Clinical trial results:
A Phase II Trial of Vinflunine chemotherapy in locally advanced and metastatic carcinoma of the penis

Summary

EudraCT number	2012-002592-34
Trial protocol	GB
Global end of trial date	06 November 2018

Results information

Result version number	v1 (current)
This version publication date	27 November 2019
First version publication date	27 November 2019

Trial information

Trial identification

Sponsor protocol code	ICR-CTSU/2012/10036

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02057913
WHO universal trial number (UTN)	-
Other trial identifiers	Sponsor Identification Number: CCR3858, ICRCTSU protocol number: ICR-CTSU/2012/10036, CRUK reference number: CRUK/12/021, Main REC reference: 13/LO/0822, MHRA CTA number: 2213810018/001{001

Notes:

Sponsors

Sponsor organisation name	The Institute of Cancer Research
Sponsor organisation address	15 Cotswold Road, Sutton, United Kingdom, SM2 5NG
Public contact	Stephanie Burnett, The Institute of Cancer Research, +44 02087224261, vincap-icrctsu@icr.ac.uk
Scientific contact	Stephanie Burnett, The Institute of Cancer Research, +44 02087224261, vincap-icrctsu@icr.ac.uk

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	01 November 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	01 November 2017
Global end of trial reached?	Yes
Global end of trial date	06 November 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The principal research objective of the VinCaP study is to determine the clinical benefit (complete response + partial response + stable disease) and toxicity of vinflunine chemotherapy in patients with inoperable (locally advanced or metastatic) cancer of the penis and thus determine whether this regimen warrants further research.

Protection of trial subjects:

For trial entry and optional tissue donation, patients were given a verbal explanation, discussion and written information. The Principal Investigator at each site was responsible for ensuring written informed consent was obtained for each patient.

Eligible patients were given as much time as they needed to consider and come to a decision about entering the trial, prior to giving consent for registration. The patient information sheet, described fully which parties would have access to their identifiable personal information and patients were asked to give consent to this.

Laxatives and dietary measures (including oral hydration) were recommended from day 1 to day 5 or 7 after each vinflunine administration in order to prevent constipation. Anti-emetics were given according to local hospital policy.

The trial was overseen by an Independent Data Monitoring Committee, who reviewed the accumulating trial data and could recommend stopping the trial if there was any cause for concern about patient safety and if this were the case the patient's oncologist would be notified.

Background therapy: -

Evidence for comparator:

Platinum-based combination chemotherapy has been in common use for the treatment of squamous carcinoma of the penis since 1990. Phase II trials of cisplatin-based regimens have reported response rates around 30% (Di Lorenzo et al, 2012), and it is not clear that there is any survival benefit accruing to such treatment. This suggests that complex chemotherapy may be justified in the neoadjuvant setting, but the relatively low response rates and high toxicity rates mean that such an approach has substantially less value for patients with metastatic disease.

Vinca alkaloids have been a component of treatment regimens for penis cancer since the mid-1970s, even though evidence for single-agent activity is lacking (Williams et al, 1974). Vinflunine is a third-generation vinca alkaloid approved by the European Medicines Agency for use as a second-line treatment in patients with urothelial carcinoma resistant to first-line platinum-containing chemotherapy (EMA; Pizzocaro et al, 2010).

Doses of older vinca alkaloids such as vincristine are limited by sensory neuropathy and constipation. Vinflunine has been shown to be tolerable in this regard. It is anticipated that single-agent use of vinflunine in penis cancer will be associated with a favourable toxicity profile combined with the potential to produce meaningful clinical response.

Actual start date of recruitment	25 June 2014
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: 25
Worldwide total number of subjects	25
EEA total number of subjects	25

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)	9
From 65 to 84 years	16
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Twenty-five patients were recruited from eight UK centres between June 2014 and May 2017.

Pre-assignment

Screening details:

Patients that met the eligibility criteria were recruited into the study.

Period 1

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

Arms

Arm title	Vinflunine Chemotherapy

Arm description:

The Vinflunine chemotherapy regimen consists of vinflunine 320mg/m2 day 1 with a cycle of 21 days, four cycles to be given in total.

Arm type	Experimental
Investigational medicinal product name	Vinflunine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

IV vinflunine 320mg/m2 day 1 with a cycle of 21 days, four cycles to be given prior to formal re-staging. Patients judged to have stable disease, partial remission or complete remission and who are fit to do so will then be able to continue on treatment until disease progression or until toxicity supervenes or until treatment is discontinued on clinician's advice or on patient preference.

Number of subjects in period 1	Vinflunine Chemotherapy
Started	25
Completed	12
Not completed	13
Adverse event, serious fatal	2
Adverse event, non-fatal	3
Did not commence treatment	3
Lack of efficacy	5

Baseline characteristics

Reporting groups

Reporting group title	Overall Trial

Reporting group description: -

Reporting group values	Overall Trial	Total	
Number of subjects	25	25	
Age categorical Units: Subjects			
Adults (18-64 years)	9	9	
From 65-84 years	16	16	
Age continuous Units: years			
median	67.9		
inter-quartile range (Q1-Q3)	60.4 to 70.4	-	
Gender categorical Units: Subjects			
Male	25	25	

Subject analysis sets

Subject analysis set title	Intention to treat population
Subject analysis set type	Intention-to-treat

Subject analysis set description:

This population includes all patients enrolled into the study regardless of whether they are later found to be ineligible, a protocol violator, never treated or evaluated. Patients for whom the primary endpoint cannot be evaluated will be treated as non-responders.

Subject analysis set title	Evaluable population
Subject analysis set type	Modified intention-to-treat

Subject analysis set description:

This population contains all enrolled patients for whom the primary endpoint can be evaluated. A patient is considered not evaluable if:
1. The patient received <1 cycle of study vinflunine chemotherapy for one of the following reasons:
Death from any cause
Withdrawal from trial due to progressive disease
Withdrawal from trial for a reason unrelated to drug or disease(e.g. patient preference, administrative reasons), regardless of the number of cycles of chemotherapy.
Or
2. Disease cannot be measured at the end of study treatment for one of the following reasons:
Death from causes other than penile cancer
Withdrawal from trial for a reason unrelated to drug or disease(e.g. patient preference, administrative reasons), regardless of the number of cycles of chemotherapy

Subject analysis set title	Measureable population
Subject analysis set type	Modified intention-to-treat

Subject analysis set description:

Patients who had a scan at 12 weeks or discontinued prior to 12 weeks due to progression. Patients who discontinued prior to 12 weeks for non-disease related reasons were excluded from this analysis.

Reporting group values	Intention to treat population	Evaluable population	Measureable population
Number of subjects	25	22	17
Age categorical Units: Subjects			
Adults (18-64 years)	9	9	9
From 65-84 years	16	13	8
Age continuous Units: years			
median	67.9	66.3	63.8
inter-quartile range (Q1-Q3)	60.4 to 70.4	59.7 to 70.4	58.9 to 70.4
Gender categorical Units: Subjects			
Male	25		

End points

End points reporting groups

Reporting group title	Vinflunine Chemotherapy

Reporting group description:

The Vinflunine chemotherapy regimen consists of vinflunine 320mg/m2 day 1 with a cycle of 21 days, four cycles to be given in total.

Subject analysis set title	Intention to treat population
Subject analysis set type	Intention-to-treat

Subject analysis set description:

This population includes all patients enrolled into the study regardless of whether they are later found to be ineligible, a protocol violator, never treated or evaluated. Patients for whom the primary endpoint cannot be evaluated will be treated as non-responders.

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Withdrawal from trial for a reason unrelated to drug or disease(e.g. patient preference, administrative reasons), regardless of the number of cycles of chemotherapy.
Or
2. Disease cannot be measured at the end of study treatment for one of the following reasons:
Death from causes other than penile cancer
Withdrawal from trial for a reason unrelated to drug or disease(e.g. patient preference, administrative reasons), regardless of the number of cycles of chemotherapy

Subject analysis set title	Measureable population
Subject analysis set type	Modified intention-to-treat

Subject analysis set description:

Patients who had a scan at 12 weeks or discontinued prior to 12 weeks due to progression. Patients who discontinued prior to 12 weeks for non-disease related reasons were excluded from this analysis.

Primary: Clinical Benefit

End point title	Clinical Benefit[1]

End point description:

The clinical benefit rate is defined as the proportion of patients having achieved partial remission, complete remission or stable disease according to RECIST criteria (v1.1) on imaging and/ or bi-dimensional clinical measurements (of skin disease) performed after 4 cycles (approximately 11-12 weeks from Day 1 of first cycle).

End point type	Primary

End point timeframe:

4 weeks from the date of commencement of the final cycle of chemotherapy

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: This is a single arm study and no comparative analysis was performed, however the system expects at least 2 groups to be identified. All methods and options specified in the analysis section apply to statistical methods and summary measures to report and compare at least 2 independent groups, which is not the case in this single arm trial. There is no way of reporting one group inference and summary values without triggering an error or reporting inaccurate information.

End point values	Vinflunine Chemotherapy	Evaluable population		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	22	22		
Units: Patients				
Clinical benefit	10	10		
No clinical benefit	12	12		

Statistical analyses

No statistical analyses for this end point

Secondary: Objective response rate

End point title	Objective response rate

End point description:

Defined as the proportion of patients having achieved partial or complete remission.

End point type	Secondary

End point timeframe:

4 weeks from the date of commencement of the final cycle of chemotherapy

End point values	Vinflunine Chemotherapy	Evaluable population	Measureable population	
Subject group type	Reporting group	Subject analysis set	Subject analysis set	
Number of subjects analysed	22	22	17	
Units: Patients				
Objective response	6	6	6	
No objective response	16	16	11	

Statistical analyses

No statistical analyses for this end point

Secondary: Progression-free survival

End point title	Progression-free survival

End point description:

Defined as time from registration until the first of clinically or radiologically documented disease progression, or death from any cause death. Kaplan-Meier curves will be drawn and estimates of median progression-free survival estimates with their 95% CI will be presented along with the proportion of patients, alive and progression free, at 6 and 12 months respectively.

End point type	Secondary

End point timeframe:

Progression free survival at 12 months

End point values	Vinflunine Chemotherapy	Intention to treat population		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	25	25		
Units: Percentage progression free				
number (confidence interval 95%)	16.7 (4.6 to 35.3)	16.7 (4.6 to 35.3)		

Statistical analyses

No statistical analyses for this end point

Secondary: Overall survival

End point title	Overall survival

End point description:

Kaplan-Meier curves will be drawn and estimates of median overall survival estimates with their 95% CI will be presented along with the proportion of patients alive, at 6 and 12 months respectively.

End point type	Secondary

End point timeframe:

Overall survival will be defined as the time from registration until death from any cause. Patients alive at time of analysis will be censored at date last seen. Patients lost to follow-up will be censored at date last seen.

End point values	Vinflunine Chemotherapy	Intention to treat population		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	25	25		
Units: months				
median (confidence interval 95%)	8.4 (3.2 to 14.1)	8.4 (3.2 to 14.1)		

Statistical analyses

No statistical analyses for this end point

Secondary: Treatment compliance

End point title	Treatment compliance

End point description:

An investigation of treatment compliance of the study treatment will involve a summary of the frequency of dose reductions and delays together with their reasons. The proportion of planned doses delivered will be summarised with a 95% CI.

End point type	Secondary

End point timeframe:

Treatment duration

End point values	Vinflunine Chemotherapy	Intention to treat population		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	25	25		
Units: Patients				
Never started	3	3		
1 cycle	4	4		
2 cycles	4	4		
3 cycles	2	2		
4 cycles	5	5		
5 cycles	1	1		
6 cycles	2	2		
7 cycles	2	2		
8 cycles	2	2		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From trial entry to 30 days after last dose of trial treatment

Adverse event reporting additional description:

AE data for patients who received at least 1 dose of experimental treatment.
In the non-serious adverse events section we report all serious and non-serious adverse events reported with grade 3 or 4 according to the CTCAE grading, that were present in more than 5% of patients.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	14

Reporting groups

Reporting group title	Safety population

Reporting group description:

Patients who received at least 1 dose of experimental treatment. In the non-serious adverse events section we report all adverse events reported at any grade according to the CTCAE grading, that were present in more than 5% of patients. Worst grade per patient is included for each event.

Serious adverse events	Safety population		
Total subjects affected by serious adverse events			
subjects affected / exposed	13 / 22 (59.09%)		
number of deaths (all causes)	18		
number of deaths resulting from adverse events	2		
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	1 / 22 (4.55%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	3 / 22 (13.64%)		
occurrences causally related to treatment / all	4 / 4		
deaths causally related to treatment / all	0 / 0		
Febrile neutropenia			
subjects affected / exposed	1 / 22 (4.55%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Neutropenia			

subjects affected / exposed	2 / 22 (9.09%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Extravasation			
subjects affected / exposed	1 / 22 (4.55%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Fatigue			
subjects affected / exposed	2 / 22 (9.09%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Pain			
subjects affected / exposed	2 / 22 (9.09%)		
occurrences causally related to treatment / all	3 / 3		
deaths causally related to treatment / all	0 / 0		
Pyrexia			
subjects affected / exposed	4 / 22 (18.18%)		
occurrences causally related to treatment / all	3 / 5		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	1 / 22 (4.55%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Haematemesis			
subjects affected / exposed	1 / 22 (4.55%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Intestinal obstruction			
subjects affected / exposed	1 / 22 (4.55%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		

Nausea			
subjects affected / exposed	1 / 22 (4.55%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Stomatitis			
subjects affected / exposed	2 / 22 (9.09%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Pulmonary embolism			
subjects affected / exposed	1 / 22 (4.55%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Skin and subcutaneous tissue disorders			
Eczema			
subjects affected / exposed	1 / 22 (4.55%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Psychiatric disorders			
Confusional state			
subjects affected / exposed	1 / 22 (4.55%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Haematuria			
subjects affected / exposed	1 / 22 (4.55%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Renal failure			
subjects affected / exposed	2 / 22 (9.09%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	1 / 1		
Endocrine disorders			
Inappropriate antidiuretic hormone secretion			

subjects affected / exposed	1 / 22 (4.55%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Groin pain			
subjects affected / exposed	1 / 22 (4.55%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Muscular weakness			
subjects affected / exposed	1 / 22 (4.55%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Infection			
subjects affected / exposed	1 / 22 (4.55%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Neutropenic sepsis			
subjects affected / exposed	2 / 22 (9.09%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	1 / 1		
Sepsis			
subjects affected / exposed	1 / 22 (4.55%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	1 / 1		
Urinary tract infection			
subjects affected / exposed	1 / 22 (4.55%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Hypercalcaemia			
subjects affected / exposed	1 / 22 (4.55%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		

Hypocalcaemia			
subjects affected / exposed	1 / 22 (4.55%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Hyponatraemia			
subjects affected / exposed	2 / 22 (9.09%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Safety population		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	12 / 22 (54.55%)		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	2 / 22 (9.09%)		
occurrences (all)	2		
Neutropenia			
subjects affected / exposed	5 / 22 (22.73%)		
occurrences (all)	5		
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	2 / 22 (9.09%)		
occurrences (all)	2		
Mucosal inflammation			
subjects affected / exposed	2 / 22 (9.09%)		
occurrences (all)	2		
Pyrexia			
subjects affected / exposed	2 / 22 (9.09%)		
occurrences (all)	2		
Respiratory, thoracic and mediastinal disorders			
Pulmonary embolism			
subjects affected / exposed	2 / 22 (9.09%)		
occurrences (all)	2		

Infections and infestations Sepsis subjects affected / exposed occurrences (all)	 2 / 22 (9.09%) 2		
Metabolism and nutrition disorders Hyponatraemia subjects affected / exposed occurrences (all)	 2 / 22 (9.09%) 2		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
21 November 2013	Removal of toxicity, bowel toxicity and adverse event monitoring assessments at the primary endpoint visit as this was a duplicated assessment (already performed at cycle 4 toxicity). • Change to liver function criteria. Added to inclusion criteria, removed from exclusion criteria. Liver function: Patients must have (with or without the presence of liver metastases): o A prothrombin time >70% NV (normal value) AND o Bilirubin <1.5xULN AND o Transaminases <2.5xULN AND o GGT <5xULN • Changes to Primary Endpoint Assessment visit. o Adverse events and toxicity assessment removed o Bowel toxicity monitoring removed. • Clarification that patients who father a child during the course of treatment must be reported as a SAE. SAEs are defined as events that occur after the commencement of study treatment and up to 30 days following the last dose of study drug.
04 March 2015	Inclusion criteria revised to ensure that patients have GFR ≥ 60ml/min. GFR to be assessed according to local practice (recommended technique of eGFR using the MDRD formula (see Appendix 2). Where GFR is 55-60ml/min please contact the trials unit for a decision to be made on patient inclusion by the Chief Investigator OR Clinical Co-ordinator. The Trial Management Group (TMG) reviewed discussed the inclusion criteria that GFR should be ≥60ml/min. The TMG and Trial Steering Committee agreed to amend the inclusion criterion to consider patients for the trial with GFR 55-60ml/min as long as all other eligibility criteria are met. The decision to include such a patient must be discussed with the Chief Investigator and/or the Clinical Coordinator. Previous safety concerns raised by Pierre Fabre (drug company for Vinflunine), about inclusion of patients with a lower GFR, in relation to renal function, originate from use of Vinflunine in bladder cancer patients where disturbance of renal function would be expected; the TMG and TSC agreed that this safety concern is not applicable to this patient group. This amendment was also supported by the pharmaceutical company, Pierre-Fabre. Added requirement to forward SAEs and SARs to the pharmaceutical company, Pierre-Fabre. Change to ICR professional address in affiliations for all ICR staff: Sutton, Surrey to London to comply with new institutional guidance.

25 June 2015	Change to the liver function criteria in line with the SmPC. Liver function parameters updated to allow patients on trial with transaminases <5xULN only in the presence of liver metastases. This accurately reflects the parameters outlined in the summary of product characteristics (SmPC). The trial management group discussed and agreed to this update on the basis that the protocol should fall in line with the SmPC recommendations for patients with hepatic impairment: Liver function: Patients must have (with or without the presence of liver metastases): o A prothrombin time >70% NV (normal value) AND o Bilirubin <1.5xULN AND o Transaminases <2.5xULN (<5xULN only in the case of liver metastases) AND o GGT <5xULN
04 May 2016	• Change to the liver function criteria - Specifying AST and/or ALT to be consistent with the wording in section 8.3 of the protocol • Changes to the exclusion criteria: o Patients who are sexually active and unwilling to use effective contraception (if they are not already surgically sterile). New exclusion criterion linked with new section – lifestyle guidelines: Update to the protocol to provide a definition of effective contraception. o Other malignancy (other than Squamous Cell Carcinoma or Basal Cell Carcinoma of non-penile skin) that has required surgical or non-surgical treatment in the last 2 years. Change from 5 to 2 years. The 5 year window was an arbitrary timeframe and two years was felt to be a more reasonable period • If a patient's performance status deteriorates to PS2, the decision to continue to treat the patient should be made by the local treating clinician. Where possible, discussion with the either the Chief Investigator or Clinical Co-ordinator is encouraged before the next cycle of vinflunine is administered. • Drug Dose Reduction Schedule - If any of the criteria for a dose reduction or delay are met, for example a grade 3 toxicity (considered severe or life threatening), but in the opinion of the treating clinician the event does not indicate a need to dose reduce at the expense of the patient deriving benefit from vinflunine, the case should be discussed with either the Chief Investigator or Clinical Co-ordinator prior to the start of the next cycle of treatment. • correction that IDMC, not TMG are responsible for reviewing evaluability of patients.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date

13 September 2016	Recruitment was halted due to a safety concern following 2 reported SAEs considered related to treatment with an outcome of death. Participant 1: Performance Status (PS) 1 patient – suffered lethargy CTC g3, Acute Kidney Injury (AKI) CTC g5 and neutropenic sepsis CTC g5. CI evaluation: all events are listed in the vinflunine SmPC however, neutropenic sepsis g3-4 has a frequency of 0.2% and the collective severity of these adverse reactions was such that they resulted in death which in the CI's judgement meant the severity of the AE than greater than expected. Participant 3: PS2 patient – suffered sepsis (non-neutropenic) CTC g5. CI evaluation: Sepsis is known to be associated with vinflunine chemotherapy and therefore this is 'expected'. IDMC opinion: There is insufficient evidence to suggest that a higher-than-expected rate of neutropenia in the study contributed to either of the patient deaths reviewed here. Neither patient had significant neutropenia with preceding cycles, suggesting that neither patient had an idiosyncratic haematological sensitivity. The IDMC did not feel there is any necessity to amend the current protocol arrangements for dose reduction. The IDMC reviewed all safety data and had no concerns. The trial was reopened to recruitment in November 2016.	25 November 2016

Notes:

Limitations and caveats

None reported