures analysis of covariance model using mixed effects and baseline score as covariate for both EQ -5D Thermometer and Utility scores. Differences between treatment groups along with 95%CI and p-values were displayed. Patient listings of EQ-5D categories, Utility Scores, and Thermometer values were produced.

Handling of missing values

All randomized patients were included in the efficacy analyses as per the ITT principle, and all events during the study were considered (as per conventions described above) regardless of whether they occurred on treatment or after treatment discontinuation. The conventions for censoring of patients for whom a RFS event occurred after extended lost-to-follow up (i.e., after period with missing data) are described in the analysis plan.

Missing data were indicated by the use of a “blank” in the patient listing displays. Answers such as “Not applicable” and “Not evaluable” were not considered to be missing data and were displayed as such.

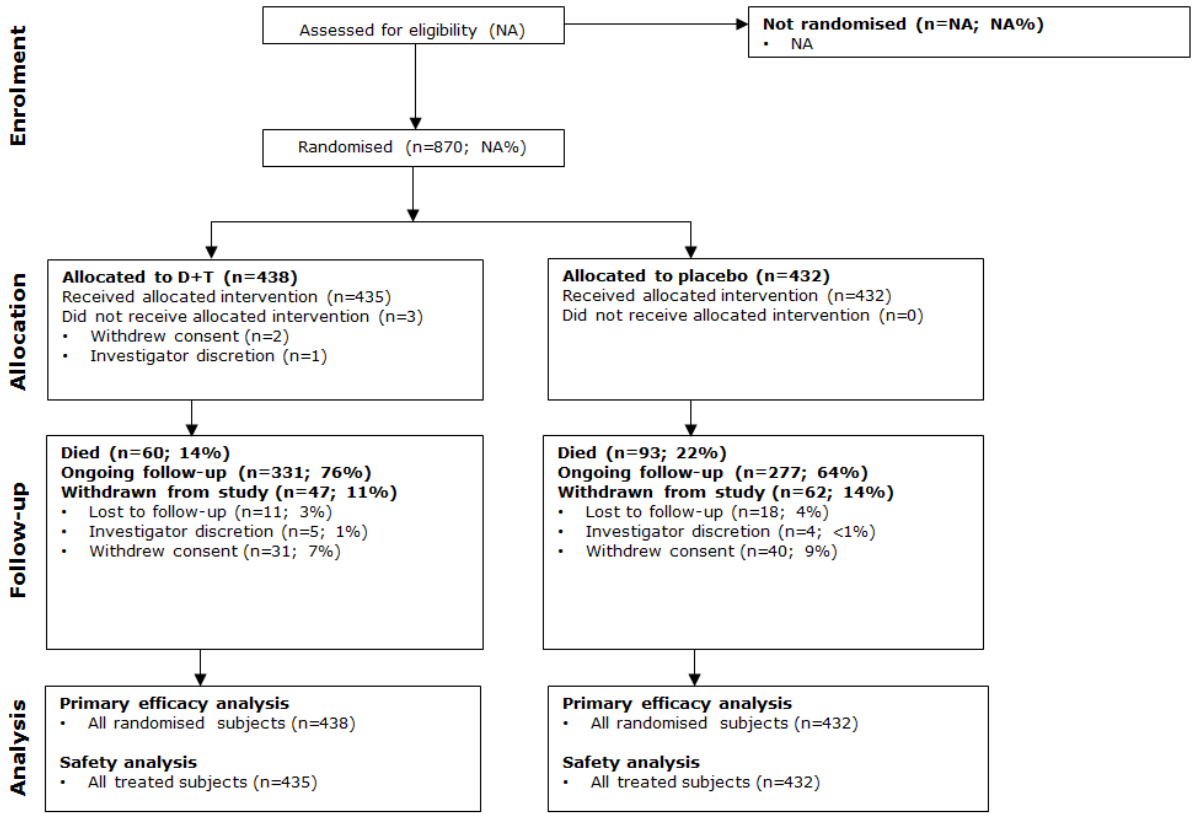
A worst-case assumption was applied to AEs and SAEs for which the treatment relationship was missing; they were imputed to be considered as related.

In general, imputed partial dates were not used to derive study day, duration (e.g. , duration of AEs), or elapsed time variables. In addition, imputed dates were not used for deriving the last contact date in the OS analysis dataset.

With the exception of a new anti-cancer medication start date for the time-to-event analysis datasets, and an exposure end date for the exposure analysis dataset, imputed dates were not kept as variables in the datasets.

Results

Participant flow



Recruitment

The study was conducted in 169 centres across 25 countries.

Conduct of the study

The most important amendment is described below.

- **Amendment 7 (31-May-2017)**

  The data cut-off for the primary endpoint analysis was changed from an event-driven time point (467 RFS events) to a follow up-driven time point (corresponding to a projected median study follow up of 3.3 years for all patients, and 2.5 years after Last patient, First dose). The new data cut-off for the primary analysis was defined on 30-Jun-2017 when approximately 410 RFS events were expected to occur providing sufficient power (92%) to detect the originally targeted HR=0.71. These changes occurred prior to study unblinding.

  An additional OS interim analysis was added to be applied when approximately 299 death events have occurred; i.e,. at 50% information fraction of the originally targeted 597 OS events in order to provide early efficacy information on survival, since the final OS will occur much later.

After pre-screening of 2258 patients, 1442 (64%) tested BRAF V600 mutation positive. A total of 870 patients were randomized between 31-Jan-2013 to 11-Dec-2014 in the study, 438 patients in the dabrafenib+trametinib arm and 432 patients in the placebo arm. A total of 3 patients were not treated, all in the dabrafenib+trametinib arm. 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 (Table 9).

Table 9: Summary of patient status and reason for study withdrawal (safety population)

	Dabrafenib+Trametinib	Placebo
Disposition **Reason**	**N=438** **n (%)**	**N=432** **n (%)**
Patients randomized		
Untreated	3 (<1)	0
Treated	435 (99)	432 (100)
Patient status		
Died	60 (14)	93 (22)
Ongoing	331 (76)	277 (64)
Follow-up	331 (76)	277 (64)
Withdrawn from study	47 (11)	62 (14)
Reasons for study withdrawal		
Lost to follow-up	11 (3)	18 (4)
Investigator discretion	5 (1)	4 (<1)
Withdrew consent	31 (7)	40 (9)

[a] Patients on study treatment at the time of the cut-off 30-June-2017.

Last patient, last dose occurred on 01-Dec-2015. By the time of data cut-off (30-Jun-2017), the median patient follow-up time was 34 months (range: 0-51 months) in the dabrafenib+trametinib arm and 33 months (range: 1-50 months) in the placebo arm. At the time of the data cut-off, all patients still in the study were off treatment and in the follow-up phase (Table 10).

Table 10: Summary of study treatment status for D+T and placebo (safety population)

	Dabrafenib + Trametinib		Placebo	
	Dabrafenib	Trametinib	Placebo to match Dabrafenib	Placebo to match Trametinib
Disposition	**N=435**	**N=435**	**N=432**	**N=432**
Reason	**n (%)**	**n (%)**	**n (%)**	**n (%)**
End of treatment	435 (100)	435 (100)	432 (100)	432 (100)
Treatment status				
Completed scheduled treatments	272 (63)	277 (64)	227 (53)	227 (53)
Prematurely discontinued	163 (37)	158 (36)	205 (47)	205 (47)
Primary reason for treatment discontinuation				
Adverse event	108 (25)	104 (24)	12 (3)	12 (3)
Protocol deviation	2 (<1)	2 (<1)	1 (<1)	1 (<1)
Lost to follow-up	1 (<1)	1 (<1)	1 (<1)	1 (<1)
Investigator discretion	2 (<1)	2 (<1)	5 (1)	5 (1)
Decision by patient or proxy	27 (6)	26 (6)	11 (3)	11 (3)
Disease recurrence	23 (5)	23 (5)	175 (41)	175 (41)

[1] Patients ongoing at the time of the cut-off 30-June-2017.
All patients had discontinued treatment by Dec 2015.

Protocol deviations

Protocol deviations were observed in both treatment arms. 407 patients (93%) and 393 patients (91%) in the dabrafenib+trametinib arm and placebo arm, respectively, had protocol deviations (Table 11).

Table 11: Summary of protocol deviations (ITT)

Criterion	Dabrafenib + Trametinib (N=438)	Placebo (N=432)
Any criteria deviations	407 (93%)	393 (91%)
Assessments and/or procedures	385 (88%)	356 (82%)
Eligibility criteria not met	53 (12%)	49 (11%)
Not withdrawn after developing withdrawal criteria	0	2 (<1%)
Other protocol deviation category	5 (1%)	11 (3%)
Prohibited medication or device	2 (<1%)	1 (<1%)
Received wrong treatment or incorrect dose	33 (8%)	25 (6%)
Visit window	267 (61%)	258 (60%)

Baseline data

Demographics

Table 12: Summary of demographic characteristics (ITT)

Demographic variable	Dabrafenib + Trametinib N=438	Placebo N=432	All patients N=870
Age (years)			
n	438	432	870
Mean (SD)	50.4 (14.17)	50.5 (13.14)	50.4 (13.66)
Median	50.0	51.0	51.0
Min-Max	18 - 89	20 - 85	18 - 89
Age category (years) – n (%)			
18 - 64	353 (81%)	359 (83%)	712 (82%)
65 - 74	73 (17%)	61 (14%)	134 (15%)
75 - 84	11 (3%)	11 (3%)	22 (3%)
≥ 85	1 (<1%)	1 (<1%)	2 (<1%)
Gender – n (%)			
n	438	432	870
Male	243 (55%)	239 (55%)	482 (55%)
Female	195 (45%)	193 (45%)	388 (45%)
Race – n (%)			
n	438	432	870
White	432 (99%)	427 (99%)	859 (99%)
Asian	6 (1%)	5 (1%)	11 (1%)

Disease characteristics and medical history

Disease characteristics are shown in Table 13.

157 patients (18%) were current smokers, 223 (26%) were former smokers and 489 patients (56%) were non-smokers. The proportion of smokers and non-smokers was balanced between the treatment arms. 56% of patients had regular alcohol consumption and the median alcohol units/week was 3.0 (0-112 units/week). 48 patients (6%) had a family history of melanoma, which was balanced between the two treatment arms.

Table 13: Summary of disease characteristics (ITT)

Disease Characteristics	Dabrafenib + Trametinib N=438	Placebo N=432	All patients N=870
Primary Tumor Type			
Melanoma	438 (100%)	432 (100%)	870 (100%)
Time Since Initial Diagnosis (months)			
n	438	432	870
1st Quartile	4	4	4
Median	5.0	6.0	5.0
3rd Quartile	19	20	20
Min. – Max.	1 – 306	0 – 351	0 - 351
Stage at Screening [1]			
IIIA	83 (19%)	71 (16%)	154 (18%)
IIIB	169 (39%)	187 (43%)	356 (41%)
IIIC	181 (41%)	166 (38%)	347 (40%)
Unknown	5 (1%)	8 (2%)	13 (1%)
Primary Tumor Ulceration			
Yes	179 (41%)	177 (41%)	356 (41%)
No	253 (58%)	249 (58%)	502 (58%)
Missing	6 (1%)	6 (1%)	12 (1%)
In-transit Disease			
Yes	51 (12%)	36 (8%)	87 (10%)
No	387 (88%)	395 (91%)	782 (90%)
Missing	0	1 (<1%)	1 (<1%)
TNM Staging: Primary Tumor			
T1a	54 (12%)	59 (14%)	113 (13%)
T1b	20 (5%)	24 (6%)	44 (5%)
T2a	80 (18%)	80 (19%)	160 (18%)
T2b	28 (6%)	22 (5%)	50 (6%)
T3a	73 (17%)	54 (13%)	127 (15%)
T3b	67 (15%)	74 (17%)	141 (16%)
T4a	29 (7%)	34 (8%)	63 (7%)
T4b	77 (18%)	72 (17%)	149 (17%)
TX	6 (1%)	8 (2%)	14 (2%)
Missing	4 (<1%)	5 (1%)	9 (1%)
TNM Staging: Regional Lymph Nodes			
N1a	82 (19%)	95 (22%)	177 (20%)
N1b	87 (20%)	81 (19%)	168 (19%)
N2a	70 (16%)	62 (14%)	132 (15%)
N2b	71 (16%)	80 (19%)	151 (17%)
N2c	18 (4%)	16 (4%)	34 (4%)
N3	110 (25%)	97 (22%)	207 (24%)
Missing	0	1 (<1%)	1 (<1%)
TNM Staging: Distant Metastasis			
M0	437 (>99%)	432 (100%)	869 (>99%)
Missing	1 (<1%)	0	1 (<1%)

[1] Actual disease stage (IIIA, IIIB, IIIC) was derived based on the primary tumor (T) stage, regional lymph nodes (N) stage, and distant metastasis (M) stage [Appendix 16.1.1-Appendix 1-Section 12.1] using data from eCRF.

Prior anti-cancer surgery

All patients underwent tumour excision prior to enrollment. The same proportion of patients (53%) in each arm had sentinel lymphadenectomy. The median number of lymph nodes removed by lymphadenectomy was similar between the treatment arms, 16 in dabrafenib+trametinib arm and 17 in placebo arm.

Stratification factors

The percentage of patients falling into each category for stratification factors of disease stage and mutation status entered into RAMOS were identical between the treatment arms. One patient had both BRAF V600E and V600K mutation and was stratified as V600K at randomization. This patient received dabrafenib+trametinib (Table 14).

Table 14: Summary of stratification factors

	Dabrafenib + Trametinib N=438	Placebo N=432	Total N=870
Data Available for all stratification factors in RAMOS[1]			
Yes	438 (100%)	432 (100%)	870 (100%)
Disease stage as per RAMOS			
IIIA	91 (21%)	90 (21%)	181 (21%)
IIIB	188 (43%)	187 (43%)	375 (43%)
IIIC	159 (36%)	155 (36%)	314 (36%)
BRAF Mutation Status as per RAMOS			
BRAF V600E Mutation Positive	400 (91%)	395 (91%)	795 (91%)
BRAF V600K Mutation Positive	38 (9%)	37 (9%)	75 (9%)

[1]Randomization was performed centrally using RAMOS (Registration And Medication Ordering System), GSK's interactive voice response system (IVRS). Patients were randomized 1:1 to each treatment arm using a randomization schedule generated by the GSK Biostatistical Department and patients were stratified according to Mutation Type (V600E or V600K) and Disease stage (IIIA, IIIB, or IIIC). One subject is both BRAF V600E and BRAF V600K mutation positive and is included in the V600K subset in this table.

Numbers analysed

All 870 randomized patients were included in the ITT population (Table 15). Three patients were not treated, all in the dabrafenib+trametinib arm, and were thus excluded from the Safety population.

Table 15: Summary of study populations

	Dabrafenib + Trametinib N=438	Placebo N=432	Total N=870
Intent-to-Treat[1]	438	432	870
Safety[2]	435	432	867
PK Population[3]	61	0	61

[1]All randomized patients are included in the Intent-to-Treat population regardless of whether or not they received study treatment.

[2]Patients are included in the Safety population if they were randomized and had taken at least one dose of study medication.

[3] All subjects included in the Safety population for whom a PK sample was obtained and analyzed.

Outcomes and estimation

Primary efficacy results - Relapse Free Survival

The primary RFS analysis was conducted at the pre-defined cut-off date of 30-Jun-2017, at which time 414 RFS events were observed; 166 events (38%) in the dabrafenib+trametinib arm and 248 events (57%) in the placebo arm. Types of recurrence considered as an event were loco-regional, distant metastases, and second primary melanoma.

The study met its primary objective. The combination of dabrafenib and trametinib demonstrated superiority over placebo for the primary endpoint of RFS per the investigator's assessment with an estimated HR of 0.47 and 95%CI 0.39-0.58 in favour of the dabrafenib+trametinib treatment arm. This result was highly statistically significant with p=1.53x10-14 (stratified Log-rank test, two-sided) (Table 16).

Using the data cut-off date of 30-Apr-2018, the median patient follow-up was 44 months in the dabrafenib+trametinib arm and 42 months in the placebo arm. The results are shown in Table 16.

Table 16: Summary of RFS (primary analysis; ITT)

	Primary analysis (data cut off 30-Jun-2017)		Updated Analysis (data cut off 30-Apr-2018)	
Category	Dabrafenib + Trametinib N=438	Placebo N=432	Dabrafenib + Trametinib N=438	Placebo N=432
Number of patients				
Relapsed (event)	163 (37%)	247 (57%)	174 (40%)	253 (59%)
Died (event)	3 (<1%)	1 (<1%)	3 (<1%)*	1 (<1%)*
Censored, follow-up ended[#]	43 (10%)	35 (8%)	45 (10%)	39 (9%)
Censored, follow-up ongoing[#]	229 (52%)	149 (34%)	216 (49%)	139 (32%)
Percentiles (95% CI) (months)				
25th percentile	17.9 (16.6, 21.4)	5.3 (3.3, 5.6)	17.9 (16.6, 21.4)	5.3 (3.3, 5.6)
Median	NE (44.5, NE)	16.6 (12.7, 22.1)	NE (46.9, NE)	16.6 (12.7, 22.1)
75th percentile	NE (NE, NE)	NE (NE, NE)	NE (NE , NE)	57.9 (57.9, NE)
Hazard ratio (95% CI) vs. placebo	0.47 (0.39, 0.58)		0.49 (0.40, 0.59)	

Hazard ratio is obtained from the stratified Pike estimator. Hazard Ratio is model adjusted for randomized strata: Disease Stage and BRAF mutation status.
NE: Not estimable.
* Includes 2 subjects whose deaths secondary to melanoma before documented disease recurrence.
[#] Patients censored with follow-up ongoing are those who were alive, did not take any anti-cancer therapy and did not withdraw from study by the time of data cut-off. Patients censored with follow-up ended are the remaining censored patients

Table 17: Summary of estimated percentages of relapse free patients by the Kaplan-Meier curves based on database cut-off 30-Apr-2018

	Dabrafenib + Trametinib N=438	Placebo N=432
1-year RFS rate (95% CI) [1]	0.88 (0.85, 0.91)	0.56 (0.51, 0.61)
2-year RFS rate (95% CI) [1]	0.67 (0.62, 0.72)	0.44 (0.40, 0.49)
3-year RFS rate (95% CI) [1]	0.59 (0.55, 0.64)	0.40 (0.35, 0.45)

[1] The RFS rate estimation is based on the Kaplan-Meier method and the confidence intervals are estimated using log transformation.

The Kaplan-Meier RFS curves are shown in Figure 6 (primary analysis) and Figure 6 (updated database lock).

Figure 5: Kaplan-Meier curve investigator-assessed RFS (primary analysis; ITT; 30-Jun-2017)

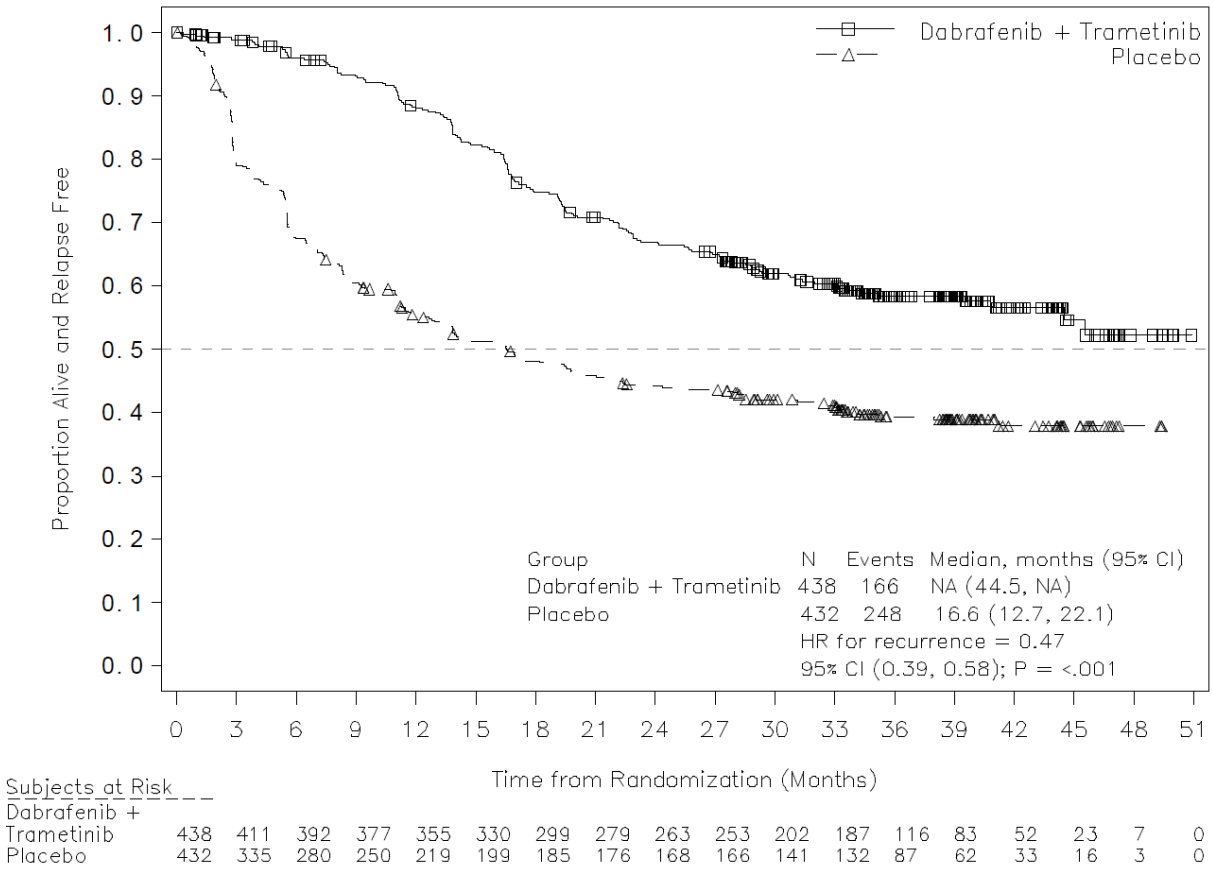
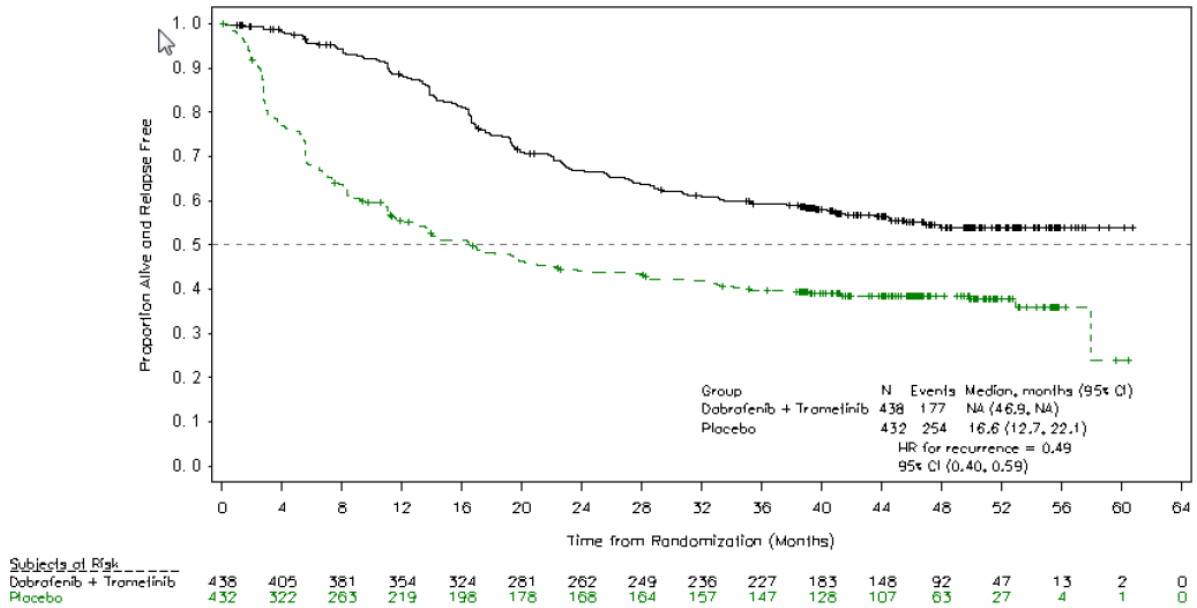


Figure 6: Kaplan-Meier curve investigator-assessed RFS (primary analysis; ITT; 30-Apr-2018)



Most of the RFS events in both the dabrafenib+trametinib arm and the placebo arm were distant recurrences (103 patients; 24% and 133 patients; 31%, respectively). More patients in the placebo arm had local or regional recurrence (114 patients; 26%) compared to the dabrafenib+trametinib arm (61 patients; 14%) (Table 16).

It should be noted that in the RFS analysis only the first occurrence is counted as an event. For example, if a patient experienced a local recurrence first followed by a distant recurrence at a later time point, only the former one is counted as an event. There were, however, several patients who experienced several types of recurrence on the same day and were thus counted in several categories of recurrence subtypes. In particular, 7 patients in each arm had both local/regional and distant recurrence observed on the same day. In addition, 1 patient in the dabrafenib+trametinib arm and 1 patient in the placebo arm had both disease recurrence and secondary primary melanoma observed on the same.

Secondary efficacy results

Overall survival

As the primary endpoint of the study was met and was statistically significant, the key secondary endpoint of OS was formally tested with an interim OS analysis performed with a total of 153 deaths; 60 in the dabrafenib+trametinib arm and 93 in the placebo arm, representing 26% of the total targeted 597 deaths required for the final OS analysis.

The estimated HR for OS was 0.57 (95%CI 0.42, 0.79) (stratified Log-rank test p=0.0006, two-sided). As the two-sided threshold for significance at this first interim analysis was p=0.000019, this result is not considered statistically significant (Table 18). The significance threshold was determined based on the observed information fraction and predefined 3-look Lan-DeMets group sequential design with an O'Brien-Fleming type boundary.

Median OS was not reached in either arm; the OS data are still immature due to the low number of events observed (Table 18). 331 (76%) patients in the dabrafenib+trametinib arm and 277 (64%) patients in the placebo arm were censored and are still being followed for OS events. Follow-up for the remaining 47 patients (11%) and 62 patients (14%) in the dabrafenib+trametinib arm and placebo arm, respectively, has ended (Table 18).

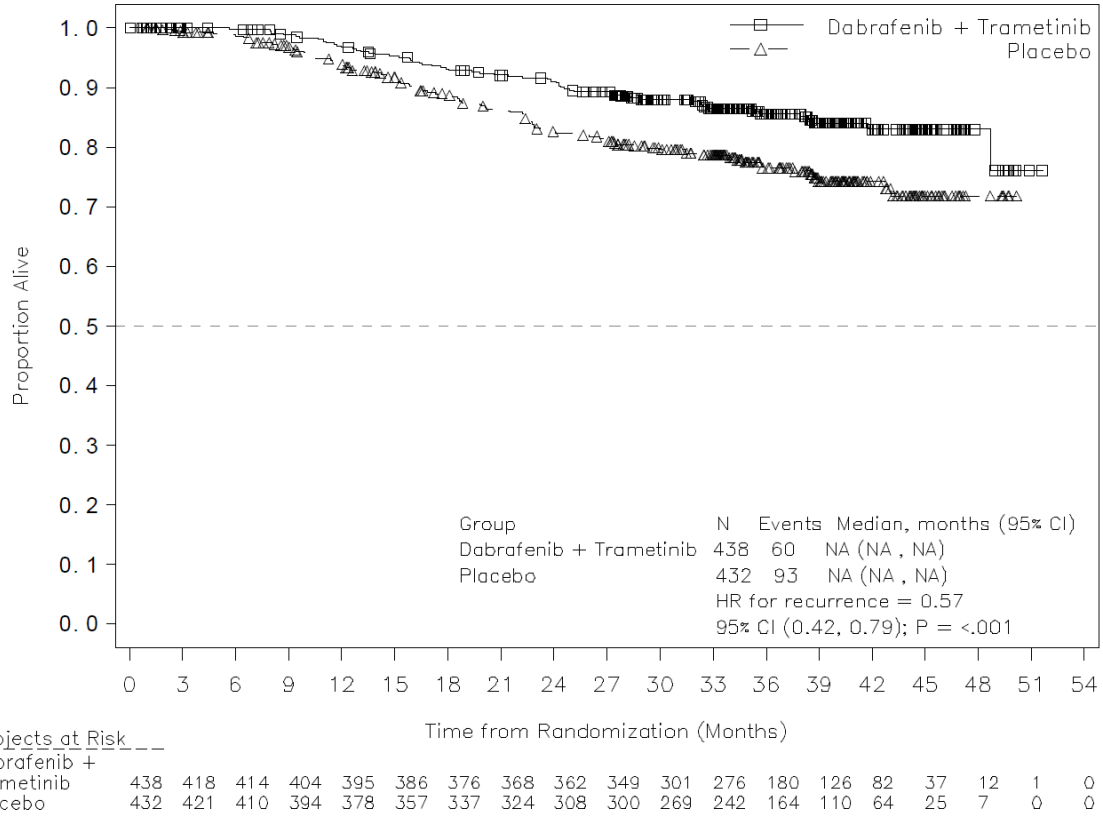
Table 18: Summary of OS (primary analysis; ITT)

Category	Dabrafenib + Trametinib N=438	Placebo N=432
Number of patients		
Died (event)	60 (14%)	93 (22%)
Censored, follow-up ended	47 (11%)	62 (14%)
Censored, follow-up ongoing	331 (76%)	277 (64%)
Percentiles (95% CI) (months)		
25th percentile	NE (48.7, NE)	38.7 (31.5, NE)
Median	NE (NE, NE)	NE (NE, NE)
75th percentile	NE (NE, NE)	NE (NE, NE)
Hazard ratio (95% CI) vs. placebo[1]	0.57 (0.42, 0.79)	
P-value[2]	6×10^{-4}	
Kaplan-Meier estimate (95% CI)		
1-year OS rate	0.97 (0.95, 0.99)	0.94 (0.92, 0.96)
2-year OS rate	0.91 (0.88, 0.94)	0.83 (0.79, 0.86)
3-year OS rate	0.86 (0.82, 0.89)	0.77 (0.72, 0.81)

[1]Hazard ratio is obtained from the stratified Pike estimator. A hazard ratio <1 indicates a lower risk with dabrafenib + trametinib compared with Placebo. Hazard Ratio and p-value from stratified log-rank test are adjusted for randomized strata: Disease stage and BRAF mutation status.
[2]P-value is obtained from the two-sided stratified logrank test.
NE: Not estimable.

The K-M curves for the first interim analysis are presented in Figure 7.

Figure 7: Kaplan-Meier OS (ITT)



A sensitivity analysis based on the Cox model which included only treatment as a covariate confirmed the results of the primary analysis for OS (HR=0.57; 95%CI 0.41, 0.79).

A stratified multivariate Cox regression analysis of OS produced treatment effect estimates adjusted for key baseline prognostic factors (covariates). The results were numerically slightly better compared to the covariate unadjusted estimate of the primary analysis (HR =0.52; 95%CI 0.37, 0.73) (see also Table 14.2-2.8 clinical study report).

An additional OS interim analysis is planned when approximately 299 death events have occurred, i.e. at 50% information fraction of the 597 OS events needed for the final OS analysis, to provide early efficacy information on survival, since the final OS analysis is expected to occur much later.

Follow-up anti-cancer therapy

Summary of post-treatment anti-cancer therapies is presented in Table 19; based on the safety dataset, which includes all patients who received at least one dose of randomized treatment. A higher proportion of patients in the placebo arm (42%) compared to the treatment arm (28%) received post-treatment anti-cancer therapy, which is primarily due to a higher number of disease relapses in the placebo arm. Median time from disease recurrence to start of subsequent anti-cancer therapy was similar between the two arms (7.1 weeks for dabrafenib+trametinib and 7.3 weeks for placebo).

Table 19: Summary of post-treatment anti-cancer therapy (safety population)

Category	Dabrafenib + Trametinib N=435	Placebo N=432
Any Anti-Cancer Therapy		
Yes	148 (34%)	217 (50%)
No	287 (66%)	215 (50%)
Type of Anti-Cancer therapy		
Any Systemic Anti-Cancer Therapy	120 (28%)	183 (42%)
Immunotherapy	86 (20%)	97 (22%)
Small Molecule Targeted Therapy	63 (14%)	137 (32%)
Any BRAF Inhibitor	63 (14%)	137 (32%)
Any MEK Inhibitor	47 (11%)	77 (18%)
Chemotherapy	20 (5%)	23 (5%)
Biologic Therapy	6 (1%)	12 (3%)
Investigational Treatment	6 (1%)	19 (4%)
Other Therapy	2 (<1%)	0
Surgery	78 (18%)	131 (30%)
Radiotherapy	60 (14%)	73 (17%)
n	117	182
Min.	0	0
1st Quartile	3.0	4.1
Median	7.1	7.3
3rd Quartile	17.6	19.7
Max.	136	78

[1] For patients who started post-treatment anti-cancer therapy, excluding radiotherapy and surgery, prior to disease recurrence the time was set to zero

Summary of post-treatment anti-cancer therapies in patients with disease recurrence (excluding death as RFS event) is presented in Table 20. This analysis (based on 163 patients in the dabrafenib+trametinib and 247 patients in the placebo arm) demonstrated that a similar proportion of patients in each arm received systemic anticancer therapy post-relapse (70% in the dabrafenib+trametinib arm and 72% in the placebo arm).

The proportion of patients receiving immunotherapy was higher in the dabrafenib+trametinib arm (52%) than in the placebo arm (38%). Conversely, the use of targeted therapy, such as BRAF and/or MEK inhibitors, was more frequently used in the placebo arm (55%) as compared to the dabrafenib+trametinib arm (37%). Chemotherapy was administered in a lower proportion of patients in both arms (12% in the dabrafenib+trametinib arm and 9% in the placebo arm).

Table 20: Summary of post-treatment anti-cancer therapy in patients with disease recurrence

Category	Dabrafenib + Trametinib N=163	Placebo N=247
Any Anti-Cancer Therapy, n(%)		
Yes	141 (87)	203 (82)
No	22 (13)	44 (18)
Type of Anti-Cancer therapy		
Any Systemic Anti-Cancer Therapy, n(%)	114 (70)	178 (72)
Immunotherapy	84 (52)	95 (38)
Small Molecule Targeted Therapy	61 (37)	135 (55)
Any Braf Inhibitor	61 (37)	134 (54)
Any Mek Inhibitor	46 (28)	76 (31)
Chemotherapy	19 (12)	22 (9)
Biologic Therapy	5 (3)	12 (5)
Investigational Treatment	6 (4)	19 (8)
Other Therapy	2 (1)	0
Surgery	70 (43)	114 (46)
Radiotherapy	58 (36)	71 (29)
Time from Disease Recurrence to Start of Subsequent Anti-Cancer Therapy (weeks)[1]		
n	114	178
Min.	0	0
1st Quartile	3.1	4.1
Median	7.1	7.2
3rd Quartile	17.6	19.7
Max.	136	78

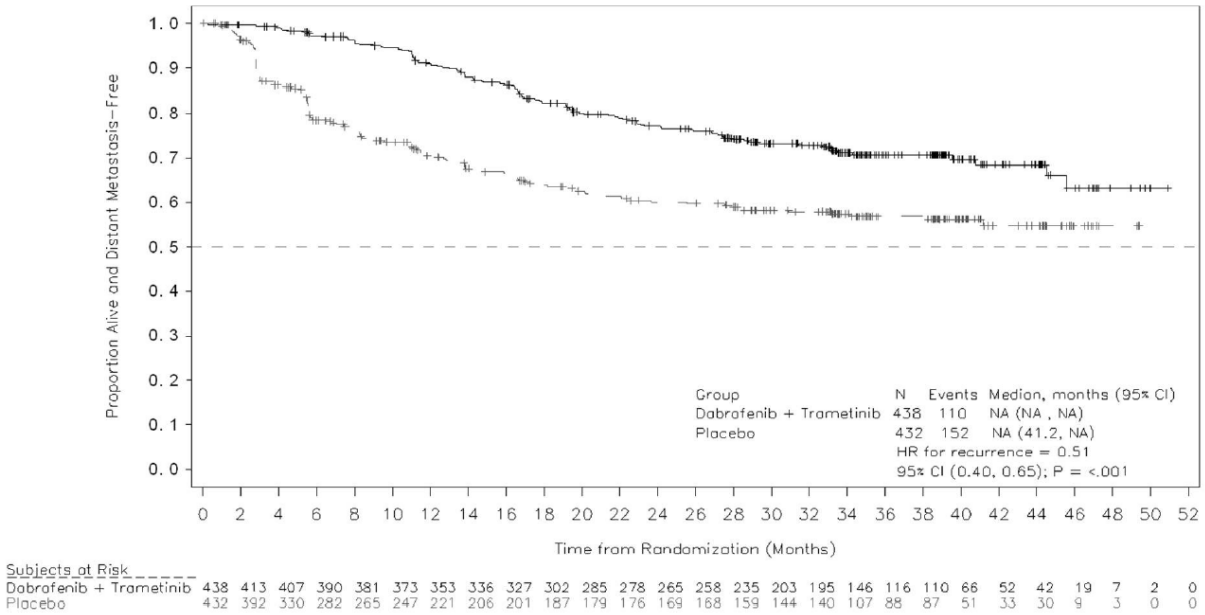
[1] For patients who started post-treatment anti-cancer therapy, excluding radiotherapy and surgery, prior to disease recurrence the time was set to zero

Distant metastasis-free survival

In the DMFS analysis, the first occurrence of distant metastasis or death (if it occurred before documented recurrence) was counted as an event.

The estimated HR based on the analysis of 30-Apr-2017 for DMFS was 0.51 (CI95 0.40, 0.65) and was in favor of the dabrafenib+trametinib arm. The DMFS event analysis included 106 relapses and 4 deaths in the dabrafenib+trametinib arm and 150 relapses and 2 deaths in the placebo arm. The median DMFS was not reached in either treatment arm due to the low event rates (Figure 9). The percentage of patients who were censored with no additional follow-up was similar between the dabrafenib+trametinib arm (23%) and the placebo arm (30%). The K-M estimated DMFS rate at 3 years was 71% (95%CI 66%, 76%) in dabrafenib+trametinib arm and 57% (95%CI 52%, 63%) in the placebo arm.

Figure 8: Kaplan-Meier investigator-assessed DMFS (secondary efficacy analysis; ITT; 30-Jun-2017)



The updated DMFS analysis (30-Apr-2018) included 114 relapses and 4 deaths in the dabrafenib+trametinib arm and 153 relapses and 2 deaths in the placebo arm. The median DMFS was not reached in either treatment arm (Figure 9) and DMFS rates are shown in Table 21.

Figure 9: Kaplan-Meier investigator-assessed DMFS (secondary efficacy analysis; ITT) – data cut off 30-Apr-2018

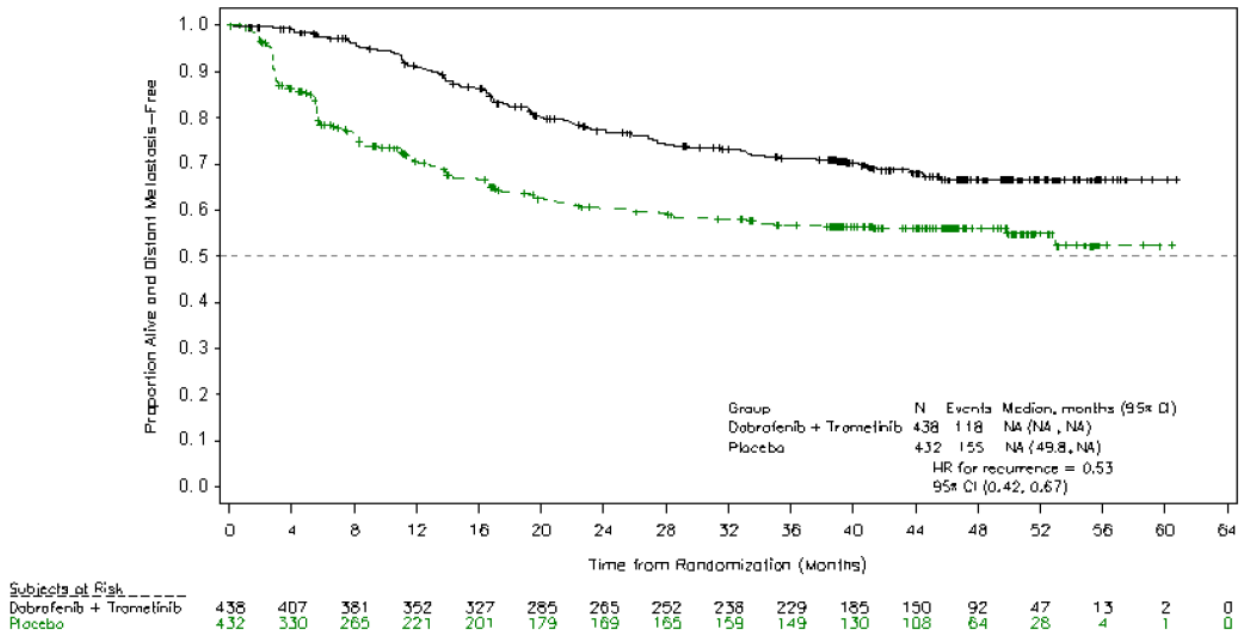


Table 21: Estimated percentages of distant metastasis-free survival patients by the Kaplan-Meier curves (30-Apr-2018)

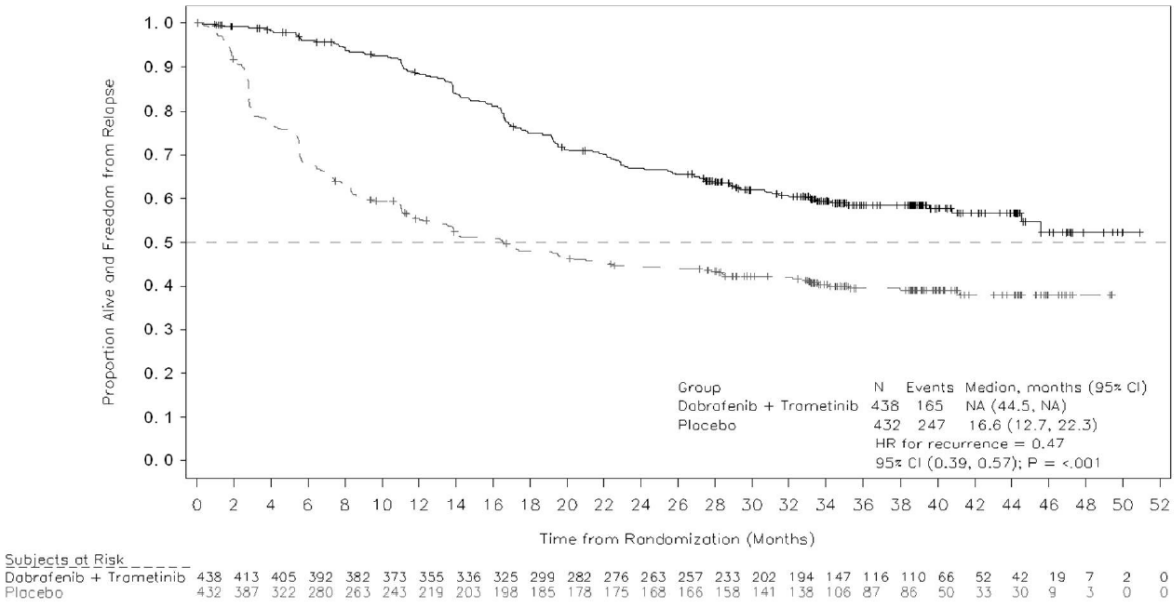
	Dabrafenib + Trametinib N=438	Placebo N=432
1-year DMFS rate (95% CI) [1]	0.91 (0.88, 0.94)	0.70 (0.66, 0.75)
2-year DMFS rate (95% CI) [1]	0.77 (0.73, 0.82)	0.60 (0.55, 0.66)
3-year DMFS rate (95% CI) [1]	0.71 (0.67, 0.76)	0.57 (0.52, 0.62)

[1] The DMFS rate estimation is based on the Kaplan-Meier method and the confidence intervals are estimated using log transformation.

Freedom from relapse

In the FFR analysis, local or distant recurrence or a new primary melanoma were counted as events, and patients who died of causes other than melanoma or treatment-related toxicity were censored. The estimated HR for FFR was 0.47 (95%CI 0.39, 0.57), in favor of the dabrafenib+trametinib arm. The FFR event analysis included a total of 412 disease- or treatment-related relapses or deaths. Among these, 163 (37%) events of relapse and 2 deaths occurred in the dabrafenib+trametinib arm, and 247 (57%) events of relapse and no deaths occurred in the placebo arm. In the FFR analysis, local or distant recurrence or a new primary melanoma were counted as events, and patients who died of causes other than melanoma or treatment-related toxicity were censored. Median FFR was 16.6 months in the placebo arm and was not reached in the dabrafenib+trametinib arm (Figure 10). The percentage of patients who were censored with no additional follow-up available was similar between the dabrafenib+trametinib arm (10%) and the placebo arm (8%).

Figure 10: Kaplan-Meier FFR (secondary efficacy analysis; ITT)



Health-related quality of life

EQ-5D questionnaire completion rates as a percentage of available patients at the time of assessment were at the month 12 assessment 93% in the dabrafenib+trametinib arm and 97% in the placebo arm; the completion rates were 92% for the first 3 years in both treatment arms.

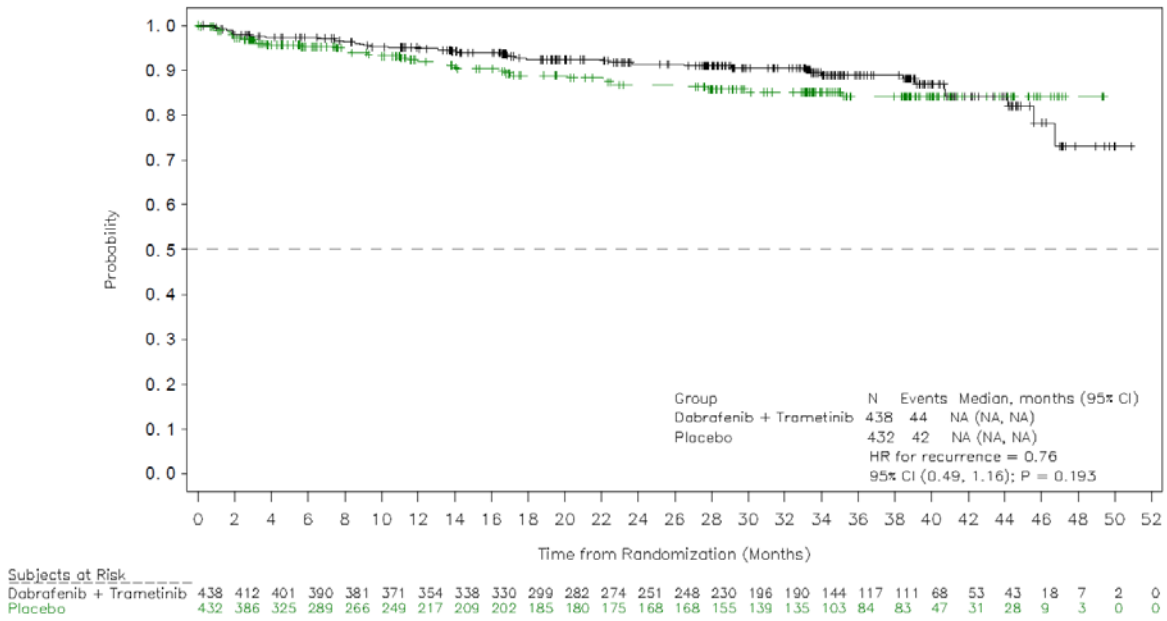
At months 6, 12, 24, 36 and 48, the number (%) of patients in the dabrabefenib+trametinib arm with EQ-5D data available were 363 (83%), 337 (77%), 254 (58%), 186 (42%), and 42 (10%), respectively. Whereas for patients in the placebo arm, data were available for 298 (69%), 236 (55%), 172 (40%), 132 (31%), and 31 (7%), respectively.

Baseline scores were comparable between arms for the thermometer scale (or visual analogue scale) and health utility scores as measured by the EQ-5D. When assessed for differences between treatment arms using mixed-model repeated measures analyses, there was no statistically significant difference in thermometer or utility scores between the two treatment arms and changes from baseline were minimal for all assessments throughout the treatment period.

ECOG performance status

All ECOG analyses were based on the ITT population. In the presence of missing data, the analysis of time-to-definitive deterioration in ECOG PS was provided. Definitive deterioration was defined as a definitive increase in PS by at least one category of the score from baseline. Deterioration was considered definitive if no improvements in the ECOG PS status were observed after an instance of deterioration. The estimated HR indicated a 24% lower risk of definitive deterioration of ECOG performance status with dabrafenib+trametinib (HR=0.76; 95%CI 0.49, 1.16) with nominal p-value equal to 0.193) (Figure 11).

Figure 11: Kaplan-Meier time to definitive deterioration in ECOG scores



Ancillary analyses

RFS censoring

A total of 272 patients (62%) in the dabrafenib+trametinib arm and 184 patients (43%) in the placebo arm were censored in the primary analysis of RFS. The reasons for censoring are detailed in Table 22.

Table 22: Summary of reasons for censoring

	Dabrafenib + Trametinib (N=438)		Placebo (N=432)	
Number of Subjects Censored	272	(62%)	184	(43%)
Event Free at Analysis Cut-off	258	(59%)	176	(41%)
Extended Loss to Follow-up	1	(<1%)	4	(<1%)
Start of New Anti-cancer Therapy	2	(<1%)	0	
No adequate post baseline assessments	11	(3%)	3	(<1%)
Evidence of unresected melanoma or distant metastatic disease at screening	0		1	(<1%)

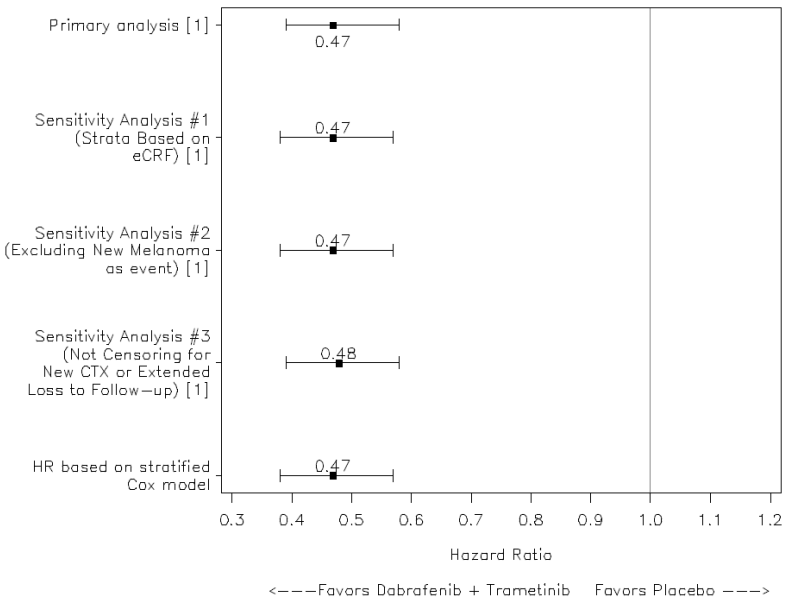
The percentages of patients censored as being event-free at the data analysis cut-off date are higher in the treatment arm corresponding to the larger number of RFS events observed in the placebo arm.

Of note, those numbers were derived as the total number of censored patients minus patients censored for other censoring reasons (extended loss to follow-up, start of new anticancer therapy, no adequate post-baseline assessment, unresected melanoma at screening) and without taking into account withdrawal from the study. Therefore, the number of patients censored as being 'event-free at the data analysis cut-off date' as presented in Table 22 are higher than the number of patient 'censored with follow-up ongoing' as presented in Table 16 in which the study withdrawals were taken into account. The impact of censoring due to extended loss to follow up and due to start of a new anti-cancer therapy was addressed by sensitivity analysis #3.

Sensitivity and supportive analyses of RFS

Results from sensitivity analyses are shown below with HR point estimate ranging between 0.47 to 0.48 (Figure 12 and Table 23).

Figure 12: HR and 95%CI for RFS sensitivity analyses



[1]: Hazard ratios were estimated using Pike estimator.

Table 23: Summary of sensitivity and supportive analyses of RFS (primary analysis; ITT)

RFS Analysis	Dabrafenib+trametinib vs placebo
Ignoring extended loss to follow-up and start of new anti-cancer therapy[1]	
Hazard Ratio	
Estimate	0.48
95% CI	(0.39, 0.58)
Stratified Log-Rank P-Value	<0.001
Excluding new melanoma as an event[1]	
Hazard Ratio	
Estimate	0.47
95% CI	(0.38, 0.57)
Stratified Log-Rank P-Value	<0.001
Based on Cox regression analysis[2]	
Hazard Ratio	
Estimate	0.47
95% CI	(0.38, 0.57)
Stratified Log-Rank P-Value	<.001
Based on Multivariate Cox regression analysis[3]	
Hazard Ratio for treatment effect	
Estimate	0.43
95% CI	(0.35, 0.53)
P-Value based on Wald Chi-square test	<.001
Using Stratification factors from eCRF[4]	
Hazard Ratio	
Estimate	0.47
95% CI	(0.38, 0.57)
Stratified Log-Rank P-Value	<0.001

A hazard ratio <1 indicates a lower risk with dabrafenib +trametinib compared with placebo.

[1]Hazard ratios are estimated using a Pike estimator. Hazard Ratio and p-value from stratified log-rank test are adjusted for randomized strata: Disease stage and BRAF mutation status.

[2]Hazard ratio is estimated using Cox model. The exact method is used to handle ties in the event times. Hazard Ratio and p-value from stratified log-rank test are adjusted for randomized strata: Disease stage and BRAF mutation status.

[3] Multivariate Cox regression model stratified by randomization stratification includes treatment and following baseline factors as covariates: gender, T stage (1, 2, 3, 4), Tumor ulceration (Y, N), N stage (N1, N2, N3), In-transit disease (Y, N), Melanoma subtype (Superficial Spreading, Nodular, Other).

[4]Hazard ratios are estimated using a Pike estimator. Hazard Ratio and p-value from stratified log-rank test are adjusted for actual strata from eCRF: Disease stage and BRAF mutation status. Actual disease stages (IIIA, IIIB, IIIC) are derived based on the primary tumor (T) stage, regional lymph nodes (N) stage and distant metastasis (M) stage (refer to protocol section 12.1) using data from eCRF.

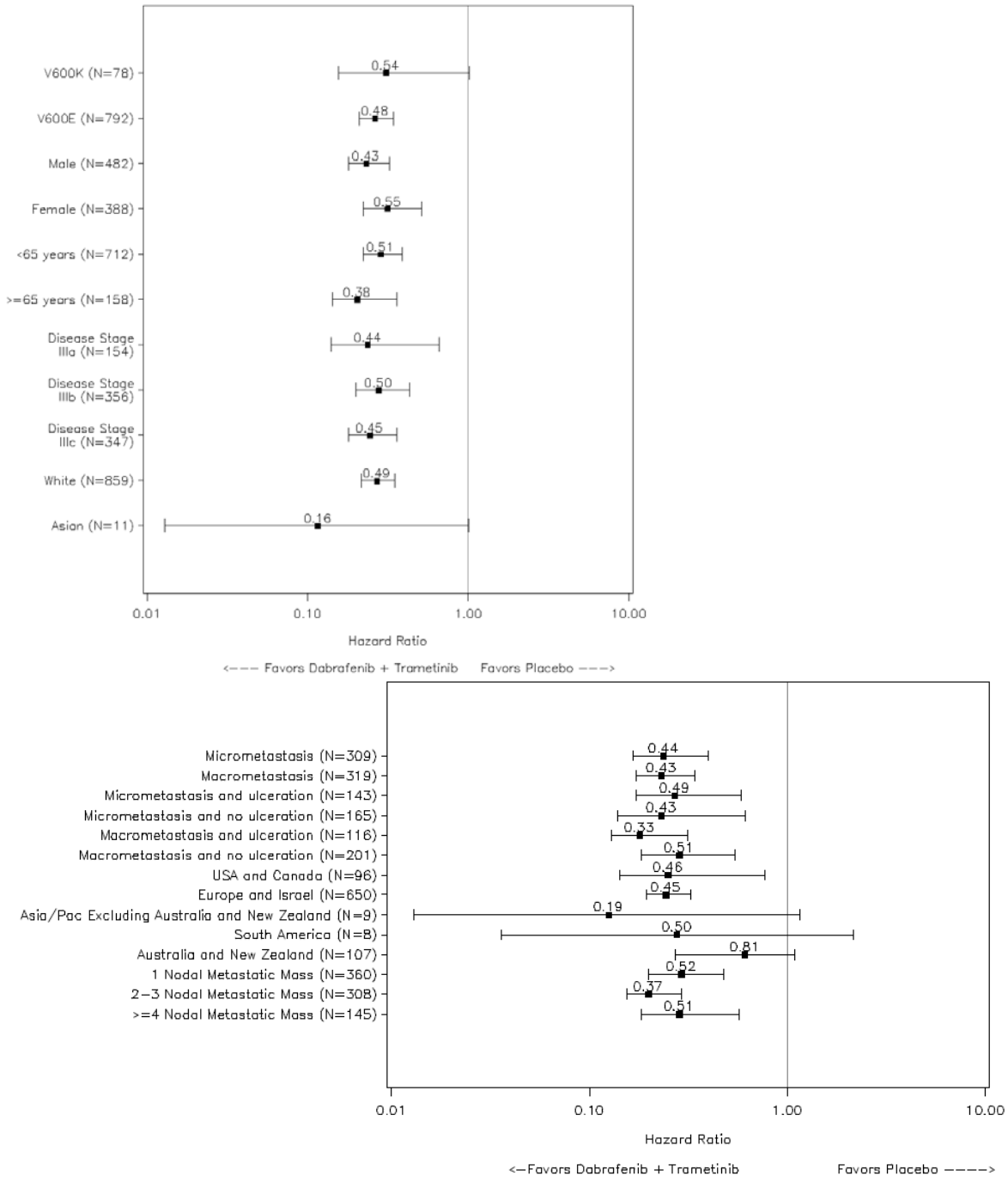
Multivariate Cox Regression

A stratified multivariate Cox model was fitted to better estimate the effects of the prognostic characteristics on RFS and their impact on the treatment effect. The multivariate model for RFS included prognostic characteristics of gender (male, female), tumour staging and ulceration, nodal stage, presence or absence of in-transit disease, and melanoma subtype (superficial spreading, nodular and other) as covariates. The HR for treatment effect after adjusting for these covariates was 0.43 (95%CI 0.35, 0.53).

Subgroup analyses for RFS

To assess homogeneity and consistency of the RFS treatment effect across pre-defined patient subsets, an RFS subgroup analysis was performed; the results are shown in Figure 13.

Figure 13: HR and 95%CI for RFS subgroups analyses (ITT)



RFS was evaluated across all stage III subgroups in Figure 14, Figure 15, Figure 16.

Figure 14: Kaplan-Meier RFS for subgroup with disease stage IIIa at initial diagnosis

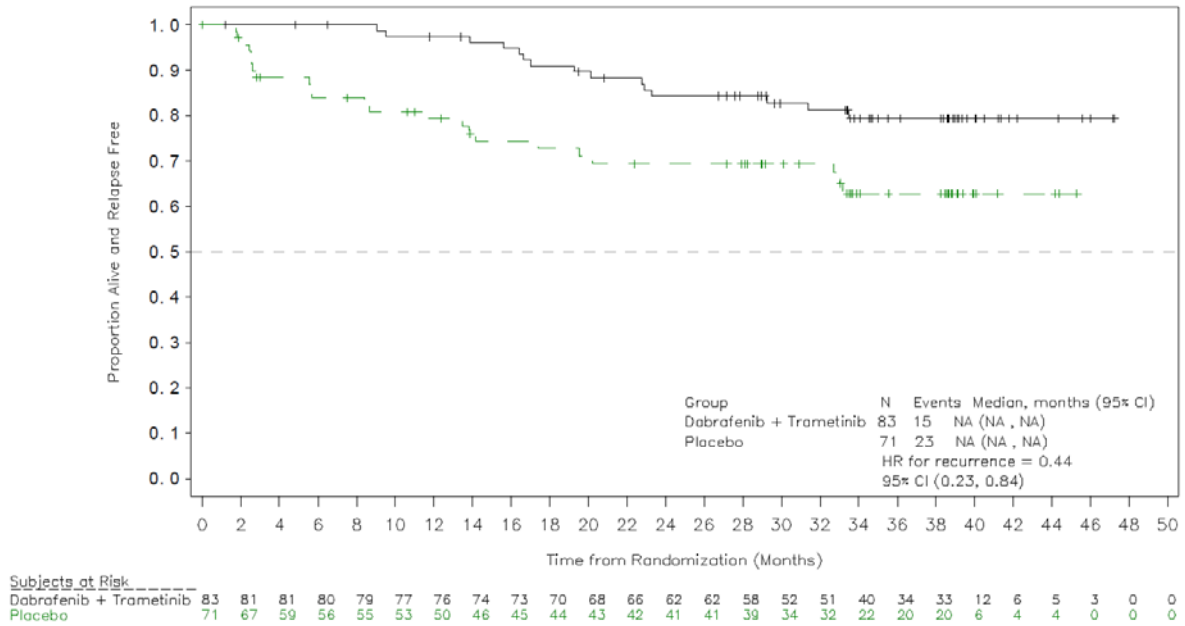


Figure 15: Kaplan-Meier RFS for subgroup with disease stage IIIb at initial diagnosis

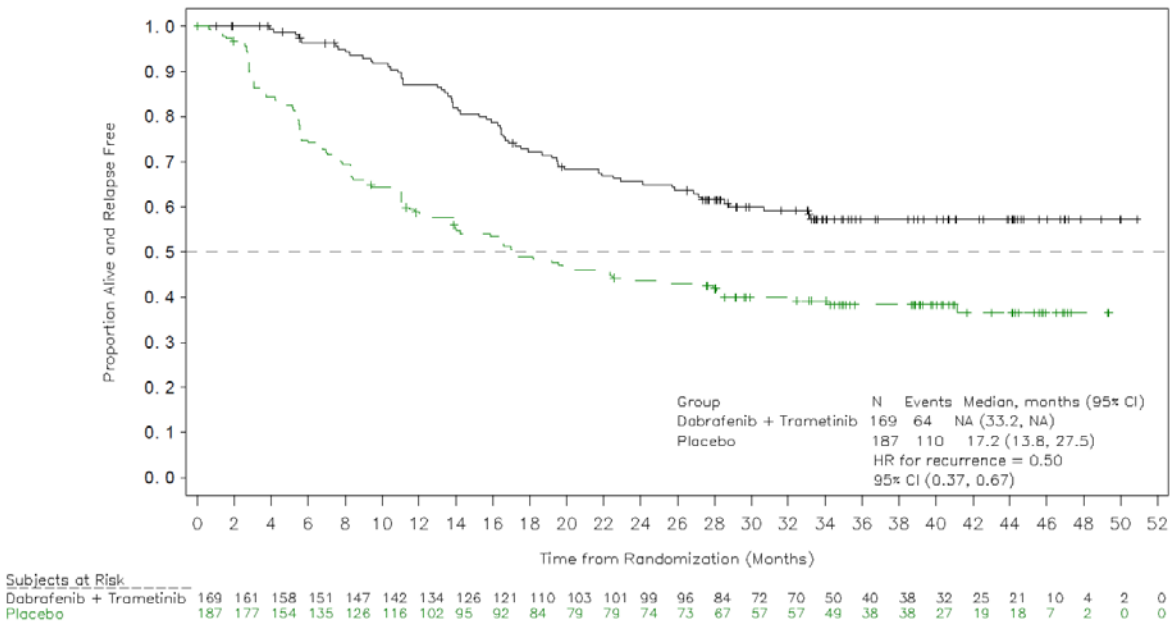
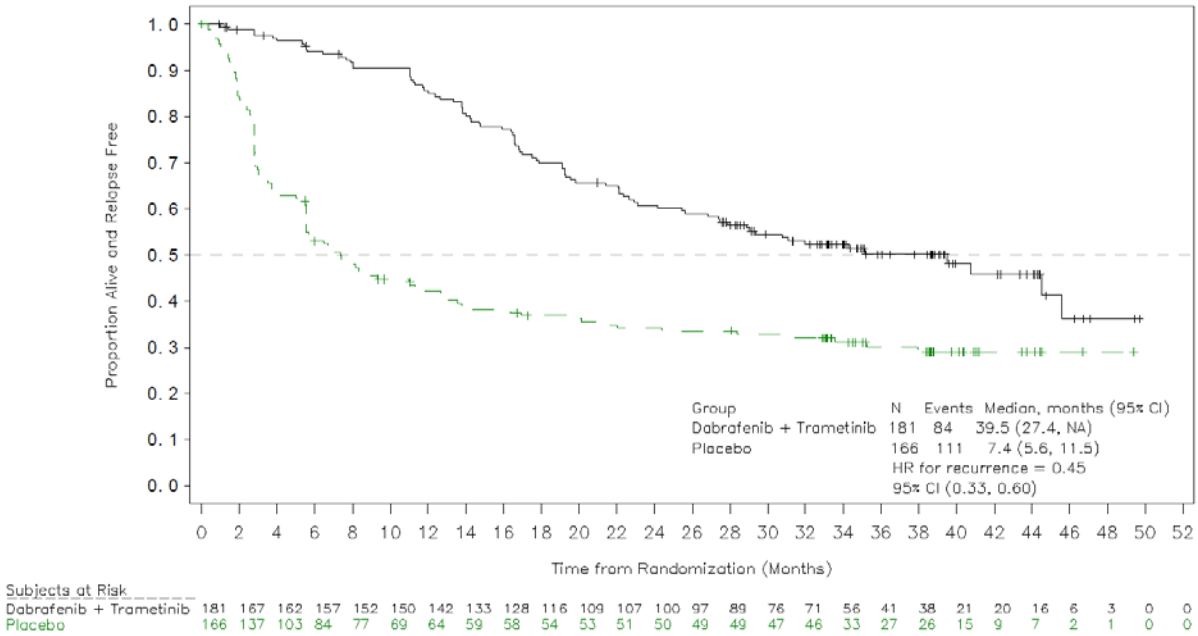


Figure 16: Kaplan-Meier RFS for subgroup with disease stage IIIc at initial diagnosis



Staging IIIA-C according to the new AJCC staging

A post-hoc subgroup analysis was performed to evaluate RFS in patients by disease stage based on AJCC 8 classification. The 870 patients, randomized to the dabrafenib+trametinib arm (n=438) and the placebo arm (n=432), were re-categorized as per AJCC 8 staging system into stage IIIA (dabrafenib+trametinib, n=50; placebo, n=39), stage IIIB dabrafenib+trametinib, n=145; placebo, n=154), stage IIIC (dabrafenib+trametinib, n=217; placebo, n=214), and stage IIID (dabrafenib+trametinib, n=22; placebo, n=17). Four patients in the dabrafenib+trametinib arm and 8 patients in the placebo arm were not recategorized to the AJCC8 classification due to missing information in T or N categories.

The results are shown in Table 24.

Table 24: Summary of RFS analysis for stage subgroups by AJCC7 and AJCC8 staging classification

	AJCC 7			AJCC 8		
	N	**Events**	**HR (95% CI)**	**N**	**Events**	**HR (95% CI)**
Stage IIIA	154	38	0.44 (0.23, 0.84)	89	17	0.46 (0.17-1.21)
Stage IIIB	356	174	0.50 (0.37, 0.67)	299	132	0.46 (0.33-0.65)
Stage IIIC	347	195	0.45 (0.33, 0.60)	431	233	0.49 (0.38-0.64)
Stage IIID	NA	NA	N/A	39	26	0.34 (0.15-0.80)

RFS stratified by AJCC 8 staging yielded HR=0.47 [95% CI, 0.39-0.58].

Summary of main study(ies)

Table 25 summarises the efficacy results from the main study supporting the present application. This summary should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 25: Summary of efficacy for trial COMBI-AD

Title: COMBI-AD: A phase III randomized double blind study of dabrafenib (GSK2118436) in COMBInation with trametinib (GSK1120212) versus two placebos in the ADjuvant treatment of high-risk BRAF V600 mutation-positive melanoma after surgical resection			
Study identifier	BRF115532/DRB436F2301		
Design	Two-arm, randomized, double-blind phase III study		
	Study initiation date: Early termination data: Study completion date:		31-Jan-2012 (first patient first visit) Not applicable Ongoing (data cut-off for primary analysis 30-Jun-2017)
Hypothesis	Superiority		
Treatments groups	Dabrafenib/trametinib		Dabrafenib 150 mg BID + trametinib 2 mg OD, 1 year, n=438
	Placebo		Matching placebo capsules for dabrafenib 150 mg BID + matching tablets for trametinib 2 mg OD, 1 year, n=432
Endpoints and definitions	Primary endpoint	RFS	Time from randomization to disease recurrence or death from any cause.
	Secondary endpoint	OS	Interval from randomization to the date of death, irrespective of the cause of death.
	Secondary endpoint	DMFS	Interval from randomization to the date of first distant metastasis or date of death, whichever occurred first
	Secondary endpoint	FFR	Interval from randomization to local or distant recurrence with censoring of patients dying from causes other than melanoma or treatment-related toxicity at the date of death.
Database lock	30-Apr-2018 for RFS and DMFS, 30-Jun-2017 for other endpoints		

Results and Analysis

Analysis description	**Primary Analysis**		
Analysis population and time point description	Intent to treat		
Descriptive statistics and estimate variability	Treatment group	Dabrafenib/trametinib	Placebo
	Number of subject	438	432
	RFS (median, months)	NE	16.6
	95%CI	46.9 - NE	12.7 – 22.1
	OS (median, months)	NE	NE
	95%CI	NE – NE	NE - NE
	DMFS (median, months)	NE	NE
	95%CI	NE – NE	49.8 - NE
	FFR (median, months)	NE	16.6
	95%CI	44.5 - NE	12.7 – 22.3
Effect estimate per comparison	Primary endpoint RFS	Comparison groups	Dabrafenib/trametinib vs placebo

		HR	0.49
		95%CI	0.40 – 0.59
		P-value	$1.53X10^{-14}$ Cave: No p-value was provided for analysis 30-Apr-2018; this p-value is applicable to primary analysis of 30-Apr-2017.
	Secondary endpoint OS	Comparison groups	Dabrafenib/trametinib vs placebo
		HR	0.57
		95%CI	0.42 – 0.79
		P-value	$6x10^{-4}$
	Secondary endpoint DMFS	Comparison groups	Dabrafenib/trametinib vs placebo
		HR	0.53
		95%CI	0.42 – 0.67
		P-value	<0.001 Cave: No p-value was provided for analysis 30-Apr-2018; this p-value is applicable to primary analysis of 30-Apr-2017.
	Secondary endpoint FFR	Comparison groups	Dabrafenib/trametinib vs placebo
		HR	0.47
		95%CI	0.39 – 0.57
		P-value	<0.001

2.3.2. Discussion on clinical efficacy

Design and conduct of clinical studies

Study design- COMBI-AD is a randomised, double-blind phase III trial to evaluate the combination of dabrafenib and trametinib versus two placebos as adjuvant treatment in high-risk BRAF V600E/K mutant melanoma after surgical resection. 870 patients were randomised 1:1 with stratification by BRAF status and disease stage. Although treatment assignment was blinded for investigators, it is likely that due to class-specific toxicity, investigators would know for at least a part of the study population that dabrafenib+trametinib was given. However, it is also regarded unavoidable in this type of trial. Physicians could request treatment unblinding post-recurrence to determine the next therapy, which is understandable to provide best patient care.

RFS was a primary endpoint with OS as a key secondary endpoint while other supportive secondary efficacy endpoints were DMFS (distant metastases or death), and FFR (local or distant recurrence with censoring of death from causes other than melanoma or treatment-related toxicity at the date of death). These endpoint were considered acceptable in the adjuvant setting. Although treatment assignment was blinded for investigators, it is likely that due to class-specific toxicity, investigators would know for at least a part of the study population that dabrafenib+trametinib was given. In that aspect, central assessment of radiological exams would have provided a more objective assessment of the results, however, given the robustness of the primary endpoint RFS, there are no uncertainties concerning the observation of radiological or clinical recurrence of disease.

The choice of placebo comparators is acceptable as there are no standard of care treatments for stage III adjuvant melanoma. Treatment was given for a maximum of 12 months or until disease recurrence, death, unacceptable toxicity, or withdrawal of consent as it is unknown what the optimal duration of treatment should be from a scientific rationale, but it is agreed as there is no evidence for an alternative to the proposal of 1-year treatment duration. For patients that relapse or do not respond to therapy, there is no evidence that prolonged treatment would be of benefit. Hence, the 1 year duration is acceptable based on clinical practice for adjuvant treatment. Overall, the study design is consistent with the scientific advice (SA) of 2012 (EMA/CHMP/SAWP/381667/2012) for the adjuvant setting in melanoma patients.

Study population-Patients with lower risk melanoma, i.e. stage IIIA with lymph node metastasis <1 mm were not included. This information has been described in section 5.1 of the SmPC.

Study conduct - There were no concerns on the conduct of the study. The MAH altered the timing of RFS and OS interim analyses including alpha spending. This change in timing of analysis was endorsed during a follow-up SA in 2017 (EMA/CHMP/SAWP/209337/2017). Apart from the planned interim OS analysis at time of the RFS analysis, an additional OS interim analysis with 299 events (50% information fraction, projected to occur in December 2019) was implemented after endorsement of the same SA. The rationale was the low event rate on OS. The type of alpha spending for OS (2 interim, one final) was proposed to be changed (from O'Brien-Fleming to Pocock), but in the end was not changed.

Efficacy data and additional analyses

Baseline characteristics- The baseline demographic and disease characteristics were balanced between the treatment arms.

Primary endpoint RFS- The study met its primary endpoint demonstrating a statistically significant effect of the treatment arm with HR 0.47 (95%CI 0.39-0.58; $p=1.53x10^{-14}$). Median time to reach RFS was 16.6 months in the placebo arm (95%CI 12.7-22.1) and not reached in the treatment arm (95%CI 44.5-NE). Also RFS rates at 1, 2, and 3 years were 0.88 v 0.56, 0.67 v 0.44 and 0.58 v 0.39 in favour of the treatment arm compared to placebo. Sensitivity analyses were all supportive of the efficacy of the dabrafenib+trametinib arm (only 14 vs 8 subjects, 3% vs 2%, were censored for potentially informative reasons). Subgroup analyses all showed HR<1 in favour of the treatment arm, including for known prognostic factors such as disease stage, nodal status and ulceration.

An additional data cut-off at 30-Apr-2018 with an extra 10 months of follow-up showed consistent results with HR 0.49 (95%CI 0.40-0.59) with the RFS Kaplan-Meier curves separating after the first assessment on study in favour of dabrafenib+trametinib. Compared to the primary RFS analysis 17 additional RFS event were recorded (11 in dabrafenib+trametinib arm and 6 in placebo arm). Median follow-up was 44 months in the dabrafenib+trametinib group and 42 months in the placebo group. The curves are interpretable until ~38 months, which is considered adequate, given that most recurrences occur <3 years. With the additional follow-up in both the placebo arm and in the dabrafenib+trametinib arm a plateau is visible, indicating cure, but importantly, at 3 years the difference in RFS rate was 19% in favour of the dabrafenib+trametinib arm. Support that the RFS data are mature is provided by the event and censoring rates. The number of events after 36 months is low in both arms and seems to stabilise.

A cure rate modelling was performed with the RFS data from the 30-Apr-2018 cut-off. The MAH did not provide the methodology on how this analysis was performed. The cure rate model seems to fit the RFS Kaplan-Meier curves.

Key secondary endpoint OS- According to the hierarchical statistical testing plan, OS was tested after statistical significance of RFS (first interim analysis) with a total 153 deaths, being 26% of the total targeted of 597 deaths required for the final analysis. The number of events was 60 (14%) in the dabrafenib+trametinib arm and 93 (22%) in the placebo arm. Median OS was immature and not reached in either arm. HR was 0.57 (95%CI 0.42-0.79) and the threshold for significance was not reached. OS rates at 1, 2, and 3 years were 0.97 v 0.94, 0.91 v 0.83 and 0.86 v 0.77 in favour of the treatment arm compared to placebo. Thus, the data are not mature yet, but they show a trend to support the favourable RFS in the experimental arm. The second interim analysis is projected to be available in 2022 with 50% information fraction planned.

Secondary endpoint DMFS- Median DMFS was not reached in either treatment arm due to low event rates, but the HR of 0.51 (95%CI 0.40-0.65) also showed a trend in support for the treatment arm, as was the 3-year DMFS rate. Based on the cut-off date of 30-Apr-2018 the estimated HR for DMFS was 0.53 (95%CI 0.42-0.67). In the Kaplan-Meier curves considerable censoring is shown, but the clear separation of the curves on this relevant secondary endpoint is supportive for the RFS benefit of dabrafenib+trametinib as adjuvant melanoma treatment.

Secondary endpoint FFR- In the FFR analysis, patients were censored for death from other causes than melanoma or treatment-related toxicity at the date of death and results are expected to be similar to the primary endpoint. Indeed the number of events and HR results were very similar to the data for RFS and are considered supportive.

Post-treatment anti-cancer therapy- For the patients with disease recurrence 87% and 82% of the patients received post-treatment anti-cancer therapy in the treatment and control arm, respectively. Systemic treatment was given in 70% and 72%, a similar proportion in both treatment arms. In the dabrafenib+trametinib arm this was mainly immunotherapy (52%), and BRAF-inhibition with or without MEK-inhibition (37%). For the placebo-treated patients these numbers were 38% and 55%. Responses to next-line systemic treatment were provided. The majority of patients with a recurrence received next-line immunotherapy or targeted therapy. There is a trend towards lower responses to immunotherapy post recurrence in the dabrafenib+trametinib arm compared to patients that were treated with placebo, however the numbers are too small to draw definitive conclusions. Complete and partial responses were observed, also after dabrafenib+trametinib. Responses were also seen after next-line targeted therapy including BRAF-MEK-inhibition and immunotherapy). RFS2 data were not collected, making it difficult to assess the efficacy of next-line treatment. Responses were observed for next-line treatment (including BRAF-MEK-inhibition and immunotherapy), which is reassuring. Due to the small numbers, definitive conclusions about increased resistance to next-line therapy after adjuvant dabrafenib+trametinib cannot be made.

Immunotherapy as well as BRAF and MEK inhibitors (as single agent or in combination) have proven to be efficacious treatments in metastatic melanoma, thus; suggesting that patients had a similar access to highly effective therapies post relapse. This observation provides additional support to the conclusion that the survival improvement observed can be attributed to the combination treatment of dabrafenib and trametinib.

Exploratory endpoint- There were no statistically significant differences in HRQOL measures between the two arms and, during the study, changes from baseline were minimal. Since disease-related symptoms are not expected in an adjuvant setting, this suggests that the treatment has no negative impact on QoL. Changes in ECOG performance scale were also similar between the two groups.

Additional expert consultation

The SAG oncology was invited to provide its expert's views on the following point:

Do you consider that the currently available results from the COMBI-AD trial, on the Mekinist-Tafinlar combination in the adjuvant treatment setting for melanoma, are sufficient to demonstrate clinical benefit?

The SAG unanimously agreed that the currently available results from the COMBI-AD trial clearly demonstrate the efficacy of the dabrafenib+trametinib combination in the adjuvant treatment of melanoma in the target population studied. This was based on clinically and statistically compelling difference in terms of the clinically relevant endpoint of recurrence-free survival (in accordance with the present anticancer guidelines); trend towards overall survival improvement and curative potential; consistent effect on distant metastasis-free survival; supportive data from the metastatic setting; acceptable safety profile with mostly with mainly reversible toxicity.

Concerning the possibility to induce resistance for subsequent treatments, the positive trend in survival is reassuring and currently data on re-challenging post-recurrence are lacking. It will be of interest to see the pattern of recurrence (on or off-treatment) to elucidate some mechanistic aspect. It was also discussed that it may be possible to further optimise dose although such studies are difficult to conduct.

There was some discussion about whether the effect observed could be extrapolated to the current stage IIIA classification (TNM classification version 8) that includes slightly better prognosis patients than those treated in the study (version 7; stage IIIA [lymph node metastasis >1 mm]). The prevalent view was that the effects observed could be extrapolated to the new staging system and that any uncertainty about treating lower-risk patients should be part of the patient-physician discussion.

In conclusion, the present data demonstrate a clearly positive benefit-risk balance.

2.3.3. Conclusions on the clinical efficacy

In conclusion, the study design of COMBI-AD is considered acceptable. The combination of dabrafenib and trametinib not only leads to a prolonged RFS benefit, but also increases cure rate. The primary endpoint is supported by a trend in OS and support from secondary endpoints DMFS, and FFR as well as subgroup analyses. The combination of dabrafenib+trametinib demonstrates a significant and relevant long-term effect in the adjuvant treatment of stage III melanoma. In the adjuvant melanoma setting, patients should be treated for a period of 12 months unless there is disease recurrence or unacceptable toxicity.

In the COMBI-AD trial patient with stage IIIA disease were only included if the lymph node metastasis was >1 mm. In the AJCC staging, both 7th and 8th edition, this cut-off is not used. It is agreed with the SAG that by using the cut-off of 1 mm in the inclusion criteria, slightly better prognosis patients with stage IIIA disease were not included in the study.

As OS data are currently immature, there is a requirement for the verification of the impact of the intervention on the OS outcome. Therefore, the CHMP expects the MAH to submit the following measures to address issues related to efficacy:

- Results from the second OS interim analysis of the COMBI AD trial with 50% of the information fraction should be submitted by Q4 2022.

The CHMP recommends the following measures in order to address issues related to efficacy:

- The MAH discussed their biomarker plan to assess baseline and relapse tissue samples. Biomarker results from all tissue samples and from plasma samples collected at time of relapse from the COMBI-AD trial should be submitted (expected to be available for submission in 2019).

2.4. Clinical safety

Introduction

The dabrafenib plus trametinib safety data described below is derived from the BRF115532 study in stage III melanoma patients in the adjuvant setting. The existing safety profile of trametinib (2 mg QD) in combination with dabrafenib (150 mg BID) in patients with BRAF V600 mutation positive unresectable or metastatic melanoma was based on two phase III studies (MEK115306 and MEK116513). The most common AEs seen at ≥ 20% included pyrexia, fatigue, nausea, chills, diarrhoea, cough, headache, hypertension, rash, vomiting, arthralgia and peripheral oedema. Most common grade 3 events were pyrexia (4-7%) and hypertension (6-14%) and most common SAEs were pyrexia (14-17%) and decreased ejection fraction (4-7%). In these studies squamous cell carcinoma of the skin (cuSCC) was reported more frequently in the BRAF inhibitor monotherapy arms compared to the combination therapy arms (4-10% vs <1%). Six fatal bleedings were observed in the combination therapy arms, to which a contribution of the therapy could not be ruled out. Haemorrhage is already addressed in section 4.4. and 4.8 of the SmPC. Toxicity was generally manageable, despite higher rates of AEs leading to dose mitigation or interruption and higher rates of SAEs observed in patients treated with combination therapy versus monotherapy components. Following assessments of PSURs, photosensitivity was identified as a common AE and acute, severe left ventricular dysfunction due to myocarditis (reversible upon stopping treatment) was added to the warning on LVEF reduction/LV dysfunction in the SmPC and colitis was added as an uncommon AE for the combination therapy.

Patient exposure

By the time of data cut-off (30-Jun-2017), the median patient follow-up time was 34 months (range: 0-51 months) in the D+T group and 33 months (range: 1-50 months) in the placebo group. At the time of the cut-off, all patients still in the study were off treatment and in the follow –up phase.

Median duration of exposure was 11 months for both dabrafenib and trametinib, and 10 months for the placebo arm. Details on exposure to study treatment are shown in Table 26 and Table 27.

Table 26: **Exposure to study treatment**

	Dabrafenib + Trametinib		Placebo	
	Dabrafenib	Trametinib	Placebo for Dabrafenib	Placebo for Trametinib
Exposure variable	N=435	N=435	N=432	N=432
Duration of exposure (months)[1]				
n	435	435	432	432
Mean (SD)	8.2 (3.97)	8.3 (3.94)	7.7 (3.88)	7.7 (3.89)
Median	11.0	11.0	10.0	10.0
Min-Max	0 - 12	0 - 12	0 – 12	0 - 12
Duration of exposure category (months) – n (%)[1, 2]				
n	435	435	432	432
<3	72 (17%)	72 (17%)	73 (17%)	73 (17%)
3-6	53 (12%)	49 (11%)	86 (20%)	87 (20%)
6-12	310 (71%)	314 (72%)	273 (63%)	272 (63%)
Average daily dose (mg)[3]				
n	435	435	432	432
Mean (SD)	251.32 (57.190)	1.81 (0.296)	291.14 (21.644)	1.97 (0.084)
Median	283.85	1.97	299.55	2.00
Min-Max	88.5 – 300.0	0.6 – 2.0	150.0 – 303.1	1.0 – 2.4
Cumulative dose (mg)				
n	435	435	432	432
Mean (SD)	66719.7 (35306.18)	476.7 (232.00)	71655.5 (33755.74)	483.8 (224.63)
Median	75600.0	598.0	94425.0	641.0
Min-Max	300 - 110550	2 - 734	2700 - 108600	18 - 726

[1]The time on study drug does not exclude dose interruptions.

[2] The treatment period is 12 months.

[3]The patient daily dose (the cumulative dose divided by the duration of exposure) is calculated for each patient first and the summary statistics are calculated based on the patient average daily dose.

Table 27: Summary of exposure by cumulative duration for D+T therapy

Study Drug	Duration of Exposure	Persons (N = 435)	Person Time (Months)
Dabrafenib + Trametinib	0-<1 month	26 (6%)	0
	>=1 month	409 (94%)	3540
	>=3 months	360 (83%)	3477
	>=6 months	316 (73%)	3306
	>=9 months	293 (67%)	3146
	Total Person Time	435 (100%)	3540

Permanent discontinuations

In the D+T group, 272 patients (63%) completed scheduled dabrafenib treatment and 277 (64%) completed scheduled trametinib treatment. In the D+T group, 163 patients (37%) discontinued dabrafenib treatment and 158 patients (36%) discontinued trametinib treatment. In the placebo group, 205 (47%) discontinued treatment prematurely.

Dose modifications

Dose reductions

Patients with dose reductions were more frequent in the D+T arm (43% (n=188) of the patients with dabrafenib and 24% (n=104) trametinib) compared to the placebo arm (12% (n=54) of the patients with dabrafenib placebo and 2% (n=8) trametinib placebo). The total number of dose reductions was 307 for dabrafenib and 62 for its placebo and 134 for trametinib vs 8 for its placebo. The most common reasons for dose reductions were AEs (98% (n=131) of the dose reductions in the dabrafenib and 74% (n=227) trametinib) vs (88% (n=7) and 13% (n=8) of the dose reductions in the respective placebo groups) and subject non-compliance in both treatment arms.

In the dabrafenib+trametinib arm, 2 or more dabrafenib dose reductions were required in 87 patients (20%) and 2 or more trametinib reductions were reported in 30 patients (7%). Most dose reductions in the placebo arm occurred once. For patients who have a dose reduction due to AEs early on in treatment, it appears that the KM RFS curve is superior to the RFS curve of patients in the placebo arm.

Dose escalations

The proportion of patients with dose escalations was similar in the dabrafenib+trametinib arm (4% dabrafenib and 4% trametinib) and in the placebo arm (2% dabrafenib placebo and 5% trametinib placebo). The most common reason for dose escalation was following AE resolution or due to patient non-compliance.

Dose interruptions

Dose interruptions are summarized in Table 28.

Table 28: Summary of dose interruptions

	Dabrafenib N=435	Trametinib N=435	Placebo for dabrafenib N=432	Placebo for trametinib N=432
Patients with Any Dose Interruption	336 (77%)	277 (64%)	217 (50%)	158 (37%)
Total Number of Dose Interruptions	2197	1020	888	396
Number of Dose Interruptions[1]				
0	98 (23%)	157 (36%)	215 (50%)	274 (63%)
1	70 (16%)	97 (22%)	88 (20%)	89 (21%)
2	40 (9%)	59 (14%)	40 (9%)	29 (7%)
3 or more	226 (52%)	121 (28%)	89 (21%)	40 (9%)
Not Evaluable	1 (<1%)	1 (<1%)	0	0
Interruption Duration (days)				
n	336	277	217	158
≤ 7	105 (31%)	101 (36%)	152 (70%)	110 (70%)
8 to 14	52 (15%)	50 (18%)	30 (14%)	24 (15%)
>14	179 (53%)	126 (45%)	35 (16%)	24 (15%)
Interruption Duration (days)				
Min	0	0	1	1
Max	177	140	153	39
1st Quartile	5.0	4.0	2.0	2.0
3rd Quartile	31.0	26.0	11.0	9.0
Median	16.5	13.0	4.0	4.0
Reasons for Interruption[2]				
n	2197	1020	888	396
Adverse Event	1224 (56%)	568 (56%)	102 (11%)	69 (17%)
Patient non-compliance	884 (40%)	408 (40%)	693 (78%)	296 (75%)
Other	89 (4%)	44 (4%)	93 (10%)	31 (8%)

[1]Not evaluable means the patient did not receive any drug in any succeeding time period after the first dose.
[2]Patients may be counted multiple times in the same 'reason' row if the patient had multiple interruptions for the same reason.

Adverse events

AEs were graded according CTCAE v4.0. AEs were coded using MedDRA version 19.1. AEs by preferred term (PTs) were summarized by frequency and percentage of patients and sorted by MedDRA System Organ Classes (SOC). Adverse Events of Special Interest (AESIs) were analysed separately.

AEs were recorded from the time the first dose of study treatment administration until 30 days after discontinuation of study treatment, with the exceptions of treatment emergent malignancies (reported regardless of the time from treatment discontinuation to occurrence of the event) and SAEs related to study treatments (reported at any follow up contact). A summary of AEs and deaths is presented in Table 29.

Table 29: Overview of AEs and death

Category	Dabrafenib + Trametinib N=435 n (%)	Placebo N=432 n (%)
Any AE	422 (97)	380 (88)
AEs related to study treatment	398 (91)	272 (63)
Grade 3 or 4	180 (41)	61 (14)
AEs leading to permanent discontinuation of study treatment	114 (26)	12 (3)
AE leading to dose reduction	167 (38)	11 (3)
AE leading to dose interruption	289 (66)	65 (15)
Any SAE	155 (36)	44 (10)
SAEs related to study treatment	117 (27)	17 (4)
Fatal SAEs	1 (<1)	0
Fatal SAEs related to study treatment	0	0

Categories are not mutually exclusive. Patients with multiple events in the same category are counted only once in that category. Patients with events in more than 1 category are counted once in each of those categories.

The most frequently reported AEs by preferred term are reported in Table 30. Grade 3/4 AEs were reported in 41% (39% grade 3, 3% grade 4) patients in the D+T treatment group and 14% (14% grade 3, grade 4 <1%) in placebo group; the most frequently reported grade 3-4 AEs in the D+T arm were hypertension (6%), pyrexia (5%), fatigue (4%), and elevated ALT (4%). Grade 3/4 AEs were not frequently reported in the placebo arm.

AEs considered treatment related

Almost all AEs in the D+T arm were considered treatment-related. The percentages of patients with AEs considered related to study treatment were higher in the dabrafenib+trametinib arm (91%) relative to the placebo arm (63%). The percentage of patients with pyrexia, fatigue, chills, nausea, headache, diarrhoea, arthralgia, rash, vomiting, increased ALT and increased AST was ≥10% higher in the D+T arm than in the placebo arm. The most common AEs related to study treatment are shown in Table 31.

In the D+T arm, 129 patients (30%) had grade 3 treatment-related events versus 20 patients (5%) in the placebo arm, and 7 patients (2%) had grade 4 events versus respectively 1 patient (<1%).

Table 30: Summary of most frequent AEs by PT in at least 10 percent of patients

	Dabrafenib + Trametinib N=435		Placebo N=432	
Preferred term	All grades n (%)	Grade 3/4 n (%)	All grades n (%)	Grade 3/4 n (%)
Any Event	**422 (97)**	**180 (41)**	**380 (88)**	**61 (14)**
Pyrexia	273 (63)	23 (5)	47 (11)	2 (<1)
Fatigue	204 (47)	19 (4)	122 (28)	1 (<1)
Nausea	172 (40)	4 (<1)	88 (20)	0
Headache	170 (39)	6 (1)	102 (24)	0
Chills	161 (37)	6 (1)	19 (4)	0
Diarrhoea	144 (33)	4 (<1)	65 (15)	1 (<1)
Vomiting	122 (28)	4 (<1)	43 (10)	0
Arthralgia	120 (28)	4 (<1)	61 (14)	0
Rash	106 (24)	0	47 (11)	1 (<1)
Cough	73 (17)	0	33 (8)	0
Myalgia	70 (16)	1 (<1)	40 (9)	0
Alanine aminotransferase increased	67 (15)	16 (4)	6 (1)	1 (<1)
Influenza like illness	67 (15)	2 (<1)	29 (7)	0
Aspartate aminotransferase increased	63 (14)	16 (4)	7 (2)	1 (<1)
Pain in extremity	60 (14)	2 (<1)	38 (9)	0
Asthenia	58 (13)	2 (<1)	42 (10)	1 (<1)
Oedema peripheral	58 (13)	1 (<1)	19 (4)	0
Dry skin	55 (13)	0	32 (7)	0
Dermatitis acneiform	54 (12)	2 (<1)	10 (2)	0
Constipation	51 (12)	0	27 (6)	0
Hypertension	49 (11)	25 (6)	35 (8)	8 (2)
Decreased appetite	48 (11)	2 (<1)	25 (6)	0
Erythema	48 (11)	0	14 (3)	0

Preferred terms are sorted in descending frequency of any grades column, as reported in the dabrafenib + trametinib arm.
A patient with multiple occurrences of an AE under one treatment is counted only once in the AE category for that treatment.

Table 31: Summary of adverse events related to study treatment

Preferred Term	Dabrafenib + Trametinib (N=435)		Placebo (N=432)	
Any Event	398	(91%)	272	(63%)
Pyrexia	244	(56%)	28	(6%)
Fatigue	170	(39%)	85	(20%)
Chills	155	(36%)	12	(3%)
Nausea	140	(32%)	52	(12%)
Headache	120	(28%)	50	(12%)
Diarrhoea	101	(23%)	42	(10%)
Arthralgia	98	(23%)	35	(8%)
Rash	98	(23%)	33	(8%)
Vomiting	95	(22%)	12	(3%)
Alanine aminotransferase increased	57	(13%)	2	(<1%)
Myalgia	55	(13%)	30	(7%)
Aspartate aminotransferase increased	51	(12%)	4	(<1%)
Dermatitis acneiform	50	(11%)	9	(2%)
Dry skin	47	(11%)	23	(5%)
Influenza like illness	45	(10%)	8	(2%)
Asthenia	43	(10%)	28	(6%)
Decreased appetite	43	(10%)	19	(4%)
Oedema peripheral	38	(9%)	4	(<1%)
Erythema	35	(8%)	6	(1%)

Table 32: Summary of severity of serious adverse events

Preferred Term	Grade 1	2	3	4	5	Unknown	Total
			Dabrafenib+Trametinib (N=435)				
Any Event	18 (4%)	56 (13%)	70 (16%)	10 (2%)	1 (<1%)	0	155 (36%)
			Placebo (N=432)				
Any Event	6 (1%)	11 (3%)	26 (6%)	1 (<1%)	0	0	44 (10%)

Table 33: Adjuvant treatment of melanoma – Adverse drug reactions for dabrafenib in combination with trametinib vs. placebo

Adverse drug reactions	Dabrafenib in combination with trametinib N=435 %		Placebo N=432 %		Frequency category (combination arm, all grades)
	All Grades	Grade 3/4	All Grades	Grade 3/4	
Infections and infestations					
Nasopharyngitis[1)]	12	<1	12	0	Very common
Blood and lymphatic system disorders					
Neutropenia[2)]	10	5	<1	0	Very common
Metabolism and nutrition disorders					
Decreased appetite	11	<1	6	0	Very common
Nervous system disorders					
Headache[3)]	39	1	24	0	Very common
Dizziness[4)]	11	<1	10	0	Very common
Eye disorders					
Uveitis	1	<1	<1	0	Common
Chorioretinopathy[5)]	1	<1	<1	0	Common
Retinal detachment[6)]	1	<1	<1	0	Common
Vascular disorders					
Haemorrhage[7)]	15	<1	4	<1	Very common
Hypertension[8)]	11	6	8	2	Very common
Respiratory, thoracic, and mediastinal disorders					
Cough[9)]	17	0	8	0	Very common

Adverse drug reactions	Dabrafenib in combination with trametinib N=435 %		Placebo N=432 %		Frequency category (combination arm, all grades)
	All Grades	Grade 3/4	All Grades	Grade 3/4	
Gastrointestinal disorders					
Nausea	40	<1	20	0	Very common
Diarrhoea	33	<1	15	<1	Very common
Vomiting	28	<1	10	0	Very common
Abdominal pain[10)]	16	<1	11	<1	Very common
Constipation	12	0	6	0	Very common
Skin and subcutaneous tissue disorders					
Rash[11)]	37	<1	16	<1	Very common
Dry skin[12)]	14	0	9	0	Very common
Dermatitis acneiform	12	<1	2	0	Very common
Erythema[13)]	12	0	3	0	Very common
Pruritus[14)]	11	<1	10	0	Very common
Palmar-plantar erythrodysaesthesia syndrome	6	<1	1	<1	Common
Musculoskeletal and connective tissue disorders					
Arthralgia	28	<1	14	0	Very common
Myalgia[15)]	20	<1	14	0	Very common
Pain in extremity	14	<1	9	0	Very common
Muscle spasms[16)]	11	0	4	0	Very common
Rhabdomyolysis	<1	<1	0	0	Uncommon
Renal and urinary disorders					
Renal failure	<1	0	0	0	Uncommon
General disorders and administration site conditions					
Pyrexia[17)]	63	5	11	<1	Very common
Fatigue[18)]	59	5	37	<1	Very common
Chills	37	1	4	0	Very common
Oedema peripheral[19)]	16	<1	6	0	Very common
Influenza like illness	15	<1	7	0	Very common
Investigations					
Alanine aminotransferase increased[20)]	17	4	2	<1	Very common
Aspartate aminotransferase increased[21)]	16	4	2	<1	Very common
Alkaline phosphatase increased	7	<1	<1	<1	Common
Ejection fraction decreased	5	0	2	<1	Common

1) Nasopharyngitis also includes pharyngitis.

2) Neutropenia also includes febrile neutropenia and cases of neutrophil count decreased that met the criteria for neutropenia.

3) Headache also includes tension headache.

4) Dizziness also includes vertigo.

5) Chorioretinopathy also includes chorioretinal disorder.

6) Retinal detachment also includes detachment of macular retinal pigment epithelium and detachment of retinal pigment epithelium.

7) Haemorrhage includes a comprehensive list of hundreds of event terms that capture bleeding events.

8) Hypertension also includes hypertensive crisis.

9) Cough also includes productive cough.

10) Abdominal pain also includes abdominal pain upper and abdominal pain lower.

Adverse drug reactions	Dabrafenib in combination with trametinib N=435 %		Placebo N=432 %		Frequency category (combination arm, all grades)
	All Grades	Grade 3/4	All Grades	Grade 3/4	

[11] Rash also includes rash maculo-papular, rash macular, rash generalized, rash erythematous, rash papular, rash pruritic, nodular rash, rash vesicular, and rash pustular.

[12] Dry skin also includes xerosis and xeroderma.

[13] Erythema also includes generalized erythema.

[14] Pruritus also includes pruritus generalized and pruritus genital.

[15] Myalgia also includes musculoskeletal pain and musculoskeletal chest pain.

[16] Muscle spasms also includes musculoskeletal stiffness.

[17] Pyrexia also includes hyperpyrexia.

[18] Fatigue also includes asthenia and malaise.

[19] Oedema peripheral also includes peripheral swelling.

[20] Alanine aminotransferase increased also includes hepatic enzyme increased, liver function test increased, liver function test abnormal, and hypertransaminasaemia.

[21] Aspartate aminotransferase increased also includes hepatic enzyme increased, liver function test increased, liver function test abnormal, and hypertransaminasaemia.

Source: [SCS Appendix 1-Table 6.0004]

Serious adverse event/deaths/other significant events

Serious adverse events

SAEs are reported in Table 34 and Table 35. In the placebo arm, SAEs rarely occurred; the only SAE occurring in at least 1% (5 patients) was decreased LVEF. SAEs leading to hospitalization occurred in 108 (25%) patients in the D+T arm and 25 (6%) patients in the placebo arm; pyrexia led to hospitalization in 11% of patients in the dabrafenib+trametinib arm.

Among the 155 subjects in the dabrafenib-trametinib arm who experienced an SAE, 145 (94%)of the patients with an SAE, recovered from the event and 7 (4.5%) were either recovering or had recovered with sequelae at the time of the data cut-off (30-Jun-2017). Two subjects had not recovered at time of the data cutoff and 1 subject died due to pneumonia, which was not considered related to study drug. SAEs recurred after rechallenge in 29 (19%) subjects.

Table 34: Summary of serious adverse events

	Dabrafenib+Trametinib (N=435)	Placebo (N=432)
No. of Subjects with 1 SAE	88 (20%)	32 (7%)
No. of Subjects with 2 SAEs	32 (7%)	11 (3%)
No. of Subjects with 3 or more SAEs	35 (8%)	1 (<1%)

Table 35: Summary of most frequent serious adverse events, in at least 1% of the population

Preferred Term	Dabrafenib +Trametinib N=435 n (%)	Placebo N=432 n(%)
Any event	155 (36)	44 (10)
Pyrexia	67 (15)	4 (<1)
Chills	13 (3)	0
Ejection fraction decreased	13 (3)	5 (1)
Erysipelas	8 (2)	1 (<1)
Hypotension	6 (1)	0
Cellulitis	5 (1)	1 (<1)
Chorioretinopathy	5 (1)	0

Deaths

As of the data cut-off (30-Jun-2017), a total of 153 patients died; 60 (14%) in the dabrafenib+trametinib and 93 (22%) in the placebo arm (Table 36). In both treatment arms, deaths were most commonly related to disease progression. Five deaths occurred within 30 days from last dose of study medication (on-treatment deaths), 4 in the dabrafenib+trametinib arm and 1 in the placebo arm. In the dabrafenib+trametinib arm, 1 death was due to pneumonia (fatal SAE), all other on-treatment deaths were due to disease progression. The investigator did not suspect a relationship between the event (pneumonia) and the study treatment (dabrafenib+trametinib).

Table 36: Summary of deaths

Primary Cause of Death	Dabrafenib + Trametinib N=435 n (%)	Placebo N=432 n (%)
Patient Status		
Dead	60 (14)	93 (22)
Alive at last contact, follow-up ended	44 (10)	62 (14)
Alive at last contact, follow-up ongoing	331 (76)	277 (64)
Disease under study	54 (12)	77 (18)
SAE possibly related to study medication	0	0
Other	3 (<1)	10 (2)
Pneumonia	1 (<1)	2 (<1)
Haemorrhage	0	1 (<1)
Trauma	1 (<1)	1 (<1)
Suicide	1 (<1)	0
Other cancer	0	4 (<1)
Heart failure	0	1 (<1)
Other: unknown	0	1 (<1)
Unknown[1]	3 (<1)	6 (1)
Time to Death from Last Dose		
≤ 30 Days	4 (<1)	1 (<1)
>30 Days	56 (13)	92 (21)
Unknown	0	0
Among all deaths		
Died after documented disease recurrence	57 (13)	91 (21)
Died without documented disease recurrence	3 (<1)	2 (<1)

Other significant adverse events

AEs leading to dose reduction

AEs leading to dose reduction were reported in 38% (n=167) of patients in the dabrafenib+trametinib arm and in 3% (n=11) of patients in the placebo arm. In the dabrafenib+trametinib arm, pyrexia (81 patients; 19%), chills (17 patients; 4%), fatigue (13 patients; 3%) and decreased ejection fraction (11 patients; 3%) arthralgia, neutropenia, increased ALT, influence like illness and vomiting (all 2%) were the most common AEs leading to dose reduction. In the placebo arm, events were observed in 3 or fewer patients each. The most dose reductions due to AEs (dabrafenib 71%; trametinib 52%) occur within the first 3 months of treatment in the dabrafenib+trametinib arm.

In the D+T arm, 113 (67%) patients had Grade 1-2 AEs which led to dose reduction versus 54 (32%) patients with a dose reduction due to Grade 3-4 AEs.

AEs leading to dose interruption

AEs leading to dose interruption are displayed in Table 37.

Table 37: Summary of AEs leading to dose interruptions in at least 2% of patients in a treatment arm

Preferred Term	Dabrafenib +Trametinib N=435 n (%)	Placebo N=432 n(%)
Any event	289 (66)	65 (15)
Pyrexia	194 (45)	14 (3)
Chills	65 (15)	0
Fatigue	27 (6)	1 (<1)
Headache	25 (6)	4 (<1)
Vomiting	23 (5)	5 (1)
Nausea	22 (5)	4 (<1)
Influenza like illness	20 (5)	1 (<1)
Alanine aminotransferase increased	16 (4)	0
Arthralgia	16 (4)	2 (<1)
Aspartate aminotransferase increased	16 (4)	0
Ejection fraction decreased	14 (3)	5 (1)
Rash	14 (3)	1 (<1)
Myalgia	13 (3)	0
Neutropenia	13 (3)	0
Diarrhoea	12 (3)	1 (<1)
Oedema peripheral	10 (2)	0
Erythema nodosum	9 (2)	0
Dizziness	8 (2)	4 (<1)
Vision blurred	8 (2)	1 (<1)
Decreased appetite	7 (2)	2 (<1)
Influenza	7 (2)	2 (<1)
Pain in extremity	7 (2)	0

AEs of special interest (AESIs)

An overview of AESIs is shown in Table 38.

Table 38: Summary of AESIs (Safety population)

	Dabrafenib +Trametinib N=435 Grade, n (%)				Placebo N=432 Grade, n (%)			
Grouped Term	1	2	3	4	1	2	3	4
Pyrexia	131 (30)	136 (31)	24 (6)	1 (<1)	50 (12)	14 (3)	2 (<1)	0
Skin related toxicities	202 (46)	65 (15)	7 (2)	0	138 (32)	27 (6)	5 (1)	0
Diarrhea	115 (26)	25 (6)	4 (<1)	0	53 (12)	11 (3)	1 (<1)	0
Hepatic Disorders	37 (9)	25 (6)	29 (7)	0	10 (2)	1 (<1)	2 (<1)	0
Hypersensitivity	70 (16)	20 (5)	4 (<1)	0	22 (5)	3 (<1)	0	0
Oedema	58 (13)	27 (6)	2 (<1)	0	34 (8)	10 (2)	1 (<1)	0
Hyperglycemia	5 (1)	5 (1)	8 (2)	0	2 (<1)	4 (<1)	3 (<1)	1 (<1)
Ocular Events	56 (13)	9 (2)	3 (<1)	1 (<1)	36 (8)	5 (1)	0	0
Uveitis	4 (<1)	6 (1)	1 (<1)	1 (<1)	0	0	0	0
Bleeding events	63 (14)	3 (<1)	1 (<1)	0	14 (3)	2 (<1)	1 (<1)	0
Hypertension	8 (2)	18 (4)	27 (6)	0	9 (2)	20 (5)	8 (2)	0
Neutropenia	6 (1)	24 (6)	21 (5)	0	2 (<1)	4 (<1)	0	0
Cardiac related event	8 (2)	14 (3)	0	0	1 (<1)	5 (1)	1 (<1)	0
Pre-renal and intrinsic renal failure	3 (<1)	2 (<1)	1 (<1)	1 (<1)	0	0	0	0
Deep vein thrombosis/Pulmonary embolism	1 (<1)	1 (<1)	5 (1)	0	0	2 (<1)	2 (<1)	1 (<1)
Pancreatitis	2 (<1)	0	3 (<1)	1 (<1)	0	0	1 (<1)	0
cuSCC including Keratoacanthoma	2 (<1)	2 (<1)	2 (<1)	0	1 (<1)	2 (<1)	2 (<1)	0
Non-cutaneous secondary/recurrent malignancies	2 (<1)	0	2 (<1)	1 (<1)	0	0	3 (<1)	0
New primary melanoma	0	0	1 (<1)	0	1 (<1)	1 (<1)	4 (<1)	0
Pneumonitis/Interstitial lung disease	0	1 (<1)	0	0	0	0	0	0

Pyrexia

Pyrexia was reported in 292 (67%) patients in the dabrafenib+trametinib arm and in 66 (15%) in the placebo arm; 8% vs 3% of these events were grade 3 and 1 event vs 0 events were grade 4 in severity in the D+T arm and placebo arm, respectively.

An SAE was reported in 24% (71/292), while in the placebo arm 6% (4/66) patients had pyrexia SAEs. In the D+T arm, 52% of the patients had 3 or more pyrexia episodes whereas in the placebo arm 68% experienced only 1 episode.

In 99% of the patients in the dabrafenib+trametinib arm, pyrexia resolved without sequelae; a similar proportion was observed in the placebo arm (97%). Dabrafenib and trametinib were discontinued due to pyrexia in 14% and 9% patients, respectively. Dose interruption/delays occurred in 69% patients for dabrafenib and 41% patients for trametinib and dose reductions in 29% and 6% respectively. Median time to onset of pyrexia events was 23 days in dabrafenib+trametinib arm compared to 53 days in the placebo arm; with a median duration of 3 days in each arm.

In the dabrafenib+trametinib arm, 30% of patients received medications for prophylactic treatment of pyrexia and 48% received medication for active treatment of pyrexia compared to 2% and 5% in the placebo arm. Most frequently used medications to treat pyrexia were NSAIDs (45%) and corticosteroids (22%) in the D+T arm. Half of the patients requiring corticosteroids required treatment over 3 weeks.

Skin-related toxicities

Skin-related toxicities occurred in 63% of patients in the dabrafenib+trametinib arm and 39% in the placebo arm. The most common skin-related toxicity was rash (24% in dabrafenib+trametinib arm and 11% in placebo arm). Most events were grade 1 or 2 in severity (98% in dabrafenib+trametinib arm and 97% in placebo arm); grade 3 events were observed in 3% patients in either arm. Skin-related SAEs were reported in 2 patients in the D+T arm. In the dabrafenib+trametinib arm 40% of patients had 1 episode and 36% of the patients had 3 or more episodes. In the placebo arm, almost half of the patients reported only 1 episode (53%). Photosensitivity was reported in 13 (3%) of the D+T patients and in 16 (4%) of the placebo patients. At the time of the cut-off skin toxicity events were resolved in 91% and 85% of patients in the dabrafenib+trametinib and placebo arms, respectively.

Dose reductions occurred in 5%, interruptions/delays in 12% and discontinuation in 3% of the patients due to skin-related toxicities in the D+T arm. Median time to onset of skin-related toxicity events was 44 days in the dabrafenib+trametinib arm and 56 days in the placebo arm. Median duration of events was similar in the dabrafenib+trametinib arm (34 days) and placebo arm (39 days). Use of prophylactic treatment for skin toxicity was reported in 10% of the patients in the D+T arm and in 3% in the placebo arm. Medication to actively treat skin toxicity was used in 34% and 14% of patients in the dabrafenib+trametinib arm and the placebo arm, respectively. Half of the patients requiring corticosteroids required treatment over 3 weeks. The median duration of skin toxicity treatment was similar between the 2 arms; 29 days and 27 days.

Diarrhoea

Diarrhoea events occurred in 33% patients in the dabrafenib+trametinib arm and 15% patients in the placebo arm. Events were mainly grade 1/2 (97% of the events in the D+T arm and 98% in the placebo arm). One patient in the D+T arm had an SAE of diarrhoea. Most patients reported only 1 occurrence of diarrhoea (74% in the D+T arm and 68% in the placebo arm). All diarrhoea events were resolved, except for 1 case in the placebo arm.

No treatment discontinuations occurred due to diarrhoea. Dabrafenib dose reductions and interruptions/delays were reported in 2% and 8 % of patients, respectively. Trametinib dose reductions and interruptions/delays were reported 1% and 7% of patients, respectively.

Time to onset of diarrhoea was 42 days in the dabrafenib+trametinib arm compared to 71 days in the placebo arm. The median duration of event was 6 days in the dabrafenib+trametinib arm and 3 days in the placebo arm.

Hepatic disorders

Hepatic disorders were reported in 91 (21%) patients in the D+T arm and 13 (3%) patients in the placebo arm. ALT and AST increased were the most frequently reported events (67 patients, 15% and 63 patients, 14%) in the D+T arm; whereas in the placebo arm ALT and AST increased were reported in 6 patients (1%) and 7 patients (2%), respectively.

In the treatment arm, 32% of the events were grade 3 events. In the placebo arm, 2/13 patients (15%) had grade 3 events, all other events were grade 1-2. Hepatic SAEs were reported in 6/91 patients (7%) in the D+T arm and no events were reported in the placebo arm.

All hepatic events either resolved or were resolving in 93% of patients in the D+T arm and 69% in the placebo arm at the time of data cut-off date. Dabrafenib and trametinib were discontinued due to hepatic disorders in 13% and 12% patients, respectively. Dose interruption/delays occurred in 25% of patients for dabrafenib and 26% of patients for trametinib. Median time to onset of hepatic disorders was 44 days in the dabrafenib+trametinib arm compared to 84 days in the placebo arm. The median duration of events was similar in both arms (dabrafenib+trametinib; 29 days and placebo arm; 29 days). A summary of liver tests is shown in Table 40 under laboratory findings.

Hypersensitivity

Hypersensitivity events occurred in 94 (22%) patients in the D+T arm, as compared to 25 (6%) patients in the placebo arm. All patients in the placebo arm had grade 1/2 events, in the D+T arm most events were grade 1/2 events and 4 patients had grade 3 events. In the D+T arm 1 patient had hypersensitivity SAEs.

In the D+T arm hypersensitivity events resolved in 98%, in the placebo arm all events were resolved. Dabrafenib dose reduction and interruption/delay was required in 7% and 16% of patients, respectively. Median time to onset of hypersensitivity events was 60 days with a median duration of events 32 days in the dabrafenib+trametinib arm and 57 days in the placebo arm with a median duration of 21 days in the placebo arm.

Oedema

Oedema events were observed in 87 (20%) patients in the dabrafenib+trametinib arm and 45 (10%) patients in the placebo arm. Grade 3 events were reported in 2 patients in the D+T arm and 1 patient in the placebo arm; all other events were grade 1 or 2.

In the D+T arm, 8% had 3 or more occurrences and in the placebo arm 1/45 patients had 3 or more occurrences. One patient in the placebo arm had an SAE of oedema. The majority of events had resolved in both arms: 72/87 (83%) patients in the D+T arm and 34/45 (76%) patients in the placebo arm. Median time to onset of oedema events was 91 days with a time to resolution of 68 days in the D+T arm and 88 days with a time to resolution of 62 days for placebo.

Hyperglycaemia

Hyperglycaemia events occurred in 18 (4%) patients in the D+T arm and 10 (2%) patients in the placebo arm. Grade 3 events occurred in 8 patients in the D+T arm and in 3 patients in the placebo arm; 1 patient in the placebo arm had a grade 4 event. In the D+T arm, 78% of patients had 1 occurrence and 22% had 2 occurrences. In the placebo arm all patients had 1 occurrence. SAEs occurred in 2 patients in the dabrafenib+trametinib arm and in 1 patient in the placebo arm.

Events resolved for 12/18 (67%) patients in the dabrafenib+trametinib arm and for 6/10 of the patients in the placebo arm. No treatment discontinuations for hyperglycaemia were reported.

Dabrafenib dose reduction and interruption/delays occurred in 2 and 4 patients, respectively and trametinib dose interruption/delays occurred in 1 and 4 patients, respectively.

Ocular events

Ocular events were observed in 69 (16%) patients in the D+T arm and 41 (9%) patients in the placebo arm. In the D+T arm 3 patients had grade 3 events and 1 had a grade 4 event; the complaints resolved after treatment discontinuation (n=2) or treatment interruption (n=2). In the placebo arm all events were grade 1/2.

Few patients had 3 or more occurrences in the D+T and placebo arm. SAEs were reported in 6 patients in the D+T arm. In the D+T arm, 60/69 (87%) patients recovered and in the placebo arm 36/41 (88%) patients recovered. Dabrafenib was discontinued in 5 patients and trametinib was discontinued in 4 patients due to ocular events. Dabrafenib dose reduction and interruptions/delays occurred in 2 and 5 patients, respectively. Trametinib dose reduction and interruptions/delays occurred in 9 and 15 patients, respectively.

Uveitis

Uveitis was observed in 12 patients (3%) in the D+T arm and none in the placebo arm. One patient had a grade 3 event and 1 had a grade 4 event; SAEs were reported in 4/12 patients. Among the 12 patients with uveitis, dabrafenib was discontinued in 4 patients (33%) and trametinib was discontinued in 5 patients (42%) due to uveitis-related events. Dabrafenib interruption/dose delays occurred in 3 patients and trametinib reduction and interruption/dose delays occurred in 2 and 6 patients, respectively. Eventually all cases resolved in the D+T arm.

Bleeding events

Bleeding events were reported in 67 (15%) patients in the dabrafenib+trametinib arm and 17 (4%) patients in the placebo arm. In the D+T arm a grade 3 SAE of haemorrhagic anaemia was observed, which resolved after 30 days, when study treatment was interrupted. In the placebo arm a grade 3 SAE of hepatic haemorrhage was observed which recovered after 3 days, no action was taken with the study treatment. All other bleeding events were grade 1 or 2. SAEs were reported in 1 patient in the D+T arm and 2 patients in the placebo arm.

Most patients in the D+T and placebo arm had 1 occurrence. Events resolved in 64/67 patients in the D+T arm and in 14/17 in the placebo arm. No patient discontinued treatment due to bleeding events. Median duration of the bleeding event was 14 days in the D+T arm and 8 days in the placebo arm.

Hypertension

Hypertension events were observed in 53 (12%) patients in the D+T arm and 37 (9%) patients in placebo arm. Grade 3 events were reported in 27/53 (51%) patients in the D+T arm and in 8/37 (22%) in the placebo arm. In the D+T arm 1 patient had 3 or more occurrences; all other patients had 1 or 2 occurrences. No SAEs were observed in either arm.

Events resolved in 41/53 patients in the dabrafenib+trametinib arm and 24/37 patients in the placebo arm. Dabrafenib dose reduction and interruptions/delays were reported in 4 and 5 patients, respectively. Trametinib dose reduction and interruptions/delays were reported in 4 and 6 patients, respectively. Median time to onset of hypertension events was 78 days in the D+T arm and 84 days in the placebo arm; median time for events to be resolved was 45 days in the D+T arm and 77 days in the placebo arm.

Neutropenia

Neutropenia events were observed in 51 (12%) patients in the D+T arm, and 6 (1%) patients in the placebo arm. In the D+T arm, 21/51 patients had grade 3 events; all events in the placebo arm were grade 1 or 2. SAEs occurred in 4 patients in the D+T arm. Febrile neutropenia (grade 3 SAE) was observed in 2 patients, which resolved in one patient after treatment modifications and in the other after the treatment was discontinued.

All neutropenia events resolved; however, study treatment was discontinued in 7 patients. Dabrafenib dose reduction and interruptions/delays occurred in 10 and 16 patients, respectively. Trametinib dose reduction and interruptions/delays occurred in 11 and 16 patients, respectively.

Median time to onset of neutropenia events in the D+T arm was 42 days with a duration of 14 days; time to onset was 73 days with a median duration of 29 days in the placebo arm.

Cardiac-related events

Cardiac-related events were reported in 22 (5%) patients in the D+T arm and 7 (2%) patients in the placebo arm. In the placebo arm, 1 patient had a grade 3 event; all other events in both arms were grade 1 or 2. In D+T arm, 2/22 patients had 2 occurrences and 1/7 patients in the placebo arm had 2 occurrences; all other patients had 1 occurrence. SAEs occurred in 13/22 patients in the D+T arm and 5/7 patients in the placebo arm.

All events had resolved at the time of data cut-off date. 2 patients discontinued treatment with dabrafenib and 3 patients discontinued treatment with trametinib due to cardiac-related events.

Dabrafenib dose reduction and interruption/delay occurred in 1 and 14 patients, respectively while trametinib dose reduction and interruptions/delays occurred in 11 and 13 patients, respectively. Median time to onset of cardiac-related events was 81 days in the D+T arm compared to 168 days in the placebo arm; median duration was 31 days in both arms.

Left ventricular ejection fraction (ECHO findings)

The specific protocol-mandated criteria required dose interruption if the LVEF was >10% below baseline and below the institutional LLN, and permanent discontinuation of study treatment if there was >20% absolute reduction from baseline.

LVEF decreases of any level occurred in 74% of patients in the D+T arm and 63% of patients in the placebo arm. Of the patients with a decrease in LVEF, a decrease of <10% was reported in 217/311 (70%) patients in the D+T arm and 209/262 (80%) in the placebo arm. A LVEF decrease of 10-19% was reported in 89/311 (29%) patients in the D+T arm and in 49/262 (19%) patients in the placebo arm. A LVEF decrease of ≥ 20% was observed in 2% of patients in both treatment arms. When sorted for worse-case-on-therapy, 15 patients (3% in the D+T arm and 8 patients (<2%) in the placebo arm had a decrease ≥10% resulting in an ejection fraction below the institution's lower limit of normal.

Pre-renal and intrinsic renal failure

Pre-renal and intrinsic renal failure occurred in 7 patients (2%) in the D+T arm and in no patients in the placebo arm, of which 2 patients with SAEs. One patient had a grade 3 event and 1 patient had a grade 4 event. One patient discontinued dabrafenib and trametinib treatment due to these events. All patients recovered. The median time to onset was 57 days and the median duration was 6 days.

Deep vein thrombosis/pulmonary embolism

DVT/pulmonary embolism were observed in 7 patients in the D+T arm, and in 5 patients in the placebo arm. SAEs were reported in 3 patients in each arm. In the D+T arm, 5 patients had grade 3 events; in the placebo arm 2 patients had grade 3 events and 1 patient had a grade 4 event. With the exception of 1 patient in the placebo arm, all patients recovered. One patient discontinued dabrafenib and trametinib treatment due to a DVT event. Median time to resolution in the D+T arm and in the placebo arm was 92 and 33 days, respectively.

Pancreatitis-related events

Pancreatitis-related events occurred in six patients in the D+T arm (1 patient had pancreatitis and 5 patients had elevations in pancreatic enzymes). One patient in the placebo arm had increased amylase levels.

One patient had a grade 3 SAE pancreatitis due to gallstones, the patient had 2 previous grade 2 SAE episodes of pancreatitis which developed after a gall bladder infection. In 1 patients with a grade 3 increased amylase and grade 4 increased lipase the study treatment was discontinued. Both events resolved within 7 days. Two patients had grade 1 elevations in pancreatic enzymes, which resolved after 29 days and 85 days, respectively. Two patients had grade 3 elevations in pancreatic enzymes, which resolved after 33 days and 8 days, respectively. The median time to resolution was 19 and 36 days in the D+T and placebo arm respectively.

Pneumonitis/interstitial lung disease

One patient in the D+T arm had a grade 2 event of pneumonitis, which was not suspected to be study treatment-related. The event resolved without any change in treatment; the event started on day 19 and last for 12 days.

Cutaneous small cell carcinoma (cuSCC) including keratoacanthoma

CuSCC were reported in 6 patients in the D+T arm and 5 patients in the placebo arm. CuSCC events had a delayed onset in both arms; 127 days in the D+T arm and 232 days in the placebo arm.

In the D+T arm patients were observed with a grade 1 Bowen's disease; a grade 2 basosquamous carcinoma, and a grade 1 SAE of Bowen's disease; a grade 2 SAE of Bowen's disease-related, grade 3 SAE of squamous cell carcinoma of skin and a grade 3 SAE of keratoacanthoma; a grade 1 keratoacanthoma; a grade 3 SAE of squamous cell carcinoma and a grade 2 SAE squamous cell carcinoma. In the placebo arm patients were observed with 2 grade 3 SAEs of squamous cell carcinoma; a grade 3 SAE of squamous cell carcinoma; a grade 2 SAE of squamous cell carcinoma; a two grade 2 SAEs: one of Bowen's disease and one of keratoacanthoma and a grade 1 SAE of Bowens disease. All events in D+T arm and placebo arm resolved.

Non-cutaneous treatment-emergent malignancies

Non-cutaneous treatment-emergent malignancies occurred in 5 patients in the D+T arm and in 3 patients in the placebo arm. Median time to onset of was 157 days versus 86 days, respectively.

In the D+T arm patients were reported to have a grade 1 SAE of endometrial adenocarcinoma; a grade 1 event of dysplastic naevus syndrome; a grade 3 SAE of B-cell lymphoma; a grade 3 SAE of prostate cancer and a grade 4 SAE of endometrial adenocarcinoma.

In the placebo arm patients were reported to have a grade 3 SAE of bladder transitional cell carcinoma; a grade 3 metastases to the central nervous system and a grade 3 SAE of renal cancer. In the D+T arm 60% of the events resolved, in the placebo arm all events resolved.

New primary melanoma

In the D+T arm 1 patient had malignant melanoma. In the placebo arm 6 patients had a new primary melanoma events. Median time of onset was 30 days in the D+T arm and 74 days in the placebo arm. In the D+T arm one patient had a grade 3 SAE malignant melanoma. In the placebo arm patients were observed with a grade 1 malignant melanoma in situ; a grade 3 SAE, malignant melanoma in situ; a grade 3 SAE malignant melanoma; a grade 2 SAE malignant melanoma; a grade 3 SAE malignant melanoma and a grade 3 SAE of lentigo maligna. Eventually all events resolved.

Laboratory findings

Haematology

The most frequently observed changes from baseline in the D+T arm were neutrophils decreased (47%), leukocyte count decreased (43%), lymphocytes decreased (26%), and haemoglobin decreased (25%). Changes in haematology laboratory values as well as grade 3 changes were more frequent in the D+T arm compared to placebo arm (Table 39).

Table 39: **Worst-case on-therapy haematology grade changes from baseline**

	Dabrafenib + Trametinib N = 435 n (%)				Placebo N = 432 n (%)			
Test	n[1]	Any Grade increase	Increase to Grade 3	Increase to Grade 4	n[1]	Any Grade increase	Increase to Grade 3	Increase to Grade 4
Hemoglobin decreased	431	107 (25%)	3 (<1%)	0	428	26 (6%)	1 (<1%)	0
Hemoglobin Increased	431	5 (1%)	0	0	428	9 (2%)	0	0
Lymphocyte Count Decreased	431	112 (26%)	23 (5%)	0	428	24 (6%)	2 (<1%)	0
Lymphocyte Count Increased	431	9 (2%)	0	0	428	3 (<1%)	0	0
Neutrophils (10^9/L)	431	204 (47%)	22 (5%)	3 (<1%)	428	51 (12%)	0	1 (<1%)
Platelets (10^9/L)	430	81 (19%)	3 (<1%)	0	428	15 (4%)	0	0
Leukocytes (10^9/L)	431	187 (43%)	10 (2%)	1 (<1%)	428	42 (10%)	0	1 (<1%)

[1]n = number of subjects with lab values at the specified planned time.
[2] For the worst-case on-therapy row, subjects are counted twice if the subject 'Decreased to Low' and 'Increased to High' during the on-therapy period.

Clinical chemistry

There were no clinically relevant changes in biochemistry parameters assessed between the 2 treatment arms. For those laboratory tests that were not graded according to NCI CTCAE criteria, an analysis was conducted using the normal ranges. Events of LDH increase above ULN (66% vs 12%), and high C-reactive protein (96% vs 70%) were more frequent in the D+T arm compared to the placebo arm..

ECG changes

At Baseline and at Month 12, most patients (>70%) in both treatment arms had normal ECG readings. Three patients (<1%) in each arm had a QTcB grade 3 increase (≥ 501 sec), with a corresponding increase of >60 msec from Baseline. All of the increases were transient. In all three patients in the D+T arm the QTcB value returned to normal at the next monthly visit, in one patient after the study treatment was interrupted, in the other two patients no dose modification were performed. In the placebo arm the treatment was interrupted in two patients and in one patient the dose was not modified.

Liver tests

A summary of liver tests is given in Table 40.

Table 40: **Summary of liver tests (safety population)**

Laboratory Criteria [1][2]	Dabrafenib + Trametinib (N=435) n (%)	Placebo (N=432) n (%)
n	430	428
ALT or AST > 3x ULN	73 (17)	6 (1)
ALT or AST > 5x ULN	30 (7)	2 (<1)
ALT or AST > 8x ULN	9 (2)	1 (<1)
n	431	428
BIL >=2x ULN [3]	3 (<1)	0
BIL >= 2x ULN and Baseline BIL < 2x ULN (or Baseline BIL missing)[3]	3 (<1)	0
n	431	428
ALT >3xULN and BIL >=2xULN [3]	3 (<1)	0
n	431	428
ALP >= 3x ULN	15 (3)	3 (<1)
ALP >= 3x ULN and Baseline ALP < 3x ULN (or Baseline ALP missing)	15 (3)	3 (<1)

[1] Subjects may be counted in more than one category of 'Laboratory Criteria'.
[2] ALT: alanine aminotransferase; AST: aspartate aminotransferase; ALP: alkaline phosphatase; BIL: total bilirubin; INR: international normalized ratio; ULN=Upper Limit of Normal.
[3] If Direct Bilirubin is available, then Direct Bilirubin must also be >= 35% when Total Bilirubin is >= 2x ULN in order to satisfy the criteria. Bilirubin value can occur up to 28 days on or after ALT value.

Three patients treated in the dabrafenib+trametinib arm showed a concomitant increase of ALT >3 x ULN and bilirubin ≥ 2x ULN.

Safety in special populations

The subgroup analysis by age included 709 patients in the age group of <65 years, and 158 patients in the age group of ≥ 65 years. The percentage of patients with any AE was slightly higher in patients < 65 (dabrafenib+trametinib vs placebo: 97% vs 87% in patients <65 years of age, and 96% vs 92% in patients ≥ 65 years of age).

In the dabrafenib+trametinib arm the proportions of patients with events in the <65 years and ≥ 65 years groups were similar or somewhat lower in patients ≥ 65 years compared to those <65 years. The most frequent AEs (≥ 20% patients) in both age subgroups (<65 years and ≥ 65 years) were: pyrexia (65% and 52%), fatigue (46% and 49%), headache (42% and 26%), nausea (41% and 33%), chills (38% and 33%), diarrhoea (34% and 29%), vomiting (29% and 26%), and rash (25% and 22%). In the placebo group, events were overall less frequently reported and were similar between the two age groups (87% vs 92%).

In the dabrafenib+trametinib arm, the incidence of grade 3 /4 events was similar between the two age subgroups (<65 years, 40% and ≥ 65 years, 45%). In the placebo group, events were also similar between the two age subgroups (<65 years, 14% and ≥ 65 years, 21%). SAEs, AEs leading to dose reduction, AEs leading to dose interruption occurred at comparable rates between patients <65 years and ≥ 65 years in the D+T arm and the placebo arm (except for SAEs which occurred more often in placebo patients ≥ 65 compared to those <65 years). AEs leading to permanent discontinuation were seen more frequently in patients ≥ 65 years compared to those <65 years (33% vs 25%), while the rates were similar in the placebo arm.

In Table 41 safety information by age group in the dabrafenib+trametinib arm is shown.

Table 41. Safety information by age group in the dabrafenib+trametinib arm

	Age <65 n=350	Age 65-74 n=73	Age 75-84 n=11	Age 85+ n=1
Total AEs	340 (97%)	71 (97%)	10 (91%)	1 (100%)
Serious AEs – Total	126 (36%)	25 (34%)	4 (36%)	0
- Fatal	0	1 (1%)	0	0
- Hospitalization/prolong existing hospitalization	90 (26%)	15 (21%)	3 (27%)	0
- Life-threatening	4 (1%)	3 (4%)	0	0
- Disability/incapacity	5 (1%)	3 (4%)	0	0
- Other (medically significant)	9 (3%)	5 (7%)	0	0
AE leading to Treatment Discontinuation	86 (25%)	24 (33%)	4 (36%)	0
Psychiatric disorders	60 (17%)	15 (21%)	2 (18%)	0
Nervous system disorders	195 (56%)	36 (49%)	2 (18%)	1 (100%)
Injury, poisoning and procedural complications	28 (8%)	12 (16%)	0	0
Cardiac disorders	22 (6%)	3 (4%)	1 (9%)	0
Vascular disorders	92 (26%)	19 (26%)	4 (36%)	1 (100%)
Cerebrovascular disorders	0	0	0	0
Infections and infestations	192 (55%)	31 (42%)	7 (64%)	1 (100%)
Anticholinergic syndrome	0	0	0	0
Sum of postural hypotension, falls, black outs, syncope, dizziness, ataxia, fractures	37 (11%)	8 (11%)	1 (9%)	0

A similar proportion of male and female patients in both treatment arms experienced at least one AE (dabrafenib+trametinib vs placebo: 96% vs 86% among male patients and 98% vs 90% among female patients). The most frequent (≥ 20% patients) AEs were comparable between genders. In the dabrafenib+trametinib arm the incidence of grade 3 /4 AEs was lower among male patients (34% grade 3 and 2% grade 4) than among female patients (44% grade 3 and 3% grade 4). In the placebo arm, a similar proportion of grade 3/4 events was observed among male (16% grade 3 and <1% grade 4) compared to female patients (11% grade 3 and no grade 4).

AEs leading to permanent discontinuation were frequently observed in women (32% vs 22%) compared to men, as were AEs leading to dose reduction (45% vs 33%). Rates of SAEs (38 vs 33%) and AEs leading to dose interruption 64% vs 70% were more or less comparable between females and males. In the placebo arm all these rates were more or less comparable between males and females. No specific AEs or cluster of AEs could be identified underlying the male-female differences in the D+T arm.

Discontinuation due to adverse events

Adverse events leading to permanent discontinuation of study treatment

AEs leading to discontinuation of study treatment were reported in 26% in the dabrafenib+trametinib arm and 3% in the placebo arm. The most common AEs leading to discontinuation of study treatment in the D+T and placebo arm are shown in Table 42. In total 40% of the patients who discontinue due to AEs, do so within the first 3 months. From the patients who permanently discontinued due to AEs, there were 71 patients (62%) with Grade 1-2 AEs versus 43 patients (38%) of Grade 3-4 AEs which led to discontinuation. In 87% of the patients experiencing any AE leading to treatment discontinuation, a complete recovery/resolution of the event was observed and in 7 patients (6%) the AE was recovering/resolving at the time of the data cut-off. In 6 patients (5%) the event was not recovered/resolved and resolved with sequelae in one patient. One patient died due to pneumonia, which was not considered to be related to study treatment. RFS curves do not appear to be influenced by discontinuations.

Table 42: Summary of adverse events leading to permanent discontinuation of study treatment in at least 1 percent of patients in a treatment arm

	Dabrafenib +Trametinib	Placebo
Preferred Term	**N=435 n (%)**	**N=432 n(%)**
Any event	114 (26)	12 (3)
Pyrexia	38 (9)	0
Chills	16 (4)	0
Fatigue	8 (2)	0
Alanine aminotransferase increased	7 (2)	0
Headache	6 (1)	0
Arthralgia	5 (1)	0
Aspartate aminotransferase increased	5 (1)	0
Nausea	5 (1)	1 (<1)
Neutropenia	5 (1)	0

Post marketing experience

The review of all new safety data and information obtained during the reporting interval of [Tafinlar PSUR 27Aug2016 to 26Aug2017] and [Mekinist PSUR 30Nov2016 to 29May2017] revealed no additional new safety signals.

Safety in comparison to pooled data from previous indications

The safety profile observed with dabrafenib+trametinib in the BRF115532 adjuvant study has been compared with that observed in the metastatic MEK115306 and MEK116513 phase III studies. A summary of AEs is shown in Table 43.

The most frequently reported AEs leading to discontinuation in adjuvant setting were pyrexia in 9% of patients and chills in 4% of patients; while in the metastatic setting were pyrexia (2% and 3%) and ejection fraction decreased (1% and 3%) in the MEK115306 and MEK116513 studies.

The proportion of AEs leading to dose reduction was similar between the adjuvant and metastatic studies (38% and 31%, respectively). The proportion of AEs leading to dose interruption was slightly higher in the adjuvant setting (66%) as compared to the metastatic setting (55%).

The most common AEs are compared between melanoma studies in Table 44.

Table 43: Comparison with dabrafenib plus trametinib in subjects with BRAF V600E/K mutation positive in adjuvant setting and metastatic melanoma

	Adjuvant Melanoma (BRF115532 study)		Metastatic Melanoma
	Dabrafenib +Trametinib N= 435 n (%)	Placebo N=432 n (%)	Pooled data (MEK115306 and MEK116513) N=559 n (%)
Any AE	422 (97)	380 (88)	546 (98)
AEs related to study treatment	398 (91)	272 (63)	501 (90)
AEs leading to permanent discontinuation of study treatment	114 (26)	12 (3)	68 (12)
AE leading to dose reduction	167 (38)	11 (3)	174 (31)
AE leading to dose interruption	289 (66)	65 (15)	310 (55)
Any SAE	155 (36)	44 (10)	219 (39)
SAEs related to study treatment	117 (27)	17 (4)	154 (28)
Fatal SAEs	1 (<1)	0	8 (1)
Fatal SAEs related to study treatment	0	0	0

Table 44: Summary of adverse events displayed by preferred term in adjuvant setting (≤10%) and metastatic melanoma

	Adjuvant Melanoma (F2301) N=435		Metastatic melanoma Pooled data (MEK115306 and MEK116513) N=559	
Preferred term	**All grades n (%)**	**Grade 3/4 n (%)**	**All grades n (%)**	**Grade 3/4 n (%)**
Any Event	422 (97)	180 (41)	546 (98)	278 (50)
Pyrexia	273 (63)	23 (5)	303 (54)	30 (5)
Fatigue	204 (47)	19 (4)	182 (33)	9 (2)
Nausea	172 (40)	4 (<1)	193 (35)	2 (<1)
Headache	170 (39)	6 (1)	170 (30)	5 (<1)
Chills	161 (37)	6 (1)	174 (31)	3 (<1)
Diarrhoea	144 (33)	4 (<1)	175 (31)	7 (1)
Vomiting	122 (28)	4 (<1)	153 (27)	6 (1)
Arthralgia	120 (28)	4 (<1)	138 (25)	5 (<1)
Rash	106 (24)	0	132 (24)	4 (<1)
Cough	73 (17)	0	113 (20)	0
Myalgia	70 (16)	1 (<1)	85 (15)	1 (<1)

	Adjuvant Melanoma (F2301) N=435		Metastatic melanoma Pooled data (MEK115306 and MEK116513) N=559	
Alanine aminotransferase increased	67 (15)	16 (4)	76 (14)	14 (3)
Influenza like illness	67 (15)	2 (<1)	47 (8)	5 (<1)
Aspartate aminotransferase increased	63 (14)	16 (4)	68 (12)	12 (2)
Pain in extremity	60 (14)	2 (<1)	65 (12)	7 (1)
Asthenia	58 (13)	2 (<1)	81 (14)	8 (1)
Oedema peripheral	58 (13)	1 (<1)	86 (15)	3 (<1)
Dry skin	55 (13)	0	55 (10)	0
Dermatitis acneiform	54 (12)	2 (<1)	42 (8)	0
Constipation	51 (12)	0	72 (13)	1 (<1)
Hypertension	49 (11)	25 (6)	144 (26)	60 (11)
Decreased appetite	48 (11)	2 (<1)	68 (12)	8 (1)
Erythema	48 (11)	0	48 (9)	0

Preferred terms are sorted in descending frequency of any grades column, as reported in the dabrafenib + trametinib group.
A patient with multiple occurrences of an AE under one treatment is counted only once in the AE category for that treatment.

2.4.1. Discussion on clinical safety

The D+T safety data is derived from the BRF115532 study in stage III melanoma patients in the adjuvant setting. The median follow up was 33-34 months, which is considered sufficient to assess the safety profile. The median average daily dose in current pivotal study was comparable between the two study arms, however, the cumulative dose was lower, while the duration of exposure was slightly longer in the D+T arm compared to the placebo arm, reflective of the dose reductions observed for D+T (discussed below) and disease progression in the placebo arm. Around two thirds of the patients in the D+T arm received at least 9 months of treatment.

In general, the toxicity profile of D+T in adjuvant melanoma setting is comparable to the known safety profile from studies in metastatic melanoma setting In the D+T arm, higher frequencies of AEs were observed compared to the placebo arm (97 vs 88%). Pyrexia was the most common AE, other AEs occurring in ≥30% of the patients in the D+T arm were fatigue, nausea, headache, chills and diarrhoea, all of which occurred more frequently compared to the placebo arm. Reported frequencies of these AEs were slightly higher in the adjuvant setting compared to the metastatic melanoma setting which could be due to differences in exposure between the two settings. Also a higher reporting AEs in the adjuvant versus the metastatic (melanoma) setting has previously been described in the literature (Eggermont 2015), thus the observed differences are not considered clinically relevant. The most frequently reported Grade 3-4 AEs in the D+T arm were hypertension, pyrexia and fatigue, in the placebo arm Grade 3/4 AEs were not frequent (overall Grade 3-4 AEs respectively 41% vs 14%). Compared to the metastatic setting the overall number of Grade 3-4 AEs was slightly lower in the adjuvant setting (respectively 50 vs 41%), which might be expected as current population are expected to have less disease-related morbidity.

The MAH updated the frequencies of the ADRs based on adverse reactions reported in the integrated safety population of trametinib in combination with dabrafenib in the studies MEK115306, MEK116513a, BRF113928, and BRF115532 (n=1076)(n=641). Several ADRs changed frequency, most notably “urinary tract infection” changed from “very common” to “common”, renal failure changed from “common” to “uncommon”, influenza-like illness changed from”very common” to “common”, uveitis from “uncommon” to “common”, pneumonitis from “common” to “uncommon” and gastrointestinal perforation from “uncommon” to “rare”.

Serious adverse events including deaths

SAEs frequently occurred in the D+T arm as 36% of the patients had at least one SAE in the D+T arm. In 25% of the patients in the D+T arm a SAE lead to hospitalization. Few patients experienced 2 or 3 or more SAEs. A considerable part of the total SAEs are Grade 1-2 AEs and thus even non-severe AEs have some impact on patients life. Almost all patients appear to recover from SAEs (94%). Few SAEs were seen in the placebo arm (10%). Most frequent SAEs in the D+T arm were pyrexia, chills and decreased ejection fraction. This is consistent with the known safety profile of D+T.

Deaths were more frequently observed in the placebo arm compared to the D+T arm. Most deaths were related to disease progression. Four patients in the D+T arm versus 1 patient in the placebo arm died within 30 days of study treatment, all but one due to disease progression. This one patient was randomised to the D+T arm and died due to an untreated pneumonia. Fatal SAEs were less frequently observed for D+T in the adjuvant melanoma setting compared to the metastatic melanoma setting (see bleeding events below).

Adverse events leading to study treatment discontinuation or dose interruption/delay or reduction

A considerable part of the patients permanently discontinued treatment due to AEs in the D+T arm (26% vs 3% in the placebo arm). The most common AEs in the D+T arm leading to discontinuation were pyrexia (9%), chills (4%) and fatigue (2%). A considerable number of D+T treated patient discontinued due to AEs within the first three months. Further, most of the AEs which led to discontinuation in this arm were low grade (Grade 1-2). Pyrexia, chills and fatigue were also the most common AEs leading to dose reduction and interruptions. Dose reduction due to AEs was reported frequently in the D+T arm (38% vs 3% in the placebo arm). Similar to the discontinuations, most dose reductions due to AEs occurred within the first three months and the reductions were mostly related to Grade 1-2 AEs. Overall, these data confirm the moderate tolerability of the D+T treatment. Also dose interruptions due to AEs were often observed; in 66% of the patients in the D+T arm compared to 15% in the placebo arm. AEs leading to permanent discontinuation and dose interruptions/reductions were seen more often in the adjuvant setting compared to the metastatic setting. Since the AEs are considered manageable, this does not cause any particular concerns.

Adverse events of special interest (AESIs)

All AESIs were observed more frequently in the D+T arm compared to placebo. Almost all AESIs resolved in the D+T arm, exceptions were hyperglycaemia (67% resolved), hypertension (77% resolved) and ocular events (87% resolved). These AEs are sufficiently covered in the SmPC. More or less comparable rates of resolving of AEs were observed in the placebo arm, though in the placebo arm in concerned fewer patients. Most AESIs occurred in similar frequencies as already observed from metastatic melanoma patients, except for skin-related toxicities (mostly rash), which occurred in 63% of patients in the D+T arm (39% in the placebo arm) and in the metastatic setting in 45-48% of the D+T treated patients. Most skin-related events reported were Grade 1 or 2 in severity and had little influence on dosing. The current SmPC adequately covers skin-related toxicities; Rash has been observed in about 60% of patients in trametinib monotherapy studies and in about 24% of patients when trametinib is used in combination with dabrafenib (see section 4.8).

One of the more challenging AEs described with D+T therapy is pyrexia. Pyrexia occurred much more frequent in the D+T arm (67% vs 15%), though Grade 3-4 events was much less frequent overall and the difference between the 2 study arms was smaller(8% vs 3% respectively). More than half of the patient experienced three or more episodes in the D+T arm, whereas in the placebo arm patients generally experienced only 1 episode. Pyrexia was also a common cause for dose modifications, interruptions in the D+T arm, confirming the difficulties in management of this AE, however 99% of the cases in the current study eventually resolved without sequelae. The SmPC adequately covers dosing advices related to pyrexia.

In prior studies of the D+T combination in metastatic setting 6 fatal bleedings were observed in the D+T arms, to which a contribution of the D+T therapy could not be ruled out. In this study no fatal bleeding event were observed, all but one (Grade 3 SAE) of the bleeding events were Grade 1-2. The current SmPC warning is still considered warranted due to observations in previous studies.

LVEF decreases were frequently observed, as is expected from the known safety profile of D+T. Most decreases in the D+T arm deviated less than 10% from baseline and few patients with a LVEF decrease of ≥20% or with a decrease ≥10% resulting in an ejection fraction below the lower limit of normal were reported. The latter two AEs were more or less balanced between the study arms. This issue is considered sufficiently covered by current SmPC.

Relating to concerns of an increased risk of development of secondary malignancies by the paradoxical stimulation of the MAPK pathway by BRAF (and MEK) inhibitors; CuSCC rates in the D+T arm were low and comparable to placebo (6 vs 5 patients), however it should be noted that CuSCC occurred earlier in the D+T arm (median 18 vs 33 weeks). In the placebo arm more new melanomas were observed compared to D+T arm (6 vs 1 patient). This might even support a protective mechanism for the experimental arm. Non-cutaneous treatment-emergent malignancies were numerically more frequently seen in the D+T compared to the placebo arm (5 vs 3 patients). The long term risk regarding development of non-cutaneous malignancies is still unclear. CuScc, new melanomas and new non-cutaneous malignancies are important identified risks for dabrafenib and are appropriately communicated through current labelling and already part of the pharmacovigilance plan for dabrafenib, hence no new measures are required.

Haemorrhagic events, including major haemorrhagic events and fatal haemorrhages, occurred in patients taking trametinib as monotherapy and in combination with dabrafenib in the unresectable or metastatic melanoma Phase III studies and NSCLC Phase II study (see SmPC section 4.8).

Special populations: AEs were generally occurred at comparable or numerically lower rates in patients of 65 years and older compared to those younger than 65. However, AEs leading to permanent discontinuation were observed more frequently in those of 65 years and older compared to those younger than 65 years. The SmPC already contains a warning relating to this subject.

A similar proportion of male and female patients in both treatment arms experienced at least one AE, however women experienced more (difference≥10%) Grade 3-4 AEs, more AEs leading to permanent discontinuation or dose reductions. No specific AE or cluster of AEs could be identified as an underlying cause of these differences.

2.4.2. Conclusions on clinical safety

No new safety concerns were identified in the current pivotal study for adjuvant treatment of stage III melanoma patients. The safety profile appears similar to the known profile in metastatic melanoma patients, however compared to the metastatic setting less severe AEs and fatal AEs were observed. It may be noted that with dabrafenib and trametinib combination therapy grade 3-4 AEs, SAEs, discontinuations and dose reductions due to AEs occur frequent. Discontinuations and dose reduction were observed early on during the treatment and are often related to low grade AEs, which underlines the toxicity associated with this regimen. Almost all AESI, SAEs and AEs which lead to discontinuation eventually resolved. The SmPC section 4.8 has been updated and no new risk minimisation activities are considered necessary (please see RMP).

2.4.3. PSUR cycle

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

2.5. Risk management plan

The CHMP received the following PRAC Advice on the submitted Risk Management Plan:

The PRAC considered that the risk management plan version 9.1 for Tafinlar and 14.1 for Mekinist is acceptable. The PRAC endorsed PRAC Rapporteur assessment report is attached.

The CHMP endorsed the Risk Management Plan version 9.1 for Tafinlar and 14.1 for Mekinist with the following content:

Safety concerns

Tafinlar

Important identified risks for dabrafenib (including combination therapy)	• New Primary/secondary malignancy • Pre-renal and Intrinsic Renal failure • Uveitis • Medicinal Products that are sensitive substrates of CYP3A4, CYP2B6, CYP2C8, CYP2C9, CYP2C19, UDP glucuronosyl transferase (UGT) and transporters. • Severe Photosensitivity

Important potential risks for dabrafenib (including combination therapy)	• Non-specific cardiac toxicity • Testicular Toxicity • Developmental toxicity • Pregnancy and risks in breast feeding
Important potential risks related to dabrafenib+ trametinib combination therapy only	• Pulmonary embolism, deep vein thrombosis
Missing Information for dabrafenib	• Safety in patients with severe renal impairment • Safety in patients with moderate to severe hepatic impairment

No changes to the list of safety concerns were introduced based on the proposed new indication. However some existing safety concerns were either removed or reclassified based on the revision of GVP module V (rev 2) and the revision of RMP template (rev. 2).

Mekinist

Important identified trametinib risks	• Left ventricular systolic dysfunction (e.g., LVEF decreased and left ventricular dysfunction) • Ocular events (e.g., retinal vein occlusion, retinal pigment epithelial detachment) • Pneumonitis/Interstitial lung disease • Hepatic events (e.g., AST, ALT increased**,** and hepatic failure) • Hemorrhagic events • Gastrointestinal disorders (diarrhea, colitis, and GI perforation).
Important potential trametinib risks	• Impaired female fertility • Developmental toxicity • Safety in children <18 years old (including potential adverse effects on skeletal maturation and sexual maturation) • Pregnancy and risks in breast-feeding.
Important potential risk related to trametinib+dabrafenib combination therapy only	• Pulmonary embolism, deep vein thrombosis
Missing information	• Use in patients with reduced cardiac function or symptomatic Class II, III, or IV heart failure (NYHA functional classification system) • Safety in patients with severe renal impairment • Safety in patients with moderate to severe hepatic impairment • Safety in patients with recent (within 6 months) acute coronary syndrome including unstable angina, coronary angioplasty, stenting or cardiac arrhythmias (except sinus arrhythmia) and treatment refractory hypertension (blood pressure of systolic >140 mmHg and/or diastolic >90 mmHg which cannot be controlled by anti-hypertensive therapy) • Drug-drug interactions (effect of trametinib on oral contraceptives).
Missing information for combination of dabrafenib and trametinib	• None

No changes to the list of safety concerns were introduced based on the proposed new indication. However some existing safety concerns were either removed or reclassified based on the revision of GVP module V (rev 2) and the revision of RMP template (rev. 2).

Pharmacovigilance plan

Tafinlar

Study/Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorization.				
None				
Category 2 – Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorization or a marketing authorization under exceptional circumstances.				
None				
Category 3 - Required additional pharmacovigilance activities				
PASS Study BRF115532 (CDRB436F2301, COMBI-AD): A Phase III study in combination with trametinib in patients with in the Adjuvant treatment of high-risk BRAF V600 mutation-positive melanoma after surgical resection. Status: Ongoing	To evaluate the efficacy of dabrafenib and trametinib combination therapy compared to two placebos with respect to relapse-free survival (RFS) in patients with completely resected, histologically confirmed, BRAF V600E/K high-risk, Stage III cutaneous melanoma. To compare overall survival (OS), distant metastasis-free survival (DMFS), freedom from relapse (FFR) in the combination therapy with the placebo.	New primary/ secondary malignancy	Second interim CSR	Q4-2023

	To evaluate safety of the combination therapy in the OS population and health related quality of life (HRQOL) in combination therapy compared to placebo.			
Study 201710: A non-interventional study to perform evaluation of secondary malignancies in patients treated with dabrafenib in randomized, controlled trials Status: Ongoing	Evaluation of secondary malignancies in patients treated with dabrafenib in randomized, controlled trials	New primary/secondary malignancy	Final report	Q4-2020
PASS Study CDRB436A2106: A Phase I, open label, multicenter, single dose study to evaluate the pharmacokinetics of dabrafenib in healthy subjects with normal renal function and subjects with impaired renal function. Status: Planned	To evaluate the pharmacokinetics of a single oral dose of dabrafenib (and metabolites) in subjects with renal impairment as compared to healthy subjects with normal renal function. To assess the safety of a single oral dose of dabrafenib in subjects with renal impairment. To assess the plasma binding of dabrafenib and pharmacokinetics expressed as unbound drug in subjects with renal	Severe renal impairment	Final report	Q1-2020

	impairment as compared to healthy subjects.			
PASS Study CDRB436A2107: A Phase I, open label, multicenter, single dose study to evaluate the pharmacokinetics of dabrafenib in healthy subjects with normal hepatic function and subjects with impaired hepatic function. Status: Planned	To evaluate the pharmacokinetics of dabrafenib and metabolites after a single oral dose of dabrafenib in subjects with hepatic impairment as compared to healthy subjects with normal hepatic function (Child-Pugh classification) To assess the safety of a single oral dose of dabrafenib in subjects with normal and impaired hepatic functions.	Moderate and severe hepatic impairment	Final report	Q1-2020

Mekinist

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Category 1 – Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorization				
None				
Category 2 – Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorization or a marketing authorization under exceptional circumstances				
None				
Category 3 – Required additional pharmacovigilance activities				

PASS Study MEC116354 – Hepatic Impairment NCI Sponsored Phase I and PK Study Status: ongoing	To obtain dosing recommendation in patients with hepatic impairment	Safety in patients with moderate to severe hepatic impairment	Final report submission	4Q 2018
Study 201711 Annual Reports for Cardiomyopathy-related adverse reactions Status: ongoing	To identify and characterize the risk of cardiomyopathy and subsequent sequelae, including safety evaluations adequate to inform labeling of patient populations at highest risk for developing these toxicities; To provide evidence-based dose modification and monitoring recommendations, in all ongoing and subsequently initiated randomized controlled clinical trials through 2020 that use trametinib alone or in combination with other anti-cancer drugs.	Left ventricular systolic dysfunction	Final report submission	4Q 2020
PASS Study BRF115532 (COMBI-AD) Phase III randomized double-blind study of dabrafenib (GSK2118436) in combination with trametinib (GSK1120212) versus two placebos in the adjuvant treatment of high-risk BRAF V600 mutation-positive melanoma after surgical resection. Status: ongoing	To evaluate the efficacy of dabrafenib and trametinib combination therapy compared to two placebos with respect to relapse-free survival (RFS) in patients with completely resected, histologically confirmed, BRAF V600E/K high-risk, Stage III cutaneous melanoma.	Hemorrhagic events	Primary study report Second interim report	4Q 2017 4Q 2023

PASS Study BRF117277 (COMBI-MB) Phase II, Open-Label, Multicentre Study of dabrafenib plus trametinib in subjects with BRAF Mutation positive melanoma that has metastasized to the brain Status: ongoing	To assess the intracranial response (IR) of subjects with locally confirmed BRAF V600E-mutation positive melanoma that has metastasized to the brain without symptoms and have not undergone prior local therapy for brain metastases, ECOG score of 0-1.	Hemorrhagic events	Final report submission	3Q 2018
PASS Study MEK116540 An Open-Label, Dose-Escalation, Phase I/II study to Investigate the safety, pharmacokinetics, pharmacodynamics and clinical activity of the MEK Inhibitor trametinib in children and adolescents subjects with cancer or plexiform neurofibromas and trametinib in combination with dabrafenib in children and adolescents with cancers harboring V600 mutations. (Trametinib PIP: EMEA-001177-PIP01-11) Status: ongoing	To determine the safe and tolerable trametinib dose(s) for chronic dosing in pediatric subjects (infants, children, and adolescents) that achieves similar exposures ($C\tau$) to the recommended adult dose.	Safety in children <18 years old (including potential adverse effects on skeletal maturation and sexual maturation)	Final report submission	4Q 2020

No changes to the Pharmacovigilance plan for either Mekinist or Tafinlar have been introduced by the MAH with this extension of indication.

The existing Pharmacovigilance plan for both Mekinist and Tafinlar remains sufficient to identify and characterise the risks of the product.

Risk minimisation measures

Tafinlar

Safety concern	Risk minimization measures	Pharmacovigilance activities
Important identified dabrafenib risks (also applicable to combination therapy)		
New primary/secondary malignancy	**Routine risk minimization measures** Dose modifications in Section 4.2 of the SmPC Undesirable effects in Section 4.8	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection**: Targeted follow-up checklist **Additional pharmacovigilance activities:**

Safety concern	Risk minimization measures	Pharmacovigilance activities
	of the SmPC **Additional risk minimization measures** None	None **Additional pharmacovigilance activities:** PASS study BRF115532 (CDRB436F2301, COMBI-AD)
Pre-Renal and Intrinsic Renal Failure	**Routine risk minimization measures** Dose modifications in Section 4.2 of the SmPC Undesirable effects in Section 4.8 of the SmPC **Additional risk minimization measures** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection**: Targeted follow-up checklist **Additional pharmacovigilance activities:** None
Uveitis	**Routine risk minimization measures** Dose modifications in Section 4.2 of the SmPC Undesirable effects in Section 4.8 of the SmPC **Additional risk minimization measures** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection**: None **Additional pharmacovigilance activities:** None
Medicinal Products that are sensitive substrates of CYP3A4, CYP2B6, CYP2C8, CYP2C9, CYP2C19, UDP glucuronosyl transferase (UGT) and transporters	**Routine risk minimization measures** Interactions with other medicinal products and other forms of interactions in Section 4.5 of the SmPC **Additional risk minimization measures** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection**: None **Additional pharmacovigilance activities:** None
Severe Photosensitivity	**Routine risk minimization measures** None **Additional risk minimization measures** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection**: None **Additional pharmacovigilance activities:** None
Important potential dabrafenib risks (also applicable to combination therapy)		
Non-specific Cardiac Toxicity	**Routine risk minimization measures** None **Additional risk minimization measures** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection**: None **Additional pharmacovigilance activities:** None
Testicular toxicity	**Routine risk minimization measures** Preclinical safety data in Section 5.3 of the SmPC **Additional risk minimization measures** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection**: None **Additional pharmacovigilance activities:** None
Developmental	**Routine risk minimization**	**Routine pharmacovigilance activities**

Safety concern	Risk minimization measures	Pharmacovigilance activities
toxicity	**measures** Fertility, pregnancy and lactation in Section 4.6 of the SmPC Preclinical safety data in Section 5.3 of the SmPC **Additional risk minimization measures** None	**beyond adverse reactions reporting and signal detection**: None **Additional pharmacovigilance activities:** None
Pregnancy and risks in breast feeding	**Routine risk minimization measures** Fertility, pregnancy and lactation in Section 4.6 of the SmPC **Additional risk minimization measures** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection**: None **Additional pharmacovigilance activities:** None
Important potential risks related to dabrafenib and trametinib combination therapy only		
Pulmonary embolism, Deep vein thrombosis	**Routine risk minimization measures** Dose modifications in Section 4.2 of the SmPC Undesirable effects in Section 4.8 of the SmPC **Additional risk minimization measures** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection**: None **Additional pharmacovigilance activities:** None
Missing dabrafenib monotherapy information		
Safety in patients with severe renal impairment	**Routine risk minimization measures** Posology and method of administration in Section 4.2 of the SmPC Pharmacokinetic properties in Section 5.2 of the SmPC **Additional risk minimization measures** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection**: None **Additional pharmacovigilance activities:** Study CDRB436A2106
Safety in patients with moderate to severe hepatic impairment	**Routine risk minimization measures** Posology and method of administration in Section 4.2 of the SmPC Pharmacokinetic properties in Section 5.2 of the SmPC **Additional risk minimization measures** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection**: None **Additional pharmacovigilance activities:** Study CDRB436A2107

Mekinist

Safety concern	Risk minimization measures	Pharmacovigilance activities
Important identified trametinib risks		
Left ventricular systolic dysfunction	**Routine risk minimization measures**	**Routine pharmacovigilance activities beyond adverse reactions reporting and**

(e.g., LVEF decreased and left ventricular dysfunction)	SmPC section 4.8 **Additional risk minimization measures** None	**signal detection:** None **Additional pharmacovigilance activities:** Annual Reports for Cardiomyopathy-related adverse reactions (Study 201711)
Ocular events (e.g., retinal vein occlusion, retinal pigment epithelial detachment)	**Routine risk minimization measures** SmPC section 4.8 **Additional risk minimization measures** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** None.
Pneumonitis/Interstitial lung disease	**Routine risk minimization measures** SmPC section 4.8 **Additional risk minimization measures** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** None.
Hepatic events (e.g., AST, ALT increased, and hepatic failure)	**Routine risk minimization measures** SmPC section 4.8 **Additional risk minimization measures** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** None.
Hemorrhagic events	**Routine risk minimization measures** SmPC section 4.8 **Additional risk minimization measures** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** PASS Study BRF117277 (Novartis trial ID: Study CDRB436B2204) and PASS Study BRF115532 (Novartis trial ID: Study CDRB436F2301)
Gastrointestinal disorders (diarrhea, colitis, and GI perforation)	**Routine risk minimization measures** SmPC section 4.4, section 4.8, and section 5.3. **Additional risk minimization measures** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** None
Important potential risks		
Impaired female fertility	**Routine risk minimization measures** SmPC section 4.6 **Additional risk minimization measures** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** None
Developmental toxicity	**Routine risk minimization measures** SmPC section 5.3 **Additional risk minimization measures** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** None
Safety in children <18 years old (including potential adverse effects on skeletal maturation	**Routine risk minimization measures** SmPC section 4.2 **Additional risk minimization**	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None

and sexual maturation)	**measures** None	**Additional pharmacovigilance activities:** Trametinib PIP: EMEA-001177-PIP01-11 (PASS Study MEK116540)
Pregnancy and risks in breast-feeding	**Routine risk communication** SmPC Section 4.6 **Additional risk minimization measures** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** None
Important potential risks related to trametinib + dabrafenib combination therapy only		
Pulmonary embolism, deep vein thrombosis	**Routine risk minimization measures** SmPC section 4.4 **Additional risk minimization measures** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** None
Missing information		
Use in patients with reduced cardiac function or symptomatic Class II, III, or IV heart failure (NYHA functional classification system)	**Routine risk minimization measures** SmPC section 4.4 **Additional risk minimization measures** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** None
Safety in patients with severe renal impairment	**Routine risk minimization measures** SmPC section 4.2 **Additional risk minimization measures** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** None
Safety in patients with moderate to severe hepatic impairment	**Routine risk minimization measures** SmPC section 4.2 **Additional risk minimization measures** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** PASS Study MEC116354 (Novartis trial ID: Study CTMT212XUS23T)
Safety in patients with recent (within 6 months) acute coronary syndrome including unstable angina, coronary angioplasty, stenting or cardiac arrhythmias (except sinus arrhythmia) and treatment refractory hypertension (blood pressure of systolic >140 mmHg and/or diastolic >90 mmHg which cannot be controlled by anti-hypertensive therapy	**Routine risk minimization measures** SmPC section 4.4 **Additional risk minimization measures** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** None
Drug-drug interactions (effect of trametinib on oral contraceptives)	**Routine risk minimization measures** SmPC section 4.6 **Additional risk minimization**	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None

	measures None	**Additional pharmacovigilance activities:** None

No changes to the risk minimisation measures for either Mekinist or Tafinlar have been introduced as part of this extension of indication.

Routine risk minimisation measures remains sufficient to manage the safety concerns of both medicinal products.

2.6. Update of the Product information

As a consequence of this new indication, sections 4.1, 4.2, 4.4, 4.8 and 5.1.of the SmPC have been updated. The Package Leaflet has been updated accordingly.

In addition, the list of local representatives in the PL has been revised to amend contact details for the representative(s) of Latvia, Estonia, Bulgaria and Lithuania.

2.6.1. User consultation

A justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the MAH and has been found acceptable for the following reasons: the changes are considered minor and do not impact the readability of the PL.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

The MAH applied for an extension of indication for trametinib in combination with dabrafenib for the adjuvant treatment of adult patients with Stage III melanoma with a BRAF V600 mutation, following complete resection.

3.1.2. Available therapies and unmet medical need

Melanoma is a malignant tumour that originates from melanocytic cells and primarily involves the skin. Using the 8th edition of the AJCC classification, 5-year melanoma-specific survival rate ranges from 93% in stage IIIA to 32% in stage IIID.

In melanoma, different activating mutations have been described, mainly resulting in an increased signalling of the Mitogen-Activated Protein Kinase (MAPK)-pathway leading to cell proliferation. About 45% of patients with cutaneous melanoma carry an activating BRAF V600 mutation.

For locoregional advanced melanomas, surgery alone is standard of care, including resection of satellite or in-transit metastases and regional lymph node dissections once tumour-positive nodes have been detected. However, prognosis for patients with high risk melanoma remains poor with 5-year survival rates of 40 to 80%. Therefore, there is a need for additional adjuvant therapy options.

Interferon alpha has been approved for the adjuvant treatment for melanoma in the EU, however due to concerns regarding toxicity, it is currently not standard of care in the EU. Recently nivolumab has been approved.

3.1.3. Main clinical studies

The application is supported by one pivotal study, a randomised, double-blind phase III study to evaluate the combination of dabrafenib and trametinib versus placebo as adjuvant treatment for 1 year in stage III BRAF V600E/K mutant melanoma after surgical resection. 870 patients were randomised 1:1 with stratification by BRAF status and disease stage. Staging of the study population was based on the previous 7th AJCC edition. Given that stage III contains patients with metastases in regional lymph nodes and non-nodal locoregional sites and without distant metastases in both the 7th and 8th edition, this is not likely to influence the results. The primary efficacy endpoint was RFS; OS was a key secondary endpoint. Other efficacy endpoints were DMFS (secondary), FFR (secondary), HRQOL (using EQ-5D; exploratory), ECOG PS (exploratory), PK (exploratory) and biomolecular analysis (exploratory).

3.2. Favourable effects

The study BRF115532 met its primary endpoint demonstrating superiority of the treatment arm for RFS with HR 0.47 (95%CI 0.39-0.58; p=1.53x10-14). Median time to reach RFS was 16.6 months in the placebo arm (95%CI 12.7-22.1) and not reached in the treatment arm (95%CI 44.5-NE) with the primary DBL of 30-Jun-2017. An additional DBL at 30-Apr-2018 with an extra 10 months of follow-up showed consistent results with HR 0.49 (95%CI 0.40-0.59). Compared to the primary RFS analysis 17 additional RFS events were recorded (11 in dabrafenib+trametinib arm and 6 in placebo arm). Median follow-up was 44 months in the dabrafenib+trametinib group and 42 months in the placebo group. When looking at the RFS Kaplan-Meier curves separation of the curves is visible after the first assessment on study in favour of dabrafenib+trametinib. The curves are interpretable until ~38 months, which is, given that most recurrences occur <3 years, considered sufficient. With the additional follow-up the curve in the dabrafenib+trametinib arm leads to a plateau, indicating that some patients may be cured. At 3 years the difference in RFS rate was 19%.

Support that the RFS data are mature is provided by the event and censoring rates. The number of events after 36 months is low in both arms and seems to stabilise.

Sensitivity analyses were all supporting the efficacy of the dabrafenib+trametinib arm. Most subgroup analyses showed a favourable HR in favour of the treatment arm, including for known prognostic factors such as disease stage, nodal status and ulceration.

The first interim analysis for OS was based on in total 153 deaths (26% of the total targeted deaths required for final analysis). The number of events was 60 (14%) in the dabrafenib+trametinib arm and 93 (22%) in the placebo arm. Median OS was not reached in either arm. HR was 0.57 (95%CI 0.42-0.79) and the threshold for significance was not reached.

Though immature, other secondary endpoints (DMFS and FFR) are considered supportive for the RFS results.

There were no statistically significant differences in HRQoL measures between the two arms and during the study changes from baseline were minimal. Changes in ECOG performance scale were also similar between the two groups.

The provided PK data in this variation support that exposure to dabrafenib and its active metabolites, as well as exposure to trametinib, with dabrafenib given at a dose of 150 mg twice daily and trametinib as 2 mg once daily, in the adjuvant melanoma setting is comparable to that in the metastatic melanoma setting.

3.3. Uncertainties and limitations about favourable effects

Secondary endpoint OS- OS data of 24-27 months are still immature. Therefore, the MAH is requested to submit the final OS study results from study BRF115532. This has been included as part of an Annex II condition.

Exploratory endpoints- In addition, results from an exploratory endpoint for biomarkers analyses have not been provided. Biomarkers could aid in the detection and follow-up of residual disease during and after treatment. Moreover, biomarkers could possibly be used for dose refinement. For circulating free (cf)DNA the predictive value is already shown in the metastatic setting[10] . Currently the mutational and gene expression profiling data are being analysed in relapsed patients. The CHMP recommends the submission of the results from the biomarker analysis in tissues and plasma.

3.4. Unfavourable effects

In general, the AEs of dabrafenib plus trametinib in the current study were comparable to the known safety profile from metastatic melanoma and advanced NSCLC patients. The most common adverse reactions (incidence ≥20%) for trametinib in combination with dabrafenib were: pyrexia, fatigue, nausea, chills, headache, diarrhoea, vomiting, arthralgia and rash. Grade 3/4 AEs were also more frequent in the D+T arm compared to placebo (41 vs 14%). The most frequent Grade 3/4 AEs in the D+T arm were hypertension, pyrexia and fatigue.

Over one third of the patients (36%) in the D+T arm experienced SAEs. The most frequently reported SAEs were pyrexia (15%), chills (3%) and decreased ejection fraction (3%) in the D+T arm. In the placebo arm, SAEs occurred infrequently. Five deaths occurred within 30 days from last dose, four were due to disease progression and one death in the D+T arm was due to an untreated pneumonia and was deemed unrelated to the treatment. In prior D+T studies in metastatic melanoma, 6 patients with fatal bleedings were observed, possibly related to D+T. In this study, no fatal bleeding events were observed and almost all bleeding events were Grade 1-2.

Dose reductions/dose interruptions and discontinuations of D+T, most often related to pyrexia, chills and fatigue, at higher frequencies compared to both placebo and the metastatic melanoma setting. Permanent discontinuations occurred in about a quarter of the patients. Most discontinuations and dose reductions due to AEs occurred within the first three months and were related to Grade 1-2 AEs.

CuSCC rates in the D+T arm were low and comparable to the placebo, however the median time to onset was earlier in the D+T arm (median 18 vs 33 weeks). Non-cutaneous treatment-emergent malignancies were reported numerically more frequent and new primary melanomas numerically less frequent in the D+T arm compared to the placebo arm.

A similar proportion of male and female patients in both treatment arms experienced at least one AE, however women experienced more Grade 3-4 AEs (Grade 3: 44% vs 34%; Grade 4: 3% vs 2%), more

[10] Santiago-Walker A, Gagnon R, Mazumdar J, Casey M, Long GV, Schadendorf D, Flaherty K, Kefford R, Hauschild A, Hwu P, Haney P, O'Hagan A, Carver J, Goodman V, Legos J, Martin AM. Correlation of BRAF Mutation Status in Circulating-Free DNA and Tumor and Association with Clinical Outcome across Four BRAFi and MEKi Clinical Trials. Clin Cancer Res. 2016 Feb 1;22(3):567-74

AEs leading to permanent discontinuation (32% vs 22%) or dose reductions (45 vs 33%) than male patients. No specific AEs or cluster of AEs could be identified underlying the male-female differences.

3.5. Uncertainties and limitations about unfavourable effects

There were no new safety concerns identified during the conduct of the clinical trial.

3.6. Effects Table

Table 45: Effects Table for dabrafenib with trametinib in stage III BRAF V600 mutation positive melanoma (data cut-off: 30-Apr-2018 for RFS and DMFS, 30-Jun-2017 for other endpoints)

Effect	Short description	Unit	Treatment	Control	Uncertainties / Strength of evidence	References
Favourable Effects						
RFS	Recurrence-free survival	Median in months (95%CI)	NE (46.9-NE)	16.6 12.7-22.1	Double-blind, placebo controlled HR 0.49 (0.40-0.59) 38 months follow up	CSR
OS	Overall survival	Median in months (95%CI)	NE (NE-NE)	NE (NE-NE)	Double-blind, placebo controlled HR 0.57 (0.42-0.79), immature 24-27 months follow up	CSR
DMFS	Distant metastasis-free survival	Median in months (95%CI)	NE (NE-NE)	NE (49.8-NE)	Double-blind, placebo controlled HR 0.53 (0.42-0.67), immature	CSR
FFR	Freedom from relapse	Median in months (95%CI)	NE (44.5-NA)	16.6 (12.7-22.3)	Double-blind, placebo controlled HR 0.47 (0.39-0.57), immature	CSR
Unfavourable Effects						
Any AE		n (%)	422 (97%)	380 (88%)		CSR
AE gr3-4		n (%)	180 (41%)	61 (14%)		CSR
SAE		n (%)	155 (36)	44 (10)	-Resolving of SAEs in 94%	CSR
Deaths		n (%)	60 (14%)	93 (22%)		CSR
	- due to disease progression	n (%)	54 (12%)	77 (18%)		CSR
	- ≤30 days	n (%)	4 (<1%)	1 (<1%)		CSR
AEs	-leading to dose reduction	n (%)	167 (38%)	11 (3%)	The most dose reductions due to AEs (dabrafenib 71%; trametinib 52%) occur within the first 3 months of treatment	CSR
	-leading to dose interruption	n (%)	289 (66%)	65 (15%)		CSR
	- leading to permanent discontinuation	n (%)	114 (26%)	12 (3%)	40% of discontinuations due to AEs occur within first three months	CSR
AESIs	-Cuscc	N	6	5	No long term data	CSR
	-non cutaneous treatment emerging malignancies	N	5	3		CSR
	-new melanomas	N	6	1		CSR

Abbreviations: AE- adverse event; AESI- adverse event of special interest; NE- not estimable; SAE- serious adverse event.

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

Melanoma is the most serious form of skin cancer and currently no standard adjuvant therapy after surgery is given in the EU. Interferon alpha is an approved treatment option, but its use is limited because of its high toxicity. In addition, the benefit of interferon in BRAF mutated patients remains unclear. Therefore, there is a need for additional adjuvant therapy options in stage III melanoma. The combination of dabrafenib+trametinib shows a significant and relevant increase in RFS compared to placebo. The RFS efficacy results are supported by a favourable trend in OS and support from secondary endpoints, DMFS, and FFR in favour of dabrafenib+trametinib as well as consistent results in the subgroup analyses. The MAH provided updated RFS results which show that the RFS benefit was maintained over a longer period of time and it also increases the cure rate. Since most relapses tend to occur within 3 years in this patient population, the 38 months follow up data is reliable enough to provide a clear demonstration of a plateau with an estimated 3-year difference in RFS of 19% compared to placebo accompanied by a decreasing event rate.

An update of OS analysis within this procedure is not likely to provide more information given the low number of events.

No new safety concerns were identified in the current pivotal study for adjuvant treatment of stage III melanoma patients. In general, the safety and tolerability appear similar to what has been described for metastatic melanoma patients however compared to the metastatic setting less severe AEs and fatal AEs were observed. Nonetheless, dabrafenib and trametinib combination therapy is associated with considerable toxicity as Grade 3-4 AEs, SAEs, dose reductions and permanent discontinuations due to AEs occur relatively frequent. The latter two occur relatively early on during the treatment and are often related to low grade AEs. It is reassuring is that almost all ADRs which lead to discontinuation eventually resolve. No new safety measures are considered necessary for this patient population.

3.7.2. Balance of benefits and risks

It has been shown that the adjuvant treatment of stage III melanoma with dabrafenib+trametinib leads to a prolonged RFS benefit as well as an increased cure rate. The results outweigh the toxicity observed with the combination treatment.

3.7.3. Additional considerations on the benefit-risk balance

It was noted that patients with lower risk melanoma, i.e. stage IIIA with lymph node metastasis <1 mm were not included in the study population. However, there is no evidence that these patients would not also derive clinical benefit. Therefore, the indication includes all stage III patients with cutaneous melanoma. Moreover, patients were recruited with cutaneous melanoma with a V600E/K mutation. It is well known that over 90% of mutations at position 600 are a substitution of the amino acid valine (V) to a glutamic acid (E) but other substitutions can also occur such as V600-D-R. Dabrafenib has shown inhibitory activity against some of these other mutations and trametinib will inhibit downstream MEK activity, hence, likewise for the metastatic setting, there is sufficient evidence to be able to extrapolate the indication to melanoma patients with tumours harbouring V600 mutations.

3.8. Conclusions

The overall B/R of the combination of Tafinlar and Mekinist is positive for the adjuvant treatment of adult patients with stage III melanoma with a BRAF V600 mutation, following complete resection.

4. Recommendations

Outcome

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends the variation to the terms of the Marketing Authorisation, concerning the following change:

Variation accepted		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB

Extension of indication to include the combination adjuvant treatment with trametinib and dabrafenib of adult patients with stage III melanoma with a BRAF V600 mutation, following complete resection. As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1 of the Mekinist and Tafinlar SmPCs are updated. The Package Leaflet and the Risk Management plan (version 14.1 for Mekinist and version 9.1 for Tafinlar, according to GVP module V revision 2) are updated in accordance. In addition, the Worksharing applicant (WSA) took the opportunity to correct some typos throughout the Mekinist and Tafinlar product information, to include a cross reference to the Mekinist SmPC in section 4.6 of the Tafinlar SmPC regarding fertility, to update the list of local representatives for Bulgaria, Hungary, Estonia, Latvia and Lithuania in the Package Leaflet of both products.

The worksharing procedure leads to amendments to the Summary of Product Characteristics and Package Leaflet and to the Risk Management Plan (RMP).

5. EPAR changes

The EPAR will be updated following Commission Decision for this variation. In particular the EPAR module 8 "*steps after the authorisation*" will be updated as follows:

Scope

Extension of indication to include the combination adjuvant treatment with trametinib and dabrafenib of adult patients with stage III melanoma with a BRAF V600 mutation, following complete resection. As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1 of the Mekinist and Tafinlar SmPCs are updated. The Package Leaflet and the Risk Management plan (version 14.1 for Mekinist and version 9.1 for Tafinlar, according to GVP module V revision 2) are updated in accordance. In addition, the Worksharing applicant (WSA) took the opportunity to correct some typos throughout the Mekinist and Tafinlar product information, to include a cross reference to the Mekinist SmPC in section 4.6 of the Tafinlar SmPC regarding fertility, to update the list of local representatives for Bulgaria, Hungary, Estonia, Latvia and Lithuania in the Package Leaflet of both products.

Summary

Please refer to the published assessment report Mekinist-Tafinlar-WS-1274: EPAR - Assessment Report – Variation

Attachments

1. SmPC and Package Leaflet (changes highlighted) as adopted by the CHMP on 26 July 2018.