RISK MANAGEMENT PLAN

Encorafenib

Active substance(s) (INN or common name):	Encorafenib
Pharmaco-therapeutic group (ATC Code):	Antineoplastic agent, protein kinase inhibitor ATC code: L01EC03
Name of Marketing Authorisation Holder or Applicant:	Pierre Fabre Médicament
Names of medicinal products to which this RMP refers:	Encorafenib
Product concerned (brand name):	BRAFTOVI

RMP version to be assessed as part of this application:

RMP Version number:	3.0
Data lock point for this RMP:	26 June 2023
Date of final sign off:	06 August 2024
Submission date:	11 October 2023
Procedure number:	EMEA/H/C/004580/WS2538/0034
Rationale for submitting an updated RMP:	Variation Type II – New indication

Summary of significant changes in this RMP:

Parts	**Modules**	**Changes**
Part I	Product Overview	Addition of information relevant to the new indication Removal of the product from the EU additional monitoring list following five years of authorisation (Procedure n°: EMEA/H/C/004580/R/0029) ATC code updated
Part II	SI, SIV	Addition of information relevant to the new indication
	SII	Update information related to drug interactions
	SIII	Updated taking into consideration the addition of the new indication population Update the cut off dates of studies for melanoma indication.
	SV	Update of the post-authorisation experience as of the DLP
	SVII	Updated taking into consideration: the population of the new indication and the updated cut off dates of studies for melanoma population. Addition of post-authorisation data
Part VI		Updated according to changes in other parts.
Part VII		Annex 7 and Annex 8 updated according to changes in other parts.

Other RMP versions under evaluation:

None

Details of the currently approved RMP:

Version number:	2.0
Approved with procedure:	EMEA/H/C/004580/WS1695/0008
Date of approval:	26 March 2020

EU QPPV name: Isabelle GEORGE

EU QPPV signature: The content of this RMP has been reviewed and approved by the marketing authorisation holder´s EU QPPV. The electronic signature is available on file.

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LIST OF ABBREVIATIONS

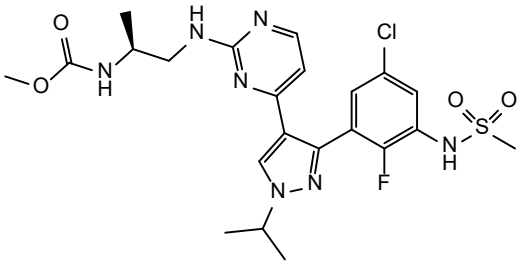
Abbreviation	Definition
ADME	Absorption, Distribution, Metabolism and Excretion
ADR	Adverse Drug Reaction
AE	Adverse Event
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
API	Active Pharmaceutical Ingredient
ASR	Age-Standardized incidence Rate
AST	Aspartate Aminotransferase
ATC	Anatomical Therapeutic Chemical
AUC	Area Under the Curve
AUC_{ss}	Area Under the Curve at Steady State
BCRP	Breast Cancer Resistance Protein
BCC	Basal Cell Carcinoma
BID	Twice Daily
BP	Broad Population
BRAF	B-Raf Proto-Oncogene, Serine/Threonine Kinase
CEA	Carcinoembryonic Antigen
CI	Confidence Interval
CK	Creatine Phosphokinase
C_{max}	Maximum Concentration
$C_{max,ss}$	Maximum Concentration at Steady State
$C_{min,ss}$	Trough Concentration at Steady State
CNS	Central Nervous System
Combo 450 RP	Combination (encorafenib 450 mg + binimetinib) Restricted Population
CrCL	Calculated Creatinine Clearance
CRC	Colorectal Cancer
CSR	Clinical Study Report
CT	Computed Tomography
CTCAE	Common Terminology Criteria for Adverse Events
cuSCC	Cutaneous Squamous Cell Carcinoma
CYP	Cytochrome P450
DDI	Drug-Drug Interaction
EAIR	Exposure-Adjusted Incidence Rate
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EEA	European Economic Area
eGFR	Estimated Glomerular Filtration Rate
EMA	European Medicines Agency
Enco 300 P	Encorafenib 300 mg Pooled population
EPAR	European Public Assessment Report
ERK	Extracellular Signal-Regulated Kinase
ESMO	European Society for Medical Oncology
EU	European Union
EUCAN	European Cancer Observatory
GMR	Geometric Mean Ratio

GGT	Gamma-Glutamyltransferase
hERG	Human Ether-A-Go-Go-Related Gene
HIV	Human Immunodeficiency Virus
HR	Heart Rate
IB	Investigator's Brochure
IC50	Half Maximal Inhibitory Concentration
ICH	International Council for Harmonization
INN	International Non-proprietary Name
INR	International Normalised Ratio
ISP	Integrated Safety population
ISS	Integrated Summary of Safety
KA	Keratoacanthoma
KRAS	V-Ki-Ras 2 Kirsten Rat Sarcoma Viral Oncogene Homolog
LDH	Lactate Dehydrogenase
LVEF	Left Ventricular Ejection Fraction
MAA	Marketing Authorisation Application
MAPK	Mitogen Activated Protein Kinase
mCRC	Metastatic Colorectal Cancer
MedDRA	Medical Dictionary for Regulatory Activities
MEK	Mitogen-Activated Protein Kinase Kinase
MUGA	Multigated Acquisition
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NM	Nodular Melanoma
NRAS	Neuroblastoma Ras Viral (V-Ras) Oncogene Homolog
NSCLC	Non-Small Cell Lung Cancer
OATP	Organic Anion Transporting Polypeptide
OCT	Organic Cation Transporter
OS	Overall Survival
PASS	Post-Authorisation Safety Studies
P-gp	P-Glycoprotein
PBRER	Periodic benefit-risk evaluation report
PIL	Patient Information Leaflet
PK	Pharmacokinetic(s)
PPES	Palmar-Plantar Erythrodysaesthesia Syndrome
PRAC	Pharmacovilance Risk assessement Committee
PS	Performance Status
PSUR	Periodic Safety Update Report
PT	Preferred Term
QD	Once Daily
QoL	Quality of life
QPPV	Qualified Person Responsible for Pharmacovigilance
QT	QT-Interval on ECG
QTc	Rate-Corrected QT Interval
QTcF	QT Interval Corrected for Heart Rate Using Fridericia's Formula
RAF	Rapidly Accelerated Fibrosarcoma
RAS	Rat Sarcoma
RMP	Risk Management Plan
RP	Restricted Population

RPED	Retinal Pigment Epithelial Detachment
RR	Relative Risk
RVO	Retinal Vein Occlusion
SAE	Serious Adverse Event
SCC	Squamous Cell Carcinoma
SmPC	Summary of Product Characteristics
SOC	System Organ Class
SSM	Superficially Spreading Melanoma
UGT	Uridine 5'-Diphospho-Glucuronosyltransferase
ULN	Upper Limit of Normal
WHO	World Health Organization
wt	Wild Type

PART I: Product overview

Table Part I.1: Product overview

Active substance(s) (INN or common name)	Encorafenib
Pharmaco-therapeutic group **(ATC Code)**	Antineoplastic agent, protein kinase inhibitor ATC code: L01EC03
Name of Marketing Authorisation Holder or Applicant	Pierre Fabre Médicament
Names of medicinal products to which this RMP refers	Encorafenib
Invented name(s) in the European Economic Area (EEA)	BRAFTOVI
Marketing authorisation procedure	Centralised
Brief description of the product:	<u>Chemical class</u> The active pharmaceutical ingredient (API) in the BRAFTOVI (LGX818) drug product is encorafenib. Chemical name: Methyl N-{(2S)-1-[(4-{3-[5-chloro-2-fluoro-3-(methanesulfonamido)phenyl]-1-(propan-2-yl)-1H-pyrazol-4-yl}pyrimidin-2-yl)amino]propan-2-yl}carbamate Appearance: White to almost white powder CAS registry number:1269440-17-6 Solubility: Slightly soluble in aqueous media at pH 1, very slightly soluble at pH 2, and insoluble at pH 3 and above. Molecular formula: C22H27ClFN7O4S Molecular mass: 540.0 (free base) Chemical structure: 
	<u>Summary of mode of action</u> Encorafenib (LGX818), is a novel oral small-molecule kinase inhibitor has potent and selective inhibitory activity against mutant BRAF kinase, a member of the RAF/MEK/ERK MAPK pathway that plays a prominent role in controlling several

	key cellular functions including growth, proliferation, and survival. Encorafenib suppresses the RAS/RAF/MEK/ERK pathway in tumour cells expressing BRAF V600 mutations, including melanoma, colorectal cancer (CRC) and non-small cell lung cancer (NSCLC) cell lines, but does not have antiproliferative activity in the majority of wild-type BRAF cell lines. As a BRAF inhibitor, this compound has the potential to benefit patients with advanced cancers harbouring a BRAF mutation by inhibiting the RAS/RAF/MEK/ERK pathway. The combination of encorafenib with the MEK inhibitor binimetinib allows concomitant inhibition of the two kinase pathways, MEK and RAF, resulting in improved inhibition of intracellular signalling and higher anti-tumour activity. Activation of EGFR has been identified as one of the mechanisms of resistance of BRAF-mutant CRC to RAF inhibitors. Therefore, in the setting of BRAF-mutant CRC, EGFR-mediated MAPK pathway activation presents with an additional therapeutic opportunity to combine MEK/RAF inhibitors with an EGFR inhibitor. Combinations of a BRAF inhibitor and agents targeting EGFR have shown to improve antitumour efficacy in non-clinical models. Combination of encorafenib and cetuximab has increased growth inhibition of the HT-29 (BRAF V600E and PIK3CAP449T double mutant) and SW1417 (BRAF V600E single mutant) tumour cells. The addition of cetuximab to the combination of encorafenib and binimetinib increased tumour growth inhibition and/or increased the number of tumour regressions (responses) and therefore resulted in the greatest tumour growth inhibition in all the non-clinical models of BRAF V600E CRC used.
	<u>Important information about its composition</u> Excipients Capsule Fill: Copovidone (E1208), poloxamer 188, cellulose microcrystalline (E460i), succinic acid (E363), Crospovidone (E1202), colloidal anhydrous silica (E468), magnesium stearate (vegetable origin) (E470b). Capsule Shell: gelatin (E441), titanium dioxide (E171), iron oxide red (E172), iron oxide yellow (E172), iron oxide black (E172), Monogramming ink (shellac (E904), iron oxide black (E172), propylene glycol (E1520) Excipients with known effect: None
Hyperlink to the Product Information:	Summary of Product Characteristics BRAFTOVI
Indication(s) in the EEA	**Current:** - Encorafenib is indicated for use in combination with binimetinib for the treatment of adult patients with

	unresectable or metastatic melanoma with BRAF V600 mutation. - Encorafenib is indicated for use in combination with cetuximab, for the treatment of adult patients with metastatic colorectal cancer (CRC) with a BRAF V600E mutation, who have received prior systemic therapy.
	Proposed: <u>Melanoma</u> Encorafenib in combination with binimetinib is indicated for the treatment of adult patients with unresectable or metastatic melanoma with a BRAF V600 mutation. <u>Colorectal cancer (CRC)</u> Encorafenib in combination with cetuximab is indicated for the treatment of adult patients with metastatic colorectal cancer with a BRAF V600E mutation, who have received prior systemic therapy. <u>Non-small cell lung cancer (NSCLC)</u> Encorafenib in combination with binimetinib is indicated for the treatment of adult patients with advanced non-small cell lung cancer with a BRAF V600E mutation. There is no proposed indication for encorafenib monotherapy.
Dosage in the EEA	**Current:** In unresectable or metastatic melanoma with a BRAF V600 mutation, the recommended dose of encorafenib is 450 mg taken orally, once daily (QD) when given in combination with binimetinib. Per current SmPC, administration of encorafenib at a dose of 450 mg once daily as a single agent is not recommended. If binimetinib is temporarily interrupted, encorafenib should be reduced at 300 mg once daily during the time of binimetinib dose interruption as encorafenib is not well-tolerated at the dose of 450 mg as a single agent. If binimetinib is permanently discontinued, encorafenib should be discontinued. In metastatic colorectal cancer, the recommended dose of encorafenib is 300 mg taken orally, once daily (QD) when used in combination with cetuximab. If encorafenib is permanently discontinued, cetuximab should be discontinued. If cetuximab is permanently discontinued, encorafenib should be discontinued.

	Treatment with encorafenib should continue until the patient no longer derives benefit or occurrence of unacceptable toxicity. If a dose of encorafenib is missed, the patient should only take the missed dose if it is more than 12 hours until the next scheduled dose. In case of vomiting after administration of encorafenib, the patient should not take an additional dose and should take the next scheduled dose. Encorafenib capsules are to be swallowed whole with water and may be taken with or without food. The concomitant administration of encorafenib with grapefruit juice should be avoided.
	Proposed: - In unresectable or metastatic melanoma with a BRAF V600 mutation: The recommended dose of encorafenib is 450 mg taken orally, once daily (QD) when used in combination with binimetinib. - In advanced non-small cell lung cancer (NSCLC) with a BRAF V600E mutation: The recommended dose of encorafenib is 450 mg taken orally, once daily (QD) when used in combination with binimetinib. As per the SmPC, administration of encorafenib at a dose of 450 mg once daily as a single agent is not recommended. If binimetinib is temporarily interrupted, encorafenib should be reduced at 300 mg once daily during the time of binimetinib dose interruption as encorafenib is not well-tolerated at the dose of 450 mg as a single agent. If binimetinib is permanently discontinued, encorafenib should be discontinued. - In metastatic colorectal cancer: The recommended dose of encorafenib is 300 mg taken orally, once daily (QD) when used in combination with cetuximab. If encorafenib is permanently discontinued, cetuximab should be discontinued. If cetuximab is permanently discontinued, encorafenib should be discontinued. Treatment with encorafenib should continue until the patient no longer derives benefit or occurrence of unacceptable toxicity. If a dose of encorafenib is missed, the patient should only take the missed dose if it is more than 12 hours until the next scheduled dose.

	In case of vomiting after administration of encorafenib, the patient should not take an additional dose and should take the next scheduled dose. Encorafenib capsules are to be swallowed whole with water and may be taken with or without food. The concomitant administration of encorafenib with grapefruit juice should be avoided.

Pharmaceutical form(s) and strengths	**Current:** Encorafenib drug product is provided as an immediate release hard gelatin capsule for oral administration. Capsules are provided in two dosage strengths of 50 mg and 75 mg.
	Proposed: No changes
Is/will the product be subject to additional monitoring in the EU?	No

Part II: Safety specification

At the time of this RMP, no indication is intended for the use of encorafenib as monotherapy.

As per the initial MAA, BRAFTOVI (encorafenib) is indicated in combination with MEKTOVI (binimetinib) for the treatment of adult patients with unresectable or metastatic melanoma with a BRAF V600 mutation.

The safety of encorafenib (450 mg orally once daily) in combination with binimetinib (45 mg orally twice daily) was evaluated in 274 patients (Combo 450 RP population; also referred to as 'Melanoma population' in this RMP) with BRAF V600 mutation-positive unresectable or metastatic melanoma, based on two phase II studies (CMEK162X2110 and CLG818X2109) and the pivotal phase III study (CMEK162B2301).

Per a variation to the initial MAA, encorafenib is indicated, in combination with cetuximab, for the treatment of adult patients with metastatic CRC with a BRAF V600E mutation, who have received prior systemic therapy.

The safety of encorafenib (300 mg orally once daily) in combination with cetuximab (at the recommended dose as per its product label) was evaluated in 216 patients with BRAF V600E mutant metastatic CRC, hereafter referred to as the doublet population represented by the doublet arm of the ARRAY-818-302 pivotal study.

The benefit/risk balance favoured the dual combination of encorafenib with cetuximab (doublet arm) over the triple combination of encorafenib with binimetinib and cetuximab for the treatment of patients BRAF-mutant mCRC.

In the newly proposed therapeutic use, encorafenib is indicated, in combination with binimetinib, for the treatment of adult patients with advanced NSCLC with a BRAF V600E mutation. In this indication, the safety of encorafenib (450 mg orally once daily) in combination with binimetinib (45 mg orally twice daily) was evaluated in 98 patients with BRAF V600E mutant advanced NSCLC enrolled and treated in the PHAROS study (C4221008, ARRAY 818-202). Encorafenib 450 mg orally QD in combination with binimetinib 45 mg orally BID is the same dosage and administration schedule as the one recommended in the melanoma indication.

The analysis of safety data pertaining to encorafenib and binimetinib combination therapy in the proposed indication (advanced BRAF V600E mutant NSCLC) did not identify any new safety concern of encorafenib as compared to the known safety concerns already included in the encorafenib RMP.

Part II: Module SI - Epidemiology of the indication(s) and target population

- **Indication: treatment of adult patients with BRAF V600 mutation unresectable or metastatic melanoma**

Incidence:

EUCAN data from 2012 indicate an age-standardised incidence rate of malignant melanoma of the skin in the EU of 13.0 per 100,000 of population per year, with Switzerland (25.8/100,000), the Scandinavian nations of Norway (25.3/100,000), the Netherlands (24.4/100,000), Denmark (24.1/100,000) and Sweden (23.9/100,000) reporting the highest rates amongst all European nations (European Cancer Information System, 2019; Steglich, 2018). Given that there are currently 508 million individuals living in the EU (European Commission), and assuming that 20% of diagnosed melanomas progress to a metastatic stage, and that approximately 50% of these cases are positive for BRAF V600E mutations (Ascierto, 2012), approximately 6,552 individuals per year will be diagnosed with BRAF V600E-mutated stage IV metastatic melanoma in Europe.

Prevalence:

The frequency of BRAF-positive mutations in patients with metastatic melanoma has been reported in several recent real-world studies conducted in the EU, ranging from as low as 29% (Lyons, 2016) to as high as approximately 62% (Rutkowski, 2014), with the variability likely due to varying sample sizes. One large study of 2,532 patients with unresectable stage IIIB–IV melanoma from France, Germany, Italy, Spain and the United Kingdom (UK) identified 50% of patients with BRAF-mutated disease (Burudpakdee, 2016). Though the incidence of melanoma is higher in countries such as Switzerland and the Scandinavian nations, real-world studies conducted in these countries have reported frequencies of BRAF-mutated disease amongst cutaneous melanoma patients of approximately 51–54% (Edlundh Rose 2006; Frauchiger, 2016), similar to rates reported for other European nations. Among the subtypes of BRAF V600-mutation positive melanomas, the V600E mutation predominates, with recent real-world studies reporting frequencies of approximately 65–92% (Rutkowski, 2014; Heinzerling, 2013, Nardin, 2015, Schlaak, 2013; Colombino, 2013), suggesting that these mutations represent upwards of 27% (Nardin, 2015) of all metastatic cutaneous melanoma cases in Europe. Similar to BRAF mutations overall, these studies suggest that countries with high melanoma incidence do not differ in terms of V600E mutation rates (Edlundh-Rose, 2006).

Demographics of the target population with unresectable, BRAF-mutated metastatic melanoma and risk factors for the disease:

Interestingly, the sex distribution of the incidence of malignant melanoma has been known to vary by geography, with some higher-latitude populations such as Scotland and Canada historically reporting higher incidence in women than men, in contrast to other mid- or low-latitude populations, such as Australia and the US, reporting higher incidence in men (Whiteman, 2011). EUCAN 2012 data report incidence rates of 11.4/100,000 and 11.0/100,000 in men and women, respectively, suggesting that in European populations, malignant melanoma occurs roughly equally amongst the sexes *(*European Cancer Information System, 2019). Indeed, this trend appears to be supported by real-world studies in Europe with regard to the distribution of BRAF-mutated disease as well, with one Polish study finding an approximately equal distribution of BRAF-mutated stage IIIC or IV metastatic melanoma between men (51%, 78/154) and women (49%, 76/154) (Rutkowski, 2014). Conversely, a small French study reported up to 66% (23/35) of male patients with stage III BRAF-mutated disease, though the sex distribution of patients with wildtype BRAF was similar, suggesting that the frequency of BRAF mutation status is unlikely to differ by sex from the overall frequency of melanoma (Picard, 2014). In addition, these patterns do not appear to differ in European countries with high melanoma incidence (Edlundh-Rose, 2006; Frauchiger, 2016).

The age at diagnosis of BRAF-mutated melanoma appears to differ from those patients with wildtype BRAF melanoma, with BRAF mutation-positive patients often significantly younger at diagnosis. European real-world studies have reported median ages at diagnosis of approximately 50 to 59 years (Frauchiger, 2016; Nardin, 2015; Moreau, 2012), in contrast to patients with wildtype BRAF disease, whose median age at diagnosis is reported from 62 to 66 years (Frauchiger, 2016; Moreau, 2012). Amongst patients with V600-mutated disease, reports have shown that approximately 31% of patients are diagnosed at <50 years of age, while only 15% of wildtype BRAF disease is diagnosed in this age range (Meckbach, 2014). One German study of 141 patients with metastatic melanoma specifically examined associations of patient characteristics with BRAF mutation status and found that younger age is strongly correlated with the risk of developing BRAF V600 mutated melanoma (Schlaak, 2013), supporting previous findings reported in US populations (Thomas, 2007).

Previously published reports conducted in the US have shown that ethnic origin may affect the incidence of cutaneous melanoma, as the incidence of the disease in Caucasians is much higher than observed in people classified as Hispanic, African-American, American Indian, or Asian (Cormier, 2006). Meta-analyses have also shown that patients with red or blond hair, blue eyes, fair skin, and those who easily develop sunburns are at higher risk for melanoma than subjects with darker hair and eyes, and skin that tans easily (Gandini, 2005). To our knowledge, there are no reports in European populations reporting associations of ethnicity or race with BRAF V600-mutated melanoma, so specific demographic characteristics associated with this mutation are currently unknown.

The existing literature has suggested a complex relationship between UV exposure and the risk of BRAF V600 mutation-positive melanoma (Thomas, 2007). An Australian study of 251 patients reported several factors that appeared to be associated with BRAF V600E mutations in melanoma, including fewer freckles (ephelides), high self-reported childhood levels of sun exposure, and more frequent pigment production in the tumour (Liu, 2007). Australian studies have also suggested that BRAF V600E-positive melanoma more frequently appeared on the trunk and distal extremities than on the head and neck, in contrast to wildtype BRAF melanoma, which appeared more frequently on the head and neck than on the trunk or extremities (Liu, 2007). Some of these findings have been supported in the Swiss study where BRAF-mutated melanoma appeared most frequently on the trunk (43%), and only 16% of patients had tumours on the head and neck area, in comparison with wildtype BRAF which appeared with similar frequency on the trunk (22%) and head/neck (17%) (Frauchiger, 2016). A Swedish study reported a similar finding, wherein primary tumours on the trunk were more likely to harbour BRAF-mutations (58%) than wildtype tumours (18%) (Edlundh-Rose, 2006). Two other real-world European reports have found similar rates of primary tumour site on the trunk and head/neck area (Rutkowski, 2014; Moreau, 2012), or indeed the opposite effect, wherein a higher frequency of BRAF wildtype primary tumours were reported on the trunk (Picard, 2014). The German Schlaak *et al.* study (Schlaak, 2013), specifically analysed clinical parameters associated with the development of BRAF V600-mutated melanoma, and found that mutated melanomas preferentially developed on areas of intermittent sun exposure such as the trunk, and that patients with more melanocytic naevi were also more likely to develop BRAF-mutated disease (Schlaak, 2013), a finding concordant with previous findings in US populations (Thomas, 2007). Interestingly, Schlaak *et al.* did not find associations of total sun burden score, use of tanning beds, sunburn or skin type with BRAF mutation status (Schlaak, 2013). Nevertheless, theories of divergent pathogenesis and clinical characteristics of BRAF V600E-positive and wildtype BRAF melanomas have been suggested in the literature (Bauer, 2011).

The main existing treatment options:

The BRAF inhibitors vemurafenib and dabrafenib and MEK inhibitors trametinib and cobimetinib are currently approved for the treatment of BRAF-mutated melanoma by the EMA. Consensus guidelines issued by European bodies' state that treatment with a combination of BRAF and MEK inhibitors is the current standard of care in patients with BRAF V600E mutation-positive metastatic melanoma, and recommends these therapies as first or second-line treatment (Garbe, 2016). real-world treatment patterns were examined from Q2 2014 to Q1 2015 of patients with unresectable stage IV metastatic melanoma from France, Germany, Italy, Spain and the UK, and found vemurafenib to be the most common first-line therapy in patients with BRAF-mutated tumours (France: 61.4%, Germany 56.3%, Italy: 75.0%, Spain: 52.8%, UK: 84.6%) (Burudpakdee, 2016). As second-line therapy, the study found that ipilimumab was the most frequently used in these countries, regardless of BRAF mutation status (Burudpakdee, 2016).

Cutaneous side effects are of concern in the treatment of BRAF-mutated metastatic melanoma. Treatment with combination BRAF and MEK inhibitors is known to have a slightly different profile of cutaneous side effects than BRAF inhibitors in monotherapy. A retrospective real-world study conducted in Australian patients treated with combination dabrafenib and trametinib (CombiDT) appeared to have a higher frequency of folliculitis (40%), but a lower frequency of cutaneous squamous cell carcinoma (26.1% with dabrafenib monotherapy versus 0% in CombiDT) and other squamo-proliferative disorders (Carlos, 2015). Smaller real-world studies conducted in Europe have reported varying rates of squamous cell carcinoma (SCC) and squamo-proliferative disorders in BRAF monotherapy, from approximately 5% (2/40) for basal cell carcinoma with dabrafenib monotherapy (Cocorocchio, 2016) and 8% (1/13) for SCC with vemurafenib monotherapy (Goppner, 2014), to as little as 0% (0/376) SCC for vemurafenib + cobimetinib (Meyer 2016). Other severe skin toxicities have also been reported in European real-world studies, with grade 3/4 rash ranging from 0% (0/48) with CombiDT in Italy (Cavalieri, 2016) to 18% (12/65) with vemurafenib in one Slovenian study (Ocvirk, 2016).

Natural history of BRAF mutated metastatic melanoma in the population, including mortality and morbidity:

EUCAN data from 2012 indicate overall mortality rates from cutaneous melanoma of 2.3/100,000 in Europe, with the highest rates seen in Norway (5.1/100,000), Slovenia (4.4/100,000), Sweden (4.0/100,000), the Netherlands (3.9/100,000) and Iceland (3.6/100.000) (European Cancer Information System, 2019). A German study reported a one-year overall survival (OS) rate of 44% (95% CI: 33.1, 53.9) amongst BRAF V600 mutation-positive patients treated with non-targeted therapies such as dacarbazine and temozolomide, and found no prognostic value of BRAF status, age or gender in these patients (Meckbach, 2014). The Swiss study of patients with stage IV metastatic melanoma found a median OS of 9.2 months (95% CI: 6.9–11.3 months) in patients with BRAF-mutated disease, which was not significantly different from the median OS of 10.6 months (95% CI: 9.1–12.2 months, p=0.25) in patients with wildtype BRAF disease (Frauchiger, 2016).These results were supported by the study conducted in Germany, which enrolled patients with stage III disease and found that once patients progressed to stage IV, median OS was not influenced by BRAF status (BRAF-mutated: 8.5 months, n=22; wildtype BRAF: 8.0 months, n=20 (Schlaak, 2013). Interestingly, another German study found that stage IV patients with BRAF V600E-mutated disease reported longer median OS (18 months, n=21) versus wildtype BRAF disease (13.5 months, n=20), although this effect was not found to be statistically significant (p=0.695) (Heinzerling, 2013).

The Swiss Frauchiger *et al.* study also examined clinical characteristics associated with OS, and found that elevated levels of lactate dehydrogenase (LDH) had a negative impact on median OS, both in BRAF-mutated (elevated LDH: 6.95 months [95% CI: 5.6–9.5 months], normal LDH: 14.2 months [95% CI: 11.2–17.3 months], p=0.01) and patients with wildtype BRAF disease (elevated LDH: 4.9 months [95% CI: 3.5–6.2 months], normal LDH: 10.7 months [95% CI: 8.5–12.8 months], p<0.01) (Frauchiger, 2016).

Analyses of differing patient characteristics between those with BRAF-mutated and wildtype BRAF disease showed a difference in the clinical subtypes of melanoma, wherein fewer patients with wildtype BRAF had nodular (NM) (31%, 21/67) and superficial spreading melanoma (SSM) (12%, 8/67) than patients with BRAF-mutated disease (NM: 36%, 32/88; SSM: 20%, 18/88) (Frauchiger, 2016). Nevertheless, the study supports previously published reports of stage IV melanoma characteristics in general, in that NM and SSM remain the most common subtypes of advanced melanoma regardless of BRAF status (Frauchiger, 2016; Garbe, 2009).

Important co-morbidities:

The impact of comorbidities is poorly studied in melanoma, and there are no known common comorbidities associated with the cancer. One large registry-based Danish study which included 23,476 patients diagnosed with melanoma from the years 1987–2009, identified that 81% of patients did not have comorbidities (Grann, 2013). Of those who did have comorbidities, the most common were cancer (excluding melanoma and non-melanoma skin cancers) at 3.9% (915/23,476) of patients, cerebrovascular disease (3.4%, 739/23,476) and chronic pulmonary disease (2.4%, 558/23,476) (Grann, 2013). The study found that standardised morality rates increased with increasing comorbidity, with interaction effects found between melanoma and comorbidity on mortality rates in the first year after diagnosis, though these effects became less pronounced after the first year if the patient survived (Grann, 2013). Stratifying by melanoma stage, the study reported that the interaction effects were concentrated in patients with distant metastases (Grann 2013). Despite the potential importance of these findings, we are unaware of any studies examining the specific comorbidities of BRAF V600E-positive disease.

- **Indication: treatment of adult patients with BRAF V600E mutant metastatic colorectal cancer**

A systematic literature review to gather the information necessary to populate this section was performed (Incidence, Prevalence, Demographics of the target population, Natural history, Main existing treatment options and Co-morbidities). Observational studies, systematic literature reviews or meta-analysis from 2009 to date in Europe and Australia were included. Since only few data are available on patients with BRAF-mutated mCRC, the systematic literature review was broaden to provide data on mCRC when data on BRAF-mutated mCRC are missing, scarce or inconclusive. A total of 66 publications on mCRC or BRAF-mCRC were finally included in this review.

Incidence:

In Europe, the age-standardized incidence rates (ASRs) (using the European standard population) in 2018 for all stages of colorectal cancer have been estimated to be 57.5 and 36.3 per 100,000 population per year in men and women respectively. This was estimated to equal approximately 378,450 new cases in 2018 – 212,170 in men and 166,280 in women (Ferlay, 2018). The highest incidence rates of colorectal cancer in males were reported in Hungary (104.2/100,000) and Slovakia (90.3/100,000), and for females in Norway (58.8/100,000), Denmark (54.7/100,000) and Hungary (54.1/100,000). Specifically, in the EU 5 countries, the ASRs of colorectal cancer for men were estimated to be 46.6/100,000 in Germany, 67.7/100,000 in Spain, 56.7/100,000 in the United Kingdom (UK), 54.3/100,000 in Italy and 55.3/100,000 in France. Similarly, the ASRs for women in these countries of interest were 32.8/100,000 in Germany, 34.4/100,000 in Spain, 39.6/100,000 in the UK, 36.7/100,000 in Italy and 36.7/100,000 in France (Ferlay, 2018).

Data on incidence arising from observational studies within the SLR scope are relatively old. In the large-scale EUROCARE study of colorectal cancer trends from 1984-2002 across Finland, Austria, Germany, Switzerland, Slovakia, Slovenia and the UK, 19% – 37% of all colorectal cancer patients had distant metastases at diagnosis (Brenner 2012). Similarly, in the large-scale registry-based CONCORD study, which drew data from 1996-98 in Estonia, Finland, France, Italy, Netherlands, Poland, Slovakia, Slovenia and Spain, 11% – 33% of all colorectal patients had Dukes Stage D (or currently known as stage VI using the Dukes' staging equivalence to TNM classification) or metastatic disease at diagnosis (Allemani, 2013). Across other large European studies, the percentage of newly diagnosed colorectal cancer patients who were diagnosed at stage IV ranged from 14% – 29% (Brouwer, 2018; Erichsen, 2013; Klein, 2011; Mantke, 2012; Schnoor, 2012; McPhail, 2015; van der Geest, 2015; Clauer, 2015; Blaker, 2019; Smeby, 2018; Benitez Majano, 2019). Similarly, an older European study of 40,613 patients from one UK and three French cancer registries found that the proportion of patients diagnosed with metastatic colorectal cancer varied from 22.1% – 22.6% (Dejardin, 2013) Lastly, a large UK study of 525,416 patients in the Public Health England cancer registry found that 20.4% of patients had stage IV colorectal cancer at diagnosis (Hippisley-Cox, 2017). Thus, the overall rate of patients diagnosed with stage IV colorectal cancers in European countries is estimated to be approximately 25% (Van Cutsem, 2014).

The Australian Cancer Agency reported that the number of newly diagnosed colorectal cancer cases in 2018 was 9,294 in males and 7,709 in females (Australian Institute of Health and Welfare, 2018). As such, the ASR of colorectal cancer incidence was estimated to be 63/100,000 population for males and 49/100,000 population for females in 2018. Data for the number of metastatic patients at diagnosis was not available for 2018, however, in 2011 the Australian Institute of Health and Welfare reported that 2,474 of the 13,993 newly diagnosed colorectal cancer patients or 17.7% were stage IV at diagnosis (Australian Institute of Health and Welfare 2019).

Various mutations have been observed in colorectal cancer, including in the KRAS, NRAS, BRAF and PIK3CA genes, and these mutations may impact both survival and response to therapy (Christensen, 2018; Van Cutsem, 2019). Amongst these, the BRAF mutation is a significant negative prognostic factor, and is estimated to occur from as low as 5% to as high as 21% of colorectal cancer cases (Troiani, 2016; Van Cutsem, 2014; Sorbye, 2015; De Roock, 2010; Clarke, 2015; Barras, 2017;

Bylsma, 2018; Davies, 2002). Similarly, the BRAF V600E mutation specifically is expected to occur in 90-95% of BRAF mutant tumours (Clarke, 2015; Ursem, 2018).

Using the estimated value of 378,450 new colorectal cancer cases diagnosed in EU countries, and assuming that 25% of newly diagnosed colorectal cancers are metastatic (Van Cutsem, 2014), and that approximately 10% of these cases are positive for BRAF V600E mutations (Troiani, 2016), it can be estimated that approximately 9,460 individuals presented with BRAF V600E-mutated stage IV colorectal cancer in 2018 across EU countries.

Using the same approach for Australia, with a 2018 diagnosed population of approximately 17,000, the number individuals per year diagnosed with BRAF V600E-mutated stage IV colorectal cancer should be 425.

Prevalence:

The rate of BRAF V600E mutations in colorectal cancers is estimated to be approximately 8.5 -12.5% (Davies, 2002; Rajagopalan, 2002), however, a large variability between studies has been observed in the mutation frequency. A recent meta-analysis found that the BRAF mutation rate in colorectal cancers ranged from 6.2% – 7.9% in European countries (Italy, Bulgaria, Croatia, and Switzerland), and 7% – 9.9% in Australia (Li, 2017). A second meta-analysis of European pathology datasets uncovered BRAF mutations in 2.7 – 14.3% of Polish and Czech samples, with an overall prevalence rate of 5.8% (Kafatos, 2017). Five additional European studies (Spain, Greece, Sweden, Norway, and Finland) reported BRAF mutation rates ranging from 12.3% to 22.4% (Seppala, 2015; Negru, 2014; Bessa, 2008; Brandstedt, 2014; Moreira, 2015; Smeby, 2018) in colorectal cancer patients. One reason for the variability in observed BRAF mutation rates may be the variation in sample sizes, where smaller studies tended to have higher overall BRAF mutation rates. For example, the two studies with the largest BRAF mutant populations (18.5% and 22.4%) also had the smallest population sizes (n=119 and n=165, respectively) (Moreira, 2015; Bessa, 2008). Other factors that varied between studies and may have impacted BRAF mutation prevalence may include the methods of mutation assessment, methods of sample analysis as some studies used older samples from 1993 onwards (Smeby, 2018), or studies imposing additional inclusion criteria such as only selecting patients with MMR deficiencies (Bessa, 2008).

In studies that looked at metastatic colorectal cancer patients specifically, the prevalence of BRAF mutations also varied widely from 6.7% (Christensen, 2018), 8.2% (Blaker, 2019), 8.5% (Kayhanian, 2018), 10.1% (Smeby, 2018), 18% (Seppala, 2015) and 25.2% (Uvirova, 2015) patients having BRAF mutations. A similar trend of higher mutation rate with smaller population size was also observed when looking at mCRC patients specifically (Seppala, 2015). Notably, the definitions of metastatic disease between studies was also inconsistent, with the study with the highest rate of BRAF mutations (25%) also being the only study to include both stage III and IV patients (Uvirova, 2015). Drawing data from only large-scale studies, the overall prevalence of BRAF mutations was similar to the canonical value of 10%, with the observed rates ranging from approximately 7% – 11%.

Notably, a 2016 Australian study of 3,693 patients in the South Australian mCRC registry reported that only 6.2% of patients in the registry had known BRAF mutation status, and of these, 12.7% had BRAF mutations (Price, 2016a). Similar results were observed in a French study of 1,269 colorectal patients wherein only 37.8% of tumours had any molecular testing, and only 128 patients (10% of the entire cohort) were tested for BRAF mutations (Thiebault, 2017). Therefore, prevalence of BRAF mutation rates must be interpreted with caution, as BRAF mutational analysis may not be systematically performed in colorectal cancer patients.

Demographics of the target population with unresectable, BRAF-mutated metastatic colorectal cancer and risk factors for the disease: As seen from European age-standardized incidence rates, colorectal cancer (regarless of mutational status) occurs at higher rates in men than in women in European Union countries (57.5/100,000 versus 36.3/100,000 respectively) (Ferlay, 2018). In other large-scale population- and cohort-based studies, the proportion of male patients varied from 47%

to 68.3% across all stages of colorectal cancer (Clauer, 2015; Uvirova, 2015; Benitez Majano, 2019; Brouwer, 2018; Christensen, 2018; Bouvier, 2015; Erichsen, 2013; White, 2018).

The epidemiology of BRAF V600E colorectal cancer, however, seems to be different as the proportion of male patients ranged from 23.4% – 37% across European studies (Blaker, 2019; Brandstedt, 2014; Seppala, 2015; Smeby, 2018; Kayhanian, 2018; de la Fouchardiere, 2019; McPhail, 2015). In 2014, a Swedish study of 584 colorectal cancer patients examined the risk of cancer development by patients' anthropometric factors such as height, weight, body-mass index, etc. (Brandstedt, 2014). This study found that the 71 (14.4%) patients with BRAF mutations were more frequently female and of higher age, but although increased weight, body fat percentage hip/waist circumference and BMI were associated with BRAF-wild-type tumours, none of the anthropometric factors were specifically associated with BRAF-mutant CRC (Brandstedt, 2014).

An Australian study found that BRAF-mutant colorectal cancer patients were less likely to have a family history of colorectal cancers than wild-type patients, but that older BRAF-mutant patients were more likely to have a family history of CRC (Buchanan, 2013).

Colorectal cancer occurs more frequently in older patients, with most cases diagnosed in people between 65-79 years old (Ait Ouakrim, 2015; Jess, 2013; Maringe, 2013; Eklof, 2013). Data from Cancer Research UK reported that at diagnosis 44% of patients were 75 years or older (Cancer Research UK, 2019). Similarly, a large French study of 3,389 colorectal cancer patients found that 44.9% of patients were 75 years or older at diagnosis (Faivre-Finn, 2002). Similar trends have been observed with BRAF mutations which were associated with older age at diagnosis than non-mutant CRC (Moreira, 2015; Blaker, 2019; Brandstedt, 2014; Seppala, 2015; Kayhanian, 2018; Christensen, 2018).

A French study of 287 BRAF-mutant patients concluded that the most frequent metastatic sites in BRAF V600E colorectal cancer were liver (51.9%), peritoneum (37.3%) and lymph nodes (31%) (de la Fouchardiere, 2019) with BRAF V600E CRC more likely to be associated with peritoneal metastases than wild-type CRC (Kayhanian, 2018; Christensen, 2018). BRAF V600E tumours were also more likely to be right-sided or found in the proximal colon (Seppala, 2015; Blaker, 2019; Moreira, 2015; Smeby, 2018; Kayhanian, 2018; Christensen, 2018; Bessa, 2008), and were more likely to be tumours with poorly differentiated histology (Moreira, 2015; Blaker, 2019).

BRAF mutations are a strong negative predictor of Lynch Syndrome (LS), a hereditary subtype of colorectal cancer characterized by mismatch repair deficient tumours and microsatellite instability (Moreira, 2015; Thiel, 2013; Bessa, 2008).

Finally, as KRAS and BRAF mutations are mutually exclusive, colorectal cancer patients with KRAS mutations are not at risk for BRAF mutations (Tie, 2011b; Smeby, 2018; Brandstedt, 2014).

Data from Australia showed similar trends, finding that BRAF-mutant tumours were more likely to be right-sided, have microsatellite instability (MSI-high) and occur in older and female patients (Tran, 2011; Tie, 2011b; Price, 2016a). As well, Australian patients with BRAF V600E colorectal cancer were also more likely to have peritoneal and distant lymph node metastases (Tran, 2011; Prasanna, 2018).

Detailed analyses of the risks of BRAF mutant colorectal cancer based on patient ethnicity were not uncovered in this review, however one 2013 UK-based study of 29 Bangladeshi and 134 Caucasian patients did report that the risks of having BRAF mutant colorectal cancer was significantly lower in Bangladeshi patients as compared to Caucasian patients (Sengupta, 2013). Additionally, a 2013 US study of 427 colorectal cancer patients found that the rate of BRAF mutations was higher in Caucasian patients (13%) than in either Asian (4%) or black (6%) patients (Hanna, 2013).

Natural history of BRAF mutated metastatic colorectal cancer in the population, including mortality and morbidity:

Natural History

The European Society for Medical Oncology (ESMO) estimates that approximately 50% of patients with colorectal cancer will develop metastases during the course of their disease (Ferlay, 2018). In turn, a 2015 study from the Netherlands reported that 20% of patients will develop metastatic disease within 5 years of diagnosis (Elferink, 2015).

A population-based study from 2017 of 19,911 patients from the New South Wales Cancer Registry examined the natural history of colorectal cancer and found that approximately 27.5% of colorectal cancer patients (stages I-III at diagnosis) developed metastatic disease after a median 5.3 years follow up. No specific data on BRAF-mutated mCRC natural history were found.

Mortality and Morbidity

In Europe, the age standardized rates of colorectal cancer mortality in 2018 have been estimated at 24.1/100,000 population in males and 14.0/100,000 population in females (Ferlay, 2018). This equals to an approximate 96,220 deaths in men and 77,010 deaths in women Europe-wide. The highest rates of mortality in men were observed in Hungary (42.8/100,000), Slovakia (47.2/100,000), and Poland (43.6/100,000). In women, the highest ASRs of mortality were observed in Hungary (22.9/100,000), Slovakia (22.6/100,000) and Croatia (19.9/100,000). Additionally, for the EU 5 countries, the 2018 age standardized mortality rates for men per 100,000 population were estimated to be 20.6 in Germany, 20.8in France, 21.5 in the UK, 26.8 in Spain and 20.6 in Italy. Similarly, for these countries of interest, the age standardized mortality rates for women were 12.4 in Germany, 12.5 in France, 14.9 in the UK, 12.7 in Spain, and 12.7 in Italy (Ferlay, 2018).

Two UK studies found that the one-year age-standardized survival rate was 44% among stage IV patients, with survival being higher in females (65% survival) than males (34% survival) (McPhail, 2015; White, 2018). Similarly, a study examining stage IV colorectal cancer patients in Denmark, England, Norway and Sweden found that the 1-year net survival ranged from 48.4% – 57.3% in colon cancer patients (Benitez Majano, 2019). Recent evidence suggests a significant improvement in survival over the last decades in stage IV colorectal cancer patients: 3-year survival rising from 12% to 20% (McDevitt 2017) and 5-year survival from 4% to 12% (Brouwer, 2018; Klein, 2011).

In a study from 2018, stage IV patients with MSS tumours with a BRAF mutation had a worse 5-year overall survival (3.4% survival) compared to wild-type (14.5% survival) patients (Smeby, 2018). Similarly, a UK study comparing BRAF mutant mCRC patients to matched controls found that median overall survival was significantly worse in BRAF V600E than wild-type patients (18.2 months and 41.1 months respectively) (Kayhanian, 2018). A 2019 French study of 66 BRAF-mutant mCRC patients with resected liver metastases found that the median survival after disease progression of BRAF-mutant patients was significantly worse than wild-type patients (23 months versus 44.3 months, respectively), but that BRAF mutations were not associated with a higher risk of relapse after resection (Bachet, 2019).

Data collected by the Australian Institute of Health and Welfare for 2011 reported a 1-year relative survival of 49.3% for patients with stage IV colorectal cancer at diagnosis, falling to 13.4% survival at 5-years post diagnosis. The 2014 Australian colorectal cancer mortality rates were 18.6/100,000 population in males and 13.0/100,000 population in women, with mortality rates showing a downward trend since the 1990s. In 2018, the burden of deaths from all-stage colorectal cancers in Australia was 4,129 deaths (2,125 for men; 2005 for women) comprising 8.5% of all cancer deaths (48,586 deaths across all cancers combined).

One Australian study of 227 colorectal cancer patients with known BRAF mutational status found that BRAF was a negative prognostic factor for survival, with median overall survival being significantly worse in BRAF-mutant than wild-type patients (14 months versus 32.9 months

respectively) (Price, 2016a). No other data was available for Australian BRAF colorectal cancer patients.

The main existing treatment options:

Across various therapeutic regimens, BRAF mutation status has been associated with poor prognosis, and ESMO guidelines recommend determining BRAF mutational status for all colorectal cancer patients, and at the same time as KRAS mutational status for metastatic CRC (Van Cutsem, 2014).

In patients which have unresectable metastases, the treatment options for mCRC regardless of mutational status include palliative care, with regimens including fluorouracil, oxaliplatin or irinotecan (van der Geest, 2015; Troiani, 2016). Targeted therapies such as epidermal growth factor receptor (EGFR) and vascular endothelial growth factor inhibitors can improve survival when used in RAS wild-type patients (van der Geest, 2015; Ferlay, 2018). However, the effectiveness of EGFR inhibitors in BRAF-mutated metastatic colorectal cancer has been shown to be low, especially in later lines of therapy, therefore ESMO consensus guidelines suggest testing for BRAF mutation status before initiation this treatment (Van Cutsem, 2014; Troiani, 2016).

The available treatment-pattern data for BRAF-mutated mCRC patients is very limited. Additionally, there is a lack of large randomized controlled trials investigating the efficacy of different treatments in BRAF-mutant mCRC patients specifically. Furthermore, in the few trials examining the efficacy and safety of various treatments in mCRC patients irrespective of mutational status, the number of patients in the BRAF mutant subgroup was small (Bennett, 2011; Price, 2016b; Carter, 2014; Bennouna, 2013; Peeters, 2009; Peeters, 2010; Amado, 2008).

One Australian study reported that the proportion of patients receiving chemotherapy was not statistically different between BRAF mutant and wild-type patients, although a greater proportion of BRAF mutant patients (41.7%) received fluoropyrimidine plus oxaliplatin chemotherapy as first line treatment than wild-type patients (24.2%) (Price, 2016a).

No other studies reporting on the real-world treatment patterns on BRAF V600E mCRC patients specifically were uncovered in this review.

Important co-morbidities:

As colorectal cancer primary occurs in older patients, many of these patients are likely to have comorbid conditions (Erichsen, 2013). A Danish study of 56,963 colorectal cancer patients found that 39% of patients had at least one comorbid condition, with the most frequent ones including cerebrovascular disease (8.8%), other tumours (8.8%), myocardial infarction (5.7%) and diabetes (5.3%) (Erichsen, 2013). Furthermore, when this study compared colorectal cancer patients to comorbidity-matched controls, the authors observed a synergistic effect between CRC and high comorbidity burden (reported as a score of 4+ on the Charlson Comorbidity Index) (Charlson, 1987).

Similarly, a large-scale UK study of 525,416 patients in the Public Health England cancer registry found that the most frequent comorbidities included cardiovascular disease (15.6% in women, 24% in men), type II diabetes (11% in women, 14.7% in men), COPD (5.5% in women, 8% in men) or presence of other cancer (8% in women, 7.7% in men) (Hippisley-Cox, 2017). Overall, the burden of comorbidities in men was greater, men were more likely to be smokers (40.1% versus 24.9%), and male patients were more likely to be prescribed statins (29.7% versus 21.6%) and aspirin (24.5% vs 17%) at diagnosis.

A 2010 German study of 17,641 colorectal cancer patients found that over 80% of patients had at least one comorbidity, with the most common comorbidities being cardiovascular disease (over 65%), diabetes (19%) and obesity (15%) (Benedix, 2010). Additionally, this study noticed that the burden of comorbidities was significantly worse in right-sided colorectal cancer patients. As mentioned previously, BRAF mutations are associated with right-sided disease, suggesting that the burden of comorbidities in BRAF V600E patients with metastatic disease could be higher (Seppala, 2015; Blaker, 2019; Moreira, 2015; Smeby, 2018; Kayhanian, 2018; Christensen, 2018; Bessa, 2008).

A 2013 Australian study of 19,415 invasive colorectal cancer cases found that the most frequently observed comorbidity was diabetes (7.6%), and that the presence of diabetes or other comorbidities increased the risk of both colorectal cancer-related mortality and non-cancer-related mortality (Dasgupta, 2013).

Despite the potential importance of these findings, no studies examining the specific comorbidities of BRAF V600E-positive disease were uncovered in this review.

- **Indication: treatment of adult patients with advanced Non-Small Cell Lung Cancer (NSCLC) with a BRAF V600E mutation**

Incidence and prevalence:

Lung cancer is the second cancer in terms of new cases and is the leading cause of cancer death worldwide. Globally, in 2020, the age-standardized incidence rates (ASRs) for all stages of lung cancer have been estimated to be 31.5 and 14.6 per 100,000 population per year in men and women respectively. This was estimated to equal approximately 2,21 million new cases in 2020 – 1,435,943 in men and 770,828 in women (Sung, 2021).

In European countries Non-small cell lung cancer is the second most common type of cancer accounted for 11.8% of all new cancer diagnoses (excluding non-melanoma skin cancer) with an incidence of about 477,500 new cases (315 100 in men and 162 500 in women) in 2020 (Dyba, 2021). For males, incidence was highest in Central and Eastern Europe–Hungary (138.3 per 100,000), Serbia (136.4), Bosnia and Herzegovina (131.3), and Latvia (127.9), and in some countries of Southern and Western Europe such as Greece (127.2), Montenegro (123.8), and Belgium (123.5). Low rates were estimated for Finland (67.1), Switzerland (64.3), and Sweden (44.8). Among females, the highest incidence rates were seen in Ireland (85.1), Denmark (85.1), Hungary (76.6), Iceland (74.3) and the United Kingdom (71.4); the lowest rates were in Eastern Europe, notably Ukraine (11.8) and Belarus (10). Specifically, in the EU 5 countries, the ASRs of lung cancer for men were estimated to be 87.1/100,00 in Germany, 99.1/100,00 in Spain, 89.3/100,000 in the United Kingdom (UK), 90.9/100,000 in Italy and 103.9/100,000 in France. Similarly, the ASRs for women in these countries of interest were 52.4/100,000 in Germany, 29.9/100,000 in Spain, 71.4/100,000 in the UK, 35.1/100,000 in Italy and 44.2/100,000 in France (Figure 9 Dyba, 2021). Tobacco smoking is the largest preventable cause of lung cancer and contributes to greater than 80% to the occurrence of this disease. The trends in cigarette smoking shape the patterns of incidence rates observed in particular populations over the decades. Among both women and men, the incidence of lung cancer is low in people aged <40 years and increases up to the age of 75–80 years in most populations.

Most newly diagnosed lung cancer patients have advanced disease: the proportion of stage IV and III disease at diagnosis differs from region to region but overall stage IV has been reported in 45.5% to 57.7% and stage III in 17% to 23% of patients (Walters, 2013). In a retrospective observational study (Minicozzi, 2018), stage at diagnosis (as TNM, condensed TNM, or Extent of Disease) was analysed for patients from 15 European countries grouped into 4 regions (Northern Europe, Central Europe, Southern Europe, and Eastern Europe), diagnosed with lung cancers between 2000 and 2007, 41% of patients had metastatic lung cancer at diagnosis. Eastern Europe had the lowest proportion of patients with metastatic disease (32% versus 41-48% in other regions) together with the highest proportion of patients with unknown stage disease (28% versus 9-18% in other regions).

Data from The European High-Resolution (HR) studies (http://hrstudies.it/) across 5 European countries (Belgium, Estonia, Portugal, Spain and Switzerland) from 2010- 2013, reported a 51.5% rate of TNM stage IV at diagnosis (ranging from 45.5% in Switzerland to 57.7% in Portugal).

An extrapolation based on European cancer registries from 12 countries reporting stage distribution of NSCLC at diagnosis estimated that 60 - 70% of patients were diagnosed at an advanced stage (Stages IIIB/C and IV) with 43 - 60% diagnosed at Stage IV. Other European studies, estimated the percentage of newly diagnosed NSCLC cancer, with stage IV ranges from

48% to 71% (Marchetti, 2011; Ilie, 2013; Brustugun, 2014; Horn, 2019; Debieuvre, 2022). Thus, the overall rate of patients diagnosed with stage IIIB/C and IV lung cancers in European countries is estimated to be approximately 60%.

About 80–85% of lung cancer is non-small cell lung cancer, and 10–15% of lung cancer is small cell lung cancer and the rest is lung carcinoid tumor and other rare lung cancers (American Cancer Society, 2021). Non-small cell lung cancer is further sub-divided into 3 subtypes (Gridelli, 2015), adenocarcinoma is the most common, accounting for around 60% of all NSCLC cases, followed by squamous cell carcinoma (around 25% of all NSCLC cases) and large cell carcinoma (around 10%) (Travis, 2015). This is correlated by 2 European publications from Portugal and France (Guerreiro, 2020; Debieuvre, 2022).

NSCLC is comprised of an expanding number of biologically distinct and clinically relevant molecular subsets. Numerous molecular alterations have been recently reported and defined as driver oncogenes following their role in transforming and maintaining cancer cells in preclinical models. The most common targetable genetic alterations in lung cancer are EGFR- and KRAS activating mutations followed by, in frequency, ALK and ROS1 rearrangements, BRAF mutations, MET exon 14 skipping mutations and MET amplifications, RET gene fusions and HER2 mutations. NTRK and NRG1 gene fusions rarely occur in NSCLC (Kris, 2014; Jordan, 2017; Leonetti, 2018).

Approximately 2% to 4% of patients with NSCLC have mutations in the BRAF gene (Hendriks, 2023a) with half of these driven by the BRAF V600E mutation (Class 1) and the other half driven by non-V600E mutations distributed throughout exons 11 and 15 collectively (Class 2 and 3) (Kris, 2014; Zheng, 2015).

The vast majority of BRAF mutations occur in adenocarcinoma and very rarely in squamous cell carcinoma (Marchetti, 2011). In the German nation-wide CRISP registry that included 3,717 patients with advanced NSCLC, BRAF mutation was found in 4.4% of NSCLC (with 1.5% V600 and 2.6% non V600 mutation) and 0.3% of SC (Griesinger, 2021).

There is a probable slight female predilection for all BRAF mutations in NSCLC, with an average female-to-male ratio of 2 to 1 for the V600E mutation (Paik, 2011;Cardella, 2013), with the exception of one Italian study that reported a dramatically higher female predilection for V600E mutations, with a female-to-male ratio of 8.6 to 1 (Marchetti, 2011). In a metanalysis (Cui, 2017) investigating the association between BRAF mutations and non-small cell lung cancer, 14 studies including 7,979 patients were analyzed for associations between the mutations of BRAF and gender. The results showed that 107 of 4,404 male patients (2.43%) were BRAF mutations positive and 108 (3.02%) of 3,575 female patients were BRAF mutations positive, indicating a significant difference of BRAF mutations between female and male (OR= 0.72, 95% CI=0.55–0.95, P=0.02). Forty-seven (32.6%) of 144 male patients were *BRAF* V600E mutations positive and 60 (62.5%) of 96 female patients were *BRAF*V600E mutations positive, indicating a significant difference in *BRAF*V600E mutations between female and male (OR=0.45, 95% CI=0.26–0.77, P=0.004).

The literature is divided as to an association with smoking status: whilst most studies conclude that BRAF mutations, in contrast to EGFR mutations, are commonly associated with a current or former status (54% to 100% of patients with BRAF mutations are current or former smokers (Yeh, 2013; O'Leary, 2019), several reports or reviews note that V600E mutation occurs most frequently in never smoker (Marchetti, 2011; Cui, 2017), whilst others find the opposite or an absence of correlation (Kinno, 2014; Cardarella, 2013; Brustugun, 2014; Villaruz, 2015).

BRAF mutations are less frequent in people of Chinese origin than in white individuals, occurring only in 0.5–2% of patients of Chinese origin affected by NSCLC (Li, 2014; Ding, 2017). A study performed on Japanese patients showed that the frequency of BRAF mutation was significantly higher in the Caucasian patients than in Asian ones (Izumi, 2020).

Histologically, BRAF V600E-mutated adenocarcinomas are mucinous with a micropapillary growth pattern and intense thyroid transcription factor-1 (TTF-1) expression (Alvarez, 2019) that is associated with shorter progression-free survival and overall survival in univariate analysis and multivariate analysis. BRAF non-V600E tumours were found to have micropapillary histology in only 12% of the cases.

Using the estimated value of 477,500 new lung cancer cases diagnosed in EU countries, and assuming that about 80% of newly diagnosed lung cancers are NSCLC, with 60% of stages IIIB/C or IV NSCLC and that approximately 3% of these cases are positive for BRAF mutations, with 50% of them driven by the BRAF V600E mutation (Class 1), it can be estimated that approximately 6,876 individuals presented with BRAF V600-mutated advanced lung cancer, of them 3,438 individuals with BRAF V600E mutation in 2020 across EU countries.

Demographics of the target population with non-small cell lung cancer (NSCLC) with a BRAF V600 mutation and risk factors for the disease:

The analysis from Globocan 2020 data identified a male to female ratio of ranging from 3 to 10 in Europe. The cumulative risk of lung cancer diagnosis before the age of 75 is also higher in males than females (5.4% for males corresponding to 1 in 19 men and 2.3% for females corresponding to 1 in 44 women (Dyba, 2021). However, a recent study (Debieuvre, 2022) showed increase in lung cancer in women and still a large proportion of patients diagnosed at metastatic or disseminated stage. In 2020, the proportion of women in patients diagnosed with lung cancer increased: 34·6% compared to 24·3% and 16·0% in 2010 and 2000 ($p<0·0001$). The proportion of non-smokers was higher in 2020 than in previous cohorts (12·6% compared to 10·9% in 2010 and 7·2% in 2000, $p<0·0001$). At diagnosis, 57·6% of patients had a metastatic/disseminated stage NSCLC. About 65.33% of men diagnosed with lung cancer are in the advanced local stage (stage III) or present metastases (stage IV) (Meza, 2015; Chen, 2014).

The myriad risk factors for lung cancer most commonly include lifestyle, environmental, and occupational exposures. The roles these factors play vary depending on geographic location, gender and race characteristics, genetic predisposition, as well as their synergistic interactions

- *Cigarette Smoking and passive Smoking*

The World Health Organization (WHO) estimates that in 2012, lung cancer is the cause of 1.59 million deaths globally per year, with 71% of them caused by smoking. Tobacco smoking remains the main cause of lung cancer and the geographical and temporal patterns of the disease largely reflect tobacco consumption during the previous decades. In countries with active tobacco control measures, the incidence of lung cancer has begun to decline in men and in young and middle-aged women (Malvezzi, 2023). About 500 000 deaths annually are attributed to lung cancer in lifetime never-smokers (Toh, 2006). Absence of any history of tobacco smoking characterises 19% of female compared with 9% of male lung carcinoma in the United States (Novello, 2014; McCarthy, 2012). However, an increase in the proportion of NSCLC in never-smokers has been observed, especially in Asian countries (Couraud, 2015). These new epidemiological data have resulted in 'non-smoking-associated lung cancer' being considered a distinct disease entity, where specific molecular and genetic tumour characteristics have been identified (Couraud, 2015).

Both smoking prevention and smoking cessation can lead to a reduction in a large fraction of lung cancers.

The epidemiological evidence and biological plausibility support a causal association between second-hand exposure to cigarette smoke and lung cancer risk in nonsmokers (Samet, 2009; Jyoti, 2016) with the excess risk in the order of 20–30% for a nonsmoker being passive smoker (Hackshaw, 1997; Boffetta; 2002). The effect of involuntary smoking appears to be present for both household exposure, mainly from spousal and workplace exposure (Boffetta, 2002; Stayner, 2007), and perhaps from involuntary childhood smoking exposure (Boffetta, 2000). Few studies have investigated the risk of lung cancer among users of smokeless tobacco products. In two large cohorts

of US volunteers, the relative risk for spit tobacco use among nonsmokers was 1.08 (95% CI 0.64–1.83) and 2.00 (95% CI 1.23–3.24), respectively (Henley, 2005).

- *Air pollution and other causes*

Other factors such as genetic susceptibility, poor diet, occupational exposures and air pollution may act independently or in concert with tobacco smoking in shaping the descriptive epidemiology of lung cancer. Moreover, novel approaches in the classification of lung cancer based on molecular techniques have started to bring new insights to its aetiology, in particular among nonsmokers. (Malhotra, 2016; Corrales, 2020; Molina, 2008; Ole, 2013).

Natural history of advanced non-small cell lung cancer (NSCLC) in the population, including mortality and morbidity:

Natural History

The European Society for Medical Oncology (ESMO) estimates that approximately 50% of patients with NSCLC will develop metastases during the course of their disease (Hendriks, 2023a).

The mortality is associated with a high degree of malignancy and late diagnosis. As many as 65.33% of men diagnosed with lung cancer are in stage III or stage IV (Meza, 2015; Chen, 2014).

Mortality and Morbidity

In Europe, the age standardized rates of NSCLC mortality in 2020 have been estimated at 81.7/100,000 population in males and 29.0/100,000 population in females (Dyba, 2021). Non-Small Cell Lung Cancer is the leading cause of cancer deaths with more than 380 000 deaths corresponding to about 20% of the cancer deaths in Europe; this equals to an approximate 260,000 deaths in men and 120,000 deaths in women Europe-wide. Lung cancer represents the first cause of cancer mortality among males in all European countries apart from Sweden, and among females in 13 countries (one-third) of the European countries (Dyba, 2021).

Data from Eurocare 5 (Sant et al, 2023) found that the one-year age-standardized survival rate was 31% among stage III-IV patients, with survival being higher in females (39.3% (95% [IC: 26.7-30.3] survival) than males (25.4% survival 95% IC 35.8-42.8]). In addition, patients with any comorbidity at diagnosis had significantly higher relative excess of risk of death (RER) than those with no comorbidity (RER 1.09, CI, 1.01–1.18). The modelisation also showed that the adjusted RER of never smokers was lower than that of current smokers (RER 0.68, CI, 0.57–0.81).

More than half of people newly diagnosed with lung cancer can be expected to die within 1 year of diagnosis (Howlader, 2020).

Important co-morbidities

With lung cancer being far more frequent in smokers and ex-smokers, these patients often have tobacco-related illnesses, mainly cardiovascular (ischaemic or hypertensive heart disease, lower limbs arteriopathy, etc.) and respiratory (chronic obstructive pulmonary disease (COPD), obstructive sleep apnoea, usual interstitial fibrosis. etc.) in nature. A Spanish real-world study assessed comorbidities at diagnosis in patients with lung cancer. In patients with non-squamous carcinoma (that includes predominantly adenocarcinoma) the following co-morbidities were most frequently reported: hypertension (42%), dyslipemia (28%), diabetes mellitus (19%), COPD (18%), cardiomyopathy (15%), depression/anxiety, former alcoholism and hypercholesterolemia (all 7%) (Provencio, 2022).

Cardiovascular diseases (CVDs) CVDs are one of the most common comorbidities in lung cancer with prevalence from 12,9% to 43% according to different studies (Islam, 2015).

A non-interventional cohort study (Linden, 2020) compared 3834 adult patients newly diagnosed with advanced NSCLC during 2006–2013 with the general population. The prevalence of analysed comorbidities was significantly higher for NSCLC patients compared to the general population, with an OR of 2.44 (95% CI 2.27–2.63). Respiratory diseases were the group of comorbidities that showed the largest difference between the cohorts with an OR of 7.22 (95% CI 6.46–8.07) where 22.7% of the patients in the regional NSCLC cohort and only 3.9% of the comparators were diagnosed. The group of comorbidities that showed the second largest OR between the two cohorts was infectious diseases with 2.50 (95% CI 2.25–2.77) followed by cardiovascular diseases with OR = 1.41 (95% CI 1.31–1.52).

The main existing treatment options for NSCLC with a BRAF-V600E mutation:

Historically, advanced NSCLC was primarily treated with platinum-based chemotherapy in first line. Advances in the understanding of tumour biology and the identification of oncogenic drivers, such as mutations in the EGFR gene and rearrangements of the ALK gene, have led to the development of targeted therapies such as tyrosine kinase inhibitors (TKIs). However, retrospective analysis exploring the activity of chemotherapy in participants with advanced NSCLC have revealed that advanced NSCLC participants harbouring a BRAF V600E mutation present a poor prognosis when treated with chemotherapy; in addition, participants with BRAF V600E mutations appear to show inferior responses to platinum-based chemotherapy when compared to BRAF non-V600E-mutated participants or wild-type participants (Barlesi, 2016; Yan, 2022; O'Leary, 2019; Cardarella, 2013). While studies on the use of immune checkpoint inhibitors (ICIs) with a longer follow-up have confirmed that immunotherapy is the new standard of care for the first-line treatment of advanced or recurrent disease regardless of oncogene-addition status (Brahmer, 2022; De Castro, 2022; Johnson, 2022), there are very few data on the benefit of ICI in the BRAF-mutated population (Hendriks, 2023a). Retrospective analyses in small series have indicated limited efficacy of ICIs in BRAF-mutant NSCLC (Tabbò, 2022). Results of the international IMMUNOTARGET study showed poor outcomes in BRAF-mutated participants (Mazieres, 2019).

Phase II trials have demonstrated the efficacy of BRAF and MEK inhibitors, for participants harbouring V600 mutation (with often no distinction between V600E and other V600 mutations). In a vemurafenib basket trial including BRAF V600-mutated NSCLC (n = 62), ORR was 38% in previously untreated participants and 37% in previously treated participants (Hyman, 2015; Subbiah, 2019). In a separate study of 101 BRAF V600-mutant patients (n = 101), ORR was 45%, mDoR 6.4 months, mPFS 5.2 months and mOS 10.0 months (Mazieres, 2020). In a Phase II study of dabrafenib in combination with trametinib in participants with BRAF V600E-mutated mNSCLC, the observed ORR was 68% (54.8-80.1) and mPFS and mDoR were 10.2 months (95% CI 6.9-16.7 months) and 9.8 months (95% CI 6.9-18.3 months), respectively in pretreated patients receiving the combination of dabrafenib and trametinib (Planchard, 2022). In treatment-naïve participants, with the combination of dabrafenib and trametinb, the ORR was 64% (46%-79%) and mPFS and mDoR were 10.8 months (95% CI 7.0-14.5 months) and 10.2 months (95% CI 8.3-15.2 months), respectively. In pretreated and treatment-naïve participants, respectively, the mOS was 18.2 months (95% CI 14.3-28.6 months; 4- and 5-year survival rates: 34% and 22%, respectively) and 17.3 months (95% CI 12.3-40.2 months; 4- and 5-year survival rates: 26% and 19%, respectively) (Planchard, 2022). The combination of dabrafenib-trametinib is approved by the EMA for the treatment of advanced NSCLC harbouring BRAF V600 mutations (Tafinlar EU SmPC-2023; Mekinist EU SmPC-2023).

The most recent ESMO and NCCN guidelines recommend dabrafenib and trametinib as first-line treatment for *BRAF* V600E mutated metastatic NSCLC in adults. Single agent vemurafenib or dabrafenib are treatment options if the preferred combination is not tolerated. If patients progress on these targeted treatments, then systemic therapy (chemotherapy and/or immunotherapy) should be offered, and the type of therapy will vary depending on tumour histology type (adenocarcinoma or squamous cell carcinoma) (Hendriks, 2023a; Planchard, 2018; NCCN, 2023). In second line

participants who have not received dabrafenib and trametinib, the ASCO guidelines (2022) consider giving dabrafenib and trametinib or dabrafenib or vemurafenib alone.

In a recent real-world study, a total of 53 patients with BRAF mutant NSCLC diagnosed between 2018 and 2022 were identified and included in the Glans-Look Lung Cancer Research database (Gibson, 2023): 35 V600E and 18 non-V600E; ICI-based systemic therapy was the most common systemic treatment chosen in the first-line setting in both V600E (44%) and non-V600E (70%) BRAF-mutant NSCLC. Among patients with a V600E mutation and advanced disease who received palliative systemic therapy, 49% received dual-targeted BRAF/MEK inhibition (dabrafenib and trametinib).

More recently (a real-life multicenter study (Perrone, 2022) conducted in consecutive NSCLC patients diagnosed between January 2018 and February 2020 identified 44 BRAF-mutant NSCLC patients: 23 V600E and 21 non-V600E. BRAF-V600E patients received first line chemotherapy (61%), targeted therapy (22%) or immunotherapy (17%). While patients treated with first-line targeted agents were excluded from the analysis, a worse performance of first-line immunotherapy versus first-line chemotherapy was observed in terms of OS in the BRAF V600E subpopulation as well as in the overall population.

The safety profile and toxicity management data of BRAFi and MEKi in NSCLC are mostly limited to the combination of dabrafenib and trametinib or translated from evidence obtained from melanoma. The toxicity profile of BRAF and MEK inhibitor combinations includes pyrexia, increases in blood levels of alanine aminotransferase, aspartate aminotransferase and creatine phosphokinase, nausea, vomiting and fatigue (Planchard, 2016; Planchard, 2017). Pyrexia (in the absence of infection) is related specifically to dabrafenib and is the most frequent adverse event (AE) reported with this treatment.

Part II: Module SII - Non-clinical part of the safety specification of encorafenib

▪ Encorafenib single agent

Table SII.1: Encorafenib: Key safety findings from non-clinical studies (toxicity, safety pharmacology)

Key safety findings	**Relevance to human usage**
TOXICITY	
• **Acute toxicity** No acute toxicity studies with encorafenib have been performed.	
• **Repeat-dose (sub-chronic) toxicity (by target organ for toxicity)** The following toxicities were seen in 13-week repeat dose studies in rats and monkeys. Repeated administration was associated with toxicity in the skin, the gastrointestinal system, and in the eyes in both sexes, and in the reproductive organs in males. All changes were partially reversible after 4 weeks without treatment. In rats, dry, scaly and thickened skin on the plantar surface of the feet, presenting histologically as slight to marked hyperkeratosis, squamous cell hyperplasia and inflammatory	 Predictive of skin lesions in patients. Potential safety concern. Weakly predictive of gastrointestinal effects in patients (humans lack non-

Key safety findings	Relevance to human usage
cell infiltration, was reported at ≥6 mg/kg/d. Lesions were dose related in terms of severity and incidence. Non-glandular stomach tissue showed hyperkeratosis and hyperplasia at ≥20 mg/kg/d. Encorafenib-related effects were clinical signs, reduced body weight parameters as well as changes in organ weights (epididymides) and microscopic pathology (testes, epididymides, stomach, skin) noted at all dose levels. All LGX818-related changes observed in testis, epididymis and skin (hind paws) occurred at lower incidence and severity at the end of the recovery phase, suggesting partial reversibility. At completion of recovery period, changes in the non-glandular stomach of males and females were still noted with similar incidence and severity. Doses ≥20 mg/kg/d resulted in tubular degeneration and cytoplasmic vacuolation of seminiferous tubules in the testes and oligospermia in the epididymides, including an absence of the later stages of spermatid maturation. In monkeys, abnormal retinas with blister-like lesions over the macular region were reported in 2 animals at 60 mg/kg/d after 13 weeks of treatment (corresponding to 1.5 -fold the mean plasma exposure in patients at the therapeutic dose in terms of AUC_{0-24}). Evidence of partial recovery was noted after 10 weeks without treatment. Histopathology findings were similar to retinopathy associated with MEK inhibitors.	glandular stomach tissue). Potential risk, not a safety concern given the target population and reversibility. Effects on male fertility not excluded. Potential risk not important given the target population. Ocular lesions in monkeys were similar to those described in humans as central serous retinopathy or central serous-like chorioretinopathy. Potential risk not an important safety concern based on the clinical data.
• **Genotoxicity/mutagenicity** Encorafenib was negative *in vitro* for mutagenicity in both bacterial [Ames Assay; Pcs-r1070208 (Covance #8229996) and mammalian (Chromosome Aberration in Human PBL Assay; Pcs-r1070206 (Covance #8229997)] cell systems, and *in vivo* in the rat bone marrow micronucleus assay (Pcs-r1270199). Taken together, the *in vitro* and *in vivo* data indicate that encorafenib is not genotoxic.	Not predictive for a safety concern.
• **Carcinogenicity** Due to the nature of the target indication, according to ICH S9, carcinogenicity studies have not been performed for encorafenib.	Not applicable.
• **Developmental and reproductive toxicity** When administered to rats during organogenesis, encorafenib induced foetotoxicity (delayed skeletal development and lower foetal weights) without embryolethality or teratogenicity at 20 mg/kg/d. The NOAEL for embryo-foetal development was 5 mg/kg/d (similar to patient exposure at the therapeutic dose). When administered to rabbits during organogenesis, encorafenib induced foetotoxicity and morphologic changes (lower foetal weights and transitory changes in skeletal development) in foetuses at the materno-toxic dose of 75 mg/kg/d. Aortic arch dilatation was observed in some fetuses. Other teratogenic effects included reduced lung lobes, absent	Predictive of embryo-foetal toxicity. Potential safety concern.

Key safety findings	Relevance to human usage
spleen, misshapen globular heart, dilation of ascending aorta, and absent interventricular septum. Although the overall incidences of litters and fetuses with malformations in all treated groups were within the historical control data range (HCDR), the percentage of litters was above the HCDR for dilatation of aortic arch and slightly above the HCDR for small/reduced lung lobe, misshapen [globular] heart, dilation of ascending aorta, absence of interventricular septum and absence of spleen. The NOAEL for embryo-foetal development was 25 mg/kg/d (79-fold the level of patient exposure at the therapeutic dose). In both species, encorafenib was detected in foetal plasma.	
SAFETY PHARMACOLOGY	
• **Cardiovascular system, including potential effect on the QT interval:** The IC_{50} for hERG inhibition was 73.4 µM, indicating an unlikely effect of encorafenib on QT prolongation. Oral administration of encorafenib in monkeys up 200 mg/kg had no effect on systemic blood pressure, electrocardiographic intervals, body temperature or qualitative evaluation of ECG waveforms. In monkeys, higher heart rates (HR) were noted at ≥50 mg/kg with an apparent lack of diurnal shift as is normally observed during the dark photo-period. A thorough QT study to evaluate the QT prolongation potential of encorafenib has not been conducted.	Not predictive for a potential safety concern. Potential risk of HR increase.
• **Central nervous system:** In rat and monkey safety studies, no significant central nervous system (CNS) effects were observed. Radiolabelled absorption, distribution, metabolism and excretion (ADME) and quantitative whole-body autoradiography studies in the rat found no meaningful CNS penetration. Single oral doses of 100 mg/kg encorafenib to rats did not cause drug-related effects on CNS.	No significant potential for abuse and not predictive for a safety concern.
• **Respiratory:** In rat and monkey safety studies, there were no significant effects on the respiratory system at single doses of 100 mg/kg in rats and 200 mg/kg in monkeys.	Not predictive for a safety concern.
3- OTHER TOXICITY-RELATED INFORMATION OR DATA	
• **Phototoxicity/Sensitisation:** Encorafenib was shown to have phototoxic potential in an in vitro 3T3 Neutral Red Uptake Test (Pcs-vh090801). Photo-irritation factor for encorafenib was greater than two fold that of the positive control article chlorpromazine. In the *in vivo* mouse contact sensitisation study (Pcs-r501817), increases in ear weights but no change in lymph node weight and cell counts were seen indicating no potential for sensitisation. Collectively, these data indicate that encorafenib has a risk of phototoxic potential and minimal risk for sensitisation at therapeutic doses in patients.	Risk of phototoxic potential and minimal risk for sensitization at therapeutic doses in patients. Not predictive for a safety concern.
• **Drug interactions:** <u>Effect of CYP enzymes on encorafenib</u>*:* Encorafenib is metabolised by CYP3A4, CYP2C19 and CYP2D6. In vitro,	Potential for CYP3A4 P450 mediated drug-drug

Key safety findings	Relevance to human usage
CYP3A4 was predicted to be the major enzyme contributing to total oxidative clearance of encorafenib in human liver microsomes (~83.3%), followed by CYP2C19 and CYP2D6 (~16.0% and 0.71%, respectively). In the clinical study ARRAY-818-105, co-administration of strong (posaconazole) and moderate (diltiazem) CYP3A4 inhibitors with encorafenib resulted in an increase in overall (AUC, 3- and 2-fold higher, respectively) and peak (C_{max}, 68% and 45% higher, respectively) encorafenib exposure. The effect of co-administering a strong CYP3A4 inducer on encorafenib exposure has not been studied in a dedicated trial. Repeat dose administration of encorafenib 450 mg once daily and binimetinib 45 mg twice daily with modafinil, a moderate CYP3A inducer, decreased encorafenib steady-state AUC by 24% and C_{max} by 20%, compared to encorafenib alone (Study ARRAY-818-103/C4221003 Arm 3). No clinically relevant differences in encorafenib exposures have been observed when binimetinib or cetuximab were co-administered with encorafenib.	interactions. Potential safety concern for over-exposure with concomitant use of strong and moderate for CYP3A4 P450 inhibitors. Limited effect on encorafenib PK with co-administration of CYP3A4 inducers. Not predictive for a safety concern for co-administration with CYP3A4 inducers.
<u>Effect of encorafenib on CYP substrates</u>*: In vitro* experiments indicate encorafenib is a relatively potent reversible inhibitor of UGT1A1, CYP2B6, CYP2C9 and CYP3A4/5, and weak inhibitory potency for CYP1A2, CYP2C8, CYP2C19 and CYP2D6 as well as a time-dependent inhibitor of CYP3A4. Encorafenib induced CYP1A2, CYP2B6, CYP2C9 and CYP3A4 in human primary hepatocytes. Repeat dose administration of encorafenib 450 mg once daily and binimetinib 45 mg twice daily with a single dose of CYP probe substrate cocktail reduced midazolam 2 mg (CYP3A4 substrate) AUC by 82% and C_{max} by 74 %. It decreased omeprazole 20 mg (CYP2C19 substrate) AUC by 17 % and did not change C_{max} and increased caffeine 50 mg (CYP1A2 substrate) AUC by 27 % and C_{max} by 13 %. It decreased the ratio of losartan metabolite E3174 to losartan (CYP2C9 substrate) concentrations in urine by 28%, and did not change the ratio of dextromethorphan metabolite (dextrorphan) to dextromethorphan (CYP2D6 substrate) concentrations in urine. A single dose of encorafenib 450 mg and binimetinib 45 mg reduced bupropion 75 mg (CYP2B6 substrate) AUC and C_{max} by ≤ 25% and repeated administration of encorafenib 450 mg daily and binimetinib 45 mg twice daily reduced bupropion AUC and C_{max} by ≤ 26 % (Study ARRAY-818-103/C4221003 Arm 2). For co-administration with UGT1A1 substrates that undergo gut extraction, a minor to moderate drug-drug-interaction (DDI) is expected. While binimetinib is a UGT1A1 substrate, it does not undergo gut extraction and therefore no DDI with encorafenib is expected. No differences in binimetinib exposure have been observed clinically when binimetinib is co-administered with encorafenib.	Encorafenib is a strong inducer of CYP3A4. Concomitant use with agents that are substrates of CYP3A4 (e.g., hormonal contraceptives) may result in loss of efficacy of these agents. No or limited effect for other CYP substrates and UGT1A1. Not predictive for a safety concern.

Key safety findings	Relevance to human usage
No clinically relevant differences in cetuximab exposures have been observed when cetuximab was co-administered with encorafenib.	
<u>Effect of transporters on encorafenib</u>*:* Encorafenib was found to be a substrate of the P-glycoprotein (P-gp) transporters. Inhibition of P-gp is unlikely to result in a clinically important increase in encorafenib concentrations as encorafenib exhibits high intrinsic permeability. Distribution into the central nervous system may be increased by P-gp inhibitors. The involvement of several uptake transporter families (OCT1, OATP1B1, OATP1B3 and OATPB1) was investigated in vitro using relevant transporter inhibitors. The data suggest that hepatic uptake transporters are not involved in encorafenib distribution into primary human hepatocytes.	Not predictive of a safety concern for use in combination with binimetinib or cetuximab.
<u>Effect of encorafenib on transporters</u>*:* Based on *in vitro* studies, there is potential for encorafenib to inhibit renal transporters OCT2, OAT1, OAT3 and hepatic transporters OCT1, OATP1B1 and OATP1B3 at clinical concentrations. Repeated administration of encorafenib 450 mg once daily and binimetinib 45 mg twice daily with a single dose of rosuvastatin (a OATP1B1, OATP1B3 and BCRP substrate) increased rosuvastatin C_{max} by 2.7-fold and AUC by 1.6-fold.	Minimal effect for P-gp and BCRP substrates. Not predictive for a safety concern.
In addition, encorafenib may inhibit P-gp in the gut and breast cancer resistance protein (BCRP) at the expected clinical concentrations and may increase oral absorption of drugs that are P-gp substrates.	Limited effect on OATP1B1, OATP1B3 and BCRP transporters. Not predictive for a safety concern. Potential effect on other transporters. Unknown clinical relevance.

▪ Encorafenib in combination use

<u>Encorafenib in combination with binimetinib</u>

When combining two compounds, the potential for overlapping toxicities based on the non-clinical data needs to be considered. No toxicity studies of encorafenib in combination with binimetinib have been conducted. A summary of an integrative assessment of the potential for additive and/or synergistic toxicity of combining encorafenib with binimetinib is described below for preclinical safety data (Table SII. 2_Combination). Some of the effects reported in this table were mainly observed in moribund or dead females at very high dose levels, and as such were not reported as relevant single agent findings.

<u>Potential synergistic toxicity from safety pharmacology data</u>

Non-clinical single agent cardiovascular safety pharmacology data for both single agent encorafenib and single agent binimetinib do not indicate a clinical risk for QTc prolongation based on the findings of the hERG assay and in vivo ECG evaluation in the GLP telemetry and repeat-dose toxicity studies in monkeys. There were no clinical signs in the encorafenib or in the binimetinib safety pharmacology and GLP repeat-dose studies in rats and monkey studies that indicate an effect on the CNS or respiratory system. Based on the safety pharmacology data, the combination of encorafenib and binimetinib is not expected to have adverse effects on the cardiovascular, CNS or respiratory systems.

<u>Potential synergistic toxicity from toxicological assessment by organ</u>

According to the resulting potential for synergistic toxicity, it appears likely that gastrointestinal intolerance/toxicity, skin toxicity and myelosuppression could be dose limiting in the clinical setting when encorafenib and binimetinib are combined.

Table SII.2: Encorafenib and binimetinib combination: Integrative toxicological assessment of the encorafenib and binimetinib combination from single agent non-clinical safety findings

Target Organ	**Encorafenib**	**Binimetinib**	**Potential impact of combination**
Adrenal	Cortical cytoplasmic vacuolation (rat)	Tissue mineralization (rat)	None predicted
Aorta	No change	Tissue mineralization (rat)	None predicted
Bone	Marrow hypocellularity (rat)	Marrow necrosis, osteopenia, thickening of the physis (rat)	Potential for synergistic toxicity
Epididymes	Oligospermia (rat)	No change	None predicted
Gastrointestinal tract	Non-glandular stomach in rat, hyperkaratosis and epithelial hyperplasia, Stomach erosions (rat)	Tissue mineralization (rat), degeneration of the absorptive mucosal epithelium and mucosal mixed cell inflammation in the cecum, colon and/or rectum (monkey)	Potential for synergistic toxicity
Heart	No change	Tissue mineralization (rat)	None predicted
Kidney	Vacuolation of tubular epithelium (rat)	Tissue mineralization (rat)	None predicted
Liver	Hepatocellular cytoplasmic vacuolation	No change	None predicted
Lung	No change	Tissue mineralization (rat)	None predicted
Ovaries	No change	Tissue mineralization (rat)	None predicted
Pancreas	Decreased zymogen, cytoplasmic vacuolation	No change	None predicted
Pituitary	No change	Tissue mineralization (rat)	None predicted
Prostate	No change	Tissue mineralization (rat)	None predicted
Retina	Blistering (CSR-like)(monkey), retinal detachment	No change	None predicted[a]
Skin	Scaly and/or thickened area of skin on plantar surfaces of rear feet: histopathology focal to multifocal areas of slight to marked hyperkeratosis, squamous cell hyperplasia and inflammatory cell infiltration (rat)	Hair loss/scabbing, erosion, inflammation and ulceration (rat)	Potential for synergistic toxicity[b]
	Phototoxic potential	Low phototoxic potential	
Spleen	Lymphoid depletion/atrophy (rats)	No change	None predicted
Testis	Tubular degeneration and cytoplasmic vacuolation of seminiferous tubules (rat)	No change	None predicted
Thymus	Lymphoid depletion	No change	None predicted

Target Organ	Encorafenib	Binimetinib	Potential impact of combination
Tongue	No change	Tissue mineralization (rat)	None predicted

[a] Human clinical experience reveals retinal findings with binimetinib as a single agent.

[b] Human clinical experience reveals less skin toxicity when encorafenib and binimetinib are dosed in combination.

Encorafenib in combination with cetuximab

When combining the two compounds, the potential for overlapping toxicities based on the non-clinical data needs to be considered. No toxicity studies of encorafenib in combination with cetuximab have been conducted. A summary of an integrative assessment of the potential for additive and/or synergistic toxicity of combining encorafenib with cetuximab is described below for preclinical safety data (Table SII.3). Some of the effects reported in this table were mainly observed in moribund or dead females at very high dose levels, and as such were not reported as relevant single agent findings.

- **Potential synergistic toxicity from safety pharmacology data**

Safety pharmacology of cetuximab was studied in Cynomolgus monkeys in a dedicated study after single administration, and as part of the 39-week toxicology study [Erbitux®, EPAR, 2019]. There were no indications of an effect of cetuximab on the cardiovascular and respiratory systems. In addition, no findings indicative of cetuximab CNS effects were observed within the 39-week repeat-dose toxicity study in Cynomolgus monkeys.

Based on the preclinical data, the combination of encorafenib and cetuximab is not expected to have adverse effects on the cardiovascular system, central nervous system or respiratory system.

- **Potential synergistic toxicity from toxicological assessment by organ**

Based on each single agent target-organ toxicities and theoretical assumptions on potentials for additive or synergistic toxicity, it appears that gastrointestinal intolerance/toxicity and skin toxicity could be regarded as potential in the clinical setting with the combination encorafenib and cetuximab.

Table SII.3: Encorafenib and cetuximab combination: Integrative toxicological assessment of the encorafenib and cetuximab combination from single agent non-clinical safety findings

Target Organ	Encorafenib	Cetuximab*	Potential impact of the combination
Adrenal	Cortical cytoplasmic vacuolation (rat). No changes considered as adverse.	No change	None predicted
Aorta	No change	No change	None predicted
Bone	Marrow hypocellularity at high dose, in moribund animals or animals found dead (rat)	No change	None predicted
Epididymes	Oligospermia (rat)	No change	None predicted
Gastrointestinal tract	Non-glandular stomach in rat, showed hyperkeratosis and hyperplasia. Stomach erosions at high dose in moribund animals or animals found dead (rat).	Diarrhoea or soft feces in monkey after single or repeated administration	**Potential for synergistic toxicity**
Kidney	Vacuolation of tubular epithelium at high dose in	Degenerative changes in the	None predicted

Target Organ	Encorafenib	Cetuximab*	Potential impact of the combination
	moribund animals or animals found dead (rat)	renal tubular epithelium due to secondary bacterial infection and septicemia	
Liver	Hepatocellular cytoplasmic vacuolation in rats not considered as adverse	No change	None predicted
Ovaries	No change	Impairment of menstrual cyclicity observed in monkeys	None predicted
Pancreas	Decreased zymogen, cytoplasmic vacuolation	No change	None predicted
Retina	Blistering central serous retinopathy-like (monkey)	No change	None predicted
Skin	Scaly and/or thickened area of skin on plantar surfaces of rear feet: histopathology focal to multifocal areas of slight to marked hyperkeratosis, squamous cell hyperplasia and inflammatory cell infiltration (rat)	Skin: primary target organ with dose-dependent severe skin reaction. Hyper-, parakeratosis, acanthosis, and acantholysis with clefts, pustules, and vesicle formation.	**Potential for synergistic toxicity**
	Phototoxic potential	Phototoxic potential not evaluated	
Spleen	Lymphoid depletion/atrophy (rats)	No change	None predicted
Testis	Tubular degeneration and cytoplasmic vacuolation of seminiferous tubules (rat)	No change	None predicted
Thymus	Lymphoid depletion at high dose in moribund animals or animals found dead (rat)	No change	None predicted
Tongue	No change	Alterations of the squamous epithelium of the tongue	None predicted

Sources: Module 2.4, section 2.4.4.8
*: Erbitux®, EPAR, 2019

Conclusions

The non-clinical safety findings of **encorafenib** as a single agent that are considered relevant and potentially important for humans, and that are thus carried forward for discussion to Sections SVII and SVIII as risks (either important or not important) are:

- Dermatologic reactions
- HR increase/tachycardia
- Embryo-foetal toxicity
- Gastrointestinal toxicity
- Ocular lesions
- Over-exposure with concomitant use of strong and moderate CYP3A4 P450 inhibitors.

The non-clinical safety findings from **encorafenib and binimetinib** compounds that are considered relevant and potentially important for humans for causing additive or synergistic toxicity when administered in combination, and that are carried forward for discussion to SVII and SVIII as risks are:

- Bone toxicity leading to myelosuppression
- Gastrointestinal toxicity
- Dermatologic reactions.

The non-clinical safety findings from the dual combination of **encorafenib and cetuximab** that are considered relevant and potentially important for humans for causing additive or synergistic toxicity when administered in combination, and that are carried forward to SVII and SVIII if considered as important risks are:

- Potential additive and synergistic gastrointestinal toxicity
- Potential additive and synergistic dermatologic reactions.

Part II: Module SIII - Clinical trial exposure of encorafenib

▪ Encorafenib single agent

Safety data from 3 clinical trials using encorafenib as a single agent in patients with unresectable or metastatic melanoma are presented in this RMP in this section.

The encorafenib single agent safety pool includes data from 217 patients with metastatic melanoma, who were previously naïve to BRAF inhibitors, enrolled at or randomised to a dose of 300 mg QD encorafenib, as summarised in the following table:

Table SIII.1: Encorafenib: Clinical studies included in safety evaluation

Single-agent encorafenib		
	Cut-off date	**Patients included in the integrated summary of safety**
CMEK162B2301	09 Nov 2016	192
CLGX818X2101	18 Aug 2014	10
CLGX818X2102	05 May 2015	15

Sources: 2.7.4 Updated Summary of Clinical Safety - LGX818/MEK162

In the safety data presentation:

- 'Enco 300' population refers to the encorafenib 300 mg QD arm patients of study CMEK162B2301 (N=192)
- 'Enco 300 P' population refers to the pooled encorafenib 300 mg QD monotherapy population (N=217).

CMEK162B2301 is the phase III pivotal study for the melanoma indication in the target population. In the trial, patients were randomised and treated in 3 arms: encorafenib 300 mg QD arm (N=192), combination encorafenib 450 mg QD and binimetinib 45 mg BID (N=192) and a vemurafenib comparator arm at the recommended dose (N=186).

A summary of overall exposure and duration of exposure is provided below for the pooled encorafenib monotherapy population, by dose, age group and gender, and by ethnic or racial origin (patient time = patient months).

1. Duration of exposure

Table SIII.2: Encorafenib: Duration of exposure

Encorafenib monotherapy safety pool (N=217)		
Duration of exposure (at least)	**Patients**	**Patient-months**
1 month	199	2231.79
3 months	176	2184.61
6 months	122	1942.80
12 months	75	1558.64
18 months	48	1150.95
24 months	24	653.47
30 months	2	63.24
Total	**217**	**2237.67**

Sources: ISS: Part1_u: Table 1.5.1.1.1b

Note: Patient-months are derived by taking the number of patients multiplied by the mean duration of exposure (days), and dividing this result by 30.4375. Duration of exposure is defined as: date of last exposure to study treatment - date of first administration of study treatment +1.

2. By dose

Table SIII.3: Encorafenib: Dose of exposure

Encorafenib monotherapy safety pool (N=217)		
Dose of exposure	**Patients**	**Patient-months**
300mg QD	217	2237.67
Total	**217**	2237.67

Sources: ISS_Part1_u: Table 1.5.1.1.2b

Note: Patient-months are derived by taking the number of patients multiplied by the mean duration of exposure (days), and dividing this result by 30.4375. Duration of exposure is defined as: date of last exposure to study treatment - date of first administration of study treatment +1.

3. By age group and gender

Table SIII.4: Encorafenib: Exposure by age group and gender

Encorafenib monotherapy safety pool (N=217) by age group and gender				
	Patients		**Patient-months**	
Age group [1]	**M**	**F**	**M**	**F**
18 - 64 years	93	79	994.37	875.10
65 - 74 years	21	12	178.96	122.78
75 - 84 years	5	6	36.17	25.69
85+ years	0	1	.	4.60
Total	**119**	**98**	**1209.49**	**1028.17**

Sources: ISS: Part1_u: Table 1.5.1.1.3b

Note: Patient-months are derived by taking the number of patients multiplied by the mean duration of exposure (days), and dividing this result by 30.4375. Duration of exposure is defined as: date of last exposure to study treatment - date of first administration of study treatment +1.

[1] Patients under 18 years was an exclusion criterion.

4. By ethnic or racial origin

Table SIII.5: Encorafenib: Exposure by ethnic or racial origin

Encorafenib monotherapy safety pool (N=217)		
Dose of exposure	**Patients**	**Patient-months**
Asian	9	82.96
Caucasian	194	2058.84
Other	4	33.41
Unknown*	10	62.46
Total	**217**	**2237.67**

Sources: ISS_Part1_u: Table 1.5.1.1.4b

Note: Patient-months are derived by taking the number of patients multiplied by the mean duration of exposure (days), and dividing this result by 30.4375. Duration of exposure is defined as: date of last exposure to study treatment - date of first administration of study treatment +1.

[1] No black patients were included in the pool (source ISS table 1.2)

*Patients with missing value were included in the unknown category.

▪ Encorafenib in combination use

Cumulative exposure data of encorafenib in combination use are first presented in all indications (Melanoma, CRC and NSCLC), they are then presented for each indication at the recommended doses.

Cumulative – All indications (Melanoma, Colorectal and NSCLC) - N=588

Table SIII.6: Encorafenib in combination use at the recommended doses: Clinical studies included in the safety evaluation

Encorafenib[a] and binimetinib combination		
Clinical trial	**Cut-off date**	**Patients included in the integrated summary of safety**
CMEK162B2301*	09 Nov 2016	192
CLGX818X2109	30 Dec 2016	75
CMEK162X2110	31 Dec 2016	7
ARRAY 818-202 (C4221008)*	22 January 2023	98
Encorafenib[b] + cetuximab combination – Doublet population		
Array-818-302 Randomized*	11 Feb 2019	216

Sources: 2.7.4 Summary of clinical safety - LGX818/MEK162- Initial Indication (melanoma indication); 2.7.4 Summary of clinical safety - LGX818/MEK162- Variation Type II (CRC indication); 2.7.4 Summary of clinical safety - Variation Type II (NSCLC indication);
[a] Enco 450 ; [b] Enco 300
* Pivotal study

1. Duration of exposure

Table SIII.7: Encorafenib Cumulative duration of exposure – All indications Pooled combination safety population (N=588)

Duration of exposure (at least)	**Persons**	**Patient-months**
1 month	553	6055.8
3 months	440	5825.1
6 months	323	5303.5
12 months	184	4090.8
18 months	131	3306.8
24 months	63	1856.9
30 months	21	726.8
Total	**588**	**6071.7**

Sources: ISS_Part1_u: Table 1.5.1.1.1c; Table 1.5.1.1.1d
ARRAY_818_302_Dossier_2019 - Version date: 11SEP2019 14:47 - File Name: T1403_010601_RMP_Doublet_expo1_add.rtf - Listing16.2.5-10.01
Cut-off date 11FEB2019 - Database lock 30APR2019 - Dataset. ADEX:10SEP19 BASEDTM1.ADSL:29JUL19 - PGM T_RMP_Doublet_expo1_add.sas 11JUL2019 10:42
Sources: W00090_NSCLC - Version date: 31MAY2023 13:52 - File Name: Sub5_2_1_c1_RMPexp_PHtreat_t.rtf
Sources: Cut-off date Melanoma: 09NOV2016 / Cut-off date Pharos: 22JAN2023 - Dataset ADSP1.ADSL:15MAY2023 - PGM Sub5_2_1_c1_RMPexp_PHtreat_t.sas 04MAY2023 11:16
Note: Patient-months are derived by taking the number of patients multiplied by the mean duration of exposure (days) and dividing this result by 30.4375. Duration of exposure is defined as: date of last exposure to study treatment - date of first administration of study treatment +1.
Total subject time, expressed in patient-months, is the sum of the duration of exposure (in months) for each patient. Duration of exposure is defined as the max exposure between that of BINI and ENCO (not CETUX).

2. By Dose

Table SIII.8: Encorafenib in combination use: Cumulative Dose of exposure (pooled target pop)

Restricted combination safety pool (N=588)		
Duration of exposure (at least)	**Persons**	**Patient-months**
Encorafenib 450mg QD and Binimetinib 45 BID	372	5135.2
Encorafenib 300mg QD and cetuximab	216	936.51
Total	**588**	**6071.7**

Sources: ISS_Part1_u: Table 1.5.1.1.2c; Table 1.5.1.1.2d
ARRAY_818_302_Dossier_2019 - Version date: 11SEP2019 14:47 - File Name: T1403_010602_RMP_Doublet_expo2_add.rtf - Listing16.2.5-10.01
Cut-off date 11FEB2019 - Database lock 30APR2019 - Dataset. ADEX:10SEP19 BASEDTM1.ADSL:29JUL19 - PGM T_RMP_Doublet_expo2_add.sas 11JUL2019 10:45
Sources: W00090_NSCLC - Version date: 31MAY2023 13:52 - File Name: Sub5_2_2_c1_RMPexpDos_PHtreat_t.rtf
Sources: Cut-off date Melanoma: 09NOV2016 / Cut-off date Pharos: 22JAN2023 - Dataset ADSP1.ADSL:15MAY2023 - PGM Sub5_2_2_c1_RMPexpDos_PHtreat_t.sas 04MAY2023 11:16
Note: Patient-months are derived by taking the number of patients multiplied by the mean duration of exposure (days) and dividing this result by 30.4375. Duration of exposure is defined as: date of last exposure to study treatment - date of first administration of study treatment +1.
Total subject time, expressed in patient-months, is the sum of the duration of exposure (in months) for each patient
Duration of exposure is defined as the max exposure between that of BINI and ENCO (not CETUX).

3. By age group and gender

Table SIII.9: Encorafenib in combination use: Cumulative Exposure by age group and gender (target pop)

Pooled Combination safety population (N=588) by age group and gender				
	Persons		**Patient-months**	
Age group [1]	**M**	**F**	**M**	**F**
18 - 64 years	209	155	2236.5	1639.1
65 - 74 years	94	75	961.2	746.2
75 - 84 years	23	28	197.1	274.3
85+ years	2	2	5.0	11.43
Total	**328**	**260**	**3399.8**	**2672.0**

Sources: ISS_Part1_u: Table 1.5.1.1.3c; Table 1.5.1.1.3d
ARRAY_818_302_Dossier_2019 - Version date: 11SEP2019 14:47 - File Name: T1403_010603_RMP_Doublet_expo3_add.rtf - Listing16.2.5-10.01
Cut-off date 11FEB2019 - Database lock 30APR2019 - Dataset. ADEX:10SEP19 BASEDTM1.ADSL:29JUL19 - PGM T_RMP_Doublet_expo3_add.sas 11JUL2019 10:27
Sources: W00090_NSCLC - Version date: 31MAY2023 13:53 - File Name: Sub5_2_3_c1_RMPexpAgSx_PHtreat_t.rtf
Sources: Cut-off date Melanoma: 09NOV2016 / Cut-off date Pharos: 22JAN2023 - Dataset ADSP1.ADSL:15MAY2023 – PGM Sub5_2_3_c1_RMPexpAgSx_PHtreat_t.sas 04MAY2023 11:16
[1] Patients under 18 years was an exclusion criterion.
Note: Patient-months are derived by taking the number of patients multiplied by the mean duration of exposure (days) and dividing this result by 30.4375. Duration of exposure is defined as: date of last exposure to study treatment - date of first administration of study treatment +1.
Total subject time, expressed in patient-months, is the sum of the duration of exposure (in months) for each patient
Duration of exposure is defined as the max exposure between that of BINI and ENCO (not CETUX).

4. By ethnic or racial origin

Table SIII.10: Encorafenib in combination use: Cumulative Exposure by ethnic or racial origin (pooled)

Pooled combination safety population (N=588)		
Racial origin [1]	**Persons**	**Patient-months**
Asian	38	261.3
Caucasian	528	5669.7
Black or African American	3	4.9
Other	8	94.5
Unknown*	11	41.3
Total	**588**	**6071.7**

Sources: ISS_Part1_u: Table 1.5.1.1.4c; Table 1.5.1.1.4d
ARRAY_818_302_Dossier_2019 - Version date: 11SEP2019 14:47 - File Name: T1403_010604_RMP_Doublet_expo4_add.rtf - Listing16.2.5-10.01
Cut-off date 11FEB2019 - Database lock 30APR2019 - Dataset .ADEX:10SEP19 .ADSL:09SEP19 - PGM T_RMP_Doublet_expo4_add.sas 11JUL2019 10:27
Sources: W00090_NSCLC - Version date: 31MAY2023 13:53 - File Name: Sub5_2_4_c1_RMPexpRace_PHtreat_t.rtf
Sources: Cut-off date Melanoma: 09NOV2016 / Cut-off date Pharos: 22JAN2023 - Dataset ADSP1.ADSL:15MAY2023 - PGM Sub5_2_4_c1_RMPExpRace_PHtreat_t.sas 04MAY2023 11:20
[1] No black patients were included in the pool, except for the NSCLC population (Pharos study)
* Patients with missing value or with value equal to 'Not reported due to confidentiality reason' were included in the unknown category
Note: Patient-months are derived by taking the number of patients multiplied by the mean duration of exposure (days) and dividing this result by 30.4375. Duration of exposure is defined as: date of last exposure to study treatment - date of first administration of study treatment +1.
Total subject time, expressed in patient-months, is the sum of the duration of exposure (in months) for each patient
Duration of exposure is defined as the max exposure between that of BINI and ENCO (not CETUX).

▪ Encorafenib in combination with binimetinib

Safety data from 5 supportive clinical trials using encorafenib in combination with binimetinib in patients with unresectable or metastatic melanoma are included in this RMP for the combination of encorafenib and binimetinib for the treatment of patients with unresectable or metastatic BRAF V600-mutant melanoma. Of them, 3 clinical trials which summarise the safety of the combination of encorafenib with binimetinib are presented below:

CMEK162B2301 is the Phase III pivotal study for the melanoma indication in the target population. Patients were randomised and treated in 3 arms: encorafenib 300 mg QD arm (N=192), combination encorafenib 450 mg QD and binimetinib 45 mg BID (N=192) and vemurafenib comparator arm at the recommended dose (N=186).

CLGX818X2109 is a Phase II, multi-center, open-label study of sequential LGX818/MEK162 combination followed by a rational combination with targeted agents after progression, to overcome resistance in adult participants with locally advanced or metastatic BRAF V600 melanoma. In Part 1 of this study, patients were treated with combination of encorafenib 450 mg QD and binimetinib 45 mg BID, a total of 158 patients were enrolled in part 1, of whom 75 were BRAF/MEK-treatment naïve.

CMEK162X2110 is a Phase Ib/II, multi-center, open-label, dose escalation study of LGX818 in combination with MEK162 in adult participants with BRAF V600 - dependent advanced solid tumours. Among the total included patients, 7 of the patients with melanoma were BRAF/MEK naive and treated with combination encorafenib 450 mg QD and binimetinib 45 mg BID.

In the safety data analyses for melanoma:

- 'Combo 450' refers to the combination of encorafenib 450 mg QD and binimetinib 45 mg BID patients in study CMEK162B2301 (N=192). When appropriate, to avoid confusion with other populations, this population is referred to as Combo 450 arm of study CMEK162B2301.
- 'Combo 450 RP' refers to the restricted combination safety pool for patients with melanoma, who received doses of encorafenib at 450 mg QD in combination with binimetinib at 45 mg BID (N=274). This population is named Combo 450 RP in the first MAA of encorafenib 450 mg QD and binimetinib 45 mg BID for the treatment of adult patients with unresectable or metastatic melanoma with a BRAF V600 mutation. This population is named the "Melanoma population" in the dossier supporting the MAA of encorafenib 450 mg QD and binimetinib 45 mg BID for the treatment of adult patients with advanced non-small cell lung cancer with a BRAFV600E mutation. In this RMP, the 2 names may be used depending on the context ("**Melanoma population" or "Combo 450 RP**").
- 'Combo BP for melanoma' refers to the broad combination safety pool for patients who received doses of encorafenib ranging from 400 mg to 600 mg QD in combination with binimetinib at 45 mg BID (N=433); Note that 4 patients were included in both CMEK162X2110 and CLGX818X2109.

The encorafenib and binimetinib combination "broad" safety population for melanoma includes data from 433 patients with metastatic melanoma, who were previously naïve to BRAF inhibitors, enrolled at or randomised to a dose of encorafenib ranging from 400 mg to 600 mg QD in combination with binimetinib at 45 mg BID as summarised in the following table:

Table SIII.11a: Encorafenib and binimetinib combination: Clinical studies relevant to safety evaluation - Combo BP for melanoma (N=433)

Encorafenib and binimetinib combination (melanoma)		
	Cut-off date	**Patients included in the integrated summary of safety for melanoma**
CMEK162B2301	09 Nov 2016	192
CLGX818X2109	30 Dec 2016	158*
CMEK162X2110	31 Dec 2016	87*

Sources: 2.7.4 Summary of clinical safety - LGX818/MEK162
* 4 patients were included in both CMEK162X2110 and CLGX818X2109

Table SIII.11b: Clinical studies Supportive for Encorafenib/Binimetinib combination therapy in Combo 450 RP (N=274) - Melanoma indication

Binimetinib and encorafenib combination (melanoma)		
	Cut-off date	**Patients included in the integrated summary of safety**
CMEK162B2301	09 Nov 2016	192
CLGX818X2109	30 Dec 2016	75
CMEK162X2110	31 Dec 2016	7
Total		**274**

Source: 2.7.4 Summary of clinical safety (NSCLC)

For advanced non-small cell lung cancer (NSCLC) with a BRAF V600E mutation, safety data from a pivotal study (PHAROS study; C4221008; ARRAY 818-202) using encorafenib (450 mg QD) in combination with binimetinib (45 mg BID) are included in this RMP. The PHAROS study is an ongoing open-label, multicentre, non-comparative, Phase 2 study to determine the safety, tolerability and antitumour activity of the combination of encorafenib and binimetinib in participants with BRAF

V600-mutant NSCLC. A total of 98 patients were enrolled in this study and received at least 1 dose of study treatment.

Safety data from the PHAROS study were integrated with data from studies in other indications using the same dosage and administration schedule of the combination of encorafenib and binimetinib. This integrated data approach is in accordance with the regulatory guidance and the currently approved labelling of encorafenib. Accordingly, 4 studies included in the analyses for encorafenib 450 mg QD in combination with binimetinib 45 mg BID are described below.

Integrated safety data are presented for 372 patients, hereafter referred to as the **Combo 450 ISP** (Integrated safety population):

- 98 patients with BRAF V600E mutant advanced NSCLC enrolled at a dose of 450 mg QD encorafenib plus 45 mg BID binimetinib from the PHAROS study referred to as the **NSCLC population** at a data cut-off of 22 January 2023.

- 274 patients with BRAF V600 mutant metastatic melanoma enrolled at or randomised to a dose of 450 mg QD encorafenib plus 45 mg BID binimetinib (192 patients from Study CMEK162B2301, 75 patients from Study CLGX818X2109 and 7 patients from Study CMEK162X2110) referred to as the Melanoma population (Combo 450 RP) and corresponding to the previously submitted safety data for the melanoma indication in the first MAA of the combination of encorafenib plus binimetinib.

As such, **Combo broad ISP population** (N= 531) includes the 'Combo BP for melanoma' (N=433) plus the 'NSCLC population' (N=98).

Table SIII.11c: Encorafenib and binimetinib combination: Supportive clinical studies for Combo 450 ISP:

Encorafenib and binimetinib combination (Combo 450 ISP)		
	Cut-off date	**Patients included in the 45 Combo ISP**
CMEK162B2301	09 Nov 2016	192
CLGX818X2109	30 Dec 2016	75
CMEK162X2110	31 Dec 2016	7
ARRAY 818-202 (C4221008)	22 Jan 2023	98
Total		**372**

Sources: 2.7.4 Summary of clinical safety - Variation Type II (NSCLC indication)

A summary of overall exposure and duration of exposure is provided below for the restricted population (i.e by indication), and the integrated combination population, by dose, age group and gender, and by ethnic or racial origin.

1. Duration of exposure

Table SIII.12a: Encorafenib and binimetinib combination: Duration of exposure (Combo 450 ISP)

Combination integrated safety population (Combo 450 ISP; N=372)		
Duration of exposure (at least)	**Persons**	**Patient-months**
1 month	353	5125.7
3 months	327	5076.3
6 months	273	4822.0
12 months	176	3967.7
18 months	130	3286.3
24 months	63	1856.9

Combination integrated safety population (Combo 450 ISP; N=372)		
Duration of exposure (at least)	**Persons**	**Patient-months**
30 months	21	726.8
Total	**372**	**5135.3**

Sources: W00090_NSCLC - Version date: 31MAY2023 13:48 - File Name: Sub5_1_1_c1_RMPexp_treat_t.rtf
Sources: Cut-off date Melanoma: 09NOV2016 / Cut-off date Pharos: 22JAN2023 - Dataset ADSP1.ADSL:15MAY2023 - PGM Sub5_1_1_c1_RMPexp_treat_t.sas 04MAY2023 11:17
Note: Total subject time, expressed in patient-months, is the sum of the duration of exposure (in months) for each patient. Duration of exposure is defined as the max exposure between Encorafenib and binimetinib.
Duration of Exposure = (date of last exposure to study drug - date of first exposure to study drug +1)/30.4375

Melanoma indication (Combo 450 RP; N=274)		
Duration of exposure (at least)	**Persons**	**Patient-months**
1 month	265	3827.02
3 months	255	3806.09
6 months	213	3606.67
12 months	133	2901.06
18 months	97	2362.84
24 months	41	1163.34
30 months	9	301.73
Total	**274**	**3831.75**

Sources: ISS_Part1_u: Table 1.5.1.1.1c
Note: Patient-months are derived by taking the number of patients multiplied by the mean duration of exposure (days) and dividing this result by 30.4375. Duration of exposure is defined as: date of last exposure to study treatment - date of first administration of study treatment +1.

NSCLC indication (N=98)		
Duration of exposure (at least)	**Persons**	**Patient-months**
1 month	88	1298.6
3 months	72	1270.2
6 months	60	1215.4
12 months	43	1066.6
18 months	33	923.4
24 months	22	693.6
30 months	12	425.1
Total	**98**	**1303.5**

Sources: W00090_NSCLC - Version date: 31MAY2023 13:52 - File Name: Sub5_2_1_c1_RMPexp_PHtreat_t.rtf
Sources: Cut-off date Melanoma: 09NOV2016 / Cut-off date Pharos: 22JAN2023 - Dataset ADSP1.ADSL:15MAY2023 - PGM Sub5_2_1_c1_RMPexp_PHtreat_t.sas 04MAY2023 11:16
Note: Total subject time, expressed in patient-months, is the sum of the duration of exposure (in months) for each patient. Duration of exposure is defined as the max exposure between Encorafenib and binimetinib.
Duration of Exposure = (date of last exposure to study drug - date of first exposure to study drug +1)/30.4375

Table SIII.12b: Encorafenib and binimetinib combination: Duration of exposure (broad)

Broad combination integrated safety population (Combo broad ISP; N=531)		
Duration of exposure (at least)	**Persons**	**Patient-months**
1 month	500	6494.3
3 months	433	6367.9
6 months	343	5957.9
12 months	214	4827.7
18 months	150	3880.8

Broad combination integrated safety population (Combo broad ISP; N=531)		
Duration of exposure (at least)	**Persons**	**Patient-months**
24 months	76	2314.4
30 months	31	1110.9
Total	**531**	**6512.2**

Sources: ISS_Part1_u: Table 1.5.1.1.1d
Sources: W00090_NSCLC - Version date: 31MAY2023 13:52 - File Name: Sub5_2_1_c1_RMPexp_PHtreat_t.rtf
Sources: Cut-off date Melanoma: 09NOV2016 / Cut-off date Pharos: 22JAN2023 - Dataset ADSP1.ADSL:15MAY2023 - PGM Sub5_2_1_c1_RMPexp_PHtreat_t.sas 04MAY2023 11:16
Note: Patient-months are derived by taking the number of patients multiplied by the mean duration of exposure (days) and dividing this result by 30.4375. Duration of exposure is defined as: date of last exposure to study treatment - date of first administration of study treatment +1.

2. By dose

Table SIII.13a: Encorafenib and binimetinib combination: Dose of exposure (Combo 450 ISP)

Combination integrated safety population (Combo 450 ISP; N=372)		
Dose of exposure (at least)	**Persons**	**Patient-months**
Encorafenib 450mg QD + Binimetinib 45 BID	372	5135.3
Total	**372**	**5135.3**

Sources: W00090_NSCLC - Version date: 31MAY2023 13:48 - File Name: Sub5_1_2_c1_RMPexpDos_treat_t.rtf
Sources: Cut-off date Melanoma: 09NOV2016 / Cut-off date Pharos: 22JAN2023 - Dataset ADSP1.ADSL:15MAY2023 - PGM Sub5_1_2_c1_RMPexpDos_treat_t.sas 04MAY2023 11:17
Note: Total subject time, expressed in patient-months, is the sum of the duration of exposure (in months) for each patient. Duration of exposure is defined as the max exposure between Encorafenib and binimetinib.
Duration of Exposure = (date of last exposure to study drug - date of first exposure to study drug +1)/30.4375

Melanoma indication (Combo 450 RP; N=274)		
Dose of exposure (at least)	**Persons**	**Patient-months**
Encorafenib 450mg QD + Binimetinib 45 BID	274	3831.75
Total	**274**	**3831.75**

Sources: ISS_Part1_u: Table 1.5.1.1.2c
Note: Patient-months are derived by taking the number of patients multiplied by the mean duration of exposure (days) and dividing this result by 30.4375. Duration of exposure is defined as: date of last exposure to study treatment - date of first administration of study treatment +1.

NSCLC indication (N=98)		
Dose of exposure (at least)	**Persons**	**Patient-months**
Encorafenib 450mg QD + Binimetinib 45 BID	98	1303.5
Total	**98**	**1303.5**

Sources: W00090_NSCLC - Version date: 31MAY2023 13:52 - File Name: Sub5_2_2_c1_RMPexpDos_PHtreat_t.rtf
Sources: Cut-off date Melanoma: 09NOV2016 / Cut-off date Pharos: 22JAN2023 - Dataset ADSP1.ADSL:15MAY2023 - PGM Sub5_2_2_c1_RMPexpDos_PHtreat_t.sas 04MAY2023 11:16
Note: Total subject time, expressed in patient-months, is the sum of the duration of exposure (in months) for each patient. Duration of exposure is defined as the max exposure between Encorafenib and binimetinib.
Duration of Exposure = (date of last exposure to study drug - date of first exposure to study drug +1)/30.4375

Table SIII.13b: Encorafenib and binimetinib combination: Dose of exposure (broad)

Broad combination integrated safety population (Combo broad ISP; N=531)		
Dose of exposure (at least)	**Persons**	**Patient-months**
Encorafenib 400mg QD + Binimetinib 45 BID	4	21.49
Encorafenib 450mg QD + Binimetinib 45 BID	465	5805.45
Encorafenib 600mg QD + Binimetinib 45 BID	62	685.27

Broad combination integrated safety population (Combo broad ISP; N=531)		
Dose of exposure (at least)	**Persons**	**Patient-months**
Total	**531**	**6512.21**

Sources: ISS_Part1_u: Table 1.5.1.1.2d
Sources: W00090_NSCLC - Version date: 31MAY2023 13:52 - File Name: Sub5_2_2_c1_RMPexpDos_PHtreat_t.rtf
Sources: Cut-off date Melanoma: 09NOV2016 / Cut-off date Pharos: 22JAN2023 - Dataset ADSP1.ADSL:15MAY2023 - PGM Sub5_2_2_c1_RMPexpDos_PHtreat_t.sas 04MAY2023 11:16
Note: Patient-months are derived by taking the number of patients multiplied by the mean duration of exposure (days) and dividing this result by 30.4375. Duration of exposure is defined as: date of last exposure to study treatment - date of first administration of study treatment +1.

3. By age group and gender

Table SIII.14a: Encorafenib and binimetinib combination: Exposure by age group and gender (Combo 450 ISP)

Combination integrated safety population (Combo 450 ISP; N=372)				
	Persons		**Patient-months**	
Age group [1]	**M**	**F**	**M**	**F**
18 - 64 years	135	95	1921.3	1402.2
65 - 74 years	61	46	830.2	598.0
75 - 84 years	17	15	162.5	212.8
85+ years	2	1	5.0	3.2
Total	**215**	**157**	**2919.1**	**2216.2**

Sources: W00090_NSCLC - Version date: 31MAY2023 13:49 - File Name: Sub5_1_3_c1_RMPexpAgSex_treat_t.rtf
Sources: Cut-off date Melanoma: 09NOV2016 / Cut-off date Pharos: 22JAN2023 - Dataset ADSP1.ADSL:15MAY2023 - PGM Sub5_1_3_c1_RMPexpAgSex_treat_t.sas 04MAY2023 11:17
Note: Total subject time, expressed in patient-months, is the sum of the duration of exposure (in months) for each patient.
Duration of exposure is defined as the max exposure between Encorafenib and binimetinib.
Duration of Exposure = (date of last exposure to study drug - date of first exposure to study drug +1)/30.4375
[1] Patients under 18 years was an exclusion criterion

Melanoma indication (Combo 450 RP; N=274)				
	Persons		**Patient-months**	
Age group [1]	**M**	**F**	**M**	**F**
18 - 64 years	116	78	1690.58	1077.78
65 - 74 years	45	20	556.55	336.20
75 - 84 years	8	6	79.87	87.56
85+ years	0	1	.	3.22
Total	**169**	**105**	**2327.00**	**1504.76**

Sources: ISS_Part1_u: Table 1.5.1.1.3c
Note: Patient-months are derived by taking the number of patients multiplied by the mean duration of exposure (days) and dividing this result by 30.4375. Duration of exposure is defined as: date of last exposure to study treatment - date of first administration of study treatment +1.
[1] Patients under 18 years was an exclusion criterion.

NSCLC indication (N=98)				
	Persons		**Patient-months**	
Age group [1]	**M**	**F**	**M**	**F**
18 - 64 years	19	17	230.8	324.4
65 - 74 years	16	26	273.7	261.8
75 - 84 years	9	9	82.6	125.2
85+ years	2	-	5.0	
Total	**46**	**52**	**592.1***	**711.5***

Sources: W00090_NSCLC - Version date: 31MAY2023 13:53 - File Name: Sub5_2_3_c1_RMPexpAgSx_PHtreat_t.rtf

Sources: Cut-off date Melanoma: 09NOV2016 / Cut-off date Pharos: 22JAN2023 - Dataset ADSP1.ADSL:15MAY2023 - PGM Sub5_2_3_c1_RMPexpAgSx_PHtreat_t.sas 04MAY2023 11:16
Note: Total subject time, expressed in patient-months, is the sum of the duration of exposure (in months) for each patient.
Duration of exposure is defined as the max exposure between Encorafenib and binimetinib.
Duration of Exposure = (date of last exposure to study drug - date of first exposure to study drug +1)/30.4375
[1] Patients under 18 years was an exclusion criterion
** Cumulative numbers may not exactly match the sum of numbers listed in the table due to rounding*

Table SIII.14b: Encorafenib and binimetinib combination: Exposure by age group and gender (broad)

Broad combination integrated safety population (Combo broad ISP; N=531)				
	Persons		**Patient-months**	
Age group [1]	**M**	**F**	**M**	**F**
18 - 64 years	204	150	2,575.7	1,868.6
65 - 74 years	79	53	946.0	643.4
75 - 84 years	22	18	186.6	241.9
85+ years	2	3	5.0	44.78
Total	**307**	**224**	**3713.4**	**2798.8**

Sources: ISS_Part1_u: Table 1.5.1.1.3d
Sources: W00090_NSCLC - Version date: 31MAY2023 13:53 - File Name: Sub5_2_3_c1_RMPexpAgSx_PHtreat_t.rtf
Sources: Cut-off date Melanoma: 09NOV2016 / Cut-off date Pharos: 22JAN2023 - Dataset ADSP1.ADSL:15MAY2023 - PGM Sub5_2_3_c1_RMPexpAgSx_PHtreat_t.sas 04MAY2023 11:16
Note: Patient-months are derived by taking the number of patients multiplied by the mean duration of exposure (days) and dividing this result by 30.4375. Duration of exposure is defined as: date of last exposure to study treatment - date of first administration of study treatment +1.
[1] Patients under 18 years was an exclusion criterion.

4. By ethnic or racial origin

Table SIII.15a: Encorafenib and binimetinib combination: Exposure by ethnic or racial origin (Combo 450 ISP)

Combination integrated safety population (Combo 450 ISP; N=372)		
Racial origin [1]	**Persons**	**Patient-months**
Asian	13	1,65.5
Black or African American	3	4.9
Caucasian	347	4,864.8
Other	5	79.1
Unknown[2]	4	21.0
Total	**372**	**5135.3**

Sources: W00090_NSCLC - Version date: 31MAY2023 13:49 - File Name: Sub5_1_4_c1_RMPexpRace_treat_t.rtf
Sources: Cut-off date Melanoma: 09NOV2016 / Cut-off date Pharos: 22JAN2023 - Dataset ADSP1.ADSL:15MAY2023 - PGM Sub5_1_4_c1_RMPexpRace_treat_t.sas 04MAY2023 11:17
Note: Total subject time, expressed in patient-months, is the sum of the duration of exposure (in months) for each patient.
Duration of exposure is defined as the max exposure between Encorafenib and binimetinib.
Note: No black patients were included in the pool of melanoma indication (source ISS table 1.2)
Duration of Exposure = (date of last exposure to study drug - date of first exposure to study drug +1)/30.4375
[1] In this table, the 'other' group does not include 'Black' origin
[2] Patients with missing value or with value equal to 'Not reported due to confidentiality reason' were included in the unknown category

Melanoma indication (Combo 450 RP; N=274)		
Racial origin [1]	**Persons**	**Patient-months**
Asian	6	72.54
Caucasian	261	3685.16
Other	4	57.79

Melanoma indication (Combo 450 RP; N=274)		
Racial origin [1]	**Persons**	**Patient-months**
Unknown*	3	16.26
Total	**274**	**3831.75**

Sources: ISS_Part1_u: Table 1.5.1.1.4c
Note: Patient-months are derived by taking the number of patients multiplied by the mean duration of exposure (days) and dividing this result by 30.4375. Duration of exposure is defined as: date of last exposure to study treatment - date of first administration of study treatment +1.
[1] No black patients were included in the pool of melanoma indication (source ISS table 1.2)
* Patients with missing value were included in the unknown category

NSCLC indication (N=98)		
Racial origin [1]	**Persons**	**Patient-months**
Asian	7	93.0
Black or African American	3	4.9
Caucasian	86	1179.7
Other	1	21.3
Unknown[2]	1	4.7
Total	**98**	**1303.5***

Sources: W00090_NSCLC - Version date: 31MAY2023 13:53 - File Name: Sub5_2_4_c1_RMPexpRace_PHtreat_t.rtf
Sources: Cut-off date Melanoma: 09NOV2016 / Cut-off date Pharos: 22JAN2023 - Dataset ADSP1.ADSL:15MAY2023 - PGM Sub5_2_4_c1_RMPExpRace_PHtreat_t.sas 04MAY2023 11:20
Note: Total subject time, expressed in patient-months, is the sum of the duration of exposure (in months) for each patient. Duration of exposure is defined as the max exposure between Encorafenib and binimetinib.
Duration of Exposure = (date of last exposure to study drug - date of first exposure to study drug +1)/30.4375
[1] In this table, the 'other' group does not include 'Black' origin
[2] Patients with missing value or with value equal to 'Not reported due to confidentiality reason' were included in the unknown category
* Cumulative numbers may not exactly match the sum of listed numbers due to rounding

Table SIII.15b: Encorafenib and binimetinib combination: Exposure by ethnic or racial origin (broad)

Broad combination integrated safety population (Combo broad ISP; N=531)		
Racial origin [1]	**Persons**	**Patient-months**
Asian	15	185.0
Caucasian	499	6,154.7
Black or African American	3	4.9
Other	10	146.6
Unknown[2]	4	20.9
Total	**531**	**6512.2**

Sources: ISS_Part1_u: Table 1.5.1.1.4d
Sources: W00090_NSCLC - Version date: 31MAY2023 13:53 - File Name: Sub5_2_4_c1_RMPexpRace_PHtreat_t.rtf
Sources: Cut-off date Melanoma: 09NOV2016 / Cut-off date Pharos: 22JAN2023 - Dataset ADSP1.ADSL:15MAY2023 - PGM Sub5_2_4_c1_RMPExpRace_PHtreat_t.sas 04MAY2023 11:20
Note: Patient-months are derived by taking the number of patients multiplied by the mean duration of exposure (days) and dividing this result by 30.4375. Duration of exposure is defined as: date of last exposure to study treatment - date of first administration of study treatment +1.
[1] No black patients were included in the pool of melanoma indication (source ISS table 1.2)
[2] Patients with missing value or with value equal to 'Not reported due to confidentiality reason' were included in the unknown category

▪ Encorafenib in combination with cetuximab

The safety of encorafenib in combination with cetuximab in the targeted indication for the treatment of BRAF V600E-mutant metastatic CRC was evaluated in 216 patients who received encorafenib at the dose of 300 mg QD in combination with cetuximab dosed as per its approved label, based on the pivotal phase III study ARRAY-818-302 doublet arm.

Array-818-302 is a multicentre, randomised, open-label, 3-arm Phase III study conducted in patients with BRAF V600E mCRC whose disease has progressed after 1 or 2 prior regimens in the metastatic setting. A total 665 of patients were randomised (1:1:1) to receive encorafenib 300 mg orally daily in combination with binimetinib 45 mg orally twice daily and cetuximab dosed as per its approved label (Triplet arm, n = 224), or encorafenib 300 mg orally daily in combination with cetuximab dosed as per its approved label (Doublet arm, n = 220) or Control therapy (irinotecan with cetuximab or irinotecan/5-fluorouracil/folinic acid (FOLFIRI) with cetuximab, Control arm, n = 221).

Patients randomized in the doublet arm received oral encorafenib at the dose of 300 mg QD with cetuximab at the recommended dose of 400 mg/m² initially and 250 mg/m² weekly IV infusion.

For the Summary of Clinical Safety, due to differences in study design and doses, safety data from multiple studies were not pooled. However safety data from Phase 1b/2 study CLGX818X2103, contributing to the understanding of the safety profile of the dual combination of encorafenib plus cetuximab were considered.

In the exposure tables presented in this section, the 'Doublet broad population' refers to patients who received doses of encorafenib ranging from 100 mg to 450 mg QD in combination with cetuximab at the standard recommended doses as per product label in the Phase 1b/2 study CLGX818X2103 (N = 76) and patients who received encorafenib at the dose of 300 mg QD in combination with cetuximab in the pivotal phase III study ARRAY-818-302 Doublet arm (N = 216).

Study CLGX818X2103 (Phase 1b/2; encorafenib + cetuximab) was conducted in patients with *BRAF* V600-mutant (V600E mutation, or any other *BRAF* V600 mutation) mCRC, treated with cetuximab dosed as per its approved label and encorafenib at different doses: 100 mg QD (N = 2); 200 mg QD (N = 57); 400 mg QD (N = 9) and 450 mg QD (N = 8) plus cetuximab (N = 76 total).

A summary of overall exposure and duration of exposure is provided below for the Array-818-302 doublet population (randomised doublet arm), by dose, age group and gender, and by ethnic or racial origin.

1. Duration of exposure

Table SIII.16: Duration of exposure (Doublet population)

Encorafenib and cetuximab - Randomized Doublet arm (N=216)		
Duration of exposure (at least)	**Patients**	**Patient-months**
1 month	200	930.27
3 months	113	748.81
6 months	50	481.48
12 months	8	123.20
18 months	1	20.63
24 months	0	.
30 months	0	.
Total	216	936.51

Note: Total subject time, expressed in patient-months, is the sum of the duration of exposure (in months) for each patient
Duration of exposure corresponds to the exposure of ENCO only (not CETUX).
For ENCO: Exposure = (date of last exposure to treatment - date of first exposure to treatment +1)/30.4375
Sources: ARRAY_818_302_Dossier_2019 - Version date: 11SEP2019 14:47 - File Name: T1403_010601_RMP_Doublet_expo1_add.rtf - Listing16.2.5-10.01
Sources: Cut-off date 11FEB2019 - Database lock 30APR2019 - Dataset .ADEX:10SEP19 BASEDTM1.ADSL:29JUL19 - PGM T_RMP_Doublet_expo1_add.sas 11JUL2019 10:42

2. By dose

Table SIII.17: Dose of exposure (Doublet population)

Encorafenib and cetuximab - Randomized Doublet arm (N=216)		
Dose of exposure	**Patients**	**Patient-months**
Encorafenib 300mg QD and Cetuximab	216	936.51
Total	216	936.51

Note: Total subject time, expressed in patient-months, is the sum of the duration of exposure (in months) for each patient
Duration of exposure corresponds to the exposure of ENCO only (not CETUX).
For ENCO: Exposure = (date of last exposure to treatment - date of first exposure to treatment +1)/30.4375
Sources: ARRAY_818_302_Dossier_2019 - Version date: 11SEP2019 14:47 - File Name: T1403_010602_RMP_Doublet_expo2_add.rtf - Listing16.2.5-10.01
Sources: Cut-off date 11FEB2019 - Database lock 30APR2019 - Dataset. ADEX:10SEP19 BASEDTM1.ADSL:29JUL19 - PGM T_RMP_Doublet_expo2_add.sas 11JUL2019 10:45

3. By age group and gender

Table SIII.18: Exposure by age group and gender (Doublet-population)

Encorafenib and cetuximab - Randomized Doublet arm (N=216) by age group and gender				
	Patients		**Patient-Months**	
Age group [1]	**F**	**M**	**F**	**M**
18 - 64 years	60	74	237.70	315.14
65 - 74 years	29	33	148.27	130.96
75 - 84 years	13	6	61.57	34.66
85+ years	1	.	8.21	.
Total	103	113	455.75	480.76

Note: Total subject time, expressed in patient-months, is the sum of the duration of exposure (in months) for each patient
Duration of exposure corresponds to the exposure of ENCO only (not CETUX).
For ENCO: Exposure = (date of last exposure to treatment - date of first exposure to treatment +1)/30.4375
[1] Patients under 18 years was an exclusion criterion
Sources: ARRAY_818_302_Dossier_2019 - Version date: 11SEP2019 14:47 - File Name: T1403_010603_RMP_Doublet_expo3_add.rtf - Listing16.2.5-10.01
Sources: Cut-off date 11FEB2019 - Database lock 30APR2019 - Dataset. ADEX:10SEP19 BASEDTM1.ADSL:29JUL19 - PGM T_RMP_Doublet_expo3_add.sas 11JUL2019 10:27

4. By ethnic or racial origin

Table SIII.19: Exposure by ethnic or racial origin (Doublet population)

Encorafenib and cetuximab - Randomized Doublet arm (N=216) by racial origin		
Racial origin [1]	**Patients**	**Patient-Months**
Asian	25	95.84
Caucasian	181	804.86
Other	3	15.44
Unknown[2]	7	20.37
Total	216	936.51

Note: Total subject time, expressed in patient-months, is the sum of the duration of exposure (in months) for each patient
Duration of exposure corresponds to the exposure of ENCO only (not CETUX).
For ENCO: Exposure = (date of last exposure to treatment - date of first exposure to treatment +1)/30.4375
[1] In this table, the 'Other' group does not include 'Black' origin
[2] Patients with missing value or with value equal to 'Not reported due to confidentiality reason' were included in the unknown category
Sources: ARRAY_818_302_Dossier_2019 - Version date: 11SEP2019 14:47 - File Name: T1403_010604_RMP_Doublet_expo4_add.rtf - Listing16.2.5-10.01
Sources: Cut-off date 11FEB2019 - Database lock 30APR2019 - Dataset. ADEX:10SEP19 .ADSL:09SEP19 - PGM T_RMP_Doublet_expo4_add.sas 11JUL2019 10:27

Part II: Module SIV - Populations not studied in clinical trials involving encorafenib

SIV.1 Exclusion criteria in pivotal clinical studies within the development programme for encorafenib

- **Encorafenib single agent**

The most relevant exclusion criteria in pivotal clinical studies within the development programme specific to encorafenib single agent are the following:

Uveal and mucosal melanoma

Reason for exclusion: BRAF mutations are only present in 10–20% of mucosal melanoma, and they are absent in uveal melanoma (Menzies, 2012; Sosman, 2012).

Is it considered to be included as missing information? No

Rationale: Patients with uveal or mucosal melanoma not exhibiting the target for a BRAF inhibitor are not candidates for treatment with encorafenib.

QTc interval >480 ms

Reason for exclusion: Non-clinical data were not predictive of clinical effect however QT prolongation has been observed in patients treated with BRAF inhibitors (e.g. vemurafenib). Therefore, patients with triplicate average baseline QTc interval >480 ms were excluded. Results from pooled clinical trials suggest encorafenib administration has the potential to result in small increases in QTc interval and mild increases in HR at a clinically relevant dose.

Is it considered to be included as missing information? No

Rationale: QT prolongation is considered an important potential risk.

Known acute or chronic pancreatitis

Reason for exclusion: Pancreatitis or asymptomatic amylase/lipase elevations have been reported with BRAF inhibitors. For a safety evaluation of pancreas-related events, patients with known acute or chronic pancreatitis were excluded from the encorafenib single agent studies in the clinical development plan to avoid confounding factors in relation to these pre-existing conditions. This exclusion criterion was considered necessary due to the potential impact on the evaluation of pancreatic toxicity. Patients with known acute or chronic pancreatitis were not however excluded in the phase III pivotal CMEK162B2301 study for Combo 450 (the first encorafenib/binimetinib combination study to do so).

Is it considered to be included as missing information? No

Rationale: Although pancreatitis is a known BRAF-related effect, in the real-life setting, patients with a medical history of acute or chronic pancreatitis and who are candidates for treatment of metastatic melanoma, are monitored as per routine clinical practice and informed (via product information) that pancreatitis may occur with encorafenib administration. A history of pancreatitis is not listed as a contra-indication.

Concomitant use of non-topical medications known to be strong inhibitors of CYP3A4

Reason for exclusion: Encorafenib is primarily metabolised by CYP3A4. Concomitant administration of encorafenib with strong CYP3A4 inhibitors may result in increased encorafenib exposure and a potential increase in toxicity.

Examples of strong CYP3A4 inhibitors include, but are not limited to, ritonavir, itraconazole, clarithromycin, telithromycin, posaconazole and grapefruit juice.

Is it considered to be included as missing information? No

Rationale: Over-exposure due to concomitant use with strong and moderate CYP3A4 inhibitors is included as an important potential risk.

- **Encorafenib in combination with binimetinib or encorafenib in combination with cetuximab in pivotal studies**

The most relevant exclusion criteria in pivotal clinical studies within the development programme that are applicable to the combination (hence due to the presence of cetuximab or binimetinib in the combination) but not specific to encorafenib single agent, are addressed below.

The following exclusion criteria are binimetinib-related:

Uncontrolled arterial hypertension despite appropriate medical therapy

Reason for exclusion: Potential for worsening of pre-existing severe and uncontrolled hypertension with potentially serious or life-threatening end-organ complications.

Is it considered to be included as missing information? No

Rationale: Hypertension was included as an important identified risk for binimetinib and was addressed in the relevant section of the binimetinib RMP. This risk was removed from the list of safety concerns of binimetinib in the last approved version of binimetinib RMP (Version 2.0; dated on 24 Apr 2020) in line with the approach of the revised GVP Module V (Rev 2), as hypertension is considered as clinically manageable and recommendations for monitoring and management of hypertension are mentioned in the binimetinib SmPC, and considered as routine pharmacovigilance activities. Furthermore, the impact to the individual is expected to be very low considering the seriousness of the advanced cancer.

Patients who are planning on embarking on a new strenuous exercise regimen and patients with neuromuscular disorders associated with elevated creatine phosphokinase (CK)

Reason for exclusion: Due to the potential impact on evaluation of MEK-induced muscular toxicity e.g. major CK elevations and potentially serious and life-threatening rhabdomyolysis, patients undergoing a strenuous exercise regimen or with known neuromuscular disorders associated with CK elevation were excluded to minimise confounding factors.

Is it considered to be included as missing information? No

Rationale: Rhabdomyolysis was included as an important identified risk and addressed in the relevant section of the binimetinib RMP. This risk was removed from the list of safety concerns of binimetinib in the last approved version of binimetinib RMP (Version 2.0; dated on 24 Apr 2020) in line with the approach of the revised GVP Module V (Rev 2) as rhabdomyolysis and CK elevation are identified as ADRs for binimetinib and are well addressed in the binimetinib SmPC. The impact to the individual is expected to be low considering the seriousness of the advanced cancer.

Impaired cardiovascular function or clinically significant cardiovascular diseases

Reason for exclusion: Left ventricular dysfunction is a known adverse effect of MEK inhibitors including binimetinib. Due to the risk of serious worsening of left cardiac dysfunction, patients with impaired cardiac function–LVEF <50%) were excluded from clinical trials. In the pivotal PHAROS study for the NSCLC indication, the exclusion criteria remained very similar, but more precise and specific wording was applied considering an older population in NSCLC setting (and thus, potentially greater risk of cardiac dysfunction) compared with the melanoma population. As such, the term "congestive heart failure requiring treatment (Grade ≥ 2)" was used in this exclusion criterion for the PHAROS study instead of "symptomatic chronic heart failure" that was used in the studies for the melanoma indication.

Is it considered to be included as missing information? No

Rationale: Use in patients with reduced cardiac function (LVEF <50%) or symptomatic chronic heart failure was considered as a missing information from a risk management planning perspective and was addressed in the relevant section of the binimetinib RMP. This risk was removed from the list of safety concerns of binimetinib in the last approved version of binimetinib RMP (Version 2.0; dated on 24 Apr 2020) in line with the approach of the revised GVP Module V (Rev 2) as specific recommendations for monitoring and management of left ventricular dysfunction are well addressed in the binimetinib SmPC, and considered as routine risk minimisation measures.

Left ventricular dysfunction is a known class-effect of MEK inhibitors. Patients with reduced cardiac function have not been included in clinical trials with binimetinib. However, if it is known that patients with reduced cardiac function or symptomatic chronic heart failure have a different safety profile to the general population for which binimetinib is indicated, any risk to these patients should be satisfactorily minimised through routine risk minimisation measures. The impact to the individual is deemed minor considering the seriousness of the advanced cancer.

History or current evidence of retinal vein occlusion (RVO or current risk factors of RVO)

Reason for exclusion: RVO is a known class effect with MEK inhibitors including binimetinib. There is a theoretical concern that patients with history of RVO or risk factors for RVO may be at higher risk of RVO during treatment.

Is it considered to be included as missing information? No

Rationale: RVO was included as an important potential risk for binimetinib when used in combination with encorafenib and was addressed in the relevant section of the binimetinib RMP. This risk was then removed from the list of safety concerns of binimetinib in the last approved version of binimetinib RMP (Version 2.0; dated on 24 Apr 2020) in line with the approach of the revised GVP Module V (Rev 2) as the risk is considered well addressed in the binimetinib SmPC and no additional pharmacovigilance activities or risk minimisation measures to address this risk are needed The impact to the individual is deemed minor considering the seriousness of the advanced cancer.

History of Gilbert's syndrome

Reason for exclusion: Gilbert's syndrome is characterised by mild unconjugated non-haemolytic hyperbilirubinemia, which does not lead to hepatic inflammation, fibrosis, chronic liver disease or liver failure. Almost 100 years after its clinical description, it was linked to a genetic variant of the human bilirubin UDP-glucuronosyltransferase (*UGT1A1)*, *UGT1A1 *28*, found in approximately 40% of Caucasoid individuals (Strassburg, 2008).

The main route of hepatic transformation of binimetinib is glucuronidation, and the use of binimetinib in patients with Gilbert's syndrome has not been studied.

Is it considered to be included as missing information? No

Rationale: Gilbert's syndrome is primarily linked to *UGT1A1*28* variants, but other variants in the promoter and coding regions are also involved in the predisposition of the disease (Kadakol, 2000) To date, more than 100 variants have been identified in the *UGT1A1* gene (Takano, 2017). Among these polymorphisms, the clinically important variants include UGT1A1*28 allelic variant (Udomuksorn, 2007).

Binimetinib is primarily metabolised through UGT1A1 mediated glucuronidation, however, in clinical study sub-analysis, there was no apparent relationship observed between binimetinib exposure and UGT1A1 mutation status. In addition, simulations to investigate the effect of 400 mg atazanavir (UGT1A1 inhibitor) on the exposure of 45 mg binimetinib predicted similar binimetinib C_{max} in the

presence or absence of atazanavir. Therefore, the possible extent of drug interactions mediated by UGT1A1 is minimal, and likely not clinically relevant.

There is a theoretical risk of over-exposure in patients with impairment of glucuronidation in Gilbert's syndrome. However, the population PK analysis (study CP16-001) suggests no substantial difference in patients with *28/*28 mutation compared to those without this genotype. Thus, cancer patients carrying the genotypes associated with Gilbert's syndrome may be possible candidates for binimetinib based therapy. In the real-life, decision for treatement with benimetinib should be made by the treating physician taking into account the individual benefit-risk in relation to the severity of the malignant metastatic disease.

The following exclusion criteria are common to combination studies in the intended indications

Any untreated CNS lesions, history of leptomeningeal metastases and symptomatic brain metastases

Reason for exclusion: Animal studies have suggested that BRAF inhibitors may have limited brain distribution due to efflux from transporters such as P-glycoprotein (P-gp), activity has been seen clinical trials (Mittapalli, 2013). Encorafenib is a substrate of (P-gp) with a high apparent passive permeability. Distribution into rat tissues was rapid but there was no distribution to the CNS (brain and spinal cord) and no retention in melanin-rich tissues.

Drug-related [14C] encorafenib radioactivity showed little or no distribution to the CNS (brain and spinal cord) *(*Encorafenib Investigator Brochure. Edition 11, 20 June 2019*).* In addition, patients with brain/leptomeningeal metastases are generally excluded from clinical trial participation because of their shortened life expectancy associated with symptomatic brain/leptomeningeal metastases and a concern that these patients would not receive adequate exposure (due so shortened duration) the study drug, making it difficult to appropriately evaluate clinical benefit and potentially confounding overall study results. However, patients with CNS lesions were not excluded from encorafenib clinical trials in melanoma if their CNS metastatic lesions were appropriately treated by surgery or radiotherapy. In the mCRC Array-818-302 study, patients with only symptomatic brain metastases were excluded. In the PHAROS study, patients with previously treated brain metastases were not excluded if they were stable for at least 28 days prior to the first dose of study treatment and neurologic symptoms had returned to baseline. Patients with untreated brain metastases were not excluded from PHAROS study if lesions were < 5 mm and were clinically stable and asymptomatic.

Is it considered to be included as missing information? No

Rationale: There is no evidence of meaningful penetration of encorafenib into the CNS, and no evident contra-indication to the treatment of patients with brain metastases due to safety reasons.

History of thromboembolic or cerebrovascular events including transient ischemic attacks, cerebrovascular accidents, deep vein thrombosis or pulmonary emboli

Reason for exclusion: Venous thromboembolism (VTE) events have been noted to occur with MEK-inhibitor treatment as a class effect (Welsh, 2015). They are also known with cetuximab use (Erbitux SmPC). Regarding arterial thromboembolic events and cetuximab, in combination with fluoropyrimidines, the frequency of cardiac ischaemia including myocardial infarction were increased compared to that with fluoropyrimidines for cetuximab (SmPC Erbitux® (cetuximab). 2019). In the CRC study Array-818-302, the exclusion criterion for patients with history of venous thromboembolic events or cerebrovascular events, which are arterial in nature, was added due to the potential impact on evaluation of safety (e.g. pulmonary embolism and cerebrovascular events) for evaluating the risk of adding cetuximab to binimetinib and encorafenib combination or to encorafenib and limiting confounding factors. Exclusion of patients with ischaemic cardiac events (history of acute myocardial infarction, acute coronary syndromes ≤ 6 months prior to start of study treatment), not specific to the mCRC population, is covered by the exclusion criteria "impaired cardiovascular function or clinically significant cardiovascular diseases and addressed" above.

Is it considered to be included as missing information? No

Rationale: VTE was addressed as an important identified risk in the relevant section of the binimetinib RMP, and is listed as an ADR for cetuximab (Erbitux SmPC). In the real-life setting, patients with BRAF-mutant melanoma, BRAF-mutant NSCLC, or BRAF-mutant mCRC and medical history of venous or arterial thromboembolic events may benefit from encorafenib and binimetinib or encorafenb and cetuximab combination, the decision to treat those patients should be made by the treating physician based on the individual benefit-risk. This risk of VTE has been removed from the list of safety concerns of binimetinib in the last approved version of binimetinib RMP (Version 2.0; dated on 24 Apr 2020) in line with the approach of the revised GVP Module V (Rev 2) as the risk was considered well addressed in the binimetinib SmPC and no additional pharmacovigilance activities or risk minimisation measures to address this risk were needed. The impact to the individual is deemed acceptable considering the seriousness of the advanced cancer.

Previous or concurrent malignancy (except for adequately treated basal cell or squamous cell carcinoma of the skin), in situ carcinoma of the cervix, treated curatively and without evidence of recurrence for at least 3 years prior to the study, and other solid tumours treated curatively, and without evidence of recurrence for at least 3 years prior to study entry

In the pivotal PHAROS study for the NSCLC indication, patients with concurrent or previous other malignancy within 2 years of study entry were excluded (except curatively treated basal or squamous cell skin cancer, prostate intraepithelial neoplasm, carcinoma in-situ of the cervix, Bowen's disease and Gleason ≤ 6 prostate cancer).

Reason for exclusion: Prior malignancies with a risk of relapse > 10% at 5 years are usually excluded from oncology clinical trials to avoid any risk that a relapse of this malignancy interferes with the interpretation of the primary efficacy endpoint of the clinical trials evaluating a new drug in a specific indication, therefore, the main aim is to exclude an important confounding factor in the interpretation of the trial end-point.

Is it considered to be included as missing information? No

Rationale: Patients with a previous malignancy who are diagnosed with metastatic melanoma or advanced NSCLC are candidates to receive encorafenib and binimetinib combination therapy. Caution should be paid to patients with prior malignancies harbouring RAS mutations due to the potential class effect of BRAF inhibitors which may promote cutaneous and non-cutaneous malignancies associated with activation of RAS through mutation or other mechanisms. In patients with a concurrent malignancy, the decision to treat the metastatic melanoma or advanced NSCLC or the concurrent cancer first will be taken by the treating physician based on individual benefit-risk assessment.

Known positive serology for HIV, active hepatitis B, and/or active hepatitis C infection

Reason for exclusion: Patients with positive serology for HIV are known to receive poly-medication including drugs with potential hepatic adverse reactions and drug-drug interactions such as anti-proteases which are CYP 3A4 inhibitors and they are also at a higher risk of different antiretroviral toxicities, including but not limited to hepatotoxicity. The exclusion criterion for patients with active hepatitis B and/or active hepatitis C is due to the potential impact on evaluation of safety e.g. hepatotoxicity.

Is it considered to be included as missing information? No

Rationale: Liver laboratory parameters have been closely monitored throughout the encorafenib clinical programme. Although transaminase elevations are considered adverse drug reactions, there is no evidence for an important identified risk. In the real-life setting, for patients diagnosed with metastatic melanoma or advanced NSCLC, the decision to treat metastatic melanoma or advanced NSCLC in patients with known positive serology for HIV, active hepatitis B, and/or active hepatitis C infection should be made by the treating physician taking into account the individual benefit-risk.

Impairment of gastrointestinal function

Reason for exclusion: Patients with impaired gastrointestinal function including active ulcerative disease, uncontrolled nausea, vomiting, diarrhoea and malabsorption syndrome were excluded due to potential unreliable administration (missed doses) and impaired absorption of the oral study drug in addition to a potential impact on evaluation of gastrointestinal toxicity. In the pivotal Array-818-302 study for the mCRC indication, history of chronic inflammatory bowel disease or Crohn's disease requiring medical intervention (immunomodulatory or immunosuppressive medications or surgery) ≤ 12 months prior to randomization was added.

Is it considered to be included as missing information? No

Rationale: In the real-life setting, the decision to treat patients with known impaired gastrointestinal function who are diagnosed with metastatic melanoma or mCRC should be made by the treating physician based on the individual benefit-risk.

Gastrointestinal toxicity (diarrhoea, nausea, vomiting) is generally manageable in routine medical practice in oncology, by symptomatic medications and fluid electrolyte replacement, and dose adjustments. No prophylaxis was required during encorafenib single agent and in encorafenib combination clinical trials.

Known acute or chronic pancreatitis

Reason for exclusion: Pancreatitis or asymptomatic amylase/lipase elevations have been reported with BRAF inhibitors. For a safety evaluation of pancreas-related events, patients with known acute or chronic pancreatitis were excluded from the studies to avoid confounding factors in relation to these pre-existing conditions. This exclusion criterion was considered necessary due to the potential impact on the evaluation of pancreatic toxicity. Patients with known acute or chronic pancreatitis were however not excluded in the phase III pivotal CMEK162B2301 study for Combo 450 (the first and only encorafenib/binimetinib combination study to do so).

Is it considered to be included as missing information? No

Rationale: Although pancreatitis is a known BRAF-related effect, in the real-life setting, patients with a medical history of acute or chronic pancreatitis and who are candidates for treatment of metastatic melanoma and advanced NSCLC are monitored as per routine clinical practice and informed (via product information) that pancreatitis may occur with encorafenib administration.

Women of child-bearing potential, unless using highly effective methods of contraception, pregnant or lactating women

Reason for exclusion: There are no data regarding the use of encorafenib in pregnant women. However, studies in animals have demonstrated reproductive toxicity.

In accordance with the ICH S9 guideline, *Nonclinical Evaluation for Anticancer Pharmaceuticals*, March 2010, fertility studies were not conducted, however, no concerns were raised in repeat-dose toxicity studies in animals.

Is it considered to be included as missing information? No

Rationale: Based on the non-clinical data, embryo-foetal toxicity was an important potential risk for encorafenib. However, this risk has been removed from the list of safety concerns of encorafenib in the last approved RMP (Version 2.0; dated on 26 March 2020) in line with the approach of the revised GVP Module V (Rev 2) as the risk is considered well addressed in the SmPC. The impact to the individual is deemed minor considering the seriousness of the advanced cancer.

Given the median age for women of the target population is over 50 years, the recommendation for effective contraception for women of childbearing potential and the severity of the disease, the use of encorafenib in pregnant or lactating women is limited.

In the event of a need for breastfeeding during treatment, the decision should be made whether to discontinue breastfeeding or to discontinue encorafenib taking into account the benefit of breast-feeding for the child and the benefit of the drug for the mother.

Paediatric population

Reason for exclusion: No patients <18 years of age were treated in any trial in the encorafenib clinical development programme.

Is it considered to be included as missing information? No

Rationale: The paediatric population is not the target indication.

SIV.2 Limitations to detect adverse reactions in clinical trial development programmes of encorafenib

- **Encorafenib single agent**

Table SIV.1: Encorafenib: Limitations for detecting adverse drug reactions (ADRs)

Ability to detect adverse reactions	Limitation of trial programme	Discussion of implications for target population
Rare adverse reactions	Based on the 217 patients of the pooled encorafenib safety set, ADRs with a true frequency ≥ 1/1000 could be detected. For N=217 and event=1, and the 95% CI = [0.0000, 0.0136]*, the safety database would not allow an ADR that occurs with a true frequency of <1% to be ruled out.	The clinical development programme is unlikely to detect rare adverse reactions (frequency ≥1/10,000 to <1/1,000). Limited impact for encorafenib single agent, and no intended indication for encorafenib monotherapy. When encorafenib is used in combination with binimetinib, if binimetinib is temporarily interrupted, encorafenib is reduced to 300 mg QD during the time of binimetinib dose interruption. If binimetinib is permanently discontinued, encorafenib should be discontinued
Adverse reactions due to prolonged exposure	In the population of 217 patients who received encorafenib single agent at the dose of 300 mg QD, the mean duration of exposure was 44.84 weeks, with 77 patients (35.5%) exposed to treatment for ≥48 weeks. The duration was limited due to the expected early progression of disease in the studied population.	Limited impact for encorafenib single agent and no intended indication for encorafenib monotherapy. When encorafenib is used in combination with binimetinib, if binimetinib is temporarily interrupted, encorafenib is reduced to 300 mg QD during the time of binimetinib dose interruption. If binimetinib is permanently discontinued, encorafenib should be discontinued.
Adverse reactions due to cumulative effects	Duration of exposure, hence cumulative dose, was limited due to expected early progression of disease in the studied population.	Limited impact for encorafenib single agent and no intended indication for encorafenib monotherapy. When encorafenib is used in combination with binimetinib, if binimetinib is temporarily interrupted, encorafenib is reduced to 300 mg QD during the time of binimetinib dose interruption. If binimetinib is permanently discontinued, encorafenib should be discontinued.

Ability to detect adverse reactions	**Limitation of trial programme**	**Discussion of implications for target population**
Adverse reactions with long latency	Duration of exposure was limited due to expected early progression of disease in the studied population.	Limited impact. At the time of this initial RMP, there is no intended indication for encorafenib monotherapy. When encorafenib is used in combination with binimetinib, if binimetinib is temporarily interrupted, encorafenib is reduced to 300 mg QD during the time of binimetinib dose interruption. If binimetinib is permanently discontinued, encorafenib should be discontinued.

**Estimated as per FDA's Guidelines*

- **<u>Encorafenib in combination with binimetinib</u>**

Table SIV.2: Encorafenib and binimetinib combination: Limitations for detecting ADRs

Ability to detect adverse reactions	**Limitation of trial programme**	**Discussion of implications for target population**
Rare adverse reactions	The specific combination of encorafenib plus binimetinib has been evaluated in 372 patients with metastatic melanoma and advanced NSCLC at the recommended doses of 450 mg QD encorafenib and 45 mg BID binimetinib. Based on the 372 patients of the pooled integrated safety population, ADRs with a true frequency ≥ 1/1000 could be detected. For N=372 and event=1, and the 95% CI= [0.0000, 0.0079]*, the safety database would allow an ADR that occurs with a true frequency of 1% to be ruled out.	The clinical development programme is unlikely to detect rare ADRs (frequency ≥1/10,000 to <1/1,000). Detection and evaluation of rare ADRs is part of routine post-marketing pharmacovigilance activities.
Adverse reactions due to prolonged exposure	Among all patients in the ISP and broad combination safety sets, the mean (SD) duration of exposure to encorafenib and binimetinib was 60.0 (42.3) weeks and 53.3 (43.4) respectively, with half of patients (50.3%) in the Combo 450 ISP safety and 231 (43.5%) patients in the broad safety set exposed to the combination for ≥48 weeks. The duration was limited due to the expected early progression of disease in the studied population.	Limited impact for the combination. Exposure in real-life situations is not expected to be longer than in clinical trials.

Ability to detect adverse reactions	**Limitation of trial programme**	**Discussion of implications for target population**
Adverse reactions due to cumulative effects	Duration of exposure, hence cumulative dose, was limited due to expected early progression of disease in the studied populations.	Limited impact for the combination. Cumulative effects in real-life situations in melanoma and NSCLC are not expected to be greater than in clinical trials as duration of exposure is not expected to be longer.
Adverse reactions with long latency	Duration of exposure was limited due to expected early progression of disease in the studied populations.	Limited impact for the combination. Patients with BRAF-mutant unresectable/metastatic melanoma and advanced NSCLC have a limited life expectancy, hence effects with long latency are unlikely to be relevant in the real-life setting.

**: Estimated as per FDA's Guidelines*

- **<u>Encorafenib in combination with cetuximab</u>**

Table SIV.3: Encorafenib in combination with cetuximab: Limitations for detecting ADRs

Ability to detect adverse reactions	**Limitation of trial programme**	**Discussion of implications for target population**
Rare adverse reactions	The specific combination of encorafenib and cetuximab has been evaluated in 216 patients with BRAF-mutant metastatic CRC at the recommended doses of 300 mg QD encorafenib. Cetuximab was administered as per product label. Based on the 216 patients of the doublet safety population, ADRs with a true frequency ≥ 1/1000 could be detected. For N=216 and event=1 and the 95% [CI=0.0000, 0.0137]*, the safety database would not allow an ADR that occurs with a true frequency of 1% to be ruled out.	The clinical development programme is unlikely to detect rare ADRs (frequency ≥1/10,000 to <1/1,000). Detection and evaluation of rare ADRs is part of routine post-marketing pharmacovigilance activities.
Adverse reactions due to prolonged exposure	Among all patients in the safety doublet population, the mean (SD) duration of exposure to encorafenib within the dual combination was 15.321 (14.0) weeks, with 14 (6.5%) exposed to the	Limited impact for the combination. Exposure in real-life situations is not expected to be longer than in clinical trials.

Ability to detect adverse reactions	Limitation of trial programme	Discussion of implications for target population
	combination for ≥48 weeks. The duration was limited due to the expected early progression of disease in the studied population and the early cut-off date for the planned analysis.	
Adverse reactions due to cumulative effects	Duration of exposure, hence cumulative dose, was limited due to expected early progression of disease in the studied population.	Limited impact for the combination. Cumulative effects in real-life situations in the BRAF-mutant mCRC indication are not expected to be greater than in clinical trials as duration of exposure is not expected to be longer.
Adverse reactions with long latency	Duration of exposure was limited due to expected early progression of disease in the studied population.	Limited impact for the combination. Patients with BRAF-mutant metastatic CRC have a limited life expectancy, hence effects with long latency are unlikely to be relevant in the real-life setting.

**: Estimated as per FDA's Guidelines*

SIV.3 Limitations with respect to populations typically under-represented in clinical trial development programmes of encorafenib

Lists of populations included but under-represented (≤5% of patients exposed) or excluded in clinical trial development programmes are provided below.

Table SIV.4: Encorafenib: Exposure of special populations included or not in clinical trial development programmes – Single agent and combination therapy with any agent

Type of special population (any included in pre-authorisation clinical development programme Yes/No)	**Patients**	**Patient-months**
Pregnant or breastfeeding women	No pregnant or breastfeeding women were enrolled or accidentally exposed to encorafenib in any clinical trials[a]	NA

Sources: Investigator's Brochure Encorafenib; version of May 2023
[a]As of 20 January 2023, a total of 2714 participants have received at least one dose of encorafenib as single agent or in all combination studies.

▪ Encorafenib single agent

Table SIV. 5: Encorafenib: Limitations with respect to under-represented populations

Type of special population (Any included in pre-authorisation clinical development program) - Encorafenib monotherapy safety pool (N=217)				
			Persons	**Patient-months**
Patients with relevant comorbidities:	Hepatic Impairment[#]	Mild	9	59.50
	Renal Impairment	Moderate (CrCl 30 and 50mL/min)	2	8.74
		Severe (CrCl<30mL/min)	1	6.05
	Cardiac Impairment	Baseline LVEF Dysfunction <50%	0	0
Patients with a disease severity different from inclusion criteria in clinical trials:		Brain metastases: Yes	8	53.59
		ECOG PS ≥ 2	0	0
Population with relevant different ethnic origin:		Asian	9	82.96
		Other	4	33.41
		Unknown*	10	62.46

Sources: ISS Part1_u: Table 1.5.1.1.5b
#Hepatic impairment calculated based on NCI definition.
Note: Patient-months are derived by taking the number of patients multiplied by the mean duration of exposure (days) and dividing this result by 30.4375. Duration of exposure is defined as: date of last exposure to study treatment - date of first administration of study treatment +1.

- **Encorafenib in combination with binimetinib**

Table SIV.6a: Encorafenib and binimetinib combination: Limitations with respect to under-represented populations in the integrated combination safety pool (Combo 450 ISP)

Type of special population (Any included in pre-authorisation clinical development program) **Combination integrated safety population (Combo 450 ISP; N=372)**				
			Persons	**Patient-months**
Patients with relevant comorbidities:	Hepatic Impairment[#]	Moderate	2	33.6
	Renal Impairment	Moderate (CrCl ≥30 and ≤50mL/min)	14	140.6
		Severe (CrCl<30mL/min)	0	0
	Cardiac Impairment	Baseline LVEF Dysfunction <50%	1	8.7
Patients with a disease severity different from inclusion criteria in clinical trials:		ECOG PS ≥ 2	1	12.0
Population with relevant different ethnic origin:		Asian	13	165.5
		Black or African American	3	4.9
		Other[1]	5	79.1
		Unknown[2]	4	21.0

Sources: ISS: Part1_u: table 1.5.1.1.5c
Sources: W00090_NSCLC - Version date: 31MAY2023 13:50 - File Name: Sub5_1_5_c1_RMPexpSpePop_treat_t.rtf
Sources: Cut-off date Melanoma: 09NOV2016 / Cut-off date Pharos: 22JAN2023 - Dataset ADSP1.ADSL:15MAY2023 - PGM Sub5_1_5_c1_RMPexpSpePop_treat_t.sas 04MAY2023 11:16Note: Total subject time, expressed in patient-months, is the sum of the duration of exposure (in months) for each patient.
Duration of exposure is defined as the max exposure between Encorafenib and binimetinib. Duration of Exposure = (date of last exposure to study drug - date of first exposure to study drug +1)/30.4375
#Hepatic impairment calculated based on NCI definition
[1] In this table, the 'other' group does not include 'Black' origin
[2] Patients with missing value or with value equal to 'Not reported due to confidentiality reason' were included in the unknown category
Pregnant women and Breastfeeding women were excluded from the trials.
No black patients were included in the pool of melanoma indication.

Table SIV.6b: Encorafenib and binimetinib combination: Limitations with respect to under-represented populations in the pooled combination safety pool (broad)

Type of special population (Any included in pre-authorisation clinical development program) **Broad combination integrated safety population (Combo broad ISP; N=531)**			**Persons**	**Patient-months**
Patients with relevant comorbidities:	Hepatic Impairment[#]	Moderate	2	33.6
	Renal Impairment	Moderate (CrCl ≥ 30 and ≤50mL/min)	17	183.5
		Severe (CrCl<30mL/min)	0	0
	Cardiac Impairment	Baseline LVEF Dysfunction <50%	2	8.8
Patients with a disease severity different from inclusion criteria in clinical trials:		ECOG PS: 2 and over	7	34.66
Population with relevant different ethnic origin:		Asian	15	185.1
		Black or African American	3	4.9
		Other [1]	10	146.6
		Unknown[2]	4	20.9

Sources: ISS_Part1_u: table 1.5.1.1.5d
Sources: W00090_NSCLC - Version date: 31MAY2023 13:54 - File Name: Sub5_2_5_c1_RMPexpSPop_PHtreat_t.rtf
*Sources: Cut-off date Melanoma: 09NOV2016 / Cut-off date Pharos: 22JAN2023 - Dataset ADSP1.ADSL:15MAY2023 - PGM Sub5_2_5_c1_RMPexpSPop_PHtreat_t.sas 10MAY2023 10:31#*Hepatic impairment calculated based on NCI definition.
[1] In this table, the 'other' group does not include 'Black' origin
[2] Patients with missing value or with value equal to 'Not reported due to confidentiality reason' were included in the unknown category
Note: Patient-months are derived by taking the number of patients multiplied by the mean duration of exposure (days) and dividing this result by 30.4375. Duration of exposure is defined as: date of last exposure to study treatment - date of first administration of study treatment +1.
Pregnant women and Breastfeeding women were excluded from the trials.
No black patients were included in the pool of melanoma indication.

- **Encorafenib in combination with cetuximab**

Table SIV.7a Limitations with respect to under-represented populations – Randomized Doublet arm (N=216)

ENCO+CETUX - Randomized Portion (N=216) **Type of special population (any included in pre-authorisation clinical development program)**			**Patients**	**Patient-Months**
Patients with relevant comorbidities:	Hepatic Impairment* Renal Impairment	Moderate	2	6.44
		Severe	2	2.46
		Severe (CrCl<30mL/min)	0	0.00
	Cardiac Impairment	Baseline LVEF Dysfunction <50%	0	0.00
Patients with a disease severity different from inclusion criteria in clinical trials:		Brain metastases at baseline** : Yes	3	12.39
		ECOG PS >= 2	4	6.31
Population with relevant different race origin:		Asian	25	95.84
		Other[1]	3	15.44
		Unknown[2]	7	20.37

Note: Total subject time, expressed in patient-months, is the sum of the duration of exposure (in months) for each patient
Duration of exposure corresponds to the exposure of ENCO only (not CETUX).
For ENCO: Exposure = (date of last exposure to study drug - date of first exposure to study drug +1)/30.4375
[1] In this table, the 'Other' group does not include 'Black' origin. / [2] Patients with missing value or with value equal to 'Not reported due to confidentiality reason' were included in the unknown category
* Hepatic impairment calculated based on NCI definition. / ** Brain metastases according to the investigator or an independant assessor before or until 15 days after first treatment intake.
Pregnant women and Breastfeeding women were excluded from the trials
Sources: ARRAY_818_302_Dossier_2019 - Version date: 19FEB2020 9:13 - File Name: T1403_010605_RMP_Doublet_expo5_add_IAcorr.rtf - Listing16.2.5-10.01
Sources: Cut-off date 11FEB2019 - Database lock 30APR2019 - Dataset WSPOSTIA.ADEX:12FEB20 WSPOSTIA.ADSL:12FEB20 - PGM T_RMP_Doublet_expo5_add_IAcorr.sas 18FEB2020 11:43

Table SIV.7b: Limitations with respect to under-represented populations - Broad Doublet population (N=292)

Broad doublet population (N=292) **Type of special population (any included in pre-authorisation clinical development program)**			**Patients**	**Patient-Months**
Patients with relevant comorbidities:	Hepatic Impairment* Renal Impairment	Moderate	2	6.44
		Severe	2	2.46
		Severe (CrCl<30mL/min)	0	0.00
	Cardiac Impairment	Baseline LVEF Dysfunction <50%	1	3.02
Patients with a disease severity different from inclusion criteria in clinical trials:		Brain metastases at baseline**: Yes	3	12.39
		ECOG PS >= 2	7	20.50
Population with relevant different race origin:		Black or African American	1	6.14
		Other	4	21.06
		Unknown[1]	8	23.36

#: Pool of ARRAY-818-302 (cut-off date=11FEB2019) and CLGX818X2103 (cut-off date=05JAN2018)
Note: Total subject time, expressed in patient-months, is the sum of the duration of exposure (in months) for each patient
Duration of exposure is defined as the ENCO exposure (excluding CETUX).
For ENCO: Exposure = (date of last exposure to study drug - date of first exposure to study drug +1)/30.4375

[1] Patients with missing value or with value equal to 'Not reported due to confidentiality reason' were included in the unknown category
* Hepatic impairment calculated based on NCI definition. / ** For ARRAY-818-302: brain mets according to the investigator or an independant assessor before or until 15 days after first treatment intake. For CLGX818X2103: brain mets according to Metastatic Sites at baseline.
Pregnant women and Breastfeeding women were excluded from the trials
Sources: ARRAY_818_302_Dossier_2019 - Version date: 21FEB2020 9:14 - File Name: A009_02_7_IA_expo_rmp_saf_D_t.rtf - ListingA009.02.8
Sources: Cut-off date 11FEB2019 - Database lock 30APR2019 - Dataset WSPOSTIA.ADEXD1P:12FEB20 WSPOSTIA.ADSLD1P:12FEB20 - PGM A009_02_7_IA_expo_rmp_saf_D_t.sas 07FEB2020 17:10

Part II: Module SV - Post-authorisation experience of encorafenib

SV.1 Post-authorisation exposure

The International Birth Date of encorafenib is 27 June 2018.

Encorafenib was first approved in the USA on 27-Jun-2018, in combination with binimetinib, for the treatment of patients with unresectable or metastatic melanoma with a BRAF V600E or V600K mutation.

Encorafenib was approved for marketing in the EU, in the same indication, on 20-Sep-2018.
A marketing authorisation was granted for encorafenib in the US on 08 April 2020 to be used in combination with cetuximab for the treatment of adult patients with metastatic colorectal cancer with a BRAF mutation who have received prior systemic therapy treatment. In the EU, this indication was approved on 02 June 2020.

As of 26 June 2023, which is the DLP of the most recent submitted Periodic Benefit-Risk Evaluation Report (PBRER/PSUR, 27-Jun-2022 to 26-Jun-2023) to EMA, encorafenib has received marketing authorisation for use in 65 countries.

SV.1.1 Method used to calculate exposure

Estimated exposure is calculated by dividing the estimated number of total capsules sold by 5, which is the average number of dosage units taken daily (based on approved prescribing information) for encorafenib (6 capsules daily for metastatic melanoma and 4 capsules daily for mCRC) and further dividing by 365.25 to obtain patient-years.

SV.1.2 Exposure

Cumulatively, the worldwide exposure to encorafenib is estimated to be 22,569 patient-years., including 11,943 patient-years in the EU countries.

From the post-marketing experience sources, no safety concern was identified in special situations including off-label use, overdose or use in special populations.

Part II: Module SVI - Additional EU requirements for the safety specification of encorafenib

Potential for misuse for illegal purposes

None for encorafenib based on non-clinical data.

Given the nature of encorafenib as an anti-cancer agent, it is considered that there is an extremely low potential for abuse. There are no significant observed psychiatric or euphoric effects associated with encorafenib which could potentially motivate its abuse. In rat and monkey studies, no significant CNS effects were observed. Radio-labelled and whole-body autoradiography studies in rats found no meaningful CNS penetration. Therefore, it is not anticipated that encorafenib will be associated with any significant potential for abuse.

Part II: Module SVII - Identified and potential risks of encorafenib

▪ Encorafenib single agent

As indicated in Part II: Module SIII above, for the clinical trial exposure of single-agent encorafenib in patients with unresectable or metastatic melanoma:

- 'Enco 300' population refers to the encorafenib 300 mg QD arm patients of Study CMEK162B2301 (N=192)
- 'Enco 300 P' population refers to the pooled encorafenib 300 mg QD monotherapy population (N=217).

▪ Encorafenib in combination with binimetinib

As indicated in Part II: Module SIII above, safety data from 6 supportive clinical trials in patients with unresectable or metastatic melanoma and NSCLC are included in this submission for the combination of encorafenib and binimetinib for the treatment of patients with unresectable or metastatic BRAF V600-mutant melanoma and BRAF V600E-mutant advanced NSCLC. Safety data from 4 clinical studies are pooled (Studies CMEK162B2301, CLGX818X2109, CMEK162X2110 and ARRAY 818-202 (C4221008)) to assess the safety of the combination at the approved dose encorafenib 450 mg QD and binimetinib 45 mg BID.

In the pooled safety analyses:

- 'Combo 450' refers to the combination of encorafenib 450 mg QD and binimetinib 45 mg BID in Study CMEK162B2301 (N=192). When appropriate, to avoid confusion with other populations, this population is referred to as Combo 450 arm of study CMEK162B2301.
- 'Combo 450 RP' (as named in the initial MAA) or the 'Melanoma population' (as named in the MAA for NSCLC indication) refers to the restricted combination safety pool for patients who received doses of encorafenib at 450 mg QD in combination with binimetinib at 45 mg BID (N=274).
- 'Combo BP for melanoma' refers to the broad combination safety pool for patients who received doses of encorafenib ranging from 400 mg to 600 mg QD in combination with binimetinib at 45 mg BID (N=433).
- 'NSCLC population' includes the patients with BRAF V600E mutant advanced NSCLC enrolled in the PHAROS study and who received doses of encorafenib at 450 mg QD in combination with binimetinib at 45 mg (N=98)
- 'Integrated safety population' (Combo 450 ISP) refers to 372 patients, including 98 patients with BRAF V600E mutant advanced NSCLC enrolled at a dose of 450 mg QD encorafenib plus 45 mg BID binimetinib from PHAROS study, referred to as the 'NSCLC population', plus 274 patients with BRAF V600 mutant metastatic melanoma enrolled at or randomised to a dose of 450 mg QD encorafenib plus 45 mg BID binimetinib (192 patients from Study CMEK162B2301, 75 patients from Study CLGX818X2109 and 7 patients from Study CMEK162X2110), referred to as the 'Melanoma population (Combo 450 RP)'.
- 'Combo broad integrated safety population' includes the 'Combo BP for melanoma' (as defined above) (N=433) plus the 98 patients with BRAF V600E mutant advanced NSCLC enrolled in the PHAROS study who received encorafenib 450 mg QD in combination with binimetinib 45 mg BID; (N= 531).

- **Encorafenib in combination with cetuximab**

As indicated in Part II: Module SIII above, safety data from the Array-818-302 clinical trial are included to assess the dual combination of encorafenib and cetuximab for the treatment of patients with metastatic BRAF V600E-mutant colorectal cancer. Safety data of the randomized doublet arm pertains to the combination of oral encorafenib at the recommended dose of 300 mg QD and cetuximab 400 mg/m² to 250 mg/m² IV infusion, as per product label.

SVII.1 Identification of safety concerns in the initial RMP submission

This section is locked as per the guidance on the format of the risk management plan accompanying the GVP Module V Revision 2 (dated 31 October 2018).

SVII.1.1 Risks not considered important for inclusion in the list of safety concerns in the RMP for encorafenib

- **Encorafenib single agent**

  - Arthralgia
  - Uveitis
  - Supraventricular tachycardia
  - Pancreatitis
  - Photosensitivity
  - Retinal pigment epithelial detachment (RPED)
  - Facial paresis
  - Renal failure

Reason for not including an identified or potential risk in the list of safety concerns for encorafenib in the RMP:

(i) Risks with minimal clinical impact on patients (in relation to the severity of the indication treated):

Arthralgia

Arthralgia is identified as an ADR for encorafenib.

Frequency and seriousness: In the Enco 300 P population, arthralgia (arthralgia, arthropathy and joint stiffness PTs) was a very common event occurring in 43.3% (94/217) of patients, regardless of causal relationship to study drug. Although arthralgia was very commonly reported with grade 3 events reported in 9.2% (20/217) of patients, encorafenib discontinuation due to arthralgia was reported in only 1 patient. Dose adjustment or interruption was implemented in 12.0% of patients who experienced arthralgia (all grades) including 7.3% grade 3. Symptomatic corrective therapy was reported in 27.2% of patients.

No serious cases of arthralgia were reported.

Benefit-risk impact: Arthralgia is a known class effect of BRAF inhibitors.

Despite the high incidence of arthralgia, there was a very limited impact of arthralgia on treatment discontinuation and the event was manageable with dose adjustment and symptomatic therapy, which does not justify including arthralgia in as an important risk for encorafenib single agent. There is no impact on the benefit-risk profile.

Uveitis

Uveitis is identified as an ADR for encorafenib.

Frequency and seriousness: Across all studies, full ophthalmic examinations including retinal examinations were performed at baseline in all patients and more frequent routine subsequent eye assessments were conducted in patients receiving encorafenib as part of their dosing regimen.

Uveitis was reported in 0.5% (1/217) patients and was Grade 2 in severity. Visual impairment, including vision blurred and reduced visual acuity, occurred in 5.5% (12/217) of patients in Enco 300 P population. Of the 12 patients with visual impairment, visual impairment was reported along with uveitis in 1 patient.

Benefit-risk impact: Uveitis is a class effect of BRAF inhibitors.

Despite the visual impairment that may be caused due to the event, BRAF-inhibitor uveitis is known to be reversible and manageable *(*Choe, 2014) with dose adjustment and corrective therapy, including in severe forms (Draganova, 2015; Guedj, 2014). For encorafenib, the incidence was low with mild to moderate severity. The routine ophthalmological monitoring recommended in the target population allows close surveillance and early management. The data do not justify including uveitis as an important risk for encorafenib in relation to the severity of the treated disease. There is no impact on the benefit-risk profile.

(ii) Adverse reactions with clinical consequences, even serious, but occurring with a low frequency and considered to be acceptable in relation to the severity of the indication treated

Supraventricular tachycardia

Supraventricular tachycardia is identified as an ADR for encorafenib.

Frequency and seriousness: In the Enco 300 P population, supraventricular tachycardia (extrasystoles and supraventricular extrasystoles, tachycardia, sinus tachycardia and tachyarrhythmia PTs) was a common ADR and occurred in 9/217 patients (4.1%) and 2/217 patients (0.9%) had a grade 3 event. No patients discontinued Enco 300 mg due to supraventricular tachycardia, but 1/217 grade 3 patient (0.5%) required dose adjustment or study drug interruption and 3 patients (1.4%) required additional therapy. Serious cases were reported in 3/217 patients (1.4%) in the Enco 300 P population.

Benefit-risk impact: In clinical trials of encorafenib, the low incidence of supraventricular tachycardia events, the multiple other possible causes in oncology practice and the absence of drug discontinuation due to supraventricular tachycardia do not justify including this ADR as an important risk. There is no impact on the benefit-risk profile.

Pancreatitis

Pancreatitis is identified as an ADR for encorafenib.

Frequency and seriousness: In the Enco 300 P population, pancreatitis was reported in 1/274 (0.5%) patients. This grade 3 case occurred on study day 2 in a diabetic patient receiving sitagliptin and was considered related. This event led to treatment discontinuation with a favourable outcome. The AEs of amylase and lipase elevation were reported in 0.5% (1/217) and 2.3% (5/217) of patients, respectively; the majority of which were in asymptomatic patients. Note that patients with pancreatitis were not excluded from the CMEK162B2301 study.

Benefit-risk impact: Pancreatitis is a class effect for BRAF inhibitors which is well known and considered manageable with routine clinical monitoring (SmPC Tafinlar® (dabrafenib), 2019; SmPC Zelboraf® (vemurafenib), 2019; Muluneh, 2013). Pancreatitis is considered as an identified risk for encorafenib but not as a safety concern based on the available data and in relation to the severity of the treated disease. There is no impact on the benefit-risk profile due to pancreatitis.

(iii) Known risks that require no further characterisation and are followed up via routine pharmacovigilance namely through signal detection and adverse reaction reporting, and for which the risk minimisation messages in the product information are adhered by prescribers (e.g. actions being part of standard clinical practice in each EU Member state where the product is authorised):

None.

(iv) Known risks that do not impact the benefit-risk profile

Photosensitivity

Photosensitivity is a known adverse effect with BRAF inhibitors (SmPC Zelboraf® (vemurafenib), 2019) and dabrafenib [Hauschild, 2012; Mattei 2012; Ascierto, 2013; Gabeff, 2015; Erfan, 2017]). Photosensitivity is identified as an ADR for encorafenib.

Encorafenib was phototoxic in an *in vitro* 3T3 Neutral Red Uptake Test. Encorafenib was not a sensitiser in the *in vivo* mouse sensitization assay. Collectively, these data indicate that encorafenib has a risk of phototoxic potential and minimal risk for sensitization at therapeutic doses in patients

Frequency and seriousness: In the Enco 300 P population, photosensitivity events (including photosensitivity reaction, sunburn and solar dermatitis PTs), regardless of relationship to study drugs were reported in 9 patients (4.1%) patients. No events were graded 3/4 or required dose adjustment/study drug interruption. Additional therapy was reported in 2 patients (0.9%). No event was serious or led to study drug discontinuation.

Benefit-risk impact: Photosensitivity reactions are strongly associated with the BRAF inhibitor vemurafenib (Gelot, 2013), occurring in approximately 33% of treated patients (SmPC Zelboraf® (vemurafenib), 2019), including 2% of patients for grade 3/4 events. In dabrafenib studies, photosensitivity was reported in 1% of patients in the phase II studies and 3% in the phase III studies (Hauschild, 2012; Ascierto, 2013). For encorafenib, preclinical data indicated a phototoxic potential and minimal risk for sensitisation at therapeutic doses in patients. Combined with the low incidence of photosensitivity events and the absence of reported severity, treatment discontinuation or seriousness in the clinical studies, photosensitivity is determined as an identified risk for encorafenib but not as a safety concern. There is no impact on the benefit-risk profile.

(v) Other reasons for considering the risks not important

Retinal pigment epithelial detachment (RPED)

Retinal pigment epithelial detachment is not identified as an ADR for encorafenib single-agent. Preclinical retinal findings did not translate into an ADR based on the available clinical data.

Frequency and seriousness: Across all studies, full ophthalmic examinations including retinal examinations were performed at baseline in all patients and more frequent routine subsequent eye assessments were conducted in patients receiving encorafenib as part of their dosing regimen.

In the Enco 300 population, RPED including PTs of RPED, retinal detachment, detachment of retinal pigment epithelium, retinopathy and retinal oedema was reported in 1.8% (4/217) of patients, all of which were grade 1 or 2. No patient discontinued due to RPED and 0.5% (1/217) had dose interruptions or dose modifications due to this event. RPED was generally reversible. Of note, intensive and full ophthalmological monitoring was performed for most patients included in clinical studies in encorafenib due to uveitis-related toxicity specific to BRAF inhibitors. In study CMEK162B2301, the incidence of RPED in the encorafenib 300 mg arm and vemurafenib arm was similar. RPED is not considered as an ADR for the approved BRAF inhibitors vemurafenib and dabrafenib.

Benefit-risk impact: RPED is not a class effect for BRAF inhibitors, unlike for MEK inhibitors. For encorafenib, the occurrence of retinal detachment (RPED) events resulting from the frequent full ophthalmic monitoring was observed with encorafenib single agent at a lower frequency (1.8%) than

predicted from preclinical observations and is not considered as a safety concern in humans. There is no impact on the benefit-risk profile.

Facial paresis

Facial paresis is identified as an ADR for encorafenib.

Frequency and seriousness: In the Enco 300 P population, facial paresis (including facial paralysis, facial nerve disorder and facial paresis PTs) was a common ADR and occurred in 16 patients (7.4%); 3 patients (1.4%) had grade 3 events. The median time to first onset of facial paresis (any grade) for patients with at least one event was 9.5 days [range 2-368 days]. Two patients (0.9%) (1 patient [0.5%] with a grade 3 event) discontinued encorafenib 300 mg due to facial paresis, 8 patients (3.7%) (1 patient [0.5%] with a grade 3 event) required dose adjustment or study drug interruption and 12 patients (5.5%) required additional therapy due to facial paresis. This ADR was reversible in the majority of first episodes of documented cases, with 10/16 (62.5%) cases having resolved at last study evaluation including the three Grade 3 cases.

Benefit-risk impact: Despite the functional discomfort that may be caused due to the event, BRAF-inhibitor-induced facial paresis (including encorafenib) is generally mild to moderate in severity, reversible and manageable with dose adjustment/interruption and corrective therapy with oral steroids. A case report by Shailesh *et al*. (Shailesh, 2014) reported that facial palsy completely resolved after withdrawal of vemurafenib. Routine clinical monitoring in the target population allows close surveillance and early management. Facial paresis has been hypothesised to be secondary to activation of the mitogen-activated protein kinase pathway, resulting in the proliferation of Schwann cells (Wisler, 2011), or be due to an autoimmune mechanism (Klein, 2013). In the proposed indication, encorafenib is not expected to be used as single agent except for short duration while binimetinib is temporarily interrupted, in which case encorafenib is reduced to 300 mg QD during the time of binimetinib dose interruption. If binimetinib is permanently discontinued, encorafenib should be discontinued. Of note, the incidence of facial paresis in the Combo 450 RP population was significantly lower than in the Enco 300 P population (0.7% vs 7.4%) reflecting a minimal risk. Routine clinical monitoring in the target population allows close surveillance and early management. The data do not justify including facial paresis as an important risk for encorafenib based on the mild to moderate severity of the treated disease and reversibility with standard treatment as there is no impact on the benefit-risk profile.

Renal failure

Renal failure and blood creatinine increased are identified as ADRs for encorafenib.

Frequency and seriousness:

In the Enco 300 P population, the ADR renal failure (including renal failure, acute kidney injury, renal impairment PTs) was reported in 2.8% (6/217) of patients and 1.4% (3/217) had a grade 3/4 event (2 grade 3 and 1 grade 4). The two grade 3 events (0.9%) led to discontinuation due to renal failure. Dose modification and additional therapy due to renal failure were reported in 0.5 (1/217) % and 1.4% (3/217) of patients, respectively. Serious cases of renal failure were reported in 1.8% (4/217) of patients in the Enco 300 P population and none was fatal.

Incidence of treatment-emergent laboratory abnormalities (changes from baseline): In the Enco 300 P population, newly occurring or worsening in serum creatinine were mostly grade 1 (71.9% of patents) or grade 2 (9.0%). One patient (0.5%) had a shift from baseline (grade 0 or 1) to post-baseline grade 3 increased creatinine values and no grade 4 hypercreatininaemia was reported in any patients. No patients had a shift from lower grades to higher grade proteinuria.

In the encorafenib 300 mg arm of the phase III study (CMEK162B2301), mild (mostly grade 1) serum creatinine elevation was noted in 76.6% of patients. One patient (0.5%) had a grade 3 event. Renal failure events were reported in 2.6% of patients. Renal failure in this arm was generally associated with vomiting and dehydration although other contributing factors in a few cases included diabetes and hypertension. Renal failure was generally reversible with dose interruption, rehydration

and other general supportive measures. There was no evidence for tubular toxicity based on urine protein shift values from baseline to post-baseline.

Based on the available data, there was no evidence for interstitial nephritis or tubular toxicity.

Benefit-risk impact: Based on the available data, no impact on the benefit-risk profile is expected at the dose of 300 mg QD for encorafenib single agent. Limited data from a dose escalation phase Ib/2 study of encorafenib in combination with binimetinib suggested a potential for renal dysfunction with high doses of encorafenib (600 to 800 mg QD). No associated proteinuria was reported. As a result, the potential for renal dysfunction due to overdose is addressed as an important potential risk for risk management plan purposes and is discussed below in the section SVII.1.2.

▪ Encorafenib in combination with binimetinib

The risks not considered important for inclusion in the list of safety concerns in the RMP for encorafenib in combination with binimetinib are:

- Neutropenia
- Gastrointestinal toxicity
- Photosensitivity

Of note, non-clinical findings were predictive of potential for synergistic skin toxicity but interestingly, the known encorafenib-related skin reactions were significantly attenuated by the combination. A comparison of Combo 450 RP vs. Enco 300 P patients showed the following frequencies: alopecia (14.6% vs. 57.1%), PPES (6.2% vs. 51.6%), hyperkeratosis (20.8% vs. 58.5%), rash (19.7% vs. 43.3%), dry skin (14.6% vs 37.8%, pruritus (11.7% vs 29.5%), erythema (8% vs 16.6%) skin hyperpigmentation (1.8% vs. 10.1%), skin exfoliation (1.1% vs. 6.5%) and dermatitis acneiform (4.4% vs. 7.8%).

Reason for not including an identified or potential risk in the list of safety concerns for the combination in the RMP:

(i) Risks with minimal clinical impact on patients (in relation to the severity of the indication treated):

Neutropenia

The following newly occurring or worsening haematology abnormalities were reported with a higher incidence (≥5% difference for any CTCAE grade) in the Combo 450 RP population than the Enco 300 P population: decreases in leukocyte count (grade 1: 12.9% vs 3.9%), decreases in neutrophil count (grade 1: 9.5% vs 3.9%) and decreases in platelet counts (grade 1: 10.1% vs 4.4%).

In the study CMEK162B2301, the incidence of treatment-emergent laboratory abnormalities (changes from baseline) occurring in ≥10% (all grades) or ≥2% (grade 3/4) of patients in the Combo 450 arm, included neutropenia in 15.1% (all grades) and 3.6% (grade 3/4). In the encorafenib 300 mg arm the incidence of neutropenia was lower, occurring in 4.7% (all grades) and 1.0% (grade 3/4) of patients.

Overall, in the Combo 450 RP population, AEs of neutropenia was reported in 11 patients (4.0%) with no associated symptoms. Febrile neutropenia was reported in 2 patients (0.7%), and in 4 patients (1.5%) neutropenia was associated with either influenza, sore throat, pharyngitis or oral herpes. No neutropenic sepsis or neutropenic severe infection was reported. Based on the available data, the risk of neutropenia, a well-known adverse reaction in oncology practice, appears minimal in relation to the severity of the treated disease. Hence, there is no impact on the benefit-risk profile.

(ii) Known risks that do not impact the benefit-risk profile

Gastrointestinal toxicity

The ADRs nausea and vomiting were very common, reported with similar rates in the Combo 450 RP population and the Enco 300 P population, with nausea in 41.6% vs 37.8% and vomiting in 28.1% vs 27.6% of patients respectively. Likewise, incidence of grade 3/4 events was similar in the two arms with nausea in 2.6% vs 3.7%; and vomiting in 2.2% vs 4.1% respectively. Despite the high frequency of these gastrointestinal events, the treatment dose intensity was high, close to 100% for both agents. Median time to first onset of nausea (any grade) for patients with at least one event was 26.0 days [range 1-680 days],

The ADR diarrhoea was reported at a higher incidence (difference >5%) in the Combo 450 RP population compared to the Enco 300 P population in 38.0% vs 12.4% of patients but with similar incidence for grade 3/4 events (3.3% vs 1.4%). Constipation and abdominal pain were also more commonly reported in the Combo 450 population than the Enco 300 population, with constipation in 24.1% vs 16.1% and abdominal pain in 27.4% vs 15.7% of patients respectively, but no severe grade events were reported in either population for constipation and the incidence of grade 3/4 abdominal pain was similar (2.6% vs 2.8% respectively).

In the Combo 450 RP population, dose adjustments were required in 7.3% of patients for nausea and in 6.2% for vomiting but no events led to treatment discontinuation. For diarrhoea, dose adjustments were required in only 4.4% of patients, and led to treatment discontinuation in 0.4% of patients.

Additional therapy was required for nausea in 20.8% of patients, for vomiting in 7.7% and for diarrhoea in 14.2%. Prophylaxis for gastrointestinal toxicity was not used in the reported clinical trials. The higher rates of diarrhoea, constipation and abdominal pain observed with the combination do not impact the benefit-risk profile.

Based on these data, the known risk of gastrointestinal toxicity with BRAF and MEK inhibitors is not considered as a safety concern in the encorafenib and binimetinib combination at the recommended dose.

Photosensitivity

Preclinical photosafety assessment indicated a low potential risk for phototoxicity with encorafenib and a minimal potential risk for phototoxicity with binimetinib.

Photosensitivity (including photosensitivity reaction, sunburn and solar dermatitis PTs) is identified as an ADR for either encorafenib single agent or in combination with binimetinib. Photosensitivity was reported at a similar low incidence in the Combo 450 RP population and the Enco 300 P population in 4% vs 4.1% of patients with exposure adjusted incidence rates 0.30 case per 100 patient-months vs 0.42 case per 100 patient-months respectively. Few events were severe (one Grade 3 vs none), required dose study drug interruption/reduction (one vs none), required additional therapy (1.8% vs 0.9%). No events were serious, or led to study drug discontinuation in either population.

In Study CMEK162B2301, photosensitivity events regardless of causality to study drugs were reported at a much lower incidence in the Combo 450 arm than in the vemurafenib arm in 4.7% vs 38.2%). Exposure adjusted incidence rate was 0.30 case per 100 patient-months vs 7.02 cases per 100 patient-months respectively. Few events were Grade 3/4 (0.5% vs 1.6%) or led to study treatment discontinuation (none vs 1.1%). Dose interruption/reduction were reported in 0.5% and 4.3% of patients. and additional therapy due to AEs in 2.6% vs 16.7% of patients in the Combo 450 and vemurafenib arms, respectively. The risk of photosensitivity, a known BRAF inhibitor adverse effect (SmPC Zelboraf® (vemurafenib), 2019 and dabrafenib [Hauschild, 2012; Mattei 2012; Ascierto, 2013; Gabeff, 2015; Erfan, 2017]), especially for vemurafenib. Photosensitivity was observed with a high incidence (>30%) and severe events with vemurafenib use (SmPC Zelboraf® (vemurafenib), 2019) and was reported in combination MEK/BRAF inhibitor therapies. For the

vemurafenib and cobimetinib combination, photosensitivity was observed in 47.3% of patients with Grade 3-4 events in 4.5% of patients in the coBRIM phase III study (Dréno, 2017). Photosensitivity is considered as an ADR for encorafenib single agent and in combination with binimetinib with an overall incidence rate <5%. Based on the data for encorafenib and binimetinib combination, there is no clinical evidence of enhanced toxicity due to the combination of encorafenib and binimetinib. The low incidence and severity of photosensitivity do not impact the benefit/risk profile of the combination. Photosensitivity is not considered as an important risk requiring a special warning in the SmPC for either encorafenib or binimetinib. Sun exposure being a known risk factor for malignant melanoma, patients treated for malignant melanoma are generally advised about sun protection in routine practice, and no additional protection measure is warranted for Combo 450.

SVII.1.2. Risks considered important for inclusion in the list of safety concerns of encorafenib in the RMP

There is no indication of encorafenib as monotherapy. Encorafenib use is only considered in the setting of the indication of combination with binimetinib for the treatment of adult patients with unresectable or metastatic melanoma with a BRAF V600 mutation. When encorafenib is used in combination with binimetinib, if binimetinib is temporarily interrupted, encorafenib is reduced to 300 mg QD during the time of binimetinib dose interruption. If binimetinib is permanently discontinued, encorafenib should be discontinued.

Important identified and potential risks and important missing information are listed below and further detailed below in the relevant section:

- Secondary skin neoplasms: cutaneous squamous cell carcinoma and new primary melanoma
- Palmar-plantar erythrodysaesthesia syndrome
- QT prolongation
- Non-cutaneous malignancies with RAS mutation
- Over-exposure due to concomitant use with strong and moderate CYP450 3A4 inhibitors
- Embryo-foetal toxicity
- Over-exposure in patients with moderate to severe hepatic impairment
- Potential for renal dysfunction due to overdose
- Use in patients with severe renal impairment.

Important identified risks:

Secondary skin neoplasms: squamous cell carcinoma and new primary melanoma

Secondary malignant skin neoplasms including cutaneous squamous cell carcinoma (cuSCC), basal cell carcinoma (BCC) and new primary melanoma are known class-effects and risks for BRAF inhibitors with common to uncommon frequency.

For encorafenib single agent, secondary skin neoplasms including cuSCC, BCC and new primary melanoma are identified as ADRs. Of note, while BCC is an ADR it is not included as a safety concern within the addressed secondary skin neoplasms due to the well-known favourable prognosis of this non-aggressive and localised malignant disease.

Frequency and seriousness:

In the Enco 300 P population, cuSCC was reported in 7.4% (16/217) patients with no Grade 3/4 events, no discontinuations or dose adjustment or study drug interruption but 4.1% of patients

required additional therapy. The median time to first onset of squamous cell carcinoma (any grade) was 84 days [range 8-364 days].

New primary melanoma occurred in 4.1% (9/217) of patients with 0.9% Grade 3/4 events. No patients required discontinuation, dose adjustment or study drug interruption and 2.8% patients required additional therapy.

Benefit-risk impact: Secondary neoplasms (cuSCC and new primary melanoma) are known class-effects of the BRAF inhibitors. Given that they can be detected at an early stage, their low frequency and the target population of the indication, the benefit-risk is considered low based on the recommended minimisation measures and the setting of the intended therapeutic use.

Details are provided in Section SVII.3.

Palmar-plantar erythrodysaesthesia syndrome (PPES)

PPES including severe PPES is identified as an ADR for encorafenib.

Frequency and seriousness: In the Enco 300 P population, PPES was reported at the high frequency of 51.6% (112/217) with grade 3 events reported in 12.4% (27/217) of patients. PPES led to discontinuation in 4.1% (9/217) of patients and to dose interruption or dose modification in 23.0% (50/217) of patients. Additional treatment was needed in 38.7% of patients, including oral nonsteroidal pain relievers, topical pain relievers such as lidocaine and prilocaine, topical moisturizing emollients such as urea and salicylic acid, oral and topical steroids, and GABA analogues (pregabalin and gabapentin).

Of note, in the combination encorafenib-binimetinib arm of study CMEK162B2301, PPES frequency and severity were considerably reduced as compared to the encorafenib 300 mg QD arm (all grades 7.3% with no grade 3 events).

No serious cases of PPES were reported during encorafenib trials.

Benefit-risk impact: PPES is a known class effect reported with the use of BRAF inhibitors *(*SmPC Zelboraf® (vemurafenib), 2019*;* SmPC Tafinlar® (dabrafenib), 2019*)*, but it is reported at lower rates with other BRAF inhibitors than what is observed with encorafenib. For encorafenib single agent, despite the high incidence and the impact on the daily activities for the severe events, no important impact on the benefit-risk is anticipated with dose adjustments and the fact that in the setting of the approved indication in combination with binimetinib, patients should not receive encorafenib as a single agent other than if binimetinib is temporarily interrupted, in which case encorafenib is reduced to 300 mg QD during the time of binimetinib dose interruption. If binimetinib is permanently discontinued encorafenib should be discontinued.

Refer to Section SVII.3 for further details.

Important potential risks:

QT prolongation

QT prolongation is a potential class-risk for BRAF inhibitors and is not identified as an ADR for encorafenib based on the available preclinical and clinical data.

Frequency and seriousness:

In the single-agent encorafenib Study CLGX818X2101, the highest mean post baseline ΔQTcF and ΔHR following the 450mg dose were 33.4 ms and 17.8 bpm, respectively. A concentration-dependent increase in QT interval was detected using a linear mixed effect analysis. At the mean observed steady-state C_{max}, an increase of 12.2 ms (18.8 ms upper-bound 2-sided 90%CI) in ΔQTcF was predicted following 450 mg BRAFTOVI.

Following encorafenib 450 mg QD in combination with 45 mg binimetinib BID across pooled studies (Study CLGX818X2109, CMEK162X2110 and CMEK162B2301), the highest mean observed post-baseline ΔQTcF was 25.2 ms (27.2 ms upper-bound 90%CI). In addition, the mean observed ΔQTcF

on Day 14 at 1.5 hours post-dose (representing the time of expected maximum steady-state concentration) was 13.7 ms (16.6 ms upper-bound 2-sided 90%CI). Overall, these results suggest encorafenib administration has the potential to result in small increases in QTc interval and mild increases in HR at a clinically relevant dose.

In the safety analysis of pooled studies for QT assesment, the incidence of new QTc >500 ms was 0.7% (2/268) in the encorafenib plus binimetinib group vs. 2.5% (5/203) in the BRAFTOVI single agent group. QT prolongation of >60 ms compared to pre-treatment values was observed in 4.9% (13/268) in the encorafenib plus binimetinib group vs. 3.4% (7/204) in the encorafenib single agent group.

No event of QTcF prolongation was reported as a serious case during clinical trials.

Benefit-risk impact: It is difficult to evaluate the risk of developing life-threatening arrhythmias from QT prolongation. There is no correlation between the prolonged QTc interval and the incidence of torsades de pointes and sudden death. Additionally, the risk of potentially fatal ventricular tachycardia is small (Brell, 2010, Haddad, 2002).

QT prolongation is a known class effect of BRAF inhibitors, however preclinical safety pharmacology data do not indicate a clinical risk of QT prolongation for encorafenib in treated patients. Small increases in QTc interval and mild increases in heart rate were apparent in the Enco 300 population. Data are insufficient to exclude a clinically significant exposure-dependent QT prolongation. Combined with the theoretical increased risk of ventricular arrhythmias including torsade de pointes associated with QT prolongation, QT prolongation is considered a potential safety concern for encorafenib for risk management plan purposes. Onset of QT prolongation can be minimized by controlling relevant serum electrolytes abnormalities prior to treatment, ECG monitoring and concomitant medications on-treatment and dose reductions, interruptions or discontinuations in the event of abnormal electrolytes and risk factors. The impact on benefit-risk is deemed low based on the available preclinical and clinical data and with regard to the minimisation measures.

Details are provided in Section SVII.3.

Non-cutaneous malignancies with RAS mutation

Frequency and seriousness: No cases of non-cutaneous malignancy with RAS mutation were identified from the pooled safety data of the clinical development program.

Benefit-risk impact: Based on its mechanism of action, encorafenib may promote malignancies associated with activation of RAS through mutation or other mechanisms. Few secondary malignancies have been reported in patients with metastatic melanoma receiving BRAF and/or MEK inhibitors. Patients with known *RAS*-mutant tumour histories should not receive BRAF inhibitors (Livingstone, 2014) and the risk benefit in these patients should be considered carefully.

Details are provided in Section SVII.3.

Over-exposure due to concomitant use with strong and moderate CYP450 3A4 inhibitors

Frequency and seriousness: Not applicable as no cases were reported.

Benefit-risk impact: Based on the pharmacokinetics of encorafenib, CYP3A4 was predicted to be the major enzyme contributing to total oxidative clearance of encorafenib in human liver microsomes (~83.3%). A drug-drug phase I study also showed increased overall and peak encorafenib exposure after a single administration. Thus, the use of concomitant strong CYP450 3A4 inhibitors was not allowed during clinical trials due to the potential risk of over-exposure of encorafenib and increased toxicities. In the real-life setting, concurrent use of strong CYP3A inhibitors during treatment with encorafenib should be avoided. If concomitant use with a strong CYP3A inhibitor is necessary, patients should be carefully monitored for safety. Caution should be exercised if a moderate CYP3A inhibitor is co-administered with encorafenib.

The benefit-risk impact is limited.

Details are provided in Section SVII.3.

Embryo-foetal toxicity

Frequency and seriousness: Not applicable as no cases were reported.

Benefit-risk impact: Studies in animals have demonstrated reproductive toxicity with embryo-foetal developmental changes and an abortifacient. In animals, encorafenib exposure was confirmed in the foetal plasma in relation to maternal exposure. There are no human clinical data or events reported suggesting reproductive toxicity. Given that the median age for women of the target population is over 50 years, that there are recommendations for effective contraception for women of childbearing potential, and not to use of encorafenib in pregnant women, the expected impact on benefit-risk impact is limited, when considering the severity of the disease. Female patients of reproductive potential are expected to adhere to effective contraceptive measures.

Details are provided in Section SVII.3.

Over-exposure in patients with moderate to severe hepatic impairment

Frequency and seriousness: Not applicable as no cases were reported. Patients with moderate to severe hepatic impairment were excluded from the pivotal trial.

Benefit-risk impact: Encorafenib is primarily metabolized and eliminated via the liver, therefore patients with hepatic impairment may have greater exposure compared to healthy patients. Results from a dedicated clinical trial indicate 25% higher total encorafenib exposure in patients with mild hepatic impairment (Child-Pugh Class A) compared with subjects with normal liver function. This translates into a 55% increase of the unbound encorafenib fraction. The PK of encorafenib has not been clinically studied in patients with moderate to severe hepatic impairment.

Encorafenib is not recommended in patients with moderate to severe hepatic impairment. Administration of encorafenib should be undertaken with caution at a reduced dose of 300 mg QD in patients with mild hepatic impairment.

The benefit-risk impact is considered limited based on the recommended minimisation measures and the setting of the intended therapeutic use. In the real-life setting, patients with hepatic impairment should be closely monitored for toxicities.

Details are provided in Section SVII.3.

Potential for renal dysfunction due to overdose

Frequency and seriousness: Grade 3 hypercreatininaemia was observed in 3 out of 14 patients treated with doses of encorafenib of 600 to 800 mg QD in combination with binimetinib and one event of acute kidney injury reported at the dose of encorafenib 800 mg QD lead to treatment discontinuation One patient received a dose of 1200 mg for 1 day by error and experienced Grade 1 events of nausea, vomiting and blurred vision all of which resolved but the patient did not experience renal dysfunction.

Benefit-risk impact: The benefit-risk impact is considered limited based on the recommended minimisation measures and the setting of the intended therapeutic use. In the real-life setting, patients receiving encorafenib overdose should be closely monitored for toxicities including renal dysfunction.

Details are provided in Section SVII.3.

Missing information

Use in patients with severe renal impairment

Severe renal impairment was defined as eGFR < 30 mL/min/1.73 m²) renal impairment. Patients with severe renal impairment were excluded from the pivotal trials.

Benefit-risk impact: Encorafenib undergoes minimal renal elimination. No formal clinical study has been conducted to evaluate the effect of renal impairment on the PK of encorafenib. In a population PK analysis, no clear trend in encorafenib CL/F was observed in patients with mild (eGFR 60 to 90 mL/min/1.73 m²) or moderate (eGFR 30 to 59 mL/min/1.73 m²) renal impairment compared with subjects with normal renal function (eGFR ≥90 mL/min/1.73 m²).

There are insufficient data to evaluate the PK in patients with severe renal impairment.

Based on the available data, no dose adjustment is recommended for patients with mild or moderate renal impairment based on a population PK analysis.

A recommended dose has not been established for patients with severe renal impairment. Encorafenib should be used with caution in these patients.

The benefit-risk impact is limited. In the real-life setting, patients with severe impairment should be closely monitored for toxicities.

Details are provided in Section SVII.3.

SVII.1.3 Additional risks considered important for inclusion in the list of safety concerns for encorafenib in combination with binimetinib

The overall safety profile of the combination of encorafenib 450 mg QD and binimetinib 45 mg BID is consistent with the mechanisms of action and the known safety profiles of BRAF and MEK inhibitors as single agents or in combination.

The safety of the combination was studied in the pivotal CMEK162B2301 controlled phase III trial in adult patients with unresectable or metastatic melanoma harbouring a BRAF V600 mutation, not previously treated with BRAF inhibitors, and in a supportive phase II study CLGX818X2109 in the same population. The CMEK162B2301 trial compared Combo 450 to vemurafenib at the recommended dose. From a safety perspective, the third arm of patients receiving encorafenib 300 mg QD was used for the comparison of the safety profiles of the combination versus encorafenib single-agent.

The combination exhibited a more favourable tolerability profile than that reported with encorafenib single agent. Despite longer median exposure to treatment in the Combo 450 RP compared to Enco 300 P population (50.64 weeks vs 29.71 weeks), fewer patients receiving Combo 450 experienced at least one Grade 3/4 AE (61.3% vs 67.7%), AEs leading to treatment discontinuation (11.7% vs 18.0%), AEs requiring dose interruption/change (52.2% vs 71.0%) and AEs requiring additional therapy (89.8% vs 94.9%) compared to patients receiving Enco 300. Most of the observed AEs in the combination were reversible and manageable with dose modifications and adequate clinical management including routine dermatological examinations, monitoring of left ventricular function with MUGA or cardiac echocardiography and complete ophthalmological assessments.

The addition of binimetinib to encorafenib allowed higher exposure to encorafenib in patients treated with Combo 450 and interestingly attenuated certain known effects of BRAF inhibitors. Encorafenib-related ADRs identified across clinical trials of encorafenib single-agent were also reported with the combination in the CMEK162B2301 pivotal trial.

The addition of binimetinib to encorafenib was associated with a lower incidence (difference ≥10% in Enco 300 P vs Combo 450 RP) of certain ADRs, in particular skin disorders (PPES, rash, alopecia, pruritus, hyperkeratosis and dry skin), pain in extremities, muscular disorders, arthralgia, and decreased appetite. Of note, one case of melanoma in situ (PT new primary melanoma) was reported in the Combo 450, and fewer patients experienced cuSCC and BCC.

The most common binimetinib-driven ADRs included skin reactions, ocular reactions (retinal detachment, visual impairment), cardiac dysfunction (left ventricular dysfunction), hypertension, and creatinine phosphokinase elevation. Certain ADRs of the Combo 450 driven by binimetinib, are potentially serious (severe hypertension, left ventricular dysfunction, venous thromboembolism, liver laboratory abnormalities, haemorrhage, ocular events and rhabdomyolysis), and are reflected

in the AEs/SAEs leading to treatment discontinuation, but were manageable with dose modifications, monitoring of left ventricular and arterial blood pressure, ophthalmological assessments and adequate clinical management with regard to individual risk factors.

The addition of binimetinib to encorafenib was associated with a numerically higher incidence of adverse events for abnormal LFTs (ALT, AST and GGT) and overall haemorrhagic events as compared to either encorafenib or binimetinib single agents. Hepatotoxicity and haemorrhage are class-effects for MEK inhibitors and considered as important identified risks for binimetinib but not for encorafenib. The reasons for the higher overall incidence of LFTs and haemorrhagic events when encorafenib is used in combination with binimetinib are unclear.

For the purposes of this RMP, safety specification information regarding hepatotoxicity and haemorrhage is provided below. In the setting of encorafenib and binimetinib combination therapy, hepatotoxicity is regarded as important potential risk. No clear causal relationship has been established at this time, therefore further characterisation is needed for the risk hepatotoxicity. Although the mechanism of haemorrhage is currently unclear with BRAF and MEK inhibitors when used in combination, the risk of haemorrhage is considered as important identified risk for encorafenib and binimetinib combination therapy.

Additional important identified and potential risks and missing information for the combination therapy are detailed below:

- Haemorrhage
- Hepatotoxicity

Important identified risks:

Haemorrhage

Haemorrhage is identified as an ADR for the combination. Haemorrhage incorporated a wide spectrum of PTs, most of them with a single event, most indicative of minor haemorrhage (low grade, epistaxis, haemorrhoidal haemorrhage, rectal haemorrhage, haematochezia, conjunctival haemorrhage).

Frequency and seriousness:

Haemorrhagic events have been observed in 17.2% (47/274) of patients in the Combo 450 RP population. The majority of these cases were Grade 1 or 2 (13.5%) with few patients requiring any dose interruptions or dose reductions (1.5% or 4/274). Haemorrhagic events led to discontinuation of treatment in 1.1% (3/274) of patients. The most frequent haemorrhagic events were gastrointestinal including rectal haemorrhage in 2.9% (8/274), haematochezia in 2.9% (8/274) and haemorrhoidal haemorrhage in 0.7% (2/274) of patients. In addition, haematuria was reported in 3.3%, retinal haemorrhage in 1.8%, cerebral haemorrhage in 1.5% and metrorrhagia (1.1%). Four fatal outcomes were reported, 3 cerebral haemorrhage (related to tumour progression and haemorrhage into tumour metastases) and one gastric ulcer haemorrhage, considered not related to Combo 450.

Benefit-risk impact:

Haemorrhagic events at various sites and mostly mild in severity were very commonly reported in patients receiving the combination therapy. The incidence rates were numerically higher in the combination population as compared to encorafenib and binimetinib single agents. Haemorrhage is a class-effect risk for MEK inhibitors including binimetinib.

Haemorrhage is identified as an ADR for the combination even though no clear causal relationship can be established due to the presence of confounding factors in severe cases and the higher overall incidence being possibly owing to the longer median duration of exposure in the Combo 450 RP population). The benefit-risk impact is low based on the risk minimisation measures and in relation to the severity of the treated disease.

Please refer to Section SVII.3 for further details.

Important potential risks:

Hepatotoxicity

Transaminases increased and gamma-glutamyl-transferase (GGT) elevations are identified as ADRs for the combination.

Frequency and seriousness:

In the Combo 450 RP population, transaminases increased (including alanine aminotransferase [ALT] increased, aspartate aminotransferase [AST] increased, transaminases increased and hepatic enzyme increased PTs) occurred in 15.7% patients, 5.5% of patients had grade 3 events. In addition, 1.8% discontinued Combo 450 due to transaminases increased, 6.2% required dose adjustment or study drug interruption and 1.5% required additional therapy.

Increased ALT >3 x upper limit of normal (ULN) were reported in 10.1% and increased ALT or AST>3 x ULN were reported in 11.7% of patients.

In the Combo 450 RP population, GGT increased was reported in 14.6% of patients and 8.4% of patients had grade 3 events. No serious cases were reported, 0.7% discontinued due to transaminases increased, 3.6% required dose adjustment or study drug interruption and 0.4% required additional therapy.

There were no cases meeting the case-finding criteria of Hy's law in the Combo 450 RP population.

Benefit-risk impact:

Hepatic events mostly grade 1 and 2 were very commonly reported in patients receiving the combination therapy. The incidence rates were higher in the combination population as compared to encorafenib and binimetinib single-agents. Hepatotoxicity is a class-effect risk for MEK inhibitors and is an important identified risk for binimetinib.

No cases of liver abnormalities meeting Hy's law criteria were observed. From the Combo 450 population, only one case of hepatic failure was reported and was assessed as not related to study drugs but to the underlying liver metastatic disease. Further risk characterisation is warranted for potential hepatotoxicity in the combination setting.

The benefit-risk impact is low based on the risk minimisation measures and in relation to the severity of the treated disease.

Please refer to Section SVII.3 for further details.

Missing information

None.

SVII.2 New safety concerns and reclassification with a submission of an updated RMP

No important identified or potential risk or missing information is re-classified, removed or added in this updated submitted version of the RMP.

SVII.3 Details of important identified risks, important potential risks and missing information for encorafenib

SVII.3.1. Presentation of important identified and important potential risks

Secondary skin neoplasms: cutaneous squamous cell carcinoma and new primary melanoma [important identified risk]

(i) Important identified risk: Cutaneous squamous cell carcinoma (cuSCC)

Potential mechanisms:

The pathogenesis of cuSCC is believed to result from paradoxical activation of the mitogen-activated protein kinase (MAPK) pathway and subsequent keratinocyte hyper-proliferation in cells that do not carry BRAF mutation (Robert, 2011; Carlos, 2015) in association with activation of signalling mediated by RAS mutations (Oberholzer, 2012; Su, 2012). CuSCCs and keratoacanthomas (KAs) from RAF inhibitor-treated patients have a distinct mutational profile as compared with cuSCCs arising sporadically or in patients treated with immunosuppressive agents. Specifically, around 20% of KAs and cuSCCs resected from patients treated with RAF inhibitors harbour activating HRAS mutations, whereas these mutations are rare in tumours that develop in naïve patients to these drugs.

Both vemurafenib and dabrafenib BRAF inhibitors induce the development of cuSCCs and KAs as frequent side effects, occurring in about 14% of dabrafenib-treated and 26% of vemurafenib-treated patients, generally within the first two months of therapy (Sosman, 2012; Larkin, 2014). However, the addition of a MEK inhibitor to a BRAF inhibitor can reduce the incidence of this hyperactivation. As shown in the first clinical trials, the rate of cuSCCs is significantly reduced (1-5% vs.15-20%) when the two BRAF and MEK inhibitors are given concurrently to patients.

Evidence source and strength of evidence:

Secondary skin neoplasms including cuSCC represent a known class-effect with the use of BRAF inhibitors.

CuSCC has been identified as an ADR for encorafenib, based on the clinical trials data.

Characterisation of the risk:

Frequency with 95% CI:

- *Encorafenib 300 mg QD*

CuSCC (including PTs of keratoacanthoma, squamous cell carcinoma, lip squamous cell carcinoma, squamous cell carcinoma of skin) occurred in 7.4% of patients in the Enco 300 population and in 8.3% of patients in the encorafenib arm of Study CMEK162B2301.

Among the cuSCC reported events, most (13/16 patients) were KAs, tumours known to have a good prognosis. The incidence of keratoacanthoma (Kas) was 6.0% and 6.8% in the Enco 300 P population and encorafenib arm of Study CMEK162B2301, respectively.

The median time to first onset of cuSCC (any grade) was 84 days [range 8-364 days] in the Enco 300 P population. Kaplan Meier plots of time to first grade ≥2 cuSCC for patients with an event showed a median time to onset for the Enco 300 population of 1.8 months.

Table SVII.1: Encorafenib: Cutaneous squamous cell carcinoma events irrespective of relationship (Enco 300 P population and Enco 300 arm of Study CMEK162B2301)

	Melanoma	**Study CMEK162B2301**
Cutaneous squamous cell carcinoma	**Enco 300 P N=217 n (%)**	**Enco 300mg QD N=192 n (%)**
Overall incidence	16 (7.4)	16 (8.3)
Related overall incidence	13 (6.0)	13 (6.8)
Grade 3-4	0	0
PT with higher incidence		
Keratoacanthoma	13 (6.0)	13 (6.8)
SAEs overall incidence	0	0
% discontinuation	0	0
% dose change/reduction	0	0
% additional therapy	9 (4.1)	9 (4.7)
EAIR (PT) [1]	0.78	0.85

*Sources: ISS Part1_u: Table 2.1.25.1-u, Table 2.1.25.2-u, Table 2.1.25.*3-u
[1] EAIR (Exposure adjusted incidence rate per 100 patient-months) = (n*100)/total exposure time (in months) of Broad Safety Set).
Melanoma: Naive to BRAF inhibitors and MEK inhibitors. Bini= Binimetinib Monotherapy safety pool; Enco= encorafenib monotherapy safety pool; A patient with multiple adverse events within a preferred term is counted only once in that preferred term. MedDRA Version 19.0 has been used for the reporting of adverse events.
PTs: Keratoacanthoma, Squamous cell carcinoma, Lip squamous cell carcinoma, Bowen's disease, Squamous cell carcinoma of skin.

- *Encorafenib 450 mg QD and binimetinib 45 mg BID*

In the Combo 450 integrated safety population (ISP), CuSCC occurred at an incidence of 3.0% of patients; in the Combo 450 RP (Melanoma population), CuSCC occurred in 3.3% of patients (Note: in the Combo 450 arm of study CMEK162B2301 it occurred in 3.6% of patients), in the NSCLC population, CuSCC occurred at an incidence of 2.0% of patients (2/98 patients; PTs: squamous cell carcinoma, and squamous cell carcinoma of skin).

In the Combo 450 RP population (Melanoma population), most (7/9) patients experienced KA, and the incidence of KAs was 2.6% both in the Combo 450 RP (Melanoma population) and in the Combo 450 arm of the Study CMEK162B2301. There was no KA reported in the NSCLC population.

The median time to first onset of squamous cell carcinoma was 176.0 days [range 30-694 days] in the Combo 450 RP population (Melanoma population), and 189.0 days [range 189-189 days] in the NSCLC population.

Table SVII.2: Encorafenib in combination with binimetinib: Cutaneous squamous cell carcinoma events irrespective of relationship (Combo 450 ISP, Combo 450 RP [Melanoma population], NSCLC population and Combo 450 arm of Study CMEK162B2301)

	Combo 450 ISP	**NSCLC Population**	**Combo 450 RP (Melanoma population)**	**Study CMEK162B2301**
Cutaneous squamous cell carcinoma	**Combo 450mg QD (N=372) n (%)**	**Combo 450mg QD (N=98) n (%)**	**Combo 450mg QD N=274 n (%)**	**Combo 450mg QD N=192 n (%)**
Overall incidence	11 (3.0)	2 (2.0)	9 (3.3)	7 (3.6)

Related overall incidence	7 (1.9)	2 (2.0)	5 (1.8)	4 (2.1)
Grade 3+	2 (0.5)	1 (1.0)	1 (0.4)	1 (0.5)
PT with higher incidence				
Keratoacanthoma	7 (1.9)	0 (0.0)	7 (2.6)	5 (2.6)
SAEs overall incidence	1 (0.3)	1 (1.0)	0	0
% discontinuation	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
% dose change/reduction	1 (0.3)	1 (1.0)	0	0
% additional therapy	6 (1.6)	2 (2.0)	4 (1.5)	2 (1.0)
EAIR (PT) [1]	0.21	0.15	0.24	0.25

Sources: W00090_NSCLC - Version date: 31MAY2023 13:56 - File Name: Sub5_3_1_c1_RMPcutSqEnBi_saf_t.rtf
Sources: Cut-off date Melanoma: 09NOV2016 / Cut-off date Pharos: 22JAN2023 - Dataset ADSP1.ADADR:15MAY2023 ADSP1.ADSL:15MAY2023 - PGM Sub5_3_1_c1_RMPcutSqEnBi_saf_t.sas 24MAY2023 10:59
[1] EAIR (Exposure adjusted incidence rate per 100 patient-months) = (n*100)/total exposure time (in months) of Safety Set MedDRA Version 25.1 has been used for the reporting of adverse events.

- *Encorafenib 300 mg QD in combination with cetuximab*

In the doublet arm for the BRAF-mutant mCRC indication, CuSCC including keratoacanthoma was observed in 1.4% (3/216) of patients.

The time to onset for each of the 3 CuSCC ADRs in the doublet arm in mCRC patients was 16 days, 17 days and 109 days respectively.

Table SVII.3: Encorafenib in combination with cetuximab: Cutaneous squamous cell carcinoma events irrespective of relationship (doublet arm of Study ARRAY-818-302)

Cutaneous squamous cell carcinoma	**Doublet arm** **N=216** **n (%)**
Overall incidence	3 (1.4)
Grade 3-4	0
PT with incidence > 10%	0
SAEs overall incidence	0
AEs leading to discontinuation [a]	0
AE leading to dose reduction/interruption [a]	0
AEs requiring additional therapy [b]	2 (0.9)

[a] Any study drug
[b] Additionnal therapy includes all non drug therapies and concomitant medications.
Sources: ARRAY_818_302_Dossier_2019 - Version date: 20DEC2019 18:37 - File Name: A009_02_1_IA_adrD_sumCuSCC_saf_D_t.rtf - ListingNA
Sources: Cut-off date 11FEB2019 - Database lock 30APR2019 - Dataset BASEDTM1.ADSL:09SEP19 WSPOSTIA.ADADRD:10SEP19 - PGM A009_02_1_IA_adrD_sumCuSCC_saf_D_t.sas 20DEC2019 18:37

In post-marketing experience, cumulatively up to 26 June 2023 (DLP of the most recent submitted PSUR), in the global safety database, there are 4 cases reporting the PTs: Keratoacanthoma, and 3 cases reporting the PT Squamous cell carcinoma of skin.

Seriousness:

One case of cuSCC was reported as serious. Due to close monitoring of skin lesions during clinical trials, early detection of these tumours and prompt excision were permitted and encorafenib was continued.

Severity:

No grade 3 or 4 CuSCC events were reported in the Enco 300 P population or the encorafenib arm of Study CMEK162B2301.

In Combo 450 ISP, 2 events (0.5%) were reported as Grade ≥ 3; one event in the melanoma population (keratoacanthoma), and one event in the NSCLC population (squamous cell carcinoma of skin).

No case led to study drug discontinuation. 4.1% in the Enco 300 P population vs 1.6% in the Combo 450 ISP, and 4.7% in the encorafenib arm vs 1.0% in the Combo 450 arm of Study CMEK162B2301 required additional therapy which included lesion excision.

Dose modification was required in 0.3% of patients in the Combo 450 ISP (one patient in the NSCLC population vs none in the Melanoma population). No case led to dose modification in the Enco 300 P population. No grade 3 or 4 CuSCC event was reported in the mCRC patients in the doublet arm of study ARRAY-818-302. Additional therapy was required in 0.9% of patients.

Event outcome:

The outcome of the cutaneous squamous cell carcinoma events in the Combo 450 ISP was recovered/resolved in most of patients.

The percentages of patients below correspond to the number of patients with a given outcome status among patients who experienced at least one keratoacanthoma or cuSCC event.

- Keratoacanthoma:
    - recovered: 76.9% all grade in both the Enco 300 P population and Enco 300 arm of Study CMEK162B2301, and 85.7% in the Combo 450 ISP.
    - recovering: 15.4% all grades in the Enco 300 mg QD pooled
    - not recovered: 7.7% in both Enco 300 P and Enco 300 mg Study CMEK162B2301, and 14.3% in the Combo 450 ISP.
- CuSCC: 100% all grades recovered in Enco 300 P, Enco 300 mg Study CMEK162B2301, and in the Combo 450 ISP.

In mCRC patients, the outcome was reported as not recovered/resolved for CuSCC in 2/3 patients in the doublet arm of study ARRAY 818 302.

Absolute risk:

The absolute risk of cuSCC events in the Enco 300 P population was 0.074.

The absolute risk of cuSCC events (all grades) in the doublet population (doublet arm of ARRAY-818-302, mCRC indication) was 0.014.

Relative risk:

In order to perform the relative risk (RR) calculations, a literature search was undertaken to identify European studies reporting the risk of secondary skin neoplasms in real-world, BRAF-mutated metastatic melanoma patients who were unexposed to encorafenib single-agent, or to any

interventions in the same therapeutic class (i.e. any BRAF inhibitor for encorafenib). Only one study was identified for non-melanoma secondary skin neoplasms and used for the RR estimation:

Table SVII. 4: Risks of cutaneous squamous cell carcinoma in the "unexposed" melanoma population

Risk	**Reference**	**Population**	**Details of risk as reported in study**	**Study location**	**Treatment (s) received by patients**	**Frequency, n/N (%)**	**RR for enco vs unexposed**
Cutaneous non-SCC Events	Li *et al*. 2016	Patients with stage IV cutaneous melanoma	CuSCC or BCC	Denmark	Not reported	140/2810 (5)	0.185

RR, relative risk

In order to perform the relative risk (RR) calculations, a literature search was undertaken to identify European studies reporting the risk of secondary skin neoplasms in real-world or clinical settings in BRAF-mutated metastatic colorectal cancer (mCRC) patients who were unexposed to encorafenib or to any interventions in the same therapeutic class (i.e. any BRAF inhibitor for encorafenib). No studies in the relevant unexposed population were identified in this search.

In order to perform the relative risk (RR) calculations, a literature search was undertaken to identify European studies reporting the risk of secondary skin neoplasms in real-world in BRAF-mutated metastatic NSCLC patients who were unexposed to encorafenib single-agent, or to any interventions in the same therapeutic class (i.e. any BRAF inhibitor for encorafenib). No studies in the relevant unexposed population were identified in this search.

Reversibility:

SCC, BCC and KA may develop from BRAF inhibitor treatment within a few days or weeks of commencing treatment (Welsh, 2015, Wu, 2017). These secondary skin toxicities are typically managed with surgical excision per local guidelines (Anforth, 2013; Trakatelli, 2014), and may generally subside within the first few months of treatment, (Welsh, 2015) suggesting therefore that these effects are transient and reversible. It is recommended that surveillance for secondary dermatological malignancies continue for up to six months after the last dose of BRAF inhibitors (SmPC Braftovi® (encorafenib), ; SmPC Tafinlar® (dabrafenib), 2019; SmPC Zelboraf® (vemurafenib), 2019).

While specific consensus guidelines are not available, published practical advice is to refer immediately to a dermatologist if the patient exhibits any rapidly growing skin lesions, KA, or lesions that are suspected to be malignant (Welsh, 2015; Sinha, 2012).

Long-term outcomes:

The impact of the risk of cuSCC and other secondary skin neoplasms are unlikely to affect the patient long-term with proper management and monitoring during treatment. At the present time, there have been no reports of any metastases resulting from secondary cuSCC associated with combination BRAF and/or MEK inhibitor treatment, suggesting minimal long-term impact.

Impact on quality of life

The fact that cuSCC developing from BRAF inhibitor treatment is diagnosed early and can be well managed means there are unlikely to be long-term impacts. No long-term effects are expected on patient quality of life during or following treatment, if managed according to local standards of care.

Risk factors and risk groups:

Associations have been reported with older age (≥65 years) for vemurafenib and dabrafenib-treated patients and prior skin cancer, and chronic sun exposure for vemurafenib-treated patients.

The median age of diagnosis of cuSCC is 61–68 years, lesions rarely appear in young patients <40 years. Patient sex does not appear to influence the rate of cuSCC development and is not a risk factor for earlier onset or more aggressive disease (Wu, 2017).

Interestingly, one study documents a distinct distribution of cuSCC occurrence in BRAF inhibitor-treated patients. In the Australian population, only one-third of BRAF inhibitor-induced cuSCCs occur on sun-exposed areas (hand, forearm, lower leg, head and neck), which is in contrast to the observation that the vast majority of sporadic cuSCCs (approximately 80%) occur on sun-exposed areas in non-BRAF inhibitor-treated patients. The disparity in their pattern of occurrence suggests that BRAF inhibitor-induced cuSCCs may be caused by factors that are less dependent on ultraviolet exposure and distinct from those that influence traditional cuSCCs (Wu, 2017).

Recent detection of several HPVs and human polyomaviruses (HPyVs) in BRAF inhibitor-induced cuSCCs has drawn much attention to the possibility that these viruses may contribute in part to the development of these lesions. This assertion is supported by the well-established role of these two viral families in the pathogenesis of proliferative cutaneous diseases (Wu, 2017).

Preventability:

Early reporting of skin symptoms through careful and ongoing dermatologic monitoring throughout treatment should lead to clinic-pathologic diagnosis and appropriate surgical intervention in a timely manner without discontinuation or withholding of dosing. Routine skin evaluation has been implemented in clinical trials. It is currently not known if intervention on pre-cancerous lesions will contribute to prevention of clinically relevant events.

Following discontinuation of encorafenib, monitoring for cutaneous malignancies is recommended to continue for up to 6 months or until initiation of another anti-neoplastic therapy. Abnormal findings should be managed according to clinical practices.

Impact on the benefit-risk balance of the product:

The risk of secondary neoplasms of cuSCC attributed to encorafenib does not outweigh the potential benefit to patients, given the target population, and is satisfactorily minimised through the routine risk minimisation measures described in Part V.

Public health impact:

Public health impact would be relevant for patients whose QoL is impacted by the development of cuSCC. However, considering the low incidence of the events, that all were detected at early stages and that a large proportion of events were recovering with local surgical treatment and no treatment interruption has been reported, public health impact is limited.

Expected population outcome:

EUCAN data from 2012 indicate an age standardised incidence rate of malignant melanoma of the skin in the EU of 13.0 per 100,000 of population per year (European Cancer Information System*).* There are currently 508 million individuals living in the EU (European Commission). Assuming that 20% of diagnosed melanomas progress to a metastatic stage, and that approximately 50% of these cases are positive for BRAF V600E mutations (Ascierto, 2012) the target population is estimated to be approximately 6,552 individuals per year if they are all treated.

Given the absolute risk of cuSCC events described above for patients treated with encorafenib alone (0.074) an estimated 485 patients receiving encorafenib, may be expected to develop cutaneous cuSCC events (with 80% of keratoacanthomas) in a population of 6,552 eligible patients each year if all of them are treated.

In Europe, the age-standardized incidence rates (ASRs) in 2018 of all stages of colorectal cancer have been estimated to be 57.5 and 36.3 per 100,000 population per year in men and women respectively (Ferlay, 2018). This was estimated to equal approximately 378,450 new cases in 2018. Using the estimated value of 378,450 new colorectal cancer cases diagnosed in EU countries, and assuming that 25% of diagnosed colorectal cancers are metastatic (Van Cutsem, 2014), and that approximately 10% of these cases are positive for BRAF V600E mutations (Troiani, 2016), approximately 9,460 individuals were diagnosed with BRAF V600E-mutated stage IV colorectal cancer in 2018 across EU countries.

Given the absolute risk of cuSCC (all grades) described above for patients treated with encorafenib and cetuximab (0.014), it is estimated that 132 of the patients receiving this therapeutic regimen may be expected to develop cuSCC events in a population of 9,460 eligible patients each year.

In Europe, using the estimated value of 477,500 new cases of lung cancer diagnosed and assuming that about 80% of newly diagnosed lung cancers are non-small cell lung cancer (American Cancer Society, 2021), 60% of NSCLC patients are diagnosed at advanced stage (stages IIIB/C or IV), and approximately 3% of these cases are positive for BRAF mutations and 50% of them driven by the BRAF V600E mutation (Class 1), it can be estimated that approximately 3,438 individuals presented with BRAF V600E-mutated advanced lung cancer in 2020 across EU countries.

Given the absolute risk of cuSCC events described above for patients treated with encorafenib alone (0.074), an estimated 254 patients receiving encorafenib, may be expected to develop cutaneous cuSCC events in a population of 3,438 eligible patients each year if all of them are treated.

It is to be noted, however, that safety data from clinical trials may not be necessarily extrapolated to the real-world target population, as patients enrolled in clinical trials from a specific, controlled subset of patients fulfilling strict inclusion criteria, without severe comorbidities and certain concomitant medications.

(ii) Important identified risk: New primary melanoma

Potential mechanisms:

The mechanism of *BRAF* inhibition on new primary melanomas remains unclear. Paradoxical activation of the RAF/MEK/ERK pathway by RAF kinase inhibitors through a CRAF activation sequence is a foreseeable effect. Alternatively, the blockade of the BRAF pathway may favour alternate signalling pathways. Although rare, *HRAS* mutations have been reported in pigmented lesions, and BRAF-inhibitors may enhance their malignant behaviour (Dalle, 2013).

Evidence source and strength of evidence:

Secondary skin neoplasms including new primary melanoma represent a known class-effect with the use of BRAF inhibitors.

New primary melanoma has been identified as an ADR for encorafenib.

Characterisation of the risk:

Frequency with 95% CI:

- *Encorafenib 300 mg QD*

In the Enco 300 P population, new primary malignant melanoma (including malignant melanoma and melanoma *in situ* PTs) was a common ADR and occurred in 4.1% (9/217) of patients. No patients required discontinuation or dose adjustment or study drug interruption and 2.8% of patients required additional therapy. New primary melanoma lesions (7 malignant melanoma, 1 with malignant melanoma *in situ* and 1 melanoma *in situ*) were managed with excision and did not require treatment modification or discontinuation.

- *Encorafenib 450 mg QD and binimetinib 45 mg BID*

In the encorafenib arm of the study CMEK163B2301, new primary melanoma events occurred in 4.7% of patients (9/192), including grade 1 in 1.6% (3/192) of patients, grade 2 in 2.1% (4/192) of patients, grade 3 and grade 4 in 0.5% of patients each. New primary melanoma lesions were managed with excision and did not require treatment modification or discontinuation.

New malignant melanoma, which was defined as a common ADR for the Enco 300 P population and a known BRAF inhibitor class effect was not considered as an ADR for Combo 450. In the Combo 450 ISP, new malignant melanoma was reported in 0.3% (1/372) of patients; this grade 3 new malignant melanoma was reported in the Combo 450 RP (Melanoma population) and it was unsure if this event was of a metastatic origin of the treated disease or an occurrence of an actual new primary melanoma. No case of new primary melanoma was reported in the NSCLC population.

- *Encorafenib 300 mg QD in combination with cetuximab*

In the doublet arm for the BRAF-mutant mCRC indication, new primary melanoma was observed in 1.4% (3/216) of patients. The time to onset for each of the 3 new primary melanoma ADRs was 72 days, 104 days and 203 days respectively.

Table SVII.5: Encorafenib in combination with cetuximab: New primary melanoma events irrespective of relationship (Doublet arm of Study ARRAY-818-302)

Overall incidence	3 (1.4)
Grade 3-4	2 (0.9)
PT with incidence > 10%	0
SAEs overall incidence	2 (0.9)
AEs leading to discontinuation [a]	0
AE leading to dose reduction/interruption [a]	1 (0.5)
AEs requiring additional therapy [b]	3 (1.4)

[a] Any study drug
[b] Additionnal therapy includes all non drug therapies and concomitant medications.
Sources: ARRAY_818_302_Dossier_2019 - Version date: 20DEC2019 18:37 - File Name: A009_02_1_IA_adrD_sumCuSCC_saf_D_t.rtf - ListingNA
Sources: Cut-off date 11FEB2019 - Database lock 30APR2019 - Dataset BASEDTM1.ADSL:09SEP19 WSPOSTIA.ADADRD:10SEP19 - PGM A009_02_1_IA_adrD_sumCuSCC_saf_D_t.sas 20DEC2019 18:37

In post-marketing experience, cumulatively up to 26 June 2023 (DLP of the most recent submitted PSUR), in the global safety database, there are 11 cases reported the PTs: malignant melanoma, and 1 case reported the PT malignant melanoma in situ. In addition, the PT: skin cancer was reported in 3 cases, and PT: neoplasm skin reported in 2 cases. Analysis of these cases did not identify a new safety information for this risk.

Seriousness:

Three cases of new primary melanoma were reported as serious. Due to close monitoring of skin lesions during clinical trials, early detection of these tumours and prompt excision were permitted and encorafenib was continued.

In the doublet arm of study ARRAY-818-302, 2 (0.9%) out of the 3 cases of new primary melanoma reported were reported as serious.

Severity:

In the Enco 300 mg arm of study CMEK163B2301, grade 3 and grade 4 events were reported in 1 patient each (0.5%).

In the doublet arm of study ARRAY-818-302 (mCRC indication), 2 (0.9%) out of the 3 cases reported were Grade 3, none of the cases led to study treatment discontinuation or dose adjustment/study drug interruption.

Event outcome:

In the Enco 300 mg arm of study CMEK163B2301, two of the nine patients with new primary melanoma were not resolved at the study cut-off date.

In the Combo 450 ISP population, new primary melanoma was not identified as an ADR.

In the doublet arm of study ARRAY-818-302 (mCRC indication), all the 3 events of new primary melanoma were considered recovered/resolved after lesion excision.

Absolute risk:

The absolute risk of new primary melanoma events in the Enco 300 P population was 0.041. There was no ADR or identified risk for new primary melanoma in the Combo 450 studies.

Relative risk:

In order to perform the relative risk (RR) calculations, a literature search was undertaken to identify European studies reporting the risk of new primary melanoma in real-world, BRAF-mutated metastatic melanoma patients who were unexposed to encorafenib single-agent, or to any interventions in the same therapeutic class (i.e. any BRAF inhibitor for encorafenib). No studies were identified for the RR calculation. The RR could not be estimated (not applicable), because no study reported the risk in a relevant, "unexposed" patient population.

In order to perform the RR calculations, a literature search was undertaken to identify European studies reporting the risk of new primary melanoma in real-world, BRAF-mutated metastatic colorectal cancer (mCRC) patients who were unexposed to encorafenib single-agent, or to any interventions in the same therapeutic class (i.e. any BRAF inhibitor for encorafenib). No studies reporting the risk of new primary melanoma in a relevant "unexposed" patient population were identified for the purposes of the encorafenib therapy RR calculations; therefore, no RR calculations could be performed.

In order to perform the relative risk (RR) calculations, a literature search was undertaken to identify European studies reporting the risk of new primary melanoma in real-world in BRAF-mutated metastatic NSCLC patients who were unexposed to encorafenib single-agent, or to any interventions in the same therapeutic class (i.e. any BRAF inhibitor for encorafenib). No studies were identified for the RR calculation. The RR could not be estimated (not applicable), because no study reported the risk in a relevant, "unexposed" patient population.

Long-term outcomes:

The impact of the risk of new primary melanoma is unlikely to affect the patient long-term with proper management and monitoring during treatment. At this time, no metastases resulting from secondary SCC associated with combination BRAF and/or MEK inhibitor treatment have been reported, suggesting minimal long-term impact.

Impact on quality of life:

The fact that new primary melanoma developing from BRAF inhibitor treatment is diagnosed early and can be well managed makes it unlikely there will be a long-term impact. No long-term effects are expected on patient quality of life during or following treatment, if managed according to local standards of care.

Risk factors and risk groups:

Associations have been reported with older age (≥65 years) for vemurafenib and dabrafenib-treated patients and prior skin cancer, and chronic sun exposure for vemurafenib-treated patients.

Preventability:

Early reporting of skin symptoms through careful and ongoing dermatologic monitoring throughout treatment should lead to clinic-pathologic diagnosis and appropriate surgical intervention in a timely manner without discontinuation or withholding of dosing. Routine skin evaluation has been implemented in clinical trials. It is currently not known if intervention on pre-cancerous lesions will contribute to prevention of clinically relevant events.

Following discontinuation of encorafenib, monitoring for cutaneous malignancies is recommended to continue for up to 6 months or until initiation of another anti-neoplastic therapy. Abnormal findings should be managed according to clinical practices.

Impact on the benefit-risk balance of the product:

The risk of secondary skin neoplasms of new primary melanoma attributed to encorafenib does not outweigh the potential benefit to patients, given the target population, and is satisfactorily minimised through the routine risk minimisation measures described in Part V.

Public health impact:

Public health impact would be relevant for patients whose QoL is impacted by the development of new primary melanoma. However, considering the low incidence of the events, that all were detected at early stages and that a large proportion of events were recovering with local surgical treatment and no treatment interruption has been reported, public health impact is limited.

Expected population outcome:

EUCAN data from 2012 indicate an age standardised incidence rate of malignant melanoma of the skin in the EU of 13.0 per 100,000 of population per year (European Cancer Information System, 2019*).* There are currently 508 million individuals living in the EU (European Commission, 2019). Assuming that 20% of diagnosed melanomas progress to a metastatic stage, and that approximately 50% of these cases are positive for BRAF V600E mutations (Ascierto, 2012), the target population is estimated to be approximately 6,552 individuals per year if they are all treated.

Given the absolute risk of new primary melanoma events described above for patients treated with encorafenib alone (0.041) an estimated 269 patients receiving encorafenib, may be expected to develop new primary melanoma in a population of 6,552 eligible patients each year if they are all treated.

In Europe, the age-standardized incidence rates (ASRs) in 2018 of all stages of colorectal cancer have been estimated to be 57.5 and 36.3 per 100,000 population per year in men and women respectively (Ferlay, 2018). This was estimated to equal approximately 378,450 new cases in 2018. Using the estimated value of 378,450 new colorectal cancer cases diagnosed in EU countries, and assuming that 25% of diagnosed colorectal cancers are metastatic (Van Cutsem, 2014), and that approximately 10% of these cases are positive for BRAF V600E mutations (Troiani, 2016), approximately 9,460 individuals were diagnosed with BRAF V600E-mutated stage IV colorectal cancer in 2018 across EU countries.

Given the absolute risk of new primary melanoma described above for patients treated with encorafenib and cetuximab (0.014), it is estimated that 132 of the patients receiving this therapeutic regimen may be expected to develop new primary melanoma events in a population of 9,460 eligible patients each year.

In Europe, using the estimated value of 477,500 new cases of lung cancer diagnosed in 2020 and assuming that about 80% of newly diagnosed lung cancers are non-small cell lung cancer (American Cancer Society, 2021), 60% of NSCLC patients diagnosed at advanced stage (stages IIIB/C or IV),and approximately 3% of these cases are positive for BRAF mutations and 50% of them driven by the BRAF V600E mutation (Class 1), it can be estimated that approximately 3,438 individuals presented with BRAF V600E-mutated advanced lung cancer in 2020 across EU countries.

Given the absolute risk of new primary melanoma events described above for patients treated with encorafenib alone (0.041) an estimated 141 patients receiving encorafenib, may be expected to develop new primary melanoma in a population of 3,438 eligible patients each year if they are all treated.

It is to be noted however, that safety data from clinical trials may not be necessarily extrapolated to the real-world target population, as patients enrolled in clinical trials from a specific, controlled subset of patients fulfilling strict inclusion criteria, without severe comorbidities and certain concomitant medications.

(iii) Important potential risk: QT prolongation

Potential mechanisms:

Proposed mechanisms include an increase in cAMP activity and phosphorylation of hERG channels and resulting decrease in their function. The other hypothesised mechanism is down-regulation of hERG channel protein quality and quantity (Bronte, 2015).

Grade ≥3 QT interval prolongation occurred in 1% of patients treated with vemurafenib monotherapy or with vemurafenib plus cobimetinib. Such negative effects on QT prolongation were not seen with dabrafenib or encorafenib, considered to be due to an additional fluorinated phenyl ring (Dummer, 2018; Nebot, 2018; Bronte, 2015; Heinzerling, 2019).

Evidence source and strength of evidence:

QT prolongation is a class effect for BRAF inhibitors. For encorafenib, the IC_{50} for hERG inhibition was determined to be 73.4 µM indicating an unlikely effect of encorafenib on QT prolongation, which did not predict a clinical risk for QT prolongation. In safety pharmacology, results suggest encorafenib administration has the potential to result in small increases in QTc interval and mild increases in HR at a clinically relevant dose.

Small increases in QTc interval and mild increases in heart rate were apparent in the Enco 300 population. Data are insufficient to exclude a clinically significant exposure-dependent QT prolongation. Despite the low level of non-clinical and clinical evidence predicting QT prolongation in patients treated with encorafenib, the theoretical risk of clinical complications (torsades de pointes, ventricular arrhythmia)

due to drug-related sustained QT prolongation remains an important potential risk from risk management plan purposes.

Characterisation of the risk:

Frequency with 95%CI:

In the Enco 300 P population, when QT interval was corrected using Fridericia's formula (QTcF), increases of >60 ms were reported in 3.4% of patients respectively. Categorical shifts in absolute QTcF values reflected increases to >480 ms and >500 ms were reported in 5.0% and 2.5% of patients respectively.

In the encorafenib arm of study CMEK162B2301, QTcF increases of >60 ms were reported in 3.9% of patients. Categorical shifts in absolute QTcF values reflected increases to >480 ms and >500 ms were reported in 4.0% and 2.8% of patients, respectively.

In the studied populations, the observed increases in QTc appear to be low and small without evidence of clinical significance.

Table SVII.6: Encorafenib: QTc events, regardless of study drug relationship (Enco 300 P population and Enco 300 arm of Study CMEK162B2301) -Summary of Newly Occurring Notable QTcB and QTcF Values

	Melanoma	**Study CMEK162B2301**
QTc	**Enco 300 P population N=217 n (%)**	**Enco 300mg QD arm N=192 n (%)**
QTcF (ms)		
Increase >30 ms	69/204 (33.8)	56/179 (31.3)
Increase >60 ms	7/204 (3.4)	7/179 (3.9)
New >450 ms	47/194 (24.2)	39/171 (22.8)
New >480 ms	10/202 (5.0)	7/177 (4.0)
New >500 ms	5/203 (2.5)	5/178 (2.8)
QTcB (ms)		
Increase >30 ms	92/204 (45.1)	74/179 (41.3)
Increase >60 ms	20/204 (9.8)	15/179 (8.4)
New >450 ms	91/180 (50.6)	76/158 (48.1)
New >480 ms	29/199 (14.6)	23/174 (13.2)
New >500 ms	11/204 (5.4)	10/179 (5.6)

Sources: ISS Part1_u: Table 4.2.2-u
Newly occurring: Patients not meeting criterion at baseline and meeting criterion post-baseline.
n: Number of patients who meet the criteria at least once.
m: Number of patients at risk for a specific category with a non-missing value at baseline and post-baseline.
N: Total number of patients in the treatment group in this analysis set

In the initial MAA for melanoma, the incidences of increased QTcB changes by >30 ms and categorical shifts to QTcB value>450 ms were reported at a higher incidence in the Enco 300 P population than in the Combo 450 RP population (43.6% vs 27.2% and 48.9% vs 34.0%, respectively). Increased QTcB changes by >60 ms were observed in 9.3% vs 6.3% of patients in the Enco 300 P and Combo 450 RP, respectively and categorical shifts to QTcB value>500 ms were observed in 5.4% vs 1.6% of patients, respectively.

In the melanoma patients, the incidences of increased QTcF changes by >30 ms and categorical shifts to QTcF value >450 ms were reported at similar incidences in the Enco 300 P and Combo 450 RP population (31.9% vs 38.4% and 22.7% vs 22.8%, respectively). Increased QTcF changes by >60 ms were observed in 3.4% vs 5.6% of patients in the Enco 300 P and Combo 450 RP, respectively. Categorical shifts to QTcF value>500 ms were observed in 2.5% vs 0.7% of patients, respectively.

In melanoma patients, KM plots of time to first newly occurring QTcF abnormality for only patients with an abnormal event showed no relevant differences between median times to onset for the Enco 300 P and Combo 450 RP populations.

In the Combo 450 ISP, QTcF increases by >60 ms were observed in 6.0% of patients, and new QTcF values >500 ms were observed in 1.1% of patients. The incidences of increased QTcF changes by >30 ms and categorical shifts to QTcF value >450 ms were reported in 36.5% and 23.0%, respectively.

In the Combo 450 ISP, median time to onset is 2 months for QTcF > 480 msec, and 5.5 months for QTcF increase > 60 msec.

In the NSCLC population, QTcF increases by >60 ms were observed in 7.3% of patients, and new QTcF values >500 ms were observed in 2.1% of patients. The incidences of increased QTcF changes by >30 ms and categorical shifts to QTcF value >450 ms were reported in 31.3% and 23.5%, respectively.

Of note, the QTcB was not calculated in the PHAROS study (NSCLC population).

Table SVII.7: Encorafenib and binimetinib combination: QTc events, regardless of study drug relationship (Combo 450 ISP, Combo 450 RP [Melanoma population], NSCLC population and Combo 450 arm of Study CMEK162B2301) -Summary of Newly Occurring Notable QTcB and QTcF Values

	Combo 450 ISP	**NSCLC population**	**Combo 450 RP (Melanoma population)**	**Study CMEK162B2301**
QTc	**Combo 450mg QD (N=372) n/m (%)**	**Combo 450mg QD (N=98) n/m (%)**	**Combo 450mg QD N=274 n/m (%)**	**Combo 450mg QD N=192 n/m (%)**
QTcF (ms)				
Increase >30 ms	133/364 (36.5)	30/96 (31.3)	103/268 (38.4)	52/186 (28.0)
Increase >60 ms	22/364 (6.0)	7/96 (7.3)	15/268 (5.6)	11/186 (5.9)
New >450 ms	79/344 (23.0)	20/85 (23.5)	59/259 (22.8)	29/178 (16.3)
New >480 ms	22/362 (6.1)	11/94 (11.7)	11/268 (4.1)	7/186 (3.8)
New >500 ms	4/363 (1.1)	2/95 (2.1)	2/268 (0.7)	1/186 (0.5)
QTcB (ms)*				
Increase >30 ms			52/191 (27.2)	49/184 (26.6)
Increase >60 ms			12/191 (6.3)	12/184 (6.5)
New >450 ms			55/162 (34.0)	51/155 (32.9)
New >480 ms			13/190 (6.8)	13/183 (7.1)
New >500 ms			3/190 (1.6)	3/183 (1.6)

Sources: ISS Part1_u: Table 4.2.2-u
Sources: W00090_NSCLC - Version date: 31MAY2023 13:59 - File Name: Sub5_4_c1_RMPQTcEnBi_saf_t.rtf
Sources: Cut-off date Melanoma: 09NOV2016 / Cut-off date Pharos: 22JAN2023 - Dataset ADSP1.ADECG:15MAY2023 ADSP1.ADSL:15MAY2023 - PGM Sub5_4_c1_RMPQTcEnBi_saf_t.sas 03MAY2023 14:27
Newly occurring: Patients not meeting criterion at baseline and meeting criterion post-baseline.
n: Number of patients who meet the criteria at least once.
m: Number of patients at risk for a specific category with a non-missing value at baseline and post-baseline.
N: Total number of patients in the treatment group in this analysis set
* QTcB was not collected in NSCLC population (PHAROS study).

For encorafenib 300 mg QD in combination with cetuximab - In Study ARRAY-818-302, new QTcF > 500 ms was reported in 3.2% of patients at risk in the doublet arm (Table SVII.7)). Of note, this event was reported in 1.2% of patients at risk in the Control arm (CSR: Table 104: Newly Occurring Clinically Notable ECG Values (Safety Set). Except for two patients (1 doublet arm, 1 control arm), all of these abnormal findings were isolated events, found at a single study visit, were without any pattern to time of onset and were not reported as AEs. In the 1 patient in the doublet arm, who was receiving amiodarone, QTcF > 500 ms occurred twice while on study treatment.

Table SVII.8: Newly Occurring Notable QT and QTcF Values (ARRAY-818-302 Safety Set)- Encorafenib in combination with cetuximab

	Study Array-818-302
Category	**Doublet arm N=216 n/m (%)**
QT (ms)	
New >450	23/210 (11.0)
New >480	6/216 (2.8)
New >500	3/216 (1.4)
Increase from baseline >30	82/216 (38.0)
Increase from baseline >60	16/216 (7.4)
QTcF (ms)	
New >450	45/196 (23.0)
New >480	16/215 (7.4)
New >500	7/216 (3.2)
Increase from baseline >30	56/216 (25.9)
Increase from baseline >60	19/216 (8.8)

Sources: ARRAY-818-302 CSR Table 14.3-7.1
CSR: clinical study report; ms: millisecond(s); QT: the time from the start of the Q wave to the end of the T wave; QTcF: QT interval corrected for heart rate using Fridericia's formula.
Newly occurring=patients not meeting criterion at baseline and meeting criterion post-baseline.
New=newly occurring post-baseline value.
n: number of patients who meet the criteria at least once.
m: number of patients at risk, i.e. with non-missing values at baseline and post-baseline, and with a baseline value that does not already meet the abnormality.
All scheduled and unscheduled visits are included.

In the post-marketing experience, cumulatively through 26 June 2023 (DLP of the most recent submitted PSUR), there were 33 cases reporting 35 events suggestive of QT prolongation from post-marketing sources. These 33 cases represent 0.4% of the cumulative post-marketing dataset. The reported PTs included: electrocardiogram QT prolonged (27 events), cardiac arrest (4), sudden death, cardio-respiratory arrest, syncope and ventricular tachycardia (1 each). No new safety information was identified for encorafenib and QT prolongation based on the analysis of the cumulative post-marketing cases.

Absolute risk: Not applicable, as potential risk.

Relative risk:

Not applicable.

Reversibility:

The majority of the cases reported with BRAF inhibitors in the studies have been reversible.

QT prolongation has been shown to be exposure-dependent with BRAF inhibitor treatment, (Livingstone, 2014; Welsh, 2015) although non-clinical safety pharmacology data do not indicate a clinical risk from encorafenib treatment for QT prolongation.

It has been recommended that patients have ECG monitoring for the entire treatment duration (Mascarucci, 2016). In patients with moderate to severe hepatic impairment (due to potential over-exposure), monitoring should be monthly for the first three months of treatment, and every three months thereafter, or more frequently if clinically indicated (Livingstone, 2014). Treatment with BRAF inhibitors is not recommended in patients with non-correctable electrolyte abnormalities (including magnesium), long QT syndrome, or for patients who are taking medications known to prolong the QT interval (Livingstone, 2014).

In general, rhythmic disturbances as result of anti-cancer treatments, are considered a consequence of metabolic changes and generally resolve after electrolyte homeostasis has been re-established (Suter 2013). In the absence of specific consensus guidelines on the management of QT prolongation arising from BRAF or MEK inhibitor treatment in metastatic melanoma, patients should be treated and managed per local guidelines. QT prolongation is typically managed according to the degree of QT interval increase and can include stopping or interrupting the BRAF and/or MEK inhibitor treatment, correction of electrolyte abnormalities and addressing any cardiac risk factors such as congestive heart failure and bradyarrhythmia (Livingstone, 2014; Welsh, 2015; Hagen, 2014; (SmPC Zelboraf® (vemurafenib), 2019).

Long-term outcomes:

The impact of the risk of QT prolongation on the individual patient is an increased risk of ventricular arrhythmias, (Livingstone, 2014) which could be life-threatening if not treated in a timely fashion. Patients with QT prolongation are also predisposed to seizures, syncope and sudden cardiac death (Hagen, 2014). However, proper monitoring and resolution following inhibitor dose modification or discontinuation can be expected; therefore, a significant impact on long-term outcomes for an individual patient is not expected.

Impact on quality of life:

QT prolongation itself is unlikely to have an impact on the quality of life of the individual patient. If detected at an early stage and managed correctly, according to local standards of care, resolution can be expected. Therefore, any long-term effects on patient quality of life are not expected in most cases.

Risk factors and risk groups:

There are several factors that can influence the prolongation of QT (Setteyova, 2016):

- Electrolyte imbalance: hypocalcaemia, hypokalaemia, hypomagnesemia
- Cardiac diseases: congestive heart failure, left ventricular hypertrophy, myocardial ischemia, myocardial infarction, myocarditis, bradyarrhythmia, complete atrioventricular block
- Endocrine abnormalities: hyperaldosteronism, hyperparathyroidism, hypothyroidism, pheochromocytoma
- Nutritional disorders: cachexia, liquid protein diet, starvation, celiac disease, gastroplasty and ileo-jejunal bypass
- Autoimmune diseases: systemic lupus erythematosus, Sjogren's syndrome, polymyositis/dermatomyositis, systemic sclerosis, rheumatoid arthritis.

Other risk factors are to be considered;

- Patients with hepatic impairment due to the risk of over-exposure for drugs primarily metabolised by the liver and that may induce QT prolongation.
- Concomitant drugs/substances with potential risk of over-exposure due to drug-drug interactions leading to an increased risk for QT prolongation.
- Concomitant drugs/substances known to be associated with the risk of QT prolongation (e.g. antiemetics, antibiotics, antipsychotics, antifungals, antihistamines, and methadone.

Preventability:

The following must be considered before treatment initiation:

- Treatment and control of disorders such as bradycardia, thyroid dysfunction or cardiovascular disease and electrolyte imbalance
- Identification of patients with risk factors including a history of QT interval prolongation, patients with hepatic impairment and patients who are taking antiarrhythmics, or patients with relevant pre-existing cardiac disease, bradycardia, or electrolyte disturbances.

Impact on the benefit-risk balance of the product:

It is difficult to evaluate the risk of developing life-threatening arrhythmias from QT prolongation. There is no correlation between the prolonged QTc interval and the incidence of torsades de pointes and sudden death. Additionally, the risk of potentially fatal ventricular tachycardia is small.

The risk of QT prolongation for encorafenib does not outweigh the potential benefit to patients and is satisfactorily minimised through the routine risk minimisation measures described in Part V.

Public health impact:

Not applicable

Expected population outcome

EUCAN data from 2012 indicate an age standardised incidence rate of malignant melanoma of the skin in the EU of 13.0 per 100,000 of population per year (European Cancer Information System, 2019*).* There are currently 508 million individuals living in the EU (European Commission, 2019). Assuming that 20% of diagnosed melanomas progress to a metastatic stage, and that approximately 50% of these cases are positive for BRAF V600E mutations (Ascierto, 2012), the target population is estimated to be approximately 6,552 individuals per year if they are all treated.

In Europe, the age-standardized incidence rates (ASRs) in 2018 of all stages of colorectal cancer have been estimated to be 57.5 and 36.3 per 100,000 population per year in men and women respectively (Ferlay, 2018). This was estimated to equal approximately 378,450 new cases in 2018. Using the estimated value of 378,450 new colorectal cancer cases diagnosed in EU countries, and assuming that 25% of diagnosed colorectal cancers are metastatic (Van Cutsem, 2014), and that approximately 10% of these cases are positive for BRAF V600E mutations (Troiani, 2016), approximately 9,460 individuals were diagnosed with BRAF V600E-mutated stage IV colorectal cancer in 2018 across EU countries.

In Europe, using the estimated value of 477,500 new cases of lung cancer diagnosed in 2020, and assuming that about 80% of newly diagnosed lung cancers are non-small cell lung cancer (American Cancer Society, 2021), 60% of NSCLC patients are diagnosed at advanced stage (stages IIIB/C or IV), and approximately 3% of these cases are positive for BRAF mutations and 50% of them driven by the BRAF V600E mutation (Class 1), it can be estimated that approximately 3,438 individuals presented with BRAF V600E-mutated advanced lung cancer in 2020 across EU countries.

The number of patients receiving encorafenib who are expected to experience QT prolongation in a population of 6,552, 9,460 or 3,438 eligible patients each year is not estimated, since there is no absolute risk for this potential risk in either targeted BRAF-mutant melanoma, CRC or NSCLC population respectively.

(iv) Important potential risk: Non-cutaneous malignancies with RAS mutation

Potential mechanisms:

Activation of MAP-kinase signalling in BRAF wild type cells which are exposed to BRAF inhibitors may lead to increased risk of non-cutaneous malignancies, including those with RAS mutations. In clinical trials with dabrafenib, non-cutaneous malignancies were reported in 1% of patients for monotherapy. Cases of RAS-driven malignancies have been seen with dabrafenib as monotherapy. Cases of RAS-driven malignancies have been seen with dabrafenib as monotherapy. Vemurafenib may cause progression of cancers associated with RAS mutations *(*SmPC Zelboraf® (vemurafenib), 2019*).*

Based on this mechanism of action, BRAF inhibitors may cause progression of cancers associated with RAS mutations.

Evidence source and strength of evidence:

Based on its mechanism of action, encorafenib may promote malignancies associated with RAS mutation associated with activation of RAS through mutation or other mechanisms. No case of non-cutaneous

malignancy with RAS mutation possibly related to encorafenib was identified from the pooled safety data of the clinical development programme, however, due to the seriousness of this class-effect risk, non-cutaneous carcinoma is considered an important potential risk for the purposes of the post-authorisation risk management plan.

Characterisation of the risk:

Frequency

No cases of non-cutaneous malignancies with RAS mutation were reported in the Enco 300 P or across all CT safety populations in combination use (Combo 450 P and Doublet populations).

However, there was 1 case involving breast cancer recurrence in in a female participant (age: 50-60 years old) enrolled in CLGX818X2109, who developed hormone receptor-positive and HER2/neu-negative carcinoma of the breast (PT Breast cancer) two years post therapy with encorafenib and binimetinib for metastatic melanoma. In the genomic deep sequencing, activating mutations in KRAS and PIK3CA were detected. There was no connection with the malignant melanoma that was known and no pathology reports were provided that confirm KRAS positivity in the initial tumor. The patient underwent surgical removal of the carcinoma and the event resolved. Treatment with study drugs was temporarily withdrawn and was restarted at the same doses. The investigator and sponsor considered the event unrelated to study drugs.

In post-marketing experience, cumulatively, there is no case reporting non-cutaneous malignancies with RAS mutation.

Absolute risk:

Not applicable, as potential risk

Relative risk as compared with "unexposed" patient populations:

On note, the occurrence of non-melanoma malignant skin lesions and non-cutaneous squamous-cell carcinoma among metastatic melanoma patients was reported in an observational cohort study in Denmark in 0.1 (3/2810) of patients (Li, 2016).

In order to perform the relative risk (RR) calculations, a literature search was undertaken to identify European studies reporting the risk of malignant lesions with RAS mutation in real-world in BRAF-mutated metastatic NSCLC patients who were unexposed to encorafenib single-agent, or to any interventions in the same therapeutic class (i.e. any BRAF inhibitor for encorafenib). No studies in the relevant unexposed population were identified in this search.

Reversibility

Non-cutaneous malignancies/cancers are rare events in patients with metastatic melanoma, with previously published results finding non-cuSCC events in the heart, bronchi, and lung (Li, 2016). In the absence of specific consensus guidelines on the management of non-cutaneous malignancies/cancers arising from BRAF inhibitor treatment in metastatic melanoma patients, non-cutaneous malignancies/cancers should be managed per local guidelines according to the site of malignancy (Livingstone, 2014). Previously published practical advice for the monitoring of non-cutaneous malignancies/cancer events includes head and neck examinations (at minimum, visual inspection of oral mucosa and lymph node palpation) prior to initiation of BRAF inhibitor treatment, with examinations every three months during treatment (Livingstone, 2014). Anal and pelvic examinations for women are also recommended before and at the end of therapy, as well as when considered clinically indicated (Livingstone 2014). Following discontinuation of BRAF inhibitor therapy, monitoring for non-cutaneous malignancies/cancers should continue for up to six months or until initiation of another anti-neoplastic therapy (Livingstone 2014). Administration of the BRAF inhibitor should be discontinued in the event of a diagnosis of non-cutaneous malignancy/cancer (Livingstone, 2014).

Few secondary malignancies have been reported in patients with metastatic melanoma receiving BRAF and/or MEK inhibitor treatment. A case report from Australia described one V600E mutation-positive melanoma patient who experienced proliferation of a KRAS-mutated colon adenocarcinoma following therapy with combination dabrafenib-trametinib (Burudpakdee, 2016). Clinical disease markers such as carcinoembryonic antigen (CEA) levels decreased following withdrawal of dabrafenib, with improvement achieved with trametinib monotherapy (Andrews, 2012). A case report from the United States observed disease progression of NRAS-mutated myelomonocytic leukaemia shortly after the initiation of vemurafenib treatment in one patient, whose melanoma and leukaemia were managed by moving the vemurafenib therapy to an intermittent dosing schedule, guided by changes in white-cell counts (Callahan, 2012). These few reports in the published literature suggest that with proper monitoring and possible discontinuation of therapy, the impact of non-cutaneous malignancies/cancers resulting from treatment with BRAF inhibitors can be minimised.

Due to the likelihood of RAS-mutant tumours proliferating as result of BRAF inhibitor therapy, it has been recommended that patients with known RAS-mutant tumour histories should not receive BRAF inhibitors (Livingstone, 2014). Thorough consideration may be given to administering combination BRAF and MEK/ERK inhibitor therapy (Holderfield, 2014).

Long-term outcomes:

While long-term results from binimetinib-encorafenib combination therapy are not available at this time, the impact of the risk of non-cutaneous malignancies/cancers can be minimised long-term with proper patient management and monitoring during treatment. As cessation of BRAF inhibitor therapy or treatment with combination BRAF and MEK/ERK inhibitors have been suggested in addition to close monitoring (Livingstone, 2014; Holderfield, 2014). Long-term outcomes are not expected to be severe in most events, though in cases of advanced secondary malignancies, death is a possibility.

Impact on quality of life:

The degree of impact of the quality of life of a patient experiencing non-cutaneous malignancies/cancers may depend on the site of the secondary tumour and whether the secondary tumour has metastasised. In severe cases where the secondary malignancy may be advanced, the impact on a patient's quality of life may be chronic and include death. However, with proper monitoring and treatment, including dose modification or discontinuation of BRAF inhibitor therapy, or combination treatment with a MEK/ERK inhibitor, a few reports have shown that patients may experience clinical improvement (Andrews, 2012; Callahan, 2012).

Risk factors and risk groups:

None identified

Preventability:

There is a large variety of non-cutaneous malignancies that may be associated with RAS mutation. The most common carcinomas harbouring RAS mutation include head and neck carcinoma and squamous cell lung carcinoma. Preventability is based on routine cancer detection and treatment as well as preventive measures for different known risk factors of different cancers.

Impact on the benefit-risk balance of the product:

The benefit-risk should be carefully considered before administering encorafenib to patients with a prior history of or concurrent *RAS*-positive non-cutaneous malignancies. Permanent discontinuation of encorafenib should be considered for patients who develop *RAS*-positive non-cutaneous malignancies. The potential risk of non-cutaneous malignancies with RAS mutation is a theoretical class risk for encorafenib and does not outweigh the potential benefit to patients, given the target population, and is satisfactorily minimised through the routine risk minimisation measures described in Part V.

Public health impact:

Public health impact would be relevant for patients whose QoL is impacted by the development of non-cutaneous malignancies/cancers with RAS mutation. However, considering the absence of the events of interest events being reported, that all patients would be monitored for early detection and therapy, public health impact is limited.

Expected population outcome:

EUCAN data from 2012 indicate an age standardised incidence rate of malignant melanoma of the skin in the EU of 13.0 per 100,000 of population per year (European Cancer Information System, 2019*).* There are currently 508 million individuals living in the EU (European Commission, 2019). Assuming that 20% of diagnosed melanomas progress to a metastatic stage, and that approximately 50% of these cases are positive for BRAF V600E mutations (Ascierto, 2012) the target population is estimated to be approximately 6,552 individuals per year.

In Europe, the age-standardized incidence rates (ASRs) in 2018 of all stages of colorectal cancer have been estimated to be 57.5 and 36.3 per 100,000 population per year in men and women respectively (Ferlay, 2018). This was estimated to equal approximately 378,450 new cases in 2018. Using the estimated value of 378,450 new colorectal cancer cases diagnosed in EU countries, and assuming that 25% of diagnosed colorectal cancers are metastatic (Van Cutsem, 2014), and that approximately 10% of these cases are positive for BRAF V600E mutations (Troiani, 2016), approximately 9,460 individuals were diagnosed with BRAF V600E-mutated stage IV colorectal cancer in 2018 across EU countries.

In Europe, using the estimated value of 477,500 new cases of lung cancer diagnosed in 2020, and assuming that about 80% of newly diagnosed lung cancers are non-small cell lung cancer (American Cancer Society, 2021), 60% of NSCLC patients are diagnosed at advanced stage (stages IIIB/C or IV), and approximately 3% of these cases are positive for BRAF mutations and 50% of them driven by the BRAF V600E mutation (Class 1), it can be estimated that approximately 3,438 individuals presented with BRAF V600E-mutated advanced lung cancer in 2020 across EU countries.

The number of patients receiving encorafenib who are expected to experience non-cutaneous malignancies/cancers with RAS mutation in a population of 6,552, 9,460 or 3,438 eligible patients each year is not estimated, since there is no absolute risk for this potential risk in either targeted BRAF-mutant melanoma, CRC or NSCLC population, respectively.

(v) Important potential risk: Over-exposure due to concomitant use with strong and moderate CYP450 3A4 inhibitors

Potential mechanisms:

Encorafenib is metabolised by CYP3A4, CYP2C19 and CYP2D6. In vitro, CYP3A4 was predicted to be the major enzyme contributing to total oxidative clearance of encorafenib in human liver microsomes (~83.3%).

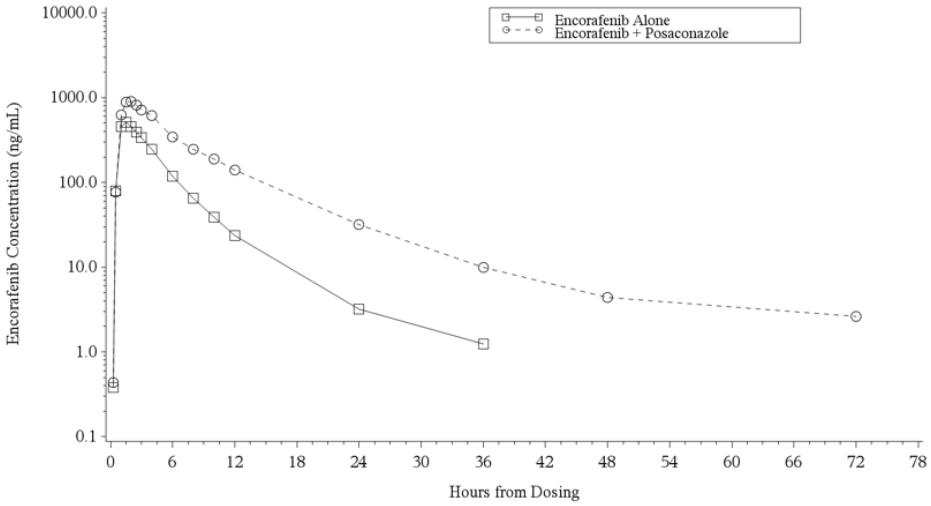
Evidence source and strength of evidence:

Encorafenib is primarily metabolised by CYP3A4. A Phase I drug-drug interaction study (ARRAY-818-105) was conducted to assess effects of strong and moderate CYP3A4 inhibitors (posaconazole and diltiazem, respectively) on the PK profile of encorafenib after single oral administration in two cohorts of 16 healthy adult males and females.

Subjects in both Part 1 and Part 2 received a single oral dose of encorafenib 50 mg as a capsule in Period 1 / Day 1 followed by a washout of 7 days. In Part 1 / Period 2, posaconazole was administered at 400 mg BID on Days 1-9, with 50 mg encorafenib co-administered on Day 7. In Part 2 / Period 2, diltiazem was administered at 240 mg QD on Days 1 to4, with 50 mg encorafenib co-administered on Day 2.

Encorafenib PK was assessed over 72 hours post-dose after each administration (i.e. alone in Period 1 / Day 1 of both Parts; and co-administered with CYP3A4 inhibitors in Period 2, on Day 7 for Part 1 and Day 2 for Part 2). Mean plasma concentration-time curves of encorafenib and an overview of the PK parameters are presented below.

Arithmetic mean plasma concentrations of encorafenib after a single oral 50 mg dose of encorafenib given either alone or co-administered with strong (posaconazole) and moderate (diltiazem) CYP3A4 inhibitors to healthy male and female subjects under fasted conditions (Study ARRAY-818-105)



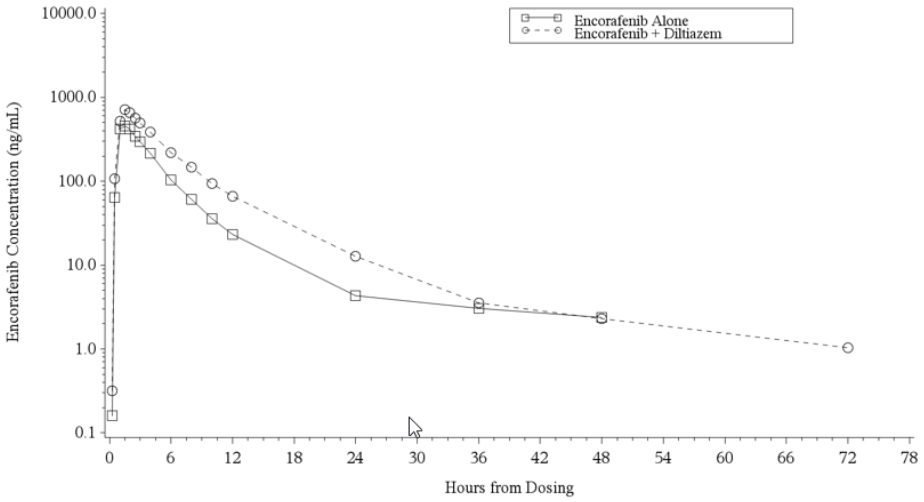


Table SVII.9: Encorafenib pharmacokinetic parameters and statistical analysis of drug-drug interaction after a single oral 50 mg dose of encorafenib given either alone or co-administered with strong (posaconazole) and moderate (diltiazem) CYP3A4 inhibitors to healthy male and female subjects under fasted conditions

	PK parameters [a]	**Encorafenib alone N = 16**	**Encorafenib + CYP3A4 inhibitor N = 16**	**Comparison (GMR [90% CI])**
Posaconazole (Part 1)	C_{max} (ng/mL)	553.5 (32.7)	932.1 (31.4)	168.39 [153.57 - 184.64]
	AUC_{inf} (ng.h/mL)	2051 (40.2)	5812 (38.3)	283.41 [254.05 - 316.16]
	$T_{1/2}$ (h)	4.309 ± 1.1034	7.264 ± 1.8634	
Diltiazem (Part 2)	C_{max} (ng/mL)	482.3 (37.6)	697.7 (40.5)	144.67 [124.14 - 168.58]
	AUC_{inf} (ng.h/mL)	1882 (42.1) n=14	3511 (49.5) n=15	183.01 [164.64 - 203.42]
	$T_{1/2}$ (h)	6.644 ± 6.0599 n=14	7.924 ± 4.7039 n=15	

Sources: Study ARRAY-818-105 Encorafenib alone: A single oral dose of encorafenib 50 mg as capsule
Encorafenib + CYP3A4 inhibitor:
In Part 1: multiple oral doses of posaconazole 400 mg BID for 9 days, with 50 mg encorafenib co-administered on Day 7
In Part 2: multiple oral doses of diltiazem 240 mg QD for 4 days, with 50 mg encorafenib co-administered on Day 4
N = number of subjects enrolled in the study, n = Number of observations used in the analysis
[a] For the C_{max} and AUC_{inf}, the geometric means (Geometric coefficient of variation) are presented. For the $T_{1/2}$, the Mean ± SD is presented
GMR = Geometric mean ratio of the least squares geometric means ratio of encorafenib administered alone relative to encorafenib co-administered with CYP3A4 inhibitor

Co-administration of strong (posaconazole) and moderate (diltiazem) CYP3A4 inhibitors with 50 mg single dose of encorafenib resulted in an increase in overall (AUC, 3- and 2-fold higher, respectively) and peak (C_{max}, 68.3% and 44.6% higher, respectively) encorafenib exposure. Based on these PK data, the use of strong CYP3A4 inhibitors was not allowed during clinical trials.

From the latest PBPK model simulations, co-administration of encorafenib 300 and 450 mg with strong CYP3A4 inhibitors posaconazole, ketoconazole and itraconazole are predicted to lead to 2.30-4. 58-fold increase of encorafenib exposure after single dose, and 2.89-5. 83-fold increase at steady state.

Physiology-based PK modelling confirmed the clinical observations in this study and predicted significant increase in encorafenib exposure if concomitant CYP3A4 strong inhibitors are administered in a clinical setting after multiple doses of encorafenib.

Concomitant administration of encorafenib and strong CYP3A4 inhibitors may lead to increased encorafenib exposure and potential increase in toxicity. Examples of strong CYP3A4 inhibitors include, but are not limited to, ritonavir, itraconazole, clarithromycin, telithromycin, posaconazole, and grapefruit juice. Moderate CYP3A4 inhibitors include, but are not limited to, amiodarone, erythromycin, fluconazole, diltiazem, delavirdine, amprenavir, imatinib.

Characterisation of the risk:

During clinical trials, the use of strong CYP450 3A4 inhibitors was not allowed and no cases of adverse effects due to drug–drug interaction were reported.

In the post-marketing experience, cumulatively up to 26 June 2023 (DLP of the most recent submitted PSUR), in the global safety database, there are 3 cases suggesting overexposure due to concomitant use with strong and moderate CYP450 3A4 inhibitors (reported potential interacting agent: verapamil, diltiazem and fluconazole; 1 each). These 3 cases represent 0.03% of the cumulative post-marketing dataset, and concerned 2 female patients and 1 male patient. Age was between 50 years old and 71years old. The reported PTs in these cases included drug interaction (3), blood creatine phosphokinase increased, blood creatinine increased, cryptococcus test positive, electrocardiogram QT prolonged, fluid intake reduced, hepatic cytolysis, lung opacity, muscular weakness, nausea, pneumonia cryptococcal and ventricular tachycardia (1 each). No new significant safety information was identified for encorafenib and overexposure due to concomitant use with strong and moderate CYP450 3A4 inhibitors based on the cumulative post-marketing data.

Frequency with 95%CI:

Not applicable.

Absolute risk:

Since no case of interactions with strong or moderate CYP450 3A4 have been reported, it is not possible to perform the relevant absolute risk calculation.

Relative risk:

In order to perform the relative risk (RR) calculations, a literature search was undertaken to identify European studies reporting the risk of over-exposure due to concomitant use with CYP450 3A4 in the real-world setting, BRAF-mutated metastatic melanoma patients who were unexposed to encorafenib single-agent, or to any interventions in the same therapeutic class (i.e. any BRAF inhibitor for encorafenib monotherapy).

No studies reporting the risk of over-exposure due to concomitant use with CYP450 3A4 in a relevant "unexposed" patient population were identified for the purposes of the encorafenib RR calculations; therefore, no RR calculations could be performed.

In order to perform the relative risk (RR) calculations, the same literature search was repeated to identify European studies reporting the risk of over-exposure due to concomitant use with CYP450 3A4 in the real-world setting, BRAF-mutated NSCLC patients who were unexposed to encorafenib single-agent, or to any interventions in the same therapeutic class (i.e. any BRAF inhibitor for encorafenib monotherapy).

No studies reporting the risk of over-exposure due to concomitant use with CYP450 3A4 in a relevant "unexposed" patient population were identified for the purposes of the encorafenib RR calculations; therefore, no RR calculations could be performed.

Seriousness:

No case of interactions with strong or moderate CYP450 3A4 have been reported in the clinical studies.

Severity:

No case of interactions with strong or moderate CYP450 3A4 have been reported in the clinical studies.

Outcome:

No case of interactions with strong or moderate CYP450 3A4 have been reported in the clinical studies.

Reversibility:

In vitro studies have shown encorafenib to be mainly metabolised by and a potent inhibitor of CYP3A4. Drug interaction studies have suggested that co-administration of encorafenib with another CYP3A4 inhibitor may decrease metabolism of encorafenib, potentially leading to an increased risk of toxicity (Wisinski, 2015). Therefore, medications such as some antibiotics and antifungals may be avoided while

patients are administered encorafenib (Welsh, 2015). In general, where these agents may need to be used, the advice is to temporarily omit the BRAF inhibitor (Welsh, 2015).

Long-term outcomes:

Awareness of drug-drug interactions with the CYP450 family of enzymes and a patient's concurrent medications may prevent serious long-term outcomes. If there is a significant inhibitory effect on the CYP450 enzymes coupled with a concurrent medication metabolised by this pathway, then there is the potential for acute or chronic toxicity. Any lasting outcomes would be dependent on the nature of this toxicity.

Impact on quality of life:

The impact on quality of life would be dependent on the degree of interaction with CYP450 enzymes and the patient's concomitant medications. If there is a significant inhibitory effect on the CYP450 enzymes coupled with a concurrent medication metabolised by this pathway, then there is the potential for acute or chronic toxicity. Any quality of life impact would very dependent on the nature of this toxicity. If carefully monitored and any necessary dose modifications or discontinuations are implemented quickly in response, impact on quality of life for the patient may be expected to be temporary.

Risk factors and risk groups:

Risk factors include any medical condition requiring the use of strong CYP3A4 inhibitors (ritonavir, itraconazole, clarithromycin, telithromycin, posaconazole, etc.) or grapefruit juice intake or moderate CYP3A4 inhibitors (amiodarone, erythromycin, fluconazole, diltiazem, delavirdine, amprenavir and imatinib) with no possibility for an alternate therapy.

Preventability:

In routine medical practice, this risk is considered manageable with the use of CYP450 3A4 inhibitors with a lesser inhibitory effect or alternate therapy. Use of strong CYP3A inhibitors during treatment with encorafenib should be avoided, and if it is considered necessary, patients should be monitored carefully for safety and discontinuation of strong CYP450 3A4 inhibitors or temporary suspension of encorafenib may be considered in relation to the individual benefit-risk in relation to the severity of the treated disease. Caution should be exercised if a moderate CYP3A inhibitor is co-administered with encorafenib.

Impact on the benefit-risk balance of the product:

The potential risk of over-exposure due to concomitant use with CYP3A4 inhibitors leading to increased toxicity of encorafenib is considered important.

However, this risk does not outweigh the potential benefit to patients and is satisfactorily minimised through the routine risk minimisation measures described in Part V.

Public health impact:

Public health impact would be relevant for patients whose QoL is impacted by increased toxicities of encorafenib due to concomitant use of strong CYP3A4 inhibitors. However, considering the general reversibility of most of the identified toxicities that all patients would be monitored for early detection and supportive therapy, public health impact is expected to be limited.

Expected population outcome:

EUCAN data from 2012 indicate an age standardised incidence rate of malignant melanoma of the skin in the EU of 13.0 per 100,000 of population per year (European Cancer Information System, 2019*).* There are currently 508 million individuals living in the EU (European Commission, 2019). Assuming that 20% of diagnosed melanomas progress to a metastatic stage, and that approximately 50% of these cases are positive for BRAF V600E mutations (Ascierto, 2012), the target population is estimated to be approximately 6,552 individuals per year.

In Europe, the age-standardized incidence rates (ASRs) in 2018 of all stages of colorectal cancer have been estimated to be 57.5 and 36.3 per 100,000 population per year in men and women respectively

(Ferlay, 2018). This was estimated to equal approximately 378,450 new cases in 2018. Using the estimated value of 378,450 new colorectal cancer cases diagnosed in EU countries, and assuming that 25% of diagnosed colorectal cancers are metastatic (Van Cutsem, 2014), and that approximately 10% of these cases are positive for BRAF V600E mutations (Troiani, 2016), approximately 9,460 individuals were diagnosed with BRAF V600E-mutated stage IV colorectal cancer in 2018 across EU countries.

In Europe, using the estimated value of 477,500 new cases of lung cancer diagnosed in 2020 and assuming that about 80% of newly diagnosed lung cancers are non-small cell lung cancer (American Cancer Society, 2021), 60% of NSCLC patients diagnosed at advanced stage (stages IIIB/C or IV), and approximately 3% of these cases are positive for BRAF mutations and 50% of them driven by the BRAF V600E mutation (Class 1), it can be estimated that approximately 3,438 individuals presented with BRAF V600E-mutated advanced lung cancer in 2020 across EU countries.

The number of patients receiving encorafenib who are expected to experience overexposure with increased toxicities due to concomitant use of CYP3A4 strong or moderate inhibitors in a population of 6,552, 9,460 or 3,438 eligible patients each year is not estimated since there is no absolute risk for this potential risk in either targeted BRAF-mutant melanoma, CRC or NSCLC population, respectively.

(vi) Important potential risk: Over-exposure in patients with moderate to severe hepatic impairment

Potential mechanisms:

Encorafenib is primarily metabolised and eliminated via the liver. A total of 6 subjects with mild hepatic impairment (Child-Pugh Class A) and 6 matched healthy subjects were dosed in study ARRAY-818-101 PK study. The results indicated an approximate 25% increase in overall exposure (AUCinf) of total encorafenib in these subjects with mild hepatic impairment compared with 6 healthy subjects. Given the increase in exposure observed in the mild cohort, and the potential for greater encorafenib exposures in the moderate and severe cohort, the study was terminated. These results for overall exposure translate into a 55% increase of the unbound encorafenib fraction. The pharmacokinetics of encorafenib has not been clinically studied in patients with moderate (Child-Pugh Class B) or severe (Child-Pugh Class C) hepatic impairment.

In the population PK analysis performed to support study CMEK162B2301 in patients with metastatic melanoma, the covariate of hepatic impairment (as defined by NCI organ dysfunction working group classification) indicated no significant trend versus encorafenib CL/F or V/F when comparing normal subjects (N=948) with patients with mild hepatic impairment (N=82) (according with National Cancer Institute Organ Dysfunction Group classification- ODWG NCI). Given the small number of patients with moderate impairment (N=3), no conclusion was drawn (Report T2019-00140). An additional physiology-based PK model was developed to predict the potential impact of hepatic impairment in mild to severe hepatic impairment on the pharmacokinetics of encorafenib, including unbound and total encorafenib exposure levels. Depending on the model assumptions, it is expected that doses of 150 to 200 mg QD encorafenib will provide similar encorafenib exposure in moderate hepatic impairment compared to normal hepatic function after 450 mg QD encorafenib. Even lower encorafenib doses are predicted to be needed in moderate to severe hepatic impairment to match patients with normal hepatic function, the results of these extrapolations using the physiology-based PK model are probably less precise. Therefore, no dosing recommendations can be made in moderate or severe hepatic impairment.

In the population PK analysis performed to support study ARRAY-818-302 in patients with mCRC, 91 patients over 300 exhibited a mild hepatic impairment. Given the limited number of subjects available in the severe and moderate hepatic impairment categories (N=1 in each category as defined by NCI organ dysfunction working group classification), no evaluation was performed in this group. The results in the mild group are similar to the results obtained with population analysis performed in patients with melanoma.

In the population PK analysis performed to support PHAROS study with patients with NSCLC, mild hepatic impairment (n=7) was assessed as a categorical covariate using the classification Organ Dysfunction

Working Group of National Cancer Institute (ODWG NCI). No impact was shown, which is consistent with previous population PK analyses performed to support the melanoma and mCRC indications. Neither baseline AST nor baseline total bilirubin laboratory values were significant covariates on encorafenib elimination.

Based on these results, encorafenib should be used with caution in patients with mild hepatic impairment at the dose of 300 mg QD for all patients. The dose of encorafenib at 300mg QD is a reduced dose for metastatic melanoma and advanced NSCLC, and the recommended dose for metastatic CRC patients.

Evidence source and strength of evidence:

The dedicated Study ARRAY-818-101 investigating the PK of encorafenib in subjects with hepatic impairment, as defined by Child-Pugh Score, versus healthy subjects and the population PK analysis showed evidence for an increased exposure in patients with mild hepatic impairment leading to the recommendation of a reduced encorafenib dose at 300 mg QD in combination with binimetinib in these patients. No formal study was conducted in patients with moderate or severe hepatic impairment and no dose adjustment can be established. A post authorisation measure (PAM) was requested by the EMA to assess the PK and the safety of encorafenib when administered in combination with binimetinib in cancer patients with moderate or severe hepatic impairment. To fulfill this PAM, the study W00090 GE 101 was established; this was an open label, multicenter, phase I study to evaluate the impact of moderate and severe hepatic impairment on the pharmacokinetics and safety of encorafenib in combination with binimetinib in adult patients with unresectable or metastatic BRAF V600-mutant melanoma. However, in agreement with the CHMP, this study was prematurely ended with no participant enrolled due to the difficulties to recruit the target patient population.

Since over-exposure with enhanced encorafenib-related toxicities may be anticipated in patients with moderate to severe hepatic impairment, as a precautionary approach, encorafenib is not recommended in these patients.

However, a literature case report (Ngo P, 2019) described a 60-year old male patient suffering from hepatic insufficiency from end-stage metastatic melanoma and NSAID-related acute renal failure who was initiated on treatment with encorafenib 450 mg QD and binimetinib 30 mg BID. After three (3) weeks of treatment and concurrent dialysis, the patient's transaminitis had improved and treatment was well tolerated. The patient was able to stop dialysis and resume binimetinib at the full dose of 45 mg BID and encorafenib 450 mg QD with no adverse effects. Not only did the patient tolerated treatment despite his organ damage, but his impairments were also reversible with treatment and was able to completely come off dialysis, suggesting encorafenib with binimetinib may be used safely and effectively even in patients with end organ damage (Ngo P, 2019).

Characterisation of the risk:
Frequency

No cases of increased risk of toxicities related to over-exposure of encorafenib were identified in clinical trials in patients with moderate or severe hepatic impairment. Patients with severe hepatic impairment were excluded from the clinical programmes. Of note, the number of patients with moderate hepatic impairment in safety populations was very low (Module SIV.3).

In the post-marketing experience, there is no case involving the use of encorafenib in a patient with confirmed severe or moderate hepatic impariement as per definition (NCI or Child-Pugh classification).

Absolute risk:

Not applicable.

Relative risk:

Not applicable.

Seriousness:

Not applicable.

Severity:

Not applicable.

Event outcome:

Not applicable since no cases identified.

Reversibility:

The conditions of reversibility of toxicities resulting from over-exposure of encorafenib in patients with moderate to severe impairment are unknown. Encorafenib clearance and terminal half-life are expected to be prolonged as compared to healthy subjects. Following a single oral dose of 100 mg [^{14}C] encorafenib in healthy subjects, radioactivity was eliminated equally in both the faeces and urine (mean of 47.2%). In urine, 1.8% of the radioactivity was excreted as encorafenib. The mean (CV %) apparent clearance (CL/F) of encorafenib was 27.9 L/h (9.15%). The median (range) encorafenib terminal half-life ($T_{1/2}$) was 6.32 h (3.74 to 8.09 h) (CLGX818A2101).

Long-term outcomes:

The impact of the risk of over-exposure in patients with moderate to severe hepatic impairment on the individual patient is likely to be dependent on the extent of over-exposure (AUC_{inf}) and whether toxicity develops.

In healthy subjects, the median (range) encorafenib terminal half-life ($T_{1/2}$) was 6.32 h (3.74 to 8.09 h). With proper recommendation to avoid encorafenib in these patients, it can be expected that most cases of over-exposure and possible resulting toxicity can be adequately minimised.

Impact on quality of life:

Over-exposure in patients with moderate to severe hepatic impairment may have a range of impacts on the quality of life of the individual patient depending on the extent of over-exposure and whether toxicity develops. If not recommended, over-exposure of a patient with moderate or severe hepatic impairment is avoidable, and therefore, is expected to have a minimal impact on patient quality of life.

Risk factors and risk groups:

Risk factors are those well known for hepatic dysfunction in routine practice including patients with baseline hepatic impairment regardless of aetiology, concurrent hepatobiliary disease/disorders and concomitant use of hepatotoxic agents. Patients with extensive liver metastatic disease with consequent associated moderate to severe liver dysfunction are unlikely to be candidates for the combination treatment as first-line therapy.

Preventability:

Clinical identification of patients with moderate to severe impairment before treatment initiation with complete laboratory liver function tests can be implemented. Encorafenib is not recommended in patients with moderate to severe hepatic impairment. Otherwise, encorafenib should be administered with caution at 300 mg QD in patients with mild hepatic impairment.

Impact on the benefit-risk balance of the product:

The potential risk of over-exposure in patients with moderate to severe hepatic impairment is considered low since encorafenib is not recommended in patients with moderate to severe hepatic impairment, while in patients with mild hepatic impairment, encorafenib can be used with caution at a reduced dose. The potential risk or overexposure in patients with moderate to severe hepatic impairment is very low and is satisfactorily minimised through the not recommended use in these patients, as reflected in routine risk minimisation measures described in Part V.

Public health impact:

No impact on public health is anticipated.

Expected population outcome

EUCAN data from 2012 indicate an age standardised incidence rate of malignant melanoma of the skin in the EU of 13.0 per 100,000 of population per year (European Cancer Information System, 2019*).* There are currently 508 million individuals living in the EU (European Commission, 2019). Assuming that 20% of diagnosed melanomas progress to a metastatic stage, and that approximately 50% of these cases are positive for BRAF V600E mutations (Ascierto, 2012), the target population is estimated to be approximately 6,552 individuals per year.

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In Europe, using the estimated value of 477,500 new cases of lung cancer diagnosed in 2020 and assuming that about 80% of newly diagnosed lung cancers are non-small cell lung cancer (American Cancer Society, 2021), 60% of NSCLC patients diagnosed at advanced stage (stages IIIB/C or IV), and approximately 3% of these cases are positive for BRAF mutations and 50% of them driven by the BRAF V600E mutation (Class 1), it can be estimated that approximately 3,438 individuals presented with BRAF V600E-mutated advanced lung cancer in 2020 across EU countries.

The number of patients with severe or moderate hepatic impairment receiving encorafenib who are expected to experience encorafenib overexposure with increased toxicities in a population of 6,552, 9,460 or 3,438 eligible patients each year is not estimated, since there is no absolute risk for this potential risk in either targeted BRAF-mutant melanoma, CRC or NSCLC population, respectively.

SVII.3.2. Presentation of missing information

Use in patients with severe renal impairment

Evidence source and strength of evidence:

Sub-acute and sub-chronic (repeat-dose) toxicity studies were not predictive of tubular and interstitial damage. In the Enco 300 P population 6/217 patients (2.8%) had an ADR of renal failure (3 patients with grade 3-4), including 4 SAE. One case of renal failure (grade 2) with positive re-challenge was reported in a male patient with medical history of diabetes and hypertension who underwent renal biopsy. The kidney parenchyma was described to be normal with no anatomo-pathological lesions.

Encorafenib undergoes minimal renal elimination. Therefore, no formal clinical study has been conducted to evaluate the effect of renal impairment on the PK of encorafenib. In a population PK analysis performed to support Phase 3 study CMEK162B2301 in patients with metastatic melanoma, no clear trend in encorafenib CL/F was observed in patients with mild (eGFR 60 to 90 mL/min/1.73 m^2) or moderate (eGFR 30 to 59 mL/min/1.73 m^2) renal impairment compared with subjects with normal renal function (eGFR ≥90 mL/min/1.73 m^2). A small decrease in CL/F (≤5%) was predicted for patients with mild and moderate renal impairment, which is unlikely to be clinically relevant. In the population PK analysis performed to support the Phase 3 Study ARRAY-818-302 in patients with mCRC, mild (N=111) and moderate (N=30) renal impairment was assessed as a categorical covariate using CRCL, limited increase in AUC and C_{max} was observed with a maximum increase of 11% in AUC in patients with moderate renal impairment compared with patients with normal renal function.

In the population PK analysis performed to support PHAROS study with patients with NSCLC, mild (n=34) and moderate (n=7) renal impairment was assessed as a continuous covariate using eGFR (mL/min/1.73m2). No impact on the PK parameters was shown, which is consistent with previous population PK analyses to support the melanoma and mCRC indications.

Based on the population PK analysis, no dose adjustment is recommended for patients with mild or moderate renal impairment analysis, however for patients with severe renal impairment who were excluded from clinical trials, so the PK of encorafenib has not been studied in this population, no dose recommendation has been established.

A report of a 60-year-old patient with severe renal impairment requiring dialysis and disease-related liver dysfunction metastatic BRAF-mutant melanoma was published (Ngo P 2019). Due to a rapid worsening of the disease, treatment was started with encorafenib at 450 mg QD in combination with binimetinib at 30 mg BID. Therapy was tolerated without significant adverse effects. Creatinine and liver function tests improved within the first week of treatment. Renal function had normalized after 2 months of therapy and dialysis was stopped.

Patients with severe renal impairment excluded from clinical trials represent a subgroup of population in need of further characterisation:

Anticipated risk/consequence of the missing information:

No formal clinical study has been conducted to evaluate the effect of severe renal impairment on the PK of encorafenib. In population PK analyses, no clear trend in encorafenib CL/F was observed in patients with mild (eGFR 60 to 90 mL/min/1.73 m^2) or moderate (eGFR 30 to 59 mL/min/1.73 m^2) renal impairment compared with subjects with normal renal function (eGFR ≥90 mL/min/1.73 m2). Small decrease in CL/F (≤5%) or increase in AUC (≤11%) were predicted for patients with mild and moderate renal impairment, which is unlikely to be clinically relevant.

Encorafenib should be used with caution in patients with severe renal impairment. Patients with severe renal impairment (eGFR < 30 mL/min/1.73 m^2) should be followed up for further characterisation of the safety profile of encorafenib in this population. Blood creatinine should be monitored as clinically indicated and managed with dose modification or discontinuation and patients should ensure adequate fluid intake during treatment.

Since encorafenib binds moderately to plasma proteins, haemodialysis is likely to be ineffective in the treatment of overdose. In the event of an overdose, recommendations are given for treatment interruption and close monitoring of renal function and adverse reactions. Symptomatic treatment and supportive care should be given as needed.

Additional missing information for encorafenib in combination with binimetinib
None.

Additional missing information for encorafenib in combination with cetuximab
None.

Part II: Module SVIII - Summary of the safety concerns of encorafenib

Table SVIII.1 Summary of safety concerns for encorafenib

Important identified risks	- Secondary skin neoplasms: cuSCC and new primary melanoma
Important potential risks	- QT prolongation - Non-cutaneous malignancies with RAS mutation - Over-exposure due to concomitant use with strong and moderate CYP450 3A4 inhibitors - Over-exposure in patients with moderate to severe hepatic impairment
Missing information	- Use in patients with severe renal impairment

Part III: Pharmacovigilance plan

III.1 Routine pharmacovigilance activities

Routine pharmacovigilance activities beyond ADR reporting and signal detection:

None

Other forms of routine pharmacovigilance activities for safety concerns:

None

III.2 Additional pharmacovigilance activities

No non-clinical, clinical, epidemiological or post-authorisation safety studies (PASS) are planned at the time of this RMP.

III.3 Summary table of additional pharmacovigilance activities

There are no planned/ongoing additional studies, imposed or required by the competent authority, in the pharmacovigilance plan.

Part IV: Plans for post-authorisation efficacy studies

There are no planned or ongoing, imposed or required post-authorisation efficacy studies.

Part V: Risk minimisation measures (including evaluation of the effectiveness of risk minimisation activities)

Risk Minimisation Plan

V.1. Routine risk minimisation measures

The table presented below includes the description of routine risk minimisation measures by safety concern for encorafenib.

The description of routine risk minimisation measures by safety concern for binimetinib or cetuximab is presented in the product specific RMP.

Table Part V.1: Description of routine risk minimisation measures by safety concern for encorafenib

Safety concern	**Routine risk minimisation activities**
Important identified risks for encorafenib	
Secondary skin neoplasms: cutaneous squamous cell carcinoma and new primary melanoma	**Routine risk communication:** Proposed text in the SmPC. • Warning in Section 4.4 of the SmPC and relevant PIL section • Listed in Section 4.8 of the SmPC and relevant PIL section **Routine risk minimisation activities recommending specific clinical measures to address the risk**: SmPC (Section 4.4): • Perform dermatologic evaluations prior to initiation of therapy, every 2 months while on therapy and for up to 6 months following discontinuation of the combination. • Manage suspicious skin lesions as appropriate. Patients told to immediately inform their physicians for any new skin lesion. Patient information leaflet (PIL); (Section 2 and Section 4): • Regular medical all-body skin examination is required. While on treatment, any noticed skin changes should be reported immediately to the treating physician for skin evaluation and lesion excision if needed. **Other risk minimisation measures beyond the Product Information**: Pack size: No specific adaptation Medicine's legal status: Prescription only medicine. Use restricted to physicians experienced in the treatment of cancer.
Important potential risks for encorafenib	
QT prolongation	**Routine risk communication:** Proposed text in the SmPC. • Dose modification recommendations in section 4.2 of the SmPC • Warning in section 4.4 of the SmPC and relevant PIL section **Routine risk minimisation activities recommending specific clinical measures to address the risk**:

Safety concern	**Routine risk minimisation activities**
	SmPC (Section 4.4): • Correct serum electrolyte abnormalities (magnesium and potassium) and control risk factors for QT prolongation (e.g. congestive heart failure, bradyarrhythmia) prior to initiating treatment and on-treatment. ECG assessments prior to initiating treatment, 1 month after initiation, and then about every 3 months or more frequently as clinically indicated. PIL (Section 2): • Before starting treatment with encorafenib, instruction to inform the treating physician about any heart disorders. • Tests to check that the heart is functioning properly before and during treatment. **Other risk minimisation measures beyond the Product Information**: Pack size: No specific adaptation Medicine's legal status: Prescription only medicine. Use restricted to physicians experienced in the treatment of cancer.
Non-cutaneous malignancies with RAS mutation	**Routine risk communication:** Proposed text in the SmPC: • Dose modification recommendations in section 4.2 of the SmPC • Warning in section 4.4 of the SmPC and relevant PIL section **Routine risk minimisation activities recommending specific clinical measures to address the risk**: SmPC (Section 4.4): • Head & neck examination, chest/abdomen CT scan, anal and pelvic examinations (for women) and complete blood cell counts prior to initiation, during and at the end of treatment. Consider history of or concurrent RAS tumours. May be discontinued in patients developing such malignancies. PIL (Section 2): • Inspection of the head, neck, mouth, and lymph glands with regular CT scans. Genital examinations (for women) and anal examinations are recommended before and at the end of treatment. • Before starting treatment with Braftovi, the treating physician should be informed about any other cancer that the patient may have (other than melanoma, large intestine cancer or NSCLC), as Braftovi may worsen certain other types of cancer. **Other risk minimisation measures beyond the Product Information**: Pack size: No specific adaptation Medicine's legal status: Prescription only medicine. Use restricted to physicians experienced in the treatment of cancer.

Safety concern	**Routine risk minimisation activities**
Over-exposure due to concomitant use with strong and moderate CYP450 3A4 inhibitors	**Routine risk communication:** Proposed text in the SmPC: • Warning in sections 4.2 and 4.4 of the SmPC and in PIL subsections 'Other medicines and Braftovi' and 'Braftovi with food and drink' • Discussion in section 4.5 of the SmPC **Routine risk minimisation activities recommending specific clinical measures to address the risk**: SmPC (Section 4.2, section 4.4 and Section 4.5): • Avoid concomitant strong inhibitors and avoid grapefruit juice intake and use moderate inhibitors with caution. Monitor patients taking strong and moderate CYP3A4 inhibitors closely. PIL (Section 2): • Warning to inform the treating physician if they are taking medicines that inhibit, stimulate or are eliminated by CYP3A4 (examples provided, including oral contraceptives) • Warning to avoid taking grapefruit juice **Other risk minimisation measures beyond the Product Information**: Pack size: No specific adaptation Medicine's legal status: Prescription only medicine. Use restricted to physicians experienced in the treatment of cancer.
Over-exposure in patients with moderate to severe hepatic impairment	**Routine risk communication:** Proposed text in the SmPC. • Dose modification recommendations in section 4.2 of the SmPC and relevant PIL section • Warning in section 4.4 of SmPC and relevant PIL section **Routine risk minimisation activities recommending specific clinical measures to address the risk**: SmPC (section 4.4): • Encorafenib is not recommended for patients with moderate to severe hepatic impairment. PIL (Section 2 and Section 3): • In case of known liver problems, the treating physician should be warned, as Encorafenib should not be used in patients with moderate to severe hepatic impairment. **Other risk minimisation measures beyond the Product Information**: Pack size: No specific adaptation Medicine's legal status: Prescription only medicine. Use restricted to physicians experienced in the treatment of cancer.
Missing information for encorafenib	

Safety concern	**Routine risk minimisation activities**
Use in patients with severe renal impairment	**Routine risk communication:** Proposed text in the SmPC. • Dosing recommendations in section 4.2 of the SmPC: • Warning in section 4.4 of the SmPC and relevant PIL section **Routine risk minimisation activities recommending specific clinical measures to address the risk**: SmPC (Section 4.2, Section 4.4): • Should be used with caution in patients with severe renal impairment who should be closely monitored for toxicities (typically associated with vomiting and dehydration). Adequate fluid intake during treatment should be ensured. PIL (Section 2): • Patient must inform treating physician of any kidney problems and keep up fluid intake on-treatment. **Other risk minimisation measures beyond the Product Information**: Pack size: No specific adaptation Medicine's legal status: Prescription only medicine. Use restricted to physicians experienced in the treatment of cancer.

V.2. Additional risk minimisation measures

No additional risk minimisation measures have been identified.

V.3 Summary of risk minimisation measures

Table Part V.3: Summary table of pharmacovigilance activities and risk minimisation activities for safety concerns of encorafenib

Safety concern	**Risk minimisation measures**	**Pharmacovigilance activities**
Important identified risks for encorafenib		
Secondary skin neoplasms: cutaneous squamous cell carcinoma and new primary melanoma	Routine: Warning in Section 4.4 of the SmPC and relevant PIL section Listed in Section 4.8 of the SmPC and relevant PIL section Prescription only medicine. Use restricted to physicians experienced in the treatment of cancer Additional: none	Routine Additional: none
Important potential risks for encorafenib		
QT prolongation	Routine: Dose modification recommendations in section 4.2 of the SmPC	Routine Additional: none

Safety concern	**Risk minimisation measures**	**Pharmacovigilance activities**
	Warning in Section 4.4 of the SmPC and relevant PIL section Prescription only medicine. Use restricted to physicians experienced in the treatment of cancer Additional: none	
Non-cutaneous malignancies with RAS mutation	Routine: Dose modification recommendations in section 4.2 of the SmPC Warning in Section 4.4 of the SmPC and relevant PIL section Prescription only medicine. Use restricted to physicians experienced in the treatment of cancer Additional: none	Routine Additional: none
Over-exposure due to concomitant use with strong and moderate CYP450 3A4 inhibitors	Routine: Warning in sections 4.2 and 4.4 of the SmPC and relevant PIL sections Discussion in section 4.5 Prescription only medicine. Use restricted to physicians experienced in the treatment of cancer Additional: none	Routine Additional: none
Over-exposure in patients with moderate to severe hepatic impairment	Routine: Dose modification recommendations in section 4.2 of the SmPC and PIL relevant section Warning in section 4.4 and relevant PIL section Prescription only medicine. Use restricted to physicians experienced in the treatment of cancer Additional: none	Routine Additional: none
Missing information for encorafenib		
Use in patients with severe renal impairment	Routine: Dosing recommendations in section 4.2 of the SmPC Warning in section 4.4 of the SmPC and relevant PIL section Prescription only medicine. Use restricted to physicians experienced in the treatment of cancer Additional: none	Routine Additional: none

Part VI: Summary of the risk management plan

Summary of the risk management plan for BRAFTOVI

This is a summary of the risk management plan (RMP) for BRAFTOVI when administered in combination with MEKTOVI or cetuximab. The RMP details important risks of BRAFTOVI in combination with MEKTOVI or cetuximab, how these risks can be minimised, and how more information will be obtained about BRAFTOVI in combination with MEKTOVI or cetuximab risks and uncertainties (missing information). Summary of product characteristics (SmPC) for BRAFTOVI and its package leaflets give essential information to healthcare professionals and patients on how BRAFTOVI should be used.

This summary of the RMP for BRAFTOVI when administered in combination with MEKTOVI or cetuximab should be read in the context of all this information including the assessment reports of the evaluation and the plain-language summary, all of which are part of the European Public Assessment Report (EPAR).

Important new concerns or changes to current concerns will be included in future updates of the RMP for BRAFTOVI.

I. The medicine and what it is used for

BRAFTOVI is authorised in combination with MEKTOVI for the treatment of adult patients with unresectable or metastatic melanoma with a BRAF V600 mutation (see SmPC for the full indication). The active substance of BRAFTOVI is encorafenib and of MEKTOVI is binimetinib and both are given by the oral route of administration.

BRAFTOVI in combination with cetuximab is authorised for the treatment of adult patients with metastatic colorectal cancer (CRC) with a BRAF V600E mutation, who have received prior systemic therapy (see SmPC for the full indication). Cetuximab is given by intravenous infusion.

BRAFTOVI in combination with MEKTOVI is proposed for the treatment of adult patients with advanced non-small cell lung cancer (NSCLC) with a BRAF V600E mutation. Both drugs are given by the oral route.

BRAFTOVI is not authorised for use as monotherapy.

Further information about the evaluation of BRAFTOVI in combination with MEKTOVI or cetuximab can be found in the BRAFTOVI EPAR, including in the plain-language summaries, available on the EMA website, under the medicine's webpage <*link to the EPAR summary landing page*>.

II. Risks associated with the medicine and activities to minimise or further characterise the risks

Important risks of BRAFTOVI in combination with MEKTOVI or cetuximab, together with measures to minimise such risks and the proposed studies if any, for learning more about the risks of BRAFTOVI in combination with MEKTOVI or cetuximab, are outlined below.

Measures to minimise the risks identified for medicinal products include:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;
- The authorised pack size - the amount of medicine in a pack is chosen so, as to ensure that the medicine is used correctly;
- The medicine's legal status - the way a medicine is supplied to the public (e.g. with or without prescription) can help to minimise its risks.

Together, these measures constitute *routine risk minimisation* measures.

In addition to these measures, information about adverse events is collected continuously and regularly analysed, including PSUR/PBRER assessments, so that immediate action and updates can be implemented as necessary. These measures constitute *routine pharmacovigilance activities*.

If important information that may affect the safe use of BRAFTOVI is not yet available, it is listed under 'missing information' below.

II.A List of important risks and missing information

Important risks of BRAFTOVI in combination with MEKTOVI or cetuximab are risks that need risk management activities to further investigate or minimise the risk, so that the medicinal product can be taken safely.

Important risks can be regarded as identified or potential.

Identified risks are concerns for which there is sufficient proof of a link with the use of BRAFTOVI as a single agent or in combination with MEKTOVI or cetuximab.

Potential risks are concerns for which an association with the use of BRAFTOVI as a single agent or in combination with MEKTOVI or cetuximab is possible based on available data, but this association has not yet been established and needs further evaluation.

Missing information refers to information on the safety of BRAFTOVI as a single agent or in combination with MEKTOVI or cetuximab that is currently missing and needs to be collected.

The following important risks are those specific to encorafenib regardless of the indication for use:

Table Part VI.1: Safety concerns for encorafenib

Important identified risks	- Secondary skin neoplasms: cutaneous squamous cell carcinoma (CuSCC) and new primary melanoma
Important potential risks	- QT prolongation - Non-cutaneous malignancies with RAS mutation - Over-exposure due to concomitant use with strong and moderate CYP450 3A4 inhibitors - Over-exposure in patients with moderate to severe hepatic impairment
Missing information	- Use in patients with severe renal impairment

II.B Summary of important risks and missing information

Important identified risk for encorafenib: Secondary skin neoplasms: cutaneous squamous cell carcinoma and new primary melanoma	
Evidence linking the risk to the medicine	Secondary skin neoplasms including cuSCC and new primary melanoma represent a known class-effect with the use of BRAF inhibitors. CuSCC and new primary melanoma have been identified as ADRs for encorafenib single agent, based on the clinical trial data.
Risk factors and risk groups	Associations have been reported with older age (≥65 years) for vemurafenib and dabrafenib-treated patients, and with prior skin cancer, and chronic sun exposure for vemurafenib-treated patients.
Risk minimisation measures	Routine risk minimisation measures: Dose modification recommendations in Section 4.2 of the SmPC Warning in section 4.4 of the SmPC and PIL relevant section Listed in section 4.8 of SmPC and PIL relevant section Prescription only medicine. Use restricted to physicians experienced in the treatment of cancer. Additional risk minimisation measures: None
Important potential risk for encorafenib: QT prolongation	
Evidence linking the risk to the medicine	QT prolongation is a class effect for BRAF inhibitors. For encorafenib, the determined IC_{50} for hERG inhibition indicates an unlikely effect of encorafenib on QT prolongation and no clinical risk is predicted for QT prolongation. Safety pharmacology results suggest encorafenib administration has the potential to result in small increases in QTc interval and mild increases in HR at a clinically relevant dose. Small increases in QTc interval and mild increases in heart rate were apparent in the Enco 300 population. Due to the theoretical risk of clinical complications (torsades de pointes, ventricular arrhythmia) due to sustained QT prolongation, QT prolongation class-effect is considered as potential.
Risk factors and risk groups	Risk factors for torsade de pointes other than QTc interval >500 ms or >60 ms increase from baseline value include uncorrected hypokalaemia, hypomagnesemia and hypocalcaemia, long QT syndrome, concomitant therapy with multiple QTc interval–prolonging drugs. Other risk factors for torsade de pointes include acute myocardial infarction, heart failure with reduced ejection fraction, diuretic therapy, age ≥65 years, female sex, family history of sudden cardiac death at <50 years, cardiac disease and history of arrhythmia or bradycardia.
Risk minimisation measures	Routine risk minimisation measures: Dose modification recommendations in section 4.2 of the SmPC Warning in Section 4.4 of the SmPC and relevant PIL section Prescription only medicine. Use restricted to physicians experienced in the treatment of cancer. Additional risk minimisation measures: None

Important potential risk for encorafenib: Non-cutaneous malignancies with RAS mutation	
Evidence linking the risk to the medicine	As for other BRAF inhibitors and based on its mechanism of action, encorafenib may promote malignancies associated with RAS mutation associated with activation of RAS through mutation or other mechanisms. No cases of non-cutaneous malignancy with RAS mutation possibly related to encorafenib were identified from the pooled safety data of the clinical development programme, however due to the seriousness of this class-effect risk, non-cutaneous carcinoma is considered an important potential risk.
Risk factors and risk groups	None identified
Risk minimisation measures	Routine risk minimisation measures: Dose modification recommendation in section 4.2 of the SmPC Warning in section 4.4 of the SmPC and PIL relevant section Additional risk minimisation measures: None
Important potential risk for encorafenib: Over-exposure due to concomitant use with strong and moderate CYP450 3A4 inhibitors	
Evidence for linking the risk to the medicine	Encorafenib is primarily metabolised by CYP3A4. Based on the PK data, the use of strong CYP3A4 inhibitors was not allowed during clinical trials. Concomitant administration of encorafenib and strong or moderate CYP3A4 inhibitors may lead to increased encorafenib exposure and potential increase in toxicity.
Risk factors and risk groups	Risk factors include any medical condition requiring the use of strong (ritonavir, itraconazole, clarithromycin, telithromycin, posaconazole, grapefruit juice, etc.) or moderate CYP3A4 inhibitors (amiodarone, erythromycin, fluconazole, diltiazem, delavirdine, amprenavir and imatinib) with no possibility for an alternate therapy.
Risk minimisation measures	Routine risk minimisation measures: Warning in sections 4.2 and 4.4 of the SmPC, and PIL relevant sections Discussion in section 4.5 of the SmPC Prescription only medicine. Use restricted to physicians experienced in the treatment of cancer. Additional risk minimisation measures: None
Important potential risk for encorafenib: Over-exposure in patients with moderate to severe hepatic impairment	
Evidence linking the risk to the medicine	Results from a dedicated clinical trial indicate a 25 % higher total encorafenib exposures in patients with mild hepatic impairment (Child-Pugh Class A) compared with subjects with normal liver function. This translates into a 55 % increase of the unbound encorafenib exposure. The pharmacokinetics of encorafenib has not been evaluated clinically in patients with moderate (Child-Pugh Class B) or severe (Child-Pugh Class C) hepatic impairment. As encorafenib is primarily metabolised and eliminated via the liver and based on PBPK modelling, patients with moderate to severe hepatic impairment may have greater increases in exposure than patients with mild hepatic impairment. No dosing recommendation can be made in moderate or severe hepatic impairment.

Risk factors and risk groups	Risk factors are those well known for hepatic dysfunction in routine practice including patients with baseline hepatic impairment regardless of aetiology, concurrent hepatobiliary disease/disorders and concomitant use of hepatotoxic agents. Patients with massive liver metastatic disease with consequent associated moderate to severe liver dysfunction are unlikely to be candidates for the combination treatment as first-line therapy.
Risk minimisation measures	Routine risk minimisation measures: Dose modification recommendations in section 4.2 of the SmPC and relevant PIL section Warning in section 4.4 of the SmPC and PIL relevant section Prescription only medicine. Use restricted to physicians experienced in the treatment of cancer Additional risk minimisation measures: None
Missing information for encorafenib: Use in patients with severe renal impairment	
Risk minimisation measures	Routine risk minimisation measures: Dosing recommendations in section 4.2 of the SmPC Warning in section 4.4 of the SmPC and relevant PIL section Prescription only medicine. Use restricted to physicians experienced in the treatment of cancer Additional risk minimisation measures: None

II.C Post-authorisation development plan

II.C.1 Studies which are conditions of the marketing authorisation

None

II.C.2 Other studies in post-authorisation development plan

None.

Part VII: Annexes

Annex 4 – Specific adverse drug reaction follow-up forms

Not applicable.

There are no specific adverse drug reaction follow-up forms.

Annex 6– Details of proposed additional risk minimisation activities

Not applicable.

There are no proposed additional risk minimisation activities.