Title:

MULTICENTRE PHASE II CLINICAL TRIAL TO EVALUATE THE ACTIVITY OF ENCORAFENIB AND BINIMETINIB BEFORE LOCAL TREATMENT IN PATIENTS WITH BRAF MUTATED MELANOMA WITH METASTASIS TO THE BRAIN.

Protocol Number:

GEM-1802

EudraCT:

2018-002530-20

Acronym:

EBRAIN-MEL

Sponsor:

Grupo Español Multidisciplinar de Melanoma - GEM

MULTIDISCIPLINARY SPANISH MELANOMA RESEARCH GROUP

Scientific Coordinators:

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Sponsor Signature Page

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EudraCT Number: 2018-002530-20

Version number and date: 5.0 4JUL2022

I have received and read the Investigator's Brochure for encorafenib and binimetinib. I have read the GEM-1802 protocol and agree to conduct the study as outlined. I agree to maintain the confidentiality of all information received or developed in connection with this protocol and I agree to conduct this trial in accordance with all provisions of the protocol, GCPs and the Declaration of Helsinki.

Sponsor's signature **Signature date**

Scientific coordinator's signature **Signature date**

Investigator's Agreement

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Investigator Printed Name

_____

Investigator Signature

_____

Date

1. SYNOPSIS

<table>
<tr><td colspan="2">Sponsor: Grupo Español Multidisciplinar en Melanoma - GEM</td></tr>
<tr><td colspan="2">Investigational Products: Encorafenib and binimetinib</td></tr>
<tr><td colspan="2">Active Ingredients: Encorafenib and binimetinib</td></tr>
<tr><td colspan="2">Title of Study: Phase II, multicentre clinical trial to evaluate the activity of encorafenib and binimetinib administered before local treatment in patients with BRAF mutant melanoma metastatic to the brain.

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EudraCT: 2018-002530-20</td></tr>
<tr><td colspan="2">Study center(s): 21 sites in Spain. In attached document</td></tr>
<tr><td colspan="2">Coordinating Investigators:

Dr. Iván Márquez Rodas - Hospital General Universitario Gregorio Marañón, Madrid.

Dr. Alfonso Berrocal Jaime - Hospital General Universitario de Valencia, Valencia.

Principal Investigators: In attached document</td></tr>
<tr><td>Studied period (years):

Estimated date first patient enrolled: 3Q 2019 (19.JUL.2019)

Estimated end of enrolment: 3Q 2022

Estimated date last patient completed: 3Q 2024</td><td>Phase of development:

II</td></tr>
<tr><td colspan="2">Objectives:

1. Primary objective:

Intracranial objective response rate assessed by the investigators using modified RECIST criteria before local treatment in cohort 1 and in cohort 2.

2. Secondary objectives:</td></tr>
</table>

*a.*Intracranial objective response rate assessed by the investigators using modified RECIST criteria. before local treatment in cohort 2.

b. Intracranial objective response rate assessed by the investigators using modified RECIST criteria. before local treatment in cohort 1.

c.The duration of the intracranial response in both cohorts assessed by the investigators using modified RECIST criteria.

d. The intracranial progression free survival assessed by the investigators using modified RECIST criteria in both cohorts.

e. Percentage of patients free of intracranial progression according to modified RECIST criteria at 6 (week 24), 12 (week 48) and 24 months (week 96) in both cohorts

f. Percentage of patients free of extracraneal progression according to RECIST criteria at 6 (week 24), 12 (week 48) and 24 months (week 96) in both cohorts

g. Overall survival in both cohorts

h.Percentage of alive patients at 6, 12 and 24 months in both cohorts

i. Toxicity of the combination until local treatment in both cohorts

I.Toxicity of the combination after local treatment in both cohorts

II. Quality of life in both cohorts

Methodology:

This is a phase II clinical trial, with two cohorts of patients included in parallel, all with melanoma BRAF mutated and brain metastases without previous local treatment in the brain. Cohort 1 will include patients with asymptomatic brain metastases and cohort 2 will include patients with symptomatic brain metastasis.

BRAF mutation status will be tested locally using a validated test before patient inclusion, patients will receive both encorafenib 450 mg/day and binimetinib 45 mg/12 h (twice a day) (COMBO450) until progression disease (PD), toxicity or death. After 56 days of treatment, a contrast enhanced brain MRI and body CT scan will be performed as the first tumour assessment. Depending on the outcome of this image test, patients undergo local radiation treatment (radiosurgery or whole brain radiotherapy (WBRT) as per local radiotherapy oncologist. Encorafenib and binimetinib will be interrupted 24h before radiotherapy and restart 24h after the last dose of radiotherapy. After local treatment encorafenib and binimetinib will be administered at same doses until PD, toxicity or death. After progression, patients will be followed only for overall survival. In the case of COMBO450 is providing a clinical benefit to any patient, treatment could be continued, after agreement with Sponsor.

This study will be carried out following good clinical practices (GCP) guidelines as per European and Spanish regulations for clinical investigations.

Number of patients (planned): At least 63 patients.

Cohort 1: N=48; Cohort 2: N=15.

Main eligibility criteria:

- Patients 18 years old
- Patients with a metastatic BRAF V600 mutated melanoma
- ECOG 0-1 in asymptomatic patients (cohort 1), 0-2 in symptomatic patients (cohort 2)
- Previous administration of BRAF and/or MEK inhibitors in the metastatic setting is not allowed. These treatments would be allowed if they were administered in the adjuvant setting, providing relapse does not occur on treatment or within 12 months of ending adjuvant treatment and/or during adjuvant treatment, moreover, any grade 3-4 prior toxicity must be resolved to grade 0 or at baseline levels.
- Previous immunotherapy treatments are allowed in any metastatic and adjuvant setting, regardless of when the patient has relapsed.
- At least one brain metastasis with 5 to 50 mm, measured by MRI
- Steroids or anticonvulsants are allowed if clinically needed and are not being administered in an increasing dose

Full list of eligibility criteria is detailed in section 6 of this protocol

Investigational products, dosage and mode of administration:

COMBO450:

- Encorafenib - Orally, 75 mg and 50 mg capsules
- Binimetinib - Orally, 15 mg tablets

In each cohort, patients will be treated with encorafenib 450 mg once daily and binimetinib (Bini) 45 mg twice daily until PD or death.

Duration of treatment:

All patients receiving COMBO450 for at least 56 days of treatment, will be evaluated with a contrast enhanced brain MRI and CT body scan, as the first tumour assessment:

- Patients with PD at first evaluation in brain MRI (per RECIST modified criteria) and /or body CT scan (per RECIST 1.1 criteria) will discontinue study drugs and will be followed for overall survival.

- Patients with intracranial complete response (CR) and no systemic PD, will be followed every two months with brain MRI and body CT scan up to 12 months. If no PD after one year, patients will be followed as per institutional criteria, and continue with the study treatment
    - Whenever is considered by the investigator, local treatment can be administered to patients with an intracranial CR.
- Patients with no CR nor PD in brain MRI per modified RECIST 1.1 criteria, and no systemic PD per RECIST 1.1, will be treated with local radiotherapy (RT) (radiosurgery or WBRT), and then they will continue COMBO 450. The first 3 patients with indication to be treated with radiotherapy will be treated in an initial running phase. These three first patients are going to be treated sequentially or at the same time depending on when radiotherapy treatment is needed. If no safety concerns appear, the rest of the patients will continue receiving local treatment when it will be medically indicated:
    - Encorafenib and binimetinib will be interrupted 24h before radiotherapy and restart 24h after the last dose of radiotherapy. The local radiation technique will be defined and indicated by the radiotherapy oncologist (local co-investigator) following the criteria defined below, regarding how to treat patients with the different techniques depending on the number of lesions and its maximum size in the last tumour assessment done during the treatment with encorafenib and binimetinib:
        - *Radiosurgery (RS) or Stereotactic radiosurgery (SRS):
            - 1 brain metastases < 4 cm
            - ≤ 3 brain metastases ≤ 3 cm
            - ≤ 4 brain metastases ≤ 2.5 cm
        - Whole brain radiotherapy (WBRT):
            - ≥ 4 brain metastases
            - Almost one brain metastasis of ≥ 4 cm
            - ≤ 4 brain metastases not eligible for RS or SRS
            - Metastases located at brain stem, midbrain, pons, and medulla or within 10 mm of the optic nerves and chiasm.

*Radiosurgery: for patients who do not meet criteria for radiosurgery (RS) or (SRS), exceptional cases are allowed after prior detailed consultation with the trial coordinators.

- After the first evaluation of the patient's intracranial response, patients without progression who received a local treatment, could receive other local treatments at the discretion of the investigator, if this is considered beneficial for the patient.
- Surgery can be done if, as per investigator criteria, is necessary for the patient's health.
- Patients with an intracranial CR not treated with radiation, if during follow up an only intracranial PD occurs, local treatment will be carried out as per protocol criteria. These patients can continue encorafenib and binimetinib treatment after local treatment if clinical benefit is considered by investigator.
- All patients progressing by RECIST 1.1 criteria in body CT scan and/or by modified RECIST 1.1. criteria in contrast enhanced brain MRI, **after having received local radiation therapy** will discontinue systemic treatment with COMBO 450.

Criteria for evaluation:

Efficacy assessment will be performed according to modified RECIST 1.1 criteria by contrast enhanced MRI for evaluating intracranial disease and according to RECIST 1.1 criteria by CT scan (PET-CT is also allowed) for evaluating systemic disease, every 8 weeks (+/-1 week) up to 12 months. If no PD during the first year, patients will be followed as per institutional criteria. Image technique should be consistent throughout the study. If no PD is observed after one year of follow up, patients will be followed as per institutional criteria, maintaining the treatment when clinical benefit is observed.

Pharmacokinetics:

No pharmacokinetic study will be performed.

Safety:

Assessment of adverse events, safety, and toxicity will be performed according to the Common Terminology Criteria for Adverse Events (CTCAE - version 4.03) at each patient visit from the time of Informed Consent is signed until the end of the study.

Quality of Life:

EORTC QLQ 30 administered at baseline, at week 8 and week 24.

Statistical methods:

The sample calculation has been done for the **primary endpoint (cohort 1)** and it's based on a Fleming's Single Stage Procedure:

We want to show that the Intracranial response rate by modified RECIST 1.1 before local treatment is superior or equal to the reference value, say, $\vartheta 0=40\%$. Under the hypothesis to have a response rate under new treatment ($\pi 1$) of 60% with α risk = 5% in one-sided test and a power of 80%, the required sample size is 38 patients.

Finally, if 20% of patients will be lost of follow up, die or progress before day 56 without doing the first tumour assessment (according data published in COMBI-MB study), the initial sample size will be 48 patients, to obtain 38 evaluable patients.

Data of study will be analysed in the following populations:

- ITT: All patients that has been enrolled in the trial
- Evaluable population (PP): All patients fulfilling all eligibility criteria and having at least two valid tumour assessments (baseline and one evaluation MRI or CT-scan) without any protocol deviation that makes the patient invalid for the primary endpoint evaluation.
- Safety population: All patients receiving at least one dose of treatment.

Cohort 2 (N=15) is exploratory and no formal sample calculation has been performed, a descriptive analysis will be performed on the same variables and population as cohort 1 (N=48). The only difference is that the population included will be symptomatic. The efficacy and safety as an overall of both cohorts in conjunction will be also addressed.

INDEX

List of Abbreviations and Definitions of Terms

The following abbreviations and specialist terms are used in this study protocol.

Abbreviation or Specialist Term	Explanation
ADL	Activities of Daily Living
ADR	Adverse drug reaction
AE	Adverse event
AP	Anatomic pathology
ASCO	American Society of Clinical Oncology
AUC	Area Under Curve
beta-hCG	Beta-human chorionic gonadotropin
BID	bis in die, (Latin for "twice daily")
BRAF	v-raf murine sarcoma viral oncogene homolog B1
CIs	Confidence intervals
CK	Creatine kinase (CK), also known as creatine phosphokinase (CPK) or phosphocreatine kinase
Cmax	Maximum (or peak) serum concentration
COMBO 450	Encorafenib 450 mg once daily and binimetinib 45 mg twice daily
CB	Clinical benefit
CDR	Control disease rate
CR	Complete Response
CSR	Central Serous Retinopathy
CTCAE	Common Terminology Criteria for Adverse Events
CT Scan	Computed Tomography Scan
DBP	Diastolic Blood Pressure
DLT	Dose Limiting Toxicity
DM	Distant metastasis
DR	Duration of response
DVP	Data Validation Plan

ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
ECG	Electrocardiogram
EMA	European Medicines Agency
ESMO	European society of Medical Oncology
FDA	US Food and Drug Administration
FFPE	Formalin-fixed paraffin-embedded
FISH	Fluorescence in situ hybridization
FU	Follow-up
GCP	Good Clinical Practice
Hb	Haemoglobin
H/E	Haematoxylin/eosin
HFSR	Hand Foot Skin Reaction
IB	Investigator Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IFN	Interferon
IMP	Investigational Medicinal Product
IRB	Institutional Review Board
ISF	Investigator Site File
ITT	Intention To Treat
KA	Keratoacanthoma
KPS	Karnofsky Performance Status
LLN	Lower Limit of Normality

LVEF	Left Ventricular Ejection Fraction
LOCF	Last Observation Carried Forward
MAP	Mitogen-Activated Protein
MASCC	Multinational Association of Supportive Care
MDM2	Mouse double minute 2 homolog
MedDRA	Medical Dictionary for Regulatory Activities
MEK	Mitogen-activated protein kinase kinase
MLPA	Multiplex ligation-dependent probe amplification
Modified RECIST	Modified Response Evaluation Criteria In Solid Tumours
MRI	Magnetic Resonance Imaging
MTD	Maximum Tolerated Dose
MUGA	Multigated Acquisition Scan
OAE	Other significant adverse event
ORR	Overall response rate
OS	Overall Survival
OTEL	Open To Enrolment Letter
PCR	Polymerase Chain Reaction
PD	Progression disease
PET-CT	Positron emission tomography–computed tomography
PFS	Progression Free Survival
PI	Principal Investigator
PK	Pharmacokinetics
PLGA	Poly (lactic-co-glycolic acid)
PP	Per Protocol
PR	Partial Response
PRT	Primary retroperitoneal tumours
PS	Performance Status

QD	Quaque die, every day “once daily”
QLQ 30	Quality of Life Questionnaire Core 30
QoL	Quality of Life
RDD	Retinal Degenerative Disease
RECIST	Response Evaluation Criteria In Solid Tumours
REEC	Registro Español de Estudios Clínicos (Spanish Registry of Clinical Studies)
RLS	Retroperitoneal Liposarcoma
RP	Retroperitoneum
RP2D	Recommended Phase II dose
RVO	Retinal Vein Occlusion
Rx	Radiography
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SAR	Serious adverse reaction
SBP	Systolic Blood Pressure
SCC	Squamous Cell Carcinoma
SD	Stable disease
SDV	Source Data Verification
SP	Safety Population
SRS	Stereotactic Radiosurgery
SUSAR	Suspected unexpected serious adverse reaction
Sx	Surgery
Tmax	Time of the sample identified as Cmax
TR	Translational Research
TTLR	Time to Local Relapse
ULN	Upper Limit of Normality
VMAT	Volumetric Modulated Arc Therapy

WBC	White Blood Count
WBRT	Whole Brain Radiotherapy
WHO	World Health Organization

2. INTRODUCTION

2.1. Disease background

Melanoma accounts for 4% of incident cancers and its mortality rate is increasing[1]. Surgical excision remains the treatment of choice for early disease, and adjuvant therapy with interferon alfa has shown benefit in some stage II and III cases[2]. Recently, adjuvant treatment with checkpoint inhibitors[3-6] and targeted therapies (BRAF and MEK inhibitors) have been approved [7-10].

However, advanced melanoma is an aggressive disease for which there are few therapies, and which portends a poor prognosis.

Previously approved drugs like interleukin-2 and dacarbazine in this setting; in clinical trials, each had response rates of 10-20% and neither showed an overall survival benefit [11,12]. More recently, ipilimumab (Yervoy), a fully humanized antibody that binds to cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) and sustains an immune attack on neoplastic cells, was approved by the FDA and EMA for use in the metastatic setting. Approval was based on a randomized study showing that ipilimumab improved survival from 6 months to 10 months compared with an experimental vaccine[13]. This advance promised new effective treatment for what was once a treatment-refractory disease and more research is underway to investigate other molecular pathways that may be targeted in an effort to produce further significant results.

The use of immune checkpoint inhibitors for the treatment of advanced melanoma has evolved beyond monotherapies to combination strategies. This combination approach results in response rates around 60% and superior progression-free survival compared with ipilimumab monotherapy (median 11.5 versus 2.9 months)[14].

2.2. BRAF in Melanoma

One potential advance that showed a lot of promise in the preclinical, and now in the clinical setting, is the targeting of the BRAF kinase in melanoma. Vemurafenib, dabrafenib and encorafenib are BRAF kinase inhibitors available in Europe and the United States. Trametinib, cobimetinib and binimetinib, a mitogen-activated extracellular signal regulated kinase (MEK) inhibitors, are also approved.

The mitogen-activated protein (MAP) kinase pathway is an important driver in melanoma and is made up of several potential targets providing therapeutic options[14]. In this pathway, the activation of RAS proteins stimulates the RAF kinases ARAF, BRAF, and RAF1. This process causes the phosphorylation of the MEK kinases, which phosphorylate the ERK kinases. Activated ERK regulates cyclin D1, which, in turn, regulates multiple cellular processes involved in cell division (see Figure 1).

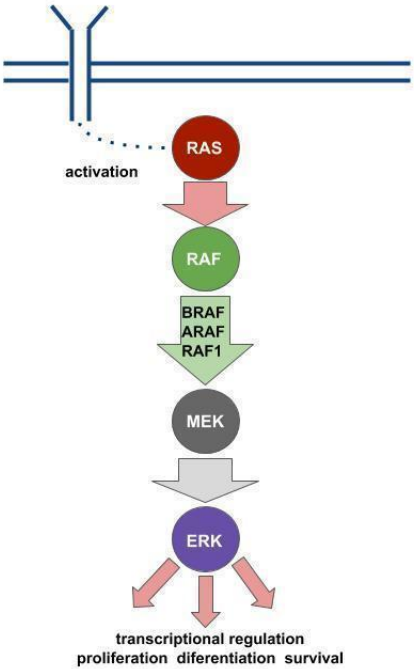


Figure 1. The mitogen-activated protein (MAP) kinase pathway.

Approximately 40-60% of melanomas contain a mutation in the gene that encodes BRAF that leads to constitutive activation of downstream signalling in the MAP kinase pathway. In 80-90% of these cases, the activating mutation consists of the substitution of glutamic acid for valine at amino acid 600 (V600E)[15,16].

BRAF-mutated melanoma tends to exhibit distinctive clinical features and is characterized by more aggressive biological behaviour than BRAF wild-type (WT) melanoma[17]. Compared with patients with BRAF WT melanoma, those with BRAF-mutated melanoma are more often younger and have tumours with superficial spreading or nodular histology and/or in anatomical regions without chronic sun damage[18]. Furthermore, BRAF-mutant tumours are more likely to metastasize to the brain than BRAF WT tumours[19]. BRAF-mutated melanoma has also been linked to shorter overall survival in patients with stage IV cancer than in those with BRAF WT disease[18-20].

2.3. Melanoma with brain metastasis

Brain metastases in patients with advanced and metastatic melanoma are a frequent complication and a significant cause of morbidity and mortality in this patient population. As the incidence of brain metastases continues to increase in patients with metastatic melanoma, it is urgent that we identify effective therapies. During the past decade, management of melanoma has continued to evolve. In the era of whole-exome and next-generation sequencing, there is a requisite role for identification of driver mutations, specifically, BRAF, given the possibility for targeted therapies and the opportunity for improved survival. Moving forward, trials that investigate multimodal treatment regimens—combinations of targeted or immunotherapies with surgery or radiation—will answer additional questions regarding the optimization of management in this growing patient population[21].

Recent data have shown an incidence of brain metastases in ≤ 50% of patients with metastatic melanoma[22]. Because this is typically a late complication of systemic disease, melanoma-related brain metastases have been associated with significant neurologic morbidity and a poor median

overall survival, with treatment, of approximately 9 months[23]. Factors that predict survival include age, performance status, and the number of brain metastases, which are summarized as the melanoma-specific graded prognostic assessment[24].

Table 1. Prognostic groups for outcome after palliative treatment of brain metastases by recursive partitioning analysis[25].

Class	Prognostic Factors	Median survival, months
I	KPS ≥70 percent	7.1
	Age <65 years	
	Controlled primary site	
	No extracranial metastases	
III	KPS <70	2.3
II	All others	4.2

KPS: Karnofsky performance status.

Table 2. Graded prognostic assessment for brain metastases from melanoma[26].

Prognostic factor	Scoring criteria			Median survival (months) by score:
	0	1.0	2.0	
Karnofsky PS	<70	70-80	90-100	0-1.0 = 3.4 1.5-2.0 = 4.7 2.5-3.0 = 8.8 3.5-4.0 = 13.2
Number of brain metastases	>3	2-3	1	

Until recently, management of brain metastases has primarily focused on local, intracranial control of disease. In cases of single metastatic lesions or large, symptomatic lesions in oligometastatic disease, resection is typically advised. For patients with more than a single brain metastasis, radiation therapy, including stereotactic radiosurgery and whole-brain radiation therapy, has been the mainstay of treatment[27]. As long-term data from post–whole-brain radiation therapy outcomes have emerged, this modality is used less frequently because of the risk of neurocognitive decline. Historically, systemic or cytotoxic therapies have not played a prominent role mainly because of the challenges of penetrating the blood-brain barrier and of achieving activity within the central nervous system (CNS). Recently, emergence of novel genomic techniques —whole-exome and next-generation sequencing— has enabled the identification of driver mutations in melanoma. Such specific targets as the neuroblastoma RAS viral oncogene homolog (NRAS) and v-RAF murine sarcoma viral oncogene homolog B (BRAF) have been exploited for therapeutic use[21]. Furthermore, immunotherapy has revolutionized the management of melanoma, specifically, with inhibition of cytotoxic T-lymphocyte antigen-4 (CTLA-4), programmed death-1 (PD-1), which is expressed on lymphocytes, and programmed death ligand-1, which is expressed on tumour cells[28].

2.3.1. Management of patients with melanoma metastatic to the brain with favourable prognosis

In favourable prognosis patients (i.e., limited or no extracranial disease, a good performance status, and a single or limited number of brain metastases), aggressive treatment to eradicate metastases in the brain is associated with an improved outcome. Surgery traditionally was used to treat patients with a single or limited number of lesions, often supplemented with WBRT. Subsequent advances have made stereotactic radiosurgery (SRS) an alternative, particularly when lesions are not surgically accessible or when multiple lesions are present.

2.3.2. Management of patients with melanoma metastatic to the brain with intermediate and poor prognosis

Patients with less favourable prognosis (*Table 1*) are generally treated with WBRT rather than surgery or SRS. However, surgery might be occasionally performed to resect a large symptomatic or life-threatening lesion.

WBRT is widely used as the treatment for intermediate/poor prognosis patients with melanoma metastatic to the brain. Even with treatment, the prognosis for these patients is poor (3-4 months)[29-32]. The Radiation Therapy Oncology Group (RTOG) conducted a series of randomized trials to determine the optimal dose and fractionation schedule for WBRT in patients with brain metastases. Patients were assigned to 40 Gy in four weeks, 40 Gy in three weeks, 30 Gy in three weeks, 30 Gy in two weeks, or 20 Gy in one week. The overall response rate (75 to 80 percent for symptom palliation) and median survival (15 to 18 weeks) were equivalent in all arms of these studies. Patients treated with larger fractions over a shorter time responded more quickly, but the duration of the clinical response and the time to progression were similar in all treatment arms. Brain metastases caused death in 40 percent of patients.

Subsequent RTOG trials exploring the use of ultra-rapid fractionation schedules, dose escalation in favourable prognosis subgroups, accelerated fractionation, and the use of radio sensitizers, failed to show any benefit over conventional radiation therapy.

2.4. Systemic therapy for melanoma patients with brain metastases

Until recently, there were few treatment options for patients with advanced or metastatic melanoma associated with significant increases in overall survival. Of these, patients with disease that has metastasized to the brain have a particularly poor prognosis and generally ineffective treatment options. Recent advances have led to the approval of ipilimumab, an antibody that blocks cytotoxic T-lymphocyte antigen-4 to augment antitumour T-cell responses, and vemurafenib, a BRAF kinase inhibitor.

Although improved understanding of the brain microenvironment and the blood–brain barrier in metastatic disease is required, data indicating both ipilimumab and vemurafenib also have activity against brain metastases are most encouraging. The next step is to investigate the optimal sequence, as well as combination treatment regimens, which will allow for further improved long-term survival without compromising safety[33].

2.4.1. Immunotherapies

As in other solid tumours, the role of immunotherapies has increased in the management of metastatic melanoma[34]. Interleukin-2 was the earliest immunotherapy agent to be used in melanoma. Unfortunately, whereas it demonstrated some efficacy, it was associated with severe toxicity, notably, fluid retention and capillary leak syndrome, which led to increased peritumoural edema[28]. Subsequently, high-dose interleukin-2 (HDIL-2) treatment was studied; however, there are little data to report on the outcome of patients with brain metastases who received HDIL-2[21].

The next generation of immunotherapy agents have focused on immune checkpoint inhibitors, such as CTLA-4, PD-1, and programmed death ligand-1 antibodies. Ipilimumab, a CTLA-4 monoclonal antibody, has demonstrated improved survival in metastatic melanoma and in patients with melanoma brain metastases.

A phase II trial of ipilimumab in patients with small and asymptomatic brain metastases—that did not require corticosteroids—demonstrated that 24% of patients achieved a partial response or stable disease[29]. In the NIBIT-M1 study, there was demonstrated clinical activity in patients with advanced melanoma who were treated with ipilimumab and fotemustine, including in patients with brain metastases[30]. A subsequent 3-year analysis demonstrated the efficacy of this combination without impairment of the immunologic activity of ipilimumab[38].

The NIBIT-M2 study, a randomized, phase III trial, will compare overall survival in treatment with fotemustine alone versus ipilimumab plus fotemustine versus ipilimumab plus nivolumab (a PD-1 inhibitor) as first-line therapy in patients with symptomatic brain metastases. In addition, the role of pembrolizumab, a PD-1 blocking antibody, is being investigated in patients with melanoma and brain metastases[39].

Although rare, there have been reports of neurologic toxicities associated with immune checkpoint blockade. Among those reported as immune-related adverse events are transient peripheral neuropathies, which have been reported in < 1% of patients who received ipilimumab[40]. Recommended management in the event of grade 2 neuropathy—no interference in daily activities—is an oral steroid taper and to continue at the same dose of ipilimumab[41]. For more severe grade 3 or 4 neuropathy, systemic corticosteroids and discontinuation of ipilimumab are recommended[41]. Other case reports of neurologic disease have described optic neuritis, aseptic meningitis, myasthenia gravis, and Guillain-Barre syndrome[42].

Data presented in ASCO 2018 data from our GEM-1202 clinical trial (NCT02115139), phase II study of Ipilimumab (IPI) and radiation (WBRT) in patients with unresectable melanoma and brain metastases[43], showed that concomitant IPI+WBRT is feasible, there were no unexpected safety issues, being one-year OS rate in this trial, higher than the historical results.

2.4.2. Targeted Therapies

BRAF mutations are present in ≤ 50% of patients with advanced melanoma and should be investigated if a patient presents at this stage. Approximately 90% of the BRAF mutations in cutaneous melanoma are valine to glutamic acid substitution (Val600Glu, V600E); there are other known activating mutations, including valine to lysine (Val600Lys, V600K), which constitute a smaller percentage[44]. Introduction of BRAF-targeted agents in patients who harbour these mutations has led to rapid systemic disease responses within weeks of initiation of therapy, which

has prompted the same investigations in the management of intracranial disease. Currently, there are three approved BRAF inhibitors available for clinical use: vemurafenib, the first agent licensed for treatment of BRAF-mutant metastatic melanoma, dabrafenib and encorafenib. It is not yet clear whether these agents have a differential effect on disease according to the specific mutation type (V600E v V600K)[44].

2.4.3. Mitogen-activated protein kinase kinase inhibitors (MEK)

Selective mitogen-activated protein kinase kinase (MEK) inhibition has also been explored as a potential therapeutic target in melanoma and has been combined with BRAF inhibitors. Results suggest an additional survival benefit compared with BRAF inhibitor therapy alone. MEK exists downstream of BRAF in the mitogen-activated protein kinase signalling pathway, which makes the combination of inhibitors an attractive therapeutic option because resistance to BRAF inhibitor monotherapy may be reduced with the addition of MEK inhibition. In phase I and II trials in BRAF V600–mutant metastatic melanoma, combination of dabrafenib and trametinib, an MEK inhibitor, resulted in a median overall survival of 2 years and a progression-free survival of 3 years compared with vemurafenib monotherapy. As expected, patients with a favourable prognostic profile experienced a more durable response[45]. In addition, there were similarities in the incidences of grade 3 or 4 toxic effects and adverse effects, which led to dose reduction. Skin-related adverse effects were less frequent in the dabrafenib and trametinib arm[46].Thus far, no data exist for use of MEK inhibitor monotherapy in patients with melanoma-related brain metastases.

2.4.4. Combination of BRAF Inhibitor and MEK Inhibitor

COMBI-MB is the first study to communicate, in a prospective manner (phase II clinical trial) the activity of the combination of a BRAF inhibitor (dabrafenib) and an MEK inhibitor (trametinib) in patients with brain metastases[47,48], providing preliminary evidence of clinical benefit with the combination of BRAF/MEK inhibitors in patients with melanoma and brain metastases.

COLUMBUS trial[49] is the first phase 3 study demonstrating that COMBO450 (ENCO 450 mg once daily (QD) + BINI 45 mg twice daily (BID) significantly improved OS, this promising approach need to be studied in patients with brain metastases.

3. TRIAL RATIONALE

As previously stated, brain metastases accounts for approximately 20% of patients with melanoma, being its frequency presumably higher in BRAF mutant melanoma[50].

Most pivotal clinical trials with both targeted therapy and immunotherapy excluded patients with active and/or untreated brain metastasis, leading to an unmet clinical need in real world practice.

In the targeted therapy field, the study COMBI-MB is the first study to communicate, in a prospective manner (phase II clinical trial) the activity of the combination of a BRAF inhibitor (dabrafenib) and an MEK inhibitor (trametinib) in patients with brain metastases. Briefly, in this study, the primary endpoint was an intracranial response of the combination in four different cohorts (being cohort A the main objective), showing these results[51].

- A) BRAFV600E-positive, asymptomatic melanoma brain metastases, with no previous local brain therapy, and an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1: **intracranial ORR 58%.**
- B) BRAFV600E-positive, asymptomatic melanoma brain metastases, with previous local brain therapy, and an ECOG performance status of 0 or 1: **intracranial ORR 56%.**
- C) BRAFV600D/K/R-positive, asymptomatic melanoma brain metastases, with or without previous local brain therapy, and an ECOG performance status of 0 or 1: **intracranial ORR 44%.**
- D) BRAFV600D/E/K/R-positive, symptomatic melanoma brain metastases, with or without previous local brain therapy, and an ECOG performance status of 0, 1, or 2: **intracranial ORR 59%.**

These results, although in an indirect comparison, are better in terms of response than treating these patients only with dabrafenib, according to the study BREAK-MB (39% in patients without previous local treatment)[52].

Thus, COMBI-MB supports the use of dabrafenib and trametinib also in BRAF mutant melanoma patients with brain metastases. However, one of the main critics to this study, is the apparently short progression free survival in the main cohort (cohort A, patients asymptomatic) in comparison with patients treated in other clinical trials with the same combination and no brain metastases: 5.6 months in COMBI MB[51] versus 11 months in COMBI-D[53]. One of the reasons could be the well-known poorer prognosis of these patients, but another one could be the fact that patients in this clinical trial, were not allowed by protocol to be treated with a local therapy (except for previously treated ones in cohort B, C and D, but always before the dabrafenib and trametinib). For those patients achieving a non-complete response, it is unknown if further local therapy (radiation, radiosurgery, surgery) could improve the duration of the responses.

Combination or sequencing of systemic (targeted) and local treatment with radiation has demonstrated a manageable toxicity profile, with some concerns regarding radio necrosis and increase in dermatitis. Most of these data, however, come from retrospective case series[54].

Finally, although encorafenib in combination with binimetinib is indicated for the treatment of adult patients with unresectable or metastatic melanoma with a BRAF V600 mutation, it is unknown the activity in patients with BRAF mutant melanoma and brain metastases.

3.0.1. Rationale for primary endpoint

COMBI-MB reported similar treatment activity of BRAF/MEK inhibitors in BRAF V600 mutated melanoma with brain metastasis regardless of symptomatology51. Moreover, recent studies on proposed setting are reporting iORR regardless of symptoms at diagnosis55,56.

We sought to determine as the primary endpoint for this trial the intracranial ORR (iORR) regardless of symptomatology. iORR will be also calculated as initially proposed by cohort, depending on symptomatology.

3.1. Rationale for dose selection

The dose selected in this trial is COMBO450 (ENCO 450 mg once daily (QD) + BINI 45 mg twice daily (BID) administered to patients in phase III COLUMBUS trial (NCT01909453)[7].

Local treatment could be radiation therapy or focused hypofractionated image guided VMAT (volumetric modulated arc therapy) for patients with ≤ 4 brain metastases of ≤ 3 cm in diameter, or whole brain radiation if patient has > 4 brain metastases and/or any lesion of > 3cm), according to local radiotherapy oncologist criteria.

4. HYPOTHESIS AND OBJECTIVES

Taking all into account, the present project will try to evaluate the role of the combination of encorafenib and binimetinib administered before local treatment that will follow, after response.

4.1. Study Hypothesis

The main hypothesis is that:

- Intracranial response rate by modified RECIST 1.1 before local treatment will be ≥40% in cohort 1 and 2.

Study will be considered positive if the main hypothesis is achieved.

4.2. Study Objectives

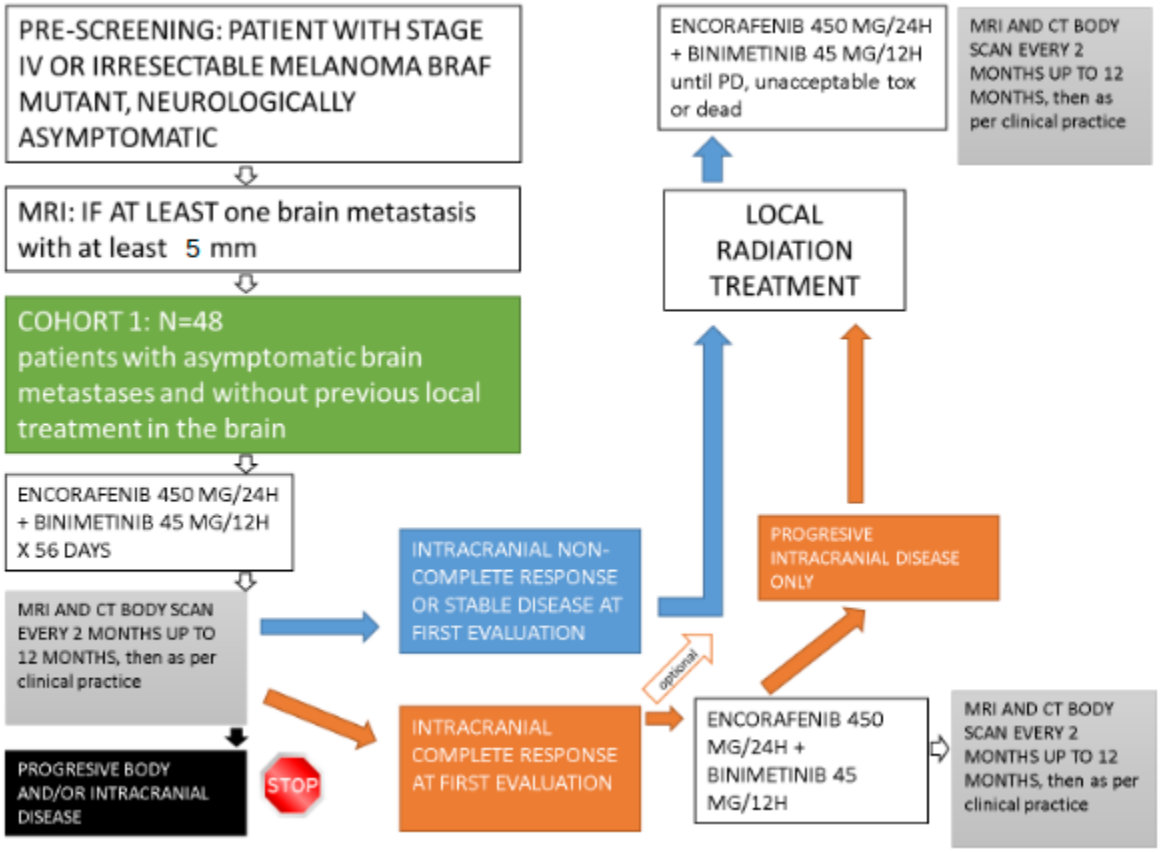
1. Primary objective:
    a. Intracranial objective response rate by modified RECIST 1.1 before local treatment in cohort 1 and in cohort 2.
2. Secondary objectives :
    a. Intracranial objective response rate assessed by the investigators using modified RECIST 1.1 before local treatment in cohort 2.
    b. Intracranial objective response rate assessed by the investigators using modified RECIST 1.1 before local treatment in cohort 1.
    c. The duration of the intracranial response in both cohorts assessed by the investigators using modified RECIST 1.1.
    d. The intracranial progression free survival by modified RECIST in both cohorts
    e. Percentage of patients free of intracranial progression according to modified RECIST at 6 (week 24), 12 (week 48) and 24 months (week 96) in both cohorts.
    f. Percentage of patients free of extracraneal progression according to RECIST 1.1 () at 6 (week 24), 12 (week 48) and 24 months (week 96) in both cohorts.
    g. Overall survival in both cohorts.
    h. Percentage of alive patients at 6, 12 and 24 months in both cohorts.
    i. Toxicity of the combination until local treatment in both cohorts:
        - Toxicity of the combination after local treatment in both cohorts.
        - Quality of life in both cohorts.

5. STUDY DESIGN

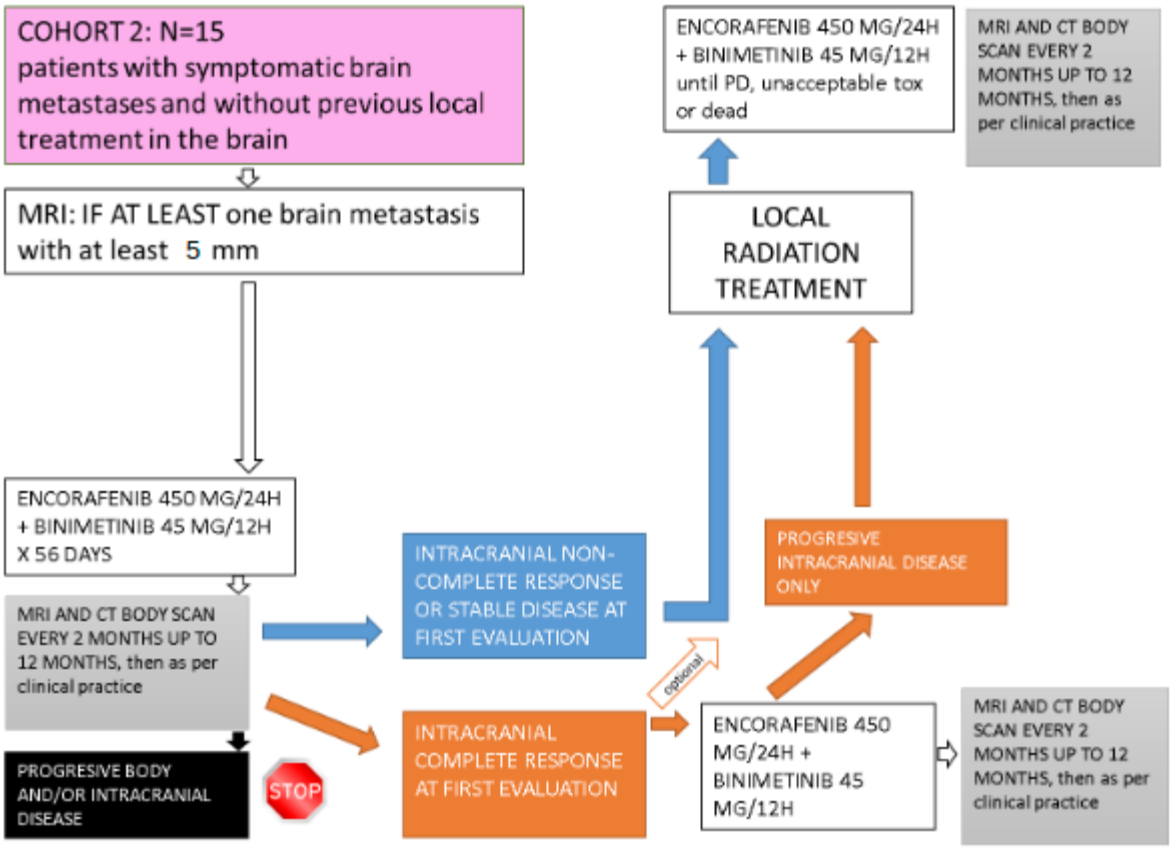
5.1. Overall Study Design

This is a phase II clinical trial with two cohorts of patients, all with melanoma BRAF mutant and brain metastases:

- **Cohort 1: patients with asymptomatic brain metastases and without previous radiotherapy (previous surgery is allowed) treatment in the brain. N=48**



- **Cohort 2: patients with symptomatic brain metastasis and without previous radiotherapy (previous surgery is allowed)treatment in the brain. N=15**



The design includes local confirmation of BRAF mutation, screening phase, systemic treatment phase, radiotherapy or radiosurgery (according to the radiotherapist criteria, following the indications included in the protocol), and quality of life assessment.

5.2. Patient Screening

Once completed all regulatory and Sponsor requirements and after received the "**O**pen **T**o **E**nrolment **L**etter" (**OTEL**), confirming that study is fully active in the corresponding site, the trial (informed consent) can be offered to potential patients.

Informed consent will be obtained prior to start of the specified screening window. Procedures conducted as part of the subject's routine clinical management (e.g., blood count determinations and imaging studies such as bone scans) prior to signing of informed consent may be used for screening or for defining baseline data, provided these procedures are conducted as specified in the protocol. Once informed consent form (ICFs) is signed, a trial screening number will be assigned to each patient after registering at Electronic Data Capture (EDC) platform. Each site will receive access to the EDC platform to register each screened case, since as per GCP guidelines it is mandatory to register every patient who signs a consent form.

Furthermore, within the Investigator Site File (ISF), a Patient Identification List will be included in order to identify patients according to local normal practice. This document will allow for immediate and unequivocal identification of patients participating in this clinical trial. This document will always be stored under Investigator staff custody at the site. The screening number will identify patients throughout the screening period while procedures needed to confirm the subjects' suitability for the trial protocol, such as clinical laboratory tests, imaging, and others are performed.

Screening determinations include obtaining informed consent, signature and registration, patient record review, local BRAF mutation status, clinical consultation, imaging procedures, and laboratory analyses including haematology, biochemistry, and urine tests. Additional information about screening procedures can be found in section 8 of this protocol.

5.3. Patient Inclusion and Cohort Assignment

During the screening (28 days before day 1 cycle 1) it should be assessed whether the patient is symptomatic (cohort 2) or asymptomatic (cohort 1).

Definition of Asymptomatic (cohort 1):.Patients without active symptoms secondary to brain metastases at the moment of inclusion.

After confirming that a patient fulfils all eligibility criteria of the study (inclusion/exclusion criteria), site staff will initiate the eCRF registration procedure.

Once procedure is fulfilled the site staff will receive the "Inclusion confirmation communication", and protocol-specific treatment can be initiated.

This is an open label, single arm study including two cohorts of patients, in each cohort, patients will be treated with encorafenib 450 mg once daily and binimetinib 45 mg twice daily.

After 56 days of treatment, a contrast enhanced brain MRI and CT body scan will be performed as first tumour assessment:

- Patients with PD at first evaluation in brain MRI (modified RECIST 1.1 criteria) and /or body CT scan (RECIST 1.1 criteria) will discontinue study treatment and will continue in the study for OS follow-up.
- Patients with CR in brain (modified RECIST 1.1) and no PD in the body (RECIST 1.1), will continue study treatment and will be followed every two months with contrast enhanced brain MRI and body CT scan up to 12 months. If no PD after one year, patients will be followed as per institutional criteria, and continue with the treatment.
    - If considered by the investigator, local treatment can be done for brain CR patients, but only after confirming no safety concerns (defined as substantial deterioration of vital signs (including ECOG PS), physical examination, ECG, Lab. Values that do not recommend RT) with the three first patients treated with radiation therapy in the running phase (for more information, please see section 9.1).
- Patients with no CR and no PD in brain MRI per modified RECIST 1.1 criteria, and no PD in body per RECIST 1.1 criteria, will be treated with local RT and/or radiosurgery, and then will continue Enco and Bini. The first 3 patients will be treated in a running

phase. These three first patients, that have achieved non-CR, non-PD in brain and no PD in body, are going to be treated sequentially or at the same time depending on when radiotherapy treatment is needed. If no safety concerns appear (defined as substantial deterioration of vital signs (including ECOG PS), physical examination, ECG, Lab. Values that do not recommend RT), the rest of patients that have achieved non-CR, non-PD in brain will begin local treatment when it will be indicated under medical criteria:

- Encorafenib and binimetinib will be interrupted 24h before radiotherapy and restart 24h after the last dose of radiotherapy.
- The local radiation technique will be defined and indicated by the radiotherapy oncologist (local co-investigator) criteria, depending on the number of lesions and its maximum size in the last tumour assessment done during the treatment with encorafenib and binimetinib:
    - *Radiosurgery (RS) or Stereotactic radiosurgery (SRS):
        - 1 brain metastases < 4 cm
        - ≤ 3 brain metastases ≤ 3 cm
        - ≤ 4 brain metastases ≤ 2.5 cm

*Radiosurgery: for patients who do not meet criteria for radiosurgery (RS) or (SRS), exceptional cases could be allowed after prior detailed consultation with the trial coordinators.

- Whole brain radiotherapy (WBRT):
    - ≥ 4 brain metastases
    - Almost one brain metastasis of ≥ 4 cm
    - ≤ 4 brain metastases not eligible for RS or SRS

Location metastases: brain stem, midbrain, pons, medulla or within 10 mm of the optic nerves and chiasm.

- After the first evaluation of the patient's intracranial response, patients without progression who received a local treatment, could receive other local treatments at the discretion of the investigator, if this is considered beneficial for the patient.
- Surgery can be done if, as per investigator criteria, is necessary for the patient's health.
- For patients in CR in the first assessment, if they were not treated with radiation, and in follow up a PD occurs **only in the brain**, brain local treatment will be carried out as per protocol. These patients can continue encorafenib and binimetinib treatment after local treatment.
- Every patient with a stable disease or response in both, brain and body, in the first assessment, when presenting a DP after local treatment in the body CT scan by RECIST 1.1. and/or brain MRI, by modified RECIST 1.1, they will discontinue the systemic treatment with encorafenib and binimetinib.

- After progression, patients will be followed only for overall survival.
    - In case of encorafenib and binimetinib are providing a clinical benefit to any patient, treatment could be continued after discussion with Sponsor [redacted] if it agrees on that. In this case, follow up will be done as per institutional criteria. In the study, these patients will be followed only for overall survival.
- *Study assessments:* in each monthly visit, adverse events will be registered, blood samples will be collected for blood cell counts and general biochemistry (including magnesium, potassium and creatinine-kinases); an ECG will be performed at baseline, after one month of treatment, and every 3 months thereafter; a left ventricular ejection fraction (LVEF) evaluation will be performed by as per institutional guidelines at baseline and every 3 months thereafter ophthalmologic anamnesis and evaluation will be performed by oncologist at baseline and in every monthly visit, if there's any alarm symptom or sign, patient will be evaluated by Ophthalmologist. Body CT-scan and contrast enhanced brain MRI will be performed baseline and every 8 weeks up to 12 months and according to normal practise thereafter. More information regarding study determination is provided in section 8 of this protocol.

6. ELIGIBILITY CRITERIA

6.1. Inclusion criteria

Patients eligible for inclusion in this study must meet all the following criteria:

1. Written informed consent of approved by the investigator's Institutional Review Board (IRB)/Independent Ethics Committee (IEC), prior to the performance of any trial activities.
2. Histologically confirmed diagnosis of unresectable metastatic cutaneous melanoma, or unknown primary melanoma with one or more brain metastasis with a diameter of 5 to 50 mm, measured by contrast enhanced MRI.
3. A documented mutation in BRAFV600 in the tumour tissue.
4. Modified Barthel Index of Activities of Daily Living > 10 (see appendix 2).
5. Subjects aged ≥ 18 years.
6. ECOG 0-1 in asymptomatic patients (cohort 1), 0-2 in symptomatic patients (cohort 2).
7. Adequate hematologic function:
    a. Haemoglobin ≥ 9 g/dL (may have been transfused).
    b. Platelet count ≥ 100 × 109/L.
    c. Absolute neutrophil count (ANC) ≥ 1.5 × 109/L.
8. Adequate hepatic function defined by a total bilirubin level ≤ 2.0 × the upper limit of normality (ULN) and AST and ALT levels ≤ 2.5 × ULN or AST and ALT levels ≤ 5 x ULN (for subjects with documented metastatic disease to the liver).
9. Serum Creatinine ≤ 2.0 x ULN or estimated creatinine clearance ≥ 30 mL/min according to the Cockcroft-Gault formula (or local institutional standard method).
10. Have evidence of at least one measurable lesion as detected by radiological or photographic methods according tto guidelines by modified RECIST 1.1.Patients with unresectable locally advanced or metastatic melanoma untreated or having progressed on or after a prior first line with antiPD1 +/- antiCTLA-4 (patients could have had brain metastasis when treated with immunotherapy). Prior immunotherapy must have ended at least 3 weeks (anti-PD1 monotherapy) or 4 weeks (anti-PD1 + anti-CTLA4) before to the cohort assignment (in case that this premise is not met, please, contact with the sponsor: i[redacted]
11. Patients relapsing to a prior adjuvant therapy (e.g. IFN, IL-2 therapy, any other immunotherapy, radiotherapy or chemotherapy) are allowed. When patients received BRAF +/- MEK inhibitors as adjuvant treatment, relapse must have occurred ≥ 12 months after the end of it. Moreover, patient mustn't present any residual grade 3-4 toxicity, including medically serious and reversible/controlled toxicities (e.g.: GGT elevation, CPK elevation, vomiting)

12. Steroids or anticonvulsants are allowed if clinically needed and once the patient is included in the trial are not being administered in an increasing dose.
13. Female subjects must either be of non-reproductive potential (e.g., post-menopausal by history: ≥60 years old and no menses for ≥1 year without an alternative medical cause; OR history of hysterectomy, OR history of bilateral tubal ligation, OR history of bilateral oophorectomy) or must have a negative urine pregnancy test upon study entry. If the result in the urine pregnancy test is positive, a serum pregnancy test should be done to confirm pregnancy.
14. Normal functioning of daily living activities.
15. Willingness and ability to attend scheduled visits, follow the treatment schedule and undergo clinical tests and other study procedures.

6.2. Exclusion criteria

Patients meeting any of the following criteria are excluded from the study:

1. Uveal or mucosal melanoma.
2. History of leptomeningeal metastases, with the exception that they are only seen in brain MRI and the patient has ECOG 0-1 and no neurological symptoms (except for cohort 2, where symptomatic patients will be allowed if ECOG is 0-2).
3. Another cancer in the last two years, except for in situ carcinoma of the cervix or squamous cell carcinoma of the skin adequately treated or limited basal cell skin cancer adequately controlled. If another cancer was diagnosed in the two previous years, it should be in complete remission and without the need for any other maintenance treatment (i.e hormonotherapy, chemotherapy, targeted therapy including monoclonal antibodies and immunotherapy)
4. History of or current evidence of central serous retinopathy (CSR), retinal vein occlusion (RVO) or history of retinal degenerative disease (RDD).
5. Any previous systemic chemotherapy treatment, brain radiotherapy, targeted therapy based on BRAF and/or MEK inhibitors for locally advanced unresectable or metastatic melanoma.
6. History of Gilbert's syndrome.
7. Previous treatment with a BRAF or MEK inhibitor in metastatic setting. This treatment will be allowed in the adjuvant setting (see above). Previous treatments with immunotherapy will be allowed in both the metastatic and adjuvant setting.
8. Known positive serology for human immunodeficiency virus, or an active hepatitis B or hepatitis C infection, or both;
9. Impaired cardiovascular function or clinically significant cardiovascular diseases “Clinically significant (i.e., active) cardiovascular disease: cerebrovascular accident/stroke (< 6 months prior to enrolment), myocardial infarction (< 6 months prior to enrolment), unstable angina, congestive heart failure (≥ New York Heart Association Classification Class II), a

LVEF < 50% evaluated as per institutional guidelines, or serious cardiac arrhythmia requiring medication or a triplicate average baseline QTc interval > 500 ms.”

10. Uncontrolled arterial hypertension despite medical treatment.
11. Moderate (Child Pugh Class B) or severe (Child Pugh Class C) hepatic impairment.
12. Impairment of gastrointestinal function.
13. Neuromuscular disorders associated with high concentrations of creatine kinase.
14. Medical, psychiatric, cognitive or other conditions that may compromise the patient's ability to understand the patient information, give informed consent, comply with the study protocol or complete the study.
15. Known hypersensitivity to encorafenib, binimetinib or their components.
16. Persisting toxicity related to prior therapy of Grade >1 NCI-CTCAE v 4.03; however, alopecia and sensory neuropathy Grade ≤ 2 is acceptable.
17. Female patients who are pregnant or breastfeeding or male or female patients of reproductive potential who are not willing to employ highly effective birth control from screening to 180 days after the last dose of study treatment.
18. Known alcohol or drug abuse.
19. Inability to swallow tablets or capsules.
20. Total lactase deficiency or glucose-galactose malabsorption.

7. TREATMENT OF SUBJECTS

7.1. Description of Study Drug

7.1.1. Encorafenib

Pharmaceutical form and route of administration: Capsules for oral use.

Strength: provided as 75 mg and 50 mg capsules.

Presentation: The encorafenib drug product is supplied as a capsule formulation in dosage strengths of 50 mg and 75 mg the dosage forms for each strength have identical formulations which are packaged into blisters in different coloured capsules per strength. Sites will provide patients enough blisters to cover the treatment until next patient's visit

7.1.2. Binimetinib

Pharmaceutical form and route of administration: Tablets for oral use.

Strength: Provided as 15 mg tablets.

Presentation: Binimetinib 15 mg will be provided as film-coated tablets and packaged into high-density polyethylene blisters. Sites will provide patients enough bottles to cover the treatment until the next patient visit.

7.1.3. COMBO 450 administration instructions

Encorafenib and binimetinib will be administered orally on a daily schedule as a flat fixed dose (not by body weight or body surface area).

Patients will be supplied during the control visit with enough number of tablets and/or capsules for all doses to be taken prior to the next scheduled visit. In addition, patients will be provided a dosing diary and should document in this diary each prescribed dose, and whether it was taken or not.

If a patient vomits at any time after dosing, the dose of study drug should not be re-administered.

Doses of binimetinib that are omitted for any reason should not be made up later if it is less than 6 hours until the next dose is due. Doses of encorafenib that are omitted any reason can be taken up to 12 hours prior to the next dose.

Patients must avoid consumption of grapefruit or grapefruit juice during the entire study and preferably 7 days before the first dose of study medications, due to potential CYP3A4 interaction with the study medications. Orange juice is allowed. Complete dosing instructions will be provided to study patients and will include the minimum times between doses and instructions for missed doses. Patients will also be instructed not to chew, crush, or dissolve tablets and/or capsules of study drugs. The investigator or responsible site personnel should instruct the patient to take the study drugs as per protocol (Sponsor compliance). All dosages prescribed and dispensed to the patient and all dose changes and all missed doses during the study must be recorded on the eCRF. Drug accountability must be performed on a regular basis. Patients will be instructed to return unused study drugs to the site at the end of each cycle. The site personnel will ensure that

the appropriate dose of each study drug is administered at each visit and will provide the patient with the correct number of drugs for subsequent dosing.

Patients should be instructed to take with a large glass of water (~250 ml) daily in the morning at approximately the same time every day the Combination of 450 mg of encorafenib and 45 mg of binimetinib (Combo 450) together. Twelve hours later, patients should take again 45 mg of binimetinib with a large glass of water (~250 ml). In total, patients should take 90 mg of binimetinib every day, if the dose has not been modified. All dose administrations may be taken with or without food, but the same method should be used consistently throughout the study. Despite this, the concomitant administration of encorafenib with grapefruit juice should be avoided.

The prescribed doses for binimetinib should be taken twice daily, approximately 12 hours apart.
On visit days when the patient is scheduled to be at the clinic, patients will take encorafenib and binimetinib (as applicable) in the clinic under the supervision of the investigator or designee on the morning. On the evening of the visit day patients will take binimetinib (as applicable) at home. On all other days, patients will take encorafenib and binimetinib (as applicable) at home. **If a patient temporarily interrupts treatment with binimetinib, the patient may continue treatment with encorafenib as monotherapy at a maximum dose of 300 mg QD**. If binimetinib is permanently discontinued, encorafenib should be discontinued. If a patient permanently discontinues treatment with encorafenib, the patient must discontinue treatment with binimetinib, complete the end of treatment visit and continue to be followed until disease progression.

7.1.4. Radiation therapy [59-62]

7.1.4.1 Whole Brain Radiation Therapy

1. Total Dose:
    - The whole brain planning target volume (PTV) will receive 30 Gy in 10 fractions.
    - Treatment will be delivered once daily, 5 fractions per week, over 2 to 2.5 weeks.
2. Immobilization, Simulation, Localization:
    - Patients will be treated in the supine position using an adequate immobilization (aquaplast mask).
    - A treatment-planning CT scan of the whole head region must be acquired with the patient in the same position and immobilization device as for treatment. Axial slice thickness not exceeding 3-5 mm will be required. Contrast IV and MRI-CT fusion are not necessary.
3. Target volumes:
    - It is not necessary to define the Gross Tumour Volume (GTV).
    - The Clinical Target Volume (CTV) is defined as the whole brain parenchyma to C1 (if no posterior fossa metastasis) or C2 (if MRI evidence of posterior fossa metastasis).
    - The PTV is defined as the CTV + 0.5 cm with clip at patient surface.
4. Treatment Planning:
    - Treatments must be delivered with 3-D planning through parallel opposed fields that cover the entire cranial contents (also it is allowed static or dynamic intensity modulation).
    - All portals will be treated daily.
    - Treatment will be delivered using megavoltage machines with photon beams ranging from 4 to 8 MV. Electron, particle, or implant therapy is not permissible.

5. Dose Specification:
    - Doses will be specified at the central axis at midplane on the brain.
      90% of the whole brain PTV must be covered by the prescription dose.
    - Maximum dose to 2% of the PTV (D2%) 37.5 Gy, and minimum dose to 98% of the PTV (D98%) 25 Gy.
    - If treatment is delivered with Helical Tomotherapy 96% of the whole brain PTV must be covered by the prescription dose. Max dose 30 Gy, 30 Gy to >=96%.
    - If LINAC-based IMRT is delivered, 92% of the whole brain PTV must be covered by the prescription dose. Max Dose 34 Gy. Min Dose: 27,6 Gy.
6. Critical Structures:
    - The lenses, orbits, optic nerves, optic chiasm and brain will be contoured.
    - Hippocampus protection is allowed in patients who do not present any nearby lesion, enabling the possibility of protecting said area.
    - Minimize the dose to the lens and orbits. Dose to any point within the optic nerves or optic chiasm cannot exceed 37.5 Gy.
    - If treatment is delivery with Helical Tomotherapy Eyes: Max Dose 8 Gy, 5 Gy <=20%. Lenses: Max Dose 3 Gy.
    - If LINAC-based IMRT Involving Static Gantry Angles: Eyes: Max Dose 7 Gy, 5 Gy <=20%. Lenses: Max Dose 5 Gy.
7. Documentation:
    - Verification of orthogonal films or portal images that localize the isocenter placement must be obtained.

7.1.4.2. Radiosurgery/Stereotactic radiosurgery

1. All participating institutions must use approved stereotactic localization procedures for imaging and treatment delivery.
2. Devices: Gamma Knife or Accelerator Linac-Based Systems (IMRT, Rapid Arc, VMAT), Cyberknife, or Tomotherapy Hi-Art system.
3. Total Dose:
    a. Dose selection must be based on previously published Radiation Therapy Oncology Group (RTOG) data, with dose modification left up to the treating physician. The total dose will depend on the size of the metastatic lesion(s) and proximity to critical structures.
    b. Suggested doses are as follows: 1 fraction x 15-25 Gy; 3 fractions x 9-11 Gy; 5 fractions x 6-7 Gy; or 6 fractions x 5-6 Gy.
    c. For GTV > 20 mm hypofractionated stereotactic radiotherapy could be prefered.
    d. Treatment will be delivered once daily, alternate-day, 3 fractions per week.
4. Immobilization, Simulation, Localization:
    a. Patients will be treated in the supine position using an adequate immobilization facemask/stereotactic frame.
    b. A treatment-planning CT scan of the whole head region must be acquired with the patient in the same position and immobilization device as for treatment. Axial slice thickness not exceeding 2-3 mm will be required to define gross tumour volumes.
    c. Administration IV contrast increases the diagnostic accuracy of CT.

    d. The MRI planning and treatment-planning CT should be fused.
5. Target volumes:
    a. GTV will be delineated on axial T1-weighted gadolinium-enhanced MRI. Areas of edema will not be considered part of the target volume.
    b. PTV will be defined as expanding GTV 1-2 mm.
6. Treatment Planning:
    a. Treatments must be delivered with Intensity-Modulated RT. Acceptable IMRT modalities include helical tomotherapy or LINAC-based IMRT involving static gantry angles or volumetric arc therapy (VMAT). It is also possible to use Gamma Knife.
7. Dose Specification:
    a. The Dose will be prescribed to the isodose surface (50-90% [maximum = 100%]), which encompasses the target, to ensure at least 95% coverage of the PTV with the prescription dose. The 100% (maximum) dose and minimum dose will be recorded for each patient.
    b. Three isodose lines should be submitted: the prescription isodose line, 90% of the prescription isodose line (not 90% of total dose) and 80% of the prescription isodose line.
        - Acceptable variation: 80% isodose line covers the target
        - Unacceptable deviation: 80% isodose line does not cover target
    c. Dose Homogeneity QA: The ratio of the maximum dose to the prescribed dose (MD/PD) will be:
        - Per protocol if <2
        - Acceptable variation if >2 but <2.5
        - Unacceptable deviation if >2.5
    d. Dose Conformity QA: The ratio of prescription isodose volume to the target volume (PI/TV) is:
        - Per protocol if between 1.0 and 2.0
        - Acceptable variation if >0.9 but <1.0 or >2.0 but <3.5
        - Unacceptable deviation if >3.5
8. Critical Structures:
    a. The lenses, orbits, optic nerves, optic chiasm and brain, will be contoured.
    b. There are no clear dose limits established for organs at risk for SR or HBRT. Gerard et al. has just published a recent compilation about dose-constraints.
9. Documentation:
    a. For all forms of dose delivery, immediately before treatment, images that localize the isocenter placement shall be obtained, with appropriate adjustment to ensure a translational position deviation less than 1 mm in any direction and minimal rotational deviation.

7.2. Dose modifications

Patients will be monitored for adverse events at each visit with the NCI CTCAE version 4.03 used for all grading. If a patient develops a toxicity, the dose may be adjusted as outlined in Table 8-9 and Table 10, which include criteria for interruption and re-initiation of encorafenib and binimetinib. All dose modifications should be based on the worst preceding toxicity (CTCAE version 4.03). All dosing interruptions and changes must be recorded on the Dosage Administration Record at eCRF.

Eye disorders should be graded according to CTCAE version 4.03 as described below in Table 3.

Table 3. CTCAE grading for eye disorders

Grade	Description
1	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated; no change in vision
2	Moderate; minimal, local or non-invasive intervention indicated; limiting instrumental ADL; best corrected visual acuity 20/40 and better or 3 lines or less decreased vision from known baseline
3	Severe or medically significant but not immediately sight threatening; limiting self-care ADL; decrease in visual acuity (best corrected visual acuity worse than 20/40 or more than 3 lines of decreased vision from known baseline, up to 20/200)
4	Sight-threatening consequences; urgent intervention indicated; best corrected visual acuity of 20/200 or worse in the affected eye
ADL = Activities of Daily Living	

Retinal detachment should be graded according to the CTCAE version 4.03 as described below in Table 4.

Table 4. CTCAE grading for retinal detachment

Grade	Description
1	-
2	Exudative and visual acuity 20/40 or better
3	Rhegmatogenous or exudative detachment; operative intervention indicated; decline in vision (worse than 20/40 but better than 20/200
4	Blindness (20/200 or worse) in the affected eye
Definition: A disorder characterized by the separation of the inner retina layers from the underlying pigment epithelium.	

Uveitis should be graded according to the CTCAE version 4.03 as described below in Table 5

Table 5. CTCAE grading for uveitis

Grade	Description
1	Anterior uveitis with trace cells
2	Anterior uveitis with 1+ or 2+ cells
3	Anterior uveitis with 3+ or greater cells; intermediate posterior or panuveitis
4	Best corrected visual acuity of 20/200 or worse in the affected eye
Definition: A disorder characterized by inflammation to the uvea of the eye.	

Palmar-plantar erythrodysesthesia syndrome should be graded according to the CTCAE version 4.03 as described below in Table 6.

Table 6. CTCAE grading for Palmar-plantar erythrodysesthesia syndrome

Grade	Description
1	Minimal skin changes or dermatitis (e.g., erythema, edema, or hyperkeratosis) without pain
2	Skin changes (e.g., peeling, blisters, bleeding, fissures, edema, or hyperkeratosis) with pain; limiting instrumental ADL
3	Severe skin changes (e.g., peeling, blisters, bleeding, fissures, edema, or hyperkeratosis) with pain; limiting self-care ADL
4	-
Definition: A disorder characterized by redness, marked discomfort, swelling, and tingling in the palms of the hands or the soles of the feet. Also known as Hand-Foot Syndrome.	

Diarrhea should be graded according to CTCAE version 4.03 as described below in Table 7.

Table 7. CTCAE grading for Diarrhea

Grade	Description
1	Increase of <4 stools per day over baseline; mild increase in ostomy output compared to baseline
2	Increase of 4 - 6 stools per day over baseline; moderate increase in ostomy output compared to baseline; limiting instrumental ADL
3	Increase of >=7 stools per day over baseline; hospitalization indicated; severe increase in ostomy output compared to baseline; limiting self-care ADL
4	Life-threatening consequences; urgent intervention indicated
5	Death
Definition: A disorder characterized by an increase in frequency and/or loose or watery bowel movements.	

7.2.1. Dose modification and dose delay for encorafenib (as monotherapy) and combination (encorafenib and binimetinib)

For patients who do not tolerate encorafenib and/or binimetinib initial dosing schedule, dose adjustment is permitted to allow the patient to continue study drug (see Table 8 for encorafenib and Table 9 for binimetinib).

A dose reduction below 100 mg QD for encorafenib and below 30 mg BID for binimetinib is not allowed. Dose interruptions of more than 28 consecutive days are not allowed unless approved by the Sponsor [redacted]

Table 8. Dose reduction for encorafenib

Dose reduction based on the highest AE grade	
Dose level	**Encorafenib***
0 (starting dose)	450 mg QD (6 capsules of 75 mg)
-1 (monotherapy dose)	300 mg QD** (4 capsules of 75 mg)
-2	200 mg QD (2 capsules of 75 mg and 1 capsule of 50 mg)
-3	100 mg QD*** (2 capsules of 50 mg)
*If binimetinib is permanently discontinued, encorafenib should be discontinued **The maximum dose of encorafenib if it is administered as monotherapy while binimetinib is temporarily interrupted ***Dose reduction below 100 mg is not allowed	

Table 9. Dose reduction for binimetinib

Dose reduction based on the highest AE grade	
Dose level	**Binimetinib**
0 (starting dose)	45 mg BID (3 pills of 15 mg)
-1	30 mg BID* (2 pills of 15 mg)
*Dose reduction below 30 mg is not allowed	

Doses of binimetinib that are omitted for any reason should not be made up later if it is less than 6 hours until the next dose is due. Doses of encorafenib that are omitted for any reason can be taken up to 12 hours prior to the next dose. For both encorafenib and binimetinib, when the toxicity that resulted in a dose reduction improves to Grade 1 or less, the dose should be re-escalated at the investigators discretion provided there are no other concomitant toxicities.

If binimetinib is dose reduced due to left ventricular dysfunction, prolonged QTcF > 500 msec or any grade 4 toxicity related to the drug, no dose re-escalation is allowed. If encorafenib is dose reduced due to prolonged QTcF > 500 msec or any grade 4 toxicity related to the drug, no dose re-escalation is allowed. Dose reduction/interruption/discontinuation decisions should be based on the CTCAE grade of the toxicity and the guidelines provided below (Table 8). In general, doses

should not be reduced or interrupted for Grade 1 toxicities, but treatment to control symptoms should be provided as appropriate. All AEs should be followed weekly or as clinically appropriate until stabilization or resolution.

If a patient temporarily interrupts treatment with binimetinib, the patient must continue treatment reducing encorafenib at dose of 300 mg QD, if patient was receiving 450 mg QD of encorafenib in combination with binimetinib (see Table 8 for encorafenib dose reductions). However, if a patient discontinues treatment with encorafenib, they must discontinue treatment with binimetinib, complete the end of treatment visit and continue to be followed until disease progression. Please refer to table 10 for dose adjustment recommendations for encorafenib and/or binimetinib induced toxicities.

Table 10. Encorafenib and binimetinib – Recommended dose modifications associated with treatment-related adverse events

Worst toxicity CTCAE v 4.03 Grade (unless otherwise specified)	**Dose adjustments of both drugs**	
Cutaneous reactions	**Encorafenib**	**Binimetinib**
Grade 2	Encorafenib and binimetinib should be maintained. If rash worsens or does not improve within 2 weeks with treatment, encorafenib and binimetinib should be withheld until being Grade 0 or 1 toxicity. Then: ● If it is the first occurrence of Grade 2, both drugs can be resumed at the same dose. ● If it is a recurrent Grade 2 toxicity, both drugs should be resumed at a reduced dose.	
Grade 3	Encorafenib and binimetinib should be withheld until improvement to Grade 0 or 1 toxicity. Then: ● If it is the first occurrence of Grade 3, both drugs can be resumed at the same dose. ● If it is a recurrent Grade 3 toxicity, both drugs should be resumed at a reduced dose.	
Grade 4	Encorafenib and binimetinib should be permanently discontinued.	
Squamous Cell Carcinoma (SCC), Keratoacanthoma (KA) or any other suspicious skin lesion	**Encorafenib**	**Binimetinib**
Grade 3-4	Encorafenib and binimetinib should be maintained at same dose and local treatment of lesion (e.g. new primary melanoma) should be done based upon institutional practice.	
Palmar-plantar erythrodysaesthesia syndrome (PPES)	**Encorafenib**	**Binimetinib**

<table>
<tr><td colspan="2">Grade 2</td><td colspan="2">Encorafenib and binimetinib should be maintained and supportive measures such as topical therapy should be instituted.
If not improvement despite supportive therapy within 2 weeks, encorafenib and binimetinib should be withheld until improvement to Grade 0 or 1 toxicity. Then, treatment should be resumed at the same dose level or at a reduced dose of encorafenib.</td></tr>
<tr><td colspan="2">Grade 3</td><td colspan="2">Encorafenib and binimetinib should be withheld, supportive measures such as topical therapy should be instituted, and patients should be reassessed weekly until improvement to Grade 0 or 1 toxicity. Then, treatment should be resumed at the same dose level or at a reduced dose of encorafenib.</td></tr>
<tr><td colspan="2">Liver laboratory abnormalities</td><td>Encorafenib</td><td>Binimetinib</td></tr>
<tr><td>Grade 2</td><td>Aspartate aminotransferase (AST) or Alanine aminotransferase (ALT) >3x - ≤5x upper limit of normal (ULN)</td><td colspan="2">Encorafenib and binimetinib should be maintained.
If no improvement within 2 weeks, binimetinib should be withheld until improved to Grade 0 or 1 or to baseline levels. At same time, encorafenib should be reduced to 300mg QD if the patient was receiving 450mg of encorafenib QD with binimetinib.
If no improvement within 4 weeks, encorafenib should be withheld until improved to Grade 0 or 1 or to baseline levels.
Then, both drugs should be resumed at the same dose.</td></tr>
<tr><td>Grade 3, first occurrence</td><td rowspan="2">AST or ALT >5x ULN + blood bilirubin >2x ULN</td><td colspan="2">Encorafenib and binimetinib should be withheld for up to 4 weeks.
● If toxicity improves to Grade 0 or 1 or to baseline levels, both drugs should be resumed at a reduced dose.
● If toxicity doesn’t improve both drugs should be permanently discontinued.</td></tr>
<tr><td>Grade 3, recurrent</td><td colspan="2">It should be considered to permanently discontinue encorafenib and binimetinib.</td></tr>
<tr><td>Grade 4, first occurrence</td><td rowspan="2">AST or ALT >20x ULN</td><td colspan="2">Encorafenib and binimetinib should be withheld for up to 4 weeks.
● If toxicity improves to Grade 0 or 1 or to baseline levels, both drugs should be resumed at a reduced dose level.
● If toxicity doesn’t improve both drugs should be permanently discontinued.
Or, encorafenib and binimetinib should be permanently discontinued.</td></tr>
<tr><td>Grade 4, recurrent</td><td colspan="2">Encorafenib and binimetinib should be permanently discontinued.</td></tr>
<tr><td colspan="2">QTc prolongation</td><td>Encorafenib</td><td>Binimetinib</td></tr>
<tr><td colspan="2">QTcF > 500 ms and has changed ≤60 ms from pre-treatment value</td><td colspan="2">Encorafenib and binimetinib should be withheld and all abnormal electrolytes and risk factors had to be controlled.
When QTcF is ≤500 ms, encorafenib and binimetinib should be resumed at a reduced dose of encorafenib.
Encorafenib and binimetinib should be discontinued if more than one</td></tr>
</table>

		recurrence happens.	
QTcF > 500 ms and has changed >60 ms from pre-treatment value		Encorafenib and binimetinib should be permanently discontinued and all abnormal electrolytes and risk factors had to be controlled.	
Left ventricular ejection fraction (LVEF) decrease		**Encorafenib**	**Binimetinib**
Grade 2	Asymptomatic and an absolute decrease >10% from baseline, that is below the lower limit of normal (LLN)	See table 8. If a patient temporarily interrupts (withheld) treatment with binimetinib, the patient may continue treatment with encorafenib as monotherapy at a maximum dose of 300 mg QD.	Binimetinib should be withheld for up to 4 weeks and LVEF should be evaluated every 2 weeks. Binimetinib should be resumed at a reduced dose if all the following are present within 4 weeks: - LVEF is at or above the LLN - Absolute decrease from baseline is ≤ 10%. If the LVEF does not recover within 4 weeks, binimetinib and encorafenib should be permanently discontinued.
Grade 3 or 4	Symptomatic left ventricular dysfunction (LVD)	See table 8. If binimetinib is permanently discontinued, encorafenib should be discontinued	Binimetinib should be permanently discontinued and LVEF should be evaluated every 2 weeks until recovery.
Hypertension		**Encorafenib**	**Binimetinib**
Severe and uncontrolled despite specific treatment		See table 8. If a patient temporarily interrupts (withheld) treatment with binimetinib, the patient may continue treatment with encorafenib as monotherapy at a maximum dose of 300 mg QD.	Binimetinib should be withheld until hypertension is controlled. Then, follow indications of dose adjustments for other adverse reactions.
Venous thromboembolism (VTE)		**Encorafenib**	**Binimetinib**
Uncomplicated deep vein thrombosis (DVT) or pulmonary embolism (PE) ≤ grade 3		See table 8. If a patient temporarily interrupts (withheld) treatment with binimetinib, the patient may continue treatment with encorafenib as monotherapy at a maximum dose of 300 mg QD.	Binimetinib should be withheld for up to 4 weeks. ● If improved to Grade 0 or 1, binimetinib should be resumed at reduced dose. ● If it is not improved within 4 weeks, binimetinib should be permanently discontinued.

Grade 4 pulmonary embolism		See table 8. If binimetinib is permanently discontinued, encorafenib should be discontinued.	Binimetinib should be permanently discontinued.
Interstitial lung disease (ILD)/Pneumonitis		**Encorafenib**	**Binimetinib**
Grade 2		See table 8. If a patient temporarily interrupts (withheld) treatment with binimetinib, the patient may continue treatment with encorafenib as monotherapy at a maximum dose of 300 mg QD.	Binimetinib should be withheld for up to 4 weeks. ● If improved to Grade 0 or 1, binimetinib should be resumed at reduced dose. ● If it is not resolved within 4 weeks, binimetinib should be permanently discontinued.
Grade 3 or 4		See table 8. If binimetinib is permanently discontinued, encorafenib should be discontinued.	Binimetinib should be permanently discontinued.
Diarrhea		**Encorafenib**	**Binimetinib**
Grade 1-2	Uncomplicated	See table 8. If a patient temporarily interrupts (withheld) treatment with binimetinib, the patient may continue treatment with encorafenib as monotherapy at a maximum dose of 300 mg QD.	Binimetinib should be withheld for up to 4 weeks. ● If improved to Grade 0 or 1, binimetinib should be resumed at same dose.
	Complicated	Encorafenib should be withheld for up to 4 weeks. ● If improved to Grade 0 or 1, encorafenib should be resumed at same dose.	Binimetinib should be withheld for up to 4 weeks. ● If improved to Grade 0 or 1, binimetinib should be resumed at reduced dose.
Grade 3-4		Encorafenib should be withheld for up to 4 weeks. ● If improved to Grade 0 or 1, encorafenib should be resumed at same dose, if in the judgment of the investigator the toxicity is unrelated to encorafenib, or at one reduced dose.	Binimetinib should be withheld for up to 4 weeks. ● If improved to Grade 0 or 1, binimetinib should be resumed at reduced dose.
Nausea/Vomiting		**Encorafenib**	**Binimetinib**

Grade 1-2		Treatment with encorafenib and binimetinib should be maintained at the current dose. Promptly institute antiemetic measures.	
Grade 3		Encorafenib should be withheld for up to 4 weeks. ● If improved to Grade 0 or 1, encorafenib should be resumed at reduced dose.	Binimetinib should be withheld for up to 4 weeks. ● If improved to Grade 0 or 1, binimetinib should be resumed at the same dose if, in the judgment of the investigator, the toxicity is unrelated to binimetinib, or at one reduced dose.
Grade 4		Encorafenib and/or binimetinib should be permanently discontinued.	
Note: Interrupt dose for ≥ grade 3 vomiting or grade 3 nausea only if the vomiting or nausea cannot be controlled with optimal antiemetics (as per local practice).			
Rhabdomyolysis/Creatine phosphokinase (CK) increase		**Encorafenib**	**Binimetinib**
Asymptomatic grade 3	CK >5 – 10x ULN	Encorafenib and binimetinib should be maintained and it should be ensured that the patient has an adequate hydration.	
Asymptomatic grade 4	CK >10x ULN	See table 8. If a patient temporarily interrupts (withheld) treatment with binimetinib, the patient may continue treatment with encorafenib as monotherapy at a maximum dose of 300 mg QD.	Binimetinib should be withheld until improved to Grade 0 or 1, moreover, an adequate hydration of the patient should be ensured.
Grade 3 or 4 with renal impairment or muscle symptoms		See table 8. If a patient temporarily interrupts (withheld) treatment with binimetinib, the patient may continue treatment with encorafenib as monotherapy at a maximum dose of 300 mg QD	Binimetinib should be withheld until improved to Grade 0 or 1, moreover, an adequate hydration of the patient should be ensured. If resolved within 4 weeks, binimetinib should be resumed at reduced dose or permanently discontinued.
Retinal pigment epithelial detachment (RPED)[a]		**Encorafenib**	**Binimetinib**
Grade 2	Symptomatic	See table 8. If a patient temporarily interrupts (withheld) treatment with binimetinib, the patient may continue treatment with encorafenib as monotherapy at a maximum	Binimetinib should be withheld for up to 2 weeks and ophthalmic monitoring should be repeated including visual acuity assessment. ● If improved to Grade 0 or 1,

		dose of 300 mg QD	binimetinib should be resumed at the same dose. ● If not improved to Grade 0 or 1, binimetinib should be resumed at a lower dose.
Grade 3	Symptomatic	See table 8. If a patient temporarily interrupts (withheld) treatment with binimetinib, the patient may continue treatment with encorafenib as monotherapy at a maximum dose of 300 mg QD	Binimetinib should be withheld for up to 2 weeks and ophthalmic monitoring should be repeated including visual acuity assessment. ● If improved to Grade 0 or 1, binimetinib should be resumed at same dose. ● If improved to Grade 2, binimetinib should be resumed at a lower dose. If not improved to Grade 2, binimetinib should be permanently discontinued.
Grade 4	Symptomatic with reduced visual acuity	See table 8. If binimetinib is permanently discontinued, encorafenib should be discontinued	Binimetinib should be permanently discontinued.
Retinal vein occlusion (RVO)[a]		**Encorafenib**	**Binimetinib**
Any grade		See table 8. If binimetinib is permanently discontinued, encorafenib should be discontinued	Binimetinib should be permanently discontinued.
Uveitis, iritis and/or iridocyclitis[a]		**Encorafenib**	**Binimetinib**
Grade 1 or 2		Initiate specific ocular therapy (e.g. topical). If Grade 1 or 2 uveitis does not respond to specific ocular therapy, encorafenib and binimetinib should be withheld and ophthalmic monitoring should be repeated within 2 weeks. ● If Grade 1 and improves to Grade 0, then treatment should be resumed at the same dose. ● If Grade 2 improves to Grade 0 or 1, then treatment should be resumed at a reduced dose.	
Grade 3		Encorafenib and binimetinib should be withheld and ophthalmic monitoring should be repeated within 2 weeks. ● If Grade 3 improves to Grade 0 or 1, then treatment should be resumed at a reduced dose. If not improved within 6 weeks, encorafenib and binimetinib should be permanently discontinued and an ophthalmologic monitoring should be performed until resolution.	

Grade 4	Encorafenib and binimetinib should be permanently discontinued and an ophthalmologic monitoring should be performed until resolution.	
[a]NOTE: Any visual acuity impairment at screening should be documented and should be considered as baseline		
Other adverse reactions	**Encorafenib**	**Binimetinib**
Recurrent or intolerable Grade 2 or First occurrence Grade 3	Encorafenib and/or binimetinib should be withheld for up to 4 weeks (see table 8 to adjust encorafenib dose as monotherapy if it was not interrupted). ● If improved to Grade 0 or 1 or to baseline levels, then, encorafenib and/or binimetinib should be resumed at a reduced dose. If not improved, encorafenib and/or binimetinib should be permanently discontinued.	
Recurrent Grade 3	It should be considered to permanently discontinue encorafenib and binimetinib.	
First occurrence Grade 4	Encorafenib and/or binimetinib should be withheld for up to 4 weeks (see table 8 to adjust encorafenib dose as monotherapy if it was not interrupted too). ● If improved to Grade 0 or 1 or to baseline levels, then encorafenib and/or binimetinib should be resumed at a reduced dose level. ● If not improved, encorafenib and binimetinib should be permanently discontinued. Or, encorafenib and/or binimetinib should be permanently discontinued.	
Recurrent Grade 4	Encorafenib and binimetinib should be permanently discontinued.	

7.2.2. Follow-up for toxicities

Patients whose treatment is interrupted or permanently discontinued due to an adverse event or clinically significant laboratory value, must be followed up at least once a week (or more frequently if required by institutional practices, or if clinically indicated) for 4 weeks, and subsequently at approximately 4-week intervals, until resolution or stabilization of the event, whichever comes first.
Appropriate clinical experts such as an Ophthalmologist, cardiologist or dermatologist should be consulted as deemed necessary. Further guidelines and recommendations for the management of specific study drug Combination induced toxicities are provided in table 10.

7.2.2.1. Management of hand foot skin reaction (HFSR)

Because HFSR has been reported for encorafenib, it is recommended that patients are educated prior to starting study treatment to avoid activities that can cause friction on hands and feet. In addition, supportive measures for prevention and/or management of HFSR should be instituted.
Clinical judgment and experience of the treating physician should guide the management plan of each patient.

Dose reduction/interruption/discontinuation decisions for HFSR should be based on the CTCAE grade of the toxicity (Section 6.4) and the guidelines provided in table 10. A visit at a podiatrist may also be recommended at the discretion of the investigator.

7.2.2.2. Follow up evaluations for appearance of keratoacanthoma (KA) and/or squamous cell carcinoma (SCC)

The skin of patients will be examined regularly to monitor for the possible development of KA and/or SCC, as these have been reported to occur under selective BRAF inhibitor treatment (Flaherty et al 2010; Kefford et al 2010; Robert et al 2011). Patients should be instructed to inform their physicians upon the occurrence of any skin changes. In case of occurrence of KA and/or SCC, treatment of these lesions will follow institutional standards.

7.2.2.3. Management of nausea and/or vomiting

Because nausea and vomiting have been reported for encorafenib and binimetinib, it is recommended that patients are educated on the possibility of occurrence of these side effects prior to starting study treatment. Patient education as well as proper management of nausea and/or vomiting at the first sign is important. Clinical judgment and experience of the treating physician should guide the management plan of each patient. Patients experiencing nausea and/or vomiting CTCAE ≥1 will receive antiemetics at the discretion of the treating physician (as per local guideline). It is recommended that patients be provided a prescription for antiemetics and are instructed on the use of antiemetics on the first day of study drug treatment. Prophylactic antiemetics such as dexamethasone 8 mg, prochlorperazine, or metoclopramide may be administered to patients on an "as needed" basis.

Dose interruption/reduction decisions for nausea and/or vomiting should be based on the CTCAE grade of the toxicity and the guidelines provided in table 10.

As a guidance for recommendations on supportive measures for the prevention and/or management of nausea and/or vomiting, the published recommendation from American Society of Clinical Oncology (ASCO) [57], the European society of Medical Oncology (ESMO) and Multinational Association of supportive Care (MASCC)[58] can be used.

7.2.2.4 Monitoring of blood pressure

All patients must monitor their blood pressure at home at Days 14 and 42 after randomization if they meet at least one of the following criteria:

- Patients with history of hypertension and/or
- Patients receiving antihypertensive drugs before onset of study treatment and/or
- Patients with a screening systolic blood pressure of ≥140 mmHg and/or
- Patients with a screening diastolic blood pressure of ≥90 mmHg.

The investigator is to educate the patient on the signs and symptoms of hypertension and to evaluate the tension after taking any hypertensive drug and resting for 5 minutes in a sitting position if they use a home blood pressure monitor. More frequent assessments during the study drug treatment period may also be performed at the discretion of the investigator and if medically indicated.

Measurements are to be taken at the same time in the morning on Study Days 14 and 42, after taking any hypertensive medications and after being at rest for 5 minutes in a sitting position. If SBP ≥160 mmHg, or DBP ≥ 100 mmHg, the patient should contact his/her investigator to have an unscheduled visit. At this unscheduled visit, the patient's blood pressure should be assessed, and these measurements must be documented in the eCRF page. Early initiation of treatment and aggressive management of emergent hypertension must be implemented after its diagnosis.

A diary will be provided for the patients to record their self-assessed blood pressure measurements and present the collected data to the investigator for evaluation and appropriate management. This diary must be maintained in the patient's source documentation.

7.3. Concomitant Medications

All concomitant medications taken by the subject during the trial, starting from the date of signature of informed consent, will be recorded. The indication, dose, frequency, and dates of treatment will be recorded in the patient's medical records and in the appropriate section of the eCRF.

All medications (prescriptions or over-the-counter medications) on-going at the start of the trial or started during the study or until 30 days from the end of the last protocol treatment and different from the study medication will be documented.

7.3.1. Permitted concomitant treatment

The patient must notify the investigational site about any new medications he/she takes after the start of the study drug. All medications (other than study drug) and significant non-drug therapies (including physical therapy, herbal/natural medications and blood transfusions) administered during the study must be listed on the Concomitant Medications or the Surgical and Medical Procedures eCRF. Patients taking concomitant medications chronically should maintain the same dose and dose schedule throughout the study if medically feasible.

Any medications that are considered necessary to protect subject welfare and will not interfere with the trial medication may be given at the Investigator's discretion.

Rescue medications may be administered to address anticipated adverse reactions or anticipated emergency situations.

7.3.2. Permitted concomitant therapy requiring caution and/or action

Encorafenib is a reversible inhibitor of CYP2B6, CYP2C9, CYP3A4 and UGT1A1. It is also a time dependent inhibitor of CYP3A4. Binimetinib is also a reversible inhibitor of CYP2B6. Permitted medications to be used with caution in this study include those that are sensitive substrates of CYP2B6, CYP2C9, CYP3A4, and UGT1A1 or those substrates that have a narrow therapeutic index (NTI). Substrates of CYP3A4 are allowed based on a lack of interaction with midazolam. There is a potential for encorafenib to induce CYP3A4 at concentrations >10-50 uM, which may reduce the effectiveness of hormonal contraception methods. Therefore, the use of at least one form of non-hormonal contraception will be needed during the participation in this study. Please see Section 6.2 exclusion criterion 18 for use of contraception methods required for this study. Caution should be used in patients receiving concomitant treatment with other drugs that are substrates of CYP3A4 as the efficacy of these drugs could be reduced when administered with encorafenib.

Encorafenib has been identified to be primarily metabolized by CYP3A4 and to a lesser extent by CYP2C19 in vitro. The use of strong inhibitors of CYP3A4 are prohibited, please see section below. Moderate inhibitors of CYP3A4 and strong inhibitors of CYP2C19 should be taken with caution when co-administered with encorafenib. Patients should be closely monitored for the occurrence of adverse events. Regular assessments will be performed as described in Table 11. If a patient develops a toxicity, encorafenib dose may be adjusted as outlined in the dose modification Table 8.

Binimetinib has been identified to be primarily metabolized by glucuronidation. It is advised that strong inhibitors of UGT1A1 should be taken with caution when co-administered with binimetinib. Patients should be closely monitored for the occurrence of adverse events. Regular assessments will be performed as described in Table 11. If a patient develops a toxicity, binimetinib dose may be adjusted as outlined in the dose modification Table 9. In vitro data showed that both binimetinib and encorafenib are substrates of P-gp. Binimetinib is also a substrate of BCRP. Thus, the use of drugs that are known to inhibit or induce P-gp and BCRP should be used with caution. Encorafenib is a BCRP inhibitor. It is also a potent inhibitor of the renal transporters OAT1, OAT3 and OCT2 and the hepatic transporters OATP1B1 and OATP1B3. Therefore, the co-administration of drugs that are known to be sensitive or NTI substrate of BCRP, OAT1, OAT3, OCT2, OATP1B1 and OATP1B3 should be used with caution.

The solubility of binimetinib and encorafenib is pH dependent and a 10-fold decrease in solubility is observed between pH 1 and 2. Patients receiving concomitant treatments that could potentially modify the gastric pH (i.e. PPI) should be instructed to take them at least two hours after the administration of binimetinib.

7.3.3. Prohibited concomitant treatment

Any other investigational treatment within the past 30 days of treatment initiation and during the trial is disallowed.

Anticancer therapies (including chemo- or biologic-therapy or radiation therapy, covering >30% of the red bone marrow reserve, and surgery) are prohibited while the patients are receiving study treatment. If such therapeutic measures are required for a patient, then the patient must be discontinued from study treatment. If local treatment, radiotherapy or surgery, is indicated by the protocol of this study, it is allowed but following the next indication regarding the study treatment. To reduce possible skin toxicity during and after radiotherapy, encorafenib and binimetinib will be interrupted 24h before radiotherapy and restart 24h after the last dose of radiotherapy.

The concomitant use of strong CYP3A4 inhibitors would likely significantly increase the exposure of encorafenib and thus should not be used during this study.

7.4. Treatment Compliance

Study drug compliance will be assessed by the Investigator and/or study personnel at each patient visit for encorafenib and binimetinib and information provided by the patient and/or caregiver will be captured in the patient records as part of source documentation at each patient visit. Corresponding drug administration information will be reported also in the eCRF.

A patient medication diary will be provided for each patient. Patients or caregivers should complete this diary during the entire study.

The investigator or designee must maintain an accurate record of the shipment and dispensing of study treatments in the IWRS system designed for this trial (access to IWRS system will be created by study monitors during site initiation visit or can be asked by email to: [redacted].

Patients will be asked to return all unused study treatment and packaging on a regular basis, at the end of the study or at the time of study treatment discontinuation.

Compliance with the IMP schema is critical for patients and trial outcomes, and any deviation from the IMP schema may jeopardize trial results or may affect patient safety; for these reasons, non-compliance may be considered as a protocol deviation. When an investigational product is dispensed in a clinical trial, the investigator or a person designated by the investigator will ensure high level of compliance with the investigational product administration procedures.

All stages from IMP since will be documented in the corresponding forms to guarantee traceability during the procedure.

For this trial, IMP compliance will be assessed by reviewing the consistency of information in the IWRS, the eCRF, patient records, nurse sheets, and in the pharmacy source documentation.

At study close-out, and, as appropriate during the study, the investigator will return all used and unused study treatment, packaging, drug labels to the Sponsor or designee's monitor or to the Sponsor address provided in the investigator folder at each site.

Upon approval from the Sponsor personnel and after accountability has been confirmed by the Sponsor or designee's monitor, the study drug supply can be destroyed by the clinical site, according their normal practise, or, when destruction in site is not possible, destroyed at Sponsor supply vendor, as appropriate.

7.5. Randomization and Blinding

Not applicable.

7.6. Study Drug Supply, labelling, dispensing and handling

7.6.1. Study Drug Supply

The Sponsor will supply encorafenib and binimetinib throughout the study period and once ended the trial to those patients who are benefiting of study treatment, as long as, medication be available for this trial by the manufacturer of the IMPs. In case that the study is suspended or completed while there are still patients under treatment with COMBO 450, the investigator or responsible should evaluate both patient's clinical status to confirm that disease is controlled and then inform to the sponsor who will make sure that based on the available information of the efficacy of the treatment, current availability of the investigational medical product and the potential benefit for the patient, will ensure that the patient continues with treatment as long as there is clinical benefit from it.

The Investigator or responsible site personnel must instruct the patient or caregiver to take the study drug as per protocol. Study drug(s) will be dispensed to the patient by authorized site

personnel only. All dosages prescribed to the patient and all dose changes during the study must be recorded on the patient record and the eCRF.

7.6.2. Study drug labelling

All drugs (encorafenib and binimetinib) will be open label. Medication labels will be in the local language and comply with the legal requirements of each country, including storage conditions for the drugs, batch number and expiration date, among others. The patient number should be hand-written by the investigator or its staff at the drug delivery time.

7.6.3. Study drug storage

Study treatments must be received by designated personnel at the study site, handled and stored safely and properly, and kept in a secured location to which only the Investigator and designated site personnel have access.

Upon receipt, the study drugs should be stored according to the instructions specified on the drug labels and Investigator's Brochure for encorafenib and binimetinib. Study medication is to be stored in a secure locked area while under the responsibility of the Investigator. Receipt and dispensing of study medication must be recorded by an authorized person at the Investigator's site.

Records of drug formulation, batch number, and number of blisters dispensed must be recorded in the IWRS system elaborated for this trial and in pharmacy source records.

7.7. End of treatment

End of treatment is defined as the last visit where the decision is made to discontinue treatment. All required procedures of the Final Visit schedule may be completed within ±7 days of the end of treatment visit. Repeat disease assessment is not required if performed within 28 days prior to the end of treatment visit.

8. STUDY ASSESSMENTS

8.1. Schedule for tests and determinations

Table 11. Schedule for tests and determinations

Visit	Baseline (D-28 to D-1)	w4	w8 (D-56)	Every 4w	Every 8w	Every 12 w	End of treatment (28 +/-4d)	FU before DP	FU after DP for OS
Informed consent	X								
Screening registration	X								
Histology confirmation of disease	X								
BRAF Status	X								
Anamnesis	X								
Demographics	X								
Physical examination / vital signs	X	X	X	X			X		
ECOG PS	X	X	X	X			X	X	
Basic neurologic examination and Modified Barthel Index	X	X	X	X			X	X	
Ophthalmologic anamnesis an evaluation by Oncologist	X	X	X	X			X		
Ophthalmologist exploration	If clinical suspicion								
ECG	X	X				X	X		
LVEF *(as per institutional guidelines)*	X					X			
Concomitant medications	X	X	X	X			X		
Inclusion/exclusion criteria	X								
QoL	X	at weeks 8 and 24							
Analytical tests									
Clinical laboratory test	X	X	X	X			X	X	
Pregnancy test	X			X			X		
Disease evaluation									
Abdominopelvic CT Scan ([1])	X		X		X ([3])			X (every 8w) ([3])	
Brain MRI ([1,2])	X		X		X ([3])			X (every 8w) ([3])	

Colour Digital Photography (including a metric ruler) of skin lesions ([1])	X		X		X ([3])			X (every 8w) ([3])	
Safety evaluation									
Adverse events and Serious Adverse events		**Every 4 weeks throughout all the study (From ICF signature up to EoT visit)**							
Study Treatment									
COMBO450 follow-up and dispensing		X		X					
Dose reduction		Throughout all the study, when applicable							
Dose delay		Throughout all the study, when applicable							
Long term FU									
OS Follow-up									X
New anti-cancer therapy									X

([1]) Out of the assessments indicated by protocol, patients can be assessed whenever the investigator considers it indicated.
([2]) Contrast enhanced MRI.
([3]) Assessments will be done every two months up to 12 months, thereafter, patients will be assessed as per institutional criteria.

Protocol specifications for trial determinations

Informed Consent Form (ICF): Determinations performed by routine clinical practice before signing the informed consent will be valid, provided they are carried out following from this protocol, if they have been performed during the period included in the table 11.

Screening registration: Any patient that sign ICF should be registered in the EDC system and have assigned a unique screening number.

Anamnesis: to be performed during the baseline period in the 2 weeks prior to inclusion. Medical history will include all active conditions and any condition diagnosed considered to be clinically significant by the investigator. Melanoma history will be recorded separately and not listed as Medical History.

Demographics: Date of birth, race, and sex.

Physical examination/vital signs: Complete physical examination, weight, height, and vital signs (pulse, respiratory rate, **blood pressure** and body temperature).

ECOG-PS: Functional status will be assessed using the ECOG score.

Neurological examination: Basic neurological assessment according to normal practice and Modified Barthel Index according to “Guidelines for the Modified Barthel Index of Activities of Daily Living”

Ophthalmologic anamnesis and evaluation by Oncologist: ophthalmologic anamnesis and evaluation performed by oncologist as a part of physical examination and it will be performed at baseline and in every monthly visit. Only if there’s any alarm symptom or sign or previous ocular antecedents, patient will be evaluated by Ophthalmologist.

Ophthalmologist examination: Patient will be evaluated by Ophthalmologist if there’s any alarm symptom or sign or previous ocular antecedents.

ECG: Standard 12-lead ECG at baseline, after 4 weeks of treatment, after every 12 weeks and in the end of treatment visit. Additional ECGs may be performed at the discretion of the investigator.

Concomitant medication: All drugs taken within 30 days before starting the trial and concomitantly during the study will be recorded in medical records and in eCRF with indication, dose information and administration dates.

Inclusion and Exclusion Criteria: Verification that patients meet all inclusion criteria and none of exclusion.

Quality of Life: EORTC QLQ 30 administered at baseline, at week 8 and week 24.

Clinical laboratory test:

- **Complete haematology:** Complete blood count that includes total white blood cell count with leukocyte formula, haemoglobin, and platelet count.
- **Complete serum biochemistry and urinalysis:** including LDH, CK (CPK), gamma-glutamyltransferase (GGT), creatinine, creatinine clearance, , total bilirubin, alkaline phosphatase, aspartate aminotransferase (AST) or GOT, alanine aminotransferase (ALT) or GPT, Calcium (Ca), Potassium (K), and Magnesium (Mg).

The analytical studies may be performed up to 72 hours before the scheduled visits to have the results at the time of the patient’s visit. Liver function tests, including GGT, ALT, AST and total bilirubin should be performed following the indications of “schedule of determinations” and when clinically indicated, with more

frequent determinations in case of increases toxicities grade 2, 3 or 4.

- **Coagulation tests:** Coagulation monitoring will be performed in patients on anticoagulant drugs treatment. During the treatment at the discretion of the investigator or if the patient is receiving anticoagulants.

Pregnancy test:

All women with reproductive capacity MUST have a negative urine pregnancy test within 72 hours before receiving study treatment. The minimum sensitivity of the pregnancy test should be 25 IU/L or equivalent units of HCG. If the urine pregnancy test is positive, a blood test should be done and if this pregnancy test in serum is positive, the patient should not receive study treatment and should not be included in the study.

Disease evaluation

- **Radiological Assessment of Tumour Lesions**

Body CT-scan and contrast enhanced brain MRI will be performed baseline and every 8 weeks (+/-1 week) up to 12 months and according to normal practise thereafter.

In addition, CT/MRI scans must be obtained of anatomic regions not covered by the chest and abdomen scans, in subjects where there is clinical suspicion for deep soft tissue metastases (e.g., lesions in the thigh). Such additional CT/MRIs will be required at Screening only when deep soft tissue disease is and must be consistently repeated at all tumour assessment visits if a deep soft tissue lesion is identified during Screening. In cases without suspicion for deep soft tissue disease, no such CT/MRIs are required.

Similar methods of tumour assessment and similar techniques must be used to characterize each identified and reported lesion at Screening during the treatment evaluation phases. Imaging-based evaluation is preferred to clinical examination. Helical (spiral) CT scans of chest and abdomen are preferred. If not available, conventional (non-spiral CT) should be used. If not contraindicated, IV contrast should be used for all studies. If IV contrast is contraindicated, MRI should be used at the Screening exam and at all tumour assessment time points. Oral contrast should be used for all applicable imaging unless contraindicated.

A reference measurement ruler must be printed on every image for scale determination. Sections should be contiguous, similarly sized and consistent from visit-to-visit. Section thickness must be based on institutional standards (e.g., from 5 to 8 mm, 10 mm cuts are not recommended). Chest x-rays and ultrasound are not acceptable methods to measure disease. Response and progression of disease must be documented by CT or MRI like the methods used at Screening.

Screening bone scans are not mandatory and should be performed as clinically indicated. Abnormal findings on Screening bone scans, consistent with malignant disease, require follow-up bone scans in specified intervals. Normal bone scans at Screening do not require follow-up bone scans, except when clinically indicated. Abnormal bone scans should be confirmed with radiographic plain films, CT or MRI. Similarly, progressive disease based only on new lesion(s) found on bone scans must be supported with plain films, CT or MRI imaging studies of the bone lesion(s) to confirm their malignant nature. Increased intensity of uptake in previously abnormal areas on bone scans is not considered progressive disease, unless the lesions seen on the correlative imaging studies confirm the finding of disease progression. New areas of abnormal uptake on a bone scan represent disease progression.

Out of the assessments indicated by protocol, patients can be assessed whenever the investigator considers it indicated.

- Intracranial tumour response evaluation of brain lesions will be conducted, according to modified RECIST 1.1 criteria until disease progression, more information is detailed in section 10.3.
-

- **Non-radiological Assessments**

Visible cutaneous lesions must be measured clinically. Digital and standardized photographic images including a ruler for scale as part of the image are recommended for documentation. All clinical assessments must be performed within proximity (± 7 days) of any protocol specified radiographic assessments

Safety evaluation: Safety assessments and adverse events include tumour-related, unrelated and treatment-related signs and symptoms. Adverse events will be documented and recorded in the CRF upon patient notification. AEs will be collected from the signing of Informed Consent until the end of treatment visit (30 days after end of treatment) or up to resolution. Classification of toxicity will be done according to the common terminology criteria for adverse events of the National Cancer Institute, version 4.03 (NCI CTCAE v. 4.03).

PFS follow-up: Body CT-scan and contrast enhanced brain MRI will be performed baseline and every 8 weeks (+/-1 week) up to 12 months and according to normal practice thereafter **until disease progression, independently of the end of treatment reason if it was not the documentation of disease progression.**

OS Follow-up: After disease progression all patients will be monitored to determine subsequent antineoplastic treatments and survival. It is recommended to maintain contacts by phone or by other methods every 4 weeks to carry out timely follow-up (up to 24 months or study closure).

New anti-cancer therapy: Information on subsequent treatments should include the list of post-treatment treatments, the drugs administered, and the date of initiation and discontinuation of each drug. All data will be recorded in the medical record and in the eCRF.

8.2. Schedule of Assessments

Prior to performing any trial assessments that are not part of routine medical care for the subject, the Investigator will obtain written informed consent as described in Section 5.2.

a) Baseline Assessments

The following assessments and procedures should be performed within 28 days before inclusion, and when applicable, as close as possible to the start of study treatment:

- Informed consent
- Screening registration
- Inclusion /exclusion criteria
- Medical history including previous cancers treatments
- Histology confirmation of disease
- BRAF mutation status (local)
- Anamnesis
- Demographics
- Physical examination and vital signs
- ECOG performance status
- Neurologic examination and Modified Barthel Index
- Ophthalmologic anamnesis and evaluation by Oncologist (if there's any alarm symptom or sign, patient will be evaluated by Ophthalmologist)
- ECG
- Concomitant medications
- Quality of Life questionnaires (QoL)

- Haematology, coagulation, serum biochemistry including CK and LDH determination (within 72 h before).
- Urine pregnancy test for woman of childbearing potential (within 72 h before), and in case this test be positive, a serum pregnancy test should be done.
- LVEF
- CT Scan
- Contrast enhanced brain MRI
- Colour Digital Photography (including a metric ruler) of the skin lesions

b) Prior treatment administration (≤7 days before day 1 (D1) of cycle 1 (C1)):

The following assessments and procedures should be performed within 7 days before start of study treatment (determination performed during "baseline assessments" can be used for the purposes of "prior treatment determination" if they are performed within 7 days before start of treatment):

- Physical examination and vital signs
- ECOG performance status
- SAEs related to study procedures (e.g. blood sampling) must be reported including screening failures (and reason for screening failure)
- Concomitant medications
- Urine pregnancy test for women of childbearing potential (within 72 h before) and in case this test be positive, a serum pregnancy test should be done
- Haematology, coagulation, serum biochemistry including CK and LDH determination (within 72 h before).

c) On treatment visits

1. - On week 4

- Physical examination
- Vital signs
- ECOG performance status
- Neurologic examination and Modified Barthel Index
- Ophthalmologic anamnesis and evaluation by Oncologist (if there's any alarm symptom or sign, patient will be evaluated by Ophthalmologist)
- ECG
- Adverse events follow-up
- Concomitant medications
- Haematology, coagulation, serum biochemistry, pregnancy test (urine test, and in case this test be positive, a serum pregnancy test should be done to confirm no pregnancy).
- COMBO450 follow up and dispensing

2. - On week 8

- Physical examination
- Vital signs
- ECOG performance status
- Neurologic examination and Modified Barthel Index

- Ophthalmologic anamnesis and evaluation by Oncologist (if there's any alarm symptom or sign, patient will be evaluated by Ophthalmologist)
- Adverse events follow-up
- Concomitant medications
- Haematology, coagulation, serum biochemistry,
- CT Scan
- Contrast enhanced brain MRI
- Colour Digital Photography (including a metric ruler) of the skin lesions
- QoL

3. - Every 4 weeks until disease progression

- Physical examination
- Vital signs
- ECOG performance status
- Neurologic examination and Modified Barthel Index
- Ophthalmologic anamnesis and evaluation by Oncologist (if there's any alarm symptom or sign, patient will be evaluated by Ophthalmologist)
- Adverse events follow-up
- Concomitant medications
- Haematology, coagulation, serum biochemistry
- Pregnancy test (urine test, and in case this test be positive, a serum pregnancy test should be done to confirm no pregnancy.)
- COMBO450 follow up and dispensing

4. - Every 8 weeks until disease progression

- CT Scan
- Contrast enhanced brain MRI
- Colour Digital Photography (including a metric ruler) of the skin lesions
- QoL (on week 24)

5. - Every 12 weeks until disease progression

- ECG
- LVEF

d) End of treatment - Safety visit (after 28 days of end of treatment)

Safety visit will be performed at day 28±4d after the end of treatment to determine patient general status and clearly identify adverse events that persists and could be related to study drug. After this visit, only SAEs that could be related to study drug should be expedited reported to the Sponsor.

- Physical examination
- Vital signs
- ECOG performance status
- Neurologic examination and Modified Barthel Index
- Ophthalmologic anamnesis and evaluation by Oncologist (if there's any alarm symptom or sign, patient will be evaluated by Ophthalmologist)
- ECG

- Adverse events follow-up
- Concomitant medications
- Haematology, coagulation, serum biochemistry,
- Pregnancy test (urine test and in case this test be positive, a serum pregnancy test should be done to confirm no pregnancy.

e) Follow-up before progression disease

- ECOG performance status
- Neurologic examination and Modified Barthel Index
- Haematology, coagulation, serum biochemistry, and pregnancy test (urine test and in case this test be positive, a serum pregnancy test should be done to confirm no pregnancy.), (only if patient it's on treatment)
- CT Scan (every two months up to 12 months, thereafter patients will be assessed as per institutional criteria)
- Contrast enhanced brain MRI (every two months up to 12 months, thereafter patients will be assessed as per institutional criteria)
- Colour Digital Photography (including a metric ruler) of the skin lesions (every two months up to 12 months, thereafter patients will be assessed as per institutional criteria).

After one year of 1st day of treatment, follow up will be performed according local normal practise.

f) Follow-up before progression disease after ending treatment:

- Subjects who no longer receive study treatment due to progression should remain in follow-up until their death or until the closure of the study (whichever comes first).
- Subjects who no longer receive study treatment due to unacceptable toxicity or at the discretion of the investigator should remain in follow up until progression. Visits will be scheduled every 8 weeks and tumor evaluation should be performed every 8 weeks until tumor progression the fist year, and after 12 months, the tumor evaluation can be done as per institutional criteria.The tests and questionnaires can be done according to the normal practise too.
- Subjects who have switched to an alternative treatment do not perform a formal follow-up, except to record the date of the death.

g) OS Long term follow-up

- New anticancer therapy

Follow-up after disease progression will be made according to local practice. Survival information may be obtained via telephone contact with the patient, patient's family or by contact with the patient's current physician. Survival data will be collected up to the time of the final overall survival (OS) analysis. At this point Investigators will be notified that no further data collection for the study is required.

The status of ongoing, withdrawn (from the study) and lost to follow up patients at the time of an overall survival analysis should be obtained by the site personnel by checking the patient notes,

hospital records, contacting the patient's general practitioner and checking publicly available death registries.

8.3. Study timetable and end of study

- Expected recruitment period: 36 months
- Expected follow-up: 24 months

8.3.1. End of Study Declaration

Last Patient Last Visit, expected on 1Q 2024. The study will be considered closed from a normative point of view after data on primary and secondary variables are sufficiently prepared for its initial publication.

8.3.2. Early study termination

This study can be terminated prematurely if in the opinion of the sponsor there is a reasonable and sufficient cause. The investigator will receive a written notification in which the sponsor motivates the interruption of the study.

Reasonsthat justify are as follows, but not limited to:

- Finding of unforeseen, considerable or unacceptable risks for the patients.
- Impossibility to include an acceptable number of patients.
- Insufficient compliance with protocol requisites.
- Plans to modify, halt or discontinue the development of study drug.
- In case of early termination of the study, all the study material must be returned to Sponsor.

9. Assessment of Safety

The safety population (SP) consists of all enrolled subjects who received at least one dose of study treatment. Patients will be monitored for safety during all stages of the study. All safety and tolerability assessments will be done at pre-dose unless otherwise specified.

Assessment of adverse events, safety, and toxicity will be performed according to the National Cancer Institute Common Toxicity Criteria (version 4.03) from the time of Informed Consent for the pre-registration phase until the end of study. The safety of study treatment will be assessed through the recording, reporting and analysing of baseline medical conditions, adverse events, and physical examination findings including vital signs, ECGs and laboratory tests.

9.1. Safety Parameters

9.1.1. Demographic/Medical History

All clinically relevant demographic and medical history data will be obtained from all patients enrolled in the study, by the investigator or qualified designee. Medical history will include all active conditions, and any condition diagnosed that are considered clinically significant by the Investigator. Melanoma history will be recorded separately and not listed as Medical History.

9.1.2. Prior Medications

The investigator or qualified designee will review prior medication use, including any protocol-specified washout requirement, and record prior medication taken by the subject within 30 days before starting the trial. Prior treatments for melanoma will be recorded.

9.1.3. Vital Signs

The investigator or qualified designee will take vital signs at screening, prior to the administration of COMBO 450 and as specified in the Table of Schedule of Assessments. Vital signs include temperature, pulse, respiratory rate, weight and blood pressure (after sitting for 5 minutes). Height will be measured at screening only.

9.1.4. Physical Examination

A standard physical examination will be performed to all patients treated with COMBO 450 as specified in the Table of Schedule of Assessments.

9.1.5. Electrocardiogram (ECG)

A standard 12-lead ECG will be performed using local standard procedures once at baseline and as specified in the Table of Schedule of Assessments. Clinically significant abnormal findings should be recorded as medical history.

9.1.6. Laboratory Assessments

Laboratory tests for haematology, chemistry and urinalysis will be performed as specified in the Table of Schedule of Assessments.

9.1.6.1. Pregnancy Screening

In any woman of childbearing potential, i.e. not > 1 year postmenopausal or surgically sterilized, a urine dipstick pregnancy test will be performed at both screening, and then (urine test) every 4 weeks and end-of-study. If the dipstick test indicates a positive result, an hCG laboratory blood test will be performed to confirm the pregnancy.

A woman of childbearing potential cannot be included in the study if any of the following occurs:

- The urine dipstick pregnancy test indicates a positive result and the pregnancy has been not yet been ruled out by the following β-HCG blood test
- No urine dipstick pregnancy test has been performed at screening
- The urine dipstick pregnancy test indicates a negative result, but early pregnancy (≤ 2 weeks from conception) is suspected by the Investigator based on anamnestic elements
- The urine dipstick pregnancy test indicates a negative result, but a pregnancy is suspected by the Investigator based on clinical elements and cannot be ruled out by further investigation.

If a positive urine dipstick pregnancy test occurs at end-of-study, or if a pregnancy is suspected at any time during the study, an hCG blood test will be performed to confirm the pregnancy.

9.1.6.2. Eastern Cooperative Oncology Group (ECOG) Performance Status

The investigator or qualified designee will assess ECOG status at screening, prior to the administration of each dose of trial treatment and as specified in the Table of Schedule of Assessments.

9.2. Adverse and Serious Adverse Events

9.2.1. Definitions

Definitions regarding safety and pharmacovigilance to be applied in this study are defined below.

9.2.1.1. Adverse Event (AE)

An AE is defined as any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. An adverse event (AE) can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product, whether considered related to the medicinal product.

9.2.1.2. Serious Adverse Event (SAE)

A serious adverse event is an AE occurring during any study phase (ie, screening, treatment, or follow-up), that fulfils one or more of the following:

- Results in death.
- It is immediately life-threatening.

- It requires in-patient hospitalization or prolongation of existing hospitalization (hospitalization should not be considered as an AE (therefore also not an SAE) when it is due to: medical or surgical procedures planned before study entry or due to social or economic reasons.
- It results in persistent or significant disability or incapacity.
- Results in a congenital abnormality or birth defect.
- It is a new cancer (that is not a condition of the study). Although new cancer is not always serious as per regulatory definitions, these should be considered and reported as such, with the seriousness criterion “important medical event”.
- It is an important medical event that may jeopardize the patient or may require medical intervention to prevent one of the outcomes listed above. Medical and scientific judgement should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition above. These should also usually be considered serious. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependence or drug abuse.

9.2.1.3. Suspected unexpected serious adverse reaction (SUSAR)

SUSARs are serious adverse reactions that could be related to the IMP and assessed as unexpected based on the applicable encorafenib and binimetinib Investigator’s Brochure (IB).

9.2.1.4. Adverse drug reaction (ADR)

All noxious and unintended responses to a medicinal product related to any dose should be considered adverse drug reactions. The phrase "responses to a medicinal products" means that a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility, i.e., the relationship cannot be ruled out.

9.2.1.5. Serious adverse reaction (SAR)

A Serious Adverse Reaction is any adverse reaction that fulfils the criteria of seriousness as defined above, therefore is an adverse reaction which results in death, is life-threatening, requires inpatient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability or incapacity, is a congenital anomaly/birth defect, is a new cancer (that is not a condition of the study) or it is an important medical event that might not be immediately life-threatening or result in death or hospitalisation but might jeopardise the patient or might require intervention to prevent one of the other outcomes listed in the definition above.

9.3. Assessment

All assessments of AEs (serious and non-serious) listed below should be recorded on the Adverse Event page of the CRF/eCRF or in the SAE form as appropriate.

9.3.1. Causality Assessment

An Investigator who is qualified in medicine must make the determination of relationship to the investigational product for each AE (Related or Unrelated). The Investigator should decide whether, in his or her medical judgment, there is a reasonable possibility that the event may have been caused by the investigational product. If no valid reason exists for suggesting a relationship, then the AE should be classified as “unrelated.” If there is any valid reason, even if undetermined, for suspecting a possible cause-and-effect relationship between the investigational product and the occurrence of the AE, then the AE should be considered “related.”

9.3.2. Expectedness assessment by the sponsors

The ‘expectedness’ of a serious adverse reaction is assessed in the light of the encorafenib and or binimetinib IB. The expectedness assessment will be performed by Sponsor according the information available in last version of study treatment IB. If information on the expectedness has been made available by the reporting investigator, this should be taken into consideration by Sponsor. If Sponsor disagrees with the investigator’s expectedness assessment, both, the opinion of the investigator and the sponsor should be provided with the report.

9.3.3. Severity assessment

Severity of AEs will be assessed according to the CTCAE which provides a descriptive terminology, which can be utilized, for Adverse Event (AE) reporting. A grading (severity) scale is provided for each AE as follows:

Grades: Grade refers to the severity of the AE. The CTCAE displays Grades 1 through 5 with unique clinical descriptions of severity for each AE based on this guideline:

- Grade 1 Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
- Grade 2 Moderate; minimal, local or non-invasive intervention indicated; limiting age-appropriate instrumental Activities of Daily Living (ADL)*
- Grade 3 Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL**
- Grade 4 Life-threatening consequences; urgent intervention indicated
- Grade 5 Death related to AE

*Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

**Self-care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

9.3.4. Action taken

All AEs should be treated appropriately. Treatment may include one or more of the following: no action taken (i.e. further observation only); study medication temporarily interrupted; study

medication permanently discontinued due to this AE; drug therapy given; non-drug therapy given, surgery, hospitalization, unknown, other.

9.3.5. Outcome

Investigators should follow-up AEs until resolution. The outcome of the AEs should be assessed as follows:

- Recovered/Resolved
- Recovering/Resolving
- Not recovered/Not resolved
- Recovered/Resolved with sequelae
- Fatal
- Unknown

9.4. Reporting

9.4.1. Reporting an Adverse Event

Adverse events (serious and non-serious) spontaneously reported by the patient and/or in response to an open question from the study personnel or revealed by observation will be recorded during the study at the investigational site. Information about AEs (including SAEs) will be collected from the signing of Informed Consent at least until the end of treatment visit or up to resolution. For each AE, the investigator will evaluate and report the onset (date and time), resolution (date and time), severity, causality, action taken, outcome, and whether it caused the patient to discontinue the study.

9.4.2. Reporting a Serious Adverse Event

Any SAEs considered related to the investigational product and discovered by the Investigator at any time after the study should be reported.

Any SAE must be reported by submitting the completed **initial report** section of the trial-specific SAE form within 24 hours of becoming aware of the event. Submission is done by sending the SAE form by fax or e-mail to [redacted]

Serious Adverse Events
All serious adverse events must be reported by fax within 24 h to [redacted]

The SAE outcome must be reported within 2 weeks after initial report by submitting the **follow-up** report (e.g. initial SAE form, updated with follow-up information) to the Pharmacovigilance as above. In case the SAE is reported as ongoing after 14 days, the follow-up report must be submitted again with the final outcome. The originals of the SAE forms (both initial and follow-up reports) are kept at the sites in the Investigator's file. The Pharmacovigilance will forward each individual SAE to the coordinating investigator, supporting coordinating investigators and to Sponsor within one working day. Wherever possible copy of summary of hospitalization, autopsy

reports, and relevant laboratory examinations should be provided. Additional follow-up information, if required or available, should all be faxed to Sponsor within one business day of receipt and this should be completed on a follow-up SAE form and placed with the original SAE information and kept with the appropriate section of the CRF and/or study file.

The Sponsor is responsible for notifying the relevant regulatory authorities of certain events. Investigators will also be notified of all unexpected, serious, drug-related events (7/15 Day Safety Reports) that occur during the clinical study.

All SAEs that occur after any patient has signed the first Informed Consent, until end of treatment visit, whether they are related to the study, must be recorded on forms provided by the Sponsor

9.4.3. Reporting Pregnancy

In case of a pregnancy notified after the first dose was received, the patient will not receive the following dose and will be followed after delivery of her child. All initial reports of pregnancies in a patient and pregnancies in partners of male patients included in the study from the screening visit must be reported to the Pharmacovigilance by the Investigator within 24 hours of knowledge of the event, using a Pregnancy Form.

Should a pregnancy occur, it must be reported and recorded on pregnancy form. Pregnancy in itself is not regarded as an AE unless there is a suspicion that an investigational product may have interfered with the effectiveness of a contraceptive medication.

Any pregnancy-related SAE (e.g. spontaneous abortion) or any other SAE experienced during pregnancy must be recorded on a separate SAE Report Form provided by Pharmacovigilance and reported to Pharmacovigilance as per SAE reporting procedures.

Abnormal pregnancy outcomes are considered SAEs and must be reported using the SAE Form. Investigators must actively follow-up, document and report to Sponsor the progress of the pregnancies until an outcome is reached. At the end of pregnancy, the Investigator will complete an End of Pregnancy Form provided by Pharmacovigilance and report it to Pharmacovigilance.

The outcome of all pregnancies (spontaneous miscarriage, elective termination, normal birth or congenital abnormality) must be followed up and documented even if the patient was discontinued from the study.

All reports of congenital abnormalities/birth defects are SAEs. Spontaneous miscarriages should also be reported and handled as SAEs. Elective abortions without complications should not be handled as AEs.

9.5. Reporting of individual SAEs and SUSARs by the Sponsor

Sponsor ensures that all reporting requirements and timelines for reporting, as defined in the applicable national law will be followed. [redacted] will distribute all SUSAR to all principal Investigators, and to each Regulatory Agency. [redacted] will forward each individual SAE to the coordinating investigator.

9.6. Periodic reporting on safety to principal investigators

The Sponsor through [redacted] ensures that the reporting requirements and timelines for reporting, as defined in the respective applicable laws, are followed. A Development Safety Update Report (DSUR) will be provided to the local investigators for filing into the investigator's file. [redacted] will submit the DSUR to the involved ECs and involved Regulatory Agencies.

10. STATISTICS

10.1. Sample size calculation

Sample size calculation:

The sample calculation has been done for the **initially proposed primary endpoint (cohort 1)** and it's based on a Fleming's Single Stage Procedure:

We want to show that the Intracranial response rate by modified RECIST 1.1 before local treatment is superior or equal to the reference value, say, ϑ0=40%. Under the hypothesis to have a response rate under new treatment (π1) of 60% with α risk = 5% in one-sided test and a power of 80%, the required sample size is 38 patients.

Finally, assuming that, 20% of patients will be lost of follow up, die or progress before day 56 without doing the first tumour assessment (according data published in COMBI-MB study), the initial sample size will be 48 patients, to obtain 38 evaluable patients.

10.2. Study endpoints

Intracranial objective response (iORR) rate by modified RECIST 1.1 before local treatment in cohort 1 and 2: iORR calculated as the proportion of patient with a best overall intracranial response of complete response (CR) or partial response (PR) before local treatment in cohort 1 and 2. The final statistical analysis of this endpoint is expected to be performed within 3 months after the local treatment of the last patient in any cohort. iORR will be also reported separately for both cohorts.

Duration of intracranial response in both cohorts (iDOR): Calculated as the time from the date of first documented CR or PR to the first documented intracranial progression or death due to underlying cancer, in patients with documented intracranial CR or PR before local treatment. The final statistical analysis of this endpoint is expected to be performed within 6 months after database closure expected at 24 months after last patient inclusion, however interim analysis might be performed when analysing other primary variables.

The intracranial progression free survival (iPFS) by modified RECIST in both cohorts: iPFS is defined as the time from the date of inclusion to the date of the first documented intracranial disease progression or death due to any cause, whichever occurs first. PFS will be determined based on tumour assessment (modified RECIST version 1.1 criteria). The local Investigator's assessments will be used for analyses. Those patients who are alive and have not progressed at the last follow-up, date of progression will be censored at the date of the last follow-up. Patient with no additional image test other than baseline will be censored to the day after to inclusion. The final statistical analysis of this endpoint is expected to be performed within 6 months after database closure expected at 24 months after last patient inclusion, however interim analysis might be performed when analysing other primary variables.

Percentage of patients free of intracranial progression at 6 (week 24), 12 (week 48) and 24 months (week 96) in both cohorts: percentage of patients free of intracranial progression assessed by modified RECIST at 6 months (week 24), 12 months (week 48) and 24-month (week 96) considering date of inclusion. The final statistical analysis of this endpoint is expected to be

performed within 6 months after database closure expected at 24 months after last patient inclusion, however interim analysis might be performed when analysing other primary variables

Percentage of patients (%) free of extracraneal progression at 6 (week 24), 12 (week 28) and 24 months (week 96): percentage of patients free of progression by RECIST 1.1 at 6 months (week 24), 12 months (week 48) and 24-month (week 96) considering date of inclusion. The final statistical analysis of this endpoint is expected to be performed within 6 months after database closure expected at 24 months after last patient inclusion, however interim analysis might be performed when analysing other primary variables.

Overall Survival in both cohorts (OS): OS is calculated as the time from date of inclusion to date of death due to any cause. The final statistical analysis of this endpoint is expected to be performed within 6 months after database closure expected at 24 months after last patient inclusion, however interim analysis might be performed when analysing other primary variables.

Percentage of patients (%) alive at 6, 12 and 24 months in both cohorts: percentage of patients alive at 6 months, 12 month and 24-month considering date of inclusion. The final statistical analysis of this endpoint is expected to be performed within 6 months after database closure expected at 24 months after last patient inclusion, however interim analysis might be performed when analysing other primary variables.

Toxicity of the combination until local treatment: Number of patients with adverse events and serious adverse events, changes in laboratory values, vital signs, electrocardiograms (ECGs), LVEF (MUGA (Multigated Acquisition Scan) / echocardiogram) and assessment of physician, dermatological and ocular examinations graded according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) v 4.03 until local treatment (local treatment D1). It will be studied using descriptive statistics techniques, such as frequency tables and contingency tables. The final statistical analysis of this endpoint is expected to be performed within 6 months after database closure expected at 24 months after last patient inclusion, however interim analysis might be performed when analysing other primary variables.

Toxicity of the combination after local treatment: Number of patients with adverse events and serious adverse events, changes in laboratory values, vital signs, electrocardiograms (ECGs), LVEF (MUGA (Multigated Acquisition Scan) / echocardiogram) and assessment of physician, dermatological and ocular examinations graded according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) v 4.03 after local treatment (after end of local treatment date). It will be studied using descriptive statistics techniques, such as frequency tables and contingency tables. The final statistical analysis of this endpoint is expected to be performed within 6 months after database closure expected at 24 months after last patient inclusion, however interim analysis might be performed when analysing other primary variables.

Quality of life: Change from baseline in the global health status score of the EORTC QLQ-C30. The final statistical analysis of this endpoint is expected to be performed within 6 months after database closure expected at 24 months after last patient inclusion, however interim analysis might be performed when analysing other primary variables.

10.3. Efficacy assessment

Magnetic contrast enhanced brain resonance imaging (MRI) and body CT scan will be performed at baseline and every 8 weeks up to 12 months and according to normal practise thereafter. All lesions selected as target and non-target lesions in the initial evaluation will be measured according to the aforementioned timeline, until disease progression. Imaging tests will be performed using the same method each time.

After local treatment, intracranial lesions (both target and non-target lesions) will be considered as non-evaluable (NE), brain MRI be performed as per protocol (every 8 weeks until first year and according to normal practise thereafter) however disease will be followed only to determine iPFS (unequivocal disease progression or new lesions).

10.3.1 Assessment of response guidelines

Table 12. Criteria for disease evaluation for target lesions

CR	Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm
PR	At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.
PD	At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progression).
SD	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.

Table 13. Criteria for disease evaluation for non-target lesions

CR	Disappearance of all non-target lesions and normalisation of tumour marker level. All lymph nodes must be non-pathological in size (<10 mm short axis).
Non-CR/non-PD	Persistence of one or more non-target lesion(s) and/or maintenance of tumour marker level above the normal limits.
PD	Unequivocal progression (see comments below) of existing non-target lesions. (Note: the appearance of one or more new lesions is also considered progression).

Table 14: Overall Response Assessment (RECIST)

Target Lesions	Non-target Lesions	New Lesions	Overall Response
CR	CR	No	CR
CR	Non-CR/non-PD	No	PR

CR	Not evaluated	No	PR
PR	Non-PD or not all evaluated	No	PR
SD	Non-PD or not all evaluated	No	SD
Not all evaluated	Non-PD	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD
CR = complete response, PR = partial response, SD = stable disease, PD = progressive disease, and NE = not evaluable			

Disease progression and response evaluations for intracranial and extracranial disease will be determined according to the definitions established in the Response Evaluation Criteria in Solid Tumours (RECIST 1. 1); Minor modifications will be applied to the assessment of intracranial lesions:

Intracranial response assessment: The Investigator modified RECIST 1.1 criteria will be used to evaluate the intracranial response. The modifications to RECIST 1.1 impact the number and the minimal size of the target lesions selected at baseline. Up to 5 intracranial lesions should be selected as target; based on size and evaluation/tracking feasibility. All the remaining brain lesions different from these 5 target lesions must be considered as non-target lesions (independently of their size). The size of target and non-target lesions must be measured. Measurable lesions are defined as those that can be accurately measured in at least one dimension with the longest diameter ≥ 5 mm when evaluated by contrast-enhanced MRI.

For intracranial response, target lesions as small as 5 mm may be selected, however the scanning should be in accordance with modified RECIST 1.1 (contiguous slices of maximum thickness corresponding to half the size of the lesion.

Contrast-enhanced MRI is the only modality accepted for the assessment of intracranial lesions For justified exceptions please, contact with the sponsor: [redacted].

10.3.2 Measurable and non-measurable definitions for response assessment

- RECIST 1.1 standard definitions will be used

10.3.3 Measurable and non-measurable definitions for intracranial response assessment

- Measurable intracranial lesion: a measure that can be accurately measured at least in one dimension with the longest diameter ≥ 5 mm when evaluated by contrast-enhanced MRI.
- Non-measurable intracranial lesion: all other lesions, including those too small to be considered measurable (longest diameter < 5 mm).
- Measurable intracranial disease: The presence of at least one measurable lesion.
- Non-measurable intracranial (only) disease: The presence of only non-measurable lesions, which at baseline excludes the patient for participation in the study.

10.4. Safety assessment

All patients included in the trial and have received at least one dose of study medication will be evaluable for safety analysis.

Safety and tolerability of study medication will be determined by evaluating the type, incidence, frequency, severity and relation to the treatment of reported adverse events, physical examinations and laboratory tests. Any signs and/or symptoms associated with the existing tumour at baseline worsening (in severity or frequency) during the trial should be reported as an adverse event. They should record all adverse events according to the NCI-CTCAE version 4.03 in each study visit.

10.5. Definition of study populations

Data of study will be analysed in the following populations:

1. *ITT:* All patients that have been enrolled in the trial.
2. *Evaluable population per protocol (PP)*: All patients fulfilling all eligibility criteria and having at least two valid tumour assessments (baseline and one evaluation MRI or CT-scan) without any protocol deviation that makes the patient invalid for the primary endpoint evaluation.
3. *Safety population*: All patients receiving at least one dose of treatment.

10.6. Statistical analysis

For each categorical variable, the results will be summarized by frequencies and percentages. For each continuous variable, the results will be summarized by descriptive statistics such as median, range, and interquartile range or by means, standard deviations and 95% confidence intervals (CIs). For proportions, point estimates and exact 95% confidence intervals will be calculated. For time to event endpoints, Kaplan-Meier estimates at selected time points and corresponding curves will be presented. Time to event is derived relative to the first study treatment administration. Laboratory values will be expressed as the absolute values and as grading (ordinal categorical variables) according to NCI CTCAE v 4.03.

Treatment-emergent AE (AEs starting after the administration of study treatment and up to study completion) will be summarized by system organ class and preferred term. Grading will be presented by type and grade in tables showing frequency and percentage of the within-patient worst grades. In addition, grade ≥3 AEs will be summarized separately. Full analysis details will be outlined in the statistical analysis plan (SAP).

10.7. Statistical Methods

Analysis will be based on observed data, and missing data for dropouts are not replaced by methods like LOCF (last option carried forward).

Continuous data will be presented with the number of observations, mean value + standard deviation, median value + minimum and maximum. Categorical data will be presented as counts and percentages. Individual subject data will be listed.

Individual and summary vital signs, ECG parameters, clinical laboratory data (haematology, serum biochemistry and urinalysis) will be presented in tabular form. For the values outside the reference range will be flagged and for the clinically significantly abnormal values will be listed in tabular form. Adverse events will be tabulated by system organ class and preferred term after medical coding using the NCI CTCAE v 4.03.

11. DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

11.1. Source data definition

Source data is defined as all data in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical trial that are necessary for the reconstruction and evaluation of the trial.

The Investigator must keep a file (medical file, original medical records) on paper or electronically for every subject in the trial. It must be possible to identify each subject by using this subject file. This file will contain the demographic and medical information for the subject listed below and should be as complete as possible.

- Subject's full name, date of birth, sex, height, weight
- Medical history and concomitant diseases
- Prior and concomitant therapies (including changes during the trial)
- Trial identification, that is, the Sponsor trial number for this clinical trial, and subject number
- Dates for entry into the trial (informed consent) and visits to the site
- Any medical examinations and clinical findings predefined in this clinical trial protocol
- All AEs
- Date that the subject left the trial including any reason for early withdrawal from the trial or IMP (if applicable).

All documents containing source data must be filed, including, but not limited to CT or MRI scan images, ECG recordings, and laboratory results. Such documents must bear the subject number and the date of the procedure. If possible, this information should be printed by the instrument used to perform the assessment or measurement. Medical evaluation of such records will be performed as necessary; all evaluations will be documented, signed, and dated by the Investigator.

Electronic subject files will be printed whenever the Monitor performs source data verification. Printouts will be signed and dated by the Investigator, countersigned by the Monitor, and will be secured in a safe place at the site.

11.2. Study Monitoring

During the study, according to monitoring plan, a monitor from [redacted] will have regular contact with the investigational site, for the following:

- Provide information and support to the investigator(s)
- Confirm that facilities remain acceptable
- Confirm that the investigational team is adhering to the protocol, data are being accurately recorded in the case report forms, and that investigational product accountability checks are being performed
- Perform source data verification. This includes a comparison of the data in the case report forms with the patient's medical records at the hospital or practice, and other records relevant to the study. This will require direct access to all original records for each patient (e.g. clinic charts).
- Record and report any protocol deviations not previously sent to [redacted]

- Confirm that AEs and SAEs have been properly documented on CRFs and confirm that all SAEs have been forwarded to MFAR, additionally, confirm that all the SAEs that met criteria for reporting have been forwarded to the IRB

The monitor will be available between visits if the investigator(s) or other staff members need information or advice.

11.3. Audits and Inspections

Authorized representatives of Sponsor, a regulatory authority, an Independent Ethics Committee or an Institutional Review Board may visit the site to perform audits or inspections, including source data verification. The purpose of a Sponsor audit or inspection is to systematically and independently examine all study-related activities and documents to determine whether these activities were conducted, and data were recorded, analysed, and accurately reported according to the protocol, Good Clinical Practice guidelines of the International Conference on Harmonization, and any applicable regulatory requirements. The investigator should contact Sponsor through [redacted] immediately if contacted by a regulatory agency about an inspection.

11.4. Independent Ethical Committee (IEC) or Institutional Review Board (IRB) Review

Prior to commencement of the trial at a given site, this clinical trial protocol will be submitted together with its associated documents to the Central IEC for its favourable opinion, which will be filed in the Investigator Site File. A copy will be filed in the Sponsor Trial Master File.

The IEC will be asked to document the date of the meeting at which the favourable opinion or approval was given and the members and voting members present. Written evidence of favourable opinion or approval that clearly identifies the trial, the clinical trial protocol version and the Subject Information and Informed Consent Form version reviewed should be provided.

Amendments to this clinical trial protocol will also be submitted to the concerned IEC or IRB, before implementation of substantial changes. Relevant safety information will be submitted to the IEC during the course of the trial in accordance with national regulations and requirements.

Initial IEC positive vote, and all materials approved by the IEC for this study including the patient consent form and recruitment materials must be maintained by the Investigator and made available for inspection.

11.5. Ethical Conduct of the Study

The study will be performed in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with ICH/Good Clinical Practice, applicable regulatory requirements.

11.6. Written Informed Consent

The Principal Investigator(s) at each centre will ensure that the patient is given full and adequate oral and written information about the nature, purpose, possible risk and benefit of the study. Patients must also be notified that they are free to discontinue from the study at any time. The patient should be given the opportunity to ask questions and allowed time to consider the

information provided. The patient’s signed and dated informed consent must be obtained before conducting any study procedures.

The Principal Investigator(s) will retain the original, signed ICF; this form will be made available for reviewing during monitoring visits. A copy of the signed ICF will be provided to the patient. The Principal Investigator will document the informed consent procedure in the patient medical records.

12. QUALITY CONTROL AND QUALITY ASSURANCE

To ensure compliance with Good Clinical Practices and all applicable regulatory requirements, the Sponsor may conduct a quality assurance audit.

13. DATA HANDLING AND RECORD KEEPING

The data will be recorded using the Electronic Data Capture software property of [redacted] which is developed and maintained with strict observance of the regulatory standards for Clinical EDC systems, with special observance of the guidelines specified at:

- CPMP/ICH/135/95. ICH E6. Note for Guidance on Good Clinical Practice.
- Good Clinical Data Management Practice, Version 4, Society for Clinical Data Management (SCDM), October 2005.
- EMEA. Reflection on expectations for electronic source documents used in clinical trials. London, 17 October 2007.
- Directive 9 Guidance for Industry. Part 11, Electronic Records; Electronic Signatures – Scope and Application (August 2003).
- FDA. Guidance for Industry. Computerized Systems Used in Clinical Investigations (May 2007).
- FDA. Guidance for Industry. Part 11, Electronic Records; Electronic Signatures – Scope and Application (August 2003)

[redacted]

All the EDC users are uniquely identified by name, all the access to the software are made through a secure, encrypted connection and all the activity is logged and audited.

All the EDC forms are built according to the CRF defined by the study protocol and is validated according the DVP (Data Validation Plan) associated.

13.1. Inspection of Records

The Sponsor will be allowed to conduct site visits to the investigation facilities for the purpose of monitoring any aspect of the study. The Investigator agrees to allow the monitor to inspect the drug storage area, study drug stocks, drug accountability records, subject charts and study source documents, and other records relative to study conduct.

13.2. Retention of Records

Upon initiation of the trial, the Investigator will be provided with an Investigator Site File containing all necessary trial documents, which will be completed throughout the trial and updated as necessary. The file must be available for review by the Monitor during Sponsor audits, and for inspection by Health Authorities during and after the trial. Moreover, the file must be safely archived for at least 25 years (as per local requirements) after the end of the trial. The documents to be archived include the Subject Identification List and the signed subject Informed Consent Forms. If archiving of the Investigator Site File is no longer possible at the site, the Investigator must notify the Sponsor/designee.

All original subject files (medical records) must be stored at the site (hospital, research institution, or practice) for the longest possible time permitted by the applicable regulations, and/or as per ICH GCP guidelines, whichever is longer (In Spain 25 years). In any case, the Investigator should ensure that no destruction of medical records is performed without the written approval of the Sponsor.

14. Publication Policy

As stated in article 42 of RD 1090/2015 of clinical trials, the Sponsor is obliged to publish both positive and negative results of the authorized clinical trials in scientific journals and with mention to the Ethical Committee of Clinical Research that approved the study.

After completion of the trial, the clinical publication will be carried out by the Coordinating Investigator in collaboration and Principal Investigators, however interim analysis of preliminary data of primary/secondary endpoints may be published by the Sponsor in scientific meetings and/or Congresses. The order of authors will strictly depend on the number of eligible patients included by the Investigators. Coordinating investigators will be first and last authors, and the number of the rest of the authors will depend on the above rule and the requirements of the congresses and/or journals.

The results will be published in two publications. It is estimated that the first publication will include the results of the analysis of the primary/secondary endpoints and will include data from the symptomatic cohort. The second publication will include the results of the analysis of the primary/secondary endpoints from the asymptomatic cohort and potential comparisons between both cohorts. The Investigator will inform the Sponsor in advance about any plans to publish or present data from the trial. Any publications and presentations of the results (abstracts in journals or newspapers, oral presentations, etc.), either in whole or in part, by Investigators or their representatives will require written authorization by the Sponsor before submission.

The anonymity of the source subjects of the data and biological samples will be maintained at all times. The results or conclusions of the study will be communicated primarily in scientific publications before being released to the non-health public. No efficacy study outcome will be reported prematurely or in a sensationalistic way. Participating investigators should not publish any patient data that is directly related to the study objectives until the trial report is published.

The trial will be registered in the Spanish Registry of Clinical Studies (REEC - Registro Español de Estudios Clínicos) and Clinical trials.gov before including the first patient.

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Anexo 1:

EORTC QLQ-C30 (versión 3)

Estamos interesados en conocer algunas cosas sobre usted y su salud. Por favor, responda a todas las preguntas personalmente, rodeando con un círculo el número que mejor se aplique a su caso. No hay contestaciones "acertadas" o "desacertadas". La información que nos proporcione será estrictamente confidencial.

Por favor ponga sus iniciales: _____

Su fecha de nacimiento (día, mes, año): _____

Fecha de hoy (día, mes, año): 31 _____

	En absoluto	Un poco	Bastante	Mucho
1. ¿Tiene alguna dificultad para hacer actividades que requierea un esfuerzo importante, como llevar una bolsa de compra pesada o una maleta?	1	2	3	4
2. ¿Tiene alguna dificultad para dar un paseo largo?	1	2	3	4
3. ¿Tiene alguna dificultad para dar un paseo corto fuera de casa?	1	2	3	4
4. ¿Tiene que permanecer en la cama o sentado/a en una silla durante el día?	1	2	3	4
5. ¿Necesita ayuda para comer, vestirse, asearse o ir al servicio?	1	2	3	4

Durante la semana pasada:

	En absoluto	Un poco	Bastante	Mucho
6. ¿Ha tenido algún impedimento para hacer su trabajo u otras actividades cotidianas?	1	2	3	4
7. ¿Ha tenido algún impedimento para realizar sus aficiones u otras actividades de ocio?	1	2	3	4

8. ¿Tuvo sensación de "falta de aire" o dificultad para respirar?	1	2	3	4
9. ¿Ha tenido dolor?	1	2	3	4
10. ¿Necesitó parar para descansar?	1	2	3	4
11. ¿Ha tenido dificultades para dormir?	1	2	3	4
12. ¿Se ha sentido débil?	1	2	3	4
13. ¿Le ha faltado el apetito?	1	2	3	4
14. ¿Ha tenido náuseas?	1	2	3	4
15. ¿Ha vomitado?	1	2	3	4
16. ¿Ha estado estreñido/a?	1	2	3	4

Por favor, continúe en la página siguiente

Durante la semana pasada:	**En absoluto**	**Un poco**	**Bastante**	**Mucho**
17. ¿Ha tenido diarrea?	1	2	3	4
18. ¿Estuvo cansado/a?	1	2	3	4
19. ¿Interfirió algún dolor en sus actividades diarias?	1	2	3	4
20. ¿Ha tenido dificultad en concentrarse en cosas como leer el periódico o ver la televisión?	1	2	3	4
21. ¿Se sintió nervioso/a?	1	2	3	4
22. ¿Se sintió preocupado/a?	1	2	3	4
23. ¿Se sintió irritable?	1	2	3	4
24. ¿Se sintió deprimido/a?	1	2	3	4
25. ¿Ha tenido dificultades para recordar cosas?	1	2	3	4
26. ¿Ha interferido su estado físico o el tratamiento médico en su vida familiar?	1	2	3	4
27. ¿Ha interferido su estado físico o el tratamiento médico en sus actividades sociales?	1	2	3	4
28. ¿Le han causado problemas económicos su estado físico o el tratamiento médico?	1	2	3	4

Por favor en las siguientes preguntas, ponga un círculo en el número del 1 al 7 que mejor se aplique a usted

29. ¿Cómo valoraría su salud general durante la semana pasada?

1	2	3	4	5	6	7
Pésima						Excelente

30. ¿Cómo valoraría su calidad de vida en general durante la semana pasada?

1	2	3	4	5	6	7
Pésima						Excelente

Appendix 2:

ÍNDICE DE BARTHEL MODIFICADO DE ACTIVIDADES BÁSICAS DE LA VIDA DIARIA

Instrucciones: Seleccione la puntuación para cada afirmación que más se ajuste al nivel de capacidad actual del paciente para cada uno de los 10 ítems siguientes. Registre la actividad actual, no la potencial. La información puede obtenerse a través del propio paciente, de una persona que esté familiarizada con las capacidades del paciente (como un familiar), o de la observación. Véase el apartado de directrices de la página siguiente para más información sobre la puntuación e interpretación.

Control de heces
0 = incontinente (o necesita que le administren enemas)
1 = accidente excepcional (uno/semana)
2 = continente
Puntuación del paciente:

Control de orina
0 = incontinente, o sondado e incapaz de cambiarse la bolsa.
1 = accidente excepcional (máximo uno/24 horas).
2 = continente (durante al menos 7 días)
Puntuación del paciente:

Aseo personal
0 = necesita ayuda con el aseo personal
1 = independiente para lavarse la cara, las manos y los dientes, y afeitarse (proporcionados los instrumentos)
Puntuación del paciente:

Uso del retrete
0 = dependiente
1 = necesita alguna ayuda, pero puede hacer algo solo
2 = independiente (entrar y salir, limpiarse y vestirse)
Puntuación del paciente:

Comer
0 = incapaz
1 = necesita ayuda para cortar, extender mantequilla, etc.
2 = independiente (la comida está al alcance de la mano)
Puntuación del paciente:

Trasladarse entre la silla y la cama
0 = incapaz, no se mantiene sentado
1 = necesita ayuda importante (una persona o dos personas, física), puede estar sentado
2 = necesita algo de ayuda (física o verbal)
3 = independiente
Puntuación del paciente:

Desplazarse
0 = inmóvil
1 = independiente en silla de ruedas, incluidas las esquinas, etc.
2 = anda con pequeña ayuda de una persona (física o verbal)
3 = independiente (pero puede usar cualquier tipo de ayuda, p. ej., bastón)
Puntuación del paciente:

Vestirse y desvestirse
0 = dependiente
1 = necesita ayuda, pero puede hacerlo a medias
2 = independiente (incluidos botones, cremalleras, cordones, etc.)
Puntuación del paciente:

Subir y bajar escaleras
0 = incapaz
1 = necesita ayuda (física o verbal, puede llevar cualquier tipo de muleta)
2 = independiente para subir y bajar
Puntuación del paciente:

Bañarse/Ducharse
0 = dependiente
1 = independiente
Puntuación del paciente:

Puntuación total:

Puntuación:
Sume las puntuaciones del paciente en cada ítem. Las puntuaciones totales posibles oscilan entre 0 y 20, y las puntuaciones más bajas indican un incremento de la incapacidad. Si se utiliza para medir la mejoría después de rehabilitación, los cambios en más de dos puntos en la puntuación total reflejan posible cambios reales, y también es probable un cambio en un ítem de completamente dependiente a independiente.

Directrices para el Índice de Barthel de actividades básicas de la vida diaria

Aspectos generales

• El índice de Barthel se debe utilizar como registro de lo que un paciente hace, NO como registro de lo que el paciente podría hacer.
• El objetivo principal es establecer el grado de independencia del paciente de cualquier tipo de ayuda, física o verbal, por mínima que sea y por cualquier razón.
• La necesidad de supervisión hace al paciente no independiente.
• La funcionalidad del paciente se debe establecer usando la mejor evidencia disponible.

Preguntar al paciente, amigos/familiares y cuidadores será la fuente habitual, pero la observación directa y el sentido común también son importantes. No obstante, no será necesaria una prueba directa.

• Por lo general, la funcionalidad del paciente durante las 24 - 48 horas anteriores es importante, pero ocasionalmente serán pertinentes periodos más largos de tiempo.
• A los pacientes con pérdida de conciencia se les puntuará con "0" en todos los ítems, aunque aún no presenten incontinencia.
• Las categoría intermedias implican que el paciente realiza más del 50 % del esfuerzo.
• Está permitido el uso de ayudas para ser independiente.

Control de heces (semana anterior)

• Si fue necesario que el cuidador aplicará un enema, se considera "incontinente".
• «Ocasional» = una vez a la semana.

Control de orina (semana anterior)

• «Ocasional» = menos de una vez al día.
• Un paciente con sonda que pueda manejar completamente la sonda por sí solo se registrará como "continente".

Aseo personal (24 - 48 horas anteriores)

• Se refiere a la higiene personal: lavarse los dientes, colocarse la dentadura postiza, peinarse, afeitarse, lavarse la cara. Los instrumentos los puede proporcionar el cuidador.

Uso del retrete

• Si es capaz de alcanzar el retrete/tapa del retrete, desvestirse de forma suficiente, limpiarse por sí mismo, vestirse y salir.
• "Con ayuda" = puede limpiarse por sí solo y hacer algunas de las tareas indicadas anteriormente

Comer

• Capaz de ingerir alimentos normales (no solo alimentos blandos). Alimentos cocinados y servidos un tercero, pero sin cortar.
• «Ayuda» = cortándole la comida, el paciente se alimenta por sí solo.

Trasladarse entre la silla y la cama

• De la cama a la silla y al revés.
• «Dependiente» = NO se mantiene sentado (incapaz de sentarse); se necesitan dos personas para levantarlo.
• "Ayuda importante" = una persona fuerte/entrenada o dos personas normales. Puede sentarse.
• "Ayuda menor" = una persona fácilmente, O necesita supervisión por motivos de seguridad.

Desplazarse

• Hace referencia a la movilidad en la casa o sala, en el interior. Puede usar ayuda. Si está en silla de ruedas, puede pasar las esquinas/puertas sin ayuda.
• «Ayuda» = por una persona no entrenada, incluida la supervisión y el apoyo moral.

Vestirse y desvestirse

• Si es capaz de seleccionar y ponerse la ropa, que puede estar adaptada.
• «A medias» = ayuda con los botones, cremalleras, etc. (¡comprobar!), pero puede ponerse alguna prendas por sí solo.

Subir y bajar escaleras

• Puede utilizar cualquier tipo de ayuda para andar para considerarse independiente.

Bañarse/Ducharse

• Por lo general, la actividad más difícil.
• Debe entrar y salir sin supervisión y lavarse por sí solo.
• Independiente en la ducha = "independiente" si no necesita supervisión/ayuda.

Referencias:
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EBRAIN-MEL GEM1802 STUDY - STATISTICAL REPORT (ANALYSIS)

JAN 2023

1. Table of Contents

2. PATIENT POPULATIONS

ITT Population:
The ITT population will include all patients who were included in the study, only screening failures are excluded.

PP Population:
The PP population will include all patients who fulfilled the inclusion and exclusion criteria and had at least 2 valid tumor evaluations (baseline + 1st assessment).

Safety Population:
The PP population will include all patients who received at least one dose of the treatment.

Table 1: ITT population

Intention to treat population
No
Yes

Table 2: ITT Population: Patients excluded

Patient number	Cohort	ITT	Exclusion reason

Table 3: PP population

PP
No
Yes

Table 4: PP Population: Patients excluded

Patient number	Cohort	PP	PP: exclusion reason

Table 5: Safety population

Safety
No
Yes

Table 6: Safety Populattion: Patients excluded

Patient number	Cohort	Safety	Safety: exclusion reason

Table 7: Analysis populations, all patients

Patient Number	Cohort	Intention to treat population	PP	ITT/PP Exclusion reason	Safety	Safety: exclusion reason

3. RESULTS

3.1. RECRUITED PATIENTS

All baseline characteristics will be performed using the ITT and PP population. In order to report the main efficacy analysis, also both the ITT and PP population will be used, meanwhile the secondary efficacy endpoints will be analyzed using the PP population. Finally the safety population will be used to report the safety results.

Table 8: Patients recruited by Hospital

Hospital
[redacted]
[redacted]
[redacted]
[redacted]

[redacted]
[redacted]
[redacted]
[redacted]
[redacted]
[redacted]
[redacted]
[redacted]
[redacted]
[redacted]

3.2. BASELINE CHARACTERISTICS

BASELINE - DEMOGRAPHIC DATA

Table 9: Baseline - Socio demographic data ITT

Age (years)
N
Mean (95%CI)
SD
Median (95%CI)
Range
Sex
Female
Male
Race
Caucasian
Latin

Table 10: Baseline - Socio demographic data PP

Age (years)
N
Mean (95%CI)
SD
Median (95%CI)
Range
Sex
Female
Male
Race

Table 11: Baseline - Physical characteristics ITT

Phototype (n(%))
Type I
Type II
Type III
Type IV
UK
Weight (kg)
N
Mean (95%CI)
SD
Median (95%CI)
Range
Height (cm)
N
Mean (95%CI)
SD
Median (95%CI)
Range
Systolic Blood Pressure (mmHg)
N
Mean (95%CI)
SD
Median (95%CI)
Range
Diastolic Blood Pressure (mmHg)
N
Mean (95%CI)
SD
Median (95%CI)
Range
Temperature (ºC)
N
Mean (95%CI)
SD
Median (95%CI)
Range
Respiratory rate (BPM)
N
Mean (95%CI)
SD
Median (95%CI)
Range
Pulse Rate (BPM)
N
Mean (95%CI)
SD
Median (95%CI)
Range

ECOG (n(%))
0
1
2
Barthel index (categorical), (n(%)), previous to November 2020
Barthel index (Arbitrary units, scale 0-100)
N
Mean (95%CI)
SD
Median (95%CI)
Range
Barthel index modified, from November 2020
Barthel index modified (Arbitrary units, scale 0-20), from November 2020
N
Mean (SD)
Median
Range
Barthel index final (all values transformed to scale 0-20) (categorical) (n(%))
Barthel index final (all values transformed to scale 0-20)
N
Mean (95%CI)
SD
Median (95%CI)
Range
Physical exam
Normal
Abnormal
Neurological exam
Normal
Abnormal
Ophthalmologic exam
Normal
Abnormal
Autoimmune concomitant diseases
Yes
No
UK

Table 12: Baseline - Physical characteristics PP

Phototype (n(%))

Type I
Type II
Type III
Type IV
UK
Weight (kg)
N
Mean (95%CI)
SD
Median (95%CI)
Range
Height (cm)
N
Mean (95%CI)
SD
Median (95%CI)
Range
Systolic Blood Pressure (mmHg)
N
Mean (95%CI)
SD
Median (95%CI)
Range
Diastolic Blood Pressure (mmHg)
N
Mean (95%CI)
SD
Median (95%CI)
Range
Temperature (ºC)
N
Mean (95%CI)
SD
Median (95%CI)
Range
Respiratory rate (BPM)
N
Mean (95%CI)
SD
Median (95%CI)
Range
PulseRate (BPM)
N
Mean (95%CI)
SD
Median (95%CI)
Range
ECOG (n(%))
0
1
2

Barthel index (categorical), (n(%)), previous to November 2020
Barthel index (Arbitrary units, scale 0-100)
N
Mean (95%CI)
SD
Median (95%CI)
Range
Barthel index modified, from November 2020
Barthel index modified (Arbitrary units, scale 0-20), from November 2020
N
Mean (SD)
Median
Range
Barthel index final (all values transformed to scale 0-20) (categorical) (n(%))
Barthel index final (all values transformed to scale 0-20)
N
Mean (95%CI)
SD
Median (95%CI)
Range
Physical exam
Normal
Abnormal
Neurological exam
Normal
Abnormal
Ophthalmologic exam
Normal
Abnormal
Autoimmune concomitant diseases
Yes
No
UK

3.3. PREVIOUS MELANOMA HISTORY

Table 13: Previous Melanoma History ITT

Time since First diagnose date until treatment started (months)
N
Mean (95%CI)

SD
Median (95%CI)
Range
Histological Subtype
NA/UK
Superficial spreading
Nodular
Lentigo maligna
Others
Histological Subtype Others
Primary Melanoma Location
NA/UK
Face
Scalp
Back
Upper extremities
Feet palms
Chest
Abdomen
Others
Primary Melanoma Location Others
Previous Multiple Nevus
Yes
No
NA/UK
Primary Melanoma Stage
In transit metastases
Yes
No
UK
Sentinel lymph node
Yes
No
UK
Lymphadenectomy
Yes
No
UK

Table 14: Previous Melanoma History PP

Time since First diagnose date until treatment started (months)
N
Mean (95%CI)
SD

Median (95%CI)
Range
Histological Subtype
NA/UK
Superficial spreading
Nodular
Lentigo maligna
Others
Histological Subtype Others
Primary Melanoma Location
NA/UK
Face
Scalp
Back
Upper extremities
Feet palms
Chest
Abdomen
Others
Primary Melanoma Location Others
Previous Multiple Nevus
Yes
No
NA/UK
Primary Melanoma Stage
In transit metastases
Yes
No
UK
Sentinel lymph node
Yes
No
UK
Lymphadenectomy
Yes
No
UK

Figure 1: Heatmap BRAF ITT

Table 15: BRAF ITT

V600E
Missing data
Mutated
Not mutated
V600K
Mutated
Not mutated
NA/UK
V600E/K
Mutated
Not mutated
NA/UK
V600R
Mutated
Not mutated
NA/UK
V600 other
Mutated
Not mutated
NA/UK
V600 (NE)
Mutated
Not mutated
NA/UK

Table 16: BRAF PP

V600E
Missing data
Mutated
Not mutated
V600K
Mutated
Not mutated
NA/UK
V600E/K
Mutated
Not mutated
NA/UK
V600R
Mutated
Not mutated
NA/UK

V600 other
Mutated
Not mutated
NA/UK
V600 non specified
Mutated
Not mutated
NA/UK

Figure 2: Heatmap BRAF PP

Table 17: Other mutations ITT

RAS
Mutated
Not mutated
NA/UK
CKIT
Mutated
Not mutated
UK
GNAQ
Mutated
Not mutated
UK

Figure 3: Heatmap Other mutations ITT

Table 18: Other mutations PP

RAS
Mutated
Not mutated
NA/UK
CKIT
Mutated
Not mutated
UK
GNAQ
Mutated
Not mutated
UK

Figure 4: Heatmap Other mutations PP

Table 19: Adjuvant therapy ITT

Adjuvant therapy
Yes
No
UK
Previous adjuvant tx: Immunotherapy
No
Yes
NA/UK
Type of previous Immunotherapy
Anti-PD1 + anti-CTLA4
Anti-PD1 monotherapy
Anti-PD1 monotherapy / Anti-PD1 monotherapy
NA/UK
Previous adjuvant tx: Interferon
No
Yes
NA/UK
Previous adjuvant tx: Radiotherapy
No
Yes
NA/UK

Table 20: Adjuvant therapy PP

Adjuvant therapy
Yes
No
UK
Previous adjuvant tx: Immunotherapy
No
Yes
NA/UK
Type of previous Immunotherapy
Anti-PD1 + anti-CTLA4
Anti-PD1 monotherapy
Anti-PD1 monotherapy / Anti-PD1 monotherapy
NA/UK
Previous adjuvant tx: Interferon
No
Yes
NA/UK

Previous adjuvant tx: Radiotherapy
No
Yes
NA/UK

Table 21: Therapy for unresectable locally advanced or metastatic melanoma ITT

Therapy for unresectable locally advanced or metastatic melanoma
Yes
No
Therapy for unresectable locally advanced or metastatic melanoma: Mts Surgery
No
Yes
NA/UK
Therapy for unresectable locally advanced or metastatic melanoma: Immunotherapy
No
Yes
NA/UK
Therapy for unresectable locally advanced or metastatic melanoma: Type of Immunotherapy
Nivolumab
Nivolumab+ipilimumab
Pembrolizumab
NA/UK
Therapy for unresectable locally advanced or metastatic melanoma: Radiotherapy
No
Yes
NA/UK
Therapy for unresectable locally advanced or metastatic melanoma: Segmentectomy
No
Yes
NA/UK
Therapy for unresectable locally advanced or metastatic melanoma: Radiosurgery
No
Yes
NA/UK

Table 22: Therapy for unresectable locally advanced or metastatic melanoma PP

Therapy for unresectable locally advanced or metastatic melanoma

Yes
No
Therapy for unresectable locally advanced or metastatic melanoma: Mts Surgery
No
Yes
NA/UK
Therapy for unresectable locally advanced or metastatic melanoma: Immunotherapy
No
Yes
NA/UK
Therapy for unresectable locally advanced or metastatic melanoma: Type of Immunotherapy
Nivolumab
Nivolumab+ipilimumab
Pembrolizumab
NA/UK
Therapy for unresectable locally advanced or metastatic melanoma: Radiotherapy
No
Yes
NA/UK
Therapy for unresectable locally advanced or metastatic melanoma: Segmentectomy
No
Yes
NA/UK
Therapy for unresectable locally advanced or metastatic melanoma: Radiosurgery
No
Yes
NA/UK

3.4. BASELINE CURRENT MELANOMA

Table 23: Baseline Current Melanoma ITT

Time since diagnosis of current melanoma until treatment started (months)
N
Mean (95%CI)
SD
Median (95%CI)
Range
Current Melanoma Histological Subtype
Superficial spreading
Nodular
Lentigo maligna
UK

Others
Histological subtype specify
Current Melanoma Stage
IV

Table 24: Baseline Current Melanoma PP

Time since diagnosis of current melanoma until treatment started (months)
N
Mean (95%CI)
SD
Median (95%CI)
Range
Current Melanoma Histological Subtype
Superficial spreading
Nodular
Lentigo maligna
UK
Others
Histological subtype specify
Current Melanoma Stage
IV

Table 25: TNM Current Melanoma ITT

Initial T Stage
T0
T1a
T1b
T2a
T2b
T3a
T3b
T4a
T4b
Tx
Initial N Stage
N0
N1a
N1b
N1c
N2a
N2b

N2c
N3b
N3c
Nx
Initial M Stage
M1d(0)
M1d(1)
Breslow (mm)
N
Mean (95%CI)
SD
Range
Mitotic Rate (mm^2)
N
Mean (95%CI)
SD
Range
Ulceration
Yes
No
UK

Table 26: TNM Current Melanoma PP

Initial T Stage
T0
T1a
T1b
T2a
T2b
T3a
T3b
T4a
T4b
Tx
Initial N Stage
N0
N1a
N1b
N1c
N2a
N2b
N2c
N3b
N3c
Nx
Initial M Stage
M1d(0)
M1d(1)

Breslow (mm)
N
Mean (95%CI)
SD
Range
Mitotic Rate (mm^2)
N
Mean (95%CI)
SD
Range
Ulceration
Yes
No
UK

Table 27: Metastases ITT

Brain Metastases
Unique
Multiple
Target Brain Metastases
1
2
3
4
5
UK
Extracranial Metastases
Yes
No
Lung Metastases
Yes
No
UK
Lung Metastases Number
1
2
3
4
>5
NA/UK
Liver Metastases
Yes
No
UK
Liver Metastases Number
1
2
3

>5
NA/UK
Skin Metastases
Yes
No
UK
Skin Metastases Number
1
2
3
>5
UK
Bone Metastases
Yes
No
UK
Bone Metastases Number
1
2
NA/UK
Pleura Metastases
Yes
No
UK
Pleural Effusion Volume
0
NA/UK
Soft Tissue Metastases
Yes
No
UK
Soft Tissue Metastases Number
1
5
NA/UK
Lymph Nodes Metastases
Yes
No
UK
Lymph Nodes Metastases Number
1
2
3
>5
UK
NA/UK
Peritoneum Metastases
Yes
No
UK
Peritoneum Metastases Number

1
NA/UK
Other Metastases
Yes
No
UK
Other Metastases Number
1
2
>5
UK
Other Metastases Specify

Table 28: Metastases PP

Brain Metastases
Unique
Multiple
Target Brain Metastases
1
2
3
4
5
UK
Extracranial Metastases
Yes
No
Lung Metastases
Yes
No
UK
Lung Metastases Number
1
2
3
4
>5
NA/UK
Liver Metastases
Yes
No
UK
Liver Metastases Number
1
2
3
>5
NA/UK
Skin Metastases

Yes
No
UK
Skin Metastases Number
1
2
3
>5
UK
Bone Metastases
Yes
No
UK
Bone Metastases Number
1
2
NA/UK
Pleura Metastases
Yes
No
UK
Pleural Effusion Volume
0
NA/UK
Soft Tissue Metastases
Yes
No
UK
Soft Tissue Metastases Number
1
5
NA/UK
Lymph Nodes Metastases
Yes
No
UK
Lymph Nodes Metastases Number
1
2
3
>5
NA/UK
Peritoneum Metastases
Yes
No
UK
Peritoneum Metastases Number
1
NA/UK
Other Metastases
Yes

No
UK
Other Metastases Number
1
2
>5
UK
Other Metastases Specify

Table 29: LDH concentration and corticosteriods ITT

LDH Concentration
Normal (≤ULN)
Elevated (>ULN)
UK
Corticosteroids Treatment
Yes
No
Corticosteroids Treatment Type
Missing data
Dexamethasone
Metilprednisolona
Prednisone
UK
Administration
Stable
Decreasing
NA

Table 30: LDH concentration and corticosteriods PP

LDH Concentration
Normal (≤ULN)
Elevated (>ULN)
UK
Corticosteroids Treatment
Yes
No
Corticosteroids Treatment Type
Missing data
Dexamethasone
Metilprednisolona
Prednisone
UK
Administration
Stable

Decreasing
NA

3.4.1. BASELINE TUMOR BURDEN

Table 31: Brain Tumor burden (mm) ITT

Brain Tumor burden (mm) intracranial Target lessions
N
Mean (95%CI)
SD
Median (95%CI)
Range

Table 32: Brain Tumor burden (mm) PP

Brain Tumor burden (mm) intracranial Target lessions
N
Mean (95%CI)
SD
Median (95%CI)
Range

3.5. TREATMENT COMPLIANCE

Upon database closure, there are 4 patients still undergoing treatment.

3.5.1. BINIMETINIB COMPLIANCE

Table 33: Incidence reason for Binimetinib

Incidence
N
No
Yes
Delay
Not available
N
No
Yes
Reduction

Not available
N
No
Yes
End of treatment[1]
Not available
N
No
Yes
Interruption due to local treatment
Not available
N
No
Yes
Interruption due to surgery
Not available
N
No
Yes

(1) The End of Treatment variable only reports 'Yes' incidents that were caused by 'End of Treatment'

Table 34: Reasons for incidence (free field to review)

PatientNumber.Inc	IncidenceStartDate	IncidenceEndDate	Incidence	Reason	End of treatment reason compiled

Table 35: Binimetinib Treatment duration (months)

Binimetinib gross duration time (months)
Missing
N
Mean (95%CI)
SD
Median (95%CI)
Range
Binimetinib net duration time (months)
Missing
N
Mean (95%CI)

SD
Median (95%CI)
Range

3.5.2. Encorafenib Compliance

Table 36: Incidence reason for Encorafenib

Incidence
N
No
Yes
Delay
Not available
N
No
Yes
Reduction
Not available
N
No
Yes
End of treatment[1]
Not available
N
No
Yes
Interruption due to local treatment
Not available
N
No
Yes
Interruption due to surgery
Not available
N
No
Yes

(1) The End of Treatment variable only reports 'Yes' incidents that were caused by 'End of Treatment'

Table 37: Encorafenib Treatment duration (months)

Encorafenib gross duration time (months)
Missing
N
Mean (95%CI)
SD
Median (95%CI)
Range
Encorafenib net duration time (months)
Missing
N
Mean (95%CI)
SD
Median (95%CI)
Range

Table 38: Reasons for incidence (free field to review)

PatientNumber.Inc	IncidenceStartDate	IncidenceEndDate	Incidence	Reason	End of treatment reason compiled

4. PRIMARY EFFICACY OBJECTIVE

4.1. ITT PRIMARY EFFICACY OBJECTIVE: RESPONSE AT 56 DAYS

Table 39: Primary Efficacy Objective. Day 56 Evaluation. ITT

intracranial Evaluation at 56 days
CR
PR
SD
PD
NE

Table 40: ITT: intracranial Objective Response Rate at 56 days

All patients: ORR intracranial response	
CR or PR	

All patients: ORR intracranial response	
SD or PD	
NE	
Total	
Cohort 1: ORR intracranial response	
CR or PR	
SD or PD	
NE	
Total	
Cohort 2: ORR intracranial response	
CR or PR	
SD or PD	
Total	

4.2. PP PRIMARY EFFICACY OBJECTIVE: RESPONSE AT 56 DAYS

Table 41: Primary Efficacy Objective. Day 56 Evaluation. PP

intracranial Evaluation at 56 days	
CR	
PR	
SD	
PD	
NE	

Table 42: PP: intracranial Objective Response Rate at 56 days

All patients: ORR intracranial response	
CR or PR	
SD or PD	

All patients: ORR intracranial response	
NE	
Total	
Cohort 1: ORR intracranial response	
CR or PR	
SD or PD	
NE	
Total	
Cohort 2: ORR intracranial response	
CR or PR	
SD or PD	
NE	
Total	

4.2.1. INTRACRANIAL RESPONSE DURATION

Table 43: Intracranial Response Duration (months) ITT

Duration of response (months)
N
Mean (95%CI)
SD
Median (95%CI)
Range

Table 44: Intracranial Response Duration (months) PP

Duration of response (months)
N
Mean (95%CI)
SD
Median (95%CI)
Range

4.3. RADIOTHERAPY TREATMENT

ITT: RADIOTHERAPY TREATMENT

Table 45: Radiotherapy treatment. ITT

Radiotherapy treatment (Local and/or Whole Brain)
N
Yes
Yes (CR)[1]
No
No (CR)
LocaL Radiation treatment
N
Yes
Yes (CR)
No
No (CR)
Local Radiation Treatment type
N
No
Radiosurgery (RS)

Stereotactic radiosurgery (SRS)
Device Used
Missing
N
Gamma Knife
Accelerator Linac-Based Systems (IMRT, Rapid Arc, VMAT)
Cyberknife
Whole Brain Radiotherapy
N
Yes
No
No (CR)

PP: RADIOTHERAPY TREATMENT

Table 46: Radiotherapy treatment. PP

Radiotherapy treatment (Local and/or Whole Brain)
N
Yes
Yes (CR)[1]
No
No (CR)
Local Radiation treatment
N
Yes
Yes (CR)
No
No (CR)
Local Radiation Treatment type
N
No
Radiosurgery (RS)
Stereotactic radiosurgery (SRS)
Device Used
Missing
N
Gamma Knife
Accelerator Linac-Based Systems (IMRT, Rapid Arc, VMAT)

Cyberknife
Whole Brain Radiotherapy
N
Yes
No
No (CR)

4.3.1. ALL PATIENTS: DETAILS OF LOCAL RADIATION TREATMENT

Table 47: Details of local radiation treatment

Patient Number	Cohort	Intention to treat population	PP	LocaL Radiation treatment	Local Radiation Treatment type	Device Used	Whole Brain Radiotherapy	Radiotherapy treatment (Local and/or Whole Brain)

4.4. LAST STATUS

Table 48: Arithmetic median for all patients

Overall
Overall follow-up since cancer diagnosis: all patients (months)
N
Mean (95%CI)
SD
Median (95%CI)
Range

Table 49: Arithmetic median for alive patients

Overall
Global follow-up since cancer diagnosis: patients alive (moths)
N
Mean (95%CI)
SD
Median (95%CI)
Range

Table 50: Follow-up since cancer diagnosis based on reverse censoring (months)

	Median	95%CI
Reverse censoring		

ITT: LAST STATUS, PD AND DEATHS

Table 51: Progression, Death. ITT

Cohort
Progression type
Only IntraPD
No PD
Both
Only ExtraPD
Death
No
Yes

PP: LAST STATUS, PD AND DEATHS

Table 52: Progression, Death. PP

Cohort
Progression type
Only IntraPD
No PD
Both
Only ExtraPD
Death
No
Yes

Table 53: Last available status

Patient Number	Cohort	Intention to treat population	PP	Last available status	Last available date	End Treatment Date	Date of last FU	Intracraneal Progression disease	Date of PD	Date of death	End Trial Date

4.5. Intracranial Overall survival (iOS).

4.5.1. ITT All patients: intracranial Overall survival (iOS).

Table 54: Events type OS

OS	N	%	95%CI
Alive			
Death			
Total			

Table 55: Median/mean OS (estimated by Kaplan-Meier)

	Median (months)	CI 95%	Mean	CI 95%
Overall survival				

Table 56: OS estimated survival ratio

OS	Events (%, total N)	Patients at risk	% estimated cumulative survival ratio	CI 95%
At 6 months				
At 12 months				
At 18 months				
At 24 months				

Figure 5: Overall survival

4.5.2. ITT - Cohort 1: intracranial Overall survival (iOS).

Table 57: Events type OS

OS	N	%	95%CI
Alive			
Death			
Total			

Table 58: Median/mean OS (estimated by Kaplan-Meier)

	Median (months)	CI 95%	Mean	CI 95%
Overall survival				

Table 59: OS estimated survival ratio

OS	Events (%, total N)	Patients at risk	% estimated cumulative survival ratio	CI 95%
At 6 months				
At 12 months				
At 18 months				
At 24 months				

Figure 6: Overall survival

4.5.3. ITT - Cohort 2: intracranial Overall survival (iOS).

Table 60: Events type OS

OS	N	%	95%CI
Alive			
Death			
Total			

Table 61: Median/mean OS (estimated by Kaplan-Meier)

	Median (months)	CI 95%	Mean	CI 95%
Overall survival				

Table 62: OS estimated survival ratio

OS	Events (%, total N)	Patients at risk	% estimated cumulative survival ratio	CI 95%
At 6 months				
At 12 months				
At 18 months				
At 24 months				

Figure 7: Overall survival

4.5.4. PP All patients: intracranial Overall survival (iOS).

Table 63: Events type OS

OS	N	%	95%CI
Alive			
Death			
Total			

Table 64: Median/mean OS (estimated by Kaplan-Meier)

	Median (months)	CI 95%	Mean	CI 95%
Overall survival				

Table 65: OS estimated survival ratio

OS	Events (%, total N)	Patients at risk	% estimated cumulative survival ratio	CI 95%
At 6 months				
At 12 months				
At 18 months				
At 24 months				

Figure 8: Overall survival

4.5.5. PP - Cohort 1: intracranial Overall survival (iOS).

Table 66: Events type OS

OS	N	%	95%CI
Alive			
Death			
Total			

Table 67: Median/mean OS (estimated by Kaplan-Meier)

	Median (months)	CI 95%	Mean	CI 95%
Overall survival				

Table 68: OS estimated survival ratio

OS	Events (%, total N)	Patients at risk	% estimated cumulative survival ratio	CI 95%
At 6 months				
At 12 months				
At 18 months				
At 24 months				

Figure 9: Overall survival

4.5.6. PP - Cohort 2: intracranial Overall survival (iOS).

Table 69: Events type OS

OS	N	%	95%CI
Alive			
Death			
Total			

Table 70: Median/mean OS (estimated by Kaplan-Meier)

	Median (months)	CI 95%	Mean	CI 95%
Overall survival				

Table 71: OS estimated survival ratio

OS	Events (%, total N)	Patients at risk	% estimated cumulative survival ratio	CI 95%
At 6 months				
At 12 months				
At 18 months				
At 24 months				

Figure 10: Overall survival

4.6. Intracranial Progression-free survival (iPFS).

Intracranial Progression-free survival (PFS), defined as the time from inclusion (first dose of treatment) until intracranial tumour progression (RECIST 1.1) or death. Patients without any of the previous events are censored at the date of the last available tumor assessment.

4.6.1. ITT All patients: intracranial Progression-free survival (iPFS).

0 patient has been censored at time 0 due to lack of tumor assessments.

Table 72: iPFS (event). ITT All patients

PFS (event)	N	%	95%CI
Censored			
Event (PD/death)			
Total			

Table 73: Median iPFS. ITT All patients

	Median	95%CI
PFS		

iPFS estimated at 3, 6 and 12 months (Kaplan-Meier)

Table 74: iPFS at 3, 6 and 12 months. ITT All patients

iPFS	Events (%, total N)	Patients at risk	% estimated cumulative survival ratio	95% IC
At 3 months				
At 6 months				
At 12 months				

[1]Estimated using Kaplan-Meier product-limit method

Figure: intracranial Progression Free Survival (ITT: All patients)

4.6.2. ITT - Cohort 1: intracranial Progression-free survival (iPFS).

Table 75: iPFS (event). ITT Cohort 1

PFS (event)	N	%	95%CI
Censored			
Event (PD/death)			

PFS (event)	N	%	95%CI
Total			

Table 76: Median iPFS. ITT Cohort 1

	Median	95%CI
PFS		

iPFS estimated at 3, 6 and 12 months (Kaplan-Meier)

Table 77: iPFS at 3, 6 and 12 months. ITT Cohort 1

iPFS	Events (%, total N)	Patients at risk	% estimated cumulative survival ratio	95% IC
At 3 months				
At 6 months				
At 12 months				

[1]Estimated using Kaplan-Meier product-limit method

Figure: intracranial Progression Free Survival (ITT Cohort 1)

4.6.3. ITT - Cohort 2: intracranial Progression-free survival (iPFS).

Table 78: iPFS (event). ITT Cohort 2

PFS (event)	N	%	95%CI
Censored			
Event (PD/death)			
Total			

Table 79: Median iPFS. ITT Cohort 2

	Median	95%CI
PFS		

iPFS estimated at 3, 6 and 12 months (Kaplan-Meier)

Table 80: iPFS at 3, 6 and 12 months. ITT Cohort 2

iPFS	Events (%, total N)	Patients at risk	% estimated cumulative survival ratio	95% IC
At 3 months				
At 6 months				
At 12 months				

[1]Estimated using Kaplan-Meier product-limit method

Figure: intracranial Progression Free Survival (ITT Cohort 2)

4.6.4. PP All patients: intracranial Progression-free survival (iPFS).

Table 81: iPFS (event). PP All patients

PFS (event)	N	%	95%CI
Censored			
Event (PD/death)			
Total			

Table 82: Median iPFS. PP All patients

	Median	95%CI
PFS		

iPFS estimated at 3, 6 and 12 months (Kaplan-Meier)

Table 83: iPFS at 3, 6 and 12 months. PP All patients

iPFS	Events (%, total N)	Patients at risk	% estimated cumulative survival ratio	95% IC
At 3 months				
At 6 months				
At 12 months				

[1]Estimated using Kaplan-Meier product-limit method

Figure: intracranial Progression Free Survival (PP: All patients)

4.6.5. PP - Cohort 1: intracranial Progression-free survival (iPFS).

Table 84: iPFS (event). PP Cohort 1

PFS (event)	N	%	95%CI
Censored			
Event (PD/death)			
Total			

Table 85: Median iPFS. PP Cohort 1

	Median	95%CI
PFS		

iPFS estimated at 3, 6 and 12 months (Kaplan-Meier)

Table 86: iPFS at 3, 6 and 12 months. PP Cohort 1

iPFS	Events (%, total N)	Patients at risk	% estimated cumulative survival ratio	95% IC
At 3 months				
At 6 months				

iPFS	Events (%, total N)	Patients at risk	% estimated cumulative survival ratio	95% IC
At 12 months				

[1]Estimated using Kaplan-Meier product-limit method

Figure: intracranial Progression Free Survival (PP Cohort 1)

4.6.6. PP - Cohort 2: intracranial Progression-free survival (iPFS).

Table 87: iPFS (event). PP Cohort 2

PFS (event)	N	%	95%CI
Censored			
Event (PD/death)			
Total			

Table 88: Median iPFS. PP Cohort 2

	Median	95%CI
PFS		

iPFS estimated at 3, 6 and 12 months (Kaplan-Meier)

Table 89: iPFS at 3, 6 and 12 months. PP Cohort 2

iPFS	Events (%, total N)	Patients at risk	% estimated cumulative survival ratio	95% IC
At 3 months				
At 6 months				
At 12 months				

[1]Estimated using Kaplan-Meier product-limit method

Figure: intracranial Progression Free Survival (PP Cohort 2)

4.7. Extracranial Progression-free survival (ePFS).

Extracranial Progression-free survival (PFS), defined as the time from inclusion (first dose of treatment) until extracranial tumour progression (RECIST 1.1) or death. Patients without any of the previous events are censored at the date of the last available tumor assessment.

4.7.1. ITT All patients: extracranial Progression-free survival (ePFS).

Table 90: Events type PFS

PFS (event)	N	%	95%CI
Censored			
Event (PD/death)			
Total			

Table 91: Median/mean PFS (estimated by Kaplan-Meier)

	Median (months)	CI 95%	Mean	CI 95%
Progression free survival				

Table 92: PFS estimated survival ratio

PFS	Events (%, total N)	Patients at risk	% estimated cumulative survival ratio	CI 95%
At 6 months				
At 12 months				
At 18 months				
At 24 months				

Figure 11: Progression free survival

4.7.2. ITT - Cohort 1: extracranial Progression-free survival (ePFS).

Table 93: Events type PFS

PFS (event)	N	%	95%CI
Censored			
Event (PD/death)			
Total			

Table 94: Median/mean PFS (estimated by Kaplan-Meier)

	Median (months)	CI 95%	Mean	CI 95%
Progression free survival				

Table 95: PFS estimated survival ratio

PFS	Events (%, total N)	Patients at risk	% estimated cumulative survival ratio	CI 95%
At 6 months				
At 12 months				
At 18 months				
At 24 months				

Figure 12: Progression free survival

4.7.3. ITT - Cohort 2: extracranial Progression-free survival (ePFS).

Table 96: Events type PFS

PFS (event)	N	%	95%CI
Censored			
Event (PD/death)			
Total			

Table 97: Median/mean PFS (estimated by Kaplan-Meier)

	Median (months)	CI 95%	Mean	CI 95%
Progression free survival				

Table 98: PFS estimated survival ratio

PFS	Events (%, total N)	Patients at risk	% estimated cumulative survival ratio	CI 95%
At 3 months				
At 6 months				
At 9 months				
At 12 months				
At 15 months				

Figure 13: Progression free survival

4.7.4. PP All patients: extracranial Progression-free survival (ePFS).

Table 99: Events type PFS

PFS (event)	N	%	95%CI
Censored			
Event (PD/death)			
Total			

Table 100: Median/mean PFS (estimated by Kaplan-Meier)

	Median (months)	CI 95%	Mean	CI 95%
Progression free survival				

Table 101: PFS estimated survival ratio

PFS	Events (%, total N)	Patients at risk	% estimated cumulative survival ratio	CI 95%
At 6 months				
At 12 months				
At 18 months				
At 24 months				

Figure 14: Progression free survival

4.7.5. PP - Cohort 1: extracranial Progression-free survival (ePFS).

Table 102: Events type PFS

PFS (event)	N	%	95%CI
Censored			
Event (PD/death)			
Total			

Table 103: Median/mean PFS (estimated by Kaplan-Meier)

	Median (months)	CI 95%	Mean	CI 95%
Progression free survival				

Table 104: PFS estimated survival ratio

PFS	Events (%, total N)	Patients at risk	% estimated cumulative survival ratio	CI 95%
At 6 months				
At 12 months				
At 18 months				
At 24 months				

Figure 15: Progression free survival

4.7.6. PP - Cohort 2: extracranial Progression-free survival (ePFS).

Table 105: Events type PFS

PFS (event)	N	%	95%CI
Censored			
Event (PD/death)			
Total			

Table 106: Median/mean PFS (estimated by Kaplan-Meier)

	Median (months)	CI 95%	Mean	CI 95%
Progression free survival				

Table 107: PFS estimated survival ratio

PFS	Events (%, total N)	Patients at risk	% estimated cumulative survival ratio	CI 95%
At 3 months				
At 6 months				
At 9 months				
At 12 months				
At 15 months				

Figure 16: Progression free survival

4.8. QUALITY OF LIFE QUESTIONARY: EORTC QLQ C-30. COHORT 2

All scores are scaled to range from 0-100, even scores based on single items. Be aware that these single-item scales still have only 4 possible values, even though they are transformed to range from 0-100. The scale name and number of items are listed below.

- **Global health status/QoL**
  QL - Global health status/QoL (revised) (from 2 items)

- **Functional Scales (higher is better functioning)**
  PF - Physical functioning (from 5 items)
  RF - Role functioning (from 2 items)
  EF - Emotional functioning (from 4 items)
  CF - Cognitive functioning (from 2 items)
  SF - Social functioning (from 2 items)

- **Symptom Scales (higher is more symptoms, worse functioning)**
  FA - Fatigue (from 3 items)
  NV - Nausea and Vomiting (from 2 items)
  PA - Pain (from 2 items)

- **Single-Item Symptom Scores (higher is more symptoms, worse functioning)**
  DY - Dyspnoea
  SL - Insomnia
  AP - Appetite Loss
  CO - Constipation

DI - Diarrhoea
FI - Financial Difficulties

- **QLQ-C30 Summary Score** (higher is better functioning, fewer symptoms) C30SUMMARY - QLQ-C30 Summary Score, composed by taking mean of all scores except for QL (Global health status/QoL) and FI (Financial Difficulties).

Reference:

https://rdrr.io/cran/PROscorer/man/qlq_c30.html

Aaronson NK, Ahmedzai S, Bergman B, Bullinger M, Cull A, Duez NJ, Filiberti A, Flechtner H, Fleishman SB, Haes JCJM de, Kaasa S, Klee M, Osoba D, Razavi D, Rofe PB, Schraub S, Sneeuw K, Sullivan M, Takeda F (1993). The European Organization for Research and Treatment of Cancer QLQ-C30: A Quality-of-Life Instrument for Use in International Clinical Trials in Oncology. JNCI J Natl Cancer Inst 85:365-376.

Fayers PM, Aaronson NK, Bjordal K, Groenvold M, Curran D, Bottomley A, on behalf of the EORTC Quality of Life Group. The EORTC QLQ-C30 Scoring Manual (3rd Edition). Published by: European Organisation for Research and Treatment of Cancer, Brussels 2001.

Giesinger JM, Kieffer JM, Fayers PM, Groenvold M, Petersen MA, Scott NW, Sprangers MAG, Velikova G, Aaronson NK (2016). Replication and validation of higher order models demonstrated that a summary score for the EORTC QLQ-C30 is robust. Journal of Clinical Epidemiology 69:79-88.

4.8.1. Global health status/QoL

4.8.1.1. QL - Global health status/QoL (revised) (from 2 items)

Table 108: Global health status/QoL

Global health status/QoL	N	Mean(SD)	Median(Min-Max)	p-value (wilcoxon test) compared with baseline
Baseline				
w8				
w16				

4.8.2. Functional Scales (higher is better functioning)

4.8.2.1. PF - Physical functioning (from 5 items)

Table 109: Physical functioning/QoL

Physical functioning/QoL	N	Mean(SD)	Median(Min-Max)	p-value (wilcoxon test) compared with baseline
Baseline				
w8				
w16				

4.8.2.2. RF - Role functioning (from 2 items)

Table 110: Role functioning/QoL

Role functioning/QoL	N	Mean(SD)	Median(Min-Max)	p-value (wilcoxon test) compared with baseline
Baseline				
w8				
w16				

4.8.2.3. EF - Emotional functioning (from 4 items)

Table 111: Emotional functioning/QoL

Emotional functioning/QoL	N	Mean(SD)	Median(Min-Max)	p-value (wilcoxon test) compared with baseline
Baseline				
w8				
w16				

4.8.2.4. CF - Cognitive functioning (from 2 items)

Table 112: Cognitive functioning/QoL

Cognitive functioning/QoL	N	Mean(SD)	Median(Min-Max)	p-value (wilcoxon test) compared with baseline
Baseline				
w8				
w16				

4.8.2.5. SF - Social functioning (from 2 items)

Table 113: Social functioning/QoL

Social functioning/QoL	N	Mean(SD)	Median(Min-Max)	p-value (wilcoxon test) compared with baseline
Baseline				
w8				
w16				

4.8.3. Symptom Scales (higher is more symptoms, worse functioning)

4.8.3.1. FA - Fatigue (from 3 items)

Table 114: Fatigue/QoL

Fatigue/QoL	N	Mean(SD)	Median(Min-Max)	p-value (wilcoxon test) compared with baseline
Baseline				
w8				
w16				

4.8.3.2. NV - Nausea and Vomiting (from 2 items)

Table 115: Nausea and Vomiting/QoL

Nausea and Vomiting/QoL	N	Mean(SD)	Median(Min-Max)	p-value (wilcoxon test) compared with baseline
Baseline				
w8				
w16				

4.8.3.3. PA - Pain (from 2 items)

Table 116: Pain/QoL

Pain/QoL	N	Mean(SD)	Median(Min-Max)	p-value (wilcoxon test) compared with baseline
Baseline				
w8				
w16				

4.8.4. Single-Item Symptom Scores (higher is more symptoms, worse functioning)

4.8.4.1. DY - Dyspnoea (from 1 item)

Table 117: Dyspnoea/QoL

Dyspnoea/QoL	N	Mean(SD)	Median(Min-Max)	p-value (wilcoxon test) compared with baseline
Baseline				
w8				
w16				

4.8.4.2. SL - Insomnia (from 1 item)

Table 118: Insomnia/QoL

Insomnia/QoL	N	Mean(SD)	Median(Min-Max)	p-value (wilcoxon test) compared with baseline
Baseline				
w8				
w16				

4.8.4.3. AP - Appetite Loss (from 1 item)

Table 119: Appetite Loss/QoL

Appetite Loss/QoL	N	Mean(SD)	Median(Min-Max)	p-value (wilcoxon test) compared with baseline
Baseline				
w8				
w16				

4.8.4.4. CO - Constipation (from 1 item)

Table 120: Constipation/QoL

Constipation/QoL	N	Mean(SD)	Median(Min-Max)	p-value (wilcoxon test) compared with baseline
Baseline				
w8				
w16				

4.8.4.5. DI - Diarrhoea (from 1 item)

Table 121: Diarrhoea/QoL

Diarrhoea/QoL	N	Mean(SD)	Median(Min-Max)	p-value (wilcoxon test) compared with baseline
Baseline				
w8				
w16				

4.8.4.6. FI - Financial Difficulties (from 1 item)

Table 122: Financial Difficulties/QoL

Financial Difficulties/QoL	N	Mean(SD)	Median(Min-Max)	p-value (wilcoxon test) compared with baseline
Baseline				
w8				
w16				

4.9. QLQ-C30 Summary Score (higher is better functioning, fewer symptoms)

4.9.1. C30SUMMARY - QLQ-C30 Summary Score, composed by taking mean of all scores except for QL (Global health status/QoL) and FI (Financial Difficulties)

Table 123: QLQ-C30 Summary Score/QoL

QLQ-C30 Summary Score/QoL	N	Mean(SD)	Median(Min-Max)	p-value (wilcoxon test) compared with baseline
Baseline				
w8				
w16				

5. SAFETY ANALYSIS

In safety population.

Table 124: Overall safety

Cohort
Adverse Events
No
Yes
AE Grade >=3
No
Yes
Toxicity: AE related to Binimetinib
No
Yes
Toxicity: AE related to Encorafenib
No
Yes
Toxicity: AE related to any treatment
No
Yes
Toxicity: AE related to all treatments
No
Yes
Toxicity grade >=3
No
Yes
Toxicity related to Binimetinib grade >=3
No
Yes
Toxicity related to Encorafenib grade >=3
No
Yes
Toxicity related to all treatments grade >=3
No
Yes
SAE
No

Cohort
Yes

Table 125: Most frequent Toxicity with 5% threshold

Toxicity	Frequency	Percentage (%)

Table 126: Grade of most frequent toxicities with 5% threshold overall

Toxicity	No	G-UK	G-1	G-2	G-3	G-4	G-5

Table 127: List of toxicities grade >=3 in all patients

Patient Number	Cohort	AE CTCAE	AE Grade	AE Related to

Table 128: Most frequent AEs with 5% threshold

AE	Frequency	Percentage (%)

Table 129: Grade of most frequent AEs with 5% threshold overall

AE	No	G-UK	G-1	G-2	G-3	G-4	G-5

Table 130: List of all SAEs

Patient Number	Cohort	AE CTCAE	AE CTCAE Other	AE Grade	AE Start Date	AE Stop Date	AE Related	AE SAE	AE Intensity	AE Related to

6. Other analysis

6.1. Dose analysis

In this section, we analyzed the pattern of Corticosteroids dosage between Assessment 1 and 2 with the aim of observing any changes in Corticosteroids usage during the second tumor assessment. To achieve this, we focused on the active Corticosteroids treatments administered during the initial and follow-up tumor assessments. Therefore, we included only those patients who had at least

one active Corticosteroids treatment during either the first or second tumor assessment.

Table 132: Frequency of Dose in Patients with Corticosteroid Treatment by Assessment

case
CortiDose
N
Mean (95%CI)
SD
Median (95%CI)
Range

Table 133: Frequencies of Corticosteroid Dose Changes between Assessment 1 and 2

Overall
Dose comparison between Assessment 1 and 2 for each patient
Decreased Dose
Increased Dose
Maintained Dose

Table 134: Dose distribution according Assessment

Dose
Mean (SD)
Range

1. Paired samples t-test

Table 135: Mean Difference in Change between Assessment 1 and Assessment 2

Overall
Dose difference between Assessment 1 and 2
N
Mean (95%CI)
SD
Median (95%CI)
Range

Figure 17: Trends in Assessment Differences

*The dose scale (mg) on the vertical axis has been plotted on a logarithmic scale to show trends more clearly.

Table 136: List of all analyzed patients with their respective tumor assessment information and ongoing corticosteroid treatment. This includes both treatment and specific tumor assessment information

Patient Number	CortiMedication Name	Corti Dose	Corti Units	CortiStart Date	Corti Stop Date	Corti Ongoing	TumAssmTargSum	TumAssmNonTargLesNA	TumAssmNonTargSum	TumAssmTargResp	TumAssmNonTargResp	TumAssmNewLes	EvlIntrCranResp	Assessment 1 date	Assessment 2 date

6.2. Neurological Symptoms

Next, we present the frequency distributions of neurological symptoms for Cohort 2 according to the three temporal moments: baseline, assessment 1, and assessment 2.

6.2.1. Overall Neurological Symptoms: Comparison between Baseline and First Two Assessments

Table 146: Comparison of Neurological Symptoms

Headache	
No	
Yes	
Epilepsy	
No	
Yes	
Motor deficit	
No	
Yes	
Sensory deficit	
No	
Yes	
Speech deficit	
No	
Yes	
Others	
No	
Yes	
Presence of at least one symptom	
No	
Yes	
Number of neurological symptoms	
1	
2	
3	
4	
0	

1. We report four p-values for each variable, separated by semicolons. The first p-value represents the comparison of the differences between the three assessments. Subsequent p-values correspond to pairwise comparisons: Baseline vs. Assessment 1, Baseline vs. Assessment 3, and Assessment 2 vs. Assessment 3. For dichotomous variables,

Cochran's Q test and McNeiman's test were used. The discrete variable 'number of symptoms' was analyzed with the Friedman and Wilcoxon tests, respectively.

7. OTHER ANALYSES REQUIRED BY THE COORDINATOR

Group A: Symptomatic patients (Those belonging tp symptomatic cohort 2).

Group B: Asymptomatic patients, both those who were not treated with corticosteroids or anticonvulsants and those who were treated without association with brain metastases.

Group C: Patients who were asymptomatic at the time of study treatment but had been treated with corticosteroids in the days before due to a symptom of the disease.

7.1. Intracranial Overall survival (iOS).

7.1.1. Symptomatic patients A+C: intracranial Overall survival (iOS).

Table 147: Events type OS

OS	
Alive	
Death	
Total	

Table 148: Median/mean OS (estimated by Kaplan-Meier)

	Median (months)	CI 95%	Mean	CI 95%
Overall survival				

Table 149: OS estimated survival ratio

OS	Events (%, total N)	Patients at risk	% estimated cumulative survival ratio	CI 95%
At 6 months				
At 12 months				
At 18 months				
At 24 months				

Figure 18: Overall survival

7.1.2. Asymptomatic patients B: intracranial Overall survival (iOS).

Table 150: Events type OS

OS	N	%	95%CI
Alive			
Death			
Total			

Table 151: Median/mean OS (estimated by Kaplan-Meier)

	Median (months)	CI 95%	Mean	CI 95%
Overall survival				

Table 152: OS estimated survival ratio

OS	Events (%, total N)	Patients at risk	% estimated cumulative survival ratio	CI 95%
At 6 months				
At 12 months				
At 18 months				
At 24 months				

Figure 19: Overall survival

7.1.3. intracranial Overall survival (iOS) vs Symptomatic.

Table 153: Events type OS

Symptomatic group
Death
Alive

1. Pearson's Chi-squared test

Table 154: Median/mean OS (estimated by Kaplan-Meier)

	Median (months)	CI 95%	Mean	CI 95%
No				
Yes				

Table 155: OS estimated survival ratio

OS	Events (%, total N)	Patients at risk	% estimated cumulative survival ratio	CI 95%
No				
At 6 months				
At 12 months				
At 18 months				
At 24 months				
Yes				
At 6 months				
At 12 months				
At 18 months				
At 24 months				

Figure 20: Overall survival vs Symptomatic group

7.2. Intracranial Progression-free survival (iPFS).

7.2.1. Symptomatic patients A+C: intracranial Progression-free survival (iPFS).

Table 156: Events type PFS

PFS	N	%	95%CI
Censored			
Event (PD/death)			
Total			

Table 157: Median/mean PFS (estimated by Kaplan-Meier)

	Median (months)	CI 95%	Mean	CI 95%
Progression-free survival				

Table 158: PFS estimated survival ratio

PFS	Events (%, total N)	Patients at risk	% estimated cumulative survival ratio	CI 95%
At 3 months				
At 6 months				
At 9 months				
At 12 months				
At 15 months				
At 18 months				
At 21 months				

Figure 21: Progression-free survival

7.2.2. Asymptomatic patients B: intracranial Progression-free survival (iPFS).

Table 159: Events type PFS

PFS	N	%	95%CI
Censored			
Event (PD/death)			
Total			

Table 160: Median/mean PFS (estimated by Kaplan-Meier)

	Median (months)	CI 95%	Mean	CI 95%
Progression-free survival				

Table 161: PFS estimated survival ratio

PFS	Events (%, total N)	Patients at risk	% estimated cumulative survival ratio	CI 95%
At 6 months				
At 12 months				
At 18 months				
At 24 months				

Figure 22: Progression-free survival

7.2.3. INTRACRANIAL PROGRESSION-FREE SURVIVAL (IPFS) VS SYMPTOMATIC.

Table 162: Events type PFS

Symptomatic group
Event (PD/death)
Censored

1. Pearson's Chi-squared test

Table 163: Median/mean PFS (estimated by Kaplan-Meier)

	Median (months)	CI 95%	Mean	CI 95%
No				
Yes				

Table 164: PFS estimated survival ratio

PFS	Events (%, total N)	Patients at risk	% estimated cumulative survival ratio	CI 95%
No				
At 6 months				
At 12 months				
At 18 months				
At 24 months				
Yes				
At 6 months				
At 12 months				
At 18 months				
At 24 months				

Figure 23: Progression-free survival vs Symptomatic group

7.3. PRIMARY EFFICACY OBJECTIVE: RESPONSE AT 56 DAYS

Table 165: Symptomatic group (A+C): intracranial Objective Response Rate at 56 days

ORR: Intracraneal Evaluation at 56 days	N	%	95%CI
CR or PR			
SD			
NE			
Total			

Table 166: Asymptomatic group (B): intracranial Objective Response Rate at 56 days

ORR: Intracraneal Evaluation at 56 days	N	%	95%CI
CR or PR			
SD			
Total			

7.3.1. INTRACRANIAL RESPONSE DURATION

Table 167: Intracranial Response Duration (months)

Duration of response (months)
N
Mean (95%CI)
SD
Median (95%CI)
Range

8. ANNEX 1

Table 168: List of all toxicities

Patient Number	Cohort	AE CTCAE	AE CTCAE Other	AE Grade	AE Start Date	AE Stop Date	AE Related	AE SAE	AE Intensity	AE Related to

EBRAIN-MEL GEM1802 STUDY - STATISTICAL REPORT (APPENDIX ANALYSIS)

JAN 2023

Table of Contents

1. BASELINE CHARACTERISTICS

BASELINE - DEMOGRAPHIC DATA

Table 1: Baseline - Socio demographic data ITT

	Symptomatic (A+C)	Asymptomatic (B)	Total
Age (years)			
N			
Mean (95%CI)			
SD			
Median (95%CI)			
Range			
Sex			
Female			
Male			
Race			
Caucasian			
Latin			

Table 2: Baseline - Physical characteristics ITT

	Symptomatic (A+C)	Asymptomatic (B)	Total
Phototype (n(%))			
Type I			
Type II			
Type III			
Type IV			
UK			
Weight (kg)			
N			
Mean (95%CI)			
SD			
Median (95%CI)			
Range			
Height (cm)			
N			
Mean (95%CI)			
SD			
Median (95%CI)			
Range			

	Symptomatic (A+C)	Asymptomatic (B)	Total
Systolic Blood Pressure (mmHg)			
N			
Mean (95%CI)			
SD			
Median (95%CI)			
Range			
Diastolic Blood Pressure (mmHg)			
N			
Mean (95%CI)			
SD			
Median (95%CI)			
Range			
Temperature (ºC)			
N			
Mean (95%CI)			
SD			
Median (95%CI)			
Range			
Respiratory rate (BPM)			
N			
Mean (95%CI)			
SD			
Median (95%CI)			
Range			
Pulse Rate (BPM)			
N			
Mean (95%CI)			
SD			
Median (95%CI)			
Range			
ECOG (n(%))			
0			
1			
2			
Barthel index (categorical), (n(%)), previous to November 2020			
Barthel index (Arbitrary units, scale 0-100)			
N			
Mean (95%CI)			
SD			
Median (95%CI)			
Range			
Barthel index modified, from November 2020			
Barthel index modified (Arbitrary units, scale 0-20), from November 2020			
N			

	Symptomatic (A+C)	Asymptomatic (B)	Total
Mean (SD)			
Median			
Range			
Barthel index final (all values transformed to scale 0-20) (categorical) (n(%))			
Barthel index final (all values transformed to scale 0-20)			
N			
Mean (95%CI)			
SD			
Median (95%CI)			
Range			
Physical exam			
Normal			
Abnormal			
Neurological exam			
Normal			
Abnormal			
Ophthalmologic exam			
Normal			
Abnormal			
Autoimmune concomitant diseases			
Yes			
No			
UK			

1.1. Baseline current melanoma

Table 3: Metastases ITT

	Symptomatic (A+C)	Asymptomatic (B)	Total
Brain Metastases			
Unique			
Multiple			
Target Brain Metastases			
1			
2			
3			
4			
5			
UK			
Extracranial Metastases			
Yes			
No			
Lung Metastases			
Yes			
No			
UK			
Lung Metastases Number			

	Symptomatic (A+C)	Asymptomatic (B)	Total
1			
2			
3			
4			
>5			
NA/UK			
Liver Metastases			
Yes			
No			
UK			
Liver Metastases Number			
1			
2			
3			
>5			
NA/UK			
Skin Metastases			
Yes			
No			
UK			
Skin Metastases Number			
1			
2			
3			
>5			
UK			
Bone Metastases			
Yes			
No			
UK			
Bone Metastases Number			
1			
2			
NA/UK			
Pleura Metastases			
Yes			
No			
UK			
Pleural Effusion Volume			
0			
NA/UK			
Soft Tissue Metastases			
Yes			
No			
UK			
Soft Tissue Metastases Number			
1			
5			
NA/UK			
Lymph Nodes Metastases			

	Symptomatic (A+C)	Asymptomatic (B)	Total
Yes			
No			
UK			
Lymph Nodes Metastases Number			
1			
2			
3			
>5			
UK			
NA/UK			
Peritoneum Metastases			
Yes			
No			
UK			
Peritoneum Metastases Number			
1			
NA/UK			
Other Metastases			
Yes			
No			
UK			
Other Metastases Number			
1			
2			
>5			
UK			
Other Metastases Specify			

Table 4: BRAF ITT

	Symptomatic (A+C)	Asymptomatic (B)	Total
V600E			
Missing data			
Mutated			
Not mutated			
V600K			
Mutated			
Not mutated			
NA/UK			
V600E/K			
Mutated			
Not mutated			
NA/UK			
V600R			
Mutated			
Not mutated			
NA/UK			
V600 other			
Mutated			

	Symptomatic (A+C)	Asymptomatic (B)	Total
Not mutated			
NA/UK			
V600 (NE)			
Mutated			
Not mutated			
NA/UK			

2. PRIMARY EFFICACY OBJECTIVE

2.1. RADIOTHERAPY TREATMENT

Table 5: Radiotherapy treatment. ITT

	Symptomatic (A+C)	Asymptomatic (B)	Total
Radiotherapy treatment (Local and/or Whole Brain)			
N			
Yes			
Yes (CR)			
No			
No (CR)			
LocaL Radiation treatment			
N			
Yes			
Yes (CR)			
No			
No (CR)			
Local Radiation Treatment type			
N			
No			
Radiosurgery (RS)			
Stereotactic radiosurgery (SRS)			
Device Used			
Missing			
N			
Gamma Knife			
Accelerator Linac-Based Systems (IMRT, Rapid Arc, VMAT)			
Cyberknife			
Whole Brain Radiotherapy			
N			
Yes			
No			
No (CR)			

2.2. OS on ITT according to Radiotherapy

Table 6: Events type OS

Radiotherapy	
Death	
Alive	

1. Pearson's Chi-squared test

Table 7: Median/mean OS (estimated by Kaplan-Meier)

	Median (months)	CI 95%	Mean	CI 95%
No				
Yes				

Table 8: OS estimated survival ratio

OS	Events (%, total N)	Patients at risk	% estimated cumulative survival ratio	CI 95%
No				
At 6 months				
At 12 months				
At 18 months				
At 24 months				
Yes				
At 6 months				
At 12 months				
At 18 months				
At 24 months				

Figure 25: Overall survival vs Radiotherapy

2.3. iPFS on ITT according to Radiotherapy

Table 9: Events type PFS

Radiotherapy	
PFS Event	
PD	
Censored	
Death (without previous PD)	

1. Pearson's Chi-squared test

Table 10: Median/mean PFS (estimated by Kaplan-Meier)

	Median (months)	CI 95%	Mean	CI 95%
No				
Yes				

Table 11: PFS estimated survival ratio

PFS	Events (%, total N)	Patients at risk	% estimated cumulative survival ratio	CI 95%
No				
At 6 months				
At 12 months				
At 18 months				
At 24 months				
Yes				
At 6 months				
At 12 months				
At 18 months				
At 24 months				

Figure 26: Progression free survival vs Radiotherapy

2.4. ePFS according to Symptomatic group

Table 12: Events type PFS

Symptomatic group	Symptomatic (A+C)	Asymptomatic (B)	Total	p value
PFS (event)				
Event (PD/death)				
Censored				

1. Pearson's Chi-squared test

Table 13: Median/mean PFS (estimated by Kaplan-Meier)

	Median (months)	CI 95%	Mean	CI 95%
Symptomatic (A+C)				
Asymptomatic (B)				

Table 14: PFS estimated survival ratio

PFS	Events (%, total N)	Patients at risk	% estimated cumulative survival ratio	CI 95%
Symptomatic (A+C)				
At 6 months				
At 12 months				
At 18 months				
At 24 months				
Asymptomatic (B)				
At 6 months				
At 12 months				
At 18 months				
At 24 months				

Figure 27: Progression free survival vs Symptomatic group

EBRAIN-MEL GEM1802 STUDY - STATISTICAL REPORT (2nd APPENDIX ANALYSIS: QUALITY OF LIFE QUESTIONARY)

JAN2023

1. Table of Contents

The database containing the results for the following report was locked on

2. ALL COHORTS

2.1. QUALITY OF LIFE QUESTIONARY: EORTC QLQ C-30

All scores are scaled to range from 0-100, even scores based on single items. Be aware that these single-item scales still have only 4 possible values, even though they are transformed to range from 0-100. The scale name and number of items are listed below.

- **Global health status/QoL**
  QL - Global health status/QoL (revised) (from 2 items)

- **Functional Scales (higher is better functioning)**
  PF - Physical functioning (from 5 items)
  RF - Role functioning (from 2 items)
  EF - Emotional functioning (from 4 items)
  CF - Cognitive functioning (from 2 items)
  SF - Social functioning (from 2 items)

- **Symptom Scales (higher is more symptoms, worse functioning)**
  FA - Fatigue (from 3 items)
  NV - Nausea and Vomiting (from 2 items)
  PA - Pain (from 2 items)

- **Single-Item Symptom Scores (higher is more symptoms, worse functioning)**
  DY - Dyspnoea
  SL - Insomnia
  AP - Appetite Loss
  CO - Constipation
  DI - Diarrhoea
  FI - Financial Difficulties

- **QLQ-C30 Summary Score** (higher is better functioning, fewer symptoms)
  C30SUMMARY - QLQ-C30 Summary Score, composed by taking mean of all scores except for QL (Global health status/QoL) and FI (Financial Difficulties).

Reference:

https://rdrr.io/cran/PROscorer/man/qlq_c30.html

Aaronson NK, Ahmedzai S, Bergman B, Bullinger M, Cull A, Duez NJ, Filiberti A, Flechtner H, Fleishman SB, Haes JCJM de, Kaasa S, Klee M, Osoba D, Razavi D, Rofe PB, Schraub S, Sneeuw K, Sullivan M, Takeda F (1993). The European Organization for Research and Treatment of Cancer QLQ-C30: A Quality-of-Life Instrument for Use in International Clinical Trials in Oncology. JNCI J Natl Cancer Inst 85:365-376.

Fayers PM, Aaronson NK, Bjordal K, Groenvold M, Curran D, Bottomley A, on behalf of the EORTC Quality of Life Group. The EORTC QLQ-C30 Scoring Manual (3rd Edition). Published by: European Organisation for Research and Treatment of Cancer, Brussels 2001.

Giesinger JM, Kieffer JM, Fayers PM, Groenvold M, Petersen MA, Scott NW, Sprangers MAG, Velikova G, Aaronson NK (2016). Replication and validation of higher order models demonstrated that a summary score for the EORTC QLQ-C30 is robust. Journal of Clinical Epidemiology 69:79-88.

2.1.1. Global health status/QoL

2.1.1.1. QL - Global health status/QoL (revised) (from 2 items)

Table 1: Global health status/QoL

Global health status/QoL	N	Mean(SD)	Median(Min-Max)	p-value (wilcoxon test) compared with baseline
Baseline				
w8				
w16				

2.1.2. Functional Scales (higher is better functioning)

2.1.2.1. PF - Physical functioning (from 5 items)

Table 2: Physical functioning/QoL

Physical functioning/QoL	N	Mean(SD)	Median(Min-Max)	p-value (wilcoxon test) compared with baseline
Baseline				
w8				

Physical functioning/QoL	N	Mean(SD)	Median(Min-Max)	p-value (wilcoxon test) compared with baseline
w16				

2.1.2.2. RF - Role functioning (from 2 items)

Table 3: Role functioning/QoL

Role functioning/QoL	N	Mean(SD)	Median(Min-Max)	p-value (wilcoxon test) compared with baseline
Baseline				
w8				
w16				

2.1.2.3. EF - Emotional functioning (from 4 items)

Table 4: Emotional functioning/QoL

Emotional functioning/QoL	N	Mean(SD)	Median(Min-Max)	p-value (wilcoxon test) compared with baseline
Baseline				
w8				
w16				

2.1.2.4. CF - Cognitive functioning (from 2 items)

Table 5: Cognitive functioning/QoL

Cognitive functioning/QoL	N	Mean(SD)	Median(Min-Max)	p-value (wilcoxon test) compared with baseline
Baseline				

Cognitive functioning/QoL	N	Mean(SD)	Median(Min-Max)	p-value (wilcoxon test) compared with baseline
w8				
w16				

2.1.2.5. SF - Social functioning (from 2 items)

Table 6: Social functioning/QoL

Social functioning/QoL	N	Mean(SD)	Median(Min-Max)	p-value (wilcoxon test) compared with baseline
Baseline				
w8				
w16				

2.1.3. Symptom Scales (higher is more symptoms, worse functioning)

2.1.3.1. FA - Fatigue (from 3 items)

Table 7: Fatigue/QoL

Fatigue/QoL	N	Mean(SD)	Median(Min-Max)	p-value (wilcoxon test) compared with baseline
Baseline				
w8				
w16				

2.1.3.2. NV - Nausea and Vomiting (from 2 items)

Table 8: Nausea and Vomiting/QoL

Nausea and Vomiting/QoL	N	Mean(SD)	Median(Min-Max)	p-value (wilcoxon test) compared with baseline
Baseline				
w8				
w16				

2.1.3.3. PA - Pain (from 2 items)

Table 9: Pain/QoL

Pain/QoL	N	Mean(SD)	Median(Min-Max)	p-value (wilcoxon test) compared with baseline
Baseline				
w8				
w16				

2.1.4. Single-Item Symptom Scores (higher is more symptoms, worse functioning)

2.1.4.1. DY - Dyspnoea (from 1 item)

Table 10: Dyspnoea/QoL

Dyspnoea/QoL	N	Mean(SD)	Median(Min-Max)	p-value (wilcoxon test) compared with baseline
Baseline				
w8				
w16				

2.1.4.2. SL - Insomnia (from 1 item)

Table 11: Insomnia/QoL

Insomnia/QoL	N	Mean(SD)	Median(Min-Max)	p-value (wilcoxon test) compared with baseline
Baseline				
w8				
w16				

2.1.4.3. AP - Appetite Loss (from 1 item)

Table 12: Appetite Loss/QoL

Appetite Loss/QoL	N	Mean(SD)	Median(Min-Max)	p-value (wilcoxon test) compared with baseline
Baseline				
w8				
w16				

2.1.4.4. CO - Constipation (from 1 item)

Table 13: Constipation/QoL

Constipation/QoL	N	Mean(SD)	Median(Min-Max)	p-value (wilcoxon test) compared with baseline
Baseline				
w8				
w16				

2.1.4.5. DI - Diarrhoea (from 1 item)

Table 14: Diarrhoea/QoL

Diarrhoea/QoL	N	Mean(SD)	Median(Min-Max)	p-value (wilcoxon test) compared with baseline
Baseline				
w8				
w16				

2.1.4.6. FI - Financial Difficulties (from 1 item)

Table 15: Financial Difficulties/QoL

Financial Difficulties/QoL	N	Mean(SD)	Median(Min-Max)	p-value (wilcoxon test) compared with baseline
Baseline				
w8				
w16				

2.2. QLQ-C30 Summary Score (higher is better functioning, fewer symptoms)

2.2.1. C30SUMMARY - QLQ-C30 Summary Score, composed by taking mean of all scores except for QL (Global health status/QoL) and FI (Financial Difficulties)

Table 16: QLQ-C30 Summary Score/QoL

QLQ-C30 Summary Score/QoL	N	Mean(SD)	Median(Min-Max)	p-value (wilcoxon test) compared with baseline
Baseline				
w8				
w16				

3. COHORTS A-C (SYMPTOMATIC PATIENTS)

Analyses were conducted exclusively on significant variables across the entire sample.

3.1.1. GLOBAL HEALTH STATUS/QOL

3.1.1.1. QL - GLOBAL HEALTH STATUS/QOL (REVISED) (FROM 2 ITEMS)

Table 17: Global health status/QoL

Global health status/QoL	N	Mean(SD)	Median(Min-Max)	p-value (wilcoxon test) compared with baseline
Baseline				
w8				
w16				

3.1.2. FUNCTIONAL SCALES (HIGHER IS BETTER FUNCTIONING)

3.1.2.1. EF - EMOTIONAL FUNCTIONING (FROM 4 ITEMS)

Table 18: Emotional functioning/QoL

Emotional functioning/QoL	N	Mean(SD)	Median(Min-Max)	p-value (wilcoxon test) compared with baseline
Baseline				
w8				
w16				

3.1.3. SINGLE-ITEM SYMPTOM SCORES (HIGHER IS MORE SYMPTOMS, WORSE FUNCTIONING)

3.1.3.1. SL - INSOMNIA (FROM 1 ITEM)

Table 19: Insomnia/QoL

Insomnia/QoL	N	Mean(SD)	Median(Min-Max)	p-value (wilcoxon test) compared with baseline
Baseline				
w8				
w16				

3.2. QLQ-C30 Summary Score (higher is better functioning, fewer symptoms)

3.2.1. C30SUMMARY - QLQ-C30 Summary Score, composed by taking mean of all scores except for QL (Global health status/QoL) and FI (Financial Difficulties)

Table 20: QLQ-C30 Summary Score/QoL

QLQ-C30 Summary Score/QoL	N	Mean(SD)	Median(Min-Max)	p-value (wilcoxon test) compared with baseline
Baseline				
w8				
w16				

4. COHORT B (Asymptomatic patients)

Analyses were conducted exclusively on significant variables across the entire sample.

4.1.1. Global health status/QoL

4.1.1.1. QL - Global health status/QoL (revised) (from 2 items)

Table 21: Global health status/QoL

Global health status/QoL	N	Mean(SD)	Median(Min-Max)	p-value (wilcoxon test) compared with baseline
Baseline				
w8				
w16				

4.1.2. Functional Scales (higher is better functioning)

4.1.2.1. EF - Emotional functioning (from 4 items)

Table 22: Emotional functioning/QoL

Emotional functioning/QoL	N	Mean(SD)	Median(Min-Max)	p-value (wilcoxon test) compared with baseline
Baseline				
w8				
w16				

4.1.3. Single-Item Symptom Scores (higher is more symptoms, worse functioning)

4.1.3.1. SL - Insomnia (from 1 item)

Table 23: Insomnia/QoL

Insomnia/QoL	N	Mean(SD)	Median(Min-Max)	p-value (wilcoxon test) compared with baseline
Baseline				
w8				
w16				

4.2. QLQ-C30 Summary Score (higher is better functioning, fewer symptoms)

4.2.1. C30SUMMARY - QLQ-C30 Summary Score, composed by taking mean of all scores except for QL (Global health status/QoL) and FI (Financial Difficulties)

Table 24: QLQ-C30 Summary Score/QoL

QLQ-C30 Summary Score/QoL	N	Mean(SD)	Median(Min-Max)	p-value (wilcoxon test) compared with baseline
Baseline				
w8				
w16				