Amsterdam, 26 March 2026
EMADOC-1700519818-2934719
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Procedure No. EMA/VR/0000278305

Medicinal products authorised through the centralised procedure

Invented name:	International non-proprietary name:
Tafinlar	Dabrafenib
Mekinist	Trametinib

Note

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

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List of abbreviations

ADR	Adverse drug reaction
AE	Adverse event
AESI	Adverse event of special interest
BID	Twice daily
BIRC	Blinded independent review committee
BOR	Best overall response
BRAF	B-Raf proto-oncogene, serine/threonine kinase
CI	Confidence interval
CL	Clearance
CMH	Cochran-Mantel-Haenszel (test)
CTCAE	Criteria for Adverse Events
CR	Complete response
CSR	Clinical study report
DCO	Data cut-off
DOR	Duration of response
D+T	Dabrafenib and trametinib
DTC	Differentiated Thyroid Cancer
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
FAS	Full Analysis Set
FPFV	First patient first visit
FTC	Follicular thyroid cancer
HR	Hazard ratio
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
K-M	Kaplan-Meier
LPLV	Last patient last visit
MAPK	Mitogen-activated protein kinase
MedDRA	Medical Dictionary for Regulatory Activities
MEK	Mitogen-activated extracellular signal-regulated kinase
mTKI	Multitarget tyrosine kinase inhibitor
NSCLC	Non-small cell lung cancer
NTRK	Neutrotrophic tyrosine receptor kinase
OCT	Optical coherence tomography
ORR	Overall response rate
OS	Overall survival
PD	Pharmacodynamic
PDTC	Oncocytic carcinoma of the thyroid
PFS	Progression free survival
PK	Pharmacokinetics
PR	Partial response
PRO	Patient-reported outcome
PSUR	Periodic Safety Update Report
PT	Preferred term
PTC	Papillary thyroid carcinoma
QD	Once daily
RAI	Radioactive iodine
RECIST	Response Evaluation Criteria in Solid Tumors

RET	Rearranged during transfection
SAE	Serious adverse event
SCE	Summary of clinical efficacy
SCS	Summary of clinical safety
SmPC	Summary of Product Characteristics
SOP	Standard operating procedure
TKI	Tyrosine Kinase Inhibitor
VAS	Visual analogue scale
VEGFR	Vascular Endothelial Growth Factor Receptor

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 25 August 2025 an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.

The following changes were proposed:

Variation(s) requested		**Type**
C.I.6.a	C.I.6.a Addition of a new therapeutic indication or modification of an approved one	Variation type II

Extension of indication to include treatment of differentiated thyroid cancer (DTC) for TAFINLAR and MEKINIST based on primary analysis from pivotal study CDRB436J12301. This is a randomized, double-blind, placebo-controlled Phase 3 study to evaluate the efficacy and safety of dabrafenib plus trametinib in previously treated patients with locally advanced or metastatic, radio-active iodine refractory BRAF V600E mutation-positive differentiated thyroid cancer. As a consequence, sections 4.1, 4.2, 4.4, 4.8 and 5.1 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 14.0 and Version 22.0 of the RMPs for Tafinlar and Mekinist, respectively, have also been submitted.

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included EMA Decisions P/0410/2020 for Tafinlar and P/0392/2020 for Mekinist on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIPs P/0410/2020 and P/0392/2020 were completed.

The PDCO issued an opinion on compliance for the PIPs P/0410/2020 and P/0392/2020.

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 MAH 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 WSA did not seek Scientific Advice at the CHMP.

1.2. Steps taken for the assessment of the product

Appointed (Co-)Rapporteurs for the WS procedure:

Rapporteur: Peter Mol

Timetable	Actual dates
Submission date	25 August 2025
Start of procedure:	13 September 2025
CHMP Rapporteur's preliminary assessment report circulated on:	6 November 2025
Joint Rapporteur's updated assessment report circulated on:	13 November 2025
PRAC RMP advice and assessment overview adopted by PRAC	27 November 2025
Request for supplementary information and extension of timetable adopted by the CHMP on:	11 December 2025
WSA's responses submitted to the CHMP on:	22 January 2026
CHMP Rapporteur's preliminary assessment report on the WSA's responses circulated on:	2 March 2026
Joint Rapporteur's updated assessment report on the WSA's responses circulated on:	19 March 2026
CHMP opinion:	26 March 2026

2. Scientific discussion

2.1. Introduction

2.1.1. Problem statement

Disease or condition

Worldwide, there were more than 800,000 new cases of thyroid cancer in 2022, making it number seven in terms of incidence among cancers (Global Cancer Observatory - Cancer Today 2022a). Differentiated thyroid carcinoma (DTC) is the most common type of thyroid cancer (> 90% of thyroid cancers), arising from follicular cells in the thyroid gland, and consists of papillary thyroid carcinoma (PTC), follicular thyroid carcinoma (FTC), and oncocytic carcinoma of the thyroid (PDTC) (Jung et al. 2022).

Claimed therapeutic indication

The initially proposed indications were:

Tafinlar

Dabrafenib in combination with trametinib is indicated for the treatment of adult patients with locally advanced or metastatic differentiated thyroid cancer with a BRAF V600E mutation, refractory to or not eligible for radioactive iodine (RAI) who have progressed during or after prior systemic therapy.

Mekinist

Trametinib in combination with dabrafenib is indicated for the treatment of adult patients with locally advanced or metastatic differentiated thyroid cancer with a BRAF V600E mutation, refractory to or not eligible for radioactive iodine (RAI) who have progressed during or after prior systemic therapy.

Biologic features

BRAF V600E is the most common molecular abnormality in thyroid cancer and is commonly found in patients with RAI-refractory DTC (Aashiq et al. 2019). The proportion of BRAF mutations is approximately 40-45% of PTC cases, which is the DTC subtype most frequently associated with the BRAF V600E mutation (Podolski et al. 2019, Subash et al. 2020). BRAF V600E mutation is rarely detected (approximately 1%) in FTC (Kebebew et al. 2007, Jung et al. 2022).

BRAF V600E mutation is an oncogenic mutation that is associated with tumour aggressiveness and poor prognosis because of the constitutive activation of the downstream mitogen-activated protein kinase (MAPK) pathway, which drives cellular differentiation and cancer progression (Prete et al. 2020, Cong et al. 2024). BRAF/MEK/MAPK pathway activation is associated with loss of expression of iodine-metabolizing genes in thyroid cancer, resulting in iodine refractoriness (Niu et al. 2024).

Clinical presentation, diagnosis and prognosis

The global incidence of thyroid cancer has been steadily rising over the last four decades, which has been attributed in part to improved detection of subclinical, indolent cancers.

DTC is typically treated with surgery and subsequent therapy with radioactive iodine (RAI) is dependent on the risk of disease recurrence. The majority of patients can be cured with this treatment strategy and have an excellent prognosis. Overall, one out of three patients with distant metastases will also be cured with RAI and have a near-normal life expectancy (Filetti et al. 2020).

Approximately 10–15% of patients with thyroid cancer eventually do not trap iodine and are considered RAI-refractory. For these patients, the 10-year survival rate is 10% from the time of detection of metastasis, with an average estimated survival of 3 to 5 years (Tan et al. 2024).

Management

DTC is typically treated with surgery and subsequent therapy is dependent on the risk of disease recurrence. RAI is a mainstay of therapy in patients who present with locally advanced or recurrent metastatic disease. However, two-thirds of patients with metastatic disease become radioiodine refractory (RAI-refractory) during their disease course, mainly due to a loss of differentiation ability of thyroid cancer cells with an impaired iodine metabolism (Leboulleux et al. 2023).

Systemic therapy for patients with RAI-refractory DTC includes multitarget tyrosine kinase inhibitors (mTKIs) targeting particularly the vascular endothelial growth factor receptor (VEGFR) family, thereby inhibiting tumour angiogenesis and causing hypoxia in malignant tissue. Systemic treatment is usually initiated for symptomatic progressive disease, after local therapy (such as surgery or radiotherapy) is no longer possible (Filetti et al. 2020).

The mTKIs sorafenib (approved on 23 May 2014) and lenvatinib (approved on 28 May 2015) were the first targeted systemic therapies approved in the European Union for advanced DTC. Sorafenib was approved based on a median PFS-benefit of 5 months compared to placebo (5.8 vs 10.8 months; HR 0.59 (0.45-0.76), Nexavar SmPC). For lenvatinib, registration was based on a benefit in median PFS over placebo of 14.7 months (3.6 vs 18.3 months; HR 0.21 (0.14-0.31); Lenvima SmPC). For both therapies, an OS benefit has not been established.

Although mTKIs have changed the therapeutic strategies and improved the prognosis for DTC, toxicity associated with VEGF pathway inhibition is common, including cardiovascular and renal events. In addition, some of the rare associated adverse events (AEs) are potentially life-threatening and can further limit utilization (Enokida, Tahara 2021). In addition, even though the mTKIs have shown clear antitumor activity in DTC, the majority of DTC patients will acquire resistance to this class of therapy and develop progressive disease (Hamidi et al. 2023).

Treatment options are limited for patients developing resistance to mTKI therapy. For patients diagnosed with RET fusion-positive thyroid cancer, the RET inhibitor selpercatinib was approved in the EU on 11 February 2021. For patients diagnosed with tumours expressing neutrotrophic tyrosine receptor kinase (NTRK) gene fusions, larotrectinib and entrectinib are possible options (larotrectinib approval date: 19 September 2019; entrectinib approval date: 31 July 2020). However, these drugs target rare and distinct molecular subtypes of DTC, and these gene fusions typically do not co-occur with the more common BRAF V600E mutation.

Despite the broadening therapeutic landscape for advanced DTC over the last decade, no selective targeted therapies directed against the BRAF V600E driver mutation are currently approved in the EU. On 29 April 2022, cabozantinib was approved in the EU as a second-line therapy for patients with locally advanced or metastatic DTC, refractory or not eligible to RAI who have progressed during or after prior systemic therapy. Approval was based on a PFS benefit compared to placebo (median PFS 1.9 months vs not reached; HR 0.22 (0.13-0.36); Cabometyx SmPC), with OS data still immature at time of approval.

For DTC patients who develop resistance to TKI therapy, options are very limited and more effective therapies with minimal toxicity are needed.

2.1.2. About the products

Dabrafenib is an orally bioavailable, potent and selective inhibitor of the V600-mutant BRAF kinase with a mode of action consistent with adenosine triphosphate-competitive inhibition. In the EU, it has been available in capsule form under the brand name Tafinlar since 2013 and is currently approved as monotherapy or in combination with trametinib for the treatment of adult patients with unresectable or metastatic melanoma with a BRAF V600 mutation and (in combination with trametinib) for the adjuvant treatment of adult patients with Stage III melanoma with a BRAF V600 mutation, following complete resection, and (in combination with trametinib) for the treatment of adult patients with advanced non-small cell lung cancer (NSCLC) with a BRAF V600 mutation. The recommended dose of dabrafenib in adult patients is 150 mg BID (corresponding to a total daily dose of 300 mg).

Trametinib is a reversible and a highly selective allosteric inhibitor of mitogen-activated extracellular signal-regulated kinase (MEK1 and MEK2 activation and kinase activity). In the EU, it has been available in tablet form under the brand name Mekinist since 2014 and is currently approved as monotherapy or in combination with dabrafenib for the treatment of adult patients with unresectable or metastatic melanoma with a BRAF V600 mutation, and in combination with dabrafenib for the adjuvant treatment of adult patients with Stage III melanoma with a BRAF V600 mutation, following complete resection, and in combination with dabrafenib for the treatment of adult patients with advanced NSCLC with a BRAF V600 mutation. The recommended dose of trametinib in adult patients is 2 mg QD.

The new applied indications are:

Tafinlar

Dabrafenib in combination with trametinib is indicated for the treatment of adult patients with locally advanced or metastatic differentiated thyroid cancer with a BRAF V600E mutation, refractory to or not eligible for radioactive iodine (RAI) who have progressed during or after prior systemic therapy.

Mekinist

Trametinib in combination with dabrafenib is indicated for the treatment of adult patients with locally advanced or metastatic differentiated thyroid cancer with a BRAF V600E mutation, refractory to or not eligible for radioactive iodine (RAI) who have progressed during or after prior systemic therapy.

2.1.3. The development programme/compliance with CHMP guidance/scientific advice

The MAH did not seek Scientific Advice from the CHMP for the development of dabrafenib and trametinib in thyroid carcinoma.

Dabrafenib and trametinib do not have an orphan indication for the treatment of thyroid carcinoma.

2.1.4. General comments on compliance with GLP, GCP

The MAH states that pivotal study J12301 was conducted in full compliance with current Good Clinical Practices.

2.2. Non-clinical aspects

No new non-clinical data have been submitted in this application, which is considered acceptable.

2.2.1. Ecotoxicity/environmental risk assessment

Table 1. Trametinib (Mekinist)-Summary of main study results Phase I

Substance (INN/Invented Name):	trametinib		
CAS-number (if available):	*1187431-43-1*		
PBT/vPvB screening			
Study type	Test protocol	Result	Conclusion

Bioaccumulation potential- log D_{ow}	OECD 107	4.04	Potential PBT: *no*

Phase I			
Parameter	Value	Unit	Conclusion
$PEC_{sw,refined\ prevalence}$	0.002	µg/L	>0.01 threshold: N
Other concerns (e.g. chemical class)			N

PECsurfacewater for trametinib is below the action limit of 0.01 µg/L. Consequently, a Phase II risk assessment is not required. No risks to the environment are to be expected when the medicinal product is used as recommended in the SmPC.

A bioaccumulation potential is not indicated based on the log KOW < 4.5. A definitive PBT/vPvB assessment is not required.

Table 2. Dabrafenib (Tafinlar) Summary of main study results Phase I

Substance (INN/Invented Name):	dabrafenib		
CAS-number (if available):	1195765-45-7		
PBT/vPvB screening			
Study type	Test protocol	Result	Conclusion
Bioaccumulation potential- log D_{ow}	OECD 107	3.229 at pH 5 3.384 at pH 7 -0.168 at pH 9	Potential PBT: *N*
PBT/vPvB assessment			
Property	Parameter	Result	Conclusion
Bioaccumulation	log D_{ow}	3.384 at pH 7	not B
	BCF_{SS}	4.38 L/kg_{ww}	Not B
Persistence	Ready biodegradability	N	potentially P
	DT_{50} at 12°C	652 d	vP
Toxicity	$NOEC_{aquatic}$ C, M, R STOT RE 1 or 2*	0.0583 mg/L Cat 2 Repro	T
PBT/vPvB statement:	dabrafenib is considered to be not PBT, nor vPvB		

Phase I			
Parameter	Value	Unit	Conclusion
$PEC_{sw,refined\ prevalence}$	0.29	µg/L	>0.01 threshold: Y

Phase I			
Other concerns (e.g. chemical class)			N

Table 3. Summary of main study results: Phase II

Phase II Physical-chemical properties and fate			
Study type	**Test protocol**	**Result**	**Remarks**
Adsorption-Desorption Soil 1 = sandy silt loam	OECD 106	 $K_{OC, soil\ 1}$ = 5819 L/kg$_{oc}$	
Soil 2 = sand		$K_{OC, soil\ 2}$ = 10615 L/kg$_{oc}$	
Soil 3 = sandy silt loam		$K_{OC, soil\ 3}$ = 1445 L/kg$_{oc}$	
Sediment 1 = sandy silt loam		$K_{OC, sediment\ 1}$ = 2345 L/kg$_{oc}$	
Sludge 1 = municipal		$K_{FOC, sludge\ 1}$ = 2460 L/kg$_{oc}$	
Ready Biodegradability Test	OECD 301B	0 % (28 d) not readily biodegradable	
Aerobic and Anaerobic Transformation in Aquatic Sediment systems Sediment 1 = silt loam	OECD 308	$DT_{50, water\ 1}$ = 16 d $DT_{50, system\ 1}$ = 307 d CO_2 = ≤0.2 % NER_{total} = 17.1 %	at 20 °C at test end at test end
Sediment 2 = sand		$DT_{50, water\ 2}$ = 28 d $DT_{50, whole\ system\ 2}$ = 162 d CO_2 = ≤0.2 % NER_{total} = 31.1 %	at 20 °C at test end at test end
Transformation products		>10% = Y TP1 (max) = 2.9 %	 at test end
Phase II Aquatic effect studies			

Study type	Test protocol	Endpoint	Value	Unit	Remarks
Algae, Growth Inhibition Test/*R. subcapitata*	OECD 201	NOEC	220	µg/L	growth rate
Daphnia sp. Reproduction Test/*D. magna*	OECD 211	NOEC	58.3	µg/L	mortality
Fish, ELS/*P. promelas*	OECD 210	NOEC	1470	µg/L	growth
Activated Sludge, Respiration Inhibition Test	OECD 209	NOEC	312500	µg/L	total respiration
Phase II Sediment effect studies					
Sediment Dwelling Organism Test/C. riparius	OECD 218	NOEC	64	mg/kg_{dw}	emergence
Phase II Other					
Bioaccumulation Test/*O. mykiss* Test 1 = 0.1 µg/L Test 2 = 0.01 µg/L	OECD 305	$BCF_{SS,1}$ $BCF_{SS,2}$	3.98 4.38	L/kg L/kg	
Risk characterisation					
Compartment	**PEC**	**PNEC**	**RQ**		**Conclusion**
STP	2.9 µg/L	31250 µg/L	<0.001		no risk
Surface water	0.29 µg/L	5.83 µg/L	0.05		no risk
Groundwater	0.073 µg/L	0.583 µg/L	0.13		no risk
Sediment	0.047 mg/kg_{dw}	0.640 mg/kg_{dw}	0.073		no risk

Considering the above data from Phase I and Phase II, dabrafenib is not expected to pose a risk to the environment.

Considering the provided data of the definitive hazard assessment, dabrafenib is not a PBT or vPvB substance.

2.2.2. Conclusion on the non-clinical aspects

Considering the provided data of the definitive hazard assessment, dabrafenib is not a PBT or vPvB substance. Considering the above data, dabrafenib and trametinib are not expected to pose a risk to the environment.

2.3. Clinical aspects

2.3.1. Introduction

GCP

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

The MAH 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 4. Overview of Study J12301

Study design, objectives, population	Phase III, multicenter, randomized, double-blind, placebo-controlled study evaluating the efficacy and safety of dabrafenib plus trametinib in adult patients with locally advanced or metastatic BRAF V600E mutation-positive DTC who are RAI-refractory and have progressed following prior VEGFR-targeted therapy.
Treatment duration	Patients received dabrafenib plus trametinib or matching placebos until disease progression as per RECIST1.1 as determined by investigator and confirmed by BIRC. Patients randomized to the placebo treatment arm were allowed to cross-over to receive open-label D+T therapy only after BIRC confirmed disease progression. D+T therapy could be continued beyond BIRC-confirmed disease progression if, in the judgment of the investigator, there was evidence of clinical benefit, and the patient wished to continue the study treatment.
No. patients Treatment(s)	Planned: 150 (2:1 randomization) Enrolled: 153 • Dabrafenib (150 mg BID) plus trametinib (2 mg QD): N=101 • Placebo: N=52

Efficacy endpoints	• **Primary**:
	  • PFS based on BIRC assessment
	• **Key secondary**:
	  • ORR based on BIRC assessment
	  • OS including death from any cause
	• **Other secondary**:
	  • DOR based on BIRC assessment

Completed/Ongoing	Ongoing FPFV: 15-Nov-2021; LPFV: 09-May-2024 DCO for the primary analysis: 22-Jan-2025

2.3.2. Pharmacokinetics

In the pivotal study for this variation, study J12301, PK sample collection was optional. Overall, 37 patients in the PK analysis set provided informed consent and had evaluable PK samples. Of these 37 patients, 30 were from non-Asian and 7 from Asian origin. The PK analysis set was defined as all patients who received at least one dose of the study treatment (dabrafenib or trametinib) and had at least one evaluable dabrafenib or trametinib PK blood sample.

PK concentrations of dabrafenib and trametinib at selected timepoints in study J12301 are shown in Table 5 and Table 6.

Table 5. Dabrafenib plasma concentrations in Study J12301

	Day 1 - 2h (ng/mL)	Week 4 predose (ng/mL)	Week 4 - 2h (ng/mL)	Week 8 predose (ng/mL)	Week 8 - 2h (ng/mL)
Asian patients	1700 (157%) [m=28]	39.1 (256%) [m=20]	1130 (174%) [m=21]	51.4 (374%) [m=16]	510 (412%) [m=16]
Non-Asian patients	2010 (123%) [m=5]	22.4 (64%) [m=4	549 (562%) [m=4]	31.9 (79%) [m=5]	1440 (124%) [m=5]
Overall population	1740 (149%) [m=33]	35.6 (219%) [m=24]	1010 (208%) [m=25]	45.9 (278%) [m=21]	653 (345%) [m=21]

Concentrations are presented as geometric mean (geometric mean variation CV%) [m].

Table 6. Trametinib plasma concentrations in Study J12301

	Day 1 - 2h (ng/mL)	Week 4 predose (ng/mL)	Week 4 - 2h (ng/mL)	Week 8 predose (ng/mL)	Week 8 - 2h (ng/mL)
Asian patients	3.7 (145%) [m=28]	11.2 (35% [m=22]	19.9 (54%) [m=23]	9.9 (30%) [m=16]	17.2 (52%) [m=17]
Non-Asian patients	5.4 (54%) [m=5]	13.5 (40%) [m=6]	19.4 (54%) [m=6]	9.7 (26%) [m=7]	16.6 (59%) [m=7]
Overall population	3.94 (132%) [m=33]	11.6 (36%) [m=28]	19.8 (53%) [m=29]	9.87 (29%) [m=23]	17.0 (53%) [m=24]

Concentrations are presented as geometric mean (geometric mean variation CV%) [m].

Further evaluation of the individual concentrations, taking into consideration individual patient characteristics (i.e. covariates) was performed via PopPK methodology. For this purpose, previously developed PopPK models of dabrafenib and trametinib were used to conduct external validation of PK data from study J12301. The results indicate that these previously established popPK models for dabrafenib and trametinib, developed using PK data primarily from a Caucasian population, adequately described the PK data from the current study J12301, in which the majority of patients are Asian.

In addition, a previous PopPK analysis indicated that disease was not deemed a relevant covariate, and that oral dabrafenib clearance (CL/F) was similar in Asian and Caucasian cancer patients with similar liver function [CDRB436E2201-2016-PopPK report].

2.3.3. Discussion on clinical pharmacology

Dabrafenib and trametinib exposure in study J12301 was in line with exposures reported in previous dabrafenib and trametinib combination therapy studies. While noting the relatively small number of non-Asian patients with evaluable PK in study J12301 (n=7), there was no evidence for a systematic trend for an increase or a decrease in exposure in the non-Asian population vs the

Asian population. In addition, the provided PopPK external validation results further indicate that the possible race effect on dabrafenib and trametinib PK is negligible.

The PK results are consistent in DTC (currently applied for), melanoma, and NSCLC patients and support an overall lack of ethnic sensitivity for dabrafenib and trametinib pharmacokinetics.

In sections 4.2 and 5.2 of the trametinib as well as the dabrafenib SmPCs the lack of significant differences in the pharmacokinetics of dabrafenib between Asian and Caucasian patients has been sufficiently reported.

2.3.4. Conclusions on clinical pharmacology

Overall, the PK results obtained in study J12301 indicate similar exposures to dabrafenib and trametinib across Asian and non-Asian ethnicities, consistent with results obtained in indications previously applied for.

3. Clinical efficacy

3.1. Dose response study

No new dose response study was performed. The proposed posology for both dabrafenib and trametinib is the same as already approved in the treatment of melanoma and NSCLC.

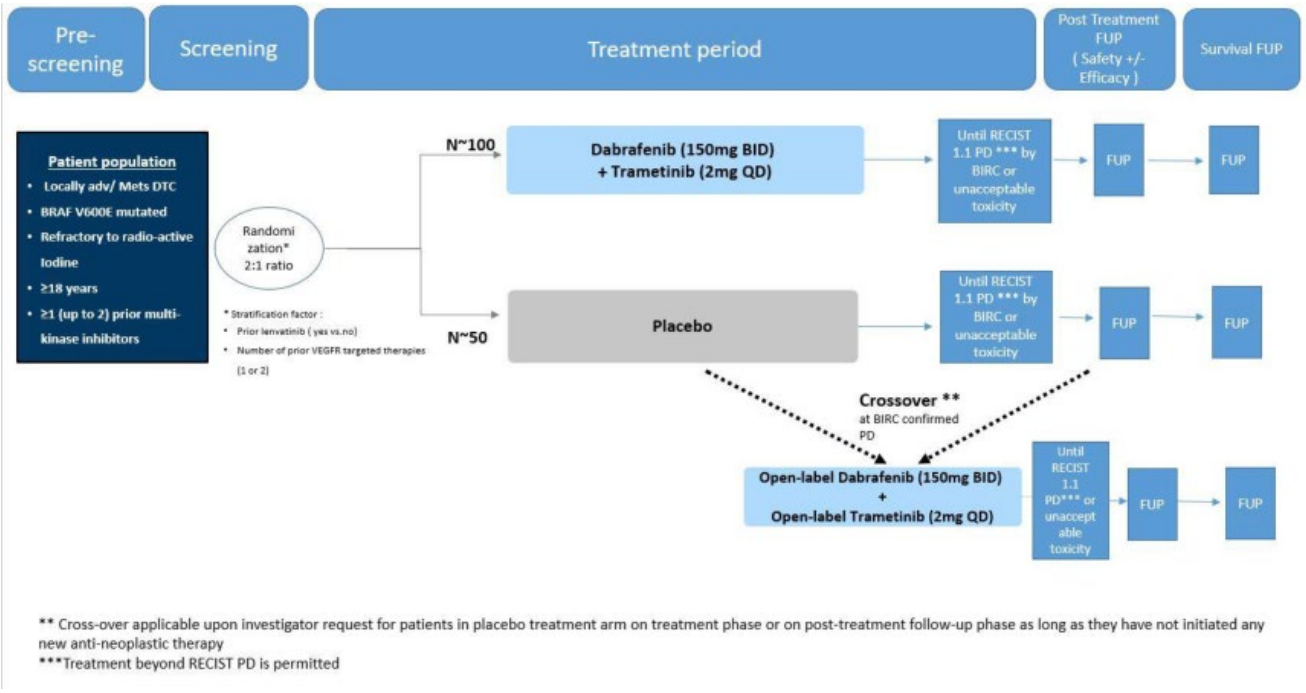
3.2. Main study

Study J12301 (CDRB436J12301; NCT04940052)

Title: A randomized, double-blind, placebo-controlled Phase III study to evaluate the efficacy and safety of dabrafenib plus trametinib in previously treated patients with

locally advanced or metastatic, radio-active iodine refractory BRAF V600E mutation-positive Differentiated Thyroid Cancer

Figure 1. Study design



Methods

Study participants

The study population includes adult patients with locally advanced or metastatic BRAF V600E mutation-positive differentiated thyroid carcinoma who are RAI-refractory and have progressed following prior VEGFR targeted therapy.

BRAF V600E mutation-positive tumour status was confirmed prior to inclusion based on central testing using the CE-marked IVD Cobas® 4800 assay.

Patients had to have progressive disease on at least 1 but not more than 2 prior VEGFR targeted therapies, an ECOG performance status ≤ 2 and adequate baseline organ function.

Patients with a tumour with a RET-fusion were excluded from treatment, as were patients previously treated with a BRAF- or MEK-inhibitor and patients with a history of or at risk of retinal vein occlusion (RVO) or central serous retinopathy.

Treatments

Interventional arm: dabrafenib (150 mg BID) plus trametinib (2 mg QD).

Control arm: matching placebo.

Treatment was continued until disease progression (as per RECIST v1.1, by investigator and confirmed by BIRC), and could be discontinued upon patient or physician decision.

In general, dose modifications were performed per the approved label for both dabrafenib and trametinib. If the patient required a dose interruption of > 28 days (> 6 weeks for uveitis or iritis)

from the previous dose for persistent grade ≥ 2 toxicity related to dabrafenib and/or trametinib, study treatment was discontinued.

Treatment could be continued beyond disease progression (confirmed by BIRC) if, in the judgment of the investigator, there was evidence of clinical benefit, and the patient wished to continue on study treatment.

Patients randomised to the placebo arm for whom disease progression was confirmed by BIRC and who met the eligibility criteria were given the option to crossover to the open-label dabrafenib plus trametinib.

Objectives

Primary objective: to compare progression free survival (PFS) between dabrafenib plus trametinib combination therapy (D+T) versus placebo.

Key secondary efficacy objectives:

- To compare objective response rate (ORR) of D+T versus placebo.
- To compare overall survival (OS) of D+T versus placebo.

Other secondary objectives were to evaluate duration of response (DOR) of D+T versus placebo, to characterise the safety and tolerability of dabrafenib and trametinib and specifically to quantify trametinib-associated serous retinopathy ocular events.

Exploratory objectives were to characterise Pharmacokinetics (PK) of dabrafenib, dabrafenib metabolites and trametinib, to identify biomarkers predictive of clinical response and/or mechanisms of resistance to treatment with D+T combination therapy, to conduct a correlative and concordance analyses for BRAF V600E detected in tumour tissue and blood samples to support potential development of a diagnostic BRAF V600E test, and to explore changes in health-related quality of life (HRQoL) and patient reported symptom severity related to pain, hoarseness, change in voice quality and difficulty swallowing through the use of the EQ-5D-5L and selected PRO-CTCAE items.

Study objectives, endpoints and estimands

Primary endpoint: PFS based on BIRC assessment using RECIST 1.1 criteria

Key secondary endpoints:

- ORR as per BIRC assessment using RECIST 1.1 criteria
- OS including all deaths from any cause.

Other secondary endpoints were DOR by BIRC assessment using RECIST v1.1 criteria, incidence and severity of AEs and SAEs, including changes in laboratory values, ECOG PS, and vital signs; and incidence, type and severity of trametinib-associated serous retinopathy ocular events.

Primary estimand

The primary clinical question of interest is: what is the relative treatment effect of dabrafenib plus trametinib versus placebo in prolonging the time to progression or death had the new antineoplastic therapies not occurred regardless of treatment discontinuation and any pandemic related events in patients with previously treated BRAF V600E mutation positive DTC.

The primary estimand is described by the following attributes:

- Population: adult patients with locally advanced or metastatic DTC, RAI-r, with BRAFV600E mutation and who have progressed following prior VEGFR-targeted therapies (no more than 2).
- Primary variable: progression-free survival as assessed by BIRC, using RECIST v1.1, defined as the time from randomisation to disease progression or death due to any cause, whichever occurs first.
- Treatment of interest: dabrafenib plus trametinib or placebo.
- Handling of the remaining intercurrent events:
    - Treatment discontinuation due to any reason will be handled using a treatment policy strategy since all PFS events will be considered as an event irrespective of the study treatment discontinuation reasons.
    - Any unforeseen intercurrent events (e.g. pandemic related events, such as COVID-19) will be handled using a treatment policy strategy.
    - Initiation of any new antineoplastic therapy started before observing any PFS event will be handled using the hypothetical strategy, i.e., as if new anticancer therapy had not been available. New antineoplastic therapy has the potential to confound the interpretation of effect of the treatment strategy, especially if this occurs more frequently in the placebo arm versus the dabrafenib plus trametinib arm.
- The summary measure is the hazard ratio (HR) for PFS between the two treatment arms, estimated using a stratified Cox proportional hazard model.

Secondary Estimands

The following two key secondary estimands for efficacy are considered. The secondary clinical question of interest is related to the treatment effect based on overall response rate between dabrafenib plus trametinib and placebo, regardless of treatment discontinuation and any unforeseen pandemic events (e.g. COVID-19), for patients with BRAF V600E mutation-positive advanced/metastatic DTC.

The secondary estimand linked to this secondary question is described by the following attributes:

- Population: adult patients with locally advanced or metastatic DTC, refractory to radioactive iodine, with BRAF V600E mutation and who have progressed following prior VEGFR-targeted therapies (no more than 2).
- Primary variable: best overall response, defined as the best response recorded from the start of the treatment up to 30 days after the last dose of study treatment or disease progression as per BIRC using RECIST 1.1 criteria, whichever occurs first, with responses after the use of new antineoplastic therapy or after the start of open-label dabrafenib and trametinib treatment following crossover for placebo patients considered as nonresponses.
- Treatment of interest: dabrafenib plus trametinib or placebo.
- Handling of the remaining intercurrent events:
    - Treatment discontinuation due to any reason will be handled using a treatment policy strategy since all response assessments occurring after treatment discontinuation and during the 30-days post-treatment follow-up period will be considered for best overall response (BOR) derivation irrespective of the study treatment discontinuation reasons.

    - Any unforeseen intercurrent events (e.g. pandemic related events, such as COVID-19) will be handled using a treatment policy strategy.

- The summary measure is the difference in ORR of the two treatments (defined as the proportion of patients with confirmed BOR of complete response (CR) or partial response (PR) based on BIRC per RECIST 1.1) and its 95% confidence interval calculated using exact method.

One other secondary clinical question of interest is the relative treatment effect of dabrafenib plus trametinib versus placebo in prolonging the survival time, regardless of treatment discontinuation, new antineoplastic therapies, any pandemic related events and crossover, for patients with BRAF V600E mutation-positive advanced or metastatic DTC.

The secondary estimand is described by the following attributes:

- Population: adult patients with locally advanced or metastatic DTC, refractory to radioactive iodine, with BRAFV600E mutation and who have progressed following prior VEGFR-targeted therapies (no more than 2).
- Primary variable: overall survival, defined as the time from randomization to death due to any cause.
- Treatment of interest: dabrafenib plus trametinib or placebo with or without any new antineoplastic therapy received post randomization as needed.
- Handling of the remaining intercurrent events:
    - Treatment discontinuation due to any reason will be handled using treatment a policy strategy since all deaths will be considered as an event irrespective of the study treatment discontinuation reasons.
    - Any unforeseen intercurrent events (e.g., pandemic related events, such as COVID-19) will be handled using a treatment policy strategy.
    - Crossover of patients from placebo to dabrafenib plus trametinib will be handled using a treatment policy strategy: all deaths will be considered as an event irrespective of the crossover.
- The summary measure is the hazard ratio (HR) for OS between the two treatment arms, estimated using stratified Cox proportional hazard model.

The following secondary estimand for safety is considered in the scope of a post-marketing requirement: what is the incidence of trametinib associated serous retinopathy ocular events while on-treatment, regardless of new antineoplastic therapies and any pandemic related events.

The secondary estimand is described by the following attributes:

- Population: adult patients with locally advanced or metastatic DTC, refractory to radioactive iodine, with BRAF V600E mutation and who have progressed following prior VEGFR-targeted therapies (no more than 2), who have received at least one dose of the study treatment and have at least two on-treatment OCT assessments.
- Primary variable: occurrence of serous retinopathy grouping event, reported in the AEs CRF (case report form) page, on-treatment, occurring from the start of study treatment and up to 30 days after last dose of study treatment, using specific case retrieval strategy for ocular events, listing the appropriate preferred terms falling into the definition of a serous retinopathy.

- Treatment of interest: dabrafenib plus trametinib.
- Handling of the remaining intercurrent events:
    - Treatment discontinuation of trametinib or dabrafenib at any time due to any reason will be handled using a treatment policy strategy since all serous retinopathy events occurring on-treatment or up to 30 days after the last dose of study treatment will be considered irrespective of the trametinib or dabrafenib discontinuation reasons.
    - Any unforeseen intercurrent events (e.g. pandemic related events, such as COVID-19) will be handled using a treatment policy strategy.
    - Any new antineoplastic therapies received during treatment or during the 30-days post treatment follow-up period will be handled using a treatment policy strategy: all serous retinopathy events will be considered regardless of the initiation of a new antineoplastic therapy.
- The summary measure is the proportion of patients with at least one serous retinopathy grouping event occurring on-treatment, over the Ocular Event Evaluable Set.

One supplementary analysis of this safety secondary estimand will be done by changing the population of interest and the summary measure attributes, using the patients included in the Safety Set.

Sample size

The sample size calculation was based on the primary estimand.

Based on lenvatinib and sorafenib data, the median PFS in the control arm was expected to be around 5 months for this study population. It was assumed that treatment with dabrafenib and trametinib would result in a 55% reduction in the PFS hazard rate, corresponding to an increase in median PFS to 11 months. With a 2:1 randomisation ratio, a recruitment period of 26 months, a gradually increasing accrual rate and an 8% annual dropout rate, 77 PFS events would have been needed to achieve 90% power to reject the null hypothesis at a one-sided 2.5% significance level using a log-rank test.

In order to estimate the incidence of serous retinopathy events with acceptable precision, 150 patients were planned to be randomised in a 2:1 ratio with at least 16-week follow-up time.

To ensure minimum follow-up time for all patients, it was estimated that the cut-off for the data analysis would occur approximately 31 months from the date of the first patient randomised in the study, at which point approximately 95 events were expected. This resulted in an increase of the power from 90% to 95%.

The primary analysis was to be performed when approximately 95 PFS events as per BIRC assessment was reached and all randomised patients completed 16 weeks of follow-up or had discontinued earlier.

The analysis for OS was to be performed at the time of the primary analysis for PFS, provided PFS and ORR are significant, at which point a total of approximately 39 deaths are expected (around 31 months from first patient randomized).

The analysis cut-off date for the final OS analysis will be established when all patients have been followed for at least 3 years. If the primary analysis of PFS does not demonstrate treatment benefit, then follow-up for OS will end.

Randomisation

Eligible patients were randomized in a 2:1 ratio to either dabrafenib plus trametinib or matching placebo.

Randomisation was stratified by prior lenvatinib treatment (yes vs no) and number of prior VEGFR-targeted therapies (1 vs 2).

Blinding (masking)

This was a double-blind study.

Unblinding was only permitted after disease progression was confirmed by BIRC and upon the investigator's request. Unblinding was permitted if it was critical to determine the optimal subsequent treatment for the patient (such as cross-over, treatment beyond progression, or subsequent treatment other than D+T combination therapy), for regulatory reporting purposes, or for patient emergencies. At time of the primary PFS analysis, investigators and patients were unblinded and crossover of patients assigned to placebo was permitted at the investigator's discretion.

3.2.1. Statistical methods

Analysis sets

- The **Full Analysis Set (FAS)** comprises all patients to whom study treatment has been assigned by randomisation. According to the intent to treat principle, patients will be analysed according to the treatment and strata they have been assigned to during the randomisation procedure. This population will be the primary population for efficacy analyses.
- The **Safety Set** includes all patients who received at least one dose of any component of the study treatment. Patients will be analysed according to the study treatment received, where treatment received is defined as the randomised/assigned treatment if the patient took at least one dose of that treatment or the first treatment received if the randomised/assigned treatment was never received.
- The **Ocular Event Evaluable Set** comprises all patients from the Safety Set who have one baseline and at least two on-treatment optical coherence tomography (OCT) assessments.
- The **pharmacokinetic analysis set (PAS)** consists of all patients who received at least one dose of the study treatment (dabrafenib or trametinib) and have at least one evaluable dabrafenib or trametinib pharmacokinetic (PK) blood sample.
- The **Crossover Population Set** may be used to summarise the analyses performed on data collected after the crossover, if applicable: it includes all patients who received at least one dose of any component of the open-label study treatment.

3.2.2. Analysis supporting primary objective(s)

3.2.2.1. Primary endpoint(s)

The primary variable of the primary estimand, PFS, is defined as the time from the date of randomisation to the date of the first documented progression according to RECIST 1.1 based on BIRC assessment, or death due to any cause. A minimum of 77 events had to be observed for 90% power, however, sample size needed to be increased to fulfil the ocular-event analysis regulatory requirement. Therefore, the primary analysis was to be performed after all randomised patients had been followed for at least 16 weeks (or had discontinued before) at which point it was expected that approximately 95 PFS events had been reported as per BIRC assessment. Data up to the cut-off date was to be used for the primary analysis. In the primary analysis, PFS was to be censored at the date of the last adequate tumour assessment before the start of a new antineoplastic therapy, if any, if no PFS event was observed prior to the analysis cut-off date using the censoring options from Table 7.

3.2.2.2. Statistical hypothesis, model, and method of analysis

The primary efficacy analysis was to be the comparison of the distribution of PFS (based on BIRC assessment of RECIST 1.1 criteria) between the two treatment groups. The following statistical hypothesis was to be tested to address the primary efficacy objective:

$$H_{01}: \theta_1 \geq 1 \text{ vs. } H_{A1}: \theta_1 < 1$$

where θ_1 is the PFS hazard ratio (dabrafenib and trametinib vs placebo). The analysis to test this hypothesis consisted of a stratified log-rank test at an overall one-sided 2.5% level of significance. Stratification was to be based on the randomisation stratification factors: prior lenvatinib treatment (yes vs no) and number of prior VEGFR targeted therapies (1 vs 2) as per IRT.

The primary efficacy variable PFS was to be analysed based on the data observed in the FAS up to the cut-off date, according to the treatment group and strata assigned at randomisation. The distribution of PFS was to be estimated using the Kaplan-Meier method. The results were to be plotted graphically by treatment group. The median and 25th and 75th percentiles of PFS along with 95% confidence intervals were to be presented by treatment group. A stratified Cox regression was to be used to estimate the hazard ratio (HR) of PFS, along with 95% confidence interval using the randomisation strata information.

3.2.2.3. Handling of missing values not related to intercurrent event

In the primary analysis, PFS was to be censored at the last adequate tumour assessment before the start of a new antineoplastic therapy, if any. If no PFS event was observed prior to the analysis cut-off date, PFS was to be censored at the last adequate tumour assessment on or before the analysis cut-off date. Clinical deterioration was not to be considered as documented disease progression.

If a PFS event was observed after two or more missing tumour assessments, then PFS was to be censored at the last adequate tumour assessment (prior to the first missing assessment and before the PFS event). If a PFS event was observed after the start of a new antineoplastic therapy, then PFS was to be censored at the last adequate tumour assessment prior to the start of the new antineoplastic therapy. Patients without any post-baseline tumour assessment and who did not die were to be censored at the time of randomisation. See Table 7 for PFS censoring rules.

Table 7. Outcome and event/censoring dates for PFS, TTP, duration of response analysis

Situation		End Date[1]	Outcome
A	No baseline assessment	Date of randomization/start of treatment[2]	Censored
B	Progression at or before next scheduled assessment	Date of progression	Progressed
C1	Progression or death after **exactly one** missing assessment	Date of progression (or death)	Progressed
C2	Progression or death after **two or more** missing assessments	Date of last adequate assessment	Censored
D	No progression	Date of last adequate assessment	Censored
E	Treatment discontinuation due to 'Disease progression' without documented progression, i.e. clinical progression based on investigator claim	Ignore clinical progression and follow situations above	As per above situations
F	New anticancer therapy given	Date of last adequate assessment prior to new anticancer therapy	Censored
[1]. = End dates are defined as 'date of death', 'date of progression', 'date of last adequate tumor assessment', 'date of next scheduled assessment'. See Protocol Section 16.1.3.2.7 for details			
[2]. =The rare exception to this is if the patient dies no later than the time of the second scheduled assessment as defined in the protocol in which case this is a PFS event at the date of death.			

3.2.2.4. Sensitivity analyses

As a sensitivity analysis to assess the impact of stratification, the two treatment groups were to be compared using the unstratified log-rank test (based on BIRC assessment of RECIST 1.1 criteria). The HR together with the associated 95% confidence interval obtained using the unstratified Cox regression model were also to be presented.

If there was a high rate of discrepancy (> 20%) between the strata classifications constructed using the eCRF data and those obtained from the IRT, a sensitivity analysis was to be performed in which a stratified Cox regression model was to be used to estimate the treatment hazard ratio and the associated 95% confidence intervals based on the eCRF-derived strata. No other inferential statistics were to be provided.

3.2.2.5. Supplementary analyses

As supplementary analyses performed in the FAS, the hazard ratio and 95% confidence interval for PFS based on independent review was to be obtained from a stratified and covariate-adjusted Cox model including as potential covariate the following: ECOG ((1 and 2) vs 0), Gender (male vs female), Age (continuous), Region (China vs rest of the world), Type of prior treatment received (Lenvatinib vs others), Number of prior VEGFR targeted therapies (1 vs 2), Baseline TSH (≤0.5 vs >0.5 mIU per liter), Baseline thyroglobulin (≤10 vs. >10 ng/ml).

An additional supplementary analysis handled the intercurrent event of a new antineoplastic therapy started using a treatment policy strategy: all PFS events were to be considered regardless of the start of a new antineoplastic therapy. The target population, the primary variable, other intercurrent events and summary measure were to be the same in this supplementary analysis as for the primary estimand.

Subgroups of interest

The primary efficacy and key secondary endpoint (PFS, ORR and OS) were to be summarised by the following subgroups to examine the homogeneity of treatment effect provided that the primary efficacy analysis based on the FAS is statistically significant:

- Gender (male vs female)
- Age (<65 vs ≥ 65 years)
- Region (China vs rest of the world)
- Type of prior treatment received (lenvatinib vs others)
- Number of prior VEGFR targeted therapies (1 vs 2)
- Baseline TSH (≤0.5 vs >0.5 mIU per liter)
- Baseline thyroglobulin (≤10 vs. >10 ng/ml).

3.2.2.6. Supportive analyses

As a supportive analysis, PFS as per local investigator assessment was to be analysed using the same analytical conventions as the primary analysis.

As a supportive analysis, the number of patients censored and reason for censoring was to be summarised by treatment group using descriptive statistics, presented separately for BIRC and local assessment.

3.2.3. Analysis supporting key secondary objectives

3.2.3.1. Key secondary endpoints

The key secondary objectives in this study were to compare the two treatment groups with respect to ORR and OS. A hierarchical testing strategy was to be used to control the overall type I error rate: ORR would only be formally tested and interpreted if the primary analysis of PFS was statistically significant. If the ORR achieved statistical significance, then the OS was to be tested and interpreted.

Overall Response rate (ORR)

Overall response rate (ORR) is defined as the proportion of patients with best overall response (BOR) of confirmed complete response (CR) or partial response (PR), as per BIRC assessment and according to RECIST 1.1. Of note, tumour assessments after the start of open-label dabrafenib and trametinib treatment following crossover for placebo patients were not considered in the BOR derivation. Responses before new anti-cancer therapy were considered.

Overall Survival (OS)

Overall survival (OS) is defined as the time from the date of randomisation to the date of death due to any cause. A cut-off date was to be established for each analysis of OS. All deaths occurring on or before the cut-off date in the FAS were to be used in the OS analysis. If a patient was not known to have died, then OS would be censored at the latest date the patient was known to be alive (on or before the cut-off date).

3.2.3.2. Statistical hypothesis, model, and method of analysis

Overall Response rate (ORR)

The null hypothesis of no difference in ORR based on BIRC assessment using RECIST 1.1 between dabrafenib plus trametinib and placebo treatment arms was to be tested using Cochran-Mantel-Haenszel (CMH) test at a 1-sided significance level of 0.025, stratified by the randomisation stratification factors: prior lenvatinib treatment (yes vs no) and number of prior VEGFR targeted therapies (1 vs 2). ORR was to be calculated based on the FAS, according to the ITT principle and strata assigned at randomisation as per IRT. The difference in ORR and its 95% confidence interval was to be reported. ORR and its 95% confidence interval based on the exact binomial distribution was to be presented by treatment group.

Overall Survival (OS)

The statistical hypothesis testing and estimations for OS were the same as for PFS. If a patient was not known to have died at the time of analysis cut-off, then OS was to be censored at the date of last known date patient was alive, i.e., last contact date.

3.2.3.3. Supportive analyses

As a supportive analysis, ORR per local investigator assessment was to be analysed using the same method as ORR by BIRC. Disease Control Rate (DCR) defined as the proportion of patients with confirmed BOR of CR or PR or SD was to be reported.

3.2.4. Analysis supporting secondary objectives

Duration of response (DOR)

DOR was to be listed and summarised by treatment group for all patients in the FAS with confirmed BOR of CR or PR. The distribution of duration of response was to be estimated using the Kaplan-Meier method and the median duration of response was to be presented along with 95% confidence interval by treatment groups. No inferential analysis that compares duration of response between the two treatment groups was to be performed.

DOR was to be listed and summarised by treatment group for all patients in the FAS with confirmed BOR of CR or PR. The distribution of duration of response was to be estimated using the Kaplan-Meier method and the median duration of response was to be presented along with 95% confidence interval by treatment groups. No inferential analysis that compares duration of response between the two treatment groups was to be performed.

Error probabilities, adjustment for multiplicity and interim analyses

There was no interim analysis (IA) for PFS.

A hierarchical testing procedure was to be adopted and the statistical test for ORR was to be performed only if the primary analysis of PFS was statistically significant. OS was to be tested only if the primary analysis of PFS and key secondary ORR endpoint were statistically significant.

For ORR, there was no interim analysis planned. The analysis was to be performed at the time of the primary analysis for PFS (and provided PFS was significant).

For OS, a maximum of two analyses were planned:

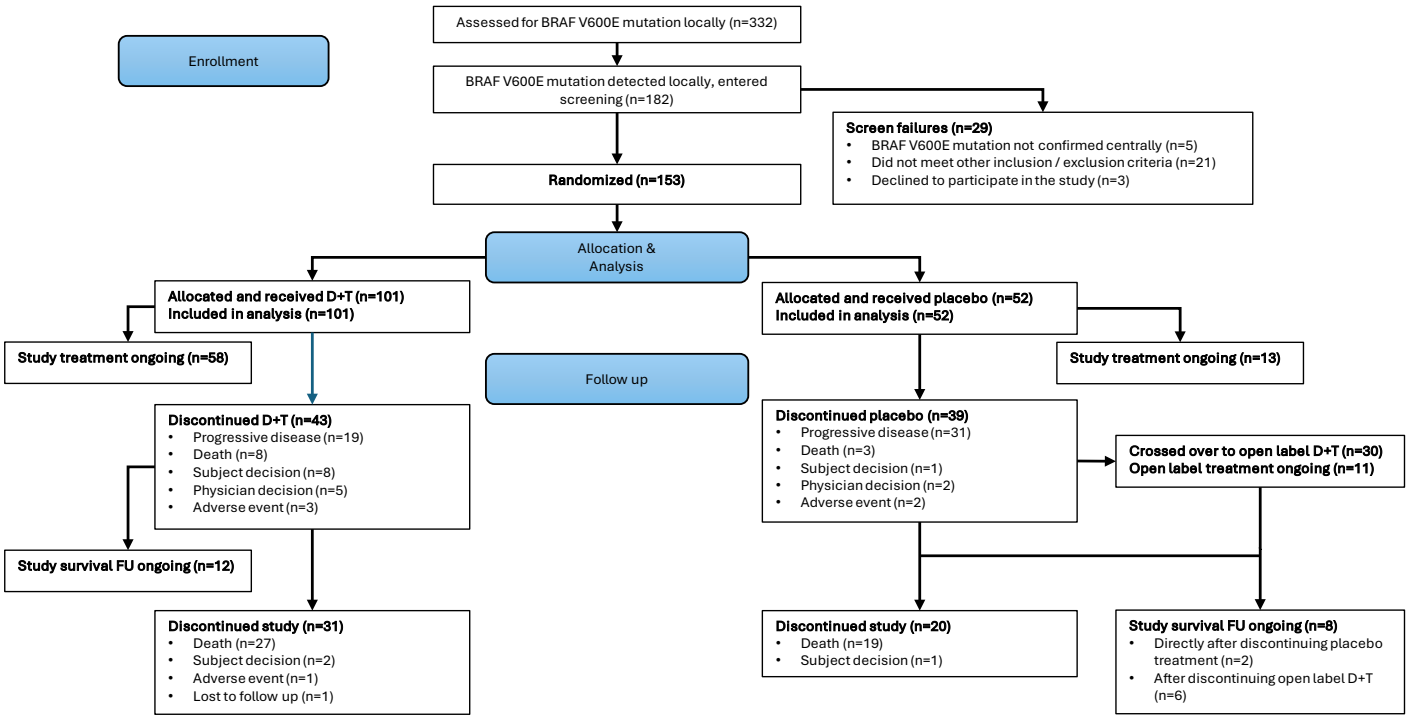
- At the time of the primary analysis for PFS (and provided PFS and ORR were significant), at which point a total of approximately 39 deaths were expected (around 31 months from first patient randomised)
- At the time of final analysis for OS when all randomised patients would have been followed for at least 3 years.

The type I error rate for OS testing was to be controlled by using a one-sided 2-look group sequential design.

Results

Participant flow

Figure 2. Participant flow of Study J12301



At the time of DCO (22 January 2025), 58 patients (57.4%) in the D+T arm and 13 patients (25.0%) in the placebo arm were still receiving the blinded treatment in the study. The median duration of exposure to the study treatment was 63.14 weeks (14.7 months; range: 0.7 to 156.4 weeks) in the D+T arm and 23.93 weeks (5.6 months; range: 0.7 to 129.0 weeks) in the placebo arm.

A total of 43 patients (42.6%) in the D+T arm and 39 patients (75.0%) in the placebo arm had discontinued blinded treatment. The primary reasons for treatment discontinuation were progressive disease in the D+T arm (18.8%) and in the placebo arm (59.6%). A total of 5 patients (3.3%) discontinued the blinded study treatment due to AE; 3 patients (3.0%) in the D+T arm and 2 patients (3.8%) in the placebo arm.

Notably, 30 patients (57.7%) from the placebo arm crossed over to receive D+T treatment. A total of 22 patients (21.8%) from the D+T arm continued treatment beyond progression, 10 of those patients were ongoing on D+T at the time of DCO.

Of the 43 patients in the D+T arm who discontinued the blinded treatment, 12 patients were ongoing in the study at the time of DCO in post-treatment FU or in survival FU, and 31 patients have discontinued from the study. Of the 39 patients in the placebo arm who discontinued the blinded treatment, 11 patients were ongoing at the time of DCO on crossover D+T treatment, 8 patients were ongoing in post-treatment FU or in survival FU, and 20 patients have discontinued from the study. Overall, 51 (33.3%) patients discontinued from the study. The main reason was death (26.7% of patients in the D+T arm and 36.5% of patients in the placebo arm).

Recruitment

First patient first visit: 15 November 2021.

Data cut-off date: 22 January 2025.

The study was conducted in 42 centers across 11 countries or regions. A total of 153 patients were randomised in a 2:1 ratio to the D+T arm (101 patients) and to the placebo arm (52 patients), between 10 Dec-ember 2021 and 09 May 2024.

The study mainly included patients in China (n=76), Korea (n=22), Taiwan (n=15), Malaysia (n=11), Brazil (n=9), India (n=6), and <5 patients each in Argentina, Canada, Turkey, US and Vietnam.

Conduct of the study

The study protocol was amended 3 times. These amendments were mainly of a clarifying nature and did not impact the main study design elements.

Post database-lock, the rank-preserving structural failure time (RPSFT) model by Robins and Tsiatis (1991) has been implemented to evaluate the potential confounding effect of crossover on OS.

Protocol deviations were observed in both treatment arms: 66 patients (65.3%) in the D+T arm and 31 patients (59.6%) in the placebo arm.

Most protocol deviations in both treatment arms were related to the "Other" category (39.6% in the D+T arm, 46.2% in the placebo arm) due to:

- Optical coherence tomography (OCT) assessments missed or not performed within protocol specified time window in 27 patients (26.7%) in D+T arm and 18 patients (34.6%) in the placebo arm. None of the missed or delayed OCT assessments impacted the ocular event evaluable set for the D+T arm as patients who had one baseline and at least two on-treatment OCT assessments were included in the Ocular Event Evaluable Set.
- At least one tumour assessment missed or not performed within the protocol specified time window in 27 patients (26.7%) in the D+T arm and 14 patients (26.9%) in the placebo arm. In total, 11 patients missed the tumor scans: 6 patients in the D+T arm and 5 patients in the placebo arm.

Additionally, treatment deviations were reported in 39 patients (38.6%) in the D+T arm and 20 patients (38.5%) in the placebo arm. These treatment deviations primarily stemmed from missed study drug administrations over several days, dosing errors (received a daily dose not in

accordance with the protocol), and mistakenly taken higher doses of the study drug (34 patients in the D+T arm and 19 patients in the placebo arm).

It was considered that none of the protocol deviations impacted the safety and efficacy for patients and nor did they compromise the integrity of the trial.

Baseline data

Table 8. Demographics and baseline characteristics (FAS)

Demographic variable	Dabrafenib + trametinib	Placebo	Total
	N=101	N=52	N=153
Age group – n (%)			
< 65 years	50 (49.5)	31 (59.6)	81 (52.9)
≥ 65 years	51 (50.5)	21 (40.4)	72 (47.1)
Age (years)			
Mean (SD)	63.1 (10.28)	61.5 (9.90)	62.6 (10.15)
Q1-Q3	56.0-70.0	55.0-69.0	56.0-70.0
Median (Min-Max)	65.0 (36-82)	63.0 (37-80)	64.0 (36-82)
Sex – n (%)			
Male	54 (53.5)	19 (36.5)	73 (47.7)
Female	47 (46.5)	33 (63.5)	80 (52.3)
Race – n (%)			
White	9 (8.9)	9 (17.3)	18 (11.8)
Black or African American	1 (1.0)	2 (3.8)	3 (2.0)
Asian	90 (89.1)	41 (78.8)	131 (85.6)
Multiple	1 (1.0)	0	1 (0.7)
Ethnicity - n (%)			
Hispanic or Latino	4 (4.0)	3 (5.8)	7 (4.6)
Not Hispanic or Latino	91 (90.1)	46 (88.5)	137 (89.5)
Not Reported	3 (3.0)	1 (1.9)	4 (2.6)
Unknown	3 (3.0)	2 (3.8)	5 (3.3)
Weight (kg)			
Mean (SD)	64.1 (13.63)	65.9 (14.14)	64.7 (13.78)
Median (Min-Max)	63.0 (39-105)	65.0 (43-121)	64.5 (39-121)
Q1-Q3	54.2-74.5	56.0-73.5	55.0-74.0
Height (cm)			
Mean (SD)	162.8 (9.72)	162.7 (9.21)	162.8 (9.52)
Median (Min-Max)	163.0 (140-179)	161.1 (147-184)	163.0 (140-184)
Q1-Q3	155.5-170.0	155.5-169.4	155.5-170.0
BMI (kg/m²)			
Mean (SD)	24.0 (3.80)	24.7 (3.86)	24.3 (3.82)
Median (Min-Max)	24.0 (16-35)	24.8 (16-36)	24.0 (16-36)
Q1-Q3	20.8-26.6	22.4-27.4	21.4-27.0
Region - n (%)			
China	53 (52.5)	23 (44.2)	76 (49.7)
Rest of the world	48 (47.5)	29 (55.8)	77 (50.3)
Centrally confirmed V600E - n (%)			
V600E	101 (100)	52 (100)	153 (100)
ECOG performance status – n (%)			
0	52 (51.5)	25 (48.1)	77 (50.3)

Demographic variable	Dabrafenib + trametinib	Placebo	Total
	N=101	N=52	N=153
1	48 (47.5)	24 (46.2)	72 (47.1)
2	1 (1.0)	3 (5.8)	4 (2.6)
Type of prior treatment received - n (%)			
Lenvatinib	32 (31.7)	15 (28.8)	47 (30.7)
Others	69 (68.3)	37 (71.2)	106 (69.3)
Prior VEGFR Targeted Therapy - n (%)*			
1	79 (78.2)	40 (76.9)	119 (77.8)
2	22 (21.8)	12 (23.1)	34 (22.2)
Lenvatinib - n (%)*			
Yes	32 (31.7)	16 (30.8)	48 (31.4)
No	69 (68.3)	36 (69.2)	105 (68.6)
TSH (mU/L) – n (%)			
≤ 0.5	74 (73.3)	38 (73.1)	112 (73.2)
> 0.5	26 (25.7)	14 (26.9)	40 (26.1)
Missing	1 (1.0)	0	1 (0.7)
Thyroglobulin (µg/L) – n (%)			
≤ 10	23 (22.8)	8 (15.4)	31 (20.3)
> 10	78 (77.2)	44 (84.6)	122 (79.7)

*Based on data obtained from IRT system

Table 9. Disease history (FAS)

	Dabrafenib + trametinib	Placebo	Total
	N=101	N=52	N=153
Predominant tumor histology/cytology – n (%)			
Papillary	101 (100.0)	52 (100.0)	153 (100.0)
Histological grade – n (%)			
Well differentiated	100 (99.0)	52 (100.0)	152 (99.3)
Poorly differentiated	1 (1.0)	0	1 (0.7)
Stage at initial diagnosis (AJCC 8) – n (%)			
I	19 (18.8)	14 (26.9)	33 (21.6)
II	34 (33.7)	18 (34.6)	52 (34.0)
III	13 (12.9)	5 (9.6)	18 (11.8)
IVA	10 (9.9)	5 (9.6)	15 (9.8)
IVB	11 (10.9)	3 (5.8)	14 (9.2)
Missing	14 (13.9)	7 (13.5)	21 (13.7)
Time since initial diagnosis to study entry (months)			
n	100	51	151
Mean (SD)	117.8 (76.84)	120.7 (70.59)	118.8 (74.56)
Median (Min-Max)	98.6 (8-413)	115.4 (17-394)	105.8 (8-413)
Q1-Q3	63.3-165.7	65.5-170.4	63.6-167.0
Time from initial diagnosis to first recurrence /progression (months)			
n	95	48	143
Mean (SD)	98.2 (76.72)	106.0 (73.46)	100.8 (75.47)

	Dabrafenib + trametinib	Placebo	Total
	N=101	N=52	N=153
Median (Min-Max)	77.7 (6-407)	90.2 (14-390)	78.3 (6-407)
Q1-Q3	48.5-140.6	49.2-147.6	48.5-140.6
Time since most recent relapse /progression to randomization (months)			
n	100	51	151
Mean (SD)	4.5 (7.75)	3.7 (4.45)	4.2 (6.81)
Median (Min-Max)	2.5 (0-64)	1.9 (0-23)	2.2 (0-64)
Q1-Q3	1.4-4.2	1.2-4.2	1.3-4.2
Stage at study entry (AJCC version 8) - n (%)			
II	17 (16.8)	10 (19.2)	27 (17.6)
III	2 (2.0)	0	2 (1.3)
IVA	8 (7.9)	4 (7.7)	12 (7.8)
IVB	74 (73.3)	38 (73.1)	112 (73.2)
Types of lesions at baseline - n (%)			
Target only	5 (5.0)	2 (3.8)	7 (4.6)
Both target and non-target	96 (95.0)	50 (96.2)	146 (95.4)
Sum of diameters at baseline (SOD) (mm)			
Mean (SD)	55.1 (40.15)	57.0 (38.99)	55.8 (39.64)
Median (Min-Max)	42.0 (11-233)	42.5 (10-170)	42.0 (10-233)
Q1-Q3	30.0-73.0	25.0-88.5	28.0-77.0
Sum of diameter at baseline (SOD) - n (%)			
< 66 mm	71 (70.3)	33 (63.5)	104 (68.0)
≥ 66 mm	30 (29.7)	19 (36.5)	49 (32.0)
Extent of disease-n (%) (metastatic sites) – n (%)			
At least one metastatic site	100 (99.0)	52 (100.0)	152 (99.3)
Number of metastatic sites - n (%)			
< 3	43 (42.6)	22 (42.3)	65 (42.5)
≥ 3	58 (57.4)	30 (57.7)	88 (57.5)

Metastatic sites are derived from CRF page of diagnosis and extent of cancer if available. Number of metastatic sites refers to number of unique sites reported per patient.

Time variables that are calculated to study entry use date of first dose of study treatment.

Numbers analysed

The number of patients included in each data analysis set is presented in Table 10. All 101 patients from the D+T arm were included in the ocular event evaluable set, while 4 patients from the placebo arm were excluded. The PK samples collection was optional and were analysed for D+T arm only. All 37 patients in the PK analysis set provided informed consent and had evaluable PK samples.

Table 10. Analysis sets (Full Analysis Set)

Analysis set	D+T N=101 n (%)	Placebo N=52 n (%)	All patients N=153 n (%)
Full analysis set	101 (100)	52 (100)	153 (100)
Safety set	101 (100)	52 (100)	153 (100)
Ocular event evaluable set	101 (100)	48 (92.3)	149 (97.4)
Pharmacokinetic analysis set	37 (36.6)	0	37 (24.2)
Crossover population set	0	30 (57.7)	30 (19.6)

Outcomes and estimation

Primary endpoint: progression free survival

The median follow-up time for PFS (by BIRC) at the DCO was 9.2 months overall, 10.4 months in the D+T arm and 3.7 in the placebo arm.

Table 11. Kaplan-Meier estimates of PFS based on BIRC assessment (FAS)

	Dabrafenib + trametinib N=101	Placebo N=52
Number of events - n (%)	54 (53.5)	43 (82.7)
Progression	53 (52.5)	39 (75.0)
Death	1 (1.0)	4 (7.7)
Number censored	47 (46.5)	9 (17.3)
Percentiles (95% CI) (months)		
25th	7.6 (3.8, 9.3)	1.9 (1.4, 2.3)
50th, median	12.8 (10.2, 21.2)	3.7 (2.3, 7.5)
75th	NE (NE, NE)	11.1 (7.5, 18.3)
Kaplan-Meier estimate (%) (95% CI)		
Month 1	100 (100, 100)	88.5 (76.1, 94.6)
Month 6	78.8 (69.3, 85.6)	40.4 (27.1, 53.3)
Month 12	51.7 (40.9, 61.4)	23.6 (12.9, 36.1)
Month 24	38.6 (27.9, 49.2)	10.6 (2.8, 24.6)
Month 36	NE (NE, NE)	NE (NE, NE)
P-value[a]	< 0.001	
Hazard ratio (95% CI) D+T vs Placebo[b]	0.38 (0.25, 0.57)	

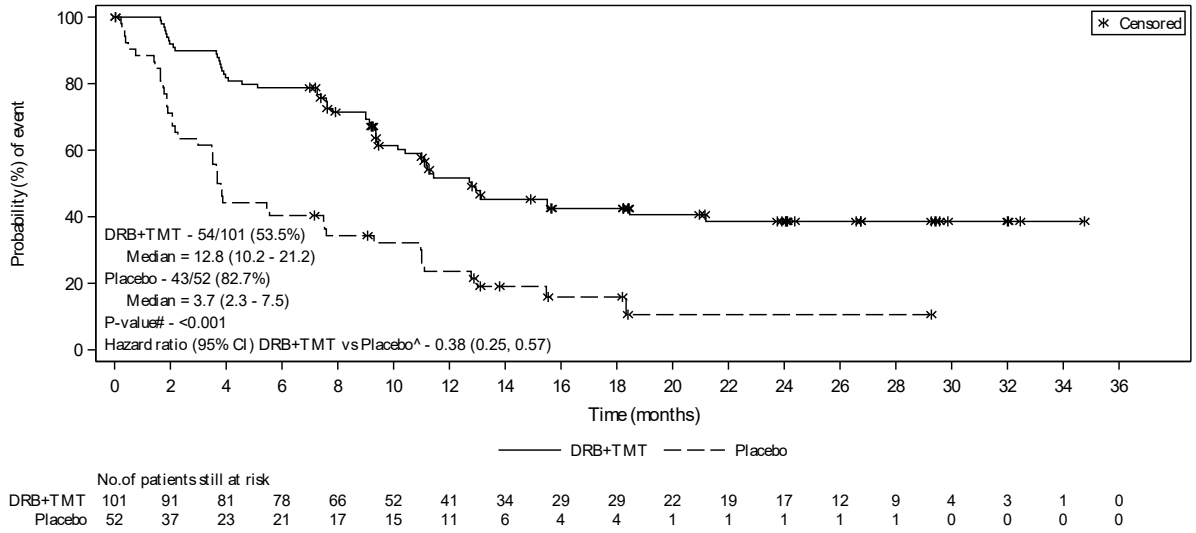
Percentiles with 95% CIs are calculated from PROC LIFETEST output using method of Brookmeyer and Crowley (1982).

% Kaplan-Meier Event-free estimate is the estimated probability that a patient will remain event-free up to the specified time point. % Event-free probability estimates are obtained from the Kaplan-Meier survival estimates for all treatment groups; Greenwood formula is used for CIs of KM event-free estimates.

a. One-sided p-value obtained from log-rank test stratified based on the randomisation stratification factors: VEGFR targeted therapy (1 vs 2) and lenvatinib treatment (Yes vs No).

b. Hazard ratio obtained from Cox PH model stratified based on the randomisation stratification factors: VEGFR targeted therapy (1 vs 2) and lenvatinib treatment (Yes vs No).

Figure 3. Kaplan-Meier plot of PFS based on BIRC assessment (FAS)



One-sided p-value obtained from log-rank test stratified based on the randomisation stratification factors: VEGFR targeted therapy (1 vs 2) and lenvatinib treatment (Yes vs No).

Hazard ratio obtained from Cox PH model stratified based on the randomisation stratification factors: VEGFR targeted therapy (1 vs 2) and lenvatinib treatment (Yes vs No).

Key secondary endpoint: ORR

As the primary endpoint of the study was met and was statistically significant, the key secondary endpoint of ORR based on BIRC assessment was formally tested.

Table 12. BOR based on BIRC assessment (FAS)

	Dabrafenib + trametinib N=101	**Placebo N=52**
BOR, n (%)		
CR	6 (5.9)	1 (1.9)
PR	52 (51.5)	1 (1.9)
SD	30 (29.7)	29 (55.8)
Progressive disease	10 (9.9)	15 (28.8)
Not Evaluable	2 (2.0)	4 (7.7)
Non-CR/Non-progressive disease	1 (1.0)	2 (3.8)
ORR (ORR: CR+PR), n (%)	58 (57.4)	2 (3.8)
95% CI	(47.2, 67.2)	(0.5, 13.2)
CMH Test p-value	< 0.001	
Odds Ratio for ORR (95% CI)	29.90 (7.02, 127.39)	
ORR Difference (%) (95% CI)	53.36 (42.25, 64.47)	
DCR, n (%)	89 (88.1)	33 (63.5)
95% CI	(80.2, 93.7)	(49.0, 76.4)

The p-value is computed from Cochran Mantel-Haenszel chi-square test statistics at a one-sided 2.5% level of significance.
CMH test, odds ratio and ORR difference are stratified by VEGFR targeted therapy (1 vs. 2) and lenvatinib treatment (Yes vs. No).
N: The total number of patients in the treatment group. It is the denominator for percentage (%) calculation.
n: Number of patients who are in the corresponding category.
The exact binomial 95% CI (Clopper and Pearson 1934) is presented.

ORR based on investigator assessment was consistent with ORR based on BIRC assessment, with a stratified difference in the ORR between the treatment groups of 42.6% (95% CI: 32.1, 53.0).

Key secondary endpoint: OS

As the key secondary endpoint of ORR was statistically significant, a planned interim analysis of the other key secondary endpoint of OS was conducted.

The median follow-up time for OS at the DCO was 17.4 months overall, 18.3 months in the D+T arm and 14.9 months in the Placebo arm.

Table 13. Kaplan-Meier estimates of OS (FAS)

	Dabrafenib + trametinib N=101	**Placebo N=52**
Number of deaths - n (%)	27 (26.7)	19 (36.5)
Number censored - n (%)	74 (73.3)	33 (63.5)
Percentiles for OS (95% CI)[a] (months)		
25th	17.2 (10.6, NE)	14.9 (6.6, 22.7)
50th, median	NE (NE, NE)	25.9 (17.1, NE)
75th	NE (NE, NE)	NE (NE, NE)
Kaplan-Meier estimate (%) (95% CI) at[b]		
Month 1	100 (100, 100)	94.2 (83.2, 98.1)
Month 12	82.1 (72.8, 88.5)	80.2 (66.2, 88.8)
Month 24	66.3 (54.0, 76.1)	57.3 (38.6, 72.2)
Cox model[c]		
Hazard ratio (95% CI)	0.658 (0.362, 1.194)	
Log-rank test[d]		
P-value (one-sided)	0.083	

a. Percentiles with 95% CIs are calculated from PROC LIFETEST output using method of Brookmeyer and Crowley (1982).

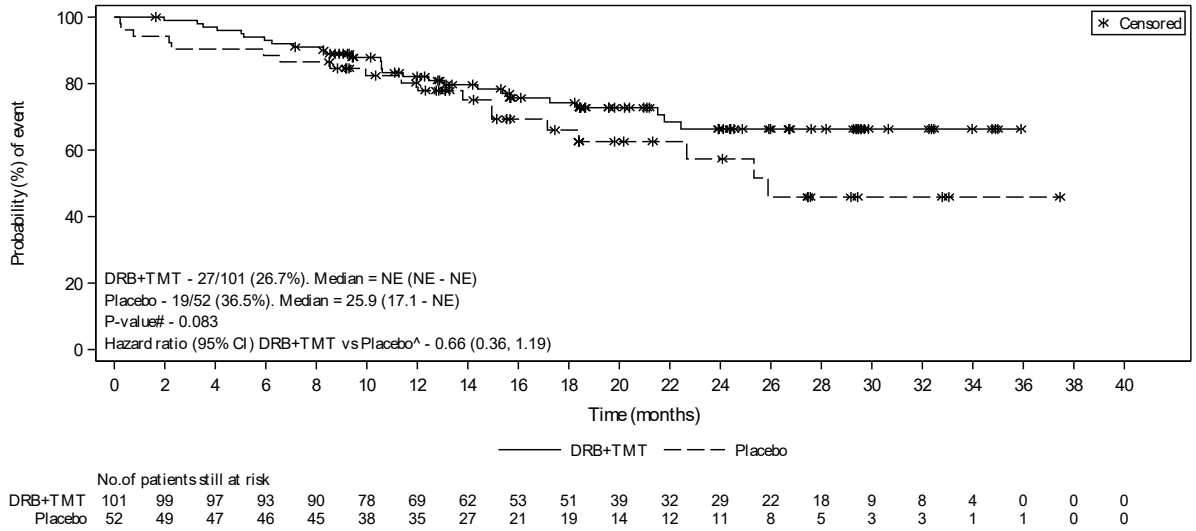
b. % Kaplan-Meier Event-free estimate is the estimated probability that a patient will remain event-free up to the specified time point.

% Event-free probability estimates are obtained from the Kaplan-Meier survival estimates for all treatment groups; Greenwood formula is used for CIs of KM event-free estimates.

c. Hazard Ratio of dabrafenib+trametinib vs. placebo.

d. Both Log-rank test and Cox PH model are stratified based on the randomisation stratification factors: VEGFR targeted therapy (1 vs 2) and lenvatinib treatment (Yes vs No).

Figure 4. Kaplan-Meier plot of OS (FAS)



NE=Not Estimable.

#One-sided p-value obtained from log-rank test stratified based on the randomisation stratification factors: VEGFR targeted therapy (1 vs. 2) and lenvatinib treatment (Yes vs. No).

^Hazard ratio obtained from Cox PH model stratified based on the randomisation stratification factors: VEGFR targeted therapy (1 vs 2) and lenvatinib treatment (Yes vs No).

The impact of the crossover of 30 patients from the placebo arm to the open-label D+T arm on the OS results was explored using a rank preserving structural failure time (RPFST) model analysis which yielded an OS HR of 0.512 (95% CI: 0.197, 1.328) when comparing the D+T arm to the reconstructed placebo arm.

Secondary endpoint: duration of response

Out of the 58 responders in the D+T arm, 21 patients reported DOR events (progressive disease or death) while the remaining 37 patients were censored. Most patients were censored due to ongoing treatment without events. In the placebo arm, the 2 responders were both censored prior to Month 9 due to treatment still ongoing at the time of the DCO.

The estimated 6-month duration of response was 88.1% (95% CI: 75.4, 94.5) and the estimated 12-month duration of response 61.6% (95% CI: 46.0, 74.0). The median DOR was not reached.

Table 14. Kaplan-Meier estimates of DOR based on BIRC assessment (FAS)

	Dabrafenib + trametinib N=101	**Placebo N=52**
Number of responders*	58 (57.4)	2 (3.8)
Number of events - n (%)	21 (36.2)	0
Number of censored	37 (63.8)	2 (100)
Percentiles (95% CI) (Months)		
25th	9.3 (6.2, 11.3)	NE (NE, NE)
50th, median	NE (11.0, NE)	NE (NE, NE)
75th	NE (NE, NE)	NE (NE, NE)
Kaplan-Meier event-free estimates (95% CI)		
Month 1	100 (100, 100)	100 (100, 100)
Month 6	88.1 (75.4, 94.5)	100 (100, 100)
Month 12	61.6 (46.0, 74.0)	NE (NE, NE)
Month 24	52.0 (35.5, 66.2)	NE (NE, NE)
Month 30	52.0 (35.5, 66.2)	NE (NE, NE)

Percentiles with 95% CIs are calculated from PROC LIFETEST output using method of Brookmeyer and Crowley (1982).

% Kaplan-Meier Event-free probability estimate is the estimated probability that a subject will remain event-free up to the specified time point.

% Kaplan-Meier Event-free probability estimates are obtained from the Kaplan-Meier survival estimates for all treatment groups;

Greenwood formula is used for CIs of KM estimates.

Event: progression disease or death due to any cause.

*Responders means the confirmed BOR is CR or PR.

Exploratory endpoint: patient-reported outcomes (PRO)

At baseline, PRO-CTCAE was completed by 94/101 (93.1%) patients in the D+T arm and 51/52 (98.1%) in the placebo arm.

The EQ-5D-5L VAS (EQ VAS) questionnaire was fully completed by 94/101 (93.1%) patients in the D+T arm and 51/52 (98.1%) patients in the placebo arm at baseline.

Patient response to the PRO-CTCAE and EQ VAS questionnaires decreased at later timepoints due to treatment discontinuation. Among these patients, PRO completion rates were similar between the D+T and placebo arms until Week 56. For example, at Week 56, EQ VAS questionnaire was completed by 55/58 patients in the D+T arm and 13/14 patients in the placebo arm.

PRO-CTCAE

Four symptomatic concepts from the PRO-CTCAE item library were selected for evaluation in this study: pain, difficulty swallowing, hoarse voice and voice changes. PRO-CTCAE attributes are scored on a 0-to-4-point scale, with higher scores representing increased symptom impact.

1) Pain

At baseline, most patients selected "never" (corresponding to a score of 0) to describe the frequency of pain (40/94 patients in the D+T arm vs. 22/51 patients in the placebo arm). At the final timepoint, of Week 56, “never” remained the most frequently selected response across both study arms (23/55 patients in the D+T arm vs. 5/13 patients in the placebo arm). The mean (SD)

pain frequency score at baseline was 1.16 (1.273) in the D+T arm and 1.20 (1.296) in the placebo arm. Mean change from baseline showed minimal deterioration in both arms.

At baseline, the most commonly selected response for pain severity was "none", reported by 46/94 patients in the D+T arm vs. 22/51 patients in the placebo arm. At Week 56, "none" remained the most frequently selected response, reported by 27/55 patients in the D+T arm vs. 6/13 patients in the placebo arm. The mean (SD) pain severity at baseline was scored at 0.80 (0.979) in the D+T arm and 1.02 (1.104) in the placebo arm. Both arms showed a general trend of minimal deterioration in mean change from baseline scores.

2) Difficulty Swallowing

At baseline the most commonly selected response for the difficulty swallowing symptom was "none", reported by 71/94 patients in the D+T arm vs. 37/51 in the placebo arm. At Week 56, "none" remained as the most frequently reported response, with 39/55 patients in the D+T arm vs. 9/13 in the placebo arm. The mean (SD) PRO-CTCAE difficulty swallowing baseline score was 0.35 (0.729) in the D+T arm and 0.35 (0.627) in the placebo arm. Mean change from baseline scores remained generally static over time with no notable difference observed between treatment and placebo arms.

3) Hoarse Voice

For hoarse voice, the most commonly selected response at baseline was "none", reported by 59/94 patients in the D+T arm vs. 35/51 patients in the placebo arm. At Week 56, "none" remained the most frequently reported response in both treatment arms, with 36/55 patients in the D+T arm vs. 9/13 patients in the placebo arm. Mean change from baseline score was largely static or showed minimal improvement across follow-up timepoints.

4) Voice Changes

For voice change, the most commonly selected response at baseline was "no", reported by 78/94 patients in the D+T arm vs. 47/51 patients in the placebo arm. At Week 56, "no" remained the most frequently selected response, with 51/55 patients in the D+T arm vs. 12/13 patients in the placebo arm.

EQ-5D-5L VAS

The EQ-5D-5L VAS (score range 0 to 100, with higher scores indicating better health) was included to capture patient reported overall health status. At baseline, EQ VAS scores were comparable between both the arms. Mean (SD) scores at baseline was 79.4 (18.73) for the D+T arm and 76.8 (14.79) for the placebo arm.

Of the 130 patients still on study at week 16, 86 patients (92.5%) in the D+T arm and 34 patients (91.9%) in the placebo arm completed the EQ VAS. Mean (SD) EQ VAS scores was 80.4 (14.31) for the D+T arm vs. 83.4 (12.52) for the placebo arm.

Of the 72 patients still on study at week 56, 55 patients (94.8%) in the D+T arm and 13 patients (92.9%) in the placebo arm completed the EQ VAS. Mean (SD) score at Week 56 was 83.4 (14.30) for the D+T arm and 85.4 (9.33) for the placebo arm. The Mean EQ VAS change from baseline scores at follow-up timepoints showed small increase in overall patient-reported health-related quality of life in both treatment arms.

In conclusion, changes for most PRO-CTCAE parameters and EQ-5D-5L VAS scores were minimal over time and similar between the treatment arms.

Ancillary analyses

Sensitivity analyses for the primary endpoint

Forty-seven patients (46.5%) in the D+T arm and 9 patients (17.3%) in the placebo arm were censored for PFS. Among these patients, only 2 in the D+T arm were censored at the initiation of a new anti-cancer therapy. There was no evidence of informative censoring, as the majority of patients were censored at the time of the DCO with treatment ongoing.

Table 15. Summary of sensitivity, supplementary and supportive analyses for PFS (FAS)

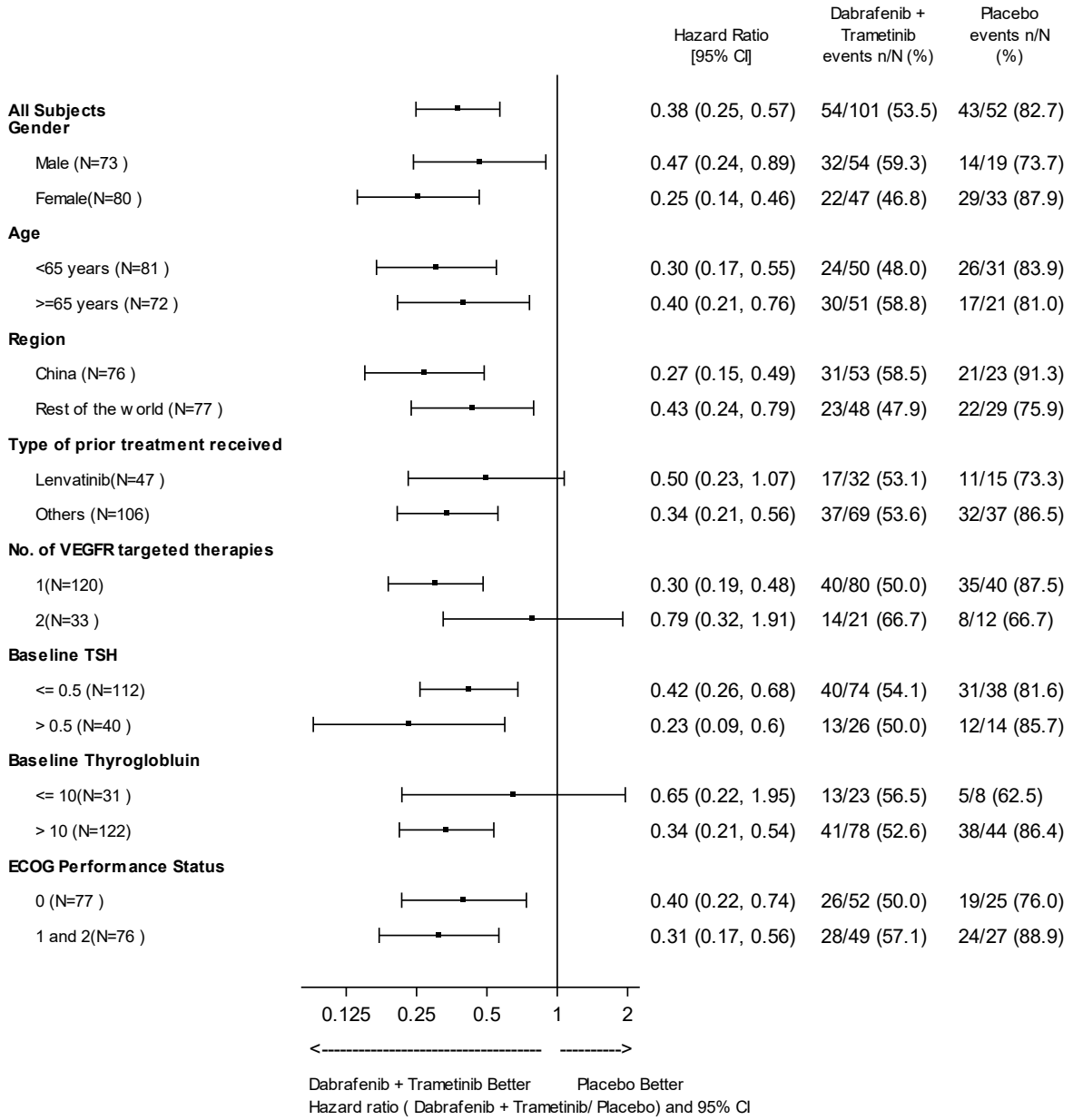
Dabrafenib + trametinib		**Placebo**		**HR between treatments**	
Median time (months)	**95% CI**	**Median time (months)**	**95% CI**	**HR**	**95% CI**
Sensitivity analysis - unstratified Log-rank test and Cox regression model for PFS based on BIRC assessment					
12.8	(10.15, 21.19)	3.7	(2.27, 7.52)	0.38[a]	(0.25, 0.57)
Supplementary analyses					
PFS based on BIRC assessment with treatment and other prognostic variables as covariates					
				0.34	(0.22, 0.51)
PFS based on BIRC assessment using treatment policy strategy					
12.9	(10.4, 21.2)	3.7	(2.3, 7.5)	0.37[b]	(0.25, 0.57)
Supportive analysis					
PFS based on local investigator assessment					
15.5	(12.7, 26.3)	5.5	(1.9, 11.0)	0.39[b]	(0.25, 0.60)
Concordance (%) analysis of PFS between local investigator and BIRC assessment					
Overall	85.0				
Dabrafenib + trametinib	86.1				
Placebo	82.7				

a. HR obtained from Unstratified Cox model

b. HR obtained from Cox PH model stratified based on the randomisation stratification factors: VEGFR targeted therapy (1 vs. 2) and lenvatinib treatment (Yes vs. No).

Subgroup analyses for PFS

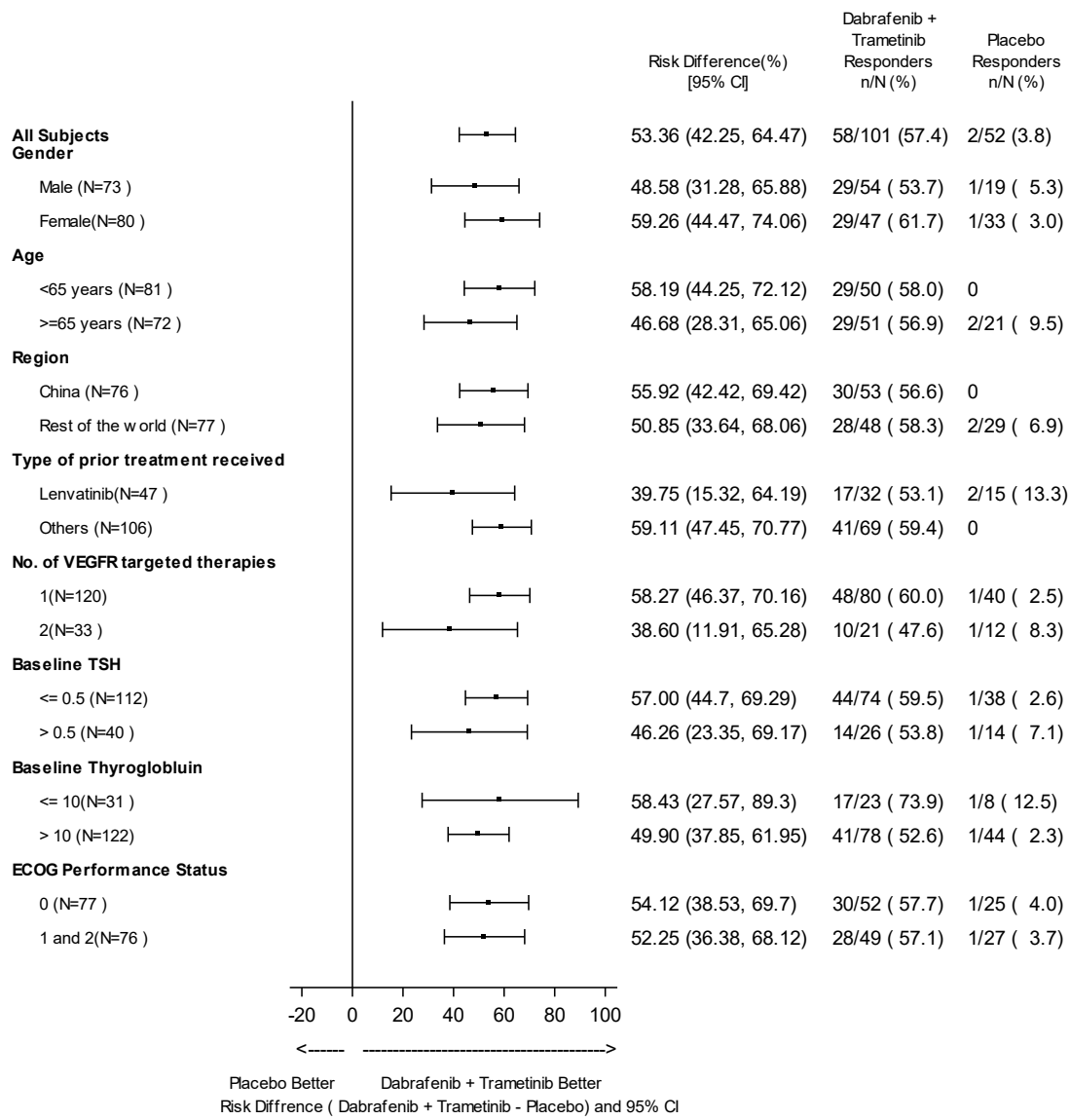
Figure 5. Forest plot of PFS based on BIRC assessment -Subgroups of interest (FAS)



Hazard ratio obtained from Cox PH model stratified based on the randomisation stratification factors: VEGFR targeted therapy (1 vs 2) and lenvatinib treatment (Yes vs No).

Subgroup analyses for ORR

Figure 6: Forest plot of ORR based on BIRC assessment - Subgroups of interest (FAS)

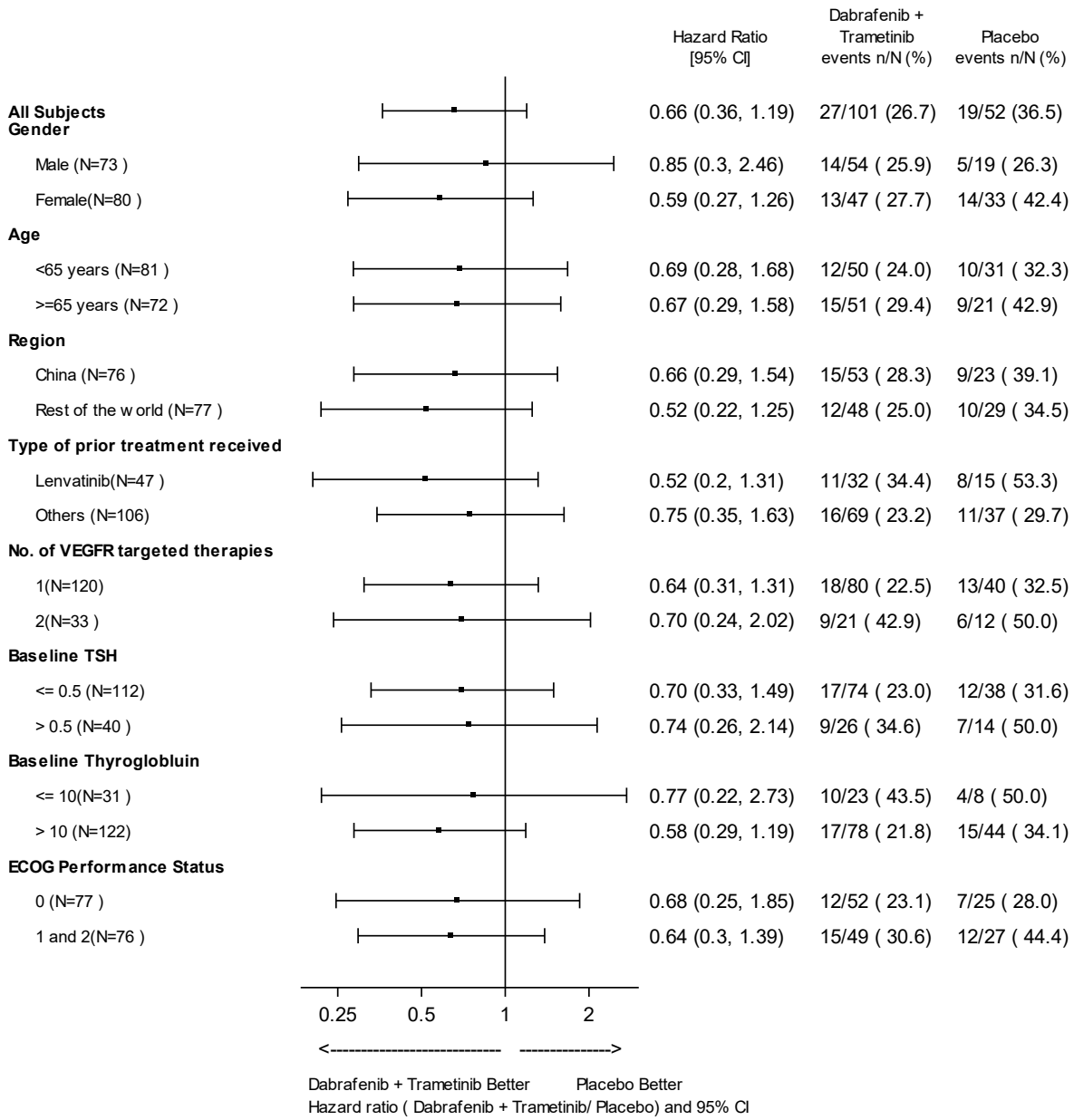


n/N=number of responders/number of patients in the subgroup.

Risk difference was calculated based on stratification factors: VEGFR targeted therapy(1 vs 2) and Lenvatinib treatment(Yes vs No).

Subgroup analyses for OS

Figure 7: Forest plot of OS - Subgroups of interest (FAS)



n/N=number of events/number of patients in the subgroup.
Hazard ratio obtained from Cox PH model stratified based on the randomization stratification factors: VEGFR targeted therapy (1 vs 2) and lenvatinib treatment (Yes vs No).

Non-Asian population

The analysis of the non-Asian subgroup was a post-hoc exploratory analysis added after the database lock. It focused on key baseline characteristics and efficacy endpoints such as PFS, ORR, and OS.

A total of 22 non-Asian patients (11 in each treatment arm) were included in this analysis. The results should be interpreted with caution due to the limited sample size. The demographic and baseline characteristics of the non-Asian population were generally consistent with those of the overall population, with a few notable differences observed. The non-Asian population had a higher

proportion of females (63.6%) compared to the overall population (52.3%). Additionally, the percentage of patients receiving prior lenvatinib was different, with 30.7% in the FAS compared to 45.5% in non-Asian patients.

Demographic and baseline characteristics of the non-Asian population across the treatment arms (D+T vs. placebo) showed notable differences. These included differences in mean age (66.5 years for the D+T arm vs. 56.5 years for placebo), a higher proportion of males in the D+T arm (54.5% vs. 18.2% in the placebo arm), ECOG performance status of 2 (0% in the D+T arm vs. 18.2% in the placebo arm), prior treatment with lenvatinib (36.4% in the D+T arm vs. 54.5% in the placebo arm), and TSH $\leq$ 0.5 mU/L (81.8% in the D+T arm vs. 54.5% in the placebo arm).

PFS results in non-Asian patients were consistent with those observed in the overall population. The HR for D+T compared to placebo was 0.13 (95% CI: 0.03, 0.49). Median PFS was substantially longer in the D+T arm at 9.4 months (95% CI: 9.0, NE) compared to 2.2 months (95% CI: 0.4, 5.5) in the placebo arm.

ORR based on BIRC assessment in the D+T arm was 63.6% (n=1 CR, n=6 PR). There were no responders in the placebo arm.

No deaths were reported in the D+T arm as of the DCO, while nearly half of the patients in the placebo arm (5/11; 45.5%) died.

Cross-over population

Thirty patients from the placebo-arm crossed over to open-label D+T treatment upon BIRC-confirmed progression. Median PFS by investigator assessment in the crossover population was 9.0 months (95% CI: 7.0, 11.1) after initiation of D+T. The percentage of deaths in the crossover population was 43.3% (13/30 patients). The K-M estimated OS rate at Month 6 after initiation of D+T was 89.3% for the crossover population vs. 93.0% in the D+T arm for FAS.

Summary of main study

The following table 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 16. Summary of Efficacy for trial J12301

Title: A randomized, double-blind, placebo-controlled Phase III study to evaluate the efficacy and safety of dabrafenib plus trametinib in previously treated patients with locally advanced or metastatic, radio-active iodine refractory BRAF V600E mutation-positive differentiated thyroid cancer		
Study identifier	CDRB436J12301; NCT04940052	
Design	multicenter, randomised, double-blind, placebo-controlled study	
	Duration of main phase:	First patient first visit: 15-Nov-2021 Data cut-off date: 22-Jan-2025
	Duration of Run-in phase:	not applicable

	Duration of Extension phase:		not applicable
Hypothesis	Superiority		
Treatment groups	Dabrafenib + Trametinib (D+T)		dabrafenib (150 mg BID) plus trametinib (2 mg QD), until disease progression, n=101
	Placebo		Matching placebo tablets, until disease progression, n=52
	Notes		Treatment was continued until disease progression (as per RECIST v1.1, by investigator and confirmed by BIRC), and could be discontinued upon patient or physician decision. Treatment could be continued beyond disease progression if there was evidence of clinical benefit.
Endpoints and definitions	Primary endpoint Progression free survival	PFS	based on BIRC assessment using RECIST 1.1 criteria time from randomisation to disease progression or death due to any cause, whichever occurs first
	Key secondary endpoint Objective response rate	ORR	proportion of patients with confirmed BOR of CR or PR based on BIRC
	Key secondary Endpoint Overall survival	OS	time from randomisation to death due to any cause
Database lock	22 January 2025		
Results and Analysis			
Analysis description	**Primary Analysis**		
Analysis population and time point description	Intention to treat Primary analysis for PFS to be performed after approximately 95 PFS events as per BIRC assessment were reached and all randomised patients have been followed for at least 16 weeks At DCO, an interim-analysis for OS was performed.		

Descriptive statistics and estimate variability	Treatment group	Dabrafenib + trametinib	Placebo
	Number of subject	n=101	N=52
	PFS (median, months)	12.8	3.7
	95% CI	10.2-21.2	2.3-7.5
	ORR PR CR	57.4% 51.5% 5.9%	3.8 1.9% 1.9%
	95% CI	47.2-67.2	0.5-13.2
	OS (median, months) 95% CI	NE NE-NE	25.9 17.1-NE
Effect estimate per comparison	Primary endpoint PFS	Comparison groups	Dabrafenib+trametinib Placebo
		Hazard ratio (HR)	0.38
		95% CI	0.25-0.57
		P-value	<0.001
	Secondary Endpoint ORR	Comparison groups	Dabrafenib+trametinib Placebo
		Stratified difference	53.4%
		95% CI	42.3-64.5
		P-value	<0.001
	Secondary endpoint OS	Comparison groups	Dabrafenib+trametinib Placebo
		HR	0.66
		95% CI	0.36-1.19
		P-value	0.083

Notes	BIRC blinded independent review committee; BOR best overall response; CI confidence interval; CR complete response; HR hazard ratio; NE not estimable; ORR objective response rate; OS overall survival; PFS progression free survival; PR partial response At the interim-analysis for OS, data maturity was 30%. 30 patients from the placebo-arm had crossed over to open-label dabrafenib+trametinib treatment (57.7%).

In vitro biomarker test for patient selection for efficacy

For the pivotal phase III trial (CDRB436J12301), the Roche cobas® 4800 BRAF V600 Mutation Test—a CE-marked in vitro diagnostic (IVD)—was selected as the predictive assay. This real-time PCR assay is designed to qualitatively detect BRAF V600 mutations in DNA extracted from formalin-fixed, paraffin-embedded (FFPE) tumour tissue. The assay is validated for use in the proposed indication and its clinical utility in patient selection for BRAF/MEK inhibitor therapy is established in other approved indications. The biomarker assay was prospectively integrated into the trial design. Only patients with centrally confirmed BRAF V600E mutation by the cobas® 4800 assay were eligible for randomisation.

This CE-marked IVD showed a high concordance with the local test for BRAF V600E mutation, as shown by the post-hoc analysis in the n=105 patients who had both a local and a central test result available.

A description of the central BRAF V600E mutation test used in the pivotal study is now included in section 5.1 of the SmPC.

3.3. Discussion on clinical efficacy

Dose response study

No new dose response study was performed. The proposed posology for both dabrafenib and trametinib is the same as already approved in the treatment of melanoma and NSCLC, which was considered acceptable.

Design and conduct of clinical studies

This application is based on the results of single pivotal study J12301. Study J12301 is a global, multicentre, randomised, double-blind, placebo-controlled phase III study to evaluate the efficacy and safety of dabrafenib plus trametinib (D+T) in patients with locally advanced or metastatic BRAF V600E mutation-positive differentiated thyroid carcinoma (DTC). The study is fully enrolled, ongoing and the last visit of the last patient is projected to occur by May 2027.

The study population includes adult patients with locally advanced or metastatic BRAF V600E mutation-positive DTC that is RAI-refractory and has progressed following prior VEGFR targeted therapy (1 or 2 treatment lines). Patients were relatively fit with an ECOG performance status ≤ 2 and adequate baseline organ function. Patients with a tumour with a RET-fusion were excluded from the study, as were patients previously treated with a BRAF- or MEK-inhibitor and patients with a history of or at risk of retinal vein occlusion (RVO) or central serous retinopathy. BRAF V600E mutation-positive tumour status was confirmed prior to inclusion based on central testing using the

CE-marked IVD Cobas® 4800 assay. This central test showed a high concordance with the local test for BRAF V600E mutation, as shown by the post-hoc analysis in the n=105 patients who had both a local and a central test result available. In section 4.1 of the SmPC a cross-reference to section 4.2 is included concerning biomarker-based patient selection.

The median time since initial diagnosis to study entry was 106 months, and most patients were randomised in the study shortly after progression/relapse on previous therapy (median 2.2 months).

The study was conducted in 42 centres across 11 countries or regions, and mainly included patients in China (n=76), Korea (n=22) and Taiwan (n=15). The pivotal study did not include any patients from the EU, and only 22 non-Asian patients (11 in each treatment arm) were enrolled. However, it is agreed that there is no indication of a differential pharmacokinetic, efficacy or safety profile in Asian versus non-Asian patients based on the available data of dabrafenib and trametinib treatment in patients with other BRAF-V600E mutated tumour types. In addition, efficacy results in the small subgroup of non-Asian patients in the pivotal trial seem comparable to those in the overall population. Baseline demographic and baseline characteristics were generally balanced between treatment arms except for sex and race, with somewhat more female patients in the placebo arm and Asian patients in the D+T arm.

In relation to the primarily Asian study population, the use of prior lenvatinib is somewhat lower than expected in the EU population based on the provided data on treatment patterns. About a quarter of the study participants had received two prior treatment lines (which following the EU ESMO guideline would mean sorafenib followed by lenvatinib) and the subgroup analysis for PFS and ORR do not indicate a difference in treatment effects in the 30.7% of the population pretreated with lenvatinib. Therefore, also in this respect, study results are considered applicable to the EU population.

Disease characteristics at baseline were well balanced between treatment arms and were consistent with what was expected from patients with advanced or metastatic DTC. All included patients had DTC of papillary histology (PTC), which is also the most prevalent subtype of DTC. Follicular thyroid carcinomas (FTC, 10-15% of DTCs) are treated the same as PTCs in the RAI-refractory setting, i.e. with mTKIs. BRAF V600E-mutations are rare in FTCs (around 1%), and no data on D+T treatment in these tumors is presented. The MAH argues that dabrafenib and trametinib have shown anti-tumour effects in BRAF V600E-mutated tumours irrespective of histology, such as in the approved indications in NSCLC and melanoma, but also in the rare aggressive subtype of anaplastic thyroid carcinoma. This can be agreed, however, the lack of data in patients with FTC with a BRAF V600E-mutation is explicitly stated in section 5.1 of the SmPC.

Considering the above, the target population defined in the indication is adequately reflected by the studied population, and it is agreed that it is this patient population with progression of disease upon treatment with an mTKI for which there remains an unmet medical need.

Around 150 patients were planned to be randomised in a 2:1 ratio to either dabrafenib capsules (150 mg BID) plus trametinib tablets (2 mg QD) or matching placebo. This posology is the same as approved for treatment of melanoma and NSCLC, and the lack of a dose finding study in the newly proposed indication is acceptable. The choice of placebo as comparator can also be followed. Cabozantinib was approved in the EU as second line treatment in DTC shortly before initiation of study J12301, but was not yet available in many of the countries where the study was conducted. Moreover, patients randomised to the placebo arm for whom disease progression was confirmed by BIRC and who met the eligibility criteria were given the option to crossover to the open-label

dabrafenib plus trametinib. Randomisation was stratified by prior lenvatinib treatment (yes vs no) and number of prior VEGFR-targeted therapies (1 vs 2). These stratification factors can be agreed.

Treatment was continued until disease progression (as per RECIST v1.1, by investigator and confirmed by BIRC), or patient or physician decision. Treatment could be continued beyond disease progression (confirmed by BIRC) if, in the judgment of the investigator, there was evidence of clinical benefit, and the patient wished to continue on study treatment. Patients randomised to the placebo arm for whom disease progression was confirmed by BIRC and who met the eligibility criteria were given the option to crossover to open-label dabrafenib plus trametinib treatment.

The primary endpoint was BIRC-assessed PFS, according to RECIST 1.1. The primary estimand is not in line with the EMA guideline for which the treatment policy strategy is preferred for the intercurrent events of use of new anticancer therapy. Supplementary analysis was pre planned and the results were consistent with the primary analysis.

Key secondary endpoints, part of the hierarchical testing strategy, were ORR and OS. In this last line treatment setting, overall survival can be considered the preferred primary endpoint. However, Cabometyx was approved in the EU in the second-line setting in a similar study population (although not selected based on BRAF V600E-mutation), based on a PFS-benefit compared to placebo, with OS data still immature at time of approval. Therefore, a benefit in PFS (and ORR) of significant magnitude could be considered clinically significant, provided that there is no sign of a detrimental effect on OS.

Results of the final OS analysis should be provided post-marketing, to which the MAH has formally committed (**REC**). The final OS analysis will be performed after completion of the study. End of study (LPLV) is defined as 3 years after last patient first treatment, i.e. by May 2027. The final CSR for study J12301 that will contain the final OS analysis is expected to be available by May 2028.

The prespecified primary analysis including safety and efficacy data was to be conducted after approximately 95 PFS events, as per the BIRC assessment, and all randomised patients had completed at least 16 weeks of follow-up. Data cut-off for the primary analysis of PFS and ORR is 22 Jan 2025. At this DCO, an interim-analysis for OS was performed.

All the proposed analysis methods are acceptable.

Efficacy data and additional analyses

Of the 182 screened patients, 29 were not randomised into the study because of screen failure. Most of these (n=21/29) did not meet the in/exclusion criteria for the study but this is not further specified. Because it concerns only 11.5% of patients, and because the characteristics of the relatively fit study population are adequately described in section 5.1 of the SmPC, this is accepted. A total of 153 patients were randomised in a 2:1 ratio to the D+T arm (101 patients) and to the placebo arm (52 patients), all of whom received their allocated intervention.

At the time of DCO (22 January 2025), the median duration of exposure to treatment was 14.7 months in the D+T arm and 5.6 months in the placebo arm. At DCO, 58 patients (57.4%) in the D+T arm and 13 patients (25.0%) in the placebo arm were still receiving blinded study treatment. A considerable proportion of patients (21.8%) from the D+T arm continued treatment beyond progression.

Based on narratives provided by the MAH, most of the participants treated beyond disease progression had progressive disease based on a new lesion or worsening of a non-target lesion, while the sum of target lesions was still below baseline. The lack of alternative treatment options

has probably influenced the decision of the treating physician to treat beyond disease progression in these participants. Because treatment until the patient no longer derives benefit (or development of unacceptable toxicity) is a reflection of the treatment strategy that was used in the pivotal study (given the relatively high percentage of participants treated beyond disease progression), the current statement in section 5.1 of the SmPC is considered acceptable.

Notably, 30 patients (57.7%) from the placebo arm crossed over to receive D+T treatment.

As of the DCO, at a median follow-up time for PFS (by BIRC) of 9.2 months, a total of 97 PFS events were observed: 54 (53.5%) in the D+T arm and 43 (82.7%) in the placebo arm. Median PFS by BIRC assessment was 12.8 months (95% CI: 10.2, 21.2) in the D+T arm and 3.7 months (95% CI: 2.3, 7.5) in the placebo arm, an absolute difference of 9.1 months. The stratified HR was 0.38 (95% CI: 0.25, 0.57; $p < 0.001$). Sensitivity analyses with PFS based on BIRC assessment using a treatment policy strategy and for PFS based on local investigator assessment showed comparable results. The chi-squared test comparing the distribution of sex between the two treatment arms yielded a p-value of 0.0457. A sensitivity analysis adding sex as a covariate or as a stratification factor. Only clinically negligibly changed the treatment effect estimate and its 95%-CI, indicating that sex does not appear to be an (important) prognostic factor in this study.

As the primary endpoint of the study was met and was statistically significant, the key secondary endpoint of ORR based on BIRC assessment was formally tested. The ORR for the D+T arm was significantly higher at 57.4% compared to the placebo arm at 3.8%. The stratified difference in ORR between the treatment arms was 53.36% (95% CI: 42.25, 64.47; p-value < 0.001). Responses are durable, with median duration of response not reached, and an estimated 12-month duration of response of 61.6%.

The reported absolute benefit in median PFS in combination with the high response rate can be considered clinically relevant in this patient population with few treatment options. Cabozantinib is approved for second line treatment (Cabometyx II/23), and, although a formal comparison cannot be made, the reported PFS results appear at least similar and the response rate for D+T is much higher in this biomarker-selected patient population.

At DCO, a planned interim analysis of the other key secondary endpoint of OS was conducted, at which time 27 patients (26.7%) in the D+T arm and 19 patients (36.5%) in the placebo group had died. Median follow-up time for OS at the DCO was 17.4 months. The median OS was not estimable for the D+T arm and 25.9 months for the placebo arm. The stratified HR for OS between the arms was 0.658 (95% CI: 0.362, 1.194). A rank preserving structural failure time (RPFST) model analysis was performed to explore the impact of crossover, showing an OS HR that was somewhat lower (0.512; 95% CI: 0.197, 1.328) but without a statistically significant difference. OS results are considered immature. The results of the final OS analysis will be provided post-approval; the CSR for study J12301 that will contain the final OS analysis is expected to be available by May 2028 **(REC)**.

Patient-reported outcomes (PRO) were assessed as exploratory endpoints. Changes for most PRO-CTCAE parameters and EQ-5D-5L VAS scores were minimal over time and similar between the treatment arms.

Subgroup analyses for PFS and ORR do not raise concerns. Subgroup analyses for OS are still considered immature to draw any firm conclusions.

A post-hoc exploratory analysis in the non-Asian population (n=22) showed a PFS-benefit (median 9.4 months vs 2.2 months) and higher ORR for D+T (ORR 63.6%), comparable to the results in the full study population. The results should be interpreted with caution due to the limited sample size.

These results do not raise concern regarding the applicability of the study findings to the EU population, as discussed above.

3.4. Conclusions on the clinical efficacy

Treatment with dabrafenib and trametinib has shown a clinically relevant prolongation of median PFS in patients with RAI-refractory BRAF V600E mutation-positive differentiated thyroid carcinoma with disease progression upon treatment with a mTKI, together with a high response rate and durable responses. Although immature, preliminary OS results do not show a detrimental effect. Therefore, from the clinical efficacy point of view, this application for an extension of the indication is approvable.

3.4.1. Clinical safety

Introduction

The safety evaluation in this application, i.e. the extension of the indication for the treatment of patients with BRAF V600E mutation positive differentiated thyroid cancer (DTC), is based primarily on the safety data collected for the primary analysis of study J12301. The safety data of this study (data cut-off (DCO); 22 January 2025) is included and discussed in the current report. The overall observation period was divided into 3 mutually exclusive segments:

- Pre-treatment period: from the day of patient's informed consent to the day before the first administration of study treatment.
- On-treatment period: from the day of the first administration of study treatment to the earlier of
    - 30 days after the date of the last administration of study treatment
    - the day prior to the start of open-label D+T treatment following crossover from placebo.
- Post-treatment period: starting from Day 31 after the last administration of study treatment or the first day of open-label D+T treatment.

Two analysis sets were submitted:

- Full analysis set: all patients to whom study treatment was assigned by randomisation. This analysis set was used for the summary of patient disposition.
- Safety set: all patients who received at least one dose of any component of the study treatment.

The safety data of study J12301 (N=101) was compared with the safety data of the established Combination Therapy Safety Pool (D + T combination), derived from 4 completed studies, in approved indication (N=1087).

Table 17. Studies included in the safety pool of approved indication

Study number	Description and population	Number of patients treated with D+T (N=1087)	Status and cut-off date
CDRB436B2301(COMBI-d)	A Phase III, randomized, double-blinded study comparing the combination of the	N=209	Completed

Study number	Description and population	Number of patients treated with D+T (N=1087)	Status and cut-off date
	BRAF inhibitor, dabrafenib and the MEK inhibitor, trametinib to dabrafenib and placebo as first-line therapy in patients with unresectable (Stage IIIC) or metastatic (Stage IV) BRAF V600E/K mutation-positive cutaneous melanoma		Cut-off: 18-Mar-2019
CDRB436B2302 (COMBI-v)	A Phase III, randomized, open-label study comparing the combination of the BRAF inhibitor dabrafenib and the MEK inhibitor trametinib to the BRAF inhibitor vemurafenib in patients with unresectable (Stage IIIC) or metastatic (Stage IV) BRAF V600E/K mutation-positive cutaneous melanoma	N=350	Completed Cut-off: 21-Jun-2019
CDRB436E2201 (E2201)	A Phase II study of the BRAF inhibitor dabrafenib as a single agent and in combination with the MEK inhibitor trametinib in patients with BRAF V600E mutation-positive metastatic (stage IV) NSCLC	N=93	Completed Cut-off: 07-Jan-2021
CDRB436F2301 (COMBI-AD)	A Phase III, randomized, double-blind study of dabrafenib in combination with trametinib versus two placebos in the adjuvant treatment of high-risk BRAF V600 mutation-positive melanoma after surgical resection	N=435	Completed Cut-off: 31-Jul-2023

Differences in demographic and baseline characteristics were observed between the patients treated with D+T in study J12301 and those in the safety pool, including:

- Age: Patients in study J12301 were generally older, with 49.5% under 65 years of age compared to 75.3% in the safety pool. The median age was 65.0 years in study J12301 vs. 54.0 years in the safety pool.
- Ethnicity: Most patients in Study J12301 were Asian (89.1%), whereas the safety pool predominantly comprised White patients (97.0%, including those of White/Caucasian/European heritage).
- Performance status: A lower proportion of patients in study J12301 had an ECOG performance status of 0 (51.5%) compared to the safety pool (76.8%), indicating a generally worse baseline functional status.

Furthermore, in study J12301, most patients (81.2%) were classified as stage IVA or IVB. In contrast, the safety pool included 41.4% of patients with stage IIIA/IIIB/IIIC disease and 39.4% with stage IV disease. Also, the median time was longer in study J12301 (98.6 months) compared to the safety pool (20.3 months), reflecting the use of D+T as a second-line treatment in study J12301, whereas the safety pool included patients who were treated in the adjuvant setting.

For the purpose of this application, the safety data of study J12301 (N=101) was pooled together with the established Combination Therapy Safety Pool (D + T combination) (N=1087), resulting in a Safety pool of N=1188.

Patient exposure

The overall safety evaluation was based on data from patients who had received D+T combination therapy (101 patients from study J12301 and 1087 patients from the safety pool; DCO 22 January 2025)

Exposure to study treatment (D+T combination therapy or placebo)

The median duration of exposure to D+T combination therapy was 63.14 weeks (range: 0.7 to 156.4). More than half of the patients (55.4%) had received combination therapy for at least 56 weeks and around 20% received at least 112 weeks of treatment. In the placebo arm the median duration of exposure was 23.93 weeks (range: 0.7 – 129.0) and 25% of patients had received treatment for at least 56 weeks.

In comparison, to D+T exposure in study J12301, a lower median exposure was observed in the safety pool: approximately 48 weeks both components and about 28% of patients received treatment for at least 56 weeks.

Table 18. Summary of exposure to dabrafenib and trametinib

	Study J12301 N=101	**Safety pool N=1087**
Dabrafenib		
Duration of exposure (weeks)		
Mean (SD)	69.70 (42.266)	70.14 (80.846)
Q1-Q3	39.3-104.1	23.4-66.3
Median (Min-Max)	63.14 (0.7-156.4)	47.83 (0.0-348.3)
Duration of exposure categories – n (%)		
< 8 weeks	3 (3.0)	96 (8.8)
8 – < 24 weeks	13 (12.9)	186 (17.1)
24 – < 56 weeks	30 (29.7)	501 (46.1)
56 – < 112 weeks	34 (33.7)	111 (10.2)
At least 112 weeks	21 (20.8)	193 (17.8)
Patient-years	134.9	1461.2
Trametinib		
Duration of exposure (weeks)		
Mean (SD)	66.27 (42.371)	69.03 (78.954)
Q1-Q3	33.1-94.6	23.9-64.9
Median (Min-Max)	56.29 (0.7-156.4)	47.83 (0.0-348.1)
Duration of exposure categories – n (%)		
< 8 weeks	4 (4.0)	96 (8.8)
8 – < 24 weeks	14 (13.9)	178 (16.4)
24 – < 56 weeks	32 (31.7)	508 (46.7)
56 – < 112 weeks	32 (31.7)	117 (10.8)
At least 112 weeks	19 (18.8)	188 (17.3)
Patient-years	128.3	1438.1

At DCO, 57.4% of patients in the D+T arm and 25.0% in the placebo arm were still receiving treatment. Treatment discontinuation rates were 42.6% in the D+T arm and 75.0% in the placebo arm, primarily due to progressive disease (18.8% vs. 59.6%). Permanent discontinuation due to AE for dabrafenib was reported for 4.0% of the patients, and for trametinib for 6.9% of the patients. In the placebo arm 3.8% of the patients had permanently discontinued treatment due to

AE. Overall, 31 patients (30.7%) in the D+T arm and 20 patients (38.5%) in the placebo arm discontinued from the study, mainly due to death (26.7% vs. 36.5%).

Thirty patients (57.7%) in the placebo arm crossed over to receive open-label D+T treatment after confirmed progression. Meanwhile, 22 patients (21.8%) in the D+T arm continued treatment beyond progression, with 10 patients ongoing at DCO.

Dose modifications in study J12301

Dabrafenib

Dose adjustments for dabrafenib (i.e. at least one dose reduction or interruption) were reported in 78.2% of patients in the D+T arm.

- Dose reductions occurred in 45.5% of patients, mostly 1 or 2 dose reductions. The most common reason for dose reduction was AE (32.7%).
- Dose interruptions occurred in 75.2% of patients, mostly more than 2 dose interruptions. The most common reason for dose interruption was AE (64.4%).

Permanent discontinuations were reported in 41.6% of patients, and the most common reason was progressive disease (18.8%).

Trametinib

Dose adjustments for trametinib (i.e. at least one dose reduction or interruption) were reported in 79.2% of patients in the D+T arm.

- Dose reductions occurred in 46.5% of patients, mostly 1 or 2 dose reductions. The most common reason for dose reductions was AE (29.7%).
- Dose interruptions occurred in 77.2% of patients, mostly more than 2 dose interruptions. The most common reason for dose interruption was AE (66.3%).

Concomitant medications or treatments

Concomitant medications were received by most patients (96.0% in the D+T arm and 88.5% in the placebo arm). There were 35.6% of patients in the D+T arm and 19.2% of patients in the placebo arm who underwent at least one surgery or procedure during the study.

AEs requiring additional therapy were reported in 93.1% of patients in the D+T arm and 78.8% of patients in the placebo arm. In the D+T arm, the most commonly reported AEs requiring additional therapy by PT (> 15%) were pyrexia (40.6%), urinary tract infection (16.8%), and pneumonia (15.8%).

Adverse events

Table 19. Overview of adverse events in Study J12301 (safety set)

Category	D+T N=101		Placebo N=52		D+T vs. Placebo Risk Difference (95% CI)	
	All grades n (%)	Grade≥3 n (%)	All grades n (%)	Grade ≥3 n (%)	All grades	Grade ≥3
Adverse events	99 (98.0)	55 (54.5)	47 (90.4)	14 (26.9)	7.6 (-0.8, 16.1)	27.5 (12.1, 43.0)
Treatment-related	87 (86.1)	28 (27.7)	30 (57.7)	2 (3.8)	28.4 (13.4, 43.5)	23.9 (13.7, 34.1)
SAEs	43 (42.6)	31 (30.7)	13 (25.0)	11 (21.2)	17.6 (2.4, 32.8)	9.5 (-4.7, 23.8)
Treatment-related	16 (15.8)	8 (7.9)	2 (3.8)	1 (1.9)	12.0 (3.2, 20.8)	6.0 (-0.5, 12.5)
Fatal SAEs	8 (7.9)	8 (7.9)	2 (3.8)	2 (3.8)	4.1 (-3.3, 11.5)	4.1 (-3.3, 11.5)
Treatment-related	1 (1.0)	1 (1.0)	0	0	1.0 (-0.9, 2.9)	1.0 (-0.9, 2.9)
AEs leading to discontinuation	8 (7.9)	2 (2.0)	3 (5.8)	2 (3.8)	2.2 (-6.1, 10.4)	-1.9 (-7.8, 4.0)
Treatment-related	6 (5.9)	2 (2.0)	1 (1.9)	0	4.0 (-1.9, 9.9)	2.0 (-0.7, 4.7)
AEs leading to dose adjustment/interruption	76 (75.2)	30 (29.7)	17 (32.7)	6 (11.5)	42.6 (27.3, 57.8)	18.2 (5.7, 30.6)
AEs requiring additional therapy	94 (93.1)	44 (43.6)	41 (78.8)	12 (23.1)	14.2 (2.1, 26.4)	20.5 (5.5, 35.5)

Numbers (n) represent counts of patients.
A patient with multiple severity grades for an AE was only counted under the maximum grade.
MedDRA version 28.0, CTCAE version 4.03.
Source: Table 14.3.1-1.1

Table 20. Overview of adverse events in comparison to safety pool

	Study J12301 N=101		Safety pool N=1087		All patients N=1188	
	All grades n (%)	Grade ≥ 3 n (%)	All grades n (%)	Grade ≥ 3 n (%)	All grades n (%)	Grade ≥ 3 n (%)
AEs	99 (98.0)	55 (54.5)	1062 (97.7)	582 (53.5)	1161 (97.7)	637 (53.6)
Treatment-related	87 (86.1)	28 (27.7)	987 (90.8)	389 (35.8)	1074 (90.4)	417 (35.1)
SAEs	43 (42.6)	31 (30.7)	488 (44.9)	324 (29.8)	531 (44.7)	355 (29.9)
Treatment-related	16 (15.8)	8 (7.9)	336 (30.9)	180 (16.6)	352 (29.6)	188 (15.8)
Fatal SAEs	8 (7.9)	8 (7.9)	21 (1.9)	21 (1.9)	29 (2.4)	29 (2.4)
Treatment-related	1 (1.0)	1 (1.0)	0	0	1 (0.1)	1 (0.1)
AEs leading to treatment discontinuation	8 (7.9)	2 (2.0)	238 (21.9)	116 (10.7)	246 (20.7)	118 (9.9)
Treatment-related	6 (5.9)	2 (2.0)	205 (18.9)	90 (8.3)	211 (17.8)	92 (7.7)
AEs leading to dose reduction	19 (18.8)	1 (1.0)	404 (37.2)	168 (15.5)	423 (35.6)	169 (14.2)
AEs leading to dose interruption	73 (72.3)	30 (29.7)	699 (64.3)	344 (31.6)	772 (65.0)	374 (31.5)

A patient with multiple severity grades for an AE is only counted under the maximum grade.
MedDRA version 28.0, CTCAE version 4.03.
Source: [Appendix 1-Table 2-1]

Common adverse events

Table 21. Adverse events by system organ class (SOC) in Study J12301 (Safety Set)

Primary SOC	Dabrafenib + trametinib N=101		Placebo N=52	
	All grades n (%)	Grade ≥ 3 n (%)	All grades n (%)	Grade ≥ 3 n (%)
Number of patients with at least one event	**99 (98.0)**	**55 (54.5)**	**47 (90.4)**	**14 (26.9)**
Investigations	72 (71.3)	16 (15.8)	30 (57.7)	3 (5.8)

	Dabrafenib + trametinib N=101		Placebo N=52	
Primary SOC	All grades n (%)	Grade ≥ 3 n (%)	All grades n (%)	Grade ≥ 3 n (%)
General disorders and administration site conditions	68 (67.3)	7 (6.9)	18 (34.6)	1 (1.9)
Infections and infestations	67 (66.3)	18 (17.8)	19 (36.5)	3 (5.8)
Metabolism and nutrition disorders	63 (62.4)	15 (14.9)	20 (38.5)	1 (1.9)
Blood and lymphatic system disorders	56 (55.4)	8 (7.9)	6 (11.5)	0
Gastrointestinal disorders	54 (53.5)	4 (4.0)	22 (42.3)	1 (1.9)
Skin and subcutaneous tissue disorders	48 (47.5)	4 (4.0)	9 (17.3)	0
Respiratory, thoracic and mediastinal disorders	46 (45.5)	8 (7.9)	18 (34.6)	5 (9.6)
Eye disorders	39 (38.6)	3 (3.0)	11 (21.2)	0
Musculoskeletal and connective tissue disorders	35 (34.7)	2 (2.0)	17 (32.7)	2 (3.8)
Renal and urinary disorders	33 (32.7)	1 (1.0)	9 (17.3)	2 (3.8)
Nervous system disorders	32 (31.7)	7 (6.9)	14 (26.9)	3 (5.8)
Cardiac disorders	26 (25.7)	3 (3.0)	10 (19.2)	2 (3.8)
Injury, poisoning and procedural complications	15 (14.9)	4 (4.0)	3 (5.8)	0
Vascular disorders	13 (12.9)	2 (2.0)	6 (11.5)	2 (3.8)
Hepatobiliary disorders	7 (6.9)	1 (1.0)	3 (5.8)	0
Psychiatric disorders	6 (5.9)	0	5 (9.6)	0
Ear and labyrinth disorders	3 (3.0)	0	0	0
Immune system disorders	3 (3.0)	1 (1.0)	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	3 (3.0)	1 (1.0)	2 (3.8)	1 (1.9)
Reproductive system and breast disorders	3 (3.0)	0	2 (3.8)	0
Congenital, familial and genetic disorders	1 (1.0)	0	0	0
Endocrine disorders	1 (1.0)	0	0	0

Only AEs that occurred from the date of first administration of any study treatment until 30 days after the date of the last actual administration of any study treatment or a day prior to start of open label were summarized.
A patient with multiple severity grades for an AE is only counted under the maximum grade.
MedDRA version 28.0, CTCAE version 4.03.

The most commonly reported AEs by preferred terms (all grades) in the D+T arm were pyrexia (47.5%), anaemia (44.6%), urinary tract infection (31.7%), hyperglycaemia (25.7%), neutrophil count decreased (25.7%), rash (25.7%), and white blood cell count decreased (25.7%).

In the placebo arm, they were hypocalcaemia (17.3%), constipation (17.3%), weight decreased (13.5%), cough (13.5%), headache (13.5%), arthralgia (11.5%), dyspnoea (11.5%), and haemoptysis (11.5%).

Table 22. Adverse events by preferred term (at least 10% in any arm) Study J12301 (Safety Set)

	D+T N=101		Placebo N=52		D+T vs. Placebo Risk Difference (95% CI)	
Preferred Term	**All grades n (%)**	**Grade ≥3 n (%)**	**All grades n (%)**	**Grade≥3 n (%)**	**All grades**	**Grade ≥3**
Number of patients with at least one event	99 (98.0)	55 (54.5)	47 (90.4)	14 (26.9)	7.6 (-0.8, 16.1)	27.5 (12.1, 43.0)
Pyrexia	48 (47.5)	4 (4.0)	5 (9.6)	0	37.9 (25.3, 50.5)	4.0 (0.2, 7.8)
Anaemia	45 (44.6)	4 (4.0)	5 (9.6)	0	34.9 (22.4, 47.5)	4.0 (0.2, 7.8)
Urinary tract infection	32 (31.7)	1 (1.0)	4 (7.7)	0	24.0 (12.4, 35.6)	1.0 (-0.9, 2.9)
Hyperglycaemia	26 (25.7)	4 (4.0)	3 (5.8)	0	20.0 (9.3, 30.6)	4.0 (0.2, 7.8)
Neutrophil count decreased	26 (25.7)	4 (4.0)	2 (3.8)	0	21.9 (11.9, 31.9)	4.0 (0.2, 7.8)
Rash	26 (25.7)	1 (1.0)	2 (3.8)	0	21.9 (11.9, 31.9)	1.0 (-0.9, 2.9)
White blood cell count decreased	26 (25.7)	4 (4.0)	5 (9.6)	0	16.1 (4.4, 27.8)	4.0 (0.2, 7.8)
Hypoalbuminaemia	25 (24.8)	1 (1.0)	3 (5.8)	0	19.0 (8.4, 29.5)	1.0 (-0.9, 2.9)
Chills	23 (22.8)	0	1 (1.9)	0	20.8 (11.9, 29.8)	NE
Lipase increased	23 (22.8)	7 (6.9)	2 (3.8)	0	18.9 (9.2, 28.6)	6.9 (2.0, 11.9)
Aspartate aminotransferase increased	22 (21.8)	0	3 (5.8)	0	16.0 (5.8, 26.3)	NE
Weight decreased	22 (21.8)	0	7 (13.5)	0	8.3 (-4.0, 20.6)	NE
Hypocalcaemia	19 (18.8)	4 (4.0)	9 (17.3)	0	1.5 (-11.3, 14.3)	4.0 (0.2, 7.8)
Upper respiratory tract infection	19 (18.8)	4 (4.0)	2 (3.8)	0	15.0 (5.7, 24.2)	4.0 (0.2, 7.8)
Blood alkaline phosphatase increased	17 (16.8)	0	4 (7.7)	0	9.1 (-1.1, 19.4)	NE
Decreased appetite	17 (16.8)	0	3 (5.8)	0	11.1 (1.4, 20.7)	NE
Nausea	17 (16.8)	1 (1.0)	4 (7.7)	1 (1.9)	9.1 (-1.1, 19.4)	-0.9 (-5.1, 3.3)
Pneumonia	17 (16.8)	8 (7.9)	2 (3.8)	1 (1.9)	13.0 (4.0, 22.0)	6.0 (-0.5, 12.5)
Blood creatine phosphokinase increased	16 (15.8)	2 (2.0)	1 (1.9)	0	13.9 (5.9, 22.0)	2.0 (-0.7, 4.7)
Cough	16 (15.8)	0	7 (13.5)	0	2.4 (-9.3, 14.1)	NE
Oedema peripheral	16 (15.8)	0	4 (7.7)	0	8.1 (-2.0, 18.3)	NE
Constipation	15 (14.9)	0	9 (17.3)	0	-2.5 (-14.9, 9.9)	NE
Diarrhoea	15 (14.9)	0	2 (3.8)	0	11.0 (2.3, 19.7)	NE
Lymphocyte count decreased	15 (14.9)	3 (3.0)	3 (5.8)	1 (1.9)	9.1 (-0.3, 18.5)	1.0 (-3.9, 6.0)
Alanine aminotransferase increased	14 (13.9)	0	4 (7.7)	0	6.2 (-3.7, 16.1)	NE
Dizziness	14 (13.9)	1 (1.0)	2 (3.8)	0	10.0 (1.5, 18.5)	1.0 (-0.9, 2.9)
Hypertriglyceridaemia	14 (13.9)	0	3 (5.8)	0	8.1 (-1.2, 17.3)	NE
COVID-19	13 (12.9)	0	3 (5.8)	0	7.1 (-2.0, 16.2)	NE
Hypercholesterolaemia	13 (12.9)	0	2 (3.8)	0	9.0 (0.7, 17.4)	NE
Hypokalaemia	13 (12.9)	0	3 (5.8)	1 (1.9)	7.1 (-2.0, 16.2)	-1.9 (-5.7, 1.8)
Proteinuria	13 (12.9)	0	2 (3.8)	1 (1.9)	9.0 (0.7, 17.4)	-1.9 (-5.7, 1.8)
Arthralgia	12 (11.9)	1 (1.0)	6 (11.5)	0	0.3 (-10.4, 11.1)	1.0 (-0.9, 2.9)
Fatigue	12 (11.9)	0	4 (7.7)	0	4.2 (-5.4, 13.8)	NE
Hypoproteinaemia	11 (10.9)	0	0	0	10.9 (4.8, 17.0)	NE
Vomiting	11 (10.9)	0	1 (1.9)	0	9.0 (1.8, 16.1)	NE
Dyspnoea	8 (7.9)	2 (2.0)	6 (11.5)	2 (3.8)	-3.6 (-13.8, 6.5)	-1.9 (-7.8, 4.0)
Headache	8 (7.9)	0	7 (13.5)	0	-5.5 (-16.2, 5.1)	NE
Haemoptysis	4 (4.0)	0	6 (11.5)	0	-7.6 (-17.1, 1.9)	NE

Numbers (n) represent counts of patients.
Only AEs that occurred from date of first administration of any study treatment until 30 days after date of last actual administration of any study treatment or a day prior to start of open label were summarized.
A patient with multiple severity grades for an AE was only counted under the maximum grade.
MedDRA version 28.0, CTCAE version 4.03.
Source: Table 14.3.1-2.3

Table 23. Adverse events by preferred term for patients treated with D+T in Study J12301 and in the safety pool

	Study J12301 N=101		Safety pool N=1087		All patients N=1188	
Preferred term	**All grades n (%)**	**Grade ≥ 3 n (%)**	**All grades n (%)**	**Grade ≥ 3 n (%)**	**All grades n (%)**	**Grade ≥ 3 n (%)**
Patients with at least one event	**99 (98.0)**	**55 (54.5)**	**1062 (97.7)**	**582 (53.5)**	**1161 (97.7)**	**637 (53.6)**
Pyrexia	48 (47.5)	4 (4.0)	648 (59.6)	63 (5.8)	696 (58.6)	67 (5.6)
Anaemia	45 (44.6)	4 (4.0)	87 (8.0)	23 (2.1)	132 (11.1)	27 (2.3)
Urinary tract infection	32 (31.7)	1 (1.0)	102 (9.4)	11 (1.0)	134 (11.3)	12 (1.0)
Hyperglycaemia	26 (25.7)	4 (4.0)	48 (4.4)	22 (2.0)	74 (6.2)	26 (2.2)
Neutrophil count decreased	26 (25.7)	4 (4.0)	36 (3.3)	9 (0.8)	62 (5.2)	13 (1.1)
Rash	26 (25.7)	1 (1.0)	294 (27.0)	9 (0.8)	320 (26.9)	10 (0.8)
White blood cell count decreased	26 (25.7)	4 (4.0)	29 (2.7)	6 (0.6)	55 (4.6)	10 (0.8)
Hypoalbuminaemia	25 (24.8)	1 (1.0)	23 (2.1)	2 (0.2)	48 (4.0)	3 (0.3)
Chills	23 (22.8)	0	372 (34.2)	11 (1.0)	395 (33.2)	11 (0.9)
Lipase increased	23 (22.8)	7 (6.9)	14 (1.3)	8 (0.7)	37 (3.1)	15 (1.3)
AST increased	22 (21.8)	0	153 (14.1)	31 (2.9)	175 (14.7)	31 (2.6)
Weight decreased	22 (21.8)	0	62 (5.7)	2 (0.2)	84 (7.1)	2 (0.2)
Hypocalcaemia	19 (18.8)	4 (4.0)	10 (0.9)	0	29 (2.4)	4 (0.3)
Upper respiratory tract infection	19 (18.8)	4 (4.0)	61 (5.6)	1 (0.1)	80 (6.7)	5 (0.4)
Blood alkaline phosphatase increased	17 (16.8)	0	93 (8.6)	13 (1.2)	110 (9.3)	13 (1.1)
Decreased appetite	17 (16.8)	0	154 (14.2)	5 (0.5)	171 (14.4)	5 (0.4)
Nausea	17 (16.8)	1 (1.0)	422 (38.8)	7 (0.6)	439 (37.0)	8 (0.7)
Pneumonia	17 (16.8)	8 (7.9)	36 (3.3)	8 (0.7)	53 (4.5)	16 (1.3)
Blood creatine phosphokinase increased	16 (15.8)	2 (2.0)	37 (3.4)	14 (1.3)	53 (4.5)	16 (1.3)
Cough	16 (15.8)	0	237 (21.8)	0	253 (21.3)	0
Oedema peripheral	16 (15.8)	0	196 (18.0)	5 (0.5)	212 (17.8)	5 (0.4)
Constipation	15 (14.9)	0	141 (13.0)	1 (0.1)	156 (13.1)	1 (0.1)
Diarrhoea	15 (14.9)	0	372 (34.2)	14 (1.3)	387 (32.6)	14 (1.2)
Lymphocyte count decreased	15 (14.9)	3 (3.0)	24 (2.2)	16 (1.5)	39 (3.3)	19 (1.6)
ALT increased	14 (13.9)	0	163 (15.0)	37 (3.4)	177 (14.9)	37 (3.1)
Dizziness	14 (13.9)	1 (1.0)	130 (12.0)	3 (0.3)	144 (12.1)	4 (0.3)
Hypertriglyceridaemia	14 (13.9)	0	4 (0.4)	1 (0.1)	18 (1.5)	1 (0.1)
COVID-19	13 (12.9)	0	0	0	13 (1.1)	0
Hypercholesterolaemia	13 (12.9)	0	7 (0.6)	0	20 (1.7)	0
Hypokalaemia	13 (12.9)	0	45 (4.1)	10 (0.9)	58 (4.9)	10 (0.8)
Proteinuria	13 (12.9)	0	3 (0.3)	0	16 (1.3)	0
Arthralgia	12 (11.9)	1 (1.0)	324 (29.8)	10 (0.9)	336 (28.3)	11 (0.9)
Fatigue	12 (11.9)	0	420 (38.6)	31 (2.9)	432 (36.4)	31 (2.6)
Hypoproteinaemia	11 (10.9)	0	1 (0.1)	0	12 (1.0)	0
Vomiting	11 (10.9)	0	329 (30.3)	14 (1.3)	340 (28.6)	14 (1.2)
Asthenia	10 (9.9)	1 (1.0)	175 (16.1)	17 (1.6)	185 (15.6)	18 (1.5)
Back pain	9 (8.9)	2 (2.0)	127 (11.7)	7 (0.6)	136 (11.4)	9 (0.8)
Pain in extremity	9 (8.9)	0	150 (13.8)	10 (0.9)	159 (13.4)	10 (0.8)
Headache	8 (7.9)	0	374 (34.4)	13 (1.2)	382 (32.2)	13 (1.1)

	Study J12301 N=101		Safety pool N=1087		All patients N=1188	
Preferred term	All grades n (%)	Grade ≥ 3 n (%)	All grades n (%)	Grade ≥ 3 n (%)	All grades n (%)	Grade ≥ 3 n (%)
Hypertension	8 (7.9)	2 (2.0)	218 (20.1)	101 (9.3)	226 (19.0)	103 (8.7)
Myalgia	6 (5.9)	0	177 (16.3)	2 (0.2)	183 (15.4)	2 (0.2)
Abdominal pain	5 (5.0)	0	117 (10.8)	5 (0.5)	122 (10.3)	5 (0.4)
Influenza like illness	5 (5.0)	0	128 (11.8)	7 (0.6)	133 (11.2)	7 (0.6)
Pruritus	5 (5.0)	0	124 (11.4)	3 (0.3)	129 (10.9)	3 (0.3)
Erythema	3 (3.0)	0	127 (11.7)	0	130 (10.9)	0
Muscle spasms	3 (3.0)	0	113 (10.4)	1 (0.1)	116 (9.8)	1 (0.1)
Dry skin	2 (2.0)	0	147 (13.5)	1 (0.1)	149 (12.5)	1 (0.1)
Nasopharyngitis	2 (2.0)	0	144 (13.2)	0	146 (12.3)	0

Only AEs that occurred from the date of first administration of any study treatment until 30 days after the date of last actual administration of any study treatment were summarized.

A patient with multiple severity grades for an AE is only counted under the maximum grade.

MedDRA version 28.0, CTCAE version 4.03.

Severity of adverse events

In study J12301, grade ≥ 3 AEs were reported in 54.5% of patients in the D+T arm (comparable to the incidence in the safety pool, 53.5%) and 26.9% of patients in the placebo arm. In the D+T arm, the most commonly reported grade ≥ 3 AEs by PT (> 5%) were pneumonia (7.9% vs 0% in the placebo arm) and lipase increased (6.9% vs 1.9% in the placebo arm). None of the other grade ≥ 3 AEs were reported in more than 5% of patients.

Adverse events of special interest

Table 24. Overview of adverse events of special interest for dabrafenib and trametinib in Study J12301 (Safety set)

	Dabrafenib + trametinib N=101		Placebo N=52	
Safety topic	All grades n (%)	Grade ≥ 3 n (%)	All grades n (%)	Grade ≥ 3 n (%)
Pyrexia	49 (48.5)	4 (4.0)	5 (9.6)	0
Skin toxicity	47 (46.5)	3 (3.0)	10 (19.2)	0
Neutropenia	36 (35.6)	8 (7.9)	5 (9.6)	0
Hyperglycemia	35 (34.7)	5 (5.0)	3 (5.8)	0
Bleeding events	33 (32.7)	4 (4.0)	16 (30.8)	2 (3.8)
Hepatic disorders	26 (25.7)	1 (1.0)	10 (19.2)	0
Pancreatitis	26 (25.7)	8 (7.9)	3 (5.8)	1 (1.9)
Ocular events	14 (13.9)	1 (1.0)	3 (5.8)	0
Cardiac related events	12 (11.9)	1 (1.0)	4 (7.7)	1 (1.9)
Hypertension	8 (7.9)	2 (2.0)	3 (5.8)	1 (1.9)
Hypersensitivity	6 (5.9)	1 (1.0)	1 (1.9)	0
New primary or secondary malignancy	2 (2.0)	1 (1.0)	1 (1.9)	0
Pneumonitis and interstitial lung disease	2 (2.0)	1 (1.0)	0	0
Pre-renal and intrinsic renal failure	2 (2.0)	1 (1.0)	0	0

	Dabrafenib + trametinib N=101		Placebo N=52	
Safety topic	All grades n (%)	Grade ≥ 3 n (%)	All grades n (%)	Grade ≥ 3 n (%)
Venous thromboembolism	2 (2.0)	1 (1.0)	0	0

A patient with multiple severity grades for an AE is only counted under the maximum grade.
MedDRA version 28.0, CTCAE version 4.03. Case retrieval strategy version released 07-May-2025 (dabrafenib) and 04-Jun-2025 (trametinib).

Pyrexia

AESIs of pyrexia were reported in 48.5% of patients in the D+T arm and 9.6% of patients in the placebo arm. In the D+T arm:

- Grade 3 events were reported in 4 patients (4.0%).
- SAEs were reported in 4 patients (4.0%).
- Treatment-related AEs were reported in 41.6% of patients.
- Pyrexia events led to study treatment discontinuation in 1 patient (1.0%), dose reduction in 9 patients (8.9%) and dose interruption in 40 patients (39.6%).

Neutropenia

AESIs of neutropenia were reported in 35.6% of patients in the D+T arm and 9.6% of patients in the placebo arm. In the D+T arm:

- Grade 3 events were reported in 7 patients (6.9%) and grade 4 in 1 patient (1.0%).
- No SAEs were reported.
- Treatment-related AEs were reported in 31.7% of patients.
- Neutropenia events led to dose reduction in 1 patient (1.0%), dose increase in 2 patients (2.0%) and dose interruption in 9 patients (8.9%).

Hyperglycaemia

AESIs of hyperglycaemia were reported in 34.7% of patients in the D+T arm and 5.8% of patients in the placebo arm. In the D+T arm:

- Grade 3 events were reported in 5 patients (5.0%).
- No SAEs were reported.
- Treatment-related AEs were reported in 10.9% of patients.
- Hyperglycaemia events led to dose interruption in 1 patient (1.0%).

Bleeding events

AESIs of bleeding events were reported in 32.7% of patients in the D+T arm and 30.8% of patients in the placebo arm. In the D+T arm:

- Grade 3 events were reported in 4 patients (4.0%).
- SAEs were reported in 4 patients (4.0%).

- Treatment-related AEs were reported in 19.8% of patients.
- Bleeding events led to study treatment discontinuation in 1 patient (1.0%) and dose interruption in 7 patients (6.9%).

Pancreatitis

AESIs of pancreatitis were reported in 25.7% of patients in the D+T arm and 5.8% of patients in the placebo arm. In the D+T arm:

- Grade 3 events were reported in 8 patients (7.9%) and grade 4 in 1 patient (1.0%).
- SAE was reported in 1 patient (1.0%).
- Treatment-related AEs were reported in 13.9% of patients.
- Pancreatitis events led to dose interruption in 4 patients (4.0%).

Skin toxicity

AESIs of skin toxicity were reported in 46.5% of patients in the D+T arm and 19.2% of patients in the placebo arm. In the D+T arm:

- Grade 3 events were reported in 3 patients (3.0%).
- SAE was reported in 1 patient (1.0%).
- Treatment-related AEs were reported in 39.6% of patients.
- Skin toxicity events led to dose reduction in 3 patients (3.0%) and dose interruption in 4 patients (4.0%).

Hepatic disorders

AESIs of hepatic disorders were reported in 25.7% of patients in the D+T arm and 19.2% of patients in the placebo arm. In the D+T arm:

- Grade 3 events were reported in 1 patient (1.0%).
- No SAEs were reported.
- Treatment-related AEs were reported in 19.8% of patients.
- Hepatic disorders events led to dose interruption in 4 patients (4.0%).

Cardiac related events

AESIs of cardiac related events were reported in 11.9% of patients in the D+T arm and 7.7% of patients in the placebo arm. In the D+T arm:

- Grade 3 events were reported in 1 patient (1.0%).
- SAEs were reported in 4 patients (4.0%).
- Treatment-related AEs were reported in 4 patients (4.0%).
- Cardiac related events led to treatment discontinuation in 3 patients (3.0%) and dose interruption in 4 patients (4.0%)
- Electrocardiograms; In Study J12301, new QTcF values > 500 ms were observed in 4.0% of patients in the D+T arm vs. 2.1% of patients in the placebo arm. New QTcF values > 480 ms and ≤ 500 ms were observed in 4.0% vs. 2.1% of patients (D+T arm vs. placebo

arm). These values were single occurrence and not reported as AEs except for one patient in the placebo arm

- Left ventricular ejection fraction; In study J12301, the LVEF% showed a decrease overtime in both treatment arms, but none of these changes were clinically significant.

Ocular AESI - serous retinopathy

Serous retinopathy AEs were reported in 7 patients (6.9%) in the D+T arm and none in the placebo arm. The PTs included: subretinal fluid in 4 patients (4.0%), detachment of retinal pigment epithelium in 2 patients (2.0%), maculopathy and retinal disorder in 1 patient each (1.0%). All these events were grade 1 or 2.

Vital signs

- Blood pressure: in the D+T arm, there were 8 patients (7.9%) with SBP ≤ 90 mmHg and decrease ≥ 20 mmHg and 2 patients (2.0%) with DBP ≤ 50 mmHg and decrease ≥ 15 mmHg.
- Pulse rate: in the D+T arm, there were 16 patients (15.8%) with pulse rate ≥ 100 bpm and increase > 25%, 1 patient (1.0%) with pulse rate ≤ 50 bpm and decrease > 25%.

ECOG performance status

Nearly all patients had an ECOG performance status of 0 or 1 at baseline, except for 1 patient (1.0%) in the D+T arm and 3 patients (5.8%) in the placebo arm, who had a baseline value of 2. In the D+T arm, the majority had a post-baseline ECOG score that matched their baseline, with 37 of 52 patients maintaining a score of 0 and 36 of 48 patients maintaining a score of 1 as their worst post-baseline ECOG score. There were no clinically significant findings.

Serious adverse event/deaths/other significant events

Serious adverse events

Table 25. Serious adverse events by preferred term (at least 2 patients in any arm for all grades) in Study J12301 (safety set)

	Dabrafenib + trametinib N=101		Placebo N=52	
Preferred term	**All grades n (%)**	**Grade ≥ 3 n (%)**	**All grades n (%)**	**Grade ≥ 3 n (%)**
Number of patients with at least one event	**43 (42.6)**	**31 (30.7)**	**13 (25.0)**	**11 (21.2)**
Pneumonia	8 (7.9)	6 (5.9)	1 (1.9)	1 (1.9)
Pyrexia	4 (4.0)	0	0	0
Dyspnoea	3 (3.0)	2 (2.0)	2 (3.8)	1 (1.9)
Ejection fraction decreased	3 (3.0)	0	0	0
Pneumonia bacterial	3 (3.0)	3 (3.0)	2 (3.8)	2 (3.8)
Back pain	2 (2.0)	2 (2.0)	0	0
Detachment of retinal pigment epithelium	2 (2.0)	0	0	0
Upper respiratory tract infection	2 (2.0)	2 (2.0)	0	0
Pleural effusion	1 (1.0)	1 (1.0)	3 (5.8)	2 (3.8)

Only AEs that occurred from the date of first administration of any study treatment until 30 days after the date of the last actual administration of any study treatment or a day prior to start of open label were summarized.

	Dabrafenib + trametinib N=101		Placebo N=52	
Preferred term	All grades n (%)	Grade ≥ 3 n (%)	All grades n (%)	Grade ≥ 3 n (%)

A patient with multiple severity grades for an AE is only counted under the maximum grade.
MedDRA version 28.0, CTCAE version 4.03.

Deaths

As of the data cut-off date for the primary analysis of study J12301, 27 patients (26.7%) in the D+T arm and 19 patients (36.5%) in the placebo arm died; the majority of deaths were due to study indication (18.8% in the D+T arm and 23.1% in the placebo arm).

Among these deaths, 17 in the D+T arm and 3 in the placebo arm were on-treatment deaths, most of which were due to study indication (10 in the D+T arm and 2 in the placebo arm).

Table 26. Summary of on-treatment deaths by system organ class and preferred term in Study J12301 (safety set)

Primary SOC Primary reason (preferred term)	Dabrafenib + trametinib N=101 n (%)	Placebo N=52 n (%)
Number of patients who died	17 (16.8)	3 (5.8)
Study indication	10 (9.9)	2 (3.8)
Other	7 (6.9)	1 (1.9)
Cardiac disorders	2 (2.0)	0
Acute myocardial infarction	1 (1.0)	0
Bradycardia	1 (1.0)	0
General disorders and administration site conditions	0	1 (1.9)
Multiple organ dysfunction syndrome	0	1 (1.9)
Infections and infestations	2 (2.0)	0
Pneumonia	2 (2.0)	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1 (1.0)	0
Squamous cell carcinoma	1 (1.0)	0
Nervous system disorders	1 (1.0)	0
Cerebrovascular accident	1 (1.0)	0
Respiratory, thoracic and mediastinal disorders	1 (1.0)	0
Respiratory failure	1 (1.0)	0

MedDRA version 28.0.

SAEs with fatal outcome were reported in 8 patients (7.9%) in the D+T arm and 2 patients (3.8%) in the placebo arm. For patients whose primary reason for death was study indication, fatal SAEs were reported in 2 patients in the D+T arm and 1 patient in the placebo arm. For patients whose primary reason for death was adverse event, fatal SAEs included pneumonia (2 patients), acute myocardial infarction, bradycardia, and squamous cell carcinoma (1 patient each) in the D+T arm and multiple organ dysfunction syndrome in the placebo arm (1 patient); none of these SAEs were considered as treatment-related. Additionally, a SAE of cerebrovascular accident was reported in 1

patient in the D+T arm whose primary reason for death was reported as "other", and this SAE was considered as treatment-related.

Adverse Drug Reactions

The AEs from study J12301 meeting any of the following criteria were assessed for inclusion as potential ADR upon fulfilment of causality criteria:

- Any new AE, which did not qualify as ADR in the approved indications but is identified in competitor labels (MEK inhibitors cobimetinib, selumetinib and binimetinib; BRAF inhibitors vemurafenib, encorafenib, tovorafenib, and sorafenib, a multi-kinase inhibitor with BRAF inhibiting properties; tyrosine kinase inhibitors cabozatinib and lenvatinib, competitors used to treat DTC)
- Any AE that is a designated medical event (DME)
- Any AE that did not fulfil above criteria but appeared in at least 10% of patients in the D+T arm
- Any AE with 10% higher frequency in the D+T arm compared to the placebo arm
- Newly reported events (not seen in the existing safety pool) which appeared in at least 3 patients

Finally, the frequency of existing ADRs in the updated safety pool (N=1188) (i.e., safety pool of approved indications (N=1087) combined with safety data of study J12301 (N=101)) were compared with the frequency in the established safety pool (i.e. safety pool of approved indications (N=1087)) to identify if there was any relevant change in frequency category for any ADR.

A total of 28 events were selected for in-depth evaluation as potential ADRs in the context of the DTC indication.

For rhabdomylosis, the frequency was changed from common (with incidence of 4.6%) to uncommon (with incidence of 0.4%). Previously the incidence of rhabdomyolysis was calculated based on reported incidence of Rhabdomyolysis and Blood creatine phosphokinase increased. Because blood creatine phosphokinase increase is included as separate ADR, the sole incidence of rhabdomyolysis is now included.

Table 27. Adverse drug reactions for dabrafenib in combination with trametinib (updated safety pool)

System organ class	Frequency (all grades)	Adverse reactions	Observed frequency (all grades), updated safety pool (N=1188)
Infections and infestations	Very common	Nasopharyngitis	14.9%
		Urinary tract infection	11.3%
	Common	Cellulitis	2.6%
		Folliculitis	4.8%
		Paronychia	2.0%
		Rash pustular	1.7%

Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Common	Cutaneous squamous cell carcinoma	2.7%
		Papilloma	2.1%
		Seborrhoeic keratosis	3.9%
	Uncommon	New primary melanoma	0.4%
		Acrochordon (skin tags)	0.6%
Blood and lymphatic system disorders	Very common	Neutropenia	14.1%
		Anaemia	11.1%
	Common	Thrombocytopenia	6.6%
		Leukopenia	8.6%
Immune system disorders	Uncommon	Hypersensitivity	0.8%
		Sarcoidosis	postmarketing event
	Rare	Haemophagocytic lymphohistiocytosis	postmarketing event
Metabolism and nutrition disorders	Very common	Decreased appetite	14.4%
	Common	Dehydration	3.1%
		Hyponatraemia	4.6%
		Hypophosphataemia	3.4%
		Hyperglycaemia	6.2%
	Not known	Tumour lysis syndrome	postmarketing event
Nervous system disorders	Very common	Headache	32.2%
		Dizziness	15.2%
	Common	Peripheral neuropathy (including sensory and motor neuropathy)	postmarketing event
Eye disorders	Common	Vision blurred	5.6%
		Visual impairment	2.6%
		Uveitis	1.8%
	Uncommon	Chorioretinopathy	0.8%
		Retinal detachment	0.8%
		Periorbital oedema	0.5%
Cardiac disorders	Common	Ejection fraction decreased	8.0%
		Bradycardia	1.9%
	Uncommon	Cardiac failure	0.3%
		Left ventricular dysfunction	0.7%
		Atrioventricular block	0.4%
	Not known	Myocarditis	postmarketing event
Vascular disorders	Very common	Hypertension	19.0%
		Haemorrhage	22.1%
	Common	Hypotension	5.1%
		Lymphoedema	5.0%
Respiratory, thoracic and mediastinal disorders	Very common	Cough	22.6%
	Common	Pneumonitis	1.0%
		Dyspnoea	9.6%
	Rare	Interstitial lung disease	0.1%

Gastrointestinal disorders	Very common	Abdominal pain	17.5%
		Constipation	13.1%
		Diarrhoea	32.6%
		Nausea	37.0%
		Vomiting	28.6%
	Common	Dry mouth	8.2%
		Stomatitis	3.3%
	Uncommon	Gastrointestinal perforation	0.3%
		Pancreatitis	0.2%
		Colitis	0.6%
Skin and subcutaneous tissue disorders	Very common	Dry skin	14.1%
		Pruritus	10.9%
		Rash	35.4%
		Erythema	10.9%
		Dermatitis acneiform	10.8%
	Common	Dermatitis exfoliative generalised	1.3%
		Actinic keratosis	3.7%
		Night sweats	5.1%
		Hyperkeratosis	5.3%
		Alopecia	6.2%
		Palmar-plantar erythrodysaesthesia syndrome	4.0%
		Skin lesion	3.8%
		Hyperhidrosis	5.7%
		Panniculitis	2.4%
		Skin fissures	1.9%
		Photosensitivity	3.6%
	Uncommon	Acute febrile neutrophilic dermatosis	postmarketing event
	Not known	Stevens-Johnson syndrome	postmarketing event
		Drug reaction with eosinophilia and systemic symptoms	postmarketing event
		Tattoo-associated skin reactions	postmarketing event
Musculoskeletal and connective tissue disorders	Very common	Arthralgia	28.3%
		Myalgia	18.9%
		Pain in extremity	13.4%
		Muscle spasms	10.6%
	Uncommon	Rhabdomyolysis	0.4%
Renal and urinary disorders	Common	Renal failure, acute kidney injury	5.8%
	Rare	Nephritis	0.1%
General disorders and administration site conditions	Very common	Fatigue	50.8%
		Chills	33.2%
		Asthenia	15.6%
		Oedema peripheral	20.6%

		Pyrexia	59.0%
		Influenza-like illness	11.2%
	Common	Mucosal inflammation	2.6%
		Face oedema	1.9%
Investigations	Very common	Alanine aminotransferase increased	17.4%
		Aspartate aminotransferase increased	17.3%
	Common	Blood alkaline phosphatase increased	9.3%
		Gamma-glutamyltransferase increased	6.5%
		Blood creatine phosphokinase increased	4.5%
Injury, poisoning and procedural complications	Common	Potentiation of radiation toxicity	postmarketing event

Laboratory findings

In study J12301, laboratory evaluations were performed in screening period, on Day 1, every 4 weeks from Weeks 4 to 56 and then every 12 weeks. Additionally, unscheduled laboratory evaluations were conducted as deemed necessary as per the investigator's judgement.

Laboratory data from local laboratories were used for analysis. The summaries included all assessments available for the laboratory parameters collected no later than 30 days after the administration date of the last study treatment.

Haematology

Table 28. Summary of worst post-baseline haematology abnormalities based on CTC grades in Study J12301 (Safety Set)

	Dabrafenib + trametinib N=101		**Placebo N=52**	
	All grades n (%)	**Grade 3/4 n (%)**	**All grades n (%)**	**Grade 3/4 n (%)**
Hemoglobin decrease	78 (77.2)	5 (5.0)	26 (50.0)	1 (1.9)
Lymphocytes decrease	57 (56.4)	11 (10.9)	17 (32.7)	1 (1.9)
Leukocytes decrease	47 (46.5)	5 (5.0)	8 (15.4)	0
Neutrophils decrease	40 (39.6)	9 (8.9)	6 (11.5)	0
Activated partial thromboplastin time increase	28 (27.7)	0	2 (3.8)	0
Platelets decrease	22 (21.8)	1 (1.0)	2 (3.8)	0
Prothrombin INR increase	17 (16.8)	0	0	0
Lymphocytes increase	2 (2.0)	0	1 (1.9)	0

"All grades" represents patients with any grade 1, 2, 3 or 4 post-baseline.
Data are presented in decreasing frequency for "all grades" column in the D+T arm.
Grades based on CTCAE version 4.03.

Clinical chemistry

Table 29. Summary of worst post-baseline biochemistry abnormalities based on CTC grades in Study J12301 (Safety Set)

	Dabrafenib + trametinib N=101		Placebo N=52	
	All grades n (%)	Grade 3/4 n (%)	All grades n (%)	Grade 3/4 n (%)
Fasting glucose increase	89 (88.1)	11 (10.9)	33 (63.5)	0
Albumin decrease	67 (66.3)	1 (1.0)	7 (13.5)	0
Creatine kinase increase	67 (66.3)	5 (5.0)	11 (21.2)	0
Triglycerides increase	61 (60.4)	2 (2.0)	23 (44.2)	0
Alkaline phosphatase increase	59 (58.4)	0	9 (17.3)	0
Sodium decrease	58 (57.4)	8 (7.9)	8 (15.4)	1 (1.9)
Cholesterol increase	53 (52.5)	0	22 (42.3)	0
Corrected calcium decrease	50 (49.5)	10 (9.9)	29 (55.8)	4 (7.7)
Pancreatic lipase increase	49 (48.5)	20 (19.8)	8 (15.4)	2 (3.8)
AST increase	48 (47.5)	0	11 (21.2)	0
Urate increase	34 (33.7)	4 (4.0)	22 (42.3)	2 (3.8)
Amylase increase	33 (32.7)	6 (5.9)	6 (11.5)	1 (1.9)
ALT increase	30 (29.7)	0	9 (17.3)	0
Phosphate decrease	30 (29.7)	0	1 (1.9)	0
Magnesium decrease	29 (28.7)	0	2 (3.8)	0
Potassium decrease	22 (21.8)	5 (5.0)	5 (9.6)	0
Creatinine increase	17 (16.8)	1 (1.0)	7 (13.5)	0
Corrected calcium increase	13 (12.9)	1 (1.0)	2 (3.8)	0
Potassium increase	9 (8.9)	0	5 (9.6)	0
Magnesium increase	7 (6.9)	1 (1.0)	2 (3.8)	0
Bilirubin increase	6 (5.9)	1 (1.0)	5 (9.6)	0
Gamma-glutamyltransferase increase	4 (4.0)	1 (1.0)	0	0
Sodium increase	4 (4.0)	0	3 (5.8)	0
Fasting glucose decrease	0	0	1 (1.9)	0

"All grades" represents patients with any grade 1, 2, 3 or 4 post-baseline.
Data are presented in decreasing frequency for "all grades" column in the D+T arm.
Grades based on CTCAE version 4.03.

In study J12301, post-baseline biochemistry abnormalities were more frequent in the D+T arm compared to the placebo arm. Most post-baseline biochemistry abnormalities were grade 1 or 2.

Liver enzymes

In study J12301, no Hy's law cases were reported. In the D+T arm, there were 3 patients with ALT > 3 × ULN, 4 patients with AST > 3 × ULN, and 1 patient with total bilirubin > 3 × ULN.

Safety in special populations

In study J12301, safety analyses were performed for China subgroup. In CMS (Chinese mainland subgroup: n=53 for the D+T group; n=23 for the placebo group), the incidence of SAEs (all grades) was similar to those observed in the overall population with 41.5% in the D+T arm and 26.1% in the placebo arm.

The most common SAEs by PT (all grades) in the D+T arm were pneumonia (9.4%), bacterial pneumonia (5.7%), and pyrexia (5.7%); and in the placebo arm was bacterial pneumonia (8.7%).

The incidence of treatment-related SAEs (17.0% in the D+T arm and 8.7% in the placebo arm) and SAEs with fatal outcome (3.8% in the D+T arm and 4.3% in the placebo arm) in CMS were consistent with those observed in the overall population.

Safety per age group

Table 30. AEs by age range

	Dabrafenib + Trametinib			Placebo		
MedDRA Terms	<65 years N=50 n (%)	65 to < 75 years N=41 n (%)	75 to < 85 years N=10 n (%)	<65 years N=31 n (%)	65 to < 75years N=19 n (%)	75 to < 85years N=2 n (%)
Total AEs	49 (98.0)	40 (97.6)	10 (100.0)	28 (90.3)	17 (89.5)	2 (100.0)
Total SAEs	19 (38.0)	20 (48.8)	4 (40.0)	6 (19.4)	7 (36.8)	0
-Fatal	5 (10.0)	2 (4.9)	1 (10.0)	1 (3.2)	1 (5.3)	0
-Hospitalization/ prolong existing hospitalization	15 (30.0)	18 (43.9)	4 (40.0)	5 (16.1)	6 (31.6)	0
-Life-threatening	2 (4.0)	2 (4.9)	0	2 (6.5)	1 (5.3)	0
-Disability/ incapacity	1 (2.0)	1 (2.4)	0	1 (3.2)	0	0
-Other (medically significant)	4 (8.0)	5 (12.2)	0	2 (6.5)	1 (5.3)	0
AE leading to discontinuation	2 (4.0)	5 (12.2)	1 (10.0)	3 (9.7)	0	0
Infections and infestations	35 (70.0)	26 (63.4)	6 (60.0)	10 (32.3)	8 (42.1)	1 (50.0)
Nervous system disorders	18 (36.0)	8 (19.5)	6 (60.0)	8 (25.8)	6 (31.6)	0
Cardiac disorders	16 (32.0)	7 (17.1)	3 (30.0)	3 (9.7)	7 (36.8)	0
Vascular disorders	8 (16.0)	3 (7.3)	2 (20.0)	2 (6.5)	4 (21.1)	0
Psychiatric disorders	2 (4.0)	4 (9.8)	0	3 (9.7)	2 (10.5)	0
Anticholinergic syndrome	0	0	0	0	0	0
Quality of life decreased	0	0	0	0	0	0
Postural hypotension, fall, black out, syncope, dizziness, ataxia, fractures	7 (14.0)	6 (14.6)	7 (70.0)	2 (6.5)	2 (10.5)	0

Numbers (n) represent counts of subjects. MedDRA version 28.0.

Safety related to drug-drug interactions and other interactions

No new information about drug interactions has been generated in support of this application.

Discontinuation due to adverse events

Table 31. Adverse events leading to discontinuation by preferred term in Study J12301 (Safety Set)

	Dabrafenib + trametinib N=101		Placebo N=52	
Preferred term	**All grades n (%)**	**Grade ≥ 3 n (%)**	**All grades n (%)**	**Grade ≥ 3 n (%)**
Number of patients with at least one event	**8 (7.9)**	**2 (2.0)**	**3 (5.8)**	**2 (3.8)**
Ejection fraction decreased	2 (2.0)	0	0	0
Retinal vein occlusion	2 (2.0)	1 (1.0)	0	0
Ascites	1 (1.0)	0	0	0
Dysphonia	1 (1.0)	0	0	0
Dyspnoea	1 (1.0)	0	0	0
Left ventricular dysfunction	1 (1.0)	1 (1.0)	0	0
Pyrexia	1 (1.0)	0	0	0
Vitreous haemorrhage	1 (1.0)	0	0	0
Electrocardiogram QT prolonged	0	0	1 (1.9)	0
Pericardial effusion	0	0	1 (1.9)	1 (1.9)
Spinal cord compression	0	0	1 (1.9)	1 (1.9)

Only AEs that occurred from the date of first administration of any study treatment until 30 days after the date of the last actual administration of any study treatment or a day prior to start of open label were summarized.

A patient with multiple severity grades for an AE is only counted under the maximum grade.

MedDRA version 28.0, CTCAE version 4.03.

Adverse events leading to dose adjustment and/or interruption

Table 32. Adverse events leading to dose adjustment and/or interruption by preferred term (at least 5% in any arm for all grades) in Study J12301 (Safety Set)

	Dabrafenib + trametinib N=101		Placebo N=52	
Preferred term	**All grades n (%)**	**Grade ≥ 3 n (%)**	**All grades n (%)**	**Grade ≥ 3 n (%)**
Number of patients with at least one event	**76 (75.2)**	**30 (29.7)**	**17 (32.7)**	**6 (11.5)**
Pyrexia	43 (42.6)	3 (3.0)	1 (1.9)	0
Chills	7 (6.9)	0	0	0
Pneumonia	7 (6.9)	5 (5.0)	0	0
White blood cell count decreased	6 (5.9)	4 (4.0)	0	0
COVID-19	5 (5.0)	0	0	0
Neutrophil count decreased	5 (5.0)	4 (4.0)	0	0
Vomiting	5 (5.0)	0	0	0
Dyspnoea	0	0	3 (5.8)	1 (1.9)

Only AEs that occurred from the date of first administration of any study treatment until 30 days after the date of the last actual administration of any study treatment or a day prior to start of open label were summarized.

A patient with multiple severity grades for an AE is only counted under the maximum grade.

MedDRA version 28.0, CTCAE version 4.03.

Post marketing experience

Since their respective first approvals, the cumulative post-marketing exposure currently exceeds 140,000 patient treatment years for dabrafenib and trametinib [Tafinlar PSUR 30 May 2024 to 29 May 2025] and [Mekinist PSUR 30 May 2024 to 29 May 2025].

Based on available data for post-marketing usage of dabrafenib plus trametinib up to 29 May 2025, the toxicities are predictable and generally manageable with standard medical treatments.

3.5. Discussion on clinical safety

The safety evaluation in this application, i.e. the extension of the indication for the treatment of patients with BRAF V600E mutation positive differentiated thyroid cancer (DTC), is based primarily on the safety data collected for the primary analysis of study J12301. The safety data of study J12301 (N=101) is compared with the AE data of established Combination Therapy Safety Pool, derived from 4 completed studies (COMBI-d, COMBI-v, E2201 and COMBI-AD) (N=1087).

Exposure

The median duration of exposure for dabrafenib was 63.1 months and for trametinib 56.3 month for patients in the study J12301 and for both dabrafenib and trametinib 47.8 months for patients in the safety pool. More than half of the patients in the D+T arm (55.4%) had received combination therapy for at least 56 weeks and around 20% received at least 112 weeks of treatment. In the placebo arm the median duration of exposure was 23.9 weeks (range: 0.7 – 129.0) and 25% of patients had received treatment for at least 56 weeks. The lower exposure in the placebo arm aligns with the fact that a significant portion of patients (57.7%) who were assigned to this arm switched to receive open-label D+T treatment following BIRC-confirmed disease progression.

Dosing for dabrafenib capsules was 50 mg BID. For trametinib tablets dosing was 2 mg QD, which is the same posology as approved for melanoma and NSCLC. In study J12301, a relatively high number of protocol deviations related to treatment administration were reported (34 patients in the D+T arm and 19 patients in the placebo arm). Among these deviations, 22 patients (12 D+T patients, 8 placebo patients and another 2 placebo patients who had crossed over to D+T following PD) were reported taking more than dabrafenib/placebo 150 mg bid and/or trametinib/placebo 2 mg OD on at least one occasion. Most of these cases (18/22, 10 D+T patients and 8 placebo patients), concerned only single incorrect intake of an additional dabrafenib/placebo 75 mg capsule and/or an additional 2 mg trametinib/placebo tablet recorded. In 4 out of the 153 patients (2/101 on D+T, 2/52 on placebo), more frequent dosing deviations were reported. These dosing errors seem not to have impacted the safety risk of D+T treatment for these patients.

Adverse events

In study J12301, the majority of patients (98.0% in the D+T arm and 90.4% in the placebo arm) experienced AEs during the study. The proportion of patients with grade ≥ 3 AEs, SAEs, AEs leading to discontinuation, AEs leading to dose adjustment or interruption, and AEs requiring additional therapy was higher in the D+T arm compared with the placebo arm (respectively 54.5 vs 26.9%, 42.6% vs 25.0%, 7.9% vs 5.8%, 75.2% vs 32.7% and 93.1% vs 78.8%).

AEs by SOC (all grades) with a higher frequency in the D+T arm compared with the placebo arm (with ≥ 10% difference) were; blood and lymphatic system disorders (55.4% vs 11.5%; Grade ≥3 7.9% vs 0%) , general disorders and administration site conditions (67.3% vs 34.6%; Grade ≥3

6.9% vs 1.9%), infections and infestations (66.3% vs 36.5%; Grade ≥3 17.8% vs 5.8%), eye disorders (38.6% vs 21.2%; Grade ≥3 3.0% vs 0%), gastrointestinal disorders (53.5% vs 42.3%; Grade ≥3 4.0% vs 1.9%), investigations (71.3% vs 57.7%; Grade ≥3 15.8% vs 5.8%), metabolism and nutrition disorders (62.4% vs 38.5%; Grade ≥3 14.9% vs 1.9%), renal and urinary disorders (32.7% vs 17.3%; Grade ≥3 1.0% vs 3.8%), respiratory, thoracic and mediastinal disorders (45.5% vs 34.6%; Grade ≥3 7.9% vs 9.6%), and skin and subcutaneous tissue disorders (47.5% vs 17.3%; Grade ≥3 4.0% vs 0%),

The most commonly reported AEs by preferred terms (all grades) in the D+T arm were; pyrexia (47.5%), anemia (44.6%), urinary tract infection (31.7%), hyperglycemia (25.7%), neutrophil count decreased (25.7%), rash (25.7%), and white blood cell count decreased (25.7%).

In the placebo arm, the most commonly reported AEs were; hypocalcemia (17.3%), constipation (17.3%), weight decreased (13.5%), cough (13.5%), headache (13.5%), arthralgia (11.5%), dyspnea (11.5%), and hemoptysis (11.5%).

AEs (all grades) with a higher frequency in the D+T arm compared with the placebo arm (with ≥ 10% difference) were: pyrexia (47.5% vs 9.6%), anemia (44.6% vs 9.6%), urinary tract infection (31.7% vs 7.7%), hyperglycemia (25.7% vs 5.8%), neutrophil count decreased (25.7% vs 3.8%), rash (25.7% vs 1.0%), hypoalbuminemia (24.8% vs 5.8%), white blood cell count decreased (25.7% vs 9.6%), chills (22.8% vs 1.9%), lipase increased (22.8% vs 3.8%), aspartate aminotransferase increased (21.8% vs 5.8%), upper respiratory tract infection (18.8% vs 3.8%), decreased appetite (16.8% vs 5.8%), pneumonia (16.8% vs 3.8%), blood creatine phosphokinase increased (15.8% vs 1.9%), dizziness (13.9% vs 3.8%) and diarrhea (14.9% vs 3.8%), and hypoproteinaemia (10.9% vs 0%).

The incidence of grade ≥ 3 AEs was higher in the D+T arm (54.5%) than the placebo arm (26.9%). Among the grade ≥ 3 AEs in the D+T arm, the incidence of lipase increased (6.9% vs 0%), and pneumonia (7.9% vs 1.9%) were ≥ 5% higher than in the placebo arm. None of the other grade ≥ 3 AEs were reported in more than 5% of patients.

In comparison to the safety pool, AEs (by preferred term (PT)) with at least a 10% higher frequency in study J12301, include: anaemia (44.6% vs 8.0%; grade ≥ 3 4.0% vs 2.1%), urinary tract infection (31.7% vs 9.4%; grade ≥ 3 1.0% vs 1.0%), hyperglycaemia (25.7% vs 4.4%; grade ≥ 3 4.0% vs 2.0%), neutrophil count decreased (25.7% vs 3.3%; grade ≥ 3 4.0% vs 0.8%), white blood cell count decrease (25.7% vs 2.7%; grade ≥ 3 4.0% vs 0.6%), hypoalbuminaemia (24.8%, 2.1%; grade ≥ 3 1.0% vs 0.2%), lipase increased (22.8% vs 1.3%; grade ≥ 3 6.9% vs 0.7%), weight decreased (21.8% vs 5.7%; grade ≥ 3 0% vs 0.2%), hypocalcaemia (18.8% vs 0.9%; grade ≥ 3 4.0% vs 0%), upper respiratory tract infection (18.8% vs 5.6%; grade ≥ 3 4.0% vs 0.1%), pneumonia (16.8% vs 3.3%; grade ≥ 3 7.9% vs 0.7%), blood creatine phosphokinase increased (15.8% vs 3.4%; grade ≥ 3 2.0% vs 1.3%), lymphocyte count decreased (14.9% vs 2.2%; grade ≥ 3 3.0% vs 1.5%), hypercholesterolaemia (12.9% vs 0.6%; grade ≥ 3 0% vs 0%), proteinuria (12.9% vs 0.3%; grade ≥ 3 0% vs 0%) and hypoproteinaemia (10.9% vs 0.1%; grade ≥ 3 0% vs 0%).

These events were generally related to laboratory abnormalities, and the difference was mainly driven by low-grade events. Except for pneumonia, the incidence of grade ≥ 3 AEs was comparatively low (< 5%) in both the D+T arm of study J12301 and safety pool. Nevertheless the high incidences of haematological abnormalities including anaemia and neutropenia, and the high incidences of infections including urinary tract infections, upper respiratory tract infections and pneumonia, were noted. This difference could be largely explained by differences in underlying disease and baseline characteristics of the patients. Differences seem not to result in high

percentage of dose discontinuation for patients in the study J12301 arm than what was reported for the safety pool.

Adverse events of special interest (AESIs)

AESIs included pyrexia (48.5% vs 9.6% placebo), skin toxicity (46.5% vs 19.2% placebo), neutropenia (35.6% vs 9.6% placebo), hyperglycemia (34.7% vs 5.8% placebo), bleeding events (32.7%%, vs 30.8% placebo), hepatic disorders (25.7%% vs 19.2%% placebo), pancreatitis (25.7% vs 5.8% placebo), ocular events (13.9% vs 5.8% placebo) , cardiac related events (11.9% vs 7.7% placebo), hypertension (7.9% vs 5.8% placebo), hypersensitivity (5.9% vs 1.9% placebo), new primary or secondary malignancy (2.0% vs 1.9% placebo), pneumonitis and interstitial lunch disease (2.0% vs 0% placebo), pre-renal and intrinsic renal failure (2.0% vs 0% placebo) and venous thromboembolism (2.0 vs 0% placebo).

In study J12301, AESIs in both treatment arms were primarily grade 1 or 2 (<5% Grade ≥ 3). Grade ≥ 3 events that occurred in > 5% of patients in the D+T arm were; neutropenia (7.9% vs 0% placebo) and pancreatitis (7.9%, vs 1.9% placebo). In the placebo arm, the incidence of grade ≥ 3 events under each safety topic was < 2%, except for bleeding events (3.8% vs 4.0% in D+T arm).

In comparison to the pooled safety data, the incidence of AESIs as reported for study J12301 was higher for 'Bleeding events AESI', 'Neutropenia AESI', 'Hyperglycaemia AESI', and 'Pancreatitis AESI'. The difference was mostly caused by differences in low grade events and for hyperglycaemia and pancreatitis by laboratory abnormalities. Differences in reported AEs could be explained by differences in reporting methods between studies.

Serious adverse events including deaths

For study J12301, SAEs were reported in 42.6% of the patients in the D+T arm and in 25.0% of the patients in the placebo arm. In the safety pool the incidence of SAEs for D+T treatment was 44.9%.

The most frequently reported SAEs were; pneumonia (7.9%), pyrexia (4%), dyspnoea (3%), ejection fraction decreased (3.0%), and pneumonia bacterial (3%). In the placebo arm, SAEs occurred infrequently. Most of these SAEs were previously reported for D+T combination therapy, but the incidence of pneumonia, seems to be higher than was seen in other studies. This can be explained by the relative high prevalence of lung metastases (88.2%) and pleural cavity metastasis (9.8%) at baseline for patients included in study J12301.

In study J12301 30.7% of the patients had a SAE Grade ≥3, in comparison to 21.2% of the patients in the placebo arm, 25% of the patients in the D+T arm a SAE led to hospitalization. In the D+T arm, the only PT with an incidence of > 5% was pneumonia (7.9%).

As of the data cut-off date for the primary analysis of study J12301, 27 patients (26.7%) in the D+T arm and 19 patients (36.5%) in the placebo arm died, the majority of deaths were due to study indication (death were considered directly related to thyroid cancer) (18.8% in the D+T arm and 23.1% in the placebo arm). Among the events of deaths, 17 in the D+T arm and 3 in the placebo arm were on-treatment deaths, most of which were due to study indication (10 in the D+T arm and 2 in the placebo arm).

SAEs with fatal outcome were reported in 8 patients (7.9%) in the D+T arm and 2 patients (3.8%) in the placebo arm. For patients whose primary reason for death was study indication, fatal SAEs were reported in 2 patients in the D+T arm and 1 patient in the placebo arm. Fatal SAEs that were reported included; pneumonia (2 patients), acute myocardial infarction, bradycardia, squamous cell

carcinoma and cerebrovascular accident (1 patient each) in the D+T arm and multiple organ dysfunction syndrome in the placebo arm (1 patient). Only the death due to cerebrovascular accident was considered as treatment-related. However, looking to the details of this patient, the cause of death was reported as unknown. Therefore, it is unknown whether this cerebrovascular accident could be a bleeding event, which is a known AE of D+T combination treatment. Further, potential confounding factors were present; history of epilepsy, hypertension, and co-medication used by the patient.

Although only one SAE with fatal outcome was considered related to D+T treatment, the incidence of fatal SAEs in study J12301 was notable higher than in the safety pool (7.9% vs 1.9%), This relative high incidence of fatal SAEs can be explained as patients with radioiodine-refractory DTC after prior VEGFR-targeted therapy have a general poor prognosis, which impacts the risk on a fatal SAE.

Adverse drug reactions

An updated ADR table was provided by the MAH and is included in the SmPC. Most of the changes are switch in frequencies (urinary tract infection, neutropenia, anaemia, dermatitis acneiform, bradycardia, gastrointestinal preformation, dermatitis exfoliative generalized, rhabdomyolysis, renal failure). Cardiac failure, and left ventricular dysfunction and interstitial lung disease, were already ADRs for Mekinist monotherapy and were mentioned also for the combination therapy in section 4.4 of the SmPC. Acute kidney injury was already included as ADR for Tafinlar monotherapy.

Safety in special populations

In study J12301, safety analyses were performed for the China subgroup. In CMS (Chinese mainland subgroup: n=53 for the D+T group; n=23 for the placebo group), the incidence of SAEs (all grades) was similar to those observed in the overall population with 41.5% in the D+T arm and 26.1% in the placebo arm. The incidence of treatment-related SAEs (17.0% in the D+T arm and 8.7% in the placebo arm) and SAEs with fatal outcome (3.8% in the D+T arm and 4.3% in the placebo arm) in CMS were consistent with those observed in the overall population.

Subgroup analysis per age groups show that the proportion of patients treated with D+T, experiencing AEs was similar in those aged <65 years and those aged ≥65 years (98.0% vs 97.6%, respectively). Patients ≥65 years were more likely to experience SAEs (38.0% vs 48.8%, respectively) and AEs leading to permanent discontinuation of medicinal product (4.0% vs 12.2%, respectively) than those <65 years.

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

In study J12301, AEs leading to treatment discontinuation were reported in 7.9% of patients in the D+T arm and 5.8% of patients in the placebo arm; few of these events were grade ≥ 3 (2.0% in the D+T arm and 3.8% in the placebo arm). The most common AEs in the D+T arm leading to discontinuation were ejection fraction decreased and retinal vein occlusion (each two patients). Further ascites, dysphonia, dyspnoea, left ventricular dysfunction, pyrexia and vitreous haemorrhage led to treatment discontinuation in the D+T arm for one patient each. The percentage of treatment discontinuation for patients in the D+T arm was lower than what was reported in the safety pool (7.9% vs 21.9%, respectively).

AEs leading to dose adjustment and/or interruption were reported more frequently in the D+T arm than in the placebo arm (percentage of patients with at least one event respectively 75.2% vs 32.7%). The incidence for the D+T arm were more or less in line with what was reported for the

safety pool (AEs leading to dose interruption 72.3% vs 64.3%; AEs leading to dose reduction 18.8% vs 37.2%, for respectively study J12301 and the safety pool).

3.6. Conclusions on clinical safety

The safety profile of D+T treatment as seen in the current pivotal study for patients with BRAF V600E mutation positive differentiated thyroid cancer (DTC) was in line with the already known profile of this combination therapy.

3.6.1. 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.

3.7. Risk management plan

The MAH submitted an updated RMP version for dabrafenib and trametinib (versions 15.0 and 23.0, respectively) with this application.

The PRAC considered that the risk management plan version (versions 15.0 and 23.0, respectively) is acceptable.

Safety concerns

Trametinib

Table 33. Summary of safety concerns

Important identified risks for trametinib	• Ocular events (e.g., retinal vein occlusion, retinal pigment epithelial detachment)
Important potential risks for trametinib	• Developmental toxicity • Long-term safety in patients < 18 years old (including potential adverse effects on skeletal maturation and sexual maturation)
Missing information for trametinib	• None

Dabrafenib

Table 34. Summary of safety concerns

Important identified risks for dabrafenib (including combination therapy)	• Pre-renal and Intrinsic Renal failure • Uveitis
Important potential risks for dabrafenib (including combination therapy)	• Testicular Toxicity • Developmental toxicity • Long-term safety in patients <18 years of age (including potential adverse effects on skeletal maturation and sexual maturation)
Missing Information for dabrafenib	• None

Pharmacovigilance plan

No new additional pharmacovigilance activities have been proposed which is found acceptable by the PRAC.

Risk minimisation measures

No new risk minimisation measures have been proposed which is found acceptable by the PRAC.

3.8. Update of the Product information

As a result of this new indication, sections 4.1, 4.2, 4.4, 4.8 and 5.1 of the Tafinlar SmPC and sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the Mekinist SmPC are being updated. The Package Leaflet (PL) for both medicinal products is updated accordingly.

3.8.1. User consultation

A justification for not performing a full user consultation with target patient groups on the package leaflet for both medicinal products has been submitted by the MAH and has been found acceptable for the following reasons: No significant changes are made to the PLs for this type II variation to add the new indication "Differentiated Thyroid Cancer". The information proposed in the PLs included in this variation maintains the currently approved layout and format and is not considered to require further consultation with target patient groups.

4. Benefit-Risk Balance

4.1. Therapeutic Context

4.1.1. Disease or condition

The claimed therapeutic indication for dabrafenib in combination with trametinib is for the treatment of adult patients with locally advanced or metastatic differentiated thyroid cancer with a BRAF V600E mutation, refractory to or not eligible for radioactive iodine (RAI) who have progressed during or after prior systemic therapy.

4.1.2. Available therapies and unmet medical need

Systemic therapy for patients with RAI-refractory DTC includes multitarget tyrosine kinase inhibitors (mTKIs) targeting particularly the vascular endothelial growth factor receptor (VEGFR) family, thereby inhibiting tumour angiogenesis and causing hypoxia in malignant tissue.

The mTKIs sorafenib and lenvatinib are targeted systemic therapies approved in the EU for first line treatment of advanced RAI-refractory DTC. Sorafenib was approved based on a median PFS-benefit of 5 months compared to placebo (Nexavar SmPC), and lenvatinib was approved based on a benefit in median PFS over placebo of 14.7 months (Lenvima SmPC). For both therapies, an OS benefit has not been established.

Cabozantinib is available as second-line therapy for patients with locally advanced or metastatic RAI-refractory DTC. Approval was based on a PFS benefit compared to placebo (median PFS 1.9 months vs not reached; HR 0.22 (0.13-0.36)), with OS data still immature at time of approval. Response rate for cabozantinib in this setting was about 10%.

Toxicity of mTKIs associated with VEGF pathway inhibition is common, including cardiovascular and renal events. In addition, the majority of DTC patients will acquire resistance to this class of therapy and develop progressive disease.

Treatment options are limited for patients developing resistance to mTKI therapy. For patients diagnosed with RET fusion-positive thyroid cancer, the RET inhibitor selpercatinib is approved in the EU (selpercatinib approval date: 29 April 2024), and for patients diagnosed with tumours expressing neutrotrophic tyrosine receptor kinase (NTRK) gene fusions, larotrectinib and entrectinib are possible options (larotrectinib approval date: 19 September 2019; entrectinib approval date: 31 July 2020). However, these drugs target rare and distinct molecular subtypes of DTC, and these gene fusions typically do not co-occur with the more common BRAF V600E mutation. No selective targeted therapies directed against the BRAF V600E driver mutation are currently approved in the EU.

4.1.3. Main clinical studies

This application is based on the results of single pivotal study J12301, see Table 4.

Study J12301 is a global, multicentre, randomized, double-blind, placebo-controlled phase III study to evaluate the efficacy and safety of D+T in adult patients with locally advanced or metastatic BRAF V600E mutation-positive DTC who are RAI-refractory and have progressed following prior VEGFR-targeted therapy.

A total of 153 eligible patients were randomized in a 2:1 ratio to either dabrafenib capsules (150 mg BID) plus trametinib tablets (2 mg QD) or matching placebo.

The primary endpoint was BIRC-assessed PFS, according to RECIST 1.1.

Key secondary endpoints, part of the hierarchical testing strategy, were ORR and OS.

Enrolment was completed on 09 May 2024. The prespecified primary analysis including safety and efficacy data was to be conducted after approximately 95 PFS events, as per the BIRC assessment, and all randomized patients had completed at least 16 weeks of follow-up. Data cut-off for the primary analysis of PFS and ORR is 22 January 2025. At this DCO, an interim-analysis for OS was performed.

The study is ongoing and the last patient last visit is set to occur by May 2027.

4.2. Favourable effects

At DCO, median PFS by BIRC assessment was 12.8 months in the D+T arm and 3.7 months in the placebo arm, an absolute difference of 9.1 months. The stratified HR was 0.38 (95% CI: 0.25, 0.57; $p < 0.001$).

The ORR for the D+T arm was significantly higher at 57.4% compared to the placebo arm at 3.8%. The stratified difference in ORR between the treatment arms was 53.36% (95% CI: 42.25, 64.47; p-value < 0.001).

As of the DCO, 27 patients (26.7%) in the D+T arm and 19 patients (36.5%) in the placebo group had died. At this interim-analysis, median OS was not estimable for the D+T arm and 25.9 months for the placebo arm. The stratified HR for OS between the arms was 0.658 (95% CI: 0.362, 1.194; p-value = 0.083). At the interim-analysis for OS, data maturity was only 30%. 30 patients from the placebo-arm had crossed over to open-label dabrafenib+trametinib treatment (57.7%). Although immature, preliminary OS results do not show a detrimental effect. The results of the final OS analysis will be provided post-approval (**REC**).

4.3. Uncertainties and limitations about favourable effects

Not applicable.

4.4. Unfavourable effects

In study J12301, the majority of patients (98.0% in the D+T arm and 90.4% in the placebo arm) experienced AEs during the study. The proportion of patients with grade ≥ 3 AEs, SAEs, AEs leading to discontinuation, AEs leading to dose adjustment or interruption, and AEs requiring additional therapy was higher in the D+T arm compared with the placebo arm.

The most commonly reported AEs (>20% all grades) in the D+T arm were; pyrexia, anaemia, urinary tract infection, hyperglycaemia, neutrophil count decreased, rash, and white blood cell count decreased. Most events were low grade.

SAEs frequently occurred in the D+T arm in 42.6% of the patients and in 25.0% of the patients in the placebo arm. In the safety pool the incidence of SAEs for D+T treatment was 44.9%.

The most frequently reported SAEs for patients in the D+T arm in study J12301, were pyrexia, dyspnea, ejection fraction decreased and pneumonitis. In the placebo arm, SAEs occurred infrequently. SAEs with fatal outcome were reported in 8 patients (7.9%) in the D+T arm and 2 patients in the placebo arm. For patients whose primary reason for death was study indication, fatal SAEs were reported in 2 patients in the D+T arm and 1 patient in the placebo arm. Fatal SAEs that were reported included pneumonitis (2 patients pneumonia), acute myocardial infraction, bradycardia, squamous cell carcinoma and cerebrovascular accident.

In study J12301, AEs leading to treatment discontinuation were reported in 7.9% of patients in the D+T arm and 5.8% of patients in the placebo arm; few of these events were grade ≥ 3. The most common AEs in the D+T arm leading to discontinuation were ejection fraction decreased and retinal vein occlusion (each two patients). Further ascites, dysphonia, dyspnoea, left ventricular dysfunction, pyrexia and vitreous haemorrhage led to treatment discontinuation in the D+T arm for one patient each. The percentage of treatment discontinuation for patients in the D+T arm was lower than what was reported in the safety pool.

In study J12301, safety analyses were performed for the subgroup of patients in Asia. The results were generally consistent with the overall population.

AEs leading to dose adjustment and/or interruption were reported more frequently in the D+T arm than in the placebo arm, however percentage of events in the D+T arm of study J12301 were comparable to the percentage of events in the safety pool.

4.5. Uncertainties and limitations about unfavourable effects

Although only one SAE with fatal outcome was considered related to D+T treatment, the incidence of fatal SAEs in study J12301 was higher than in the safety pool (7.9% vs 1.9%). This relatively high incidence of fatal SAEs can be explained as patients with radioiodine-refractory DTC after prior VEGFR-targeted therapy are generally more frail compared to target population of the already approved indications.

4.6. Effects Table

Table 35. Effects Table for dabrafenib in combination with trametinib for the treatment of adult patients with locally advanced or metastatic differentiated thyroid cancer with a BRAF V600E

mutation, refractory to or not eligible for radioactive iodine (RAI) who have progressed during or after prior systemic therapy (data cut-off: 22-Jan-2025)

Effect	Short description	Unit	Treatment Dabrafenib + trametinib	Control Placebo	Uncertainties / Strength of evidence	References
Favourable Effects ITT population n=153			n=101	n=52		
Primary endpoint **PFS**	Progression-free survival by BIRC per RECIST v1.1	Median (95% CI) in months	12.8 (10.2-21.2)	3.7 (2.3-7.5)	<u>Strengths:</u> - Derived from randomized, double blind phase 3 study <u>Uncertainties:</u> - OS data are immature - cross-over of 57.7% from placebo to D+T, hampering interpretation of OS-data	
			PFS HR= 0.38 95% CI 0.25-0.57 p-value <0.001			
Key secondary endpoint **ORR**	Objective response rate	% PR CR	57.4 51.5 5.9	3.8 1.9 1.9		
			ORR difference 53.4% 95% CI 42.3-64.5 p-value <0.001			
Key secondary endpoint **OS**	Overall survival	Median (95% CI) in months	NE (NE-NE)	25.9 (17.1-NE)		
			OS HR= 0.66 95% CI 0.36-1.19 p-value 0.083			
Unfavourable Effects						
SAEs		n(%)	43(42.6)	13(25.0)		

Effect	Short description	Unit	Treatment Dabrafenib + trametinib	Control Placebo	Uncertainties / Strength of evidence	References
Deaths	Fatal SAEs	n(%)	8(7.9)	2(3.8)		
AEs	Leading to dose adjustment/interruption	n(%)	76(75.2)	17(32.7)		
	Leading to permanent discontinuation	n(%)	8(7.9)	2(3.8)		
	AEs requiring additional therapy	n(%)	94(93.1)	41(78.8)		

Abbreviations: BIRC blinded independent review committee; CI confidence interval; CR complete response; HR hazard ratio; ITT intention to treat; NE not estimable; ORR objective response rate; OS overall survival; PFS progression free survival; PR partial response

4.7. Benefit-risk assessment and discussion

4.7.1. Importance of favourable and unfavourable effects

Treatment options are limited for DTC patients that develop resistance to mTKI therapy. Selpercatinib is approved for patients diagnosed with RET fusion-positive thyroid cancer, and larotrectinib and entrectinib are possible options for patients diagnosed with tumours expressing neutrotrophic tyrosine receptor kinase (NTRK) gene fusions. Cabozantinib is approved in the EU as a second-line therapy for patients with locally advanced or metastatic DTC, refractory or not eligible to RAI who have progressed during or after prior systemic therapy (median PFS 1.9 months vs not reached; HR 0.22 (0.13-0.36); Cabometyx SmPC), with OS data still immature at time of approval.

Despite the broadening therapeutic landscape for advanced DTC over the last decade, no selective targeted therapies directed against the BRAF V600E driver mutation are currently approved in the EU. Treatment with dabrafenib and trametinib has shown a clinically relevant prolongation of median PFS (12.8 vs 3.7; HR= 0.38; 95% CI 0.25-0.57) in patients with RAI-refractory BRAF V600E mutation-positive differentiated thyroid carcinoma with disease progression upon treatment with a mTKI. As this concerns a late-line patient population with often symptomatic disease, the high response rate and durable responses are also considered important. The OS data are not yet mature but do not show a sign of detrimental effect. The results of the final OS analysis will be provided post-approval (REC).

The safety profile of D+T treatment as seen in the current pivotal study for patients with BRAF V600E mutation positive differentiated thyroid cancer (DTC) was in line with the already known profile of this combination therapy.

4.7.2. Balance of benefits and risks

The benefits of a significantly prolonged median PFS outweigh the known safety profile of D+T combination therapy.

4.7.3. Additional considerations on the benefit-risk balance

Not applicable.

4.7.4. Conclusions

The worksharing variation to include treatment of differentiated thyroid cancer (DTC) with a BRAF V600E mutation, for Tafinlar and Mekinist is acceptable. Overall B/R of dabrafenib and trametinib is positive.

5. Recommendations

Outcome

Based on the review of the submitted data, the CHMP considers the following 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 Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB

Extension of indication to include treatment of differentiated thyroid cancer (DTC) for Tafinlar and Mekinist based on primary analysis from pivotal study CDRB436J12301. This is a randomized, double-blind, placebo-controlled phase 3 study to evaluate the efficacy and safety of dabrafenib plus trametinib in previously treated patients with locally advanced or metastatic, radio-active iodine refractory BRAF V600E mutation-positive differentiated thyroid cancer. As a consequence, sections 4.1, 4.2, 4.4, 4.8 and 5.1 of the Tafinlar SmPC and sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the Mekinist SmPC are updated. The Package Leaflet is updated in accordance. Version 15.0 and Version 23.0 of the RMPs for Tafinlar and Mekinist, respectively, have also been submitted.

The variation worksharing procedure procedure leads to amendments to the annexes I and IIIB and to the Risk Management Plan (RMP).

Amendments to the marketing authorisation

In view of the data submitted with the variation worksharing procedure amendments to Annexes I and IIIB and to the Risk Management Plan are recommended.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

- **Risk management plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

In addition, an updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.