



Clinical trial results:

A Phase II study of Gemcitabine and Bexarotene (GemBex) in the treatment of cutaneous T-cell lymphoma

Summary

EudraCT number	2006-000591-33
Trial protocol	GB
Global end of trial date	23 January 2014

Results information

Result version number	v1 (current)
This version publication date	22 October 2017
First version publication date	22 October 2017

Trial information

Trial identification

Sponsor protocol code	UCL/06/009
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Additional study identifiers

ISRCTN number	ISRCTN18563749
ClinicalTrials.gov id (NCT number)	NCT00660231
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	JRO, University College London
Sponsor organisation address	Joint Research Office, Gower Street, London, United Kingdom, WC1E 6BT
Public contact	Public contact, CRUK and UCL Cancer Trials Centre, ctc.sponsor@ucl.ac.uk
Scientific contact	Scientific contact, CRUK and UCL Cancer Trials Centre, ctc.sponsor@ucl.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	17 October 2013
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	23 January 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary research question is to confirm the feasibility and efficacy of using a combination of Gemcitabine and Bexarotene for the treatment of cutaneous T-cell lymphoma (CTCL) in patients who have disease that is no longer controlled by skin-directed therapy and who have had at least one prior systemic therapy.

Protection of trial subjects:

The risks to the safety of the participants were those generally associated with chemotherapy treatment, including nausea, alopecia, myelotoxicity and potential cardiotoxicity with high dosage. Adverse events were monitored throughout treatment and for 30 days post treatment.

Bexarotene is also associated with lipid abnormalities; therefore patients were started on lipid-lowering therapy one week prior to the initiation of Bexarotene therapy and periodic monitoring was mandated to ensure lipid levels were adequate for patients to continue treatment. A corresponding schedule of permitted dose modifications was also provided with the aim of stabilizing lipid levels. Patients were asked to abstain from or minimise alcohol consumption during the course of treatment and to ensure they remained well-hydrated with a view to avoiding pancreatitis; which is an uncommon consequence of hyperlipidaemia.

Women who could become pregnant were informed that they must use two effective forms of contraception during the course of the study and for at least six months after stopping treatment; and male patients were informed that they must use barrier contraception throughout and for six months after stopping treatment; because treatment might interfere with normal functioning of the female egg or male sperm.

Background therapy:

Prophylactic oral fenofibrate 160mg – 200mg daily for 7 days before commencing cycle 1.

Evidence for comparator:

N/A

Actual start date of recruitment	29 July 2008
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: 36
Worldwide total number of subjects	36
EEA total number of subjects	36

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)	19
From 65 to 84 years	17
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

First patient recruited: 29/07/2008

Last patient recruited: 25/03/2011

Recruiting sites: Christie Hospital, Guys and St. Thomas' Hospital, Leicester Royal Infirmary, Nottingham City Hospital, Royal Bournemouth General Hospital, St James's University Hospital, Royal Liverpool University Hospital, Royal Cornwall Hospital, St Bartholomew's Hospital

Pre-assignment

Screening details:

Patients were screened for eligibility for inclusion 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	GemBex
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Arm description:

Four cycles of Gemcitabine 1000 mg/m² (at days 1 and 8 of 21 day cycles)

Bexarotene 300 mg/m² daily concurrently

At 12 weeks responding patients maintained on Bexarotene 300 mg/m² until disease progression or until the drug could no longer be tolerated

NB: One patient was registered but found to be ineligible and did not commence trial treatment.

Arm type	Experimental
Investigational medicinal product name	Gemcitabine Hydrochloride
Investigational medicinal product code	L01BC05
Other name	
Pharmaceutical forms	Powder for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

1000 mg/m² intravenously on day 1 and day 8 of 21 day cycles for a maximum of four cycles.

Investigational medicinal product name	Bexarotene
Investigational medicinal product code	L01XX25
Other name	
Pharmaceutical forms	Capsule, soft
Routes of administration	Oral use

Dosage and administration details:

Given for 14 days orally at 150mg/m² orally. If tolerated, increased to 300mg/m² orally daily from days 15-84.

At 12 weeks responding patients maintained on 300mg/m² orally daily until PD or until Bexarotene can no longer be tolerated.

Number of subjects in period 1	GemBex
Started	36
Completed	35
Not completed	1
Patient ineligible; did not start trial treatment	1

Baseline characteristics

Reporting groups

Reporting group title	Overall trial (overall period)
Reporting group description:	
<ul style="list-style-type: none"> - Aged ≥ 18 years - Histologically confirmed diagnosis of CTCL, including mycosis fungoides and Sézary syndrome - CTCL stages Ib, IIa, IIb, III, IVa and IVb. - Failed standard skin-directed therapy and have had at least one course of prior systemic therapy, to which they have either failed to respond or have subsequently progressed - Bexarotene naïve or previous response to single-agent bexarotene, but ≥3 months since last treatment - No treatment for lymphoma in the 4 weeks prior to study entry (except patients on stable low dose steroids; local radiotherapy allowed until 2 weeks prior to study entry) - Life expectancy > 6 months - Written informed consent - ECOG performance status 0-1 - Adequate bone marrow, hepatic & pancreatic function - HIV negative - Not pregnant or breastfeeding - No coexistent or prior malignancy in 5 years prior to study entry 	

Reporting group values	Overall trial (overall period)	Total	
Number of subjects	36	36	
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)	19	19	
From 65-84 years	17	17	
85 years and over	0	0	
Age continuous			
Units: years			
median	65		
full range (min-max)	38 to 83	-	
Gender categorical			
Units: Subjects			
Female	11	11	
Male	25	25	
ECOG performance status			
Units: Subjects			
ECOG 0	20	20	
ECOG 1	16	16	
Clinical stage at study entry			
Units: Subjects			
Ib	5	5	
IIa	2	2	

I Ib	8	8	
III	8	8	
IVa	13	13	
T skin			
Units: Subjects			
T1	1	1	
T2	7	7	
T3	11	11	
T4	17	17	
N lymph nodes			
Units: Subjects			
N0	14	14	
N1	9	9	
N2	2	2	
N3	11	11	
B peripheral blood			
Units: Subjects			
B0	18	18	
B1	17	17	
Missing	1	1	
M visceral organ involvement			
Units: Subjects			
M0	36	36	
M1	0	0	
Lymphadenopathy			
Units: Subjects			
No	12	12	
Yes	24	24	
Erythrodermic			
Units: Subjects			
No	19	19	
Yes	17	17	
Pruritus			
0-10 continuous scale			
Units: unit(s)			
median	7.5		
full range (min-max)	0 to 10	-	
mSWAT score			
Modified Severity Weighted Assessment Tool (mSWAT) for Mycosis Fungoides and Sezary Syndrome			
Units: unit(s)			
median	103		
full range (min-max)	13 to 203	-	

End points

End points reporting groups

Reporting group title	GemBex
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Reporting group description:

Four cycles of Gemcitabine 1000 mg/m² (at days 1 and 8 of 21 day cycles)

Bexarotene 300 mg/m² daily concurrently

At 12 weeks responding patients maintained on Bexarotene 300 mg/m² until disease progression or until the drug could no longer be tolerated

NB: One patient was registered but found to be ineligible and did not commence trial treatment.

Primary: Objective Response Rate

End point title	Objective Response Rate ^[1]
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End point description:

Objective Primary Disease Response Evaluation Criteria (OPDREC) combines the disease response observed in skin, lymph nodes, viscera and blood to a global disease response category. To be defined as CCR, CR or PR, the response must be confirmed with a repeat assessment at least 1 month after the initial assessment.

End point type	Primary
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End point timeframe:

The rate of objective response was assessed at 24 weeks, defined as the proportion of patients with confirmed CR, clinical complete response (CCR) or PR, as determined by OPDREC.

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: Justification: As advised on 23/06/16 by Chersoni Raffaella from the EMA service desk, we can post the result without specifying details of the statistical analyses done because the system currently cannot accommodate one arm studies.

End point values	GemBex			
Subject group type	Reporting group			
Number of subjects analysed	35 ^[2]			
Units: Patients				
Confirmed Complete Response (CR)	0			
Clinical Complete Response (CCR)	0			
Partial Response (PR)	5			
Stable Disease (SD)	8			
Progressive Disease (PD)	19			
Not Evaluable (NE)	3			

Notes:

[2] - All subjects were analysed with only 5 subjects reaching the end point definition

Statistical analyses

No statistical analyses for this end point

Secondary: Reduction change from baseline in mSWAT score

End point title	Reduction change from baseline in mSWAT score
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End point description:

Within 2 weeks of starting treatment, during the initial 12-week combination and subsequently at weeks 13, 17, and 24, and every 8 weeks thereafter, patients underwent various assessments including disease assessment using the modified Severity-Weighted Assessment Tool (mSWAT) score that represents the product of the percentage Total Body Surface Area (%TBSA) involvement of each lesion type multiplied by a weighting factor.

The Change from baseline in mSWAT score is defined as the difference in mSWAT score at the assessment time point and the score at baseline. A reduction in mSWAT at week 12 was observed in this group of patients. the data shows the number of patients with reduced mSWAT scores.

End point type	Secondary
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End point timeframe:

The modified Severity-Weighted Assessment Tool (mSWAT) scores used for this end point are those assessed at baseline and at week 12, end of combination treatment

End point values	GemBex			
Subject group type	Reporting group			
Number of subjects analysed	35			
Units: Patients	28			

Statistical analyses

No statistical analyses for this end point

Secondary: Median Progression Free Survival

End point title	Median Progression Free Survival
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End point description:

Out of the 35 patients that were analysed, 30 had either died (n=15) or were alive with progression (n=15)

End point type	Secondary
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End point timeframe:

Progression free survival (PFS) defined as the time from the first date of treatment to the date of first progression or death due to any cause, whichever one comes first.

End point values	GemBex			
Subject group type	Reporting group			
Number of subjects analysed	35			
Units: months				
median (full range (min-max))	5.3 (0 to 21)			

Statistical analyses

No statistical analyses for this end point

Secondary: Median Overall Survival

End point title	Median Overall Survival
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End point description:

End point type	Secondary
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End point timeframe:

Overall Survival (OS) defined as the time from the first date of treatment to the date of death due to any cause.

End point values	GemBex			
Subject group type	Reporting group			
Number of subjects analysed	35			
Units: months				
median (full range (min-max))	21.2 (0 to 35)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

All adverse events that occurred between informed consent and 28 days post last trial treatment administration had to be reported

Adverse event reporting additional description:

Trial subjects were assessed for adverse events prior the start of each treatment cycle. All adverse events (AEs) were recorded in the patient notes and the trial CRFs. Those meeting the definition of SAEs were also reported using the trial specific SAE Reporting template.

Assessment type	Systematic
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Dictionary used

Dictionary name	NCI - CTCAE
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Dictionary version	3.0
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Reporting groups

Reporting group title	GemBex
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Reporting group description:

Four cycles of Gemcitabine 1000 mg/m² (at days 1 and 8 of 21 day cycles)

Bexarotene 300 mg/m² daily concurrently

At 12 weeks responding patients maintained on Bexarotene 300 mg/m² until disease progression or until the drug could no longer be tolerated

NB: One patient was registered but found to be ineligible and did not commence trial treatment.

Serious adverse events	GemBex		
Total subjects affected by serious adverse events			
subjects affected / exposed	13 / 35 (37.14%)		
number of deaths (all causes)	15		
number of deaths resulting from adverse events	2		
Investigations			
Creatinine Increased			
subjects affected / exposed	1 / 35 (2.86%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Tumour pain			
subjects affected / exposed	1 / 35 (2.86%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Confusion			

subjects affected / exposed	1 / 35 (2.86%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Syncope			
subjects affected / exposed	1 / 35 (2.86%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	1 / 35 (2.86%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Fever			
subjects affected / exposed	2 / 35 (5.71%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Febrile neutropenia			
subjects affected / exposed	1 / 35 (2.86%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	1 / 35 (2.86%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Obstruction, GI			
subjects affected / exposed	1 / 35 (2.86%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Obstruction, Small bowel NOS			
subjects affected / exposed	1 / 35 (2.86%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		

Renal and urinary disorders			
Renal failure			
subjects affected / exposed	1 / 35 (2.86%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Infection			
subjects affected / exposed	3 / 35 (8.57%)		
occurrences causally related to treatment / all	3 / 3		
deaths causally related to treatment / all	0 / 1		
Lung infection			
subjects affected / exposed	1 / 35 (2.86%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Metabolism and nutrition disorders			
Hypertriglyceridaemia			
subjects affected / exposed	2 / 35 (5.71%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	GemBex		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	35 / 35 (100.00%)		
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	21 / 35 (60.00%)		
occurrences (all)	21		
Pyrexia			
subjects affected / exposed	8 / 35 (22.86%)		
occurrences (all)	8		
Chills			
subjects affected / exposed	4 / 35 (11.43%)		
occurrences (all)	4		
Pain			

subjects affected / exposed occurrences (all)	3 / 35 (8.57%) 3		
Respiratory, thoracic and mediastinal disorders Dyspnoea subjects affected / exposed occurrences (all)	6 / 35 (17.14%) 6		
Psychiatric disorders Insomnia subjects affected / exposed occurrences (all)	6 / 35 (17.14%) 6		
Investigations Alanine aminotransferase increased subjects affected / exposed occurrences (all) Aspartate aminotransferase increased subjects affected / exposed occurrences (all) White blood cell count decreased subjects affected / exposed occurrences (all) Neutrophil count decreased subjects affected / exposed occurrences (all) weight loss subjects affected / exposed occurrences (all)	5 / 35 (14.29%) 5 4 / 35 (11.43%) 4 18 / 35 (51.43%) 18 23 / 35 (65.71%) 23 2 / 35 (5.71%) 2		
Cardiac disorders cardiac disorders other, cardiac subjects affected / exposed occurrences (all)	2 / 35 (5.71%) 2		
Nervous system disorders Dizziness subjects affected / exposed occurrences (all) Headache	4 / 35 (11.43%) 4		

subjects affected / exposed occurrences (all)	4 / 35 (11.43%) 4		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	26 / 35 (74.29%)		
occurrences (all)	26		
Oedema			
subjects affected / exposed	9 / 35 (25.71%)		
occurrences (all)	9		
Platelet count decreased			
subjects affected / exposed	8 / 35 (22.86%)		
occurrences (all)	8		
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	6 / 35 (17.14%)		
occurrences (all)	6		
Diarrhoea			
subjects affected / exposed	4 / 35 (11.43%)		
occurrences (all)	4		
Dry mouth			
subjects affected / exposed	6 / 35 (17.14%)		
occurrences (all)	6		
Nausea			
subjects affected / exposed	11 / 35 (31.43%)		
occurrences (all)	11		
Vomiting			
subjects affected / exposed	3 / 35 (8.57%)		
occurrences (all)	3		
Skin and subcutaneous tissue disorders			
Dry skin			
subjects affected / exposed	3 / 35 (8.57%)		
occurrences (all)	3		
Pruritus			
subjects affected / exposed	21 / 35 (60.00%)		
occurrences (all)	21		
Alopecia			

subjects affected / exposed occurrences (all)	6 / 35 (17.14%) 6		
Rash subjects affected / exposed occurrences (all)	7 / 35 (20.00%) 7		
Pigmentation disorder subjects affected / exposed occurrences (all)	2 / 35 (5.71%) 2		
Nail disorder subjects affected / exposed occurrences (all)	2 / 35 (5.71%) 2		
Pain of skin subjects affected / exposed occurrences (all)	2 / 35 (5.71%) 2		
Endocrine disorders Hypothyroidism subjects affected / exposed occurrences (all)	21 / 35 (60.00%) 21		
Musculoskeletal and connective tissue disorders Pain, other - aching muscles and joints subjects affected / exposed occurrences (all)	10 / 35 (28.57%) 10		
Bone pain subjects affected / exposed occurrences (all)	2 / 35 (5.71%) 2		
Arthralgia subjects affected / exposed occurrences (all)	2 / 35 (5.71%) 2		
Myalgia subjects affected / exposed occurrences (all)	3 / 35 (8.57%) 3		
Infections and infestations Infection subjects affected / exposed occurrences (all)	9 / 35 (25.71%) 9		
Metabolism and nutrition disorders			

Cholesterol, serum-High subjects affected / exposed occurrences (all)	21 / 35 (60.00%) 21		
Hypertriglyceridaemia subjects affected / exposed occurrences (all)	4 / 35 (11.43%) 4		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
14 February 2007	The protocol was amended to use a more appropriate method of skin disease assessment known as the Severity Weighted Assessment Tool (SWAT). A Quality of Life Assessment was also added to the study as it is felt that Cutaneous T-Cell Lymphoma has a substantial impact on the quality of life of these patients due to the very nature of the disease.
10 August 2007	<p>The address of where to send histology specimens was changed in the protocol. Changes were also made to the PIS, Consent form and an additional appendix (addition of skindex).</p> <p>The PIS was updated with additional information regarding patient anonymity when taking photographs of the disease and also included information on the use of photos for publication with consent, a statement was included asking for patient permission. Appendix 8 was been added to incorporate a QOL element to the study given the disease and the impact it's 'visibility' can have on a patients physical and/or psychological wellbeing.</p>
20 December 2007	<p>Several changes were made to the protocol to assist site staff with various aspects of the study including:</p> <ol style="list-style-type: none">1. The assessment of patients using the Severity-Weighted Assessment Tool (SWAT) - Appendix 14 provided sites with a guide to skin scoring patients using SWAT2. The updated guidelines for the management of patients who experienced hyperlipidamia prior and during Bexarotene therapy was added to section 6.33. The Safety Reporting section of the protocol was amended to provide sites with comprehensive information regarding the current regulatory requirements that were in place and how adverse events should have been assessed and reported. Two additional appendices were also added which detailed the expected adverse events that arose from treatment with Gemcitabine and Bexarotene. This information was compiled from the Summary of Product Characteristics available for both drugs. Information on Pregnancy was also added.
03 December 2008	Patient diary cards were introduced allowing clinicians give written instructions to the patient about the dose of bexarotene that they should take each day, and also to allow patients to record whether the full dose was taken each day.

21 July 2009	<p>Following the start of the trial, Bexarotene had become more widely used in standard clinical practise, including prolonged maintenance, therefore it was decided to bring the trial in line with standard clinical practice in terms of the duration of maintenance, and also in allowing patients previously treated with single agent Bexarotene to be entered into the trial. Various other practical issues arising from the first year of recruitment into the trial were also addressed.</p> <ul style="list-style-type: none"> o Bexarotene maintenance no longer stopped at week 20, but continued until the patient either had disease progression, or could no longer tolerate bexarotene o Bone marrow aspirates /trephines and baseline chest x-ray were no longer required for the purposes of the trial o CT scan was only required at end of chemo and maintenance if patient had an abnormal CT scan at baseline o Photography requirements significantly reduced to baseline, end of combination chemo, week 24 and disease progression o Rules governing concomitant use of steroids changed so patients on a stable, low dose of steroids were allowed to enter the trial
23 June 2010	<p>An audit of the patient information sheet (PIS) showed that contraception guidelines given to patients in the PIS was not accurate thus leading to an Urgent Safety Measure being taken.</p> <p>The Patient information sheet was updated advising patients to use adequate contraception during the duration of the study and for at least 6 months after stopping trial treatment (as suggested in the SmPC for Gemcitabine, which is one of the trial drugs for the study).</p> <p>A paragraph justifying the need of using contraception and listing examples of reliable forms of contraception was also added.</p> <p>The PIS was further modified to emphasise that the study doctor should be notified also in cases where a male trial patient's partner became pregnant.</p>
02 February 2011	<p>The Bexarotene labels were amended to comply with Annexe 13 and labelling exemption for Gemcitabine was proposed as it was provided from hospital stock. The sponsor believed it fell under the remit of Regulation 46(2) of the Medicines for Human Use (Clinical Trials) Regulations</p>

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

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

Non serious AEs: 'occurrences all number' cannot be given as only highest grade experienced by patients were collected on CRFs; Subjects affected number is entered instead.
 Serious and non-serious AEs are listed under non-serious adverse events

Notes:

Online references

<http://www.ncbi.nlm.nih.gov/pubmed/24136145>