Clinical trial results:
Phase II, open-label, single arm, multicenter study of encorafenib, binimetinib plus cetuximab in subjects with previously untreated BRAFV600E-mutant metastatic colorectal cancer.

Summary

EudraCT number	2018-000271-32
Trial protocol	FR ES BE NL GB AT IT
Global end of trial date	

Results information

Result version number	v1 (current)
This version publication date	16 December 2021
First version publication date	16 December 2021

Trial information

Trial identification

Sponsor protocol code	W00090GE201

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03693170
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Pierre Fabre Médicament
Sponsor organisation address	45 Place Abel Gance , Boulogne, France, F-92654
Public contact	Isabelle Klauck, MD, Pierre Fabre Médicament, isabelle.klauck@pierre-fabre.com
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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	Interim
Date of interim/final analysis	29 June 2020
Is this the analysis of the primary completion data?	Yes
Primary completion date	29 June 2020
Global end of trial reached?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the antitumor activity of the combination of encorafenib, binimetinib and cetuximab by assessing the confirmed overall response rate (cORR) by local radiologist/investigator assessment in adult subjects with previously untreated BRAFV600E-mutant (BRAFV600E) metastatic colorectal cancer (mCRC).

Protection of trial subjects:

The trial was conducted in compliance with the ethical principles derived from the Declaration of Helsinki and the International Council for Harmonisation (ICH) Good Clinical Practice (GCP) Guidelines.
All the local regulatory requirements pertaining to safety of trial subjects were also followed during the conduct of the trial;

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	17 January 2019
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Austria: 1
Country: Number of subjects enrolled	Belgium: 9
Country: Number of subjects enrolled	France: 13
Country: Number of subjects enrolled	Italy: 15
Country: Number of subjects enrolled	Netherlands: 1
Country: Number of subjects enrolled	Spain: 29
Country: Number of subjects enrolled	United Kingdom: 13
Country: Number of subjects enrolled	United States: 3
Country: Number of subjects enrolled	Japan: 11
Worldwide total number of subjects	95
EEA total number of subjects	68

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)	43
From 65 to 84 years	52
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

95 (41 in Stage 1 and 54 in Stage 2) subjects were enrolled in the study and assigned to treatment between 17 January 2019 and 27 December 2019.

Pre-assignment

Screening details:

125 subjects were screend for inclusion in the study.
30 subjects were excluded (29 due to eligibility criteria not met and 1 due to adverse event).

Period 1

Period 1 title	Stage 1 + Stage 2 (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Encorafenib + Binimetinib + Cetuximab

Arm description: -

Arm type	Experimental
Investigational medicinal product name	Encorafenib
Investigational medicinal product code	
Other name	Braftovi (Tradename)
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

300 mg once daily (QD)

Investigational medicinal product name	Binimetinib
Investigational medicinal product code	
Other name	Mektovi (Tradename)
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

45 mg twice daily (BID)

Investigational medicinal product name	Cetuximab
Investigational medicinal product code	
Other name	Erbitux (Tradename)
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

- 400 mg/m2 administered as a 120-min infusion on Cycle 1 Day 1, followed by 250 mg/m2 administered as a 60-min infusion once weekly (QW) for the first 28 weeks.
- 500 mg/m2 administered as a 120-min infusion twice weekly (Q2W) from Week 29 (Cycle 8 Day 1) onward.

Following implementation of an Urgent Safety Measure on 26 Mar 2020 due to the outbreak of COVID-19 pandemic, cetuximab infusions could be administered Q2W regardless of the cycle number, after investigator’s evaluation of the benefit/risk ratio for the subject, with regards to COVID-19 pandemic.

Number of subjects in period 1	Encorafenib + Binimetinib + Cetuximab
Started	95
Completed	20
Not completed	75
Adverse event, serious fatal	1
Consent withdrawn by subject	1
Physician decision	6
Adverse event, non-fatal	16
Non-compliance with study drug	1
Progressive disease	48
Protocol deviation	2

Baseline characteristics

Reporting groups	
Reporting group title	Encorafenib + Binimetinib + Cetuximab

Reporting group description: -

Reporting group values	Encorafenib + Binimetinib + Cetuximab	Total	
Number of subjects	95	95	
Age categorical			
Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	43	43	
From 65-84 years	52	52	
85 years and over	0	0	
Age continuous			
Units: years			
median	65.0		
inter-quartile range (Q1-Q3)	57.0 to 70.0	-	
Gender categorical			
Units: Subjects			
Female	51	51	
Male	44	44	
Race			
Units: Subjects			
White	71	71	
Asian	11	11	
American Indian or Alaska Native	0	0	
Black or African American	0	0	
Native Hawaiian or Other Pacific Islander	0	0	
Unknown or not reported	13	13	
Ethnicity			
Units: Subjects			
Not Hispanic or Latino	73	73	
Hispanic or Latino	8	8	
Unknown or not reported	14	14	
Primary tumor location			
The category "right-sided/transverse" includes "Colon, Right " and "Colon, Transverse" tumour locations". The category "left-sided/transverse" includes "Colon, Left " and "Rectum" tumour locations".			
Units: Subjects			
Right-sided/transverse	57	57	

Left-sided/rectum	37	37	
Other	1	1	
Number of metastatic organs Units: Subjects			
1 metastatic organ	23	23	
2 metastatic organs	33	33	
> 2 metastatic organs	39	39	
ECOG-PS			
Eastern Cooperative Oncology Group (ECOG) performance status (PS).			
Units: Subjects			
ECOG-PS 0	43	43	
ECOG-PS 1	52	52	
BRAFV600E mutation based on local assessment Units: Subjects			
Positive	95	95	
Negative	0	0	
BRAFV600E mutation based on central assessment Units: Subjects			
Positive	92	92	
Negative	2	2	
Indeterminate	1	1	

End points

End points reporting groups

Reporting group title	Encorafenib + Binimetinib + Cetuximab
Reporting group description: -	
Subject analysis set title	Efficacy Set (ES)
Subject analysis set type	Modified intention-to-treat
Subject analysis set description:	
Includes all subjects in the Full Analysis Set (FAS) with a BRAFV600E mutation confirmed by central laboratory results. This analysis set was used for efficacy analyses, including the analysis of the primary endpoint.	
Subject analysis set title	Per Protocol Set (PP Set)
Subject analysis set type	Per protocol
Subject analysis set description:	
Includes all subjects in the Full Analysis Set (FAS) without any major protocol deviation. Subjects with no central confirmation of the BRAFV600E mutation status are excluded from this analysis set. This analysis set was used for supportive analyses of the primary endpoint.	
Subject analysis set title	Full Analysis Set (FAS)
Subject analysis set type	Full analysis
Subject analysis set description:	
Includes all subjects who received at least one dose of study treatment (partial dose - defined as at least one dose of encorafenib, binimetinib or cetuximab - or full dose). This analysis set was used for analysis of efficacy, safety and quality of life.	
Subject analysis set title	FAS Responders by local review
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Includes subjects from the Full Analysis Set (FAS) with a confirmed response (complete response and partial response) as assessed by local radiologist/investigator review.	
Subject analysis set title	FAS Responders by central review
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Includes subjects from the Full Analysis Set (FAS) with a confirmed response (complete response and partial response) as assessed by central radiologist review.	

Primary: Confirmed overall response rate (cORR) by local review

End point title	Confirmed overall response rate (cORR) by local review[1]
End point description:	
The confirmed overall response rate (cORR) is the percentage of confirmed responses, defined as complete response (CR) or partial response (PR), as assessed by local radiologist/investigator review based on the Response Evaluation Criteria in Solid Tumors (RECIST 1.1). cORR was assessed when all subjects had the opportunity to complete at least 4 post-baseline tumor assessments and after subjects with an initial objective response had the opportunity to have a confirmation scan.	
End point type	Primary
End point timeframe:	
Tumor evaluations were performed every 6 weeks for the first 12 weeks and then every 8 weeks.	

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: The cORR was provided with a corresponding Clopper-Pearson (exact) binomial 95% CI for the Efficacy Set. If 37 or more confirmed responses were observed in the 90 treated subjects with a centrally confirmed BRAFV600E mutation, corresponding to a lower limit of Clopper-Pearson (exact) binomial 95% CI exceeding 30%, the study was considered to have met its primary endpoint. If more than 90 subjects were enrolled, the lower limit of Clopper-Pearson was to be used for decision.

End point values	Efficacy Set (ES)			
Subject group type	Subject analysis set			
Number of subjects analysed	92			
Units: Percentage				
number (confidence interval 95%)	47.8 (37.3 to 58.5)			

Statistical analyses

No statistical analyses for this end point

Secondary: Confirmed overall response rate (cORR) by central review

End point title	Confirmed overall response rate (cORR) by central review

End point description:

The confirmed overall response rate (cORR) is the percentage of confirmed responses, defined as complete response (CR) or partial response (PR), as assessed by central radiologist review based on the Response Evaluation Criteria in Solid Tumors (RECIST 1.1). CORR was assessed when all subjects had the opportunity to complete at least 4 post-baseline tumor assessments and after subjects with an initial objective response had the opportunity to have a confirmation scan.

End point type	Secondary

End point timeframe:

Tumor evaluations were performed every 6 weeks for the first 12 weeks and then every 8 weeks.

End point values	Efficacy Set (ES)			
Subject group type	Subject analysis set			
Number of subjects analysed	92			
Units: Percentage				
number (confidence interval 95%)	45.7 (35.2 to 56.4)			

Statistical analyses

No statistical analyses for this end point

Secondary: Overall response rate (ORR) by local review

End point title	Overall response rate (ORR) by local review

End point description:

The overall response rate (ORR) is the percentage of responses (confirmed and unconfirmed), as assessed by local radiologist/investigator review based on the Response Evaluation Criteria in Solid Tumors (RECIST 1.1). ORR was ssessed when all subjects had the opportunity to complete at least 4 post-baseline tumor assessments and after subjects with an initial objective response had the opportunity to have a confirmation scan.

End point type	Secondary

End point timeframe:

Tumor evaluations were performed every 6 weeks for the first 12 weeks and then every 8 weeks.

End point values	Efficacy Set (ES)			
Subject group type	Subject analysis set			
Number of subjects analysed	92			
Units: Percentage of patients				
number (confidence interval 95%)	62.0 (51.2 to 71.9)			

Statistical analyses

No statistical analyses for this end point

Secondary: Overall response rate (ORR) by central review

End point title	Overall response rate (ORR) by central review

End point description:

The overall response rate (ORR) is the percentage of responses (confirmed and unconfirmed), as assessed by central radiologist review based on the Response Evaluation Criteria in Solid Tumors (RECIST 1.1). ORR was assessed when all subjects had the opportunity to complete at least 4 post-baseline tumor assessments and after subjects with an initial objective response had the opportunity to have a confirmation scan.

End point type	Secondary

End point timeframe:

Tumor evaluations were performed every 6 weeks for the first 12 weeks and then every 8 weeks.

End point values	Efficacy Set (ES)			
Subject group type	Subject analysis set			
Number of subjects analysed	92			
Units: Percentage of patients				
number (confidence interval 95%)	60.9 (50.1 to 70.9)			

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of response (DOR) by local review

End point title	Duration of response (DOR) by local review

End point description:

Duration of response (DOR) is defined as the time from the first radiographic evidence of response (complete response and partial response), as assessed by local radiologist/investigator review, to the

earliest documented date of progression or death due to underlying disease.

End point type	Secondary

End point timeframe:

Duration of the study period.

End point values	FAS Responders by local review			
Subject group type	Subject analysis set			
Number of subjects analysed	45			
Units: months				
median (confidence interval 95%)	5.1 (3.7 to 6.9)			

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of response (DOR) by central review

End point title	Duration of response (DOR) by central review

End point description:

Duration of response (DOR) is defined as the time from the first radiographic evidence of response (complete response and partial response), as assessed by central radiologist review to the earliest documented date of progression or death due to underlying disease.

End point type	Secondary

End point timeframe:

Duration of the study period.

End point values	FAS Responders by central review			
Subject group type	Subject analysis set			
Number of subjects analysed	42			
Units: months				
median (confidence interval 95%)	5.1 (3.4 to 5.5)			

Statistical analyses

No statistical analyses for this end point

Secondary: Time to response (TTR) by local review

End point title	Time to response (TTR) by local review

End point description:

Time to response (TTR) is defined as the time from the first study treatment administration until the first documented radiographic evidence of response (complete response or partial response) as assessed by local radiologist/investigator review.

End point type	Secondary

End point timeframe:

Duration of study period.

End point values	FAS Responders by local review			
Subject group type	Subject analysis set			
Number of subjects analysed	45			
Units: months				
median (confidence interval 95%)	1.4 (1.4 to 1.5)			

Statistical analyses

No statistical analyses for this end point

Secondary: Time to response (TTR) by central review

End point title	Time to response (TTR) by central review

End point description:

Time to response (TTR) is defined as the time from the first study treatment administration until the first documented radiographic evidence of response (complete response or partial response) as assessed by central radiologist review.

End point type	Secondary

End point timeframe:

Duration of the study period.

End point values	FAS Responders by central review			
Subject group type	Subject analysis set			
Number of subjects analysed	42			
Units: months				
median (confidence interval 95%)	1.4 (1.3 to 1.4)			

Statistical analyses

No statistical analyses for this end point

Secondary: Progression-free survival (PFS) by local review

End point title	Progression-free survival (PFS) by local review

End point description:

Progression-free survival (PFS) is defined as the time from the first dose of study treatment to the earliest documented date of disease progression, as assessed by local radiologist/investigator review, or death due to any cause.

End point type	Secondary

End point timeframe:

Duration of the study period.

End point values	Efficacy Set (ES)			
Subject group type	Subject analysis set			
Number of subjects analysed	92			
Units: months				
median (confidence interval 95%)	5.8 (4.6 to 6.4)			

Statistical analyses

No statistical analyses for this end point

Secondary: Progression-free survival (PFS) by central review

End point title	Progression-free survival (PFS) by central review

End point description:

Progression-free survival (PFS) was defined as the time from the first dose of study treatment to the earliest documented date of disease progression, as assessed by central radiologist review, or death due to any cause.

End point type	Secondary

End point timeframe:

Duration of the study period.

End point values	Efficacy Set (ES)			
Subject group type	Subject analysis set			
Number of subjects analysed	92			
Units: months				
median (confidence interval 95%)	5.0 (4.6 to 6.4)			

Statistical analyses

No statistical analyses for this end point

Secondary: Overall survival (OS)

End point title	Overall survival (OS)

End point description:

Overall survival (OS) is defined as the time from the first dose of study treatment to death due to any cause.
Note: the number of subjects with events was too low to calculate the upper limit of the 95% CI. The value for the upper limit of the 95%CI has been arbitrarily set at 99.9 for the purpose of data reporting in this record.

End point type	Secondary

End point timeframe:

Duration of the study period.

End point values	Full Analysis Set (FAS)			
Subject group type	Subject analysis set			
Number of subjects analysed	95			
Units: months				
median (confidence interval 95%)	17.2 (14.1 to 99.9)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in EORTC QLQ-C30 over time

End point title	Change from baseline in EORTC QLQ-C30 over time

End point description:

The European Organization for Research and Treatment of Cancer Quality of Life Questionnaire for cancer subjects (EORTC QLQ-C30) includes a global health status/QoL scale, 5 functional scales (physical, role, cognitive, emotional, social) and 9 symptom scales (nausea and vomiting, pain, fatigue, dyspnea, insomnia, appetite loss, constipation, diarrhea, financial difficulties). Each scale of the EORTC QLQ-C30 questionnaire was scored 0 to 100 according to the EORTC recommendations. Changes from baseline in EORTC QLQ-C30 global health status/quality of life (QoL) over time are presented in this record. Higher scores on the global health status/QoL scale indicate higher QoL.
Note: changes from baseline are shown up to Cycle 10 Day 1 (C10D1) and for the 30-day safety follow-up period. Beyond C10D1, less than 10 subjects filled the questionnaire.

End point type	Secondary

End point timeframe:

The EORTC QLQ-C30 was administered at the Cycle 1 Day 1 (C1D1) Visit (baseline), at the the Day 1 Visit of subsequent cycles (CnD1), at the End of Treatment (EOT) Visit and at the 30-day Safety Follow-up Visit.

End point values	Full Analysis Set (FAS)			
Subject group type	Subject analysis set			
Number of subjects analysed	95			
Units: Score on a scale				
arithmetic mean (standard deviation)				
C2D1, n=79	-2.64 (± 19.270)			

C3D1, n=71	-0.35 (± 20.866)			
C4D1, n=69	0.97 (± 20.238)			
C5D1, n=56	-0.89 (± 18.026)			
C6D1, n=52	-1.92 (± 22.544)			
C7D1, n=34	-5.39 (± 22.834)			
C8D1, n=27	-4.63 (± 21.225)			
C9D1, n=18	-1.85 (± 15.274)			
C10D1, n=13	-7.69 (± 17.167)			
30-day Safety Follow-up, n=40	-15.42 (± 25.775)			

Attachments (see zip file)	QLQ-C30 mean changes from

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in EQ-5D-5L over time

End point title	Change from baseline in EQ-5D-5L over time

End point description:

The EQ-5D-5L consists of the EQ-5D descriptive system and the EQ visual analogue scale (EQ VAS). The EQ-5D-5L VAS records the patient's self-rated health on a vertical visual analogue scale numbered from 0 ("The worst health you can imagine") to 100 ("The best health you can imagine"). Changes from baseline in EQ-5D-5L VAS over time are presented in this record.
Note: changes from baseline are shown up to Cycle 10 Day 1 (C10D1) and for the 30-day safety follow-up period. Beyond C10D1, less than 10 subjects filled the questionnaire.

End point type	Secondary

End point timeframe:

The EQ-5D-5L was administered at the Cycle 1 Day 1 (C1D1) Visit (baseline), at the the Day 1 Visit of subsequent cycles (CnD1), at the End of Treatment (EOT) Visit and at the 30-day Safety Follow-up Visit.

End point values	Full Analysis Set (FAS)			
Subject group type	Subject analysis set			
Number of subjects analysed	95			
Units: Score on a scale				
arithmetic mean (standard deviation)				
C2D1, n=78	0.04 (± 19.707)			
C3D1, n=71	0.35 (± 21.668)			
C4D1, n=68	2.66 (± 19.400)			

C5D1, n=55	3.73 (± 17.052)			
C6D1, n= 52	1.69 (± 18.421)			
C7D1, n=35	1.31 (± 18.903)			
C8D1, n=28	2.89 (± 15.882)			
C9D1, n=19	-2.32 (± 21.945)			
C10D1, n=13	-4.00 (± 12.503)			
30-day Safety Follow-up, n=40	-9.35 (± 23.585)			

Attachments (see zip file)	EQ-5D-5L VAS mean changes over

Statistical analyses

No statistical analyses for this end point

Secondary: PGIC scores over time

End point title	PGIC scores over time

End point description:

The Patient Global Impression of Change (PGIC) is a measure of patients' perceptions of change in their symptoms over time. For this assessment, subjects answered the following question: "Since starting treatment, my colorectal cancer symptoms are: (1) very much improved, (2) much improved, (3) minimally improved, (4) no change, (5) minimally worse, (6) much worse or (7) very much worse." Note: PGIC scores are shown up to Cycle 10 Day 1 (C10D1) and for the 30-day safety follow-up period. The number of subjects who filled the questionnaire was 11 at C11D1 and less than 10 beyond C11D1.

End point type	Secondary

End point timeframe:

The PGIC questionnaire was administered during at the Cycle 1 Day 1 (C1D1) Visit (baseline), at the Day 1 Visit of subsequent cycles (CnD1), at the End of Treatment (EOT) Visit and at the 30-day Safety Follow-up Visit.

End point values	Full Analysis Set (FAS)			
Subject group type	Subject analysis set			
Number of subjects analysed	95			
Units: Percent				
number (not applicable)				
C2D1 (n=91), very much improved	5.5			
C2D1 (n=91), much improved	16.5			
C2D1 (n=91), minimally improved	18.7			
C2D1 (n=91), no change	31.9			
C2D1 (n=91), minimally worse	3.3			
C2D1 (n=91), much worse	0			
C2D1 (n=91), very much worse	0			
C2D1 (n=91), not done/missing	24.2			
C3D1 (n=81), very much improved	12.3			

C3D1 (n=81), much improved	34.6			
C3D1 (n=81), minimally improved	13.6			
C3D1 (n=81), no change	24.7			
C3D1 (n=81), minimally worse	0			
C3D1 (n=81), much worse	0			
C3D1 (n=81), very much worse	0			
C3D1 (n=81), not done/missing	14.8			
C4D1 (n=77), very much improved	11.7			
C4D1 (n=77), much improved	40.3			
C4D1 (n=77), minimally improved	15.6			
C4D1 (n=77), no change	20.8			
C4D1 (n=77), minimally worse	0			
C4D1 (n=77), much worse	0			
C4D1 (n=77), very much worse	0			
C4D1 (n=77), not done/missing	11.7			
C5D1 (n=65), very much improved	15.4			
C5D1 (n=65), much improved	29.2			
C5D1 (n=65), minimally improved	16.9			
C5D1 (n=65), no change	20.0			
C5D1 (n=65), minimally worse	3.1			
C5D1 (n=65), much worse	0			
C5D1 (n=65), very much worse	0			
C5D1 (n=65), not done/missing	15.4			
C6D1 (n=57), very much improved	12.3			
C6D1 (n=57), much improved	31.6			
C6D1 (n=57), minimally improved	22.8			
C6D1 (n=57), no change	22.8			
C6D1 (n=57), minimally worse	0			
C6D1 (n=57), much worse	0			
C6D1 (n=57), very much worse	0			
C6D1 (n=57), not done/missing	10.5			
C7D1 (n=43), very much improved	9.3			
C7D1 (n=43), much improved	30.2			
C7D1 (n=43), minimally improved	16.3			
C7D1 (n=43), no change	25.6			
C7D1 (n=43), minimally worse	0			
C7D1 (n=43), much worse	0			
C7D1 (n=43), very much worse	0			
C7D1 (n=43), not done/missing	18.6			
C8D1 (n=33), very much improved	12.1			
C8D1 (n=33), much improved	33.3			
C8D1 (n=33), minimally improved	15.2			
C8D1 (n=33), no change	15.2			
C8D1 (n=33), minimally worse	6.1			
C8D1 (n=33), much worse	0			
C8D1 (n=33), very much worse	0			
C8D1 (n=33), not done/missing	18.2			
C9D1 (n=20), very much improved	5.0			
C9D1 (n=20), much improved	45.0			
C9D1 (n=20), minimally improved	10.0			
C9D1 (n=20), no change	25.0			
C9D1 (n=20), minimally worse	0			

C9D1 (n=20), much worse	0			
C9D1 (n=20), very much worse	0			
C9D1 (n=20), not done/missing	15.0			
C10D1 (n=14), very much improved	14.3			
C10D1 (n=14), much improved	28.6			
C10D1 (n=14), minimally improved	28.6			
C10D1 (n=14), no change	28.6			
C10D1 (n=14), minimally worse	0			
C10D1 (n=14), much worse	0			
C10D1 (n=14), very much worse	0			
C10D1 (n=14), not done/missing	0			
30-day Safety Follow-up (n=72), very much improved	4.2			
30-day Safety Follow-up (n=72), much improved	16.7			
30-day Safety Follow-up (n=72), minimally improve	6.9			
30-day Safety Follow-up (n=72), no change	12.5			
30-day Safety Follow-up (n=72), minimally worse	8.3			
30-day Safety Follow-up (n=72), much worse	8.3			
30-day Safety Follow-up (n=72), very much worse	0			
30-day Safety Follow-up (n=72), not done/missing	43.1			

Attachments (see zip file)	PGIC over time/t11_4_1_2_15_1_pgic_fas.rtf

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

AEs were collected from informed consent signing date up to 30 days after last study treatment administration.
Note: disease progression documented ony by medical imaging techniques, with no new or worsening symptoms, was not reported as an AE/SAE.

Adverse event reporting additional description:

Only TEAEs defined as events that started during the treatment period (from first treatment administration up to last administration date +30 days) or that worsened during the study period are reported. All AEs (not only TEAEs) leading to death are reported. Only deaths occurring during the treatment period are reported.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	23.0

Reporting groups

Reporting group title	Encorafenib + Binimetinib + Cetuximab

Reporting group description: -

Serious adverse events	Encorafenib + Binimetinib + Cetuximab		
Total subjects affected by serious adverse events			
subjects affected / exposed	49 / 95 (51.58%)		
number of deaths (all causes)	4		
number of deaths resulting from adverse events	3		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Tumour associated fever			
subjects affected / exposed	1 / 95 (1.05%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	2 / 95 (2.11%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Asthenia			

subjects affected / exposed	1 / 95 (1.05%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
General physical health deterioration				
subjects affected / exposed	1 / 95 (1.05%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Respiratory, thoracic and mediastinal disorders				
Pleural effusion				
subjects affected / exposed	1 / 95 (1.05%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pneumonia aspiration				
subjects affected / exposed	1 / 95 (1.05%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pneumonitis				
subjects affected / exposed	1 / 95 (1.05%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	1 / 1			
Respiratory failure				
subjects affected / exposed	1 / 95 (1.05%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Investigations				
Alanine aminotransferase increased				
subjects affected / exposed	1 / 95 (1.05%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Blood bilirubin increased				
subjects affected / exposed	1 / 95 (1.05%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			

Blood creatine phosphokinase increased				
subjects affected / exposed	1 / 95 (1.05%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Gamma-glutamyl transferase increased				
subjects affected / exposed	1 / 95 (1.05%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Injury, poisoning and procedural complications				
Diversion colitis				
subjects affected / exposed	1 / 95 (1.05%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 0			
Femoral neck fracture				
subjects affected / exposed	1 / 95 (1.05%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Infusion related reaction				
subjects affected / exposed	1 / 95 (1.05%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Lumbar vertebral fracture				
subjects affected / exposed	1 / 95 (1.05%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Cardiac disorders				
Cardiac failure				
subjects affected / exposed	1 / 95 (1.05%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Myocardial infarction				

subjects affected / exposed	1 / 95 (1.05%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Myocarditis				
subjects affected / exposed	1 / 95 (1.05%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Nervous system disorders				
Dizziness				
subjects affected / exposed	1 / 95 (1.05%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Blood and lymphatic system disorders				
Anaemia				
subjects affected / exposed	2 / 95 (2.11%)			
occurrences causally related to treatment / all	1 / 2			
deaths causally related to treatment / all	0 / 0			
Eye disorders				
Detachment of retinal pigment epithelium				
subjects affected / exposed	1 / 95 (1.05%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Gastrointestinal disorders				
Large intestinal obstruction				
subjects affected / exposed	6 / 95 (6.32%)			
occurrences causally related to treatment / all	0 / 6			
deaths causally related to treatment / all	0 / 0			
Intestinal obstruction				
subjects affected / exposed	5 / 95 (5.26%)			
occurrences causally related to treatment / all	0 / 5			
deaths causally related to treatment / all	0 / 1			
Nausea				

subjects affected / exposed	5 / 95 (5.26%)			
occurrences causally related to treatment / all	4 / 5			
deaths causally related to treatment / all	0 / 0			
Abdominal pain				
subjects affected / exposed	4 / 95 (4.21%)			
occurrences causally related to treatment / all	1 / 4			
deaths causally related to treatment / all	0 / 0			
Diarrhoea				
subjects affected / exposed	4 / 95 (4.21%)			
occurrences causally related to treatment / all	4 / 4			
deaths causally related to treatment / all	0 / 0			
Small intestinal obstruction				
subjects affected / exposed	4 / 95 (4.21%)			
occurrences causally related to treatment / all	0 / 5			
deaths causally related to treatment / all	0 / 0			
Vomiting				
subjects affected / exposed	4 / 95 (4.21%)			
occurrences causally related to treatment / all	3 / 4			
deaths causally related to treatment / all	0 / 0			
Abdominal pain upper				
subjects affected / exposed	1 / 95 (1.05%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Diverticulum				
subjects affected / exposed	1 / 95 (1.05%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Enteritis				
subjects affected / exposed	1 / 95 (1.05%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Enterocolitis				

subjects affected / exposed	1 / 95 (1.05%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Intra-abdominal fluid collection				
subjects affected / exposed	1 / 95 (1.05%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Large intestine perforation				
subjects affected / exposed	1 / 95 (1.05%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Lower gastrointestinal haemorrhage				
subjects affected / exposed	1 / 95 (1.05%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pancreatitis acute				
subjects affected / exposed	1 / 95 (1.05%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 0			
Subileus				
subjects affected / exposed	1 / 95 (1.05%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Hepatobiliary disorders				
Bile duct stenosis				
subjects affected / exposed	1 / 95 (1.05%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Cholangitis				
subjects affected / exposed	1 / 95 (1.05%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Cholecystitis				

subjects affected / exposed	1 / 95 (1.05%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hepatic function abnormal			
subjects affected / exposed	1 / 95 (1.05%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	6 / 95 (6.32%)		
occurrences causally related to treatment / all	6 / 8		
deaths causally related to treatment / all	1 / 1		
Renal failure			
subjects affected / exposed	2 / 95 (2.11%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Haematuria			
subjects affected / exposed	1 / 95 (1.05%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nephritis			
subjects affected / exposed	1 / 95 (1.05%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Nephrolithiasis			
subjects affected / exposed	1 / 95 (1.05%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	1 / 95 (1.05%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Infections and infestations			
Appendicitis			
subjects affected / exposed	1 / 95 (1.05%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Bacteraemia			
subjects affected / exposed	1 / 95 (1.05%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Biliary tract infection			
subjects affected / exposed	1 / 95 (1.05%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cellulitis			
subjects affected / exposed	1 / 95 (1.05%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Escherichia sepsis			
subjects affected / exposed	1 / 95 (1.05%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Lymph node tuberculosis			
subjects affected / exposed	1 / 95 (1.05%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory tract infection			
subjects affected / exposed	1 / 95 (1.05%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Sepsis			
subjects affected / exposed	1 / 95 (1.05%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Streptococcal bacteraemia			

subjects affected / exposed	1 / 95 (1.05%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Tuberculosis			
subjects affected / exposed	1 / 95 (1.05%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Urinary tract infection			
subjects affected / exposed	1 / 95 (1.05%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	1 / 95 (1.05%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Hypokalaemia			
subjects affected / exposed	1 / 95 (1.05%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Encorafenib + Binimetinib + Cetuximab		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	93 / 95 (97.89%)		
Investigations			
Lipase increased			
subjects affected / exposed	12 / 95 (12.63%)		
occurrences (all)	24		
Amylase increased			
subjects affected / exposed	10 / 95 (10.53%)		
occurrences (all)	17		
Blood creatinine increased			

subjects affected / exposed	9 / 95 (9.47%)		
occurrences (all)	11		
Weight decreased			
subjects affected / exposed	6 / 95 (6.32%)		
occurrences (all)	8		
Blood creatine phosphokinase increased			
subjects affected / exposed	5 / 95 (5.26%)		
occurrences (all)	7		
Nervous system disorders			
Dysgeusia			
subjects affected / exposed	12 / 95 (12.63%)		
occurrences (all)	13		
Headache			
subjects affected / exposed	10 / 95 (10.53%)		
occurrences (all)	11		
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	30 / 95 (31.58%)		
occurrences (all)	67		
Fatigue			
subjects affected / exposed	18 / 95 (18.95%)		
occurrences (all)	38		
Pyrexia			
subjects affected / exposed	12 / 95 (12.63%)		
occurrences (all)	19		
Mucosal inflammation			
subjects affected / exposed	6 / 95 (6.32%)		
occurrences (all)	6		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	23 / 95 (24.21%)		
occurrences (all)	60		
Eye disorders			
Vision blurred			
subjects affected / exposed	13 / 95 (13.68%)		
occurrences (all)	17		

Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	64 / 95 (67.37%)		
occurrences (all)	145		
Nausea			
subjects affected / exposed	42 / 95 (44.21%)		
occurrences (all)	83		
Vomiting			
subjects affected / exposed	34 / 95 (35.79%)		
occurrences (all)	59		
Abdominal pain			
subjects affected / exposed	31 / 95 (32.63%)		
occurrences (all)	43		
Constipation			
subjects affected / exposed	25 / 95 (26.32%)		
occurrences (all)	26		
Dyspepsia			
subjects affected / exposed	8 / 95 (8.42%)		
occurrences (all)	8		
Stomatitis			
subjects affected / exposed	8 / 95 (8.42%)		
occurrences (all)	16		
Abdominal pain upper			
subjects affected / exposed	7 / 95 (7.37%)		
occurrences (all)	11		
Abdominal discomfort			
subjects affected / exposed	6 / 95 (6.32%)		
occurrences (all)	6		
Rectal haemorrhage			
subjects affected / exposed	6 / 95 (6.32%)		
occurrences (all)	8		
Flatulence			
subjects affected / exposed	5 / 95 (5.26%)		
occurrences (all)	5		
Respiratory, thoracic and mediastinal disorders			

Dyspnoea subjects affected / exposed occurrences (all)	15 / 95 (15.79%) 23		
Cough subjects affected / exposed occurrences (all)	8 / 95 (8.42%) 9		
Dysphonia subjects affected / exposed occurrences (all)	6 / 95 (6.32%) 8		
Skin and subcutaneous tissue disorders			
Dermatitis acneiform subjects affected / exposed occurrences (all)	38 / 95 (40.00%) 77		
Rash subjects affected / exposed occurrences (all)	38 / 95 (40.00%) 56		
Dry skin subjects affected / exposed occurrences (all)	30 / 95 (31.58%) 35		
Pruritus subjects affected / exposed occurrences (all)	12 / 95 (12.63%) 16		
Skin fissures subjects affected / exposed occurrences (all)	11 / 95 (11.58%) 17		
Hypertrichosis subjects affected / exposed occurrences (all)	6 / 95 (6.32%) 6		
Erythema subjects affected / exposed occurrences (all)	5 / 95 (5.26%) 5		
Palmar-plantar erythrodysaesthesia syndrome subjects affected / exposed occurrences (all)	5 / 95 (5.26%) 6		
Psychiatric disorders			

Insomnia subjects affected / exposed occurrences (all)	5 / 95 (5.26%) 6		
Musculoskeletal and connective tissue disorders Back pain subjects affected / exposed occurrences (all) Arthralgia subjects affected / exposed occurrences (all) Myalgia subjects affected / exposed occurrences (all) Muscle spasms subjects affected / exposed occurrences (all)	 9 / 95 (9.47%) 9 8 / 95 (8.42%) 14 6 / 95 (6.32%) 8 5 / 95 (5.26%) 5		
Infections and infestations Paronychia subjects affected / exposed occurrences (all)	 11 / 95 (11.58%) 11		
Metabolism and nutrition disorders Decreased appetite subjects affected / exposed occurrences (all) Hypoalbuminaemia subjects affected / exposed occurrences (all) Hypomagnesaemia subjects affected / exposed occurrences (all) Hyperkalaemia subjects affected / exposed occurrences (all)	 22 / 95 (23.16%) 36 7 / 95 (7.37%) 13 6 / 95 (6.32%) 9 5 / 95 (5.26%) 6		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
08 February 2019	The aim of this global substantial protocol amendment (PA02) was to consolidate monitoring of subject's safety, implement changes in subject population and corrections/clarifications following requests from Competent Authorities/Ethics Committees following their evaluation of protocol version 1.
02 July 2019	The aim of this global substantial protocol amendment (PA03) was to implement changes in subject population (changes in inclusion/exclusion criteria), add recommendations on cetuximab discontinuation, increase retention duration of tumor samples for future analysis, and add some clarifications.
14 April 2020	The aim of this global substantial protocol amendment (PA05) was to implement changes following the Urgent Safety Measures released on 26MAR2020 due to the COVID-19 pandemic outbreak.
17 July 2020	The aim of this global substantial protocol amendment (PA06) was to implement a Study extension period to continue to provide access to study treatment to all subjects whom the investigator considers were continuing to benefit from study treatment.

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.

The absence of a comparator arm should be noted as a limitation. In addition, the short duration of the follow-up at the data cut-off date does not allow a robust estimate of OS results.

Notes: