Clinical trial results:
Multicentric 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.

Summary

EudraCT number	2018-002530-20
Trial protocol	ES
Global end of trial date	31 July 2023

Results information

Result version number	v1 (current)
This version publication date	24 April 2025
First version publication date	24 April 2025

Trial information

Trial identification

Sponsor protocol code	GEM-1802

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03898908
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Grupo Español Multidisciplinar de Melanoma (GEM)
Sponsor organisation address	Velázquez, 7, 3ª planta, Madrid, Spain, 28001
Public contact	Technical Secretary, Grupo Español Multidisciplinar de Melanoma (GEM), secretaria@groupgem.es
Scientific contact	Technical Secretary, Grupo Español Multidisciplinar de Melanoma (GEM), secretaria@groupgem.es

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	31 July 2023
Is this the analysis of the primary completion data?	Yes
Primary completion date	10 October 2022
Global end of trial reached?	Yes
Global end of trial date	31 July 2023
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Intracranial objective response rate by RECIST 1.1 before local treatment

Protection of trial subjects:

The study protocol already included measures to protect trial subjects.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	18 July 2019
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Spain: 48
Worldwide total number of subjects	48
EEA total number of subjects	48

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	48
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

the initial sample size was set at 48 patients, to ensure obtaining 38 evaluable patients. The cohort of symptomatic patients was exploratory and no formal sample calculation was performed, anticipating the inclusion of up to 15 patients. An interim analysis revealed no differences between cohorts. The trial was amended to analyze the full dataset.

Pre-assignment

Screening details:

Between July 2019 and October 2022, 48 patients were enrolled

Period 1

Period 1 title	Overall study period (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Blinding implementation details:

Single arm study. No blinding applicable. No randomization.

Arms

Arm title	COMBO450

Arm description:

Encorafenib 450 mg daily orally and binimetinib 45 mg twice a day orally until progression of the disease, unacceptable toxicity or death.
local radiation treatment started after start of treatment. Suggested doses are as follow: 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.

Arm type	Experimental
Investigational medicinal product name	Encorafenib
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

75 mg and 50 mg capsules

Investigational medicinal product name	Binimetinib
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

15 mg tablets

Number of subjects in period 1	COMBO450
Started	48
Completed	48

Baseline characteristics

Reporting groups

Reporting group title	Overall study period

Reporting group description: -

Reporting group values	Overall study period	Total	
Number of subjects	48	48	
Age categorical Units: Subjects			
In utero		0	
Preterm newborn infants (gestational age < 37 wks)		0	
Newborns (0-27 days)		0	
Infants and toddlers (28 days-23 months)		0	
Children (2-11 years)		0	
Adolescents (12-17 years)		0	
Adults (18-64 years)		0	
From 65-84 years		0	
85 years and over		0	
Age continuous Units: years			
median	54		
full range (min-max)	18 to 88	-	
Gender categorical Units: Subjects			
Female	24	24	
Male	24	24	
Eastern cooperative oncology group (ECOG) performance status (PS) at baseline			
Measure Description: The ECOG PS score describes a patient’s level of functioning in terms of their ability to care for themself, daily activity, and physical ability (walking, working, etc.). The score ranges from 0 (Fully active, able to carry on all pre-disease performance without restriction) to 5 (dead)			
Units: Subjects			
Score 0	26	26	
Score 1	20	20	
Score 2	2	2	
Barthel Index			
Measure Description: Scale used to assess a patient's functional status and monitor their progress. The scale measures a person's ability to perform 10 basic activities of daily living, thereby providing a quantitative estimate of their degree of independence. Lower values indicate worse performance and more dependency.			
Units: Subjects			
Total dependent (0-4)	3	3	
Severe dependent (5-12)	4	4	
Moderate dependent (13-18)	6	6	
Slight dependent (19-20)	33	33	
Not applicable	2	2	
BRAF genotype			

BRAF genotype refers to changes or mutations in the BRAF gene, which is located on chromosome 7. These changes may be linked to cancer.			
Units: Subjects			
V600E mutated	41	41	
V600E not mutated	7	7	
Brain symptoms			
Patients who experience symptoms related to the presence of brain metastasis, including (among others): Headaches. Seizures. Weakness in the arms or legs. Loss of balance. Memory loss. Speech disturbance/problems talking.			
Units: Subjects			
Asymptomatic	25	25	
Symptomatic	23	23	
Number of brain target lesion Units: Subjects			
1 intracranial lesion	21	21	
2 intracranial lesions	15	15	
3 or more intracranial lesions	12	12	
Extracranial metastases			
Presence of extracranial disease.			
Units: Subjects			
Yes	41	41	
No	7	7	
Lactate dehydrogenase (LDH) levels			
LDH is determined in blood samples. this biomarker is indicative of inflammatory processes and in metastatic melanoma is considered a prognostic factor. Elevated levels of LDH are correlated with worse outcomes.			
Units: Subjects			
≤ upper limit normal (ULN)	26	26	
> ULN	21	21	
Unknown	1	1	
Corticosteroids use at baseline			
Number of patients having corticosteroids at baseline. Corticcosteroids are ofter prescribed to mitigate the symptoms of brain metastasis.			
Units: Subjects			
Yes	33	33	
No	15	15	
Previous anti- PD-1 based immunotherapy			
PD-1 inhibitors and PD-L1 inhibitors are a group of checkpoint inhibitor anticancer drugs that block the activity of PD-1 and PDL1 immune checkpoint proteins. These treatments have an anticancer effect by promoting the activation of the immune system against tumor cells.			
Units: Subjects			
Anti PD-1	11	11	
Anti PD-1 / anti CTLA-4	5	5	
No previous PD-L1	32	32	
Radiotherapy received in the E-BRAIN trial			
ype of radiation therapy scheduled during this trial. The radiotherapy type was chosen according to the principal investigator criteria and local standard procedures.			
Units: Subjects			
Radiosurgery (RS)	10	10	
Fractioned stereotactic radiotherapy (FSRT)	6	6	
Whole brain radiotherapy (WBRT)	15	15	

None	17	17	

Sum of longest diameters of intracranial target lesions			
This endpoint is a surrogate of the intracranial tumor burden. Here we show the sum of the longest diameter of intracranial metastasis			
Units: millimetre(s)			
median	26.5		
full range (min-max)	6 to 134	-	
Corticosteroid dose			
The corticosteroids are collected as dexametasone equivalent. Here we report the daily dose prescribed. Measure Analysis Population Description: The dose of corticosteroids is only reported in patients receiving corticosteroids (N=33).			
Units: milligram(s)/24 hours			
median	8		
full range (min-max)	1 to 16	-	

End points

End points reporting groups

Reporting group title	COMBO450

Reporting group description:

Encorafenib 450 mg daily orally and binimetinib 45 mg twice a day orally until progression of the disease, unacceptable toxicity or death.
local radiation treatment started after start of treatment. Suggested doses are as follow: 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.

Primary: Intracranial Objective Response (iORR) by Modified RECIST 1.1 Before Local Radiotherapy Treatment in Full Dataset

End point title	Intracranial Objective Response (iORR) by Modified RECIST 1.1 Before Local Radiotherapy Treatment in Full Dataset[1]

End point description:

iORR calculated as the proportion of patient with a best overall intracranial response of complete response (CR) or partial response (PR) before local treatment according to modified RECIST 1.1.
Modified RECIST 1.1 consists of:
Up to 5 intracranial lesions could be selected as target lesions Target lesions might have a longest diameter ≥ 5 mm when evaluated by contrast-enhanced MRI
This endpoint was also independently reported in patients with symptomatic and asymptomatic brain metastasis.

End point type	Primary

End point timeframe:

24 months after start of treatment

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: This is a single arm study. No statistical comparison was planned. The results are indirectly compared with the current state of the art in the pathology.

End point values	COMBO450			
Subject group type	Reporting group			
Number of subjects analysed	48			
Units: Patients				
Patients with intracranial response	34			
Patients with NO intracranial response	13			
Not evaluable	1			

Statistical analyses

No statistical analyses for this end point

Primary: iORR by Modified RECIST 1.1 Before Local Radiotherapy Treatment in asymptomatic

End point title	iORR by Modified RECIST 1.1 Before Local Radiotherapy Treatment in asymptomatic[2]

End point description:

iORR calculated as the proportion of patient with a best overall intracranial response of complete

response (CR) or partial response (PR) before local treatment according to modified RECIST 1.1.
Modified RECIST 1.1 consists of:
Up to 5 intracranial lesions could be selected as target lesions Target lesions might have a longest diameter ≥ 5 mm
when evaluated by contrast-enhanced MRI
This endpoint was also independently reported in patients with symptomatic and asymptomatic brain metastasis.

End point type	Primary

End point timeframe:

24 months after start of treatment

Notes:

[2] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: This is a single arm study. No statistical comparison was planned. The results are indirectly compared with the current state of the art in the pathology.

End point values	COMBO450			
Subject group type	Reporting group			
Number of subjects analysed	25[3]			
Units: Patients				
Patients with intracranial response	20			
Patients with NO intracranial response	5			
Not evaluable	0			

Notes:

[3] - Patients without symptoms of brain metastasis (Asymptomatic cohort)

Statistical analyses

No statistical analyses for this end point

Primary: iORR by Modified RECIST 1.1 Before Local Radiotherapy Treatment in symptomatic

End point title	iORR by Modified RECIST 1.1 Before Local Radiotherapy Treatment in symptomatic[4]

End point description:

iORR calculated as the proportion of patient with a best overall intracranial response of complete response (CR) or partial response (PR) before local treatment according to modified RECIST 1.1.
Modified RECIST 1.1 consists of:
Up to 5 intracranial lesions could be selected as target lesions Target lesions might have a longest diameter ≥ 5 mm
when evaluated by contrast-enhanced MRI
This endpoint was also independently reported in patients with symptomatic and asymptomatic brain metastasis.

End point type	Primary

End point timeframe:

24 months after start of treatment

Notes:

[4] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: This is a single arm study. No statistical comparison was planned. The results are indirectly compared with the current state of the art in the pathology.

End point values	COMBO450			
Subject group type	Reporting group			
Number of subjects analysed	23[5]			
Units: Patients				
Patients with intracranial response	14			
Patients with NO intracranial response	8			
Not evaluable	1			

Notes:

[5] - Patients with symptoms of brain metastasis (symptomatic)

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Intracranial Response

End point title	Duration of Intracranial Response

End point description:

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 accoridng to modified RECIST 1.1, in patients with documented intracranial CR or PR before local treatment.

End point type	Secondary

End point timeframe:

Throughout the study period, up to approximately 24 months

End point values	COMBO450			
Subject group type	Reporting group			
Number of subjects analysed	34[6]			
Units: month				
median (confidence interval 95%)	5.6 (3.6 to 7.5)			

Notes:

[6] - Only patients with a response were analyzed

Statistical analyses

No statistical analyses for this end point

Secondary: Intracranial Progression-free Survival (iPFS) by RECIST 1.1

End point title	Intracranial Progression-free Survival (iPFS) by RECIST 1.1

End point description:

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 was determined based on tumor assessment (modified RECIST version 1.1 criteria). The local Investigator's assessments was used for analyses. Those patients who were alive and had not progressed at the last follow-up, date of progression was censored at the date of the last follow-up. Patients with no additional image test other than baseline were censored the day after inclusion.

End point type	Secondary

End point timeframe:

Throughout the study period, up to approximately 24 months

End point values	COMBO450			
Subject group type	Reporting group			
Number of subjects analysed	48			
Units: month				
median (confidence interval 95%)	8.5 (6.4 to 11.8)			

Statistical analyses

No statistical analyses for this end point

Secondary: Extracranial Progression-free Survival (ePFS) in Both Cohorts

End point title	Extracranial Progression-free Survival (ePFS) in Both Cohorts

End point description:

Defined as the time from the date of inclusion to the date of the first documented extracranial disease progression or death due to any cause, whichever occurs first. PFS was determined based on tumor assessment (RECIST version 1.1 criteria). The local Investigator's assessments was used for analyses. Those patients who were alive and had not progressed at the last follow-up, date of progression was censored at the date of the last follow-up. Patients with no additional image test other than baseline were censored the day after inclusion.

End point type	Secondary

End point timeframe:

Throughout the study period, up to approximately 24 months

End point values	COMBO450			
Subject group type	Reporting group			
Number of subjects analysed	48			
Units: month				
median (confidence interval 95%)	7.7 (6.1 to 11.8)			

Statistical analyses

No statistical analyses for this end point

Secondary: Intracranial Progression-free Rates

End point title	Intracranial Progression-free Rates

End point description:

Proportion 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 estimated through Kaplan-Meier method

End point type	Secondary

End point timeframe:

at 6 months (week 24), 12 months (week 48) and 24-month (week 96)

End point values	COMBO450			
Subject group type	Reporting group			
Number of subjects analysed	48			
Units: Percentage of patients				
number (confidence interval 95%)				
6 months	66.8 (54.4 to 82.1)			
12 months	29.5 (18.2 to 47.6)			
24 months	5.5 (0.9 to 32)			

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival

End point title	Overall Survival

End point description:

Calculated as the time from date of inclusion to date of death due to any cause.

End point type	Secondary

End point timeframe:

Throughout the study period, up to approximately 24 months

End point values	COMBO450			
Subject group type	Reporting group			
Number of subjects analysed	48			
Units: month				
median (confidence interval 95%)	15.9 (10.7 to 21.4)			

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival Rates

End point title	Overall Survival Rates

End point description:

Proportion of of patients alive at 6 months, 12 month and 24-month considering date of inclusion estimated using Kaplan-Meier

End point type	Secondary

End point timeframe:

at 6 months, 12 month and 24-month

End point values	COMBO450			
Subject group type	Reporting group			
Number of subjects analysed	48			
Units: Percentage of patients				
number (confidence interval 95%)				
6 months	91.6 (84.1 to 99.8)			
12 months	59.2 (46.2 to 76)			
24 months	15.5 (6.7 to 35.8)			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With Treatment-related Adverse Events as Assessed by CTCAE v4.0

End point title	Number of Participants With Treatment-related Adverse Events as Assessed by CTCAE v4.0

End point description:

Number of patients experiencing treatment related adverse events. These events were graded accrding to CTCAE, a scale that ranges from 0 (less intense; no event) to 5 (death).

End point type	Secondary

End point timeframe:

Throughout the study period, up to approximately 24 months

End point values	COMBO450			
Subject group type	Reporting group			
Number of subjects analysed	48			
Units: Patients				
Experienced Toxicity	40			
Do NOT experienced toxicity	8			

Statistical analyses

No statistical analyses for this end point

Secondary: Change on Quality of Life at Week 8 in Both Cohorts Based on the EORTC QLQ 30 Scale

End point title	Change on Quality of Life at Week 8 in Both Cohorts Based on the EORTC QLQ 30 Scale

End point description:

The EORTC QLQ-C30 questionnaire is validated for cancer. It is composed of 30 questions or items that assess QoL. The questionnaire is structured in 5 functional scales physical functioning, daily activities, emotional functioning, cognitive functioning and social functioning), 3 symptom scales (fatigue, pain and nausea, vomiting), 1 global health status scale, and 6 independent items (dyspnea, insomnia, anorexia, constipation, diarrhea and economic impact). Values between 1 and 4 (1: not at all, 2: a little, 3: quite, 4: a lot) are assigned according to the patient's responses to the item, only in items 29 and 30 are they evaluated with a score of 1 to 7 (1: dreadful, 7: excellent).
The scores obtained are standardized and a score between 0 and 100 is obtained, which determines the level of impact of the cancer on the patient on each of the scales. Higher values indicate better performance

End point type	Secondary

End point timeframe:

8 weeks

End point values	COMBO450			
Subject group type	Reporting group			
Number of subjects analysed	36[7]			
Units: arbitrary units				
median (full range (min-max))				
Baseline	78.4 (29.3 to 98.7)			
Week 8	85.5 (48.6 to 99.4)			

Notes:

[7] - Patients with QoL completed

Statistical analyses

No statistical analyses for this end point

Secondary: Change on Quality of Life at Week 24 in Both Cohorts Based on the EORTC QLQ 30 Scale

End point title	Change on Quality of Life at Week 24 in Both Cohorts Based on the EORTC QLQ 30 Scale

End point description:

The EORTC QLQ-C30 questionnaire is validated for cancer. It is composed of 30 questions or items that assess QoL. The questionnaire is structured in 5 functional scales physical functioning, daily activities, emotional functioning, cognitive functioning and social functioning), 3 symptom scales (fatigue, pain and nausea, vomiting), 1 global health status scale, and 6 independent items (dyspnea, insomnia, anorexia, constipation, diarrhea and economic impact). Values between 1 and 4 (1: not at all, 2: a little, 3: quite, 4: a lot) are assigned according to the patient's responses to the item, only in items 29 and 30 are they evaluated with a score of 1 to 7 (1: dreadful, 7: excellent).
The scores obtained are standardized and a score between 0 and 100 is obtained, which determines the level of impact of the cancer on the patient on each of the scales. Higher values indicate better performance

End point type	Secondary

End point timeframe:

24 weeks

End point values	COMBO450			
Subject group type	Reporting group			
Number of subjects analysed	26[8]			
Units: Arbitrary units				
number (confidence interval 95%)				
Baseline	78.4 (29.3 to 98.7)			
Week 24	74.9 (47.3 to 97.9)			

Notes:

[8] - Patients who completed QoL questionnaires

Statistical analyses

No statistical analyses for this end point

Secondary: Extracranial Progression-free Rates

End point title	Extracranial Progression-free Rates

End point description:

Proportion of patients free of extracranial progression assessed by modified RECIST at 6 months (week 24), 12 months (week 48) and 24-month (week 96) considering date of inclusion estimated through Kaplan-Meier method

End point type	Secondary

End point timeframe:

at 6 months (week 24), 12 months (week 48) and 24-month (week 96)

End point values	COMBO450			
Subject group type	Reporting group			
Number of subjects analysed	48			
Units: Percentage of patients				
number (confidence interval 95%)				
6 months	64.1 (51.4 to 79.9)			
12 months	31.2 (19.6 to 49.6)			
24 months	5.8 (1 to 33.8)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Throughout the study period, up to approximately 24 months	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	19

Reporting groups	
Reporting group title	COMBO450

Reporting group description:

Encorafenib 450 mg daily orally and binimetinib 45 mg twice a day orally until progression of the disease, unacceptable toxicity or death.
local radiation treatment started after start of treatment. Suggested doses are as follow: 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.

Serious adverse events	COMBO450		
Total subjects affected by serious adverse events			
subjects affected / exposed	22 / 48 (45.83%)		
number of deaths (all causes)	33		
number of deaths resulting from adverse events	0		
Investigations			
Creatinine increased			
subjects affected / exposed	1 / 48 (2.08%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Surgical and medical procedures			
Brain metastasis surgery			
subjects affected / exposed	1 / 48 (2.08%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Epileptic status			
subjects affected / exposed	1 / 48 (2.08%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Eplectic seizures			

subjects affected / exposed	1 / 48 (2.08%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Focal seizures				
subjects affected / exposed	1 / 48 (2.08%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Headache				
subjects affected / exposed	2 / 48 (4.17%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 0			
Instability				
subjects affected / exposed	1 / 48 (2.08%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Movements involuntary				
subjects affected / exposed	1 / 48 (2.08%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Seizure				
subjects affected / exposed	1 / 48 (2.08%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Blood and lymphatic system disorders				
Anemia				
subjects affected / exposed	2 / 48 (4.17%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
General disorders and administration site conditions				
Acute pain in rib zone irradiated to legs				
subjects affected / exposed	1 / 48 (2.08%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			

Encorafenib overdose				
subjects affected / exposed	1 / 48 (2.08%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Febrile syndrome of unknown origin				
subjects affected / exposed	1 / 48 (2.08%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Left Hemiparesis				
subjects affected / exposed	1 / 48 (2.08%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pain				
subjects affected / exposed	1 / 48 (2.08%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Immune system disorders				
Anaphylaxis				
subjects affected / exposed	1 / 48 (2.08%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Gastrointestinal disorders				
Clostridium Difficile infectious diarrhea				
subjects affected / exposed	1 / 48 (2.08%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Diarrhea				
subjects affected / exposed	2 / 48 (4.17%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Digestive bleeding				
subjects affected / exposed	1 / 48 (2.08%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			

Pancreatitis				
subjects affected / exposed	1 / 48 (2.08%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Upper gastrointestinal hemorrhage				
subjects affected / exposed	1 / 48 (2.08%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Vomiting				
subjects affected / exposed	1 / 48 (2.08%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Respiratory, thoracic and mediastinal disorders				
Amigdalitis				
subjects affected / exposed	1 / 48 (2.08%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pneumonitis				
subjects affected / exposed	1 / 48 (2.08%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pulmonary thromboembolism				
subjects affected / exposed	1 / 48 (2.08%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Respiratory sepsis				
subjects affected / exposed	1 / 48 (2.08%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
ight pleural empyema by streptococcus constellatus				
subjects affected / exposed	1 / 48 (2.08%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			

Renal and urinary disorders			
Acute renal insufficiency			
subjects affected / exposed	1 / 48 (2.08%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	COMBO450		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	48 / 48 (100.00%)		
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	9 / 48 (18.75%)		
occurrences (all)	9		
Aspartate aminotransferase increased			
subjects affected / exposed	8 / 48 (16.67%)		
occurrences (all)	8		
CPK increased			
subjects affected / exposed	3 / 48 (6.25%)		
occurrences (all)	3		
Creatinine increased			
subjects affected / exposed	3 / 48 (6.25%)		
occurrences (all)	3		
GGT increased			
subjects affected / exposed	8 / 48 (16.67%)		
occurrences (all)	8		
Other not specified			
subjects affected / exposed	6 / 48 (12.50%)		
occurrences (all)	6		
Nervous system disorders			
Dysgeusia			
subjects affected / exposed	5 / 48 (10.42%)		
occurrences (all)	5		
Blood and lymphatic system disorders			

Anemia			
subjects affected / exposed	8 / 48 (16.67%)		
occurrences (all)	8		
Lymphocyte count decreased			
subjects affected / exposed	3 / 48 (6.25%)		
occurrences (all)	3		
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	5 / 48 (10.42%)		
occurrences (all)	5		
Fatigue			
subjects affected / exposed	12 / 48 (25.00%)		
occurrences (all)	12		
Fever			
subjects affected / exposed	7 / 48 (14.58%)		
occurrences (all)	7		
Eye disorders			
Other not specified			
subjects affected / exposed	3 / 48 (6.25%)		
occurrences (all)	3		
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	3 / 48 (6.25%)		
occurrences (all)	3		
Constipation			
subjects affected / exposed	5 / 48 (10.42%)		
occurrences (all)	5		
Diarrhea			
subjects affected / exposed	13 / 48 (27.08%)		
occurrences (all)	13		
Nausea			
subjects affected / exposed	11 / 48 (22.92%)		
occurrences (all)	11		
Other not specified			
subjects affected / exposed	4 / 48 (8.33%)		
occurrences (all)	4		

Vomiting subjects affected / exposed occurrences (all)	5 / 48 (10.42%) 5		
Skin and subcutaneous tissue disorders Other not specified subjects affected / exposed occurrences (all) Pruritus subjects affected / exposed occurrences (all)	 7 / 48 (14.58%) 7 3 / 48 (6.25%) 3		
Musculoskeletal and connective tissue disorders Arthralgia subjects affected / exposed occurrences (all)	 4 / 48 (8.33%) 4		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
14 November 2019	- Update of information regarding the treatment of toxicities associated with the investigational product encorafenib. - Update of safety aspects of the investigational product, encorafenib, following the update of information reflected in the investigator's manual version 11 of June 20, 2019 (new version 2.0 of the patient information sheet and informed consent form of August 29, 2019). - Change of the principal investigator of the study at the Virgen de la Macarena Hospital. Dr. Maria del Carmen Álamo de la Gala replaces Dr. Luis de la Cruz Merino.
17 January 2020	- Update of information regarding the discontinuation time of encorafenib + binimetinib during local treatment (radiotherapy). - Correction of an error regarding the specified dose for radiotherapy administration when using intensity-modulated radiotherapy (IMRT). - Correction of an error to standardize the test to be performed to detect possible pregnancies before and during participation in the trial in women of childbearing age. - Change of the study's principal investigator at the Clínica Universidad de Navarra. Dr. Miguel Fernández de Sanmamed Gutiérrez replaces Dr. Salvador Martín Algarra.
03 November 2020	- Change of IB, and update of information in the protocol and HIP-CI. - Update of the PI at the Canary Islands center. - The protocol changes refer to changes in inclusion criteria and data analysis.
29 March 2021	- A new participating center joins the study: ICO Hospitalet - A new principal investigator joins the study at ICO L'Hospitalet: Dr. Juan Martín Liberal
29 November 2021	Reduce the discontinuation of the trial treatment combination to 24 hours before and after the administration of local treatment. Modification of secondary objectives: the overall response objective is eliminated. Radiosurgery: For patients who do not meet criteria for radiosurgery (RS) or (SRS), the possibility of allowing certain cases is added after prior consultation with the trial coordinators, and specifically with the radiotherapy coordinator. Whole-cranial radiotherapy: The possibility of allowing hippocampal protection is added. The design titles of both cohort 1 and cohort 2 are modified (pages 27 and 28), specifying that patients who have received prior surgery can be included (instead of indicating prior local treatment). The definition of the asymptomatic cohort has been updated (page 29). Regulations have been made regarding inconsistencies detected. BUN has been eliminated. A paragraph has been added to clarify the protocol-required follow-up for patients who complete treatment due to treatment toxicity, according to inquiries received regarding this issue. Exclusion criterion 3 has been modified. The increase in the estimated recruitment period has been indicated.

11 November 2022	- Modification of the primary endpoint of the study: We request to study the intracranial objective response rate according to the modified RECIST 1.1 criteria before local treatment in cohort 1 and cohort 2. - This change is based on: - Various interim analyses (published in ESMO) have shown that the response rates of symptomatic and asymptomatic patients are similar, so it makes little sense to assess them separately as a primary endpoint. The joint analysis gives us greater statistical power (higher n). - At the level of clinical interest, it is more relevant to study both cohorts together, as has been recently reported in several clinical trials in this setting: TRICOTEL and COMBI-MB. - Incorporation of a new secondary endpoint: We request to incorporate the previous primary endpoint as a secondary endpoint: the intracranial objective response rate according to the modified RECIST 1.1 criteria before local treatment in cohort 1.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

Not applicable

Notes: