



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: 4.0
Data lock point for this RMP: 26 June 2025
Date of final sign off: 26 May 2026
Submission date: 13 October 2025
Procedure number: EMA/VR/0000304994
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
Part II	SI	Update the information relevant to epidemiology of colorectal cancer target population
	SIII	Updated taking into consideration the addition of the new indication population Update the cutoff date of BEACON CRC study, and update of relevant study data as per the new cutoff date.
	SIV	Addition of information relevant to the new indication, Update the information of BEACON CRC study as per the updated cutoff date
	SV	Update of the post-authorisation experience as of the DLP
	SVII	Updated taking into consideration: the population of the new indication, the updated cutoff date of BEACON CRC study, and post-authorisation data.
Part VI		Updated according to changes in other parts.
Part VII		Annex 7 and Annex 8 updated, as applicable.



Other RMP versions under evaluation:

None

Details of the currently approved RMP:

Version number:	3.0
Approved with procedure:	EMA/H/C/004580/WS2538/0034
Date of approval:	25 July 2024

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.



Table of contents

Table of contents.....	4
Tables.....	6
LIST OF ABBREVIATIONS	8
PART I: Product overview.....	11
Part II: Safety specification.....	16
Part II: Module SI - Epidemiology of the indication(s) and target population	17
Part II: Module SII - Non-clinical part of the safety specification of encorafenib	32
Part II: Module SIII - Clinical trial exposure of encorafenib.....	40
Part II: Module SIV - Populations not studied in clinical trials involving encorafenib	60
SIV.1 Exclusion criteria in pivotal clinical studies within the development programme for encorafenib	60
SIV.2 Limitations to detect adverse reactions in clinical trial development programmes of encorafenib	66
SIV.3 Limitations with respect to populations typically under-represented in clinical trial development programmes of encorafenib.....	71
Part II: Module SV - Post-authorisation experience of encorafenib	76
SV.1 Post-authorisation exposure	76
SV.1.1 Method used to calculate exposure	76
SV.1.2 Exposure.....	76
Part II: Module SVI - Additional EU requirements for the safety specification of encorafenib.....	77
Part II: Module SVII - Identified and potential risks of encorafenib.....	78
SVII.1 Identification of safety concerns in the initial RMP submission	79
SVII.1.1 Risks not considered important for inclusion in the list of safety concerns in the RMP for encorafenib	79
SVII.1.2. Risks considered important for inclusion in the list of safety concerns of encorafenib in the RMP	85
SVII.1.3 Additional risks considered important for inclusion in the list of safety concerns for encorafenib in combination with binimetinib	89
SVII.2 New safety concerns and reclassification with a submission of an updated RMP	92
SVII.3 Details of important identified risks, important potential risks and missing information for encorafenib	93
SVII.3.1. Presentation of important identified and important potential risks	93
SVII.3.2. Presentation of missing information	123
Part II: Module SVIII - Summary of the safety concerns of encorafenib .	125
Part III: Pharmacovigilance plan	125
III.1 Routine pharmacovigilance activities.....	125



III.2	Additional pharmacovigilance activities	125
III.3	Summary table of additional pharmacovigilance activities.....	125
Part IV: Plans for post-authorisation efficacy studies		125
Part V: Risk minimisation measures (including evaluation of the effectiveness of risk minimisation activities)		126
V.1.	Routine risk minimisation measures.....	126
V.2.	Additional risk minimisation measures	129
V.3	Summary of risk minimisation measures.....	129
Part VI: Summary of the risk management plan.....		131
I.	The medicine and what it is used for	131
II.	Risks associated with the medicine and activities to minimise or further characterise the risks.....	131
II.A	List of important risks and missing information.....	132
II.B	Summary of important risks and missing information	133
II.C	Post-authorisation development plan	135
II.C.1	Studies which are conditions of the marketing authorisation.....	135
II.C.2	Other studies in post-authorisation development plan	135
Part VII: Annexes.....		136
Annex 1	– EudraVigilance Interface.....	137
Annex 2	– Tabulated summary of planned, ongoing, and completed pharmacovigilance study programme	138
Annex 3	– Protocols for proposed, ongoing and completed studies in the pharmacovigilance plan	139
Annex 4	– Specific adverse drug reaction follow-up forms.....	140
Annex 5	– Protocols for proposed and ongoing studies in RMP part IV	141
Annex 6	– Details of proposed additional risk minimisation activities	142
Annex 7	– Other supporting data (including referenced material)	143
Annex 8	– Summary of changes to the risk management plan over time	157



Tables

Table Part I.1: Product overview	11
Table SII.1: Encorafenib: Key safety findings from non-clinical studies (toxicity, safety pharmacology)	32
Table SII.2: Encorafenib and binimetinib combination: Integrative toxicological assessment of the encorafenib and binimetinib combination from single agent non-clinical safety findings.....	36
Table SII.3: Encorafenib and cetuximab combination: Integrative toxicological assessment of the encorafenib and cetuximab combination from single agent non-clinical safety findings.....	37
Table SIII.1: Encorafenib: Clinical studies included in safety evaluation	40
Table SIII.2: Encorafenib: Duration of exposure	40
Table SIII.3: Encorafenib: Dose of exposure	41
Table SIII.4: Encorafenib: Exposure by age group and gender.....	41
Table SIII.5: Encorafenib: Exposure by ethnic or racial origin	41
Table SIII.6: Encorafenib in combination use at the recommended doses: Clinical studies included in the safety evaluation.....	42
Table SIII.7: Encorafenib Cumulative duration of exposure – All indications Pooled combination safety population (N=847)	43
Table SIII.8: Encorafenib in combination use: Cumulative Dose of exposure (pooled target pop)	43
Table SIII.9: Encorafenib in combination use: Cumulative Exposure by age group and gender (target pop).....	44
Table SIII.10: Encorafenib in combination use: Cumulative Exposure by ethnic or racial origin (pooled)	44
Table SIII.11a: Encorafenib and binimetinib combination: Clinical studies relevant to safety evaluation - Combo BP for melanoma (N=433)	46
Table SIII.11b: Clinical studies Supportive for Encorafenib/Binimetinib combination therapy in Combo 450 RP (N=274) - Melanoma indication	46
Table SIII.11c: Encorafenib and binimetinib combination: Supportive clinical studies for Combo 450 ISP:	47
Table SIII.12a: Encorafenib and binimetinib combination: Duration of exposure (Combo 450 ISP)	47
Table SIII.12b: Encorafenib and binimetinib combination: Duration of exposure (broad).....	48
Table SIII.13a: Encorafenib and binimetinib combination: Dose of exposure (Combo 450 ISP)	48
Table SIII.13b: Encorafenib and binimetinib combination: Dose of exposure (broad).....	49
Table SIII.14a: Encorafenib and binimetinib combination: Exposure by age group and gender (Combo 450 ISP)	49
Table SIII.14b: Encorafenib and binimetinib combination: Exposure by age group and gender (broad)	50
Table SIII.15a: Encorafenib and binimetinib combination: Exposure by ethnic or racial origin (Combo 450 ISP)	50
Table SIII.15b: Encorafenib and binimetinib combination: Exposure by ethnic or racial origin (broad) ..	51
Table SIII.16: Duration of exposure (Doublet population of BEACON CRC study- indication: mCRC in previously treated patients)	53
Table SIII.17: Dose of exposure (Doublet population of BEACON CRC study- indication: mCRC in previously treated patients)	53
Table SIII.18: Exposure by age group and gender (Doublet-population of BEACON CRC study- indication: mCRC in previously treated patients)	53
Table SIII.19: Exposure by ethnic or racial origin (Doublet population of BEACON CRC study- indication: mCRC in previously treated patients).....	54
Table SIII.20: Duration of exposure (EC population of BREAKWATER study).....	54
Table SIII.21: Dose of exposure (EC population of BREAKWATER study).....	55
Table SIII.22: Exposure by age group and gender (EC population of BREAKWATER study)	55
Table SIII.23: Exposure by ethnic or racial origin (EC population of BREAKWATER study)	55
Table SIII.24: Duration of exposure (Doublet broad population)	56
Table SIII.25: Dose of exposure (Doublet broad population)	56
Table SIII.26: Exposure by age group and gender (Doublet broad population).....	56
Table SIII.27: Exposure by ethnic or racial origin (Doublet broad population).....	57
Table SIII.28: Duration of exposure for BREAKWATER study (EC-FOLFOX pooled Population (EC-FOLFOX-P), indication: mCRC in previously untreated patients)	58
Table SIII.29: Dose of exposure for BREAKWATER study (EC-FOLFOX pooled Population (EC-FOLFOX-P), indication: mCRC in previously untreated patients)	58
Table SIII.30: Exposure by age group and gender for BREAKWATER study (EC-FOLFOX pooled Population (EC-FOLFOX-P), indication: mCRC in previously untreated patients)	58



Table SIII.31: Exposure by ethnic or racial origin for BREAKWATER study (EC-FOLFOX pooled Population (EC-FOLFOX-P), indication: mCRC in previously untreated patients)	59
Table SIV.1: Encorafenib: Limitations for detecting adverse drug reactions (ADRs)	66
Table SIV.2: Encorafenib and binimetinib combination: Limitations for detecting ADRs	67
Table SIV.3: Encorafenib in combination with cetuximab: Limitations for detecting ADRs	68
Table SIV.4: Encorafenib in combination with cetuximab and FOLFOX: Limitations for detecting ADRs	69
Table SIV.5: Encorafenib: Exposure of special populations included or not in clinical trial development programmes – Single agent and combination therapy with any agent.....	71
Table SIV. 6: Encorafenib: Limitations with respect to under-represented populations	71
Table SIV.7a: Encorafenib and binimetinib combination: Limitations with respect to under-represented populations in the integrated combination safety pool (Combo 450 ISP)	72
Table SIV.7b: Encorafenib and binimetinib combination: Limitations with respect to under-represented populations in the pooled combination safety pool (broad)	73
Table SIV.8a Limitations with respect to under-represented populations – Randomized Doublet arm (N=216)	74
Table SIV.8b: Limitations with respect to under-represented populations - Doublet Broad population (N=368)	74
Table SIV.9 Limitations with respect to under-represented populations in EC-FOLFOX pooled Population; EC-FOLFOX-P (N= 259)	75
Table SVII.1: Encorafenib: Cutaneous squamous cell carcinoma events irrespective of relationship (Enco 300 P population and Enco 300 arm of Study CMEK162B2301)	94
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)	94
Table SVII.3: Encorafenib in combination with cetuximab: Cutaneous squamous cell carcinoma events irrespective of relationship (doublet arm of Study ARRAY-818-302)	95
Table SVII.4: Encorafenib in combination with cetuximab: Cutaneous squamous cell carcinoma events irrespective of relationship (EC arm of Study C4221015 study).....	96
Table SVII.5: Encorafenib in combination with cetuximab and FOLFOX: Cutaneous squamous cell carcinoma events irrespective of relationship (EC-FOLFOX-P)	96
Table SVII. 6: Risks of cutaneous squamous cell carcinoma in the "unexposed" melanoma population.....	98
Table SVII.7: Encorafenib in combination with cetuximab: New primary melanoma events irrespective of relationship (Doublet arm of Study ARRAY-818-302)	101
Table SVII.8: Encorafenib in combination with cetuximab: New primary melanoma events irrespective of relationship (EC arm of Study C4221015).....	102
Table SVII.9: Encorafenib in combination with cetuximab and FOLFOX: New primary melanoma events irrespective of relationship (EC-FOLFOX-P)	102
Table SVII.10: 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	106
Table SVII.11: 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....	107
Table SVII.12: Newly Occurring Notable QT and QTcF Values (ARRAY-818-302 Safety Set)- Encorafenib in combination with cetuximab	108
Table SVII.13: Newly Occurring Notable QTcF Values (C4221015-EC arm)- Encorafenib in combination with cetuximab	108
Table SVII.14: Newly Occurring Notable QTcF Values (C4221015; EC-FOLFOX-P)- Encorafenib with cetuximab in combination with FOLFOX	109
Table SVII.15: 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.....	116
Table SVIII.1 Summary of safety concerns for encorafenib.....	125
Table Part V.1: Description of routine risk minimisation measures by safety concern for encorafenib	126
Table Part V.3: Summary table of pharmacovigilance activities and risk minimisation activities for safety concerns of encorafenib.....	129
Table Part VI.1: Safety concerns for encorafenib.....	132



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
CL/F	Total Clearance
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
DPD	dihydropyrimidine dehydrogenase
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
ODWG	Organ Dysfunction Working Group
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 Erythrodysesthesia Syndrome
PRAC	Pharmacovigilance Risk assessment 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: The chemical structure of Encorafenib (LGX818) is shown. It features a central pyrimidine ring substituted with a 4-((3-((2S)-1-((4-((3-chloro-2-fluorophenyl)amino)propan-2-yl)carbamoyl)pyrazol-4-yl)pyrimidin-2-yl)amino)propan-2-yl group at position 2 and a 3-((2S)-1-((4-((3-chloro-2-fluorophenyl)amino)propan-2-yl)carbamoyl)pyrazol-4-yl)pyrimidin-2-yl group at position 4. The pyrazole ring is substituted with a 3-((2S)-1-((4-((3-chloro-2-fluorophenyl)amino)propan-2-yl)carbamoyl)pyrimidin-2-yl)pyrazol-4-yl group at position 4. The pyrimidine ring is substituted with a 4-((3-((2S)-1-((4-((3-chloro-2-fluorophenyl)amino)propan-2-yl)carbamoyl)pyrazol-4-yl)pyrimidin-2-yl)amino)propan-2-yl group at position 2 and a 3-((2S)-1-((4-((3-chloro-2-fluorophenyl)amino)propan-2-yl)carbamoyl)pyrazol-4-yl)pyrimidin-2-yl group at position 4.
	<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 binimetinib for the treatment of adult patients with advanced non-small cell lung cancer with a BRAF V600E 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. - Encorafenib in combination with cetuximab and FOLFOX is indicated for the first line treatment of adult patients with metastatic colorectal cancer with a BRAF V600E mutation. <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 and 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 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 with a BRAF V600E mutation in patient who have received prior systemic therapy, 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 (weekly administration), or in combination with cetuximab (bi-weekly administration) and FOLFOX.



	If encorafenib is permanently discontinued, cetuximab should be discontinued. FOLFOX alone may be continued per standard of care. If cetuximab is permanently discontinued, encorafenib should be discontinued. FOLFOX alone may be continued per standard of care. If FOLFOX is permanently discontinued, the combination of encorafenib and cetuximab may be continued. 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 (administered weekly), for the treatment of adult patients with metastatic CRC (mCRC) with a BRAF V600E mutation, who have received prior systemic therapy (previously treated patients). 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 of BEACON CRC study 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 who have received prior systemic therapy.

Per a further variation to the MAA, 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.

In the newly proposed therapeutic use, encorafenib is indicated, in combination with cetuximab and FOLFOX (5-fluorouracil (5-FU), leucovorin (folinic acid), and oxaliplatin), for the first line treatment of adult patients with BRAF V600E-mutant mCRC. In this indication, the safety of encorafenib (300 mg orally once daily) in combination with cetuximab (administered bi-weekly) and FOLFLOX (5-fluorouracil/leucovorin/oxaliplatin) at the recommended doses as per their respective product labels and according to the mFOLFOX6 regimen ([Cheeseman, 2002](#)) was evaluated in 259 patients with BRAF V600E-mutant mCRC enrolled and treated in the BREAKWATER study (C4221015), hereafter referred to as EC-FOLFOX pooled population (EC-FOLFOX-P) of the BREAKWATER pivotal study. The analysis of safety data pertaining to encorafenib in combination with cetuximab and FOLFLOX in the proposed indication 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 ([Cavaliere, 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. Since only few data are available on patients with BRAF-mutated mCRC, the systematic literature review was broadened to provide data on mCRC when data on BRAF-mutated mCRC are missing, scarce or inconclusive.

Incidence:

In Europe, the age-standardized incidence rates (ASRs) (using the European standard population) in 2022 for all stages of colorectal cancer have been estimated to be 37.7 and 24.8 per 100,000 population per year in men and women respectively. This was estimated to equal approximately 538,262 new cases in 2022; 289,049 in men and 249,213 in women ([Ferlay, 2024](#)). The highest incidence rates of colorectal cancer in males were reported in Hungary (62.4/100,000), Croatia (55.9/100,000) and Denmark (55.1/100,000), and for females in Norway (43.6/100,000) and Denmark (41.9/100,000). Specifically, in the EU 5 countries, the ASRs of colorectal cancer for men were estimated to be 31.2/100,000 in Germany, 44.7/100,000 in Spain, 35.1/100,000 in the United Kingdom (UK), 36.0/100,000 in Italy and 37.6/100,000 in France. Similarly, the ASRs for women in these countries of interest were 20.5/100,000 in Germany, 24.2/100,000 in Spain, 27.1/100,000 in the UK, 26.0/100,000 in Italy and 27.4/100,000 in France ([Ferlay, 2024](#)).

Globally, CRC is the third most diagnosed cancer worldwide, with about 1.93 million new cases and over 900,000 deaths in 2022 according to the GLOBOCAN database ([Bray, 2024](#)). It is also the second most common type of cancer and the second deadliest cancer in Europe with an estimated 538,262 new cases diagnosed in 2022 and around 247,842 deaths ([Bray, 2024](#)), which is one of the highest incidence (30.5 for 100 000) and the highest mortality (12.1 for 100 000) in the world considering age-standardized rate ([Ferlay, 2024](#)).

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 IV 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](#)).



According to Bray 2024, incidence rates of CRC are three to four times higher in transitioned relative to transitioning countries, with approximately 10-fold variation in incidence rates by world region in men and women, respectively, and the highest rates in Europe, Australia/New Zealand, and Northern America, with Denmark and Norway ranking first in men and women, respectively. Alcohol consumption, smoking, consumption of red or processed meat, and body fatness increase the disease risk overall. CRC incidence increased by 1%–4% per year among younger adults (younger than 50 years at diagnosis) in many high-income countries ([Bray, 2024](#)).

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](#)). More recent data on stage at diagnosis or extent of disease at diagnosis showed broadly similar stage profiles compared with 2011 ([VCR, 2023](#); [Cancer Institute NSW 2022](#)). As per ([Ferlay, 2024](#)), 17088 new cases are estimated in Australia, with ASR incidence of 37.8/100,000 for male and 31.7/100,000 for female.

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](#); [Tabernero, 2022](#)). 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 538,262 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 13,456 individuals presented with BRAF V600E-mutated stage IV colorectal cancer in 2022 across EU countries.

Using the same approach for Australia, with a 2018 diagnosed population of approximately 17,088, the number individuals per year diagnosed with BRAF V600E-mutated stage IV colorectal cancer should be 427.

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 were 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 (regardless of mutational status) occurs at higher rates in men than in women in European Union countries (37.7/100,000 versus 24.8/100,000 respectively) ([Ferlay, 2024](#)). 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](#); [Gonsalves, 2014](#)).

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](#)). BRAF V600 mutant CRC is considered a distinct subtype of CRC that has unique clinical characteristics and is associated with a worse prognosis, with a negative impact on both overall survival (OS) and progression-free survival (PFS) ([Cremolini, 2015](#); [Cohen, 2021](#); [Stintzing, 2023](#)).

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](#)). The updated ESMO estimation showed that approximately 15%-30% of patients with colorectal cancer present with metastases, and 20%-50% of patients with initially localised disease will develop metastases ([Cervantes, 2023](#)).

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 2022 have been estimated at 15.7/100,000 population in males and 9.4/100,000 population in females ([Ferlay, 2024](#)). This equals to an approximate 133,532 deaths in men and 114,310 deaths in women Europe-wide. The highest rates of mortality in men were observed in Hungary (62.4/100,000), Croatia (55.9/100,000), and Denmark (51.1/100,000). In women, the highest ASRs of mortality were observed in Norway (43.6/100,000) and Denmark (41.9/100,000). Additionally, for the EU 5 countries, the 2022 age standardized mortality rates for men per 100,000 population were estimated to be 31.2 in Germany, 37.6 in France, 235.1 in the UK, 44.7 in Spain and 36.0 in Italy. Similarly, for these countries of interest, the age standardized mortality rates for women were 20.5 in Germany, 27.4 in France, 27.1 in the UK, 24.2 in Spain, and 26.0 in Italy ([Ferlay, 2024](#)).

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](#)).

According to the GLOBOCAN database, over 900,000 deaths in 2022 worldwide were estimated due to CRC. CRC is the second deadliest cancer in Europe with an estimated 538,262 new cases diagnosed in 2022 and around 247,842 deaths ([Bray, 2024](#)).

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.

Despite major treatment advances over the past decades, metastatic colorectal cancer (mCRC) remains a serious, life-threatening condition, with significant years of potential life lost and substantial losses in productivity due to high incidence rates ([Bradley, 2011](#); [Darba, 2020](#), [Ortega-Ortega, 2023](#)).

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](#)).

A challenge with estimating the efficacy of current standard of care treatment in first-line BRAF V600E-mutant mCRC is that there have been limited prospective trials in this population. No specific treatments are indicated for patients with BRAF V600E-mutant mCRC in the first line setting ([Cervantes, 2023](#)). In the first line setting, patients with BRAF V600E-mutant mCRC are typically treated with standard-of-care regimens for KRAS wild-type (KRAS^{wt}) mCRC i.e. a combination of chemotherapy (based on fluoropyrimidine/leucovorin (5-FU/LV) or capecitabine with or without irinotecan, oxaliplatin, or in combination with both) with targeted agents (monoclonal antibodies targeting the vascular endothelial growth factor (VEGF), i.e. bevacizumab or the epidermal growth factor receptor (EGFR), i.e. panitumumab and cetuximab) ([Vogel, 2018](#), [Cervantes, 2023](#)). The common regimens approved in Europe and used in patients with mCRC include FOLFOX, FOLFIRI, FOLFOXIRI (usually reserved to fit patients), and CAPOX each with or without bevacizumab ([Cervantes, 2023](#); [NCCN, 2021](#)). Standard therapy for BRAF wild-type mCRC, even with the more intensive regimens, produces substantially poorer outcomes in patients with BRAF V600E-mutant mCRC than in patients with BRAF wild-type disease in the first-line, with a negative impact on both overall survival (OS) and progression-free survival (PFS) ([Cremolini, 2015](#); [Cohen, 2021](#); [Stintzing 2023](#)). There is currently no first-line activation pathway-targeted treatment indicated for patients with BRAF V600E-mutant mCRC; therefore, a treatment that can demonstrate improved efficacy in the first-line setting is needed given the poor prognosis compared with BRAF wild-type mCRC ([Kopetz, 2025](#)).

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](#)).

According to GLOBOCAN 2022, alcohol consumption, smoking, consumption of red or processed meat, and body fatness increase the overall risk of CRC ([Bray, 2024](#)).

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](#)). CRC data in the South Australian Cancer Registry (SACR) for 2004–2013 showed that for the 8462 CRC cases in this study, diabetes, peptic ulcer disease, and previous cancers were the most commonly recorded co-existing conditions in CRC patients ([Gheybi, 2022](#)).



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) 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, 2019](#)). 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 trametinib, 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 cell infiltration, was reported at ≥ 6 mg/kg/day. Lesions were dose related in terms of severity and incidence. Non-glandular stomach tissue showed hyperkeratosis and hyperplasia at ≥ 20 mg/kg/day. 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/day 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/day after 13 weeks of treatment (corresponding to 1.5 -fold the mean plasma exposure in patients at the therapeutic dose in terms of AUC₀₋₂₄). Evidence of partial recovery was noted after 10 weeks without treatment. Histopathology findings were similar to retinopathy associated with MEK inhibitors.	Predictive of skin lesions in patients. Potential safety concern. Weakly predictive of gastrointestinal effects in patients (humans lack non-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	



Key safety findings	Relevance to human usage
Encorafenib was negative <i>in vitro</i> 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 <i>in vivo</i> in the rat bone marrow micronucleus assay (Pcs-r1270199). Taken together, the <i>in vitro</i> and <i>in vivo</i> 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 embryoletality or teratogenicity at 20 mg/kg/day. The NOAEL for embryo-foetal development was 5 mg/kg/day (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 fetuses at the materno-toxic dose of 75 mg/kg/day. Aortic arch dilatation was observed in some fetuses. Other teratogenic effects included reduced lung lobes, absent 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/day (79-fold the level of patient exposure at the therapeutic dose). In both species, encorafenib was detected in foetal plasma.	Predictive of embryo-foetal toxicity. Potential safety concern.
SAFETY PHARMACOLOGY	
Cardiovascular system, including potential effect on the QT interval: The IC₅₀ 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.



Key safety findings	Relevance to human usage
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 <i>in vivo</i> 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, 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, cetuximab or mFOLFOX6 were co-administered with encorafenib. <u>Effect of encorafenib on CYP substrates:</u> <i>In vitro</i> 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	Potential for CYP3A4 P450 mediated drug-drug 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. 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
dextromethorphan metabolite (dextrophan) 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 $\leq 25\%$ and repeated administration of encorafenib 450 mg daily and binimetinib 45 mg twice daily reduced bupropion AUC and C_{max} by $\leq 26\%$ (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. No clinically relevant differences in cetuximab and in oxaliplatin exposures have been observed when encorafenib was co-administered with cetuximab $\pm$ mFOLFOX6. Based on their elimination pathways, no impact of encorafenib on 5-Fluorouracil (5-FU), leucovorin (folinic acid) is expected. <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. <u>Effect of encorafenib on transporters:</u> Based on <i>in vitro</i> 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. 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.	Not predictive of a safety concern for use in combination with binimetinib or cetuximab or oxaliplatin. Minimal effect for P-gp and BCRP substrates. Not predictive for a safety concern. 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**

Encorafenib in combination with binimetinib

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.

Potential synergistic toxicity from safety pharmacology data

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.

Potential synergistic toxicity from toxicological assessment by organ

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, hyperkeratosis 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



Target Organ	Encorafenib	Binimetinib	Potential impact of combination
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
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 [Erbix®, 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 moribund animals or animals found dead (rat)	Degenerative changes in the renal tubular epithelium due to secondary bacterial infection and septicemia	None predicted
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



Target Organ	Encorafenib	Cetuximab*	Potential impact of the combination
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 for humans 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 for humans for causing additive or synergistic toxicity when administered in combination 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 for humans for causing additive or synergistic toxicity when administered in combination 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				
Age group [1]	Patients		Patient-months	
	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, mCRC in previously treated patients (doublet population of BEACON CRC), NSCLC, and mCRC in previously untreated patients (EC-FOLFOX pooled Population of BREAKWATER (EC-FOLFOX-P))), they are then presented for each indication at the recommended doses.

Cumulative – All indications (Melanoma, previously treated mCRC (doublet population of BEACON CRC), NSCLC, and previously untreated mCRC (EC-FOLFOX-P) in BREAKWATER study) - N=847

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 Jan 2023	98
Encorafenib^b + cetuximab combination – Doublet population of BEACON CRC		
Array-818-302 Randomized*	15 Aug 2019	216
Encorafenib^b + cetuximab + FOLFOX combination (EC-FOLFOX-P Population of BREAKWATER)		
C4221015* (SLI portion)	22 Dec 2023	27
C4221015* (Phase 3 portion)	06 Jan 2025	232

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); 2.7.4 Summary of clinical safety - Variation Type II (first line treatment of mCRC 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=847)

Duration of exposure (at least)	Persons	Patient-months
1 month	808	9590.0
3 months	694	9353.0
6 months	543	8658.9
12 months	309	6586.8
18 months	197	4923.8
24 months	90	2664.6
30 months	35	1182.1
Total	847	9606.8*

Sources: ISS_Part1_u: Table 1.5.1.1.1c; Table 1.5.1.1.1d

ARRAY_818_302_Dossier_2019 - Version date: 13MAR2020 15:00- File Name: T1403_010601_RMP_Doublet_expo1_add.rtf - Listing16.2.5-10.01

Cut-off date 15AUG2019 - Database lock 05NOV2019 - Dataset. ADEX: 12MAR20 BASEDTM3.ADSL: 28NOV19 - PGM T_RMP_Doublet_expo1_add.sas 29JAN2020 17:16

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

Sources: CRC1L - Version date: 01AUG2025 11:04 - File Name: tsub6_06_01_02_c1_expdurtrp_saf.rtf

Sources: Cut-off date BREAKWATER_RAN: 06JAN2025 / Cut-off date BREAKWATER_SLI: 22DEC2023 / Cut-off date POOL_PFE: 06JAN2025 - Dataset ADSP1.ADSL:31JUL2025 - PGM tsub6_06_01_02_c1_expdurtrp_saf.sas 01JUL2025 11:06

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 or mFOLFOX6).

* Cumulative numbers may not exactly match the sum of numbers listed in the table due to rounding

2. By Dose

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

Restricted combination safety pool (N=847)		
Duration of exposure (at least)	Persons	Patient-months
Encorafenib 450mg QD and Binimetinib 45 BID	372	5135.2
Encorafenib 300mg QD and cetuximab	216	1237.6
Encorafenib 300mg QD + Cetuximab + FOLFOX	259	3234.0
Total	847	9606.8

Sources: ISS_Part1_u: Table 1.5.1.1.2c; Table 1.5.1.1.2d

ARRAY_818_302_Dossier_2019 - Version date: 13MAR2020 14:46 - File Name: T1403_010602_RMP_Doublet_expo2_add.rtf - Listing16.2.5-10.01

Cut-off date 15AUG2019 - Database lock 05NOV2019 - Dataset. ADEX: 12MAR20 BASEDTM1.ADSL: 28NOV19 - PGM T_RMP_Doublet_expo2_add.sas 29JAN2020 17:16

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

Sources: CRC1L - Version date: 01AUG2025 11:03 - File Name: tsub6_06_01_01_c1_expdostrp_saf.rtf

Sources: Cut-off date BREAKWATER_RAN: 06JAN2025 / Cut-off date BREAKWATER_SLI: 22DEC2023 / Cut-off date POOL_PFE: 06JAN2025 - Dataset ADSP1.ADSL:31JUL2025 - PGM tsub6_06_01_01_c1_expdostrp_saf.sas 01JUL2025 11:10

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 or mFOLFOX6).



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=847) by age group and gender				
Age group ^[1]	Persons		Patient-months	
	M	F	M	F
18 - 64 years	298	232	3343.9	2788.6
65 - 74 years	127	116	1468.8	1252.1
75 - 84 years	32	38	334.2	401.8
85+ years	2	2	5.0	11.43
Total*	459	388	5151.9	4454.9

Sources: ISS_Part1_u: Table 1.5.1.1.3c; Table 1.5.1.1.3d

ARRAY_818_302_Dossier_2019 - Version date: 13MAR2020 14:46 - File Name: T1403_010603_RMP_Doublet_expo3_add.rtf - Listing16.2.5-10.01

Cut-off date 15AUG2019 - Database lock 05NOV2019 - Dataset. ADEX: 12MAR20 BASEDTM1.ADSL: 28NOV19 - PGM

T_RMP_Doublet_expo3_add.sas 29JAN2020 17:16

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

Sources: CRC1L - Version date: 01AUG2025 11:09 - File Name: tsub6_06_01_03_c1_expagsxtrp_saf.rtf

Sources: Cut-off date BREAKWATER_RAN: 06JAN2025 / Cut-off date BREAKWATER_SLI: 22DEC2023 / Cut-off date POOL_PFE: 06JAN2025 - Dataset ADSP1.ADSL:31JUL2025 - PGM tsub6_06_01_03_c1_expagsxtrp_saf.sas 01JUL2025 15:09

^[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 or mFOLFOX6).

* Cumulative numbers may not exactly match the sum of numbers listed in the table due to rounding

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=847)		
Racial origin ^[1]	Persons	Patient-months
Asian	131	1552.4
Caucasian	687	7827.0
Black or African American	3	4.9
Other	8	100.6
Unknown*	18	122.0
Total**	847	9606.8

Sources: ISS_Part1_u: Table 1.5.1.1.4c; Table 1.5.1.1.4d

ARRAY_818_302_Dossier_2019 - Version date: 13MAR2020 14:46 - File Name: T1403_010604_RMP_Doublet_expo4_add.rtf - Listing16.2.5-10.01

Cut-off date 15AUG2019 - Database lock 05NOV2019 - Dataset .ADEX: 12MAR20 .ADSL: 12MAR20 - PGM

T_RMP_Doublet_expo4_add.sas 29JAN2020 17:17

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

Sources: CRC1L - Version date: 01AUG2025 11:10 - File Name: tsub6_06_01_04_c1_expractrp_saf.rtf

Sources: Cut-off date BREAKWATER_RAN: 06JAN2025 / Cut-off date BREAKWATER_SLI: 22DEC2023 / Cut-off date POOL_PFE: 06JAN2025 - Dataset ADSP1.ADSL:31JUL2025 - PGM tsub6_06_01_04_c1_expractrp_saf.sas 04JUL2025 14:07

^[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

** Cumulative numbers may not exactly match the sum of numbers listed in the table due to rounding

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 or mFOLFOX6).



▪ **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 naïve 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
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
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
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)

Age group ^[1]	Persons		Patient-months	
	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)

Age group ^[1]	Persons		Patient-months	
	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)

Age group ^[1]	Persons		Patient-months	
	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)

Age group ^[1]	Persons		Patient-months	
	M	F	M	F
18 - 64 years	204	150	2,575.7	1868.6
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	165.5
Black or African American	3	4.9
Caucasian	347	4864.8
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
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	6154.7



Broad combination integrated safety population (Combo broad ISP; N=531)

Racial origin ^[1]	Persons	Patient-months
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 (EC) in the indication for the treatment of BRAF V600E-mutant metastatic CRC after prior systemic therapy (i.e previously treated BRAF V600E mCRC patients) 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 (BEACON CRC study) 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 for the indication of mCRC after prior systemic therapy (i.e in previously treated patients), 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. 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).

The doublet arm (Encorafenib + Cetuximab arm; EC arm) of BREAKWATER is taken into consideration in the exposure tables presented in this section for the '**Doublet broad population**' which refers, thus, to 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 (**Doublet population of BEACON CRC study**; N = 216) and patients who received encorafenib at the dose of 300 mg QD in combination with cetuximab in the pivotal study C4221015 (**EC arm of BREAKWATER study**; N= 152). As such, the **Doublet broad population** is composed of 368 patients.

A summary of overall exposure and duration of exposure is provided below for the doublet; EC population by study (i.e BEACON CRC study and BREAKWATER study, separately), and then the Doublet broad population, by dose, age group and gender, and by ethnic or racial origin.



Summary of overall exposure and duration of exposure for the ARRAY-818-302 (BEACON CRC) doublet population (Doublet population of BEACON CRC study) by dose, age group and gender, and by ethnic or racial origin:

1. Duration of exposure

Table SIII.16: Duration of exposure (Doublet population of BEACON CRC study- indication: mCRC in previously treated patients)

Encorafenib and cetuximab - Randomized Doublet arm (N=216)		
Duration of exposure (at least)	Patients	Patient-months
1 month	205	1235.22
3 months	140	1093.75
6 months	85	849.48
12 months	14	222.03
18 months	2	46.03
24 months	0	.
30 months	0	.
Total	216	1237.59

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: 13MAR2020 15:00 - File Name:

T1403_010601_RMP_Doublet_expo1_add.rtf - Listing16.2.5-10.01

Sources: Cut-off date 15AUG2019 - Database lock 05NOV2019 - Dataset .ADEX: 12MAR20 BASEDTM3.ADSL: 28NOV19 - PGM
T_RMP_Doublet_expo1_add.sas 29JAN2020 17:16

2. By dose

Table SIII.17: Dose of exposure (Doublet population of BEACON CRC study- indication: mCRC in previously treated patients)

Encorafenib and cetuximab - Randomized Doublet arm (N=216)		
Dose of exposure	Patients	Patient-months
Encorafenib 300mg QD and Cetuximab	216	1237.59
Total	216	1237.59

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: 13MAR2020 14:46 - File Name:

T1403_010602_RMP_Doublet_expo2_add.rtf - Listing16.2.5-10.01

Sources: Cut-off date 15AUG2019 - Database lock 05NOV2019 - Dataset .ADEX: 12MAR20 BASEDTM3.ADSL: 28NOV19 - PGM
T_RMP_Doublet_expo2_add.sas 29JAN2020 17:16

3. By age group and gender

Table SIII.18: Exposure by age group and gender (Doublet-population of BEACON CRC study- indication: mCRC in previously treated patients)

Encorafenib and cetuximab - Randomized Doublet arm (N=216) by age group and gender				
Age group ^[1]	Patients		Patient-Months	
	F	M	F	M
18 - 64 years	61	73	350.65	396.35
65 - 74 years	29	33	171.66	183.20
75 - 84 years	13	6	74.87	52.63
85+ years	1	.	8.21	.
Total	104	112	605.40	632.18

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: 13MAR2020 14:46 - File Name:

T1403_010603_RMP_Doublet_expo3_add.rtf - Listing16.2.5-10.01

Sources: Cut-off date 15AUG2019 - Database lock 05NOV2019 - Dataset. ADEX: 12MAR20 BASEDTM3.ADSL: 28NOV19 - PGM T_RMP_Doublet_expo3_add.sas 29JAN2020 17:16

4. By ethnic or racial origin

Table SIII.19: Exposure by ethnic or racial origin (Doublet population of BEACON CRC study- indication: mCRC in previously treated patients)

Encorafenib and cetuximab - Randomized Doublet arm (N=216) by racial origin		
Racial origin ^[1]	Patients	Patient-Months
Asian	25	149.42
Caucasian	181	1030.11
Other	3	21.52
Unknown ²	7	36.53
Total	216	1237.59

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: 13MAR2020 14:46 - File Name:

T1403_010604_RMP_Doublet_expo4_add.rtf - Listing16.2.5-10.01

Sources: Cut-off date 15AUG2019 - Database lock 05NOV2019 - Dataset. ADEX: 12MAR20 .ADSL: 12MAR20 - PGM T_RMP_Doublet_expo4_add.sas 29JAN2020 17:17

Summary of overall exposure and duration of exposure for the EC arm of C4221015 (BREAKWATER) study (N= 153) by dose, age group and gender, and by ethnic or racial origin:

1. Duration of exposure

Table SIII.20: Duration of exposure (EC population of BREAKWATER study)

Encorafenib and cetuximab – BREAKWATER EC arm (N=153*)		
Duration of exposure (at least)	Patients	Patient-months
1 month	145	1381.98
3 months	131	1351.85
6 months	78	1101.60
12 months	34	734.72
18 months	21	543.97
24 months	12	360.21
30 months	5	168.67
Total	152	1383.85

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 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

* In the EC arm of BREAKWATER, 153 patients received at least one dose of study drug, but 152 patients exposed to encorafenib.

Sources: CRC1L - Version date: 01AUG2025 11:08 - File Name: tsub6_06_01_02_c1_expdurdbl_saf.rtf

Sources: Cut-off date BREAKWATER_RAN: 06JAN2025 / Cut-off date BREAKWATER_SLI: 22DEC2023 / Cut-off date POOL_PFE: 06JAN2025 - Dataset ADSP1.ADSL:31JUL2025 - PGM tsub6_06_01_02_c1_expdurdbl_saf.sas 23JUL2025 14:36



2. By dose

Table SIII.21: Dose of exposure (EC population of BREAKWATER study)

Encorafenib and cetuximab - BREAKWATER EC arm (N=153*)		
Dose of exposure	Patients	Patient-months
Encorafenib 300mg QD and Cetuximab	152	1383.85
Total	152	1383.85

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

* In the EC arm of BREAKWATER, 153 patients received at least one dose of study drug, but 152 patients exposed to encorafenib

Sources: CRC1L - Version date: 01AUG2025 11:03 - File Name: tsub6_06_01_01_c1_expdosdbl_saf.rtf

Sources: Cut-off date BREAKWATER_RAN: 06JAN2025 / Cut-off date BREAKWATER_SLI: 22DEC2023 / Cut-off date POOL_PFE: 06JAN2025 - Dataset ADSP1.ADSL:31JUL2025 - PGM tsub6_06_01_01_c1_expdosdbl_saf.sas 23JUL2025 14:36

3. By age group and gender

Table SIII.22: Exposure by age group and gender (EC population of BREAKWATER study)

Encorafenib and cetuximab - BREAKWATER EC arm (N=153*) by age group and gender				
Age group ^[1]	Patients		Patient-Months	
	F	M	F	M
18 - 64 years	46	54	462.39	441.33
65 - 74 years	22	16	218.81	146.00
75 - 84 years	9	5	79.51	35.81
85+ years	0	0	0.00	0.00
Total	77	75	760.71	623.15

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

* In the EC arm of BREAKWATER, 153 patients received at least one dose of study drug, but 152 patients exposed to encorafenib.

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

Sources: CRC1L - Version date: 01AUG2025 11:09 - File Name: tsub6_06_01_03_c1_expagsxdbl_saf.rtf

Sources: Cut-off date BREAKWATER_RAN: 06JAN2025 / Cut-off date BREAKWATER_SLI: 22DEC2023 / Cut-off date POOL_PFE: 06JAN2025 - Dataset ADSP1.ADSL:31JUL2025 - PGM tsub6_06_01_03_c1_expagsxdbl_saf.sas 23JUL2025 14:36

4. By ethnic or racial origin

Table SIII.23: Exposure by ethnic or racial origin (EC population of BREAKWATER study)

Encorafenib and cetuximab - BREAKWATER EC arm (N=153*) by racial origin		
Racial origin ^[1]	Patients	Patient-Months
Asian	61	524.94
Caucasian	85	798.88
Black or African American	1	8.28
Other	1	6.93
Unknown ²	4	44.81
Total	152	1383.85

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

* In the EC arm of BREAKWATER, 153 patients received at least one dose of study drug, but 152 patients exposed to encorafenib.

^[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: CRC1L - Version date: 01AUG2025 11:10 - File Name: tsub6_06_01_04_c1_expracdbl_saf.rtf

Sources: Cut-off date BREAKWATER_RAN: 06JAN2025 / Cut-off date BREAKWATER_SLI: 22DEC2023 / Cut-off date POOL_PFE: 06JAN2025 - Dataset ADSP1.ADSL:31JUL2025 - PGM tsub6_06_01_04_c1_expracdbl_saf.sas 23JUL2025 14:36



A summary of overall exposure and duration of exposure is provided below for the Doublet broad population (doublet population of BEACON CRC study + EC arm of BREAKWATER study), by dose, age group and gender, and by ethnic or racial origin.

1. Duration of exposure

Table SIII.24: Duration of exposure (Doublet broad population)

Encorafenib and cetuximab - Doublet broad population (N=368)		
Duration of exposure (at least)	Patients	Patient-months
1 month	350	2617.2
3 months	271	2445.6
6 months	163	1951.1
12 months	48	956.8
18 months	23	590.0
24 months	12	360.21
30 months	5	168.67
Total	368	2621.4

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: 13MAR2020 15:00 - File Name:

T1403_010601_RMP_Doublet_expo1_add.rtf - Listing16.2.5-10.01

Sources: Cut-off date 15AUG2019 - Database lock 05NOV2019 - Dataset.ADEX: 12MAR20 BASEDTM3.ADSL: 28NOV19 - PGM
T_RMP_Doublet_expo1_add.sas 29JAN2020 17:16

Sources: CRC1L - Version date: 01AUG2025 11:08 - File Name: tsub6_06_01_02_c1_expdudbl_saf.rtf

Sources: Cut-off date BREAKWATER_RAN: 06JAN2025 / Cut-off date BREAKWATER_SLI: 22DEC2023 / Cut-off date POOL_PFE:
06JAN2025 - Dataset ADSP1.ADSL:31JUL2025 - PGM tsub6_06_01_02_c1_expdudbl_saf.sas 23JUL2025 14:36

2. By dose

Table SIII.25: Dose of exposure (Doublet broad population)

Encorafenib and cetuximab - Doublet broad population (N=368)		
Dose of exposure	Patients	Patient-months
Encorafenib 300mg QD and Cetuximab	368	2621.4
Total	368	2621.4

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: 13MAR2020 14:46 - File Name:

T1403_010602_RMP_Doublet_expo2_add.rtf - Listing16.2.5-10.01

Sources: Cut-off date 15AUG2019 - Database lock 05NOV2019 - Dataset.ADEX: 12MAR20 BASEDTM3.ADSL: 28NOV19 - PGM
T_RMP_Doublet_expo2_add.sas 29JAN2020 17:16

Sources: CRC1L - Version date: 01AUG2025 11:03 - File Name: tsub6_06_01_01_c1_expdosdbl_saf.rtf

Sources: Cut-off date BREAKWATER_RAN: 06JAN2025 / Cut-off date BREAKWATER_SLI: 22DEC2023 / Cut-off date POOL_PFE:
06JAN2025 - Dataset ADSP1.ADSL:31JUL2025 - PGM tsub6_06_01_01_c1_expdosdbl_saf.sas 23JUL2025 14:36

3. By age group and gender

Table SIII.26: Exposure by age group and gender (Doublet broad population)

Encorafenib and cetuximab - Doublet broad population (N=368) by age group and gender				
Age group ^[1]	Patients		Patient-Months	
	F	M	F	M
18 - 64 years	107	127	813.0	837.7
65 - 74 years	51	49	390.5	329.2
75 - 84 years	22	11	154.4	88.4
85+ years	1	.	8.21	.



Encorafenib and cetuximab - Doublet broad population (N=368) by age group and gender

Age group ^[1]	Patients		Patient-Months	
	F	M	F	M
Total	181	187	1366.1	1255.3

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: 13MAR2020 14:46 - File Name:

T1403_010603_RMP_Doublet_expo3_add.rtf - Listing16.2.5-10.01

Sources: Cut-off date 15AUG2019 - Database lock 05NOV2019 - Dataset. ADEX: 12MAR20 BASEDTM3.ADSL: 28NOV19 - PGM T_RMP_Doublet_expo3_add.sas 29JAN2020 17:16

Sources: CRC1L - Version date: 01AUG2025 11:09 - File Name: tsub6_06_01_03_c1_expagsxdbl_saf.rtf

Sources: Cut-off date BREAKWATER_RAN: 06JAN2025 / Cut-off date BREAKWATER_SLI: 22DEC2023 / Cut-off date POOL_PFE: 06JAN2025 - Dataset ADSP1.ADSL:31JUL2025 - PGM tsub6_06_01_03_c1_expagsxdbl_saf.sas 23JUL2025 14:36

4. By ethnic or racial origin

Table SIII.27: Exposure by ethnic or racial origin (Doublet broad population)

Encorafenib and cetuximab - Doublet broad population (N=368) by racial origin		
Racial origin ^[1]	Patients	Patient-Months
Asian	86	674.4
Caucasian	266	1829.0
Black or African American	1	8.28
Other	4	28.5
Unknown ²	11	81.34
Total	368	2621.4*

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

* Cumulative numbers may not exactly match the sum of numbers listed in the table due to rounding

Sources: ARRAY_818_302_Dossier_2019 - Version date: 13MAR2020 14:46 - File Name:

T1403_010604_RMP_Doublet_expo4_add.rtf - Listing16.2.5-10.01

Sources: Cut-off date 15AUG2019 - Database lock 05NOV2019 - Dataset. ADEX: 12MAR20. ADSL: 12MAR20 - PGM T_RMP_Doublet_expo4_add.sas 29JAN2020 17:17

Sources: CRC1L - Version date: 01AUG2025 11:10 - File Name: tsub6_06_01_04_c1_expracdbl_saf.rtf

Sources: Cut-off date BREAKWATER_RAN: 06JAN2025 / Cut-off date BREAKWATER_SLI: 22DEC2023 / Cut-off date POOL_PFE: 06JAN2025 - Dataset ADSP1.ADSL:31JUL2025 - PGM tsub6_06_01_04_c1_expracdbl_saf.sas 23JUL2025 14:36

▪ Encorafenib in combination with cetuximab and FOLFOX

The safety of encorafenib in combination with cetuximab (EC) and FOLFOX (EC + FOLFOX) was evaluated in the EC-FOLFOX pooled Population (EC-FOLFOX-P; N= 259 patients) who received encorafenib at the dose of 300 mg QD in combination with cetuximab 500 mg/m² bi-weekly and FOLFOX (5-fluorouracil (5-FU), leucovorin (folinic acid) and oxaliplatin; dosed as per their approved labels, with the mFOLFOX6 regimen [Cheeseman 2002]), based on the pivotal phase III study C4221015 (BREAKWATER) study.

Study C4221015 (BREAKWATER) is an open-label, multicenter, 3-arm, randomized Phase III study of combination of encorafenib with cetuximab alone (EC arm of BREAKWATER) or encorafenib plus cetuximab in combination with chemotherapy (EC + mFOLFOX6 arm) versus standard-of-care chemotherapies (Control arm) in first-line treatment of patients with BRAF V600E-mutant mCRC.

In the randomized Phase 3 portion of the study, 236 patients were randomized to the EC + mFOLFOX6 arm and 243 participants were randomized to the Control arm. Of the patients randomized, 232 in the EC + mFOLFOX6 arm received at least 1 dose of study intervention at the data cutoff date of 06 January 2025.



Prior to the randomized Phase 3 portion, a Safety Lead In (SLI) was conducted at a limited number of sites to evaluate the safety/tolerability and PK of EC in combination with either FOLFIRI or mFOLFOX6 (Cohort 1 and Cohort 2, respectively). EC in combination with mFOLFOX6 (Cohort 2; N=27) from the SLI portion of BREAKWATER study to the data cutoff date of 22 December 2023 (N=27) is considered as supportive safety data for the EC-FOLFOX combination selected for use in the Phase 3 portion.

A pooling of safety data from patients receiving EC + FOLFOX in the randomized Phase 3 portion (232 patients) and SLI portion of BREAKWATER who received EC + mFOLFOX6 (27 patients) constitute the BREAKWATER EC-FOLFOX pooled Population (EC-FOLFOX-P); N=259.

Summary of overall exposure and duration of exposure is provided below for the BREAKWATER EC-FOLFOX pooled Population (EC-FOLFOX-P), by dose, age group and gender, and by ethnic or racial origin.

1. Duration of exposure

Table SIII.28: Duration of exposure for BREAKWATER study (EC-FOLFOX pooled Population (EC-FOLFOX-P), indication: mCRC in previously untreated patients)

EC-FOLFOX-P; BREAKWATER study (N=259)		
Duration of exposure (at least)	Patients	Patient-months
1 month	250	3229.34
3 months	227	3182.95
6 months	185	2987.43
12 months	119	2397.21
18 months	65	1591.56
24 months	27	807.66
30 months	14	455.33
Total	259	3234.00

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 of ENCO only (neither CETUX nor mFOLFOX6).

For ENCO: Exposure = (date of last exposure to study drug - date of first exposure to study drug + 1) / 30.4375

Sources: CRC1L - Version date: 01AUG2025 11:04 - File Name: tsub6_06_01_02_c1_expdurtrp_saf.rtf

Sources: Cut-off date BREAKWATER_RAN: 06JAN2025 / Cut-off date BREAKWATER_SLI: 22DEC2023 / Cut-off date POOL_PFE: 06JAN2025 - Dataset ADSP1.ADSL:31JUL2025 - PGM tsub6_06_01_02_c1_expdurtrp_saf.sas 01JUL2025 11:06

2. By dose

Table SIII.29: Dose of exposure for BREAKWATER study (EC-FOLFOX pooled Population (EC-FOLFOX-P), indication: mCRC in previously untreated patients)

EC-FOLFOX-P; BREAKWATER study (N=259)		
Duration of exposure	Patients	Patient-months
Encorafenib 300mg QD + Cetuximab + mFOLFOX6	259	3234.00
Total	259	3234.00

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 (neither CETUX nor mFOLFOX6).

For ENCO: Exposure = (date of last exposure to study drug - date of first exposure to study drug + 1) / 30.4375

Sources: CRC1L - Version date: 01AUG2025 11:03 - File Name: tsub6_06_01_01_c1_expdostrp_saf.rtf

Sources: Cut-off date BREAKWATER_RAN: 06JAN2025 / Cut-off date BREAKWATER_SLI: 22DEC2023 / Cut-off date POOL_PFE: 06JAN2025 - Dataset ADSP1.ADSL:31JUL2025 - PGM tsub6_06_01_01_c1_expdostrp_saf.sas 01JUL2025 11:10

3. By age group and gender

Table SIII.30: Exposure by age group and gender for BREAKWATER study (EC-FOLFOX pooled Population (EC-FOLFOX-P), indication: mCRC in previously untreated patients)

EC-FOLFOX-P; BREAKWATER study (N=259) exposure by age and gender				
Age group^[1]	Patients		Patient-months	
	F	M	F	M
18 - 64 years	76	90	1036.62	1026.20
65 - 74 years	41	33	482.50	455.43
75 - 84 years	10	9	114.17	119.10



EC-FOLFOX-P; BREAKWATER study (N=259) exposure by age and gender

Age group ^[1]	Patients		Patient-months	
	F	M	F	M
85+ years	0	0	0.00	0.00
Total	127	132	1633.28	1600.72

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 (neither CETUX nor mFOLFOX6).

For ENCO: 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.

Sources: CRC1L - Version date: 01AUG2025 11:09 - File Name: tsub6_06_01_03_c1_expagsxtrp_saf.rtf

Sources: Cut-off date BREAKWATER_RAN: 06JAN2025 / Cut-off date BREAKWATER_SLI: 22DEC2023 / Cut-off date POOL_PFE: 06JAN2025 - Dataset ADSP1.ADSL:31JUL2025 - PGM tsub6_06_01_03_c1_expagsxtrp_saf.sas 01JUL2025 15:09

4. By ethnic or racial origin

Table SIII.31: Exposure by ethnic or racial origin for BREAKWATER study (EC-FOLFOX pooled Population (EC-FOLFOX-P), indication: mCRC in previously untreated patients)

EC-FOLFOX-P; BREAKWATER study (N=259) by racial origin

Racial origin ^[1]	Patients	Patient-months
Asian	93	1237.49
Caucasian	159	1932.06
Black or African American	0	0.00
Other	0	0.00
Unknown ²	7	64.46
Total	259	3234.00

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 (neither CETUX nor mFOLFOX6).

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.

Sources: CRC1L - Version date: 01AUG2025 11:10 - File Name: tsub6_06_01_04_c1_expractrp_saf.rtf

Sources: Cut-off date BREAKWATER_RAN: 06JAN2025 / Cut-off date BREAKWATER_SLI: 22DEC2023 / Cut-off date POOL_PFE: 06JAN2025 - Dataset ADSP1.ADSL:31JUL2025 - PGM tsub6_06_01_04_c1_expractrp_saf.sas 04JUL2025 14:07



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 contraindication.

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, encorafenib in combination with cetuximab, or encorafenib in combination with cetuximab and chemotherapy 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, binimetinib or chemotherapy 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 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 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 missing information was removed from the list of safety concerns of binimetinib in the 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 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 treatment with binimetinib 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 and C4221015 studies, 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 (Erbix 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 Erbix® \(cetuximab\). 2019](#)). In the CRC study Array-818-302 and C4221015 studies, 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 (Erbix 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 encorafenib 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 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 not treated curatively and with a risk a relapse

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, advanced NSCLC or metastatic CRC are candidates to receive encorafenib in 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, metastatic CRC 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, metastatic CRC or advanced NSCLC, the decision to treat these malignancies 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 and C4221015 study for the mCRC indications, 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, advanced NSCLC or metastatic CRC 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, metastatic CRC 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 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 populations 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.

Exclusion criteria related to chemotherapy:

Known dihydropyrimidine dehydrogenase (DPD) deficiency

In the C4221015 (BREAKWATER) study, patients with known dihydropyrimidine dehydrogenase (DPD) deficiency were excluded, and the investigators were recommended to refer to the local fluorouracil/capecitabine labels, or local clinical guidance regarding DPD status prior to starting treatment.



Reason for exclusion: Patients with DPD deficiency are at increased risk for acute early-onset toxicity and serious (including fatal) adverse reactions (e.g., mucositis, diarrhoea, neutropenia, and neurotoxicity) due to fluorouracil and capecitabine.

Is it considered to be included as missing information? No

Rationale: In the real-life setting, and as per the local clinical guidances and labels, the patients who are candidates to receive treatment with fluorouracil should be tested for DPD deficiency before initiating the treatment. Patients with known DPD deficiency are informed (via product information) to alert their physician before the start of treatment.

This is also applicable in Europe; the EMA recommended (EMA/229267/2020) that patients should be tested for the DPD enzyme deficiency before starting cancer treatment with fluorouracil, and fluorouracil medicines must not be given to patients with complete DPD deficiency. A reduced starting dose should be considered in patients with identified partial DPD deficiency.

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 $\geq 1/1000$ could be detected. For $N=217$ and $\text{event}=1$, and the $95\% \text{ CI} = [0.0000, 0.0136]^*$, 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 $\geq 1/10,000$ 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.



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 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 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

▪ **Encorafenib in combination with binimetinib**

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 $\geq 1/1000$ 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 $\geq 1/10,000$ to $<1/1,000$). Detection and evaluation of rare ADRs is part of routine post-marketing pharmacovigilance activities.



Ability to detect adverse reactions	Limitation of trial programme	Discussion of implications for target population
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.
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

▪ **Encorafenib in combination with cetuximab**

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 $\geq 1/1000$ could be detected.	The clinical development programme is unlikely to detect rare ADRs (frequency $\geq 1/10,000$ to $< 1/1,000$).



Ability to detect adverse reactions	Limitation of trial programme	Discussion of implications for target population
	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.	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 24.9 (18.3) weeks, with 26 (12.0%) exposed to the 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.	Limited impact for the combination. Exposure in real-life situations is not expected to be longer than in clinical trials.
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

▪ **Encorafenib in combination with cetuximab and FOLFOX**

Table SIV.4: Encorafenib in combination with cetuximab and FOLFOX: 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 with cetuximab and FOLFOX has been evaluated in 259 patients with BRAF V600E-mutant metastatic CRC at the recommended doses of 300 mg QD encorafenib. Cetuximab was administered at a dose of 500mg/m² biweekly and FOLFOX was administered as per the respective products' labels with FOLFOX administered according to the mFOLFOX6 regimen (Cheeseman, 2002). Based on the 259 patients of the combination safety population, ADRs with a true frequency $\geq 1/1000$ could be detected. For N=259 and event=1 and the 95% [CI=0.0000, 0.0114]*, 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 $\geq 1/10,000$ 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 EC-FOLFOX pooled Population (EC-FOLFOX-P), the mean (SD) duration of exposure to encorafenib within the EC-FOLFOX-P was 54.3 (37.4) weeks, with 133 (51.4%) exposed to the combination for ≥ 48 weeks. The clinical development programmes are, in general, unlikely to detect certain types of adverse reactions such as those caused by prolonged exposure.	Limited impact for the combination. Exposure in real-life situations is not expected to be longer than in clinical trials.
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. The clinical development programmes are, in general, unlikely to detect certain types of adverse reactions such as those caused by cumulative exposure.	Limited impact for the combination. Cumulative effects in real-life situations in the BRAF V600E-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. The clinical development programmes are, in general, unlikely to detect certain types of adverse reactions such as those caused with long latency.	Limited impact for the combination. Patients with BRAF V600E-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 ($\leq 5\%$ of patients exposed) or excluded in clinical trial development programmes are provided below.

Table SIV.5: 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 2024

^aAs of 20 January 2024, a total of 3142 participants have received at least one dose of encorafenib as single agent or in all combination studies.

▪ **Encorafenib single agent**

Table SIV. 6: 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
	Moderate (CrCl 30 and 50mL/min)	2	8.74
	Renal Impairment 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.7a: 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.7b: 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.8a 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*	Moderate	2	6.44
		Severe	2	2.56
	Renal Impairment	Severe (CrCl<30mL/min)	0	0.00
		Cardiac Impairment	Baseline LVEF Dysfunction <50%	0
Patients with a disease severity different from inclusion criteria in clinical trials:	Brain metastases at baseline**:		3	12.39
	Yes			
	ECOG PS >= 2		4	8.94
Population with relevant different race origin:	Asian		25	149.42
	Other ¹		3	21.52
	Unknown ²		7	36.53

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 independent 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: 13MAR2020 14:46 - File Name:

T1403_010605_RMP_Doublet_expo5_add_IACorr.rtf - Listing16.2.5-10.01

Sources: Cut-off date 15AUG2019 - Database lock 05NOV2019 - Dataset .ADEX: 12MAR20 .ADSL: 12MAR20 - PGM

T_RMP_Doublet_expo5_add.sas 18FEB2020 11:28

Table SIV.8b: Limitations with respect to under-represented populations - Doublet Broad population (N=368)

Doublet Broad population (N=368)				
Type of special population (any included in pre-authorisation clinical development program)				
			Patients	Patient-Months
Patients with relevant comorbidities:	Hepatic Impairment*	Moderate	3	23.9
		Severe	2	2.56
	Renal Impairment	Severe (CrCl<30mL/min)	0	0.00
		Cardiac Impairment	Baseline LVEF Dysfunction <50%**	0
Patients with a disease severity different from inclusion criteria in clinical trials:	Brain metastases at baseline***: Yes		3	12.39
	ECOG PS >= 2		4	8.94
Population with relevant different race origin:	Black or African American		1	8.28
	Asian		86	674.36
	Other ¹		4	28.45
	Unknown ²		11	81.34

#: Pool of ARRAY-818-302 (cut-off date=15AUG2019) and C4221015 (cut-off date=06JAN2025)

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 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.

**Baseline LVEF Dysfunction <50% was only available for BEACON CRC study (not available for BREAKWATER study)

*** Brain metastases according to the investigator or an independent 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: 13MAR2020 14:46 - File Name:

T1403_010605_RMP_Doublet_expo5_add.rtf - Listing16.2.5-10.01

Sources: Cut-off date 15AUG2019 - Database lock 05NOV2019 - Dataset.ADEXD: 12MAR20.ADSL: 12MAR20 - PGM

T_RMP_Doublet_expo5_add.sas 18FEB2020 11:28

Sources: CRC1L - Version date: 01AUG2025 11:14 - File Name: tsub6_06_01_05_c1_expspecdbl_saf.rtf

Sources: Cut-off date BREAKWATER_RAN: 06JAN2025 / Cut-off date BREAKWATER_SLI: 22DEC2023 / Cut-off date POOL_PFE:

06JAN2025 - Dataset ADSP1.ADSL:31JUL2025 - PGM tsub6_06_01_05_c1_expspecdbl_saf.sas 23JUL2025 14:36

▪ **Encorafenib in combination with cetuximab and FOLFOX**

Table SIV.9 Limitations with respect to under-represented populations in EC-FOLFOX pooled Population;
EC-FOLFOX-P (N= 259)

ENCO+CETUX+FOLFOX (EC-FOLFOX-P; N=259)

Type of special population (any included in pre-authorisation clinical development program)

			Patients	Patient-months
Patients with relevant comorbidities:	Hepatic Impairment*	Moderate	0	0.00
		Severe	0	0.00
	Renal Impairment	Severe (CrCl <30 mL/min)	0	0.00
	Cardiac Impairment	Baseline cardiac risk: Yes	123	1459.45
Patients with a disease severity different from inclusion criteria in clinical trials:		Brain metastases at baseline** : Yes	1	10.87
		ECOG PS ≥ 2	0	0.00
Population with relevant different race origin:		Asian	93	1237.49
		Black or African American	0	0.00
		Other	0	0.00
		Unknown ¹	7	64.46

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 (neither CETUX nor mFOLFOX6).

For ENCO: Exposure = (date of last exposure to study drug - date of first exposure to study drug + 1) / 30.4375

Baseline cardiac risk: if the patient reports history of hypertension, diabetes, dyslipidaemia, cardiac disorders, arteriosclerosis, ischaemic heart disease in the medical history page, the patient is considered to have baseline cardiac risk.

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.

** Brain metastases according to the investigator or an independent assessor before or until 15 days after first treatment intake.

Pregnant women and Breastfeeding women were excluded from the trials.

Sources: CRC1L - Version date: 01AUG2025 11:13 - File Name: tsub6_06_01_05_c1_expspectrp_saf.rtf

Sources: Cut-off date BREAKWATER_RAN: 06JAN2025 / Cut-off date BREAKWATER_SLI: 22DEC2023 / Cut-off date POOL_PFE:

06JAN2025 - Dataset ADSP1.ADSL:31JUL2025 - PGM tsub6_06_01_05_c1_expspectrp_saf.sas 22JUL2025 15:43



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 V600E mutation who have received prior systemic therapy treatment. In the EU, this indication was approved on 02 June 2020.

Additionally, a marketing authorization was granted for encorafenib in US on 11 October 2023 to be used in combination with binimetinib for the treatment of adult patients with metastatic non-small cell lung cancer (NSCLC) with a BRAF V600E mutation. In the EU, the indication of encorafenib in combination with binimetinib for the treatment of adult patients with advanced BRAF V600E-mutant NSLC was approved on 29 August 2024.

On 20 December 2024, encorafenib received accelerated approval in US in combination with cetuximab and mFOLFOX6, for the treatment of patients with mCRC with a BRAF V600E mutation.

As of 26 June 2025, the DLP of the most recent Periodic Benefit-Risk Evaluation Report submitted in Europe (PBRER/PSUR, 27-Jun-2024 to 26-Jun-2025), encorafenib has received marketing authorisation for use in 69 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 (4 capsules daily or 6 capsules daily, depending on the indication) and further dividing by 365.25 to obtain patient-years.

SV.1.2 Exposure

Cumulatively, the worldwide exposure to encorafenib is estimated to be 40,669 patient-years, including 22,189 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 after prior systemic therapy. 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.

▪ **Encorafenib in combination with cetuximab and FOLFOX**

As indicated in Part II: Module SIII above, safety data from the C4221015 clinical trial are included to assess the EC + FOLFOX combination of encorafenib 300 mg QD with cetuximab and FOLFOX (doses as per the approved labels, and FOLFOX administered according to the mFOLFOX6 regimen ([Cheeseman, 2002](#))) for the treatment of patients with metastatic BRAF V600E-mutant colorectal cancer (previously untreated). Safety data from participants receiving encorafenib with cetuximab and mFOLFOX6 in the Phase 3 portion and in SLI portion of the study are pooled into EC-FOLFOX pooled Population (EC-FOLFOX-P; N=259) to assess the safety of this combination.

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. **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.

(iv) 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 ($\geq 5\%$ 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 $\geq 10\%$ (all grades) or $\geq 2\%$ (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 erythrodysesthesia 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 erythrodysesthesia 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.

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 Δ QTcF and Δ HR 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 Δ QTcF 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 Δ QTcF was 25.2 ms (27.2 ms upper-bound 90%CI). In addition, the mean observed Δ QTcF 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.

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.

Missing information

Use in patients with severe renal impairment

Severe renal impairment was defined as $\text{eGFR} < 30 \text{ mL/min/1.73 m}^2$) 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 ($\text{eGFR} 60 \text{ to } 90 \text{ mL/min/1.73 m}^2$) or moderate ($\text{eGFR} 30 \text{ to } 59 \text{ mL/min/1.73 m}^2$) renal impairment compared with subjects with normal renal function ($\text{eGFR} \geq 90 \text{ mL/min/1.73 m}^2$).

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 $\geq 10\%$ 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.

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.

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 previously treated 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 Additional therapy includes all non drug therapies and concomitant medications.

Sources: ARRAY_818_302_Dossier_2019 - Version date: 17MAR2020 9:43 - File Name:

A009_02_1_UP_adrD_sumCuSCC_saf_D_t.rtf - ListingNA

Sources: Cut-off date 15AUG2019 - Database lock 05NOV2019 - Dataset BASEDTM3.ADSL: 28NOV19 .ADADRD:12MAR20 - PGM

A009_02_1_UP_adrD_sumCuSCC_saf_D_t.sas 29JAN2020 16:04

In the EC arm of C4221015 (BREAKWATER) study, CuSCC was observed in 2.0% (3/153) of patients.

The time to onset for each of the 3 CuSCC ADRs in the EC arm of BREAKWATER study was 112,113 and 128 days, respectively.



Table SVII.4: Encorafenib in combination with cetuximab: Cutaneous squamous cell carcinoma events irrespective of relationship (EC arm of Study C4221015 study)

Cutaneous squamous cell carcinoma	EC arm
	N=153 n (%)
Overall incidence	3 (2.0)
Grade 3-4	0 (0.0)
PT with incidence > 10%	0 (0.0)
SAEs overall incidence	0 (0.0)
AEs leading to discontinuation ^a	0 (0.0)
AE leading to dose reduction/interruption ^a	0 (0.0)
AEs requiring additional therapy ^b	2 (1.3)

^a Any study drug

^b Additional therapy includes all non-drug treatments and concomitant medications.

Sources: CRC1L - Version date: 12SEP2025 9:03 - File Name: tsub6_06_03_01_c1_adrcscctrp_saf.rtf

Sources: Cut-off date BREAKWATER_RAN: 06JAN2025 / Cut-off date BREAKWATER_SLI: 22DEC2023 / Cut-off date POOL_PFE: 06JAN2025 - Dataset ADSP1.ADADR:11SEP2025 ADSP1.ADSL:02SEP2025 - PGM tsub6_06_03_01_c1_adrcscctrp_saf.sas 11SEP2025 19:18

- Encorafenib in combination with cetuximab and FOLFOX

In the EC-FOLFOX pooled Population (EC-FOLFOX-P) for the BRAF V600E-mutant mCRC indication (previously untreated), CuSCC, including keratoacanthoma and squamous cell carcinoma of skin, was observed in 1.2% (3/259) of patients.

The time to onset for the 3 CuSCC ADRs in the EC-FOLFOX-P in BREAKWATER study was 16 days, 57 days and 188 days, respectively.

Table SVII.5: Encorafenib in combination with cetuximab and FOLFOX: Cutaneous squamous cell carcinoma events irrespective of relationship (EC-FOLFOX-P)

Cutaneous squamous cell carcinoma	EC-FOLFOX-P
	N=259 n (%)
Overall incidence	3 (1.2)
Grade 3-4	2 (0.8)
PT with incidence > 10%	0 (0.0)
SAEs overall incidence	1 (0.4)
AEs leading to discontinuation ^a	0 (0.0)
AE leading to dose reduction/interruption ^a	0 (0.0)
AEs requiring additional therapy ^b	2 (0.8)

^a Any study drug

^b Additional therapy includes all non-drug treatments and concomitant medications.

Sources: CRC1L - Version date: 12SEP2025 9:03 - File Name: tsub6_06_03_01_c1_adrcscctrp_saf.rtf

Sources: Cut-off date BREAKWATER_RAN: 06JAN2025 / Cut-off date BREAKWATER_SLI: 22DEC2023 / Cut-off date POOL_PFE: 06JAN2025 - Dataset ADSP1.ADADR:11SEP2025 ADSP1.ADSL:02SEP2025 - PGM tsub6_06_03_01_c1_adrcscctrp_saf.sas 11SEP2025 19:18

In post-marketing experience, cumulatively up to 26 June 2025 (DLP of the most recent submitted PSUR), in the global safety database, there are 9 cases reporting the PT Keratoacanthoma, and 8 cases reporting the PT Squamous cell carcinoma of skin.



Seriousness:

Two cases of cuSCC were reported as serious in the clinical trials. 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. No grade 3 or 4 CuSCC event was reported in the mCRC patients in the doublet arm of study ARRAY-818-302 and in the EC arm of BREAKWATER (C4221015) study. In the EC-FOLFOX-P population of BREAKWATER study, grade 3-4 events were reported in 0.8% (2/259) patients.

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. Additional therapy (including lesion excision) required in 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, and in 0.9% in the mCRC patients in the doublet arm of study ARRAY 818 302. In C4221015 study, additional therapy was required in 1.3% and 0.8% of patients in the EC arm and in the EC-FOLFOX-P population, respectively.

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, in doublet arm of study ARRAY 818 302, in the EC arm of C4221015 study or in the EC-FOLFOX-P population of C4221015 study.

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:
 - o recovered: 76.9% all grade in both the Enco 300 P population and Enco 300 arm of Study CMEK162B2301, in 85.7% in the Combo 450 ISP, and 100% in EC-FOLFOX-P of C4221015 study.
 - o recovering: 15.4% all grades in the Enco 300 mg QD pooled
 - o 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, in the Combo 450 ISP, and in EC-FOLFOX-P of C4221015 study.

In mCRC patients, the outcome was reported as not recovered/not 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 after prior therapy) was 0.014.

The absolute risk of cuSCC events in the Combo 450 ISP was 0.03.

The absolute risk of cuSCC events in the EC-FOLFOX-P of C4221015 study was 0.012.



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. 6: 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 <i>et al.</i> 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. 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 2022 of all stages of colorectal cancer have been estimated to be 37.7 and 24.8 per 100,000 population per year in men and women respectively



([Ferlay, 2024](#)). This was estimated to equal approximately 538,262 new cases in 2022. Using the estimated value of 538,262 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 13,456 individuals were diagnosed with BRAF V600E-mutated stage IV colorectal cancer in 2022 across EU countries.

Given the absolute risk of cuSCC (all grades) described above for patients treated with encorafenib and cetuximab (0.014) and for patients treated by encorafenib with cetuximab and FOLFOX (0.012), it is estimated that 188 and 161 of the patients receiving these therapeutic regimens respectively may be expected to develop cuSCC events in a population of 13,456 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.

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.

- Encorafenib 450 mg QD and binimetinib 45 mg BID

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 after prior therapy (BEACON CRC study), new primary melanoma was observed in 1.9% (4/216) of patients. Grade 3-4 occurred in 0.9% (2/216) patients. No patient required treatment discontinuation. Dose adjustment required in one patient (0.5%), and the 4 patients (1.9%) required additional therapy. The time to onset for each of the 4 new primary melanoma ADRs was 72 days, 104 days, 106 days and 203 days respectively.

Table SVII.7: Encorafenib in combination with cetuximab: New primary melanoma events irrespective of relationship (Doublet arm of Study ARRAY-818-302)

New primary melanoma	Doublet arm N=216 n (%)
Overall incidence	4 (1.9)
Grade 3-4	2 (0.9)
PT with incidence > 10%	0
SAEs overall incidence	3 (1.4)
AEs leading to discontinuation ^a	0
AE leading to dose reduction/interruption ^a	1 (0.5)
AEs requiring additional therapy ^b	4 (1.9)

^a Any study drug

^b Additional therapy includes all non drug therapies and concomitant medications.

Sources: ARRAY_818_302_Dossier_2019 - Version date: 30MAY2024 17:46 - File Name:

A009_02_9_UP_adrD_sumNewPrimaryMelanoma_saf_D_t.rtf - ListingNA

Sources: Cut-off date 15AUG2019 - Database lock 05NOV2019 - Dataset BASEDTM3.ADSL: 28NOV19.ADADR: 12MAR20 - PGM A009_02_9_UP_adrD_sumNewPrimaryMelanoma_saf_D_t.sas 30MAY2024 17:33

In the EC arm of BREAKWATER study, new primary melanoma was observed in 0.7% (1/153) of patients, with no grade 3-4 events. The new primary melanoma in this patient did not require treatment discontinuation or dose adjustment. The new primary melanoma event in this patient required additional therapy. The time to onset was 13 days.



Table SVII.8: Encorafenib in combination with cetuximab: New primary melanoma events irrespective of relationship (EC arm of Study C4221015)

New primary melanoma	EC arm N=153 n (%)
Overall incidence	1 (0.7)
Grade 3-4	0 (0.0)
PT with incidence > 10%	0 (0.0)
SAEs overall incidence	0 (0.0)
AEs leading to discontinuation ^a	0 (0.0)
AE leading to dose reduction/interruption ^a	0 (0.0)
AEs requiring additional therapy ^b	1 (0.7)

^a Any study drug

^b Additional therapy includes all non-drug treatments and concomitant medications.

Sources: CRC1L - Version date: 12SEP2025 9:05 - File Name: tsub6_06_03_02_c1_adrnpmptrp_saf.rtf

Sources: Cut-off date BREAKWATER_RAN: 06JAN2025 / Cut-off date BREAKWATER_SLI: 22DEC2023 / Cut-off date POOL_PFE: 06JAN2025 - Dataset ADSP1.ADADR:11SEP2025 ADSP1.ADSL:02SEP2025 - PGM tsub6_06_03_02_c1_adrnpmptrp_saf.sas 11SEP2025 19:18

- Encorafenib in combination with cetuximab and FOLFOX

In the EC-FOLFOX Pooled Population (EC-FOLFOX-P) for the BRAF V600E-mutant mCRC indication (previously untreated), new primary melanoma was observed in 0.8% (2/259) of patients, both had Grade 3-4 events. No patient required treatment discontinuation. Dose adjustment required in one patient (0.4%), and both patients required additional therapy. The times to onset were 43 days and 134 days.

Table SVII.9: Encorafenib in combination with cetuximab and FOLFOX: New primary melanoma events irrespective of relationship (EC-FOLFOX-P)

New primary melanoma	EC-FOLFOX-P N=259 n (%)
Overall incidence	2 (0.8)
Grade 3-4	2 (0.8)
PT with incidence > 10%	0 (0.0)
SAEs overall incidence	2 (0.8)
AEs leading to discontinuation ^a	0 (0.0)
AE leading to dose reduction/interruption ^a	1 (0.4)
AEs requiring additional therapy ^b	2 (0.8)

^a Any study drug

^b Additional therapy includes all non-drug treatments and concomitant medications.

Sources: CRC1L - Version date: 12SEP2025 9:05 - File Name: tsub6_06_03_02_c1_adrnpmptrp_saf.rtf

Sources: Cut-off date BREAKWATER_RAN: 06JAN2025 / Cut-off date BREAKWATER_SLI: 22DEC2023 / Cut-off date POOL_PFE: 06JAN2025 - Dataset ADSP1.ADADR:11SEP2025 ADSP1.ADSL:02SEP2025 - PGM tsub6_06_03_02_c1_adrnpmptrp_saf.sas 11SEP2025 19:18

In post-marketing experience, cumulatively up to 26 June 2025 (DLP of the most recent submitted PSUR), in the global safety database, there are 17 cases reporting the PTs malignant melanoma, and 3 cases reported the PT malignant melanoma stage 0. In addition, the PTs skin cancer and neoplasm skin were reported in 6 cases (each). Analysis of these cases did not identify a new safety information for this risk.



Seriousness:

Five cases of new primary melanoma were reported as serious in the clinical trials. 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, 3 (1.4%) out of the 4 cases of new primary melanoma reported were reported as serious, and in the EC-FOLFOX-P population of the C4221015 study both reported cases were 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 after prior systemic therapy), 2 (0.9%) out of the 4 cases reported were Grade 3-4, none of the cases led to study treatment discontinuation, and one case (0.5%) required dose adjustment/study drug interruption. In the EC arm of C4221015 study, no grade 3-4 events were reported, and the unique reported event did not lead to study treatment discontinuation or dose adjustment.

In the EC-FOLFOX pooled Population (EC-FOLFOX-P) for the BRAF V600E-mutant mCRC indication (previously untreated), both reported events of new primary melanoma were Grade 3-4. None of the cases led to study treatment discontinuation, and dose adjustment/study drug interruption was required in one patient (0.4%).

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; previously treated), all the 4 events of new primary melanoma were considered recovered/resolved after lesion excision.

In the EC-FOLFOX pooled Population (EC-FOLFOX-P) of C4221015 study (mCRC indication; previously untreated), both observed events were considered recovered/resolved.

Absolute risk:

The absolute risk of new primary melanoma events in the Enco 300 P population was 0.041.

The absolute risk of new primary melanoma events in the doublet population (doublet arm of ARRAY 818 302, mCRC indication after prior therapy) was 0.019.

The absolute risk of new primary melanoma events in the EC + FOLFOX P of C4221015 study was 0.008.

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 2022 of all stages of colorectal cancer have been estimated to be 37.7 and 24.8 per 100,000 population per year in men and women respectively ([Ferlay, 2024](#)). This was estimated to equal approximately 538,262 new cases in 2022. Using the estimated value of 538,262 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 13,456 individuals were diagnosed with BRAF V600E-mutated stage IV colorectal cancer in 2022 across EU countries.

Given the absolute risk of new primary melanoma described above for patients treated with encorafenib and cetuximab (0.019) and for patients treated by encorafenib with cetuximab and FOLFOX (0.008), it is estimated that 256 and 108 of the patients receiving these therapeutic regimens respectively may be expected to develop new primary melanoma events in a population of 13,456 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](#); [Neboit, 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:

- Encorafenib 300 mg QD

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.10: 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	Enco 300mg QD arm
	N=217	N=192
	n (%)	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

- Encorafenib 450 mg QD and binimetinib 45 mg BID

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.11: 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).

- Encorafenib 300 mg QD in combination with cetuximab

For encorafenib 300 mg QD in combination with cetuximab - In Study ARRAY-818-302, new QTcF > 500 ms was reported in 2.8% of patients at risk in the doublet arm (Table SVII.12)). 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.12: 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	27/209 (12.9)
New >480	7/216 (3.2)
New >500	5/216 (2.3)
Increase from baseline >30	95/216 (44.0)
Increase from baseline >60	21/216 (9.7)
QTcF (ms)	
New >450	48/196 (24.5)
New >480	18/214 (8.4)
New >500	6/216 (2.8)
Increase from baseline >30	69/216 (31.9)
Increase from baseline >60	19/216 (8.8)

Sources: ARRAY-818-302 CSR OS Addendum (COD 15 AUG2019) 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, which is used to calculate the percentage.

All scheduled and unscheduled visits are included

In the EC arm of BREAKWATER (C4221015) study, new QTcF > 500 ms was reported in 3.3% of patients. QTcF increases by >60 ms were observed in 7.3% of patients. The incidences of increased QTcF changes by >30 ms and categorical shifts to QTcF value >450 ms were reported in 40.7% and 22.7%, respectively.

Table SVII.13: Newly Occurring Notable QTcF Values (C4221015-EC arm)- Encorafenib in combination with cetuximab

Category	Study C4221015
	EC arm N=153 n/N (%)
QTcF (ms)	
New >450	34/150 (22.7)
New >480	9/150 (6.0)
New >500	5/150 (3.3)
Increase from baseline >30	61/150 (40.7)
Increase from baseline >60	11/150 (7.3)

Sources: Table 14.3.6.2.1 – CSR of C4221015 study;

CSR: clinical study report; ms: millisecond(s);

N: number of participants evaluated against criteria.

n=number of participants that met criteria.



- Encorafenib in combination with cetuximab and FOLFOX

In the EC-FOLFOX pooled Population (EC-FOLFOX-P) for the BRAF V600E-mutant mCRC indication (previously untreated), new QTcF > 500 ms was reported in 4.0% of patients. QTcF increases by >60 ms were observed in 11.5% of patients. The incidences of increased QTcF changes by >30 ms and categorical shifts to QTcF value >450 ms were reported in 51.8% and 32.4%, respectively. All abnormal findings were isolated events, found at a single study visit. There was no pattern for time of onset.

Table SVII.14: Newly Occurring Notable QTcF Values (C4221015; EC-FOLFOX-P)- Encorafenib with cetuximab in combination with FOLFOX

Category	Study C4221015
	EC-FOLFOX-P N=259 n/N (%)
QTcF (ms)	
New >450	82/253 (32.4)
New >480	21/253 (8.3)
New >500	10/253 (4.0)
Increase from baseline >30	131/253 (51.8)
Increase from baseline >60	29/253 (11.5)

Sources: Table 14.3.6.2.1 – CSR of C4221015 study;

Sources: Table 14.3.6.2.2 – CSR of C4221015 study;

CSR: clinical study report; ms: millisecond(s);

N: number of participants evaluated against criteria.

n=number of participants that met criteria.

In the post-marketing experience, cumulatively through 26 June 2025 (DLP of the most recent submitted PSUR), there were 45 cases reporting 48 events suggestive of QT prolongation from post-marketing sources. These 45 cases represent 0.5% of the cumulative post-marketing dataset. The reported PTs included: electrocardiogram QT prolonged (35 events), cardiac arrest (6 events), sudden death, ventricular tachycardia (2 events each), cardio-respiratory arrest, syncope and ventricular fibrillation (1 event each). No new safety information was identified for encorafenib and QT prolongation based on the analysis of the cumulative post-marketing cases.

Absolute risk:

In the Enco 300 P population, the absolute risk of increased QTcF >60 ms is 0.034, the new QTcF increases to >480 ms is 0.05, and >500 ms is 0.025.

In the doublet population (doublet arm of ARRAY 818 302, mCRC indication after prior therapy), the absolute risk of increased QTcF >60 ms is 0.088, the new QTcF increases to >480 ms is 0.084, and >500 ms is 0.028.

In the Combo 450 ISP, the absolute risk of increased QTcF >60 ms is 0.06, the new QTcF increases to >480 ms is 0.061, and >500 ms is 0.011.

In the EC-FOLFOX-P of C4221015 study, the absolute risk of increased QTcF >60 ms is 0.115, the new QTcF increases to >480 ms is 0.083, and >500 ms is 0.04.

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, ([Livingstone2014](#)) 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, gastropasty 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.

Given the absolute risk of increased QTcF >60 ms, the new QTcF increases to >480 ms, and >500 ms described above for patients treated with encorafenib alone (0.034, 0.05, and 0.025, respectively), an estimated 223, 328, and 164 patients receiving encorafenib, may be expected to develop the risk in a population of 6,552 eligible patients each year if they are all treated.

In Europe, the age-standardized incidence rates (ASRs) in 2022 of all stages of colorectal cancer have been estimated to be 37.7 and 24.8 per 100,000 population per year in men and women respectively ([Ferlay, 2024](#)). This was estimated to equal approximately 538,262 new cases in 2022. Using the estimated value of 538,262 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 13,456 individuals were diagnosed with BRAF V600E-mutated stage IV colorectal cancer in 2022 across EU countries.

Given the absolute risk of increased QTcF >60 ms, the new QTcF increases to >480 ms, and >500 ms described above for patients treated with encorafenib and cetuximab (0.088, 0.084, and 0.028, respectively), an estimated 1184, 1130 and 377 patients receiving encorafenib, may be expected to develop the risk in a population of 13,456 eligible patients each year if they are all treated.

Using the same approach, given the absolute risk of increased QTcF >60 ms, the new QTcF increases to >480 ms, and >500 ms for patients treated by encorafenib with cetuximab and FOLFOX (0.115, 0.083, and 0.04, respectively), an estimated 1547, 1117 and 538 patients receiving encorafenib, may be expected to develop the risk in a population of 13,456 eligible patients each year if they are all treated.

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.

Given the absolute risk of increased QTcF >60 ms, the new QTcF increases to >480 ms, and >500 ms described above for patients treated with encorafenib alone (0.034, 0.05, and 0.025), an estimated 117, 172 and 86 patients receiving encorafenib, may be expected to develop the risk 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.

(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, Doublet populations and EC-FOLFOX-P).

However, there was 1 case involving breast cancer recurrence 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 recurrent) 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 tumour. 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 through 26 June 2025 (DLP of the most recent submitted PSUR), there is no case reporting non-cutaneous malignancies with RAS mutation.

Absolute risk:

Not applicable.

Relative risk as compared with "unexposed" patient populations:



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 2022 of all stages of colorectal cancer have been estimated to be 37.7 and 24.8 per 100,000 population per year in men and women respectively ([Ferlay, 2024](#)). This was estimated to equal approximately 538,262 new cases in 2022. Using the estimated value of 538,262 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 13,456 individuals were diagnosed with BRAF V600E-mutated stage IV colorectal cancer in 2022 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, 13,456 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%).

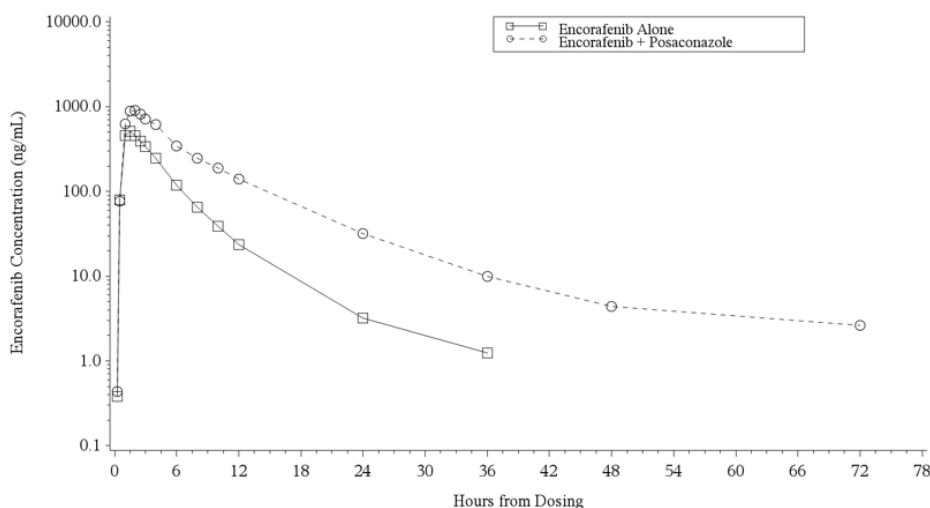
Evidence source and strength of evidence:

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 to 4, 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)



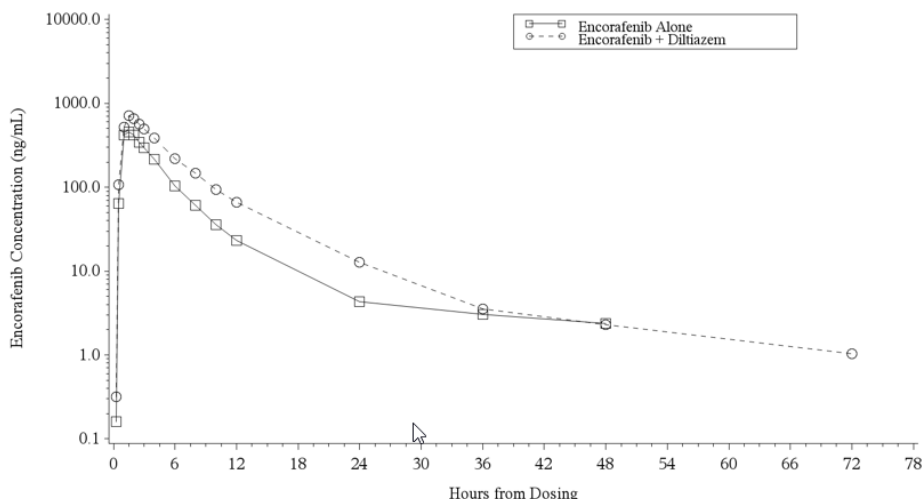


Table SVII.15: Encorafenib pharmacokinetic parameters and statistical analysis of drug-drug interaction after a single oral 50 mg dose of encorafenib given either alone or co-administered with strong (posaconazole) and moderate (diltiazem) CYP3A4 inhibitors to healthy male and female subjects under fasted 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 2025 (DLP of the most recent submitted PSUR), in the global safety database, there are 7 cases suggesting overexposure due to concomitant use with strong and moderate CYP450 3A4 inhibitors (reported potential interacting agent: diltiazem (3), verapamil, fluconazole, grapefruit juice, nirmatrelvir and ritonavir; 1 each). These 7 cases represent 0.07% of the cumulative post-marketing dataset, and concerned 3 female patients and 4 male patients. Age (when reported) was between 50 years old and 82 years old. The reported PTs in these cases included drug interaction (5), blood creatine phosphokinase increased, blood creatinine increased, cryptococcus test positive, diarrhoea, electrocardiogram QT prolonged, fluid intake reduced, hepatic cytolysis, food interaction, labelled drug-drug interaction medication error, lung opacity, muscular weakness, nausea, neoplasm progression, 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 2022 of all stages of colorectal cancer have been estimated to be 37.7 and 24.8 per 100,000 population per year in men and women respectively ([Ferlay, 2024](#)). This was estimated to equal approximately 538,262 new cases in 2022. Using the estimated value of 538,262 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 13,456 individuals were diagnosed with BRAF V600E-mutated stage IV colorectal cancer in 2022 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, 13,456 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 (AUC_{inf}) 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.

In a Global population PK analysis including 9 clinical studies and successfully validated with BREAKWATER PK data, none of the baseline associated safety laboratory measurements (albumin, alanine aminotransferase, or bilirubin) were found to be statistically significant covariates in the final model. Mild hepatic impairment was shown to have no major impact on encorafenib exposure (ODWG NCI classification, mild [N = 153], moderate [N = 7], and severe [N = 1]). No conclusion was drawn for moderate and severe impairment.

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 fulfil 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. In April 2025, this PAM has been considered by EMA as closed with no encorafenib SmPC modification.

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, cumulatively up to 26 June 2025 (DLP of the most recent submitted PSUR), in the global safety database there are two cases involving the use of encorafenib in patients with reported information about the severity of the relevant medical history using Child Pugh classification (Child Pugh A and Child Pugh B, one case each). No new significant safety information was identified for encorafenib and overexposure in patients with moderate to severe hepatic impairment based on the post-marketing experience.

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 [¹⁴C] 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.

In Europe, the age-standardized incidence rates (ASRs) in 2022 of all stages of colorectal cancer have been estimated to be 37.7 and 24.8 per 100,000 population per year in men and women respectively ([Ferlay, 2024](#)). This was estimated to equal approximately 538,262 new cases in 2022. Using the estimated value of 538,262 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 13,456 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 with severe or moderate hepatic impairment receiving encorafenib who are expected to experience encorafenib overexposure with increased toxicities in a population of 6,552, 13,456 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 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). 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.

In a Global population PK analysis including 9 clinical studies and successfully validated with BREAKWATER PK data, baseline estimated glomerular filtration rate was not found to have a statistically significant influence on encorafenib apparent clearance (CL/F); mild and moderate renal impairment were shown to have no major impact on encorafenib exposure (according to the National Kidney Foundation Kidney Disease Outcomes Quality Initiative, mild [N = 524], moderate [N = 83], and severe [N = 1]).

Based on the population PK analyses, no dose adjustment is recommended for patients with mild or moderate renal impairment, 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 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). 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 m²) 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, cetuximab or individual products that comprise the mFOLFOX6 regimen are presented in the product specific RMPs.

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 cetuximab (with or without FOLFOX) or with MEKTOVI. The RMP details important risks of BRAFTOVI in combination with cetuximab (with or without FOLFOX) or MEKTOVI, how these risks can be minimised, and how more information will be obtained about BRAFTOVI in combination with MEKTOVI or cetuximab (with or without FOLFOX) 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 (with or without FOLFOX) 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 (mCRC) 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 authorised 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 in combination with cetuximab and FOLFOX is proposed for the first line treatment of adult patients with metastatic colorectal cancer (mCRC) with a BRAF V600E mutation (see SmPC for the full indication). Cetuximab and FOLFOX are given by intravenous infusion.

BRAFTOVI is not authorised for use as monotherapy.

Further information about the evaluation of BRAFTOVI in combination with MEKTOVI, or with cetuximab (with or without FOLFOX) 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 with cetuximab (with or without FOLFOX), 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 with cetuximab (with or without FOLFOX) 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 (with or without FOLFOX).

Potential risks are concerns for which an association with the use of BRAFTOVI as a single agent or in combination with MEKTOVI or with cetuximab (with or without FOLFOX) 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 with cetuximab (with or without FOLFOX) 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	<u>Routine risk minimisation measures:</u> 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. <u>Additional risk minimisation measures:</u> 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	<u>Routine risk minimisation measures:</u> 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. <u>Additional risk minimisation measures:</u> 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	<u>Routine risk minimisation measures:</u> Dose modification recommendation in section 4.2 of the SmPC Warning in section 4.4 of the SmPC and PIL relevant section <u>Additional risk minimisation measures:</u> 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	<u>Routine risk minimisation measures:</u> 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. <u>Additional risk minimisation measures:</u> 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	<u>Routine risk minimisation measures:</u> 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 <u>Additional risk minimisation measures:</u> None
Missing information for encorafenib: Use in patients with severe renal impairment	
Risk minimisation measures	<u>Routine risk minimisation measures:</u> 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 <u>Additional risk minimisation measures:</u> 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.



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.



Annex 7 – Other supporting data (including referenced material)

Ait Ouakrim D, Pizot C, Boniol M, et al. Trends in colorectal cancer mortality in Europe: retrospective analysis of the WHO mortality database. *Bmj*. Oct 6 2015;351:h4970.

Allemani C, Rachet B, Weir HK, et al. Colorectal cancer survival in the USA and Europe: a CONCORD high-resolution study. *BMJ Open*. Sep 10 2013;3(9):e003055.

Alvarez JGB, Otterson GA. Agents to treat BRAF-mutant lung cancer. *Drugs in Context* 2019; 8: 212566. DOI: 10.7573/dic.212566.

Amado RG, Wolf M, Peeters M, et al. Wild-type KRAS is required for panitumumab efficacy in patients with metastatic colorectal cancer. *J Clin Oncol*. Apr 1 2008;26(10):1626-1634.

American Cancer Society (2021). <https://www.cancer.org/cancer/lung-cancer/about/what-is.html>. Accessed 15 June 2021 [Ref list]

Andrews M, Behren A, Chiohn F, et al. Colorectal cancer promoted in a melanoma patient receiving dabrafenib (GSK2118436) in combination with MEK1/2 inhibitor trametinib (GSK1120212). *Pigment Cell & Melanoma Research* 2012;25(6):842.

Anforth R, Fernandez-Penas P and Long GV. Cutaneous toxicities of RAF inhibitors. *Lancet Oncology* 2013;14(1):e11-8.

Ascierto PA, Kirkwood JM, Grob JJ, et al. The role of BRAF V600 mutation in melanoma. *J Transl Med*. 2012 Jul 9;10:85.

Ascierto PA, Minor D, Ribas A, et al. Phase II Trial (BREAK-2) of the BRAF Inhibitor Dabrafenib (GSK2118436) in Patients With Metastatic Melanoma. *J Clin Oncol*. 2013 Sep 10;31(26):3205-11.

Australian Institute of Health and Welfare 2018. National Bowel Cancer Screening Program: monitoring report 2018. Cat. no. CAN 112. Canberra: AIHW. <https://www.aihw.gov.au/getmedia/df120b1a-1bda-49c1-8611-17a7256e61d0/aihw-can-12.pdf.aspx?inline=true>. Accessed on September 2019

Australian Institute of Health and Welfare 2019. Cancer in Australia 2019. Cancer series no.119. Cat. no. CAN 123. Canberra: AIHW. <https://www.aihw.gov.au/getmedia/8c9fcf52-0055-41a0-96d9-f81b0feb98cf/aihw-can-123.pdf.aspx?inline=true> . Accessed in September 2019

Bachet JB, Moreno-Lopez N, Vigano L, et al. BRAF mutation is not associated with an increased risk of recurrence in patients undergoing resection of colorectal liver metastases. *Br J Surg*. 2019 Aug;106(9):1237-1247.

Barlesi F, Mazieres J, Merlio JP, Debieuvre D, Mosser J, Lena H, et al. Routine Molecular Profiling of Patients With Advanced Non-Small-Cell Lung Cancer: Results of a 1-Year Nationwide Programme of the French Cooperative Thoracic Intergroup (IFCT). *Lancet* (2016) 387:1415–26. doi: 10.1016/S0140-6736(16)00004-0.

Barras D, Missiaglia E, Wirapati P, et al. BRAF V600E Mutant colorectal cancer subtypes based on gene expression. *Clin Cancer Res* 2017;23(1):104-15.

Bauer J, Buttner P, Murali R, et al. BRAF mutations in cutaneous melanoma are independently associated with age, anatomic site of the primary tumor, and the degree of solar elastosis at the primary tumor site. *Pigment Cell Melanoma Res* 2011;24(2):345-51.

Benedix F, Kube R, Meyer F, et al. Comparison of 17,641 patients with right- and left-sided colon cancer: differences in epidemiology, perioperative course, histology, and survival. *Dis Colon Rectum*. Jan 2010;53(1):57-64.

Benitez Majano S, Di Girolamo C, Rachet B, et al. Surgical treatment and survival from colorectal cancer in Denmark, England, Norway, and Sweden: a population-based study. *Lancet Oncol*. Jan 2019;20(1):74-87.



Bennett L, Zhao Z, Barber B, et al. Health-related quality of life in patients with metastatic colorectal cancer treated with panitumumab in first- or second-line treatment. *Br J Cancer*. Nov 8 2011;105(10):1495-1502.

Bennouna J, Sastre J, Arnold D, et al. Continuation of bevacizumab after first progression in metastatic colorectal cancer (ML18147): a randomised phase 3 trial. *Lancet Oncol*. Jan 2013;14(1):29-37.

Bessa X, Balleste B, Andreu M, et al. A prospective, multicenter, population-based study of BRAF mutational analysis for Lynch syndrome screening. *Clin Gastroenterol Hepatol*. Feb 2008;6(2):206-214.

Blaker H, Alwers E, Arnold A, et al. The Association Between Mutations in BRAF and Colorectal Cancer-Specific Survival Depends on Microsatellite Status and Tumor Stage. *Clin Gastroenterol Hepatol*. Feb 2019;17(3):455-462 e456.

Boffetta P. Involuntary smoking and lung cancer. *Scand J Work Environ Health* 2002; 28: Suppl. 2, 30-40.

Boffetta P, Trédaniel J, Greco A . Risk of childhood cancer and adult lung cancer after childhood exposure to passive smoke: a meta-analysis. *Environ Health Perspect* 2000; 108: 73.

Bouvier AM, Launoy G. [Epidemiology of colorectal cancer]. *Rev Prat*. Jun 2015;65(6):767-773.

Bradley C, Lansdorp-Vogelaar I, Yabroff R et al Productivity Savings from Colorectal Cancer Prevention and Control Strategies. *Am J Prev Med*. 2011 Aug; 41(2): e5-e14.

Brahmer JR, Lee J, Ciuleanu T, et al. Five-Year Survival Outcomes With Nivolumab Plus Ipilimumab Versus Chemotherapy as First-Line Treatment for Metastatic Non-Small Cell Lung Cancer in CheckMate 227. *J Clin Oncol*. 2022 Oct 12. Doi: 10.1200/JCO.22.01503. Online ahead of print.

Brandstedt J, Wangefjord S, Nodin B, et al. Associations of anthropometric factors with KRAS and BRAF mutation status of primary colorectal cancer in men and women: a cohort study. *PLoS One*. 2014;9(2):e98964.

Bray F, Laversanne M, Sung H et al. Global cancer statistics 2022: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin*. 2024 May-Jun;74(3):229-263.

Brell JM. Prolonged QTc Interval in Cancer Therapeutic Drug Development: Defining Arrhythmic Risk in Malignancy. *Prog Cardiovasc Dis*. 2010 Sep-Oct; 53(2): 164-172.

Brenner H, Bouvier AM, Foschi R, et al. Progress in colorectal cancer survival in Europe from the late 1980s to the early 21st century: the EURO CARE study. *Int J Cancer*. Oct 1 2012;131(7):1649-1658.

Bronte E, Bronte G, Novo G, Bret, al. What links BRAF to the heart function? New insights from the cardiotoxicity of BRAF inhibitors in cancer treatment. *Oncotarget*. 2015 Nov 3;6(34):35589-601.

Brouwer NPM, Bos A, Lemmens V, et al. An overview of 25 years of incidence, treatment and outcome of colorectal cancer patients. *Int J Cancer*. Dec 1 2018;143(11):2758-2766.

Brustugun OT, Khatkhat AM, Trømborg AK, Beigi M, Beiske K, Lund-Iversen M, Helland Å. BRAF-mutations in non-small cell lung cancer. *Lung Cancer*. 2014 Apr;84(1):36-8.

Buchanan DD, Win AK, Walsh MD, et al. Family history of colorectal cancer in BRAF p.V600E-mutated colorectal cancer cases. *Cancer Epidemiol Biomarkers Prev*. May 2013;22(5):917-926.

Burudpakdee C, Zhao Z, Seetasith A, et al. Treatment patterns of metastatic melanoma in five European countries. *Value in Health* 2016;19 (3):A172.

Bylsma LC, Gillezeau C, Garawin T et al. Prevalence of RAS and BRAF mutations in metastatic colorectal cancer (mCRC) patients by tumor location. *J Clin Oncol* 2018;36(4)_suppl:681.

Callahan MK, Rampal R, Harding JJ, et al. Progression of RAS-mutant leukemia during RAF inhibitor treatment. *N Engl J Med* 2012;367(24):2316-21.

Cancer Institute NSW (2022) Cancer statistics NSW – Cancer incidence, mortality and relative survival-external site opens in new window, NSW government, accessed 31 January 2024.



Cancer Research UK. Bowel cancer incidence statistics. . Last reviewed: 20 June 2019. Accessed on September 2019.

Cardarella S, Ogino A, Nishino M, Butaney M, Shen J, Lydon C, Yeap BY, Sholl LM, Johnson BE, Jänne PA. Clinical, pathologic, and biologic features associated with BRAF mutations in non-small cell lung cancer. Clin Cancer Res. 2013 Aug 15;19(16):4532-40.

Carlos G, Anforth R, Clements A, et al. Cutaneous Toxic Effects of BRAF Inhibitors Alone and in Combination With MEK Inhibitors for Metastatic Melanoma. JAMA Dermatol 2015;151(10):1103-9.

Carter NJ. Regorafenib: a review of its use in previously treated patients with progressive metastatic colorectal cancer. Drugs Aging. Jan 2014;31(1):67-78.

Cavalieri S, Di Guardo L, Cimminiello C, et al. Combined therapy with dabrafenib and trametinib in BRAF-mutated metastatic melanoma in a real-life setting: the INT Milan experience. Tumori 2016;102(5):501-507.

Cervantes A, R. Adam, S. Roselló, D. Arnold, N. Normanno, J. Taïeb, J. Seligmann, T. De Baere, P. Osterlund, T. Yoshino, E. Martinelli. Metastatic colorectal cancer: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up. Annals of Oncology, Volume 34, Issue 1, 2023, Pages 10-32

Charlson ME, Pompei P, Ales KL, et al. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis. 1987;40(5):373-83.

Chen V.W., Ruiz B.A., Hsieh M.-C., Wu X.-C., Ries L.A.G., Lewis D.R. Analysis of stage and clinical/prognostic factors for lung cancer from SEER registries: AJCC staging and collaborative stage data collection system. Cancer. 2014;120:3781–3792. doi: 10.1002/cncr.29045.

Cheeseman SL, Joel SP, Chester JD, Wilson G, Dent JT, Richards FJ, Seymour MT. A "modified de Gramont" regimen of fluorouracil, alone and with oxaliplatin, for advanced colorectal cancer. Br J Cancer (2002) 87: 393–399

Choe CH, McArthur GA, Caro I, et al. Ocular Toxicity in BRAF Mutant Cutaneous Melanoma Patients Treated With Vemurafenib. Am J Ophthalmol. 2014 Oct;158(4):831-837.e2.

Christensen TD, Palshof JA, Larsen FO, et al. Associations between primary tumor RAS, BRAF and PIK3CA mutation status and metastatic site in patients with chemo-resistant metastatic colorectal cancer. Acta Oncol. Aug 2018;57(8):1057-1062.

Clarke CN, Kopetz ES. BRAF mutant colorectal cancer as a distinct subset of colorectal cancer: clinical characteristics, clinical behavior, and response to targeted therapies. J Gastrointest Oncol. 2015 Dec;6(6):660-7.

Clauer U, Schafer J and Roder J. [Morbidity, mortality and analysis of prognostic factors for colorectal cancer]. Chirurg. Jun 2015;86(6):561-569.

Cocorocchio E, Gandini S, Alfieri S, et al. Dabrafenib in metastatic melanoma: a monocentric 'real life' experience. Ecancermedalscience 2016;10:624.

Cohen R, Liu H, Fiskum J, et al. BRAFV600E Mutation in First-Line Metastatic Colorectal Cancer: An Analysis of Individual Patient Data from the ARCAD Database.J Natl Cancer Inst. 2021 October 01; 113(10): 1386–1395

Colombino M, Lissia A, Capone M, et al. Heterogeneous distribution of BRAF/NRAS mutations among Italian patients with advanced melanoma. J Transl Med. 2013 Aug 29;11:202.

Cormier JN, Xing Y, Ding M, et al. Ethnic differences among patients with cutaneous melanoma. Arch Intern Med 2006;166(17):1907-14.

Corrales L, Rosell R, Cardona AF, Martín C, Zatarain-Barrón ZL, Arrieta O. Lung cancer in never smokers: The role of different risk factors other than tobacco smoking. Crit Rev Oncol Hematol. 2020 Apr;148:102895. doi: 10.1016/j.critrevonc.2020.102895. Epub 2020 Jan 31. PMID: 32062313.



Couraud S, Souquet PJ, Paris C, Do P, et al. French Cooperative Intergroup. BioCAST/IFCT-1002: epidemiological and molecular features of lung cancer in never-smokers. *Eur. Respir. J.*, 45 (5) (2015), pp. 1403-1414.

Cremolini C, Loupakis F, Antoniotti C et al. FOLFOXIRI plus bevacizumab versus FOLFIRI plus bevacizumab as first-line treatment of patients with metastatic colorectal cancer: updated overall survival and molecular subgroup analyses of the open-label, phase 3 TRIBE study. *Lancet Oncol* 2015;16:1306-15.

Cui G, Liu D, Li W, et al. A meta-analysis of the association between BRAF mutation and nonsmall cell lung cancer. *Medicine (Baltimore)*. 2017;96:e6552.

Dalle S, Poulalhon N, Debarbieux S, et al. Tracking of Second Primary Melanomas in Vemurafenib-Treated Patients. *JAMA Dermatol*. 2013;149(4):488-490.

Darba J, Marsa A. Evaluation of productivity losses due to premature mortality from colorectal cancer *PLoS One*. 2020 Dec 23; doi: 10.1371/journal.pone.0244375. eCollection 2020

Dasgupta P, Youlden DR and Baade PD. An analysis of competing mortality risks among colorectal cancer survivors in Queensland, 1996-2009. *Cancer Causes Control*. May 2013;24(5):897-909.

Davies H, Bignell GR, Cox C, et al. Mutations of the BRAF gene in human cancer. *Nature*. 2002 Jun 27;417(6892):949-54.

Debieuvre D, Molinier O, Falchero L, et al. Lung cancer trends and tumor characteristic changes over 20 years (2000-2020): Results of three French consecutive nationwide prospective cohorts' studies. *Lancet Reg Health Eur*. 2022 Aug 29;22:100492.

Dejardin O, Rachet B, Morris E, et al. Management of colorectal cancer explains differences in 1-year relative survival between France and England for patients diagnosed 1997-2004. *Br J Cancer*. Mar 5 2013;108(4):775-783.

De Castro G Jr, Kudaba I, Wu YL, et al. Five-Year Outcomes With Pembrolizumab Versus Chemotherapy as First-Line Therapy in Patients With Non-Small-Cell Lung Cancer and Programmed Death Ligand-1 Tumor Proportion Score $\geq 1\%$ in the KEYNOTE-042 Study. *J Clin Oncol*. 2022 Oct 28. Doi: 10.1200/JCO.21.02885. Online ahead of print.

de la Fouchardiere C, Cohen R, Malka D, et al. Characteristics of BRAF (V600E) Mutant, Deficient Mismatch Repair/Proficient Mismatch Repair, Metastatic Colorectal Cancer: A Multicenter Series of 287 Patients. *Oncologist*. May 31 2019;pii: theoncologist.2018-0914.

De Roock W, Claes B, Bernasconi D, et al. Effects of KRAS, BRAF, NRAS, and PIK3CA mutations on the efficacy of cetuximab plus chemotherapy in chemotherapy-refractory metastatic colorectal cancer: a retrospective consortium analysis. *Lancet Oncol*. Aug 2010;11(8):753-762.

Ding X, Zengli Z, Tao J, et al. Clinicopathologic characteristics and outcomes of Chinese patients with non-small-cell lung cancer and BRAF mutation. *Cancer Med*. 2017;6:555-562.

Draganova D, Kerger J, Caspers L, et al. Severe bilateral panuveitis during melanoma treatment by Dabrafenib and Trametinib. *J Ophthalmic Inflamm Infect*. 2015 Jun 9;5:17.

Dréno B, Ribas A, Larkin J, et al. Incidence, course, and management of toxicities associated with cobimetinib in combination with vemurafenib in the coBRIM study. *Ann Oncol*. 2017 May 1;28(5):1137-1144.

Dummer R, Ascierto PA, Gogas HJ, et al. Encorafenib plus binimetinib versus vemurafenib or encorafenib in patients with BRAF-mutant melanoma (COLUMBUS): a multicentre, open-label, randomised phase 3 trial. *Lancet Oncol*. 2018 May;19(5):603-615.

Dyba T, Randi G, Bray F, Martos C, Giusti F, Nicholson N, Gavin A, Flego M, Neamtiu L, Dimitrova N, Negrão Carvalho R, Ferlay J, Bettio M. The European cancer burden in 2020: Incidence and mortality estimates for 40 countries and 25 major cancers. *Eur J Cancer*. 2021 Nov;157:308-347.



Edlundh-Rose E, Egyhazi S, Omholt K, et al. NRAS and BRAF mutations in melanoma tumours in relation to clinical characteristics: A study based on mutation screening by pyrosequencing. *Melanoma Research* 2006;16(6):471-478.

Eklof V, Wikberg ML, Edin S, et al. The prognostic role of KRAS, BRAF, PIK3CA and PTEN in colorectal cancer. *Br J Cancer*. May 28 2013;108(10):2153-2163.

Elferink MA, de Jong KP, Klaase JM, et al. Metachronous metastases from colorectal cancer: a population-based study in North-East Netherlands. *Int J Colorectal Dis*. Feb 2015;30(2):205-212.

Encorafenib Investigator's Brochure. Array BioPharma/Ono Pharmaceutical/Pierre Fabre Médicament. 20 June 2019. Edition 11.

Erbitux. EPAR. https://www.ema.europa.eu/documents/procedural-steps-after/erbitux-epar-procedural-steps-taken-scientific-information-after-authorisation_en.pdf. Last update September 2019.

European Cancer Information System. <https://ecis.jrc.ec.europa.eu/>. Last accessed September 2019.

European Commission. https://ec.europa.eu/info/index_en. Last accessed September 2019.

Erfan G, Puig S, Carrera C, et al. Development of Cutaneous Toxicities During Selective Anti-BRAF Therapies: Preventive Role of Combination with MEK Inhibitors. *Acta Derm Venereol* 2017; 97: 258–260.

Erichsen R, Horvath-Puho E, Iversen LH, et al. Does comorbidity interact with colorectal cancer to increase mortality? A nationwide population-based cohort study. *Br J Cancer*. Oct 1 2013;109(7):2005-2013.

Faivre-Finn C, Bouvier-Benhamiche AM, Phelip JM, et al. Colon cancer in France: evidence for improvement in management and survival. *Gut*. Jul 2002;51(1):60-64.

Ferlay J, Colombet M, Soerjomataram I, et al. Cancer incidence and mortality patterns in Europe: Estimates for 40 countries and 25 major cancers in 2018. *Eur J Cancer*. Nov 2018;103:356-387.

Ferlay J, Ervik M, Lam F, Laversanne M, Colombet M, Mery L, Piñeros M, Znaor A, Soerjomataram I, Bray F (2024). *Global Cancer Observatory: Cancer Today*. Lyon, France: International Agency for Research on Cancer. Available from: <https://gco.iarc.who.int/today>, accessed [accessed September 2025]

Frauchiger AL Mangana J, Rechsteiner M, et al. Prognostic relevance of lactate dehydrogenase and serum S100 levels in stage IV melanoma with known BRAF mutation status. *Br J Dermatol*. 2016 Apr;174(4):823-30.

Gabeff R, Dutartre H, Khammari A, et al. Phototoxicity of B-Raf inhibitors: exclusively due to UVA radiation and rapidly progressive. *Eur J Dermatol*. 2015 Sep-Oct;25(5):452-6.

Gandini S, Sera F, Cattaruzza MS, et al. Meta-analysis of risk factors for cutaneous melanoma: III. Family history, actinic damage and phenotypic factors. *Eur J Cancer* 2005;41(14):2040-59.

Garbe C and Leiter U. Melanoma epidemiology and trends. *Clin Dermatol* 2009;27(1):3-9.

Garbe C, Peris K, Hauschild A, et al. Diagnosis and treatment of melanoma. European consensus-based interdisciplinary guideline - Update 2016. *Eur J Cancer* 2016;63:201-17.

Gelot P, Dutartre H, Khammari A, et al. Vemurafenib: an unusual UVA-induced photosensitivity. *Exp Dermatol*. 2013 Apr;22(4):297-8.

Gheybi K, Buckley E, et al. Occurrence of comorbidity with colorectal cancer and variations by age and stage at diagnosis. *Cancer epidemiology* 80 (2022) 102246

Griesinger F, Eberhardt W, Nusch A, Reiser M, et al. Biomarker testing in non-small cell lung cancer in routine care: Analysis of the first 3,717 patients in the German prospective, observational, nation-wide CRISP Registry (AIO-TRK-0315). *Lung Cancer*. 2021 Feb;152:174-184.

Gibson AJW, Pabani A, Dean ML, Martos G, Cheung WY, Navani V. Real-World Treatment Patterns and Effectiveness of Targeted and Immune Checkpoint Inhibitor-Based Systemic Therapy in BRAF Mutation-Positive NSCLC. *JTO Clin Res Rep*. 2023 Jan 10;4(3):100460



Gonsalves WI, Mahoney MR, Sargent DJ et al. Patient tumour characteristics and BRAF and KRAS mutations in colon cancer, NCCTG/Alliance. N0147. J Natl Cancer Inst 2014; 106: 8.

Goppner D, Muller J, Kruger S, et al. High incidence of naevi-associated BRAF wild-type melanoma and dysplastic naevi under treatment with the class I BRAF inhibitor vemurafenib. Acta Dermato-Venereologica 2014;94(5):517-20.

Grann AF, Froslev T, Olesen AB, et al. The impact of comorbidity and stage on prognosis of Danish melanoma patients, 1987-2009: a registry-based cohort study. Br J Cancer 2013;109(1):265-71.

Gridelli C, Rossi A, Carbone D, et al. Non-small-cell lung cancer. Nat Rev Dis Primers. 2015;1:15009. doi: 10.1038/nrdp.2015.9.

Guedj M, Queant A, Funck-Brentano E, et al. Uveitis in patients with late-stage cutaneous melanoma treated with vemurafenib. JAMA Ophthalmology 2014;132(12):1421-5.

Guerreiro T, Antunes L, Bastos J, Mayer A, Forjaz G, Araujo A, Nunes C. Lung Cancer: A Nationwide Study to Characterize Sex Differences, Incidence, and Spatial Patterns in Portugal. In Vivo. 2020 Sep-Oct;34(5):2711-2719.

Hackshaw AK, Law MR, Wald NJ . The accumulated evidence on lung cancer and environmental tobacco smoke. BMJ 1997; 315: 980-988.

Haddad PM and Anderson IM. Antipsychotic-related QTc prolongation, torsade de pointes and sudden death. Drugs. 2002;62(11):1649-71.

Hagen B, Trinh VA. Managing Side Effects of Vemurafenib Therapy for Advanced Melanoma. Journal of the Advanced Practitioner in Oncology 2014;5(6):400-10.

Hanna MC, Go C, Roden C, et al. Colorectal cancers from distinct ancestral populations show variations in BRAF mutation frequency. PLoS One. 2013;8(9):e74950.

Hauschild A, Grob JJ, Demidov LV, et al. Dabrafenib in BRAF-mutated metastatic melanoma: a multicentre, open-label, phase 3 randomised controlled trial. Lancet. 2012 Jul 28;380(9839):358-65.

Henley SJ, Thun MJ, Connell C, et al. Two large prospective studies of mortality among men who use snuff or chewing tobacco (United States). Cancer Causes Control 2005; 16: 347-358.

Heinzerling L, Baiter M, Kuhnappel S, et al. Mutation landscape in melanoma patients clinical implications of heterogeneity of BRAF mutations. British Journal of Cancer 2013;109(11):2833-2841.

Heinzerling L, Eigentler TK, Fluck M, et al. Tolerability of BRAF/MEK inhibitor combinations: adverse event evaluation and management. ESMO Open. 2019 May 23;4(3):e000491.

Hendriks LE, Kerr KM, Menis J, Mok TS, Nestle U, Passaro A, Peters S, Planchard D, Smit EF, Solomon BJ, Veronesi G, Reck M; ESMO Guidelines Committee. Oncogene-addicted metastatic non-small-cell lung cancer: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up. Ann Oncol. 2023a Jan 23:S0923-7534(22)04781-0.

Hippisley-Cox J and Coupland C. Development and validation of risk prediction equations to estimate survival in patients with colorectal cancer: cohort study. Bmj. Jun 15 2017;357:j2497.

Holderfield M, Nagel TE and Stuart DD. Mechanism and consequences of RAF kinase activation by small-molecule inhibitors. Br J Cancer 2014;111(4):640-5.

Horn L, Bauml J, Forde PM, et al. Real-world treatment patterns and survival of patients with BRAF V600-mutated metastatic non-small cell lung cancer. Lung Cancer. 2019;128:74-90. doi:10.1016/j.lungcan.2018.12.003.

Howlader N, Forjaz G, Mooradian MJ, et al. The Effect of Advances in Lung-Cancer Treatment on Population Mortality N Engl J Med 2020;383:640-9.

<http://hrstudies.it>

Hyman DM, Puzanov I, Subbiah V, Faris JE, Chau I, Blay JY, Wolf J, Raje NS, Diamond EL, Hollebecque A, Gervais R, Elez-Fernandez ME, Italiano A, Hofheinz RD, Hidalgo M, Chan E, Schuler M, Lasserre SF,



Makrutzki M, Sirzen F, Veronese ML, Tabernero J, Baselga J. Vemurafenib in Multiple Nonmelanoma Cancers with BRAF V600 Mutations. *N Engl J Med.* 2015 Aug 20;373(8):726-36. doi: 10.1056/NEJMoa1502309. Erratum in: *N Engl J Med.* 2018 Oct 18;379(16):1585.

Ilie M, Long E, Hofman V, et al. Diagnostic value of immunohistochemistry for the detection of the BRAFV600E mutation in primary lung adenocarcinoma Caucasian patients. *Ann Oncol.* 2013;24(3):742-748.

Islam KM, Jiang X, Anggondowati T, Lin G, Ganti AK. Comorbidity and survival in lung cancer patients. *Cancer Epidemiol Biomarkers Prev* 2015; 24: 1079–1085. doi: 10.1158/1055- 9965.EPI-15-0036.

Izumi M. *J Thorac Dis.* 2020 Jul;12(7):3776-3784. doi: 10.21037/jtd.2019.08.61. PMID: 32802457.

Jess P, Hansen IO, Gamborg M, et al. A nationwide Danish cohort study challenging the categorisation into right-sided and left-sided colon cancer. *BMJ Open.* May 28 2013;3(5).

Johnson ML, Cho BC, Luft A, et al. Durvalumab With or Without Tremelimumab in Combination With Chemotherapy as First-Line Therapy for Metastatic Non-Small-Cell Lung Cancer: The Phase III POSEIDON Study. *J Clin Oncol.* 2022 Nov 3. Doi: 10.1200/JCO.22.00975. Online ahead of print.

Jordan EJ, Kim HR, Arcila ME, et al. Prospective comprehensive molecular characterization of lung adenocarcinomas for efficient patient matching to approved and emerging therapies. *Cancer Discov.* 2017;7(6):596-609.

Jyoti Malhotra, Matteo Malvezzi, Eva Negri, Carlo La Vecchia, Paolo Boffetta. *European Respiratory Journal* Sep 2016, 48 (3) 889-902.

Kadakol A, Ghosh SS, Sappal BS, et al. Genetic lesions of bilirubin uridine-diphosphoglucuronate glucuronosyltransferase (UGT1A1) causing Crigler-Najjar and Gilbert syndromes: correlation of genotype to phenotype. *Hum Mutat.* 2000;16(4):297–306.

Kafatos G, Niepel D, Lowe K, et al. RAS mutation prevalence among patients with metastatic colorectal cancer: a meta-analysis of real-world data. *Biomark Med.* Sep 2017;11(9):751-760.

Kayhanian H, Goode E, Sclafani F, et al. Treatment and Survival Outcome of BRAF-Mutated Metastatic Colorectal Cancer: A Retrospective Matched Case-Control Study. *Clin Colorectal Cancer.* Mar 2018;17(1):e69-e76.

Kinno T, Tsuta K, Shiraishi K, Mizukami T, Suzuki M, Yoshida A, Suzuki K, Asamura H, Furuta K, Kohno T, Kushima R. Clinicopathological features of nonsmall cell lung carcinomas with BRAF mutations. *Ann Oncol.* 2014 Jan;25(1):138-42.

Klein F, Schlesinger-Raab A, Schubert-Fritschle G, et al. Epidemiologie kolorektaler Karzinome. *Tumor Diagnostik & Therapie* 2011; 32(03): 136-140.

Klein O, Ribas A, Chmielowski B, et al. Facial palsy as a side effect of vemurafenib treatment in patients with metastatic melanoma. *J Clin Oncol* 2013;31:e215-7

Kopetz S, Yoshino T, Van Cutsem E, et al. Encorafenib, cetuximab and chemotherapy in BRAF-mutant colorectal cancer: a randomized phase 3 trial. *Nat Med* 31, 901–908 (2025)

Kris MG, Johnson BE, Berry LD, Kwiatkowski DJ, Iafrate AJ, Wistuba II, et al. Using Multiplexed Assays of Oncogenic Drivers in Lung Cancers to Select Targeted Drugs. *Jama* (2014) 311:1998–2006. doi: 10.1001/jama.2014.3741.

Larkin J, Del Vecchio M, Ascierto PA, et al. Vemurafenib in patients with BRAF(V600) mutated metastatic melanoma: an open-label, multicentre, safety study. *Lancet Oncol* 15(4):436-444, 2014.

Leonetti A, Facchinetti F, Rossib G, et al. BRAF in non-small cell lung cancer (NSCLC): Pickaxing another brick in the wall. *Cancer Treat Rev.* 2018;66:82-94.

Li H, Pedersen L, Norgaard M, et al. The occurrence of non-melanoma malignant skin lesions and non-cutaneous squamous-cell carcinoma among metastatic melanoma patients: an observational cohort study in Denmark. *BMC Cancer* 2016;16:295.



Li S, Li L, Zhu Y, et al. Coexistence of EGFR with KRAS, or BRAF, or PIK3CA somatic mutations in lung cancer: a comprehensive mutation profiling from 5125 Chinese cohorts. *Br J Cancer*. 2014;110:2812–2820.

Li Y and Li W. BRAF mutation is associated with poor clinicopathological outcomes in colorectal cancer: A meta-analysis. *Saudi J Gastroenterol*. May-Jun 2017;23(3):144-149.

Linden S, Redig J, Banos Hernaez A, Nilsson J, Bartels DB, Justo N. Comorbidities and relevant outcomes, commonly associated with cancer, of patients newly diagnosed with advanced non-small-cell lung cancer in Sweden. *Eur J Cancer Care (Engl)*. 2020 Jan;29(1):e13171. doi: 10.1111/ecc.13171. Epub 2019 Oct 2. PMID: 31578054.

Liu W, Kelly JW, Trivett M, et al. Distinct clinical and pathological features are associated with the BRAF T1799A(V600E) mutation in primary melanoma. *Journal of Investigative Dermatology* 2007;127(4):900-905.

Livingstone E, Zimmer L, Vaubel J, et al. BRAF, MEK and KIT inhibitors for melanoma: adverse events and their management. *Chinese Clinical Oncology* 2014;3(3):29.

Lyons T, O'Brien O, Murphy S, et al. A screening test for BRAF mutant melanoma: Immunohistochemical (IHC) analysis of BRAF V600E mutation. *Journal of Clinical Oncology* 2016;34(Suppl):e21076.

Malhotra J, Malvezzi M, Negri E, La Vecchia C, Boffetta P. Risk factors for lung cancer worldwide. *European Respiratory Journal* Sep 2016, 48 (3) 889-902.

Malvezzi M, C. Santucci, P. Boffetta, G. Collatuzzo, F. Levi. European cancer mortality predictions for the year 2023 with focus on lung cancer. *Annals of oncology*, March 05, 2023.

Mantke R, Schmidt U, Wolff S, et al. Incidence of synchronous liver metastases in patients with colorectal cancer in relationship to clinico-pathologic characteristics. Results of a German prospective multicentre observational study. *Eur J Surg Oncol*. Mar 2012;38(3):259-265.

Marchetti A, Felicioni L, Malatesta S, et al. Clinical Features and Outcome of Patients With Non-Small-Cell Lung Cancer Harboring BRAF Mutations. *Clin Oncol* 2011; 29 (26): 3574-3579.

Maringe C, Walters S, Rachet B, et al. Stage at diagnosis and colorectal cancer survival in six high-income countries: a population-based study of patients diagnosed during 2000–2007. *Acta Oncol*. Jun 2013;52(5):919-932.

Mascarucci M, Bruni F, Maio M, et al. Acute heart failure due to reversible cardiomyopathy in patient under b-raf inhibitor for metastatic melanoma. *European Journal of Heart Failure* 2016;18(Suppl1):1858.

Mattei PL, Alora-Palli MB, Kraft S, et al. Cutaneous effects of BRAF inhibitor therapy: a case series. *Ann Oncol*. 2013 Feb;24(2):530-7.

Mazieres J, Drilon A, Lusque A. et al. Immune checkpoint inhibitors for patients with advanced lung cancer and oncogenic driver alterations: results from the IMMUNOTARGET registry. *Ann Oncol*. 2019; 30: 1321-1328.

McCarthy W, Meza R, Jeon J, Moolgavkar S. Chapter 6: Lung cancer in never smokers: epidemiology and risk prediction models. *Risk Anal* 2012; 32(Suppl 1): S69.

McDevitt J, Comber H and Walsh PM. Colorectal cancer incidence and survival by sub-site and stage of diagnosis: a population-based study at the advent of national screening. *Ir J Med Sci*. Feb 2017;186(1):113-121.

McPhail S, Johnson S, Greenberg D, et al. Stage at diagnosis and early mortality from cancer in England. *Br J Cancer*. Mar 31 2015;112 Suppl 1:S108-115.

Meckbach D, Keim U, Richter S, et al. BRAF-V600 mutations have no prognostic impact in stage IV melanoma patients treated with monotherapy. *PLoS ONE* 2014;9(2):e89218.

Menzies AM, Long GV and Murali R. Dabrafenib and its potential for the treatment of metastatic melanoma. *Drug Des Devel Ther*. 2012; 6: 391–405.



Meyer N, Anne-Benedicte DM, Dreno B, et al. Cobimetinib plus vemurafenib to treat unresectable or metastatic melanoma: Data from the French temporary authorization for use. *Annals of Oncology*. Conference: 41st European Society for Medical Oncology Congress, ESMO 2016;27(no pagination).

Meza R., Meernik C., Jeon J., Cote M.L. Lung cancer incidence trends by gender, race and histology in the United States, 1973-2010. *PLoS ONE*. 2015;10:e0121323. doi: 10.1371/journal.pone.0121323.

Minicozzi Pamela et al. Is low survival for cancer in Eastern Europe due principally to late stage at diagnosis? *European Journal of Cancer*, 2018. Volume 93, 127 - 137.

Mittapalli RK, Vaidhyanathan S, Dudek AZ, Elmquist WF. Mechanisms limiting distribution of the threonine-protein kinase B-RaF(V600E) inhibitor dabrafenib to the brain: implications for the treatment of melanoma brain metastases. *J Pharmacol Exp Ther*. 2013 Mar;344(3):655-64.

Molina JR, Yang P, Cassivi SD, Schild SE, Adjei AA. Non-small cell lung cancer: epidemiology, risk factors, treatment, and survivorship. *Mayo Clin Proc*. 2008 May;83(5):584-94. doi: 10.4065/83.5.584. PMID: 18452692; PMCID: PMC2718421.

Moreau S, Saiag P, Aegerter P, et al. Prognostic value of BRAF(V600) mutations in melanoma patients after resection of metastatic lymph nodes. *Annals of Surgical Oncology* 2012;19(13):4314-21.

Moreira L, Munoz J, Cuatrecasas M, et al. Prevalence of somatic mutl homolog 1 promoter hypermethylation in Lynch syndrome colorectal cancer. *Cancer*. May 1 2015;121(9):1395-1404.

Muluneh B, Buie LW and Collichio F. Vemurafenib-associated pancreatitis: Case report. *Pharmacotherapy* 2013; 33:43-44.

Nardin C, Puzenat E, Pretet JL, et al. BRAF mutation screening in melanoma: is sentinel lymph node reliable? *Melanoma Research* 2015;25(4):328-34.

National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®): Colon cancer, Version 2.2021.

NCCN. Non-Small Cell Lung Cancer, Version 3. 2023, NCCN Clinical Practice Guidelines in Oncology. Journal of the National Comprehensive Cancer Network (jncn.org).

Nebot N, Arkenau HT, Infante JR, et al. Evaluation of the effect of dabrafenib and metabolites on QTc interval in patients with BRAF V600-mutant tumours. *Br J Clin Pharmacol*. 2018 Apr;84(4):764-775.

Negru S, Papadopoulou E, Apessos A, et al. KRAS, NRAS and BRAF mutations in Greek and Romanian patients with colorectal cancer: a cohort study. *BMJ Open*. May 23 2014;4(5):e004652.

Ngo P, Bycroft R. Encorafenib and binimetinib for the treatment of BRAF-mutated metastatic melanoma in the setting of combined hepatic and renal impairment. *BMJ Case Reports CP* 2019;12:e230974.

Novello S, Stabile L, Siegfried J. Gender-related Differences in Lung Cancer. The IASLC Multidisciplinary Approach to Thoracic Oncology. Aurora, CO: IASLC Press 2014.

O'Leary CG, Andelkovic V, Ladwa R, Pavlakis N, et al. Targeting BRAF mutations in non-small cell lung cancer. *Transl Lung Cancer Res* 2019;8(6):1119-1.

Oberholzer PA, Kee D, Dziunycz P, et al. RAS Mutations Are Associated With the Development of Cutaneous Squamous Cell Tumors in Patients Treated With RAF Inhibitors. *J Clin Oncol*. 2012 Jan 20;30(3):316-21.

Ocvirk J, Boc M, Mesti T, et al. Treatment with vemurafenib in patients with metastatic melanoma. *Journal of Clinical Oncology*. Conference 2016;34(no pagination).

Ole Raaschou-Nielsen, Air pollution and lung cancer incidence in 17 European cohorts: prospective analyses from the European Study of Cohorts for Air Pollution Effects (ESCAPE), *The Lancet Oncology*, Volume 14, Issue 9, 2013, Pages 813-822, ISSN 1470-2045,

Ortega-Ortega M, Hanly P, Pearce A et al. Projected Impact on Labour Productivity Costs of Cancer Related Premature Mortality in Europe 2018-2040. *Applied Health Economics and Health Policy*; Published: 08 August 2023; Volume 21, pages 877-889, (2023)



Paik PK, Arcila ME, Fara M, Sima CS, Miller VA, Kris MG, Ladanyi M, Riely GJ. Clinical characteristics of patients with lung adenocarcinomas harboring BRAF mutations. *J Clin Oncol.* 2011 May 20;29(15):2046-51. doi: 10.1200/JCO.2010.33.1280.

Peeters M, Siena S, Van Cutsem E, et al. Association of progression-free survival, overall survival, and patient-reported outcomes by skin toxicity and KRAS status in patients receiving panitumumab monotherapy. *Cancer.* Apr 1 2009;115(7):1544-1554.

Peeters M, Price TJ, Cervantes A, et al. Randomized phase III study of panitumumab with fluorouracil, leucovorin, and irinotecan (FOLFIRI) compared with FOLFIRI alone as second-line treatment in patients with metastatic colorectal cancer. *J Clin Oncol.* 2010 Nov 1;28(31):4706-13.

Perrone F, Mazzaschi G, Minari R. Multicenter Observational Study on Metastatic Non-Small Cell Lung Cancer Harboring BRAF Mutations: Focus on Clinical Characteristics and Treatment Outcome of V600E and Non-V600E Subgroups. *Cancers (Basel).* 2022 Apr 16;14(8):2019. doi: 10.3390/cancers14082019.

Picard M, Pham Dang N, D'Incan M, et al. Is BRAF a prognostic factor in stage III skin melanoma? A retrospective study of 72 patients after positive sentinel lymph node dissection. *British Journal of Dermatology* 2014;171(1):108-14.

Planchard D., Kim T.M., Mazieres J., et al. Dabrafenib in patients with BRAF(V600E)-positive advanced non-small-cell lung cancer: a single-arm, multicentre, open-label, phase 2 trial. *Lancet Oncol.* 2016; 17: 642-650.

Planchard D, Smit EF, Groen HJM et al. Dabrafenib plus trametinib in patients with previously untreated BRAFV600E-mutant metastatic non-small-cell lung cancer: an open-label, phase 2 trial *Lancet Oncol* 2017;18(10):1307-16.

Planchard D, Johnson BE. BRAF Adds an Additional Piece of the Puzzle to Precision Oncology-Based Treatment Strategies in Lung Cancer. *Arch Pathol Lab Med* (2018) 142:796–7. Doi: 10.5858/arpa.2018-0088-ED.

Planchard D, Besse B, Groen HJM, Hashemi SMS, Mazieres J, Kim TM, Quoix E, Souquet PJ, Barlesi F, Baik C, Villaruz LC, Kelly RJ, Zhang S, Tan M, Gasal E, Santarpia L, Johnson BE. Phase 2 Study of Dabrafenib Plus Trametinib in Patients With BRAF V600E-Mutant Metastatic NSCLC: Updated 5-Year Survival Rates and Genomic Analysis. *J Thorac Oncol.* 2022 Jan;17(1):103-115. doi: 10.1016/j.jtho.2021.08.011.

Prasanna T, Karapetis CS, Roder D, et al. The survival outcome of patients with metastatic colorectal cancer based on the site of metastases and the impact of molecular markers and site of primary cancer on metastatic pattern. *Acta Oncol.* Nov 2018;57(11):1438-1444.

Price TJ, Beeke C, Townsend AR, et al. BRAF Mutation Testing and Metastatic Colorectal Cancer in the Community Setting: Is There an Urgent Need for More Education? *Mol Diagn Ther.* Feb 2016a;20(1):75-82.

Price T, Kim TW, Li J, et al. Final results and outcomes by prior bevacizumab exposure, skin toxicity, and hypomagnesaemia from ASPECCT: randomized phase 3 non-inferiority study of panitumumab versus cetuximab in chemorefractory wild-type KRAS exon 2 metastatic colorectal cancer. *Eur J Cancer.* 2016b Nov;68:51-59.

Provencio M, Cobo M, Rodriguez-Abreu D, Calvo V, et al. Determination of essential biomarkers in lung cancer: a real-world data study in Spain with demographic, clinical, epidemiological and pathological characteristics. *BMC Cancer.* 2022 Jul 5;22(1):732.

Rajagopalan H, Bardelli A, Lengauer C, et al. Tumorigenesis: RAF/RAS oncogenes and mismatch-repair status. *Nature.* 2002 Aug 29;418(6901):934.

Robert C, Arnault JP and Mateus C. RAF inhibition and induction of cutaneous squamous cell carcinoma. *Curr Opin Oncol.* 2011 Mar;23(2):177-82.

Rutkowski P, Gos A, Jurkowska M, et al. Molecular alterations in clinical stage III cutaneous melanoma: Correlation with clinicopathological features and patient outcome. *Oncology Letters* 2014;8(1):47-54.



- Samet JM, Avila-Tang E, Boffetta P, Hannan LM, Olivo-Marston S, Thun MJ, Rudin CM. Lung cancer in never smokers: clinical epidemiology and environmental risk factors. Clin Cancer Res. 2009 Sep 15;15(18):5626-45. doi: 10.1158/1078-0432.CCR-09-0376.
- Sant M Patterns of care and survival for lung cancer: Results of the European population-based high-resolution study frontiers in Epidemiology; Vol3 2023
- Schlaak M, Bajah A, Podewski T, et al. Assessment of clinical parameters associated with mutational status in metastatic malignant melanoma: a single-centre investigation of 141 patients. British Journal of Dermatology 2013;168(4):708-16.
- Schnoor M, Waldmann A, Eberle A, et al. Colorectal cancer incidence in Germany: stage-shift 6 years after implementation of a colonoscopy screening program. Cancer Epidemiol. Oct 2012;36(5):417-420.
- Sengupta N, Yau C, Sakthianandeswaren A, et al. Analysis of colorectal cancers in British Bangladeshi identifies early onset, frequent mucinous histotype and a high prevalence of RBFOX1 deletion. Mol Cancer. Jan 3 2013;12:1.
- Seppala TT, Bohm JP, Friman M, et al. Combination of microsatellite instability and BRAF mutation status for subtyping colorectal cancer. Br J Cancer. Jun 9 2015;112(12):1966-1975.
- Setteyova L, Bacharova L and Mladosičevićová B. QT prolongation due to targeted anticancer therapy. OncoReview. 2016;6(3):A103-112.
- Shailesh F, Singh M, Tiwari U, et al. Vemurafenib-induced bilateral facial palsy. J Postgrad Med 2014;60:187-8.
- Sinha R, Edmonds K, Newton-Bishop JA, et al. Cutaneous adverse events associated with vemurafenib in patients with metastatic melanoma: practical advice on diagnosis, prevention and management of the main treatment-related skin toxicities. The British Journal of Dermatology 2012;167(5):987-94.
- Smeby J, Sveen A, Merok MA, et al. CMS-dependent prognostic impact of KRAS and BRAFV600E mutations in primary colorectal cancer. Ann Oncol. May 1 2018;29(5):1227-1234.
- Sorbye H, Dragomir A, Sundstrom M, et al. High BRAF Mutation Frequency and Marked Survival Differences in Subgroups According to KRAS/BRAF Mutation Status and Tumor Tissue Availability in a Prospective Population-Based Metastatic Colorectal Cancer Cohort. PLoS One. 2015;10(6):e0131046.
- Sosman JA., Kim KB, Schuchter L, et al. Survival in BRAF V600-Mutant Advanced Melanoma Treated with Vemurafenib. N Engl J Med. 2012 Feb 23; 366(8): 707-714.
- Stayner L, Bena J, Sasco AJ, et al. Lung cancer risk and workplace exposure to environmental tobacco smoke. Am J Public Health 2007; 97: 545.
- Steglich RB, Coelho KMPA, Cardoso S, et al. Epidemiological and histopathological aspects of primary cutaneous melanoma in residents of Joinville, 2003-2014. An Bras Dermatol.2018 Jan-Feb;93(1):45-53.
- Stintzing S, Heinrich K, Tougeron D et al. FOLFOXIRI Plus Cetuximab or Bevacizumab as First-Line Treatment of BRAFV600E-Mutant Metastatic Colorectal Cancer: The Randomized Phase II FIRE-4.5 (AIO KRK0116) Study J Clin Oncol. 2023 Sep 1;41(25):4143-4153.
- Strassburg CP. Pharmacogenetics of Gilbert's syndrome. Pharmacogenomics. 2008 Jun;9(6):703-15.
- Su F, Viros A, Milagre C, et al. RAS Mutations in Cutaneous Squamous-Cell Carcinomas in Patients Treated with BRAF Inhibitors. N Engl J Med. 2012 Jan 19; 366(3): 207-215.
- Subbiah V, Gervais R, Riely G, et al. Efficacy of vemurafenib in patients with non-small-cell lung cancer with BRAF V600 mutation: an open-label, single-arm cohort of the histology-independent VE-BASKET study. JCO Precis Oncol. 2019; 3 (PO.18.00266).
- Summary of Product Characteristics Braftovi® (encorafenib). European Medicines Agency. Available at: https://www.ema.europa.eu/en/documents/product-information/braftovi-epar-product-information_en.pdf. Last accessed September 2023.



Summary of Product Characteristics Cotellic® (cobimetinib). European Medicines Agency. Available at: https://www.ema.europa.eu/en/documents/product-information/cotellic-epar-product-information_en.pdf. Last accessed September 2019.

Summary of Product Characteristics Erbitux® (cetuximab). European Medicines Agency. Available at: https://www.ema.europa.eu/en/documents/product-information/erbitux-epar-product-information_en.pdf. Last accessed September 2019.

Summary of Product Characteristics Mekinist® (trametinib). European Medicines Agency. Available at: https://www.ema.europa.eu/en/documents/product-information/mekinist-epar-product-information_en.pdf. Last accessed September 2019.

Summary of Product Characteristics Tafinlar® (dabrafenib). European Medicines Agency. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_Product_Information/human/002604/WC500149671.pdf; Last accessed September 2019.

Summary of Product Characteristics Zelboraf® (vemurafenib). European Medicines Agency. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_Product_Information/human/002409/WC500124317.pdf; Last accessed September 2019.

Summary of Product Characteristics Tafinlar® (dabrafenib). European Medicines Agency. Available at: [tafinlar-epar-product-information_en.pdf \(europa.eu\)](https://www.ema.europa.eu/en/documents/product-information/tafinlar-epar-product-information_en.pdf). Last accessed September 2023.

Summary of Product Characteristics Mekinist® (trametinib). European Medicines Agency. Available at: https://www.ema.europa.eu/en/documents/product-information/mekinist-epar-product-information_en.pdf. Last accessed September 2023.

Sung H, Ferlay J, Siegel RL, et al. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2021;71(3):209–249.

Suter TM and Ewer MS. Cancer drugs and the heart: importance and management. European Heart Journal 2013;34(15):1102-11.

Tabbò F, Pisano C, Mazieres J, Mezquita L, Nadal E et al. How far we have come targeting BRAF-mutant non-small cell lung cancer (NSCLC) Cancer Treatment Reviews 103 (2022) 102335.

Takano M and Sugiyama T. UGT1A1 polymorphisms in cancer: impact on irinotecan treatment. Pharmgenomics Pers Med. 2017 Feb 28;10:61-68.

Tabernero J, Rose J, Elez E. The Evolving Treatment Landscape in BRAFV600E- Mutated Metastatic Colorectal Cancer. Am Soc Clin Oncol Educ Book 42, 254-263(2022).

Thiebault Q, Defossez G, Karayan-Tapon L, et al. Analysis of factors influencing molecular testing at diagnostic of colorectal cancer. BMC Cancer. Nov 14 2017;17(1):765.

Thiel A, Heinonen M, Kantonen J, et al. BRAF mutation in sporadic colorectal cancer and Lynch syndrome. Virchows Arch. Nov 2013;463(5):613-621.

Thomas NE, Edmiston SN, Alexander A, et al. Number of nevi and early-life ambient UV exposure are associated with BRAF-mutant melanoma. Cancer Epidemiol Biomarkers Prev 2007;16(5):991-7.

Tie J, Lipton L, Desai J, et al. KRAS mutation is associated with lung metastasis in patients with curatively resected colorectal cancer. Clin Cancer Res. 2011b Mar 1;17(5):1122-1130.

Trakatelli M, Morton C, Nagore E, et al. Update of the European guidelines for basal cell carcinoma management. European Journal of Dermatology 2014;24(3):312-29.

Toh CK, Gao F, Lim WT et al. Never-smokers with lung cancer: epidemiologic evidence of a distinct disease entity. J Clin. Oncol 2006; 24: 2245–2251.

Tran B, Kopetz S, Tie J, et al. Impact of BRAF mutation and microsatellite instability on the pattern of metastatic spread and prognosis in metastatic colorectal cancer. Cancer. 2011 Oct 15;117(20):4623-4632.



Travis WD, Brambilla E, Nicholson AG, et al. The 2015 World Health Organization Classification of Lung Tumors: Impact of Genetic, Clinical and Radiologic Advances Since the 2004 Classification. *J Thorac Oncol*. 2015 Sep;10(9):1243-1260.

Troiani T, Napolitano S and Normanno, N. BRAF in Colorectal Cancer: ESMO Biomarker Factsheet. <https://oncologypro.esmo.org/Education-Library/Factsheets-on-Biomarkers/BRAF-in-Colorectal-Cancer>. Last update: 08 September 2016. Last accessed September 2019.

Udomuksorn W, Elliot DJ, Lewis BC, et al. Influence of mutations associated with Gilbert and Crigler-Najjar type II syndromes on the glucuronidation kinetics of bilirubin and other UDP-glucuronosyltransferase 1A substrates. *Pharmacogenet Genomics*. 2007;17(12):1017-1029.

Ursem C, Atreya CE and Van Loon K. Emerging treatment options for BRAF-mutant colorectal cancer. *Gastrointest Cancer*. 2018;8:13-23.

Uvirova M, Simova J, Kubova B, et al. Comparison of the prevalence of KRAS-LCS6 polymorphism (rs61764370) within different tumour types (colorectal, breast, non-small cell lung cancer and brain tumours). A study of the Czech population. *Biomed Pap Med Fac Univ Palacky Olomouc Czech Repub*. Sep 2015;159(3):466-471.

Van Cutsem E, Cervantes A, Nordlinger B, et al. Metastatic colorectal cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol*. 2014 Sep;25 Suppl 3:iii1-9.

Van Cutsem E, Huijberts S, Grothey A, et al. Binimetinib, Encorafenib, and Cetuximab Triplet Therapy for Patients With BRAF V600E-Mutant Metastatic Colorectal Cancer: Safety Lead-In Results From the Phase III BEACON Colorectal Cancer Study. *J Clin Oncol*. 2019 Jun 10;37(17):1460-1469.

van der Geest LG, Lam-Boer J, Koopman M, et al. Nationwide trends in incidence, treatment and survival of colorectal cancer patients with synchronous metastases. *Clin Exp Metastasis*. 2015 Jun;32(5):457-465.

VCR (Victorian Cancer Registry) (2023) Cancer in Victoria- external site opens in new window, Cancer Council Victoria, accessed 31 January 2024.

Villaruz LC, Socinski MA, Abberbock S, et al. Clinicopathologic features and outcomes of patients with lung adenocarcinomas harboring BRAF mutations in the Lung Cancer Mutation Consortium. *Cancer*. 2015 February 1; 121(3): 448-456.

Vogel, A. & Kirstein, M. First-line molecular therapies in the treatment of metastatic colorectal cancer – a literature-based review of phases II and III trials. *Innovative Surgical Sciences* 3, no 2 (27 juin 2018): 85-86

Walters S, Maringe C, Coleman MP, et al. Lung cancer survival and stage at diagnosis in Australia, Canada, Denmark, Norway, Sweden and the UK: a population-based study, 2004-2007. *Thorax*. 2013;68(6):551-564., 2013.

Welsh SJ and Corrie PG. Management of BRAF and MEK inhibitor toxicities in patients with metastatic melanoma. *Therapeutic Advances in Medical Oncology* 2015;7(2):122-36.

White A, Ironmonger L, Steele RJC, et al. A review of sex-related differences in colorectal cancer incidence, screening uptake, routes to diagnosis, cancer stage and survival in the UK. *BMC Cancer*. 2018 Sep 20;18(1):906.

Whiteman D and Green A. Epidemiology of Malignant Melanoma. In: Dummer R, Pittelkow MR, Iwatsuki K, Green A, Elwan NM, eds. *Skin Cancer - A World-Wide Perspective*. Berlin: Springer-Verlag, 2011:13-26.

Wisinski KB, Cantu CA, Eickhoff J, et al. Potential cytochrome P-450 drug-drug interactions in adults with metastatic solid tumors and effect on eligibility for Phase I clinical trials. *American Journal of Health-System Pharmacy* 2015;72(11):958-65.

Wisler JA, Afshari C, Fielden M, et al. RAF inhibition causes extensive multiple tissue hyperplasia and urinary bladder neoplasia in the rat. *Toxicol Pathol* 2011;39:809-22



Wu JH, Cohen DN, Rady PL, et al. BRAF inhibitor-associated cutaneous squamous cell carcinoma: new mechanistic insight, emerging evidence for viral involvement and perspectives on clinical management. *Br J Dermatol*. 2017 Oct;177(4):914-923.

Yan N, Guo S, Zhang H, Zhang Z, Shen S, Li X. BRAF-Mutated Non-Small Cell Lung Cancer: Current Treatment Status and Future Perspective. *Front Oncol*. 2022 Mar 31;12:863043. doi: 10.3389/fonc.2022.863043. PMID: 35433454; PMCID: PMC9008712.

Yeh I, von Deimling A, Bastian BCYeh. Clonal BRAF Mutations in Melanocytic Nevi and Initiating Role of BRAF in Melanocytic Neoplasia. *J Natl Cancer Inst*;2013;105:917-919.

Zheng G, Tseng L-H, Chen G, et al. Clinical detection and categorization of uncommon and concomitant mutations involving BRAF. *BMC Cancer*. 2015;15:779.