Clinical trial results:
A Phase II Trial of PLX3397 in the Treatment of KIT Mutated Advanced Acral and Mucosal Melanoma (PIANO)

Summary

EudraCT number	2013-002073-22
Trial protocol	GB
Global end of trial date	01 March 2021

Results information

Result version number	v1 (current)
This version publication date	27 September 2024
First version publication date	27 September 2024

Trial information

Trial identification

Sponsor protocol code	11_DOG12_56

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02071940
WHO universal trial number (UTN)	-
Other trial identifiers	clinicaltrials.gov: NCT02071940

Notes:

Sponsors

Sponsor organisation name	The Christie NHS Foundation Trust
Sponsor organisation address	550 Wilmslow Road, Manchester, United Kingdom, M20 4BX
Public contact	Clare Griffin, The Christie NHS Foundation Trust, +44 01619187771, the-christie.sponsoredresearch@nhs.net
Scientific contact	Clare Griffin, The Christie NHS Foundation Trust, +44 01619187771, the-christie.sponsoredresearch@nhs.net

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	27 July 2022
Is this the analysis of the primary completion data?	Yes
Primary completion date	01 March 2021
Global end of trial reached?	Yes
Global end of trial date	01 March 2021
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study is to evaluate the efficacy and safety of PLX3397 in patients with KIT mutated advanced mucosal and acral melanoma. Response to the treatment is measured by tumour progression free survival at 6 months and overall patient survival rate are key objectives of the study.

Protection of trial subjects:

Patients are assigned a unique trial ID via the MCTU trials line which was used throughout their participation in the trial. Any personal data recorded will is regarded as confidential, and any information which would allow individual patients to be identified have not be released into the public domain. Each investigator should keep a separate Trial ID and screening log of all participants consented and screen status. The investigator must maintain this screening log and all other trial documents (including participant's written consent forms) which are to be held at the participating centres, in strictest confidence. The investigator must ensure the patients' confidentiality is maintained.
The MCTU will maintain the confidentiality of all patients and will not reproduce or disclose any information by which patients could be identified. The Investigator and trial site staff involved with this trial may not disclose or use for any purpose other than performance of the trial, any data, record, or other unpublished, confidential information disclosed to those individuals for the purpose of the trial.
All Investigators and trial site staff involved with the trial must comply with the requirements of the Data Protection Act 1998 with regard to the collection, storage, processing and disclosure of personal information and will uphold the Act's core principles. Patient notes and trial files at site must be kept in a secure storage area with limited access. Computers used to collate the data will have limited access measures via user names and passwords.
Published results will not contain any personal data that could allow identification of individual patients.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	01 June 2015
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	United Kingdom: 9
Worldwide total number of subjects	9
EEA total number of subjects	0

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)	4
From 65 to 84 years	5
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

A total of 9 participants with histologically proven KIT mutated advanced mucosal or acral melanoma not associated with PLX3397 resistance were recruited over the course of the trial. Patients were recruited from outpatient oncology clinics and were required to have given written informed consent after a period of time.

Pre-assignment

Screening details:

Once eligibility was established, screening assessments included demographic details, medical and surgical history, RECIST v1.1 tumour evaluation, current medications, vital signs and standard physical examination, ECOG performance status, lab investigations including full blood count and liver function tests, pregnancy testing and ECG.

Period 1

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

Blinding implementation details:

The PIANO trial is an open-label, single-arm, multicentre phase II trial.

Arms

Arm title	Single-arm PLX3397

Arm description:

Following consent and successful screening, patients will receive PLX3397 capsules 1000mg/day as monotherapy, and will remain on therapy as long as they are deriving clinical benefit. Patients will be seen every 4 weeks during treatment to monitor response and toxicity.

Arm type	Experimental
Investigational medicinal product name	PLX3397
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Patients will be started on treatment of PLX3397, 1000mg/day divided into two doses: one dose in the morning (three 200 mg capsules) and a dose in the evening (two 200mg capsules)

Number of subjects in period 1	Single-arm PLX3397
Started	9
Completed	9

Baseline characteristics

Reporting groups

Reporting group title	Overall Trial

Reporting group description: -

Reporting group values	Overall Trial	Total	
Number of subjects	9	9	
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)	4	4	
From 65-84 years	5	5	
85 years and over	0	0	
Gender categorical Units: Subjects			
Female	5	5	
Male	4	4	

End points

End points reporting groups

Reporting group title	Single-arm PLX3397

Reporting group description:

Following consent and successful screening, patients will receive PLX3397 capsules 1000mg/day as monotherapy, and will remain on therapy as long as they are deriving clinical benefit. Patients will be seen every 4 weeks during treatment to monitor response and toxicity.

Primary: Evaluation of overall survival rate

End point title	Evaluation of overall survival rate[1]

End point description:

Survival status at point of end of trial.

End point type	Primary

End point timeframe:

Patients are kept on treatment as soon as they are consented and eligible to participate for the duration of the trial (4 years). Patients will be offered the trial drug until closure of the trial or until confirmation of disease progression.

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: Because of the slow recruitment, we tried unsuccessfully to extend the study to other countries in Europe. In the meantime, the pharmaceutical company Plexxicon was aquired by another company which made a decision not to progress development of the drug for this disease. In addition, the preliminary data did not indicate a strong signal to extend the trial.

End point values	Single-arm PLX3397			
Subject group type	Reporting group			
Number of subjects analysed	9			
Units: Number of participants				
Alive at End of Trial	2			
Died on Trial	7			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

All AEs, both related and unrelated to the drug, and whether observed by the Investigator or patient reported during the study period, must be recorded up to and including those which occurred one month after study drug administration.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	27.0

Reporting groups

Reporting group title	Single arm intervention

Reporting group description: -

Serious adverse events	Single arm intervention		
Total subjects affected by serious adverse events			
subjects affected / exposed	4 / 9 (44.44%)		
number of deaths (all causes)	1		
number of deaths resulting from adverse events	1		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Progressive Malignant Melanoma	Additional description: Progressive Malignant Melanoma		
subjects affected / exposed	1 / 9 (11.11%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Pyrexia	Additional description: Pyrexia		
subjects affected / exposed	1 / 9 (11.11%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Small Intestinal Obstruction	Additional description: Small Intestinal Obstruction		
subjects affected / exposed	1 / 9 (11.11%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Musculoskeletal and connective tissue disorders			
Suspected Spinal Cord Compression	Additional description: Suspected Spinal Cord Compression		

subjects affected / exposed	1 / 9 (11.11%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	Single arm intervention		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	9 / 9 (100.00%)		
Vascular disorders			
Hypertension	Additional description: Hypertension		
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
General disorders and administration site conditions			
Face oedema	Additional description: Face oedema		
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Fatigue	Additional description: Fatigue		
subjects affected / exposed	7 / 9 (77.78%)		
occurrences (all)	7		
Oedema peripheral	Additional description: Oedema peripheral		
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Pain	Additional description: Pain		
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Pyrexia	Additional description: Pyrexia		
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Reproductive system and breast disorders			
Vaginal Spotting	Additional description: Vaginal Spotting		
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Respiratory, thoracic and mediastinal disorders			

Dyspnoea	Additional description: Dyspnoea		
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Cough	Additional description: Cough		
subjects affected / exposed	2 / 9 (22.22%)		
occurrences (all)	2		
Psychiatric disorders			
Depression	Additional description: Depression		
subjects affected / exposed	2 / 9 (22.22%)		
occurrences (all)	2		
Insomnia	Additional description: Insomnia		
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Investigations			
Alkaline Phosphatase Increased	Additional description: Alkaline Phosphatase Increased		
subjects affected / exposed	2 / 9 (22.22%)		
occurrences (all)	2		
Alanine Aminotransferase Increased	Additional description: Alanine Aminotransferase Increased		
subjects affected / exposed	2 / 9 (22.22%)		
occurrences (all)	2		
Blood creatinine increased	Additional description: Blood creatinine increased		
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Aspartate Aminotransferase Increased	Additional description: Aspartate Aminotransferase Increased		
subjects affected / exposed	2 / 9 (22.22%)		
occurrences (all)	2		
Electrocardiogram QT prolonged	Additional description: Electrocardiogram QT prolonged		
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Eosinophil count decreased	Additional description: Eosinophil count decreased		
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Gamma-glutamyltransferase increased	Additional description: Gamma-glutamyltransferase increased		
subjects affected / exposed	2 / 9 (22.22%)		
occurrences (all)	2		
Hepatic Enzymes Increased	Additional description: Hepatic Enzymes Increased		

subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Lymphocyte count decreased	Additional description: Lymphocyte count decreased		
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Weight decreased	Additional description: Weight decreased		
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Injury, poisoning and procedural complications			
Contusion	Additional description: Contusion		
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Stoma site haemorrhage	Additional description: Stoma site haemorrhage		
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Nervous system disorders			
Ataxia	Additional description: Ataxia		
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Dysgeusia	Additional description: Dysgeusia		
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Dysesthesia	Additional description: Dysesthesia		
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Dizziness	Additional description: Dizziness		
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Blood and lymphatic system disorders			
Anaemia	Additional description: Anaemia		
subjects affected / exposed	2 / 9 (22.22%)		
occurrences (all)	2		
Eye disorders			
Periorbital oedema	Additional description: Periorbital oedema		
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		

Visual Loss	Additional description: Visual Loss		
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Gastrointestinal disorders			
Abdominal Pain	Additional description: Abdominal Pain		
subjects affected / exposed	3 / 9 (33.33%)		
occurrences (all)	3		
Abdominal distension	Additional description: Abdominal distension		
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Dysphagia	Additional description: Dysphagia		
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Dyspepsia	Additional description: Dyspepsia		
subjects affected / exposed	2 / 9 (22.22%)		
occurrences (all)	3		
Diarrhoea	Additional description: Diarrhoea		
subjects affected / exposed	4 / 9 (44.44%)		
occurrences (all)	4		
Gastroesophageal reflux disease	Additional description: Gastroesophageal reflux disease		
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Intestina stoma leak	Additional description: Intestina stoma leak		
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Mucositis Oral	Additional description: Mucositis Oral		
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Nausea	Additional description: Nausea		
subjects affected / exposed	6 / 9 (66.67%)		
occurrences (all)	6		
Vomiting	Additional description: Vomiting		
subjects affected / exposed	3 / 9 (33.33%)		
occurrences (all)	3		
Skin and subcutaneous tissue disorders			

Erythema Multiforme	Additional description: Erythema Multiforme		
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Erythema nodosum	Additional description: Erythema nodosum		
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Hair Depigmented	Additional description: Hair Depigmented		
subjects affected / exposed	3 / 9 (33.33%)		
occurrences (all)	3		
Hyperhidrosis	Additional description: Hyperhidrosis		
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Rash Maculo-Papular	Additional description: Rash Maculo-Papular		
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Skin ulceration	Additional description: Skin ulceration		
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Renal and urinary disorders			
Proteinuria	Additional description: Proteinuria		
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Musculoskeletal and connective tissue disorders			
Back Pain	Additional description: Back Pain		
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Metabolism and nutrition disorders			
Anorexia	Additional description: Anorexia		
subjects affected / exposed	5 / 9 (55.56%)		
occurrences (all)	5		
Hyperkalaemia	Additional description: Hyperkalaemia		
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Hyponatremia	Additional description: Hyponatremia		
subjects affected / exposed	2 / 9 (22.22%)		
occurrences (all)	2		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
16 July 2015	Pregnancy testing frequency was changed from monthly to every visit due to costing issues.
11 May 2016	PI change - Christine Parkinson (Addenbrookes Hospital)
13 December 2016	?Various updates to protocol including minor changes to contact details, protocol updated to show that LFTs should be repeated every week for the first 8 weeks, minor update separating blood samples for PK/PD tests, updated with information from the most recent IB, upated drug distributor details and changes in SAEs being reported from registration rather than from consent.
04 October 2017	Immediate halt of patient recruitment as of 4th October 2017 due to pending safety review by Daiichi Sankyo, the parent company of the IMP manufacturer.
12 January 2018	Updated Protocol, IB and corresponding patient documents to reopen the study to recruitment.
02 October 2019	Updates to multiple trial documents including; updated IB to v10.0, updated Protocol to reference updated IB v10.0, updated PIS to v7.0 to include updated risk language and updated ICF to v6.0 to reference updated PIS

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported