Clinical trial results:
A Phase Ib /II Multicenter, Open Label, Dose Escalation Study of WNT974, LGX818 and Cetuximab in Patients with BRAFV600-mutant Metastatic Colorectal Cancer Harboring Wnt Pathway Mutations.

Summary

EudraCT number	2014-002826-11
Trial protocol	BE ES NL FR
Global end of trial date	10 July 2017

Results information

Result version number	v1 (current)
This version publication date	01 July 2018
First version publication date	01 July 2018

Trial information

Trial identification

Sponsor protocol code	CWNT974X2102C

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Array BioPharma Inc.
Sponsor organisation address	3200 Walnut Street, Boulder, Colorado, United States, 80301
Public contact	Victor Sandor, MD Chief Medical Officer, Array BioPharma Inc., +34 900353036, info@arraybiopharma.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	Final
Date of interim/final analysis	25 August 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	10 July 2017
Global end of trial reached?	Yes
Global end of trial date	10 July 2017
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The purpose of this study was to assess the safety and antitumor activity of the triple combination of WNT974, encorafenib and cetuximab in patients with KRAS WT BRAF v600 mutant mCRC with RNF43 mutations or RSPO fusions.

Main objective:
Phase Ib: To estimate the MTD(s) and/or RP2D(s) of the triple combination of WNT974, LGX818 and cetuximab in patients with BRAFV600-mutant CRC harboring upstream Wnt pathway mutations.
Phase II: To estimate the preliminary anti-tumor activity of the RP2D(s) of WNT974 in combination with LGX818 and cetuximab in patients with BRAFV600-mutant CRC harboring upstream Wnt pathway mutations.

Note:
Further enrollment to the study has been discontinued as of 21 March 2016. Therefore, references to phase II study design and objectives are no longer relevant. Phase 2 of this study was not initiated and this objective was not achieved.

Protection of trial subjects:

All AEs suspected to be related to study drug were to be followed up weekly, or as clinically indicated, until resolution or stabilization. In addition, after the 30-day safety follow-up, monitoring of the levels of magnesium and additional electrolytes (i.e., calcium, chloride, potassium and sodium) was to be performed according to institutional and published guidelines and as per the locally applicable cetuximab label.
Before the first patient was dosed with the triple combination, the Bayesian model was updated with the most recent data from the ongoing dose-escalation studies utilizing the combination drugs to confirm that the proposed starting doses were still appropriate (fulfilled the EWOC criteria).

Background therapy:

Medications that are sensitive substrates of CYP2B6, CYP2C9, CYP3A4 and UGT1A1 or those substrates that have a narrow therapeutic index were permitted to be used with caution.

Evidence for comparator: -

Actual start date of recruitment	11 March 2015
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy
Long term follow-up duration	18 Months
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Netherlands: 4
Country: Number of subjects enrolled	Spain: 6
Country: Number of subjects enrolled	Belgium: 2

Country: Number of subjects enrolled	Singapore: 2
Country: Number of subjects enrolled	United States: 2
Country: Number of subjects enrolled	Italy: 3
Country: Number of subjects enrolled	Israel: 1
Worldwide total number of subjects	20
EEA total number of subjects	15

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)	13
From 65 to 84 years	7
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

This study was conducted at 16 clinical sites: 7 sites in Europe, 3 sites in the United States, 3 sites in Canada and 1 site each in Australia, Israel and Singapore. When the required mutational status was known, patients were to sign the Main Study ICF and be evaluated against study inclusion and exclusion criteria and safety assessments.

Pre-assignment

Screening details:

To be considered eligible for this study, patients must have had written documentation of KRAS-WT, BRAFV600 mutation, as well as RNF43 mutation and/or RSPO fusions. Central testing included analysis of a cancer related multigene panel and determination of study eligibility.

Period 1

Period 1 title	Phase 1 (overall period)
Is this the baseline period?	Yes
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

Blinding implementation details:

This study was open-label and therefore blinding was not used.

Arms

Are arms mutually exclusive?	Yes
Arm title	WNT974 5mg + LGX818+ Cetuximab

Arm description:

WNT974 5 mg QD + LGX818 200 mg QD + Cetuximab

Arm type	Experimental
Investigational medicinal product name	WNT974
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

WNT974 capsules were administered orally QD at the assigned dose. WNT974 was supplied as capsules for oral use at dosage strengths of 2.5 mg, 10 mg and 50 mg.
WNT974 and encorafenib were always to be dosed together orally QD as a flat-fixed dose and not by body weight or body surface area (BSA).

Investigational medicinal product name	Encorafenib
Investigational medicinal product code	LGX818
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Encorafenib was supplied as capsules for oral use packed in bottles. Encorafenib capsules were formulated in 2 dosage strengths: 50 mg and 100 mg. Encorafenib at the dosage strengths of 10 mg and 25 mg were also supplied if required.
WNT974 and encorafenib were always to be dosed together orally QD as a flat-fixed dose and not by body weight or body surface area (BSA).

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

Dosage and administration details:

Cetuximab was administered by IV infusion once weekly (QW) at 400 mg/m2 (initial infusion) and 250 mg/m2 (subsequent infusions). Cetuximab was supplied locally. Cetuximab was to be administered IV QW on Days 1, 8, 15 and 22 (± 3 days) of every cycle at the study site according to institutional standards.

Premedication was to be administered as described in compliance with institutional standards 30 minutes prior to cetuximab infusion. A complete treatment cycle was defined as 28 days of uninterrupted continuous treatment with the study drug combinations. Cycle 1 Day 1 was defined as the day that the first dose of WNT974 and encorafenib were administered. Commercially available vials of cetuximab were used in this study according to local regulations in each participating country.

Arm title	WNT974 7.5 mg+LGX818+Cetuximab

Arm description:

WNT974 7.5 mg QD + LGX818 200 mg QD + Cetuximab

Arm type	Experimental
Investigational medicinal product name	WNT974
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

WNT974 capsules were administered orally QD at the assigned dose. WNT974 was supplied as capsules for oral use at dosage strengths of 2.5 mg, 10 mg and 50 mg.

Arm title	WNT974 10 mg+LGX818+Cetuximab

Arm description:

WNT974 10 mg QD + LGX818 200 mg QD + Cetuximab

Arm type	Experimental
Investigational medicinal product name	WNT974
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

WNT974 capsules were administered orally QD at the assigned dose. WNT974 was supplied as capsules for oral use at dosage strengths of 2.5 mg, 10 mg and 50 mg.

Number of subjects in period 1	WNT974 5mg + LGX818+ Cetuximab	WNT974 7.5 mg+LGX818+Cetuximab	WNT974 10 mg+LGX818+Cetuximab
Started	10	6	4
Completed	0	0	0
Not completed	10	6	4
Physician decision	1	-	-
Adverse event, non-fatal	1	1	1
Death	-	-	1
Progressive desease	8	5	2

Baseline characteristics

Reporting groups	
Reporting group title	WNT974 5mg + LGX818+ Cetuximab
Reporting group description: WNT974 5 mg QD + LGX818 200 mg QD + Cetuximab	
Reporting group title	WNT974 7.5 mg+LGX818+Cetuximab
Reporting group description: WNT974 7.5 mg QD + LGX818 200 mg QD + Cetuximab	
Reporting group title	WNT974 10 mg+LGX818+Cetuximab
Reporting group description: WNT974 10 mg QD + LGX818 200 mg QD + Cetuximab	

Reporting group values	WNT974 5mg + LGX818+ Cetuximab	WNT974 7.5 mg+LGX818+Cetuximab	WNT974 10 mg+LGX818+Cetuximab
Number of subjects	10	6	4
Age categorical Units: Subjects			
Adults < 65	6	3	4
Adults ≥ 65	4	3	0
Age continuous Units: years			
median	63.5	60.5	60.5
full range (min-max)	50 to 70	51 to 75	60 to 61
Gender categorical Units: Subjects			
Female	6	4	1
Male	4	2	3

Reporting group values	Total		
Number of subjects	20		
Age categorical Units: Subjects			
Adults < 65	13		
Adults ≥ 65	7		
Age continuous Units: years			
median			
full range (min-max)	-		
Gender categorical Units: Subjects			
Female	11		
Male	9		

Subject analysis sets	
Subject analysis set title	Full Analysis Set
Subject analysis set type	Full analysis

Subject analysis set description:

Full Analysis Set (FAS) comprises all patients who received at least one full or partial dose of assigned combination of drugs.

Subject analysis set title	Safety Analysis Set
Subject analysis set type	Safety analysis

Subject analysis set description:

Safety Analysis Set included all patients from the FAS who received at least 1 dose of WNT974, encorafenib or cetuximab and had at least 1 valid postbaseline safety assessment.

Subject analysis set title	Dose-Determining Set
Subject analysis set type	Sub-group analysis

Subject analysis set description:

The dose-determining set (DDS) consisted of all patients in the Safety Analysis Set who either met the minimum exposure criterion and had sufficient safety evaluations or experienced a DLT during Cycle 1.

Subject analysis set title	PK Analysis Set
Subject analysis set type	Sub-group analysis

Subject analysis set description:

The PK analysis set included all patients with at least 1 available valid PK concentration measurement who received at least 1 dose of study drug.

Reporting group values	Full Analysis Set	Safety Analysis Set	Dose-Determining Set
Number of subjects	20	20	18
Age categorical Units: Subjects			
Adults < 65	13		
Adults ≥ 65	7		
Age continuous Units: years			
median	61.0		
full range (min-max)	50 to 75		
Gender categorical Units: Subjects			
Female	11		
Male	9		

Reporting group values	PK Analysis Set		
Number of subjects	20		
Age categorical Units: Subjects			
Adults < 65			
Adults ≥ 65			
Age continuous Units: years			
median			
full range (min-max)			
Gender categorical Units: Subjects			
Female			
Male			

End points

End points reporting groups

Reporting group title	WNT974 5mg + LGX818+ Cetuximab
Reporting group description:	
WNT974 5 mg QD + LGX818 200 mg QD + Cetuximab	
Reporting group title	WNT974 7.5 mg+LGX818+Cetuximab
Reporting group description:	
WNT974 7.5 mg QD + LGX818 200 mg QD + Cetuximab	
Reporting group title	WNT974 10 mg+LGX818+Cetuximab
Reporting group description:	
WNT974 10 mg QD + LGX818 200 mg QD + Cetuximab	
Subject analysis set title	Full Analysis Set
Subject analysis set type	Full analysis
Subject analysis set description:	
Full Analysis Set (FAS) comprises all patients who received at least one full or partial dose of assigned combination of drugs.	
Subject analysis set title	Safety Analysis Set
Subject analysis set type	Safety analysis
Subject analysis set description:	
Safety Analysis Set included all patients from the FAS who received at least 1 dose of WNT974, encorafenib or cetuximab and had at least 1 valid postbaseline safety assessment.	
Subject analysis set title	Dose-Determining Set
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
The dose-determining set (DDS) consisted of all patients in the Safety Analysis Set who either met the minimum exposure criterion and had sufficient safety evaluations or experienced a DLT during Cycle 1.	
Subject analysis set title	PK Analysis Set
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
The PK analysis set included all patients with at least 1 available valid PK concentration measurement who received at least 1 dose of study drug.	

Primary: PK Parameters for WNT974

End point title	PK Parameters for WNT974[1]
End point description:	
Incidence of DLTs; exposure to WNT974 and encorafenib as measured by PK parameters. In the Phase 1b dose-escalation part of the study, cohorts of patients were treated with the combination until the MTD and/or RP2D of the triple combination was identified. Duration of exposure for encorafenib and WNT974 QD was defined as Duration of exposure (days) = (study drug end date) – (study drug start date) + 1.	
End point type	Primary
End point timeframe:	
The study treatment was to be administered during 28-day cycles. The PK parameters were calculated as appropriate using non-compartmental method(s) for WNT974, its active metabolite LHA333 and encorafenib. Steady state was assumed to be reached by Day 15	

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 PK parameters were calculated as appropriate using non-compartmental method(s) for WNT974. This was summarized for all relevant pharmacokinetic and pharmacodynamics measurements using descriptive statistics (n, mean, standard deviation, median, minimum, and maximum) for quantitative data and contingency tables. No formal statistical hypothesis was tested.

End point values	WNT974 5mg + LGX818+ Cetuximab	WNT974 7.5 mg+LGX818+C etuximab	WNT974 10 mg+LGX818+C etuximab	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	10[2]	6[3]	4[4]	
Units: C max (ng/ml)				
arithmetic mean (standard deviation)				
Cycle 1 Day 1	42.0 (± 22.8)	66.0 (± 30.1)	66.0 (± 27.3)	
Cycle 1 Day 15	51.0 (± 23.2)	93.4 (± 55.7)	42.9 (± 37.1)	

Notes:

[2] - 9 subjects in Day 15

[3] - 5 subjects in Day 15

[4] - 3 subjects in day 15

Statistical analyses

No statistical analyses for this end point

Primary: PK Parameters for Encorafenib

End point title	PK Parameters for Encorafenib[5]

End point description:

Dose limiting toxicities will be listed by dose level. The maximum tolerated dose (MTD) is defined as the highest dose for a given schedule that causes DLTs in no more than 35% of patients during the first cycle of treatment.

End point type	Primary

End point timeframe:

The study treatment was to be administered during 28-day cycles. The PK parameters were calculated as appropriate using non-compartmental method(s) for WNT974, its active metabolite LHA333 and encorafenib. Steady state was assumed to be reached by Day 15.

Notes:

[5] - 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 PK parameters were calculated as appropriate using non-compartmental method(s) for encorafenib. This was summarized for all relevant pharmacokinetic and pharmacodynamics measurements using descriptive statistics (n, mean, standard deviation, median, minimum, and maximum) for quantitative data and contingency tables. No formal statistical hypothesis was tested.

End point values	WNT974 5mg + LGX818+ Cetuximab	WNT974 7.5 mg+LGX818+C etuximab	WNT974 10 mg+LGX818+C etuximab	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	10[6]	6[7]	4[8]	
Units: C max (ng/ml)				
arithmetic mean (standard deviation)				
Cycle 1 Day 1	3510 (± 2110)	3620 (± 1000)	2830 (± 1550)	
Cylce 1 Day 15	3080 (± 1440)	3250 (± 1170)	1440 (± 1340)	

Notes:

[6] - 9 subjects / Day 15

[7] - 5 subjects / Day 15

[8] - 3 subjects/ Day 15

Statistical analyses

No statistical analyses for this end point

Primary: Incidence of Dose-Limiting Toxicity

End point title	Incidence of Dose-Limiting Toxicity[9]

End point description:

The primary endpoint was the incidence of DLTs in the first cycle of treatment. Estimation of the Maximum tolerated dose (MTD) /Recommended phase 2 dose (RP2D) was based upon the Bayesian logistic regression model (BLRM) of the probability of a DLT in the first cycle of treatment for patients in the Dose Determining Set (DDS).

A Dose-Limiting Toxicity (DLT) was defined as an Adverse Event (AE) or abnormal laboratory value assessed as unrelated to disease, disease progression, intercurrent illness or concomitant medications that occurred within the first 28 days of treatment with the triple combination of WNT974, encorafenib and cetuximab and met any of the criteria included in protocol.

End point type	Primary

End point timeframe:

The primary endpoint was the incidence of Dose-Limiting Toxicity (DLTs) in the first cycle of treatment (Day 28).

Notes:

[9] - 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: An adaptive Bayesian logistic regression model (BLRM) guided by the escalation with overdose control (EWOC) principle was used to make dose recommendations and estimate the Maximum Tolerated Dose (MTD(s)/ recommended phase 2 dose (RP2D(s) during the escalation. Only the Phase 1b component of this study was conducted and the CSR only contains study information and results for the Phase 1b part. No formal statistical hypothesis was tested.

End point values	WNT974 5mg + LGX818+ Cetuximab	WNT974 7.5 mg+LGX818+C etuximab	WNT974 10 mg+LGX818+C etuximab	Dose-Determining Set
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	10	4	4	18
Units: number of patients				
Lipase increased	0	0	1	1
Hypercalcaemia	0	1	0	1
Dysgeusia	0	0	1	1

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Only adverse events occurring during treatment or within 30 days of the last study medication are reported. Deaths occurring 30 days after end of treatment were not included.

Adverse event reporting additional description:

A patient with multiple adverse events within a primary system organ class is counted only once in the total row. Patients with multiple events in the same category were counted only once in that category. Patients with events in more than 1 category were counted once in each of those categories.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	19.0

Reporting groups

Reporting group title	WNT974 5mg + LGX818+ Cetuximab

Reporting group description:

WNT974 5 mg QD + LGX818 200 mg QD + Cetuximab

Reporting group title	WNT974 7.5 mg+LGX818+Cetuximab

Reporting group description:

WNT974 7.5 mg QD + LGX818 200 mg QD + Cetuximab

Reporting group title	WNT974 10 mg+LGX818+Cetuximab

Reporting group description:

WNT974 10 mg QD + LGX818 200 mg QD + Cetuximab

Serious adverse events	WNT974 5mg + LGX818+ Cetuximab	WNT974 7.5 mg+LGX818+Cetuximab	WNT974 10 mg+LGX818+Cetuximab
Total subjects affected by serious adverse events			
subjects affected / exposed	8 / 10 (80.00%)	4 / 6 (66.67%)	3 / 4 (75.00%)
number of deaths (all causes)	8	4	3
number of deaths resulting from adverse events	0	0	0
Investigations			
Blood bilirubin increased			
subjects affected / exposed	0 / 10 (0.00%)	1 / 6 (16.67%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Rib fracture			
subjects affected / exposed	1 / 10 (10.00%)	2 / 6 (33.33%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	1 / 1	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Spinal compression fracture			

subjects affected / exposed	1 / 10 (10.00%)	1 / 6 (16.67%)	1 / 4 (25.00%)
occurrences causally related to treatment / all	1 / 1	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hip fracture			
subjects affected / exposed	0 / 10 (0.00%)	1 / 6 (16.67%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infusion related reaction			
subjects affected / exposed	0 / 10 (0.00%)	1 / 6 (16.67%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Headache			
subjects affected / exposed	1 / 10 (10.00%)	0 / 6 (0.00%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Seizure			
subjects affected / exposed	1 / 10 (10.00%)	0 / 6 (0.00%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Disseminated intravascular coagulation			
subjects affected / exposed	1 / 10 (10.00%)	0 / 6 (0.00%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrial fibrillation			
subjects affected / exposed	1 / 10 (10.00%)	0 / 6 (0.00%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Disease progression			

subjects affected / exposed	0 / 10 (0.00%)	1 / 6 (16.67%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General physical health deterioration			
subjects affected / exposed	1 / 10 (10.00%)	0 / 6 (0.00%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pain			
subjects affected / exposed	1 / 10 (10.00%)	0 / 6 (0.00%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyrexia			
subjects affected / exposed	1 / 10 (10.00%)	0 / 6 (0.00%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Abdominal distension			
subjects affected / exposed	1 / 10 (10.00%)	0 / 6 (0.00%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intestinal obstruction			
subjects affected / exposed	1 / 10 (10.00%)	0 / 6 (0.00%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Small intestinal obstruction			
subjects affected / exposed	0 / 10 (0.00%)	0 / 6 (0.00%)	1 / 4 (25.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Subileus			
subjects affected / exposed	0 / 10 (0.00%)	0 / 6 (0.00%)	1 / 4 (25.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			

Bile duct obstruction			
subjects affected / exposed	0 / 10 (0.00%)	0 / 6 (0.00%)	1 / 4 (25.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatic haemorrhage			
subjects affected / exposed	1 / 10 (10.00%)	0 / 6 (0.00%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Jaundice			
subjects affected / exposed	0 / 10 (0.00%)	0 / 6 (0.00%)	1 / 4 (25.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Pleural effusion			
subjects affected / exposed	1 / 10 (10.00%)	1 / 6 (16.67%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	0 / 10 (0.00%)	1 / 6 (16.67%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal failure			
subjects affected / exposed	0 / 10 (0.00%)	0 / 6 (0.00%)	1 / 4 (25.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	0 / 10 (0.00%)	1 / 6 (16.67%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bone pain			

subjects affected / exposed	1 / 10 (10.00%)	0 / 6 (0.00%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Groin pain			
subjects affected / exposed	1 / 10 (10.00%)	0 / 6 (0.00%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pathological fracture			
subjects affected / exposed	0 / 10 (0.00%)	1 / 6 (16.67%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Abdominal infection			
subjects affected / exposed	1 / 10 (10.00%)	0 / 6 (0.00%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis			
subjects affected / exposed	0 / 10 (0.00%)	1 / 6 (16.67%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	1 / 10 (10.00%)	0 / 6 (0.00%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract infection			
subjects affected / exposed	0 / 10 (0.00%)	0 / 6 (0.00%)	1 / 4 (25.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Hypercalcaemia			
subjects affected / exposed	1 / 10 (10.00%)	0 / 6 (0.00%)	1 / 4 (25.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	WNT974 5mg + LGX818+ Cetuximab	WNT974 7.5 mg+LGX818+Cetuximab	WNT974 10 mg+LGX818+Cetuximab
Total subjects affected by non-serious adverse events			
subjects affected / exposed	10 / 10 (100.00%)	6 / 6 (100.00%)	4 / 4 (100.00%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Haemangioma			
subjects affected / exposed	2 / 10 (20.00%)	0 / 6 (0.00%)	0 / 4 (0.00%)
occurrences (all)	2	0	0
Melanocytic naevus			
subjects affected / exposed	1 / 10 (10.00%)	0 / 6 (0.00%)	1 / 4 (25.00%)
occurrences (all)	1	0	1
Skin papilloma			
subjects affected / exposed	2 / 10 (20.00%)	0 / 6 (0.00%)	0 / 4 (0.00%)
occurrences (all)	2	0	0
Haemangioma of skin			
subjects affected / exposed	1 / 10 (10.00%)	0 / 6 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Keratoacanthoma			
subjects affected / exposed	0 / 10 (0.00%)	0 / 6 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1
Seborrhoeic keratosis			
subjects affected / exposed	1 / 10 (10.00%)	0 / 6 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Vascular disorders			
Flushing			
subjects affected / exposed	0 / 10 (0.00%)	1 / 6 (16.67%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Haematoma			
subjects affected / exposed	1 / 10 (10.00%)	0 / 6 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Hypertension			
subjects affected / exposed	0 / 10 (0.00%)	0 / 6 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1
General disorders and administration site conditions			

Fatigue			
subjects affected / exposed	6 / 10 (60.00%)	2 / 6 (33.33%)	3 / 4 (75.00%)
occurrences (all)	6	2	3
Pyrexia			
subjects affected / exposed	5 / 10 (50.00%)	2 / 6 (33.33%)	1 / 4 (25.00%)
occurrences (all)	5	2	1
Oedema peripheral			
subjects affected / exposed	3 / 10 (30.00%)	0 / 6 (0.00%)	4 / 4 (100.00%)
occurrences (all)	3	0	4
Chills			
subjects affected / exposed	2 / 10 (20.00%)	1 / 6 (16.67%)	1 / 4 (25.00%)
occurrences (all)	2	1	1
Pain			
subjects affected / exposed	3 / 10 (30.00%)	0 / 6 (0.00%)	0 / 4 (0.00%)
occurrences (all)	3	0	0
Asthenia			
subjects affected / exposed	2 / 10 (20.00%)	0 / 6 (0.00%)	0 / 4 (0.00%)
occurrences (all)	2	0	0
Influenza like illness			
subjects affected / exposed	0 / 10 (0.00%)	2 / 6 (33.33%)	0 / 4 (0.00%)
occurrences (all)	0	2	0
Non-cardiac chest pain			
subjects affected / exposed	1 / 10 (10.00%)	1 / 6 (16.67%)	0 / 4 (0.00%)
occurrences (all)	1	1	0
Catheter site ulcer			
subjects affected / exposed	1 / 10 (10.00%)	0 / 6 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Localised oedema			
subjects affected / exposed	1 / 10 (10.00%)	0 / 6 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Xerosis			
subjects affected / exposed	1 / 10 (10.00%)	0 / 6 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Immune system disorders			
Hypersensitivity			

subjects affected / exposed	1 / 10 (10.00%)	0 / 6 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Reproductive system and breast disorders			
Breast pain			
subjects affected / exposed	1 / 10 (10.00%)	0 / 6 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Penile pain			
subjects affected / exposed	0 / 10 (0.00%)	0 / 6 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	2 / 10 (20.00%)	2 / 6 (33.33%)	0 / 4 (0.00%)
occurrences (all)	2	2	0
Epistaxis			
subjects affected / exposed	2 / 10 (20.00%)	1 / 6 (16.67%)	0 / 4 (0.00%)
occurrences (all)	2	1	0
Cough			
subjects affected / exposed	1 / 10 (10.00%)	1 / 6 (16.67%)	0 / 4 (0.00%)
occurrences (all)	1	1	0
Nasal congestion			
subjects affected / exposed	0 / 10 (0.00%)	2 / 6 (33.33%)	0 / 4 (0.00%)
occurrences (all)	0	2	0
Dysphonia			
subjects affected / exposed	0 / 10 (0.00%)	0 / 6 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1
Pleural effusion			
subjects affected / exposed	1 / 10 (10.00%)	0 / 6 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Psychiatric disorders			
Anxiety			
subjects affected / exposed	1 / 10 (10.00%)	0 / 6 (0.00%)	2 / 4 (50.00%)
occurrences (all)	1	0	2
Insomnia			
subjects affected / exposed	2 / 10 (20.00%)	0 / 6 (0.00%)	1 / 4 (25.00%)
occurrences (all)	2	0	1
Claustrophobia			

subjects affected / exposed	1 / 10 (10.00%)	0 / 6 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Confusional state			
subjects affected / exposed	1 / 10 (10.00%)	0 / 6 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Depression			
subjects affected / exposed	1 / 10 (10.00%)	0 / 6 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Encopresis			
subjects affected / exposed	1 / 10 (10.00%)	0 / 6 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Investigations			
Weight decreased			
subjects affected / exposed	1 / 10 (10.00%)	2 / 6 (33.33%)	2 / 4 (50.00%)
occurrences (all)	1	2	2
Aspartate aminotransferase increased			
subjects affected / exposed	2 / 10 (20.00%)	1 / 6 (16.67%)	1 / 4 (25.00%)
occurrences (all)	2	1	1
Blood creatinine increased			
subjects affected / exposed	0 / 10 (0.00%)	1 / 6 (16.67%)	3 / 4 (75.00%)
occurrences (all)	0	1	3
Alanine aminotransferase increased			
subjects affected / exposed	2 / 10 (20.00%)	1 / 6 (16.67%)	0 / 4 (0.00%)
occurrences (all)	2	1	0
Blood alkaline phosphatase increased			
subjects affected / exposed	1 / 10 (10.00%)	1 / 6 (16.67%)	1 / 4 (25.00%)
occurrences (all)	1	1	1
Blood bilirubin increased			
subjects affected / exposed	1 / 10 (10.00%)	1 / 6 (16.67%)	1 / 4 (25.00%)
occurrences (all)	1	1	1
Lipase increased			
subjects affected / exposed	1 / 10 (10.00%)	1 / 6 (16.67%)	1 / 4 (25.00%)
occurrences (all)	1	1	1
Amylase increased			

subjects affected / exposed	0 / 10 (0.00%)	1 / 6 (16.67%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Injury, poisoning and procedural complications			
Rib fracture			
subjects affected / exposed	3 / 10 (30.00%)	1 / 6 (16.67%)	1 / 4 (25.00%)
occurrences (all)	3	1	1
Infusion related reaction			
subjects affected / exposed	1 / 10 (10.00%)	1 / 6 (16.67%)	1 / 4 (25.00%)
occurrences (all)	1	1	1
Spinal compression fracture			
subjects affected / exposed	1 / 10 (10.00%)	0 / 6 (0.00%)	1 / 4 (25.00%)
occurrences (all)	1	0	1
Foot fracture			
subjects affected / exposed	1 / 10 (10.00%)	0 / 6 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Lumbar vertebral fracture			
subjects affected / exposed	1 / 10 (10.00%)	0 / 6 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Cardiac disorders			
Palpitations			
subjects affected / exposed	0 / 10 (0.00%)	1 / 6 (16.67%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Nervous system disorders			
Dysgeusia			
subjects affected / exposed	2 / 10 (20.00%)	2 / 6 (33.33%)	3 / 4 (75.00%)
occurrences (all)	2	2	3
Headache			
subjects affected / exposed	2 / 10 (20.00%)	2 / 6 (33.33%)	0 / 4 (0.00%)
occurrences (all)	2	2	0
Peripheral sensory neuropathy			
subjects affected / exposed	1 / 10 (10.00%)	2 / 6 (33.33%)	1 / 4 (25.00%)
occurrences (all)	1	2	1
Neuropathy peripheral			
subjects affected / exposed	1 / 10 (10.00%)	0 / 6 (0.00%)	1 / 4 (25.00%)
occurrences (all)	1	0	1
Dysaesthesia			

subjects affected / exposed	1 / 10 (10.00%)	0 / 6 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Nerve root compression			
subjects affected / exposed	1 / 10 (10.00%)	0 / 6 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Peripheral motor neuropathy			
subjects affected / exposed	0 / 10 (0.00%)	1 / 6 (16.67%)	1 / 4 (25.00%)
occurrences (all)	0	1	1
Sciatica			
subjects affected / exposed	0 / 10 (0.00%)	1 / 6 (16.67%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Spinal claudication			
subjects affected / exposed	1 / 10 (10.00%)	0 / 6 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Transient ischaemic attack			
subjects affected / exposed	0 / 10 (0.00%)	1 / 6 (16.67%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Visual field defect			
subjects affected / exposed	0 / 10 (0.00%)	0 / 6 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1
Bradyphrenia			
subjects affected / exposed	1 / 10 (10.00%)	0 / 6 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	5 / 10 (50.00%)	2 / 6 (33.33%)	3 / 4 (75.00%)
occurrences (all)	5	2	3
Lymph node pain			
subjects affected / exposed	0 / 10 (0.00%)	1 / 6 (16.67%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Thrombocytopenia			
subjects affected / exposed	0 / 10 (0.00%)	0 / 6 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1
Ear and labyrinth disorders			
Deafness unilateral			

subjects affected / exposed	0 / 10 (0.00%)	0 / 6 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1
Dysacusis			
subjects affected / exposed	1 / 10 (10.00%)	0 / 6 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Ear discomfort			
subjects affected / exposed	1 / 10 (10.00%)	0 / 6 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Tinnitus			
subjects affected / exposed	0 / 10 (0.00%)	0 / 6 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1
Eye disorders			
Abnormal sensation in eye			
subjects affected / exposed	1 / 10 (10.00%)	0 / 6 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Conjunctival haemorrhage			
subjects affected / exposed	5 / 10 (50.00%)	0 / 6 (0.00%)	0 / 4 (0.00%)
occurrences (all)	5	0	0
Dry eye			
subjects affected / exposed	0 / 10 (0.00%)	0 / 6 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1
Eye pruritus			
subjects affected / exposed	1 / 10 (10.00%)	0 / 6 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Lacrimation increased			
subjects affected / exposed	1 / 10 (10.00%)	0 / 6 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Vitreous detachment			
subjects affected / exposed	0 / 10 (0.00%)	0 / 6 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	5 / 10 (50.00%)	2 / 6 (33.33%)	2 / 4 (50.00%)
occurrences (all)	5	2	2
Nausea			

subjects affected / exposed	4 / 10 (40.00%)	4 / 6 (66.67%)	1 / 4 (25.00%)
occurrences (all)	4	4	1
Vomiting			
subjects affected / exposed	4 / 10 (40.00%)	2 / 6 (33.33%)	2 / 4 (50.00%)
occurrences (all)	4	2	2
Abdominal pain			
subjects affected / exposed	2 / 10 (20.00%)	2 / 6 (33.33%)	2 / 4 (50.00%)
occurrences (all)	2	2	2
Diarrhoea			
subjects affected / exposed	3 / 10 (30.00%)	1 / 6 (16.67%)	1 / 4 (25.00%)
occurrences (all)	3	1	1
Abdominal distension			
subjects affected / exposed	0 / 10 (0.00%)	1 / 6 (16.67%)	1 / 4 (25.00%)
occurrences (all)	0	1	1
Stomatitis			
subjects affected / exposed	1 / 10 (10.00%)	1 / 6 (16.67%)	0 / 4 (0.00%)
occurrences (all)	1	1	0
Abdominal pain upper			
subjects affected / exposed	0 / 10 (0.00%)	0 / 6 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1
Ascites			
subjects affected / exposed	1 / 10 (10.00%)	0 / 6 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Colonic fistula			
subjects affected / exposed	1 / 10 (10.00%)	0 / 6 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Dry mouth			
subjects affected / exposed	1 / 10 (10.00%)	0 / 6 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Faecaloma			
subjects affected / exposed	1 / 10 (10.00%)	0 / 6 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Gastritis			
subjects affected / exposed	1 / 10 (10.00%)	0 / 6 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Haematochezia			

subjects affected / exposed	1 / 10 (10.00%)	0 / 6 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Lip dry			
subjects affected / exposed	1 / 10 (10.00%)	0 / 6 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Mouth haemorrhage			
subjects affected / exposed	0 / 10 (0.00%)	1 / 6 (16.67%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Oesophagitis			
subjects affected / exposed	1 / 10 (10.00%)	0 / 6 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Salivary duct inflammation			
subjects affected / exposed	0 / 10 (0.00%)	1 / 6 (16.67%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Sensitivity of teeth			
subjects affected / exposed	0 / 10 (0.00%)	1 / 6 (16.67%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Toothache			
subjects affected / exposed	1 / 10 (10.00%)	0 / 6 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Hepatobiliary disorders			
Hepatic pain			
subjects affected / exposed	1 / 10 (10.00%)	0 / 6 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Skin and subcutaneous tissue disorders			
Dry skin			
subjects affected / exposed	1 / 10 (10.00%)	2 / 6 (33.33%)	0 / 4 (0.00%)
occurrences (all)	1	2	0
Rash maculo-papular			
subjects affected / exposed	1 / 10 (10.00%)	1 / 6 (16.67%)	1 / 4 (25.00%)
occurrences (all)	1	1	1
Dermatitis acneiform			
subjects affected / exposed	0 / 10 (0.00%)	1 / 6 (16.67%)	1 / 4 (25.00%)
occurrences (all)	0	1	1
Papule			

subjects affected / exposed	1 / 10 (10.00%)	1 / 6 (16.67%)	0 / 4 (0.00%)
occurrences (all)	1	1	0
Pruritus			
subjects affected / exposed	1 / 10 (10.00%)	0 / 6 (0.00%)	1 / 4 (25.00%)
occurrences (all)	1	0	1
Hyperkeratosis			
subjects affected / exposed	1 / 10 (10.00%)	0 / 6 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Nail dystrophy			
subjects affected / exposed	1 / 10 (10.00%)	0 / 6 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Nail ridging			
subjects affected / exposed	1 / 10 (10.00%)	0 / 6 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Pruritus generalised			
subjects affected / exposed	1 / 10 (10.00%)	0 / 6 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Rash			
subjects affected / exposed	0 / 10 (0.00%)	0 / 6 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1
Rash papular			
subjects affected / exposed	1 / 10 (10.00%)	0 / 6 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Skin hyperpigmentation			
subjects affected / exposed	1 / 10 (10.00%)	0 / 6 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Renal and urinary disorders			
Urinary retention			
subjects affected / exposed	1 / 10 (10.00%)	0 / 6 (0.00%)	2 / 4 (50.00%)
occurrences (all)	1	0	2
Nocturia			
subjects affected / exposed	1 / 10 (10.00%)	0 / 6 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Musculoskeletal and connective tissue disorders			

Arthralgia			
subjects affected / exposed	5 / 10 (50.00%)	4 / 6 (66.67%)	4 / 4 (100.00%)
occurrences (all)	5	4	4
Back pain			
subjects affected / exposed	3 / 10 (30.00%)	3 / 6 (50.00%)	2 / 4 (50.00%)
occurrences (all)	3	3	2
Myalgia			
subjects affected / exposed	3 / 10 (30.00%)	2 / 6 (33.33%)	2 / 4 (50.00%)
occurrences (all)	3	2	2
Osteoporosis			
subjects affected / exposed	2 / 10 (20.00%)	2 / 6 (33.33%)	1 / 4 (25.00%)
occurrences (all)	2	2	1
Pain in extremity			
subjects affected / exposed	2 / 10 (20.00%)	1 / 6 (16.67%)	2 / 4 (50.00%)
occurrences (all)	2	1	2
Osteopenia			
subjects affected / exposed	1 / 10 (10.00%)	1 / 6 (16.67%)	0 / 4 (0.00%)
occurrences (all)	1	1	0
Bone pain			
subjects affected / exposed	0 / 10 (0.00%)	1 / 6 (16.67%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Fibromyalgia			
subjects affected / exposed	1 / 10 (10.00%)	0 / 6 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Hypercreatinaemia			
subjects affected / exposed	1 / 10 (10.00%)	0 / 6 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Joint stiffness			
subjects affected / exposed	1 / 10 (10.00%)	0 / 6 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Joint swelling			
subjects affected / exposed	1 / 10 (10.00%)	0 / 6 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Neck pain			
subjects affected / exposed	1 / 10 (10.00%)	0 / 6 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0

Pathological fracture			
subjects affected / exposed	1 / 10 (10.00%)	0 / 6 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	1 / 10 (10.00%)	1 / 6 (16.67%)	0 / 4 (0.00%)
occurrences (all)	1	1	0
Urinary tract infection			
subjects affected / exposed	2 / 10 (20.00%)	0 / 6 (0.00%)	0 / 4 (0.00%)
occurrences (all)	2	0	0
Abdominal infection			
subjects affected / exposed	1 / 10 (10.00%)	0 / 6 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Catheter site infection			
subjects affected / exposed	1 / 10 (10.00%)	0 / 6 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Conjunctivitis			
subjects affected / exposed	0 / 10 (0.00%)	1 / 6 (16.67%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Cystitis			
subjects affected / exposed	0 / 10 (0.00%)	0 / 6 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1
Gastroenteritis			
subjects affected / exposed	1 / 10 (10.00%)	0 / 6 (0.00%)	1 / 4 (25.00%)
occurrences (all)	1	0	1
Gingivitis			
subjects affected / exposed	1 / 10 (10.00%)	0 / 6 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Herpes zoster			
subjects affected / exposed	0 / 10 (0.00%)	1 / 6 (16.67%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Labyrinthitis			
subjects affected / exposed	1 / 10 (10.00%)	0 / 6 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Nail infection			

subjects affected / exposed	1 / 10 (10.00%)	0 / 6 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Paronychia			
subjects affected / exposed	1 / 10 (10.00%)	0 / 6 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Rash pustular			
subjects affected / exposed	1 / 10 (10.00%)	0 / 6 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Scrotal infection			
subjects affected / exposed	0 / 10 (0.00%)	0 / 6 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1
Sinusitis			
subjects affected / exposed	0 / 10 (0.00%)	1 / 6 (16.67%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Skin infection			
subjects affected / exposed	0 / 10 (0.00%)	0 / 6 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1
Tracheitis			
subjects affected / exposed	1 / 10 (10.00%)	0 / 6 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Upper respiratory tract infection			
subjects affected / exposed	1 / 10 (10.00%)	0 / 6 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Urethritis			
subjects affected / exposed	0 / 10 (0.00%)	0 / 6 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1
Metabolism and nutrition disorders			
Hypercalcaemia			
subjects affected / exposed	5 / 10 (50.00%)	5 / 6 (83.33%)	4 / 4 (100.00%)
occurrences (all)	5	5	4
Hypophosphataemia			
subjects affected / exposed	4 / 10 (40.00%)	2 / 6 (33.33%)	2 / 4 (50.00%)
occurrences (all)	4	2	2
Decreased appetite			
subjects affected / exposed	3 / 10 (30.00%)	2 / 6 (33.33%)	2 / 4 (50.00%)
occurrences (all)	3	2	2

Hypokalaemia			
subjects affected / exposed	3 / 10 (30.00%)	2 / 6 (33.33%)	2 / 4 (50.00%)
occurrences (all)	3	2	2
Hypomagnesaemia			
subjects affected / exposed	3 / 10 (30.00%)	1 / 6 (16.67%)	3 / 4 (75.00%)
occurrences (all)	3	1	3
Hypocalcaemia			
subjects affected / exposed	1 / 10 (10.00%)	1 / 6 (16.67%)	3 / 4 (75.00%)
occurrences (all)	1	1	3
Dehydration			
subjects affected / exposed	1 / 10 (10.00%)	0 / 6 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Hypercreatininaemia			
subjects affected / exposed	1 / 10 (10.00%)	0 / 6 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Hyperglycaemia			
subjects affected / exposed	0 / 10 (0.00%)	0 / 6 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1
Hyperkalaemia			
subjects affected / exposed	1 / 10 (10.00%)	0 / 6 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Hypoalbuminaemia			
subjects affected / exposed	1 / 10 (10.00%)	0 / 6 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Hypovitaminosis			
subjects affected / exposed	1 / 10 (10.00%)	0 / 6 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
18 September 2014	Protocol Amendment 01: The reason for this current amendment was to comply with health authority request for better defining some DLT criteria grade 4 (hypertension, diarrhea, infections and fever and laboratory abnormalities) and clarifying the sequence of drug administration. In addition, minor changes for consistency and clarification were implemented. The sequence of drug administration (QD regimen) was revised to clarify that WNT974 and encorafenib were to be taken in the fasted state, at least 1 hour after or 2 hours before a meal as recommended by the health authority. The criteria for defining some DLT criteria Grade 4 (hypertension, diarrhea, infections and fever and laboratory abnormalities) were revised.
13 July 2015	Protocol Amendment 02: The purpose of this amendment was to document a change in study sponsorship from Novartis to Array BioPharma. Study design and procedures were not affected.
19 April 2016	Protocol Amendment 03: • Added notification of the decision to discontinue further enrollment in Phase 1b and to not initiate the Phase 2 portion of the study due to evidence of bone toxicity and lack of improved efficacy of the triple combination, WNT974 + encorafenib + cetuximab over the dual combination, encorafenib + cetuximab. • Additional monitoring and treatment of bone-related toxicities were incorporated into the protocol following observations of bone toxicity. • Added notification of the decision that survival follow-up would continue until/unless the Sponsor decided to discontinue such assessments. • Added information to clarify that in exceptional cases, if WNT974 was discontinued due to toxicity and if the patient might benefit from continuing encorafenib and cetuximab, the patient may have remained on study following discussion with the Sponsor's Medical Monitor. Also added that due to the lack of demonstrated activity with single-agent encorafenib or cetuximab, patients who could not tolerate the dual combination were discontinued from the study. • Added dose modification information for bone toxicity. • Added DEXA scans (at screening, at Cycle 3 Day 1, every 16 weeks and as clinically indicated) to the "Visit Evaluation Schedule" to assess bone toxicity.
30 May 2017	Administrative letter: The frequency of tumor assessments in an ongoing patient was reduced to minimize the burden on patients and reduce radiation exposure.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported