GemBex

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

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Authorised by:

Name: Professor Tim Illidge Role: Chief Investigator
Signature Date: 09.07.09

Name: Professor Jonathan Ledermann Role: Representative of the Sponsor
Signature 10 July 2009

General Information

This document describes the *GemBex* trial and provides information about procedures for entering patients into it. The protocol should not be used as an aide-memoire or guide for the treatment of other patients; every care was taken in its drafting, but corrections or amendments may be necessary. These will be circulated to the registered investigators in the trial, but centres entering patients for the first time are advised to contact the Haematology Trials Group, CR-UK & UCL Cancer Trials Centre, London to confirm they have the most up to date version. Clinical problems relating to this trial should be referred to the relevant Chief Investigator.

- **Compliance**
  The study will be conducted in compliance with the protocol, GCP, EU Directive 2001, Data Protection Act (UCL data protection reference Z6364106/2006/3/36), NHS Research Governance and other regulatory requirements as appropriate.
- **Sponsor**
  University College London
- **Authorisation**
  Professor Tim Illidge (Chief Investigator); Professor Jonathan Ledermann (Sponsor's Representative)

Main Contacts

- **Medical expert and Chief Investigator**
  Professor Tim Illidge
  Consultant Oncologist
  Christie Hospital NHS Trust
  Wilmslow Road, Manchester, M20 4BX

- **Trial Management Group**
  Dr Sean Whittaker
  Consultant Dermatologist
  St. Thomas' Hospital
  Lambeth Palace Road, London, SE1 7EH

  Dr Richard Cowan
  Consultant Clinical Oncologist
  Christie Hospital NHS Trust
  Wilmslow Road, Manchester M20 4BX

  Dr. Julia Scarisbrick
  Consultant Dermatologist
  St. Thomas' Hospital
  Lambeth Palace Road, London, SE1 7EH

  Dr Dianne Gilson
  Consultant Clinical Oncologist
  St James' University Hospital
  Beckett Street, Leeds LS9 7TF

- **Trial Management**
  Haematology Trials Group (6th Floor)
  Cancer Research UK and UCL Cancer Trials Centre
  90 Tottenham Court Road, London, W1T 4TJ

- **Trial statistician**
  Wendi Qian
  Medical Statistician
  MRC Clinical Trial Unit
  222 Euston Road, London, NW1 2DA

	REGISTRATIONS	
	Tel: 020 7679 9860 (Mon - Fri, 09:00 – 17:00)	
	Fax: 020 7679 9861	

CONTENTS

LIST OF TABLES

LIST OF FIGURES

APPENDICES

ABBREVIATIONS AND GLOSSARY

Table 1: Abbreviations and Glossary

Abbreviation	Term
ADR	Adriamycin
ALP	Alkaline phosphatase
ALT	Alanine transaminase
ANC	Absolute neutrophil count
ASCO	American Society of Clinical Oncology
AST	Aspartate transaminase
AUC	Area under the curve
Bpm	Beats per minute
BSA	Body surface area
BUN	Blood urea nitrogen
CBC	Complete blood count
CCR	Complete clinical response
CIN	Cervical intraepithelial neoplasm
CK	Creatine kinase
C_{max}	Maximum concentration of drug
CPK	Creatinine phosphokinase
CR	Complete response
CRA	Clinical research associate
CRF	Case report form
C_{ss}	Steady-state concentration
CT	Computed tomography
CTCAE	Common terminology criteria for adverse events
CTCL	Cutaneous T-cell lymphoma
CV	Curriculum vitae
DLT	Dose limiting toxicity
DMC	Data Monitoring Committee
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EDTA	Ethylenediamine tetraacetic acid
EPOCH	A chemotherapy regimen of: etoposide, prednisone, vincristine (Oncovin), cyclophosphamide, doxorubicin (hydroxyadriamycin)
FACS	Fluorescence Activated Cell Sorting
FBC	Full blood count
FDA	Food and Drug Agency
GCP	Good Clinical Practice
HCT	Haematocrit
HGB	Haemoglobin
HIV	Human immunodeficiency virus
ICAF	Informed Consent /Authorisation Form
ICH	International Conference on Harmonisation
IDB	Investigator's Drug Brochure
IEC	Independent Ethics Committee
IUCD	Intrauterine contraceptive device
i.p.	Intraperitoneally
i.v.	Intravenous
LD	Longest diameter
LDH	Lactate dehydrogenase

Abbreviation	Term
LFT	Liver function test
LHRH	Luteinizing hormone-releasing hormone
LVEF	Left ventricular ejection fraction
MedDRA	Medical Dictionary for Regulatory Activities
MRI	Magnetic resonance imaging
MTD	Maximum tolerated dose
MUGA	Multiple gated acquisition
NCI	National Cancer Institute
OPDREC	Objective Primary Disease Response Evaluation Criteria (protocol-defined)
PBMC	Peripheral blood mononuclear cells
PD	Progressive disease
PLT	Platelet count
PPK	Population pharmacokinetics
PR	Partial response
PUVA	Psoralen plus ultraviolet A
PTCL	Peripheral T-cell lymphoma
RBC	Red blood cell
RECIST	Response Evaluation Criteria in Solid Tumours
SAE	Serious adverse event
SC	Subcutaneously
SCID	Severe combined immunodeficiency disease
SD	Stable disease, standard deviation
SGOT	Serum glutamic oxaloacetic transaminase
SGPT	Serum glutamic pyruvic transaminase
SVT	Supraventricular tachycardia
T4	Thyroxine
TFT	Thyroid function test
TSH	Thyroid stimulating hormone
U&E	Urea & electrolytes
UCL CTC	Cancer Research UK & UCL Cancer Trials Centre
ULN	Upper limit of normal
VAS	Visual analogue scale
VCR	Vincristine
WBC	White blood cell
WHO	World Health Organisation

1. SUMMARY

1.1 Lay summary

Peripheral and cutaneous T-cell lymphoma accounts for 5-10% of all malignant lymphomas in western countries[1]. Gemcitabine is a chemotherapy drug frequently used amongst the oncology community in the UK. It has been found to be well tolerated with minimal toxicity but with good response rates in the treatment of solid tumours including lung, pancreas, breast, ovary and bladder cancer. Bexarotene is a novel tablet based chemotherapy drug that has proved to be highly effective in the treatment of relapsed or refractory cutaneous T-cell lymphoma. The results from these early stage clinical studies led to the US and EU regulatory authorities granting approval for the drug in the treatment of cutaneous T-cell lymphoma (CTCL) that has relapsed after skin directed therapies. Bexarotene forms an important drug for relapsed CTCL and is now routinely used in regional centres of expertise across the UK. Further data regarding expected responses, time to response and duration of response have become available in the post licensing era and expert recommendations on the optimal use recommend continued maintenance of the drug in responding patients. In summary both Bexarotene and Gemcitabine have demonstrated encouraging responses as single agents in clinical trials and in clinical practice. This study aims to confirm the feasibility and efficacy of using a combination of Gemcitabine and Bexarotene for the treatment of cutaneous T-cell lymphoma in patients who have disease that is no longer controlled by skin-directed therapy and who have had at least one prior systemic therapy.

The study will also assess whether the combination of Gemcitabine and Bexarotene leads to an improvement in patient assessed Quality of Life (QoL). The study will examine whether there is a correlation between clinical response and an improvement in QoL and also determine the effect on QoL in all patients receiving this combination therapy.

1.2 Abstract and summary of trial design

Type of design

This is a phase II, non-randomised, open-label, single arm trial that will be conducted throughout the UK. This study is designed on the basis of objective disease control (CR, CCR and PR, and SD for 6 months) and objective disease response (CR, CCR and PR) and its duration as the measures of efficacy, in patients who have received at least two cycles of therapy.

Disease / patients studied

The study will recruit patients with histologically confirmed cutaneous T-cell lymphoma (CTCL) including its variants e.g. mycosis fungoides and Sézary syndrome. Patients must have developed progressive disease after receiving, or have been refractory to, standard skin-directed therapy and at least one prior systemic therapy.

For more details refer to Section 4.

Trial interventions and study duration

Patients will receive Gemcitabine 1000 mg/m^2 d1, 8, for 4 cycles each of 21 days duration, for a total duration of 12 weeks during which Bexarotene 300 mg/m^2 daily will be administered concurrently. At 12 weeks responding patients will be maintained on Bexarotene 300 mg/m^2 until disease progression or until the patient ceases to tolerate the drug. Cephalon Pharmaceuticals will provide a total of 20 weeks' worth of Bexarotene at 50% cost for each patient. Any toxicity from a prior cycle must have improved to at least grade 1 (NCI Common Terminology Criteria for Adverse Events v.3 [CTCAE]) or baseline value prior to the start of each treatment unless otherwise indicated. Dose reductions may be performed due to toxicity. Only one dose reduction is allowed and, if further toxicity occurs, the patient must be withdrawn. For more details refer to Section 6.

Outcome measures (endpoints)

Primary Outcome

- To confirm the feasibility and efficacy of the combination of Bexarotene and Gemcitabine in patients with CTCL whose disease is no longer controlled on skin-directed therapy and who have had at least one prior systemic therapy.

Secondary Outcomes

- To evaluate the rate of objective disease control.
- To evaluate duration and durability of objective disease response, and time to objective disease progression.
- To evaluate the safety of Bexarotene and Gemcitabine in terms of adverse events, clinical laboratory data, physical examinations, rate of neutropenic fever and sepsis, blood transfusions, and treatment compliance.
- To measure changes in patient-assessed Quality of Life (QoL).

Data recorded directly on Case Report Forms (CRF)

Data will be recorded on the Case Report Forms, where the original wet ink copy should be sent to the Haematology Trials Group at the CR-UK and UCL Cancer Trials Centre and a copy should remain at site in a designated patient trial file. The type of data to be recorded is detailed in the Assessments and Procedures Section 7.

2. BACKGROUND

2.1 Introduction

Peripheral T-cell and cutaneous T-cell lymphomas account for between 5 and 10% of all malignant lymphomas in western countries[1]. The estimated incidence rate of cutaneous T-cell lymphoma (CTCL) in the US is stable at 0.4 per 100000 person-years[2] and a similar rate is likely in Europe.

A variety of single agent and combination chemotherapy regimens have been reported in small patient groups in CTCL and although high overall response rates have been reported the duration of response is short. Zackheim and Epstein reported an overall response rate of 76% and a 5-year survival of 71% in a group of 17 patients who received weekly, low dose methotrexate[3]. The intravenous use of the purine analogues (2-deoxycoformycin (pentostatin), 2-chlorodeoxyadenosine and fludarabine) has achieved complete response (CR) rates of up to 33%[4]. Pentostatin has demonstrated an overall response rate of 71%, and a complete response rate of 25%, in a group of 28 heavily pre-treated patients with MF/SS or peripheral T cell lymphomas with prominent cutaneous disease[5]. Doxorubicin has been shown to be active but not curative in the treatment of advanced CTCL. However a side-effect profile, which includes alopecia, myelotoxicity and the potential for cardiotoxicity at higher cumulative doses means its widespread use in a palliative setting has been limited. The liposomal formulations of this anthracycline are being studied in this disease, and appear to show high response rates and reduced cardiac toxicity[6]. Pegylated liposomal doxorubicin has been shown to have significant activity in advanced MF. In a study reported by Kim, 9 out of 10 patients responded with a median time to progression of 15 months[7]. Denileukin diftitox (DAB389IL-2) has also been shown to be active in cutaneous T cell lymphoma. Saleh et al showed an objective response rate of 37% and CR rate of 14%[8].

Gemcitabine (2'2'-deifluorodeoxycyitidine) is a novel pyrimidine anti-metabolite with demonstrable efficacy, a low toxicity profile and widespread usage in a number of solid tumours including lung, bladder, pancreas, breast and ovary. A small Phase II study confirmed high activity in pre-treated CTCL, with 70% response rates (PR 60%, CR 10% n=30)[9]. This promising data has led many haemato-oncologists across the world to prescribe Gemcitabine in routine clinical practice, in the absence of any additional published data to confirm these high response rates. Furthermore the disease assessment has been

criticised in this study and this has led to the requirement for further multi-centre clinical studies with robust disease assessment involving Gemcitabine.

Bexarotene is a synthetic retinoid ligand for the retinoid X receptor (RXR) that in the "pivotal" studies demonstrated in relapsed or refractory CTCL a response rate of ~45%[10,11]. These encouraging results were achieved in patients that were "refractory" to therapy, defined as resistance to therapy due to lack of at least 50% improvement or progression of disease on therapy after an initial response. The initial responses to Bexarotene are often slow with around a 12% response rate within the first 4 weeks in the pivotal study but with the majority of responses seen by 16 weeks. The duration of responses in the phase II and III studies compared very favourably with cytotoxic chemotherapy and the median time to relapse 43 weeks. This data led to the US and EU regulatory authorities granting approval for Bexarotene in the treatment of cutaneous T-cell lymphoma (CTCL) that has relapsed after skin directed therapies. Bexarotene has become established as an important drug for relapsed CTCL and is now routinely used in regional centres of expertise across the UK. Further data regarding expected responses, time to response and duration of response has become available in the post licensing era and with that recommendations on the optimal use[24, 25]. Bexarotene may take between 12 – 16 weeks to achieve a maximum response and in patients responding to and tolerating this therapy, the recommended clinical practice is to continue it maintenance of the drug until the disease becomes refractory or the patient is no longer tolerating this[24, 25].

The slow initial responses seen with Bexarotene contrast with the more rapid responses seen with Gemcitabine making this combination of drugs suitable for the majority of patients with CTCL, including those where rapid disease control is paramount that may be excluded from having Bexarotene.

More recently data is beginning to emerge combining Bexarotene with Interferon and Denileukin diftitox in small numbers of patients in single institution studies from the US. Bexarotene and the combination of Bexarotene and Interferon-α showed the same response rates as Bexarotene alone Strauss et al[23] a small Phase I study including 14 patients using the combination of Bexarotene and denlileukin diftitox reported a response rate of 67%[12]. There are currently no national or international studies looking at combination therapy involving Bexarotene in CTCL. There is an urgent need to further investigate Gemcitabine in CTCL and the aim of this study is to assess the feasibility and efficacy of the combination of

Gemcitabine and Bexarotene. Therefore an improved response rate, an improved time to best response (achieving rapid disease control) and an increased duration of response will thus define improvements over Bexarotene alone and be the basis of a subsequent randomised study.

Demierre and colleagues have demonstrated that CTCL has significant impact on the quality of life of patients[21]. Sixty-six percent of patients reported that their disease made them tired while the same proportion also experienced difficulty sleeping. The majority of patients also experienced a psychosocial impact from their disease in particular depression, frustration, anger and embarrassment. Demierre et al[21] concluded that "in light of the serious impact of CTCL on patients' emotional well being, HRQOL assessment should be incorporated as a routine part of the evaluation of patients with CTCL and of their enrollment in clinical trials." It is possible that effects on quality of life could be independent of therapeutic response, whereby QoL could improve in patients with no objective clinical response or deteriorate in patients with objective clinical responses. Therefore a critical part of the evaluation of this study will be a thorough assessment of patients QoL in addition to the measurement of objective clinical responses.

2.2 Population

The study will recruit male and female patients with histologically confirmed cutaneous T-cell lymphoma (CTCL) including its variants e.g. mycosis fungoides and Sézary syndrome. Patients must have developed progressive disease after receiving, or have been refractory to, standard skin-directed therapy and at least one prior systemic therapy.
For more details refer to Section 4.

Investigational product / intervention(s)

Gemcitabine (2'2'-deifluorodeoxycyitidine) is a novel pyrimidine anti-metabolite with demonstrable efficacy, a low toxicity profile and widespread usage in a number of solid tumours including lung, bladder, pancreas, breast and ovary. A small Phase II study confirmed high activity in pre-treated CTCL, with 70% response rates (PR 60%, CR 10% n=30)[9].

More recent novel approaches have included Bexarotene which is a synthetic retinoid ligand for the retinoid X receptor (RXR) and has been shown to be a highly active agent in the

treatment of relapsed or refractory CTCL with a response rate of ~ 45%[10, 11]. These encouraging results have led to US FDA and more recently EU approval for the drug in the treatment of CTCL that has relapsed after skin directed therapies.

2.3 Rationale and objectives

Based on the published results of the efficacy and safety of both Gemcitabine and Bexarotene it is apparent that have both have demonstrable activity, with distinct mechanisms of action and potentially non-overlapping toxicity. It is therefore logical to combine the two agents and to use Bexarotene to consolidate the response in responders.
The formal list of outcome measures is presented in Section 9.3 .

2.4 Relevant studies / trials

The Cochrane Collaboration has not performed a systematic review. A search of the NCI PDQ trials database has not revealed any ongoing trials or closed trials similar to this proposed trial. No similar trials have been found on the IRCP website. A search on PubMed using the keywords cutaneous lymphoma, Bexarotene and Gemcitabine produced one result, which was a review article.

2.5 Risks and benefits

The risks to the safety of the participants are those associated with all chemotherapy treatment, including nausea, alopecia, myelotoxicity and potential cardiotoxicity with high dosage. However both Bexarotene and Gemcitabine are thought to demonstrate reduced cardiotoxicity but increased response rates compared to their doxorubicin counterparts.
In addition Bexarotene is associated with lipid abnormalities. These are usually manageable with a combination of careful monitoring, lipid lowering drugs, and if necessary, reduction or interruption of the Bexarotene dose. The hyperlipaemia is also generally reversible when the Bexarotene capsules are stopped so lipid lowering drugs can be stopped at the same time.

All patients who receive at least one dose of Gemcitabine and Bexarotene will be assessed for toxicity. Patients will be monitored for adverse events during trial treatment and until 30 days after the last dose of trial treatment or until all toxicities have resolved. Any abnormal haematology or biochemistry laboratory value, which the investigator considers may have a significant clinical impact on the welfare of the patient, should also be recorded as an adverse event. Adverse events will be graded according to the NCI CTCAE v.3.0 (see

http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/ctcaev3.pdf) and recorded on CRFs.

Complete details of reporting adverse events, including the definition of drug-related adverse events, are given in Section 10.

2.6 Assessment of skin disease

Accurate measurement of disease burden and any changes resulting from treatment are an essential part of clinical trials. The standard methods for assessing response in lymphoma are primarily based on measuring changes in the size of involved lymph nodes. These methods are inappropriate for evaluating disease burden in CTCL where most of the disease is in the skin.

A number of methods have been used for evaluating CTCL and these include

i. Physicians Global Assessment (PGA) of disease on a 0-3 scale where 0=no disease, 1=mild disease, 2=moderate disease and 3=severe disease.
ii. Percentage total body surface area (%TBSA) involved with disease to be evaluated using the following table

Adults	
Anatomic structure	**Surface area**
Head	9%
Anterior torso	18%
Posterior torso	18%
Each leg	18%
Each arm	9%
Genital/perineum	1%

Both of these methods have shortcomings. The PGA is a 4 point scoring system which provides little flexibility and sensitivity. %TBSA also lack sensitivity because it takes no account of the severity of the disease.

In this trial we will use the Severity-Weighted Assessment Tool (SWAT) as proposed by Stevens et al[22] to evaluate Mycosis Fungoides type CTCL. The SWAT score represents the product of the %TBSA involvement of each lesion type multiplied by a weighting factor. The tumour types and their respective weighting factors are as follows:

Patch	1
Plaque	2
Tumour or ulceration	3

This SWAT score can then be calculated according to the following formula

SWAT=(patch %TBSA x 1) + (plaque %TBSA x 2) + (tumour or ulcer %TBSA x 3)

Using this formula derives a score of 0-300 and by measuring SWAT at each visit it is possible to determine the percentage change from the baseline score and use this to measure response.

For patients with erythrodermic CTCL a modified version of the SWAT will be used where the degree of oedema or infiltration will be used to map skin severity. The following weighting will be used

Erythroderma with mild infiltration mapped as patch disease x1 erythema but no oedema or fissuring
Erythroderma with moderate infiltration mapped as plaques x2 erythema with oedema, or exudation
Erythroderma with tumourous infiltration or ulceration (including fissuring) mapped as tumors or ulceration x3 erythema with tumourous lesions or ulceration

The SWAT score for patients with erythrodermic CTCL can then be calculated using the following formula

SWAT = (mild %TBSA x 1) + (moderate %TBSA x 2) + (tumorous or ulcerative %TBSA x 3).

Please note that at least one member of the clinical team will be required to attend a SWAT training session or view the SWAT training DVD prior to opening their site to recruitment. The GemBex trial team at the UCL CTC should be contacted to obtain the SWAT training DVD if required..

Please see Appendix 10 for further information relating to the SWAT assessment of patients.

3. SELECTION OF CENTRES/CLINICIANS

Before any patients can be registered into the study, the Study Site Centre and Principal Investigator must fulfil the following criteria:

3.1 Centre/Clinician inclusion criteria

i. Registered with Haematology Trials Group, CR-UK & UCL Cancer Trials Centre

ii. Confirmation of ethics approval (site-specific assessment). For further details on ethical approval, refer to Section 11.

iii. Completed Clinical Trial Site Agreement signed by the institution Principal Investigator and designated signatories

iv. Confirmation of Research and Development approval

v. Submitted training log proving that at least one member of the clinical team has attended a SWAT training session or viewed the SWAT training DVD

4. SELECTION OF PATIENTS

4.1 Patient inclusion criteria

i. Males or non-pregnant females aged ≥18 years;

ii. Histologically confirmed diagnosis of CTCL, including mycosis fungoides and Sézary syndrome;

iii. Patients with CTCL stages Ib, IIa, IIb, III,IVa and IVb (see Appendix 2). Staging is to take place within 1 month of obtaining full written informed consent;

iv. Patients who have failed standard skin-directed therapy and have had at least 1 course of prior systemic therapy, such as interferon, chemotherapy, Denileukin diftitox (Ontak®) which they have either failed to respond to or have subsequently progressed;

v. Anticipated life expectancy greater than six months;

vi. Written informed consent to participate in the study;

vii. Bexarotene naïve or previous response to single-agent bexarotene, but ≥3 months since last treatment with bexarotene.

Patient exclusion criteria

i. ECOG Performance Status >1 (see Appendix 7);

ii. Patients who have not received at least 1 course of prior systemic therapy for CTCL;

iii. CD30 + (Ki1+ve) anaplastic large cell lymphoma;

iv. Patients who have failed previous treatment with Bexarotene (Targretin®);

v. Patients who have previously experienced a severe adverse reaction to Bexarotene;

vi. Concomitant use of any anti-cancer therapy;

vii. Concomitant use of any investigational agent;

viii. Use of any investigational agent within 4 weeks of study entry;

ix. Clinically significant active infection;

x. Known infection with human immunodeficiency virus (HIV), hepatitis B, or hepatitis C;

xi. Excessive alcohol consumption;

xii. Uncontrolled diabetes mellitus;

xiii. Biliary tract disease;

xiv. History of pancreatitis;

xv. Concomitant drug therapy with other medications that can elevate triglycerides or cause pancreatic toxicity e.g. Gemfibrozil;

xvi. Inadequate bone marrow or other organ function, as evidenced by: Unsupported haemoglobin <9.0 g/dL (transfusions and/or erythropoietin are permitted); Absolute neutrophil count (ANC) $\leq$1.5 x 10^9/L; Platelet count <100 x 10^9/L;

xvii. Total bilirubin >1.25 x upper limit of normal (ULN) for institution, aspartate transaminase/glutamic oxaloacetic transaminase (AST/SGOT) and alanine transaminase/ glutamic pyruvic transaminase (ALT/SGPT) >2.0 x ULN, serum creatinine >2 x ULN for age and sex;

xviii. Coexistent second malignancy or history of prior malignancy within previous 5 years (excluding basal or squamous cell carcinoma of the skin or cervical epithelial neoplasm [CIN1, carcinoma in situ] that has been treated curatively);

xix. Any significant medical or psychiatric condition that might prevent the patient from complying with all study procedures;

xx. Patients who are pregnant or breast-feeding (all women of child-bearing potential must use the contraceptive pill or intrauterine contraceptive device (IUCD) during the treatment period and for at least 1 month thereafter). Male patients must use a barrier method of contraception during the treatment period and for at least 1 month thereafter;

xxi. Any treatment for lymphoma, including photopheresis, within the 4 weeks prior to entering the study. For patients receiving long-term corticosteroid therapy, the dose should ideally be stopped and if this is not feasible reduced to as low as possible. If steroids cannot be stopped, patients who have been on stable doses less than or equal to 20mg for at least 3 months can be entered into the study. Local radiotherapy to isolated symptomatic tumour nodules requiring immediate treatment may be given until 2 weeks prior to entering the study;

xxii. Warfarin.

4.2 Number and source of patients

For patient numbers refer to section 9.4.

4.3 Screening procedures and pre-registration investigations

Before entering the study, patients will be evaluated to ensure that eligibility requirements are met, as specified in Section 4.1. Patients not meeting these criteria must not be entered into the study. Screening assessments must be performed within 2 weeks prior to the start of study therapy unless indicated below and the following assessments will be performed. The investigator must review the results of this screening sample before the patient is registered to ensure that the entry criteria are met. Any delay to entry must be documented on the CRF. Other screening assessments should be repeated, if possible, to comply with the appropriate time window.

- Complete medical history (all significant conditions which have previously existed and are now resolved as well as current conditions);
- Documentation of concomitant medications (including alternative medications) and medications taken in the 4 weeks prior to study entry;
- Physical examination;
- Body weight, height, and vital signs (pulse, blood pressure, temperature);
- 12 lead ECG;
- CT of chest, abdomen and pelvis within 4 weeks of study entry;
- Complete blood count (CBC) to include haemoglobin, red cell count, white cell count, haematocrit, platelet count and white cell differential;
- Peripheral blood CD4+ cell count (see also Section 4.4);
- Blood chemistry profile to include urea, creatinine, sodium, potassium, bicarbonate, ALP, AST/ALT, bilirubin, total protein, albumin, calcium, phosphate, LDH
- Urinalysis;
- Urine pregnancy test in female patients of child bearing age;
- ECOG performance status;
- Patient assessed Quality of Life measured using Skindex 29 and EORTC QLQ-C30;
- Measurement of skin disease and calculation of SWAT score;

4.4 Baseline Disease Assessment

Tumour Measurement

Patients with Mycosis Fungoides CTCL disease will be assessed using the Severity-Weighted Assessment Tool (SWAT) method of skin scoring as outlined in section 2.6. For patients with erythrodermic CTCL the modified SWAT scoring outlined in section 2.6 will be used.

Standardised Photography

Standardised photography of skin lesions at baseline and during study will be used to document skin lesions. Further details are given in Appendix 8.

Pruritus

Pruritus will be assessed using a visual analogue scale (see Appendix 5).

Biopsy specimens and central histological review

Blood All patients' peripheral blood should be examined by flow cytometry immunophenotyping using a standard T cell panel, which should include CD3, CD4 & CD8 **even when the absolute lymphocyte count, blood film and all other blood cell measurements are normal**. CD4+ count will also be evaluated. The clearing of Sézary cells in blood will be used as a measure of disease response.

Skin Histological diagnostic specimens of CTCL should be taken to confirm eligibility for the study. Wherever possible fresh skin biopsies should be obtained within 1 month prior to study entry, however, if it is not possible to obtain fresh skin biopsies, historical biopsies (obtained within 1 year prior to screening) can be used.

Nodes Lymph node biopsy is strongly recommended in all patients with palpable adenopathy (lymph nodes >1 cm) and in all patients with new adenopathy (lymph nodes >1 cm diameter) seen on CT scans done within 6 months prior to trial entry where the clinician has a high index of suspicion that this is related to lymphoma.

Histology

All histological specimens (skin lesions of all types – plaque/patch/tumour and lymph node biopsies) must be reviewed and confirmed by Dr Alistair Robson (St. Thomas' Hospital, London).

Samples should be sent to:

GemBex, Haematology Trials Group

CR-UK & UCL Cancer Trials Centre

90 Tottenham Court Road

London

W1T 4TJ

where they will be logged and forwarded to Dr. Robson.

Confirmation of diagnosis from Dr. Robson is not required prior to the start of therapy. In the event that the diagnosis differs from the local report, registered patients must be withdrawn and treated according to local protocol.

5. REGISTRATION & ENROLMENT PROCEDURE

Full written informed consent must be obtained from a patient before they can be registered for the GemBex study. The Investigator (or designated study personnel) should check that all eligibility criteria are met and the Registration forms should be completed. The completed forms should then be faxed to UCL CTC on 020 7679 9861. All eligibility criteria will be checked and patient will be allocated a trial number. Patient numbers will be allocated strictly sequentially as patients enter the trial. Once a number has been assigned, no attempt should be made to use that number again if, for example, a patient is withdrawn from the trial. No patient should be entered into the trial more than once. As this is a single arm study, all patients registered will receive the same therapy. Written confirmation of a patient entering into the trial will be sent to you within one week. Following registration, the baseline Quality of Life questionnaire should be sent immediately to UCL CTC. If any results were pending at the time of registration, an updated registration form should be sent to UCL CTC as soon as the data are available.

REGISTRATION

Tel: 020 7679 9860 (Mon - Fri, 09:00 – 17:00)
Fax: 020 7679 9861

6. TREATMENT OF PATIENTS

6.1 Introduction

This is a single arm open label study and therefore all patients registered will receive treatment with Gemcitabine and Bexarotene.

Drug supply

Bexarotene is a routine approved therapy in this indication and is prescribed for this indication by many centres in the UK. Cephalon Limited (previously known as Zeneus Pharmaceuticals) hold the European marketing rights for the Bexarotene and have agreed to support 50% of the cost of the drug for 20 weeks of treatment. All drugs supplied will be manufactured and imported according to the requirements of Directive 2001/20/EC[13]. All packaging and labelling operations will be performed according to the requirements of Directive 2001/20/EC[13] and in accordance with Good Manufacturing Practice for Medicinal Products. Gemcitabine and all prophylactic drugs will be supplied from commercial hospital stock.

Treatment schedule

Patients will commence prophylactic fenofibrate 160mg – 200mg po daily 7 days before commencing cycle 1. Patients will receive Gemcitabine 1000 mg/m^2 iv on d1, and d8 for 4 21-day cycles. Patients will receive Bexarotene 150mg/m^2 po daily in weeks 1 and 2. If this is tolerated, the dose of Bexarotene will be increased to 300mg/m^2 po daily in weeks 3-12 (see Figure 1). Gemcitabine should be dose capped at 2m^2; Bexarotene should not be dose capped. Dose banding is permitted. At 12 weeks responding patients will be maintained on Bexarotene 300mg/m^2 po daily until their disease progresses or they can no longer tolerate Bexarotene. During maintenance, patients will be assessed in clinic at weeks 13, 17, 24 and every 8 weeks thereafter. Any toxicity from a prior cycle must have improved to at least grade 1 (or baseline value prior to the start of each treatment unless otherwise indicated). Dose reductions may be performed due to toxicity (for details see sections 6.2 and 6.3). Only one dose reduction is allowed and, if further toxicity occurs, the patient must be withdrawn.

Dispensing

Once a patient has been registered on the study, the pharmacy department at the participating centre will be contacted with details of the patient's trial number. Pharmacy must fax Cephalon to order drug for the patient, allowing up to 3 working days for delivery.

Details of the number of capsules required to make up the correct dose can be found in section 4.2 of the Bexarotene SmPC.

Patients will be issued with a diary card instructing them how many Bexarotene capsules they need to take each day in order to make up the required dose. Patients should record the dose taken each day on the diary card, and this should be returned to the investigator at the end of treatment and used as source data to verify that the correct dose has been taken.

Accountability and unused drugs/devices

On receipt of the clinical trial supplies, the pharmacist will conduct an inventory of the supplies and complete a supplies receipt. This receipt must be retained in the site's Pharmacy File and must be made available to UCL CTC on request. The Trial Coordinator may check the inventory of clinical trial supplies at each study site at any time during the study.

6.2 Gemcitabine Specific Instructions

Investigations prior to each Gemcitabine treatment

Gemcitabine will be given as 4 cycles; each cycle consisting of 2 treatment sessions. Prior to each infusion of Gemcitabine a full blood and electrolyte count must be done. The following criteria must be fulfilled:

- WCC >2.0 x 10^9/l, ANC >1.0 x 10^9/l, platelets ≥75 x 10^9/l
- Serum creatinine concentration ≤ 1.5 x ULN
- AST (SGOT) and ALT (SGPT) ≤2.0 x ULN, bilirubin concentration ≤1.25 x ULN
- Recovery of any drug-related non-haematological toxicity to grade 1 or less, or to baseline values unless otherwise indicated.

If any of these criteria are not fulfilled, then administration of study drugs should be delayed as detailed below

Dose modifications - Gemcitabine

Toxicity	Gemcitabine dose
Haematological toxicity	
Platelet count x10^9/l	
50-75	Defer until unsupported count > 75
<50	Defer until unsupported count > 75 and reduce dose 500mg/m^2 **for all further cycles**
Recurrent <10 despite dose modification	Withdraw from study
Neutrophil count x10^9/l	
0.5-1.0	Defer until count > 1.0
<0.5	Defer until count > 1.0
<0.5 with fever >38°C	Defer until count > 1.0 and reduce dose 500mg/m^2 **for all further cycles**
Recurrent < 0.5	Defer until count > 1.0 and reduce dose 500mg/m^2 **for all further cycles.** If persistent despite dose reduction then withdraw from study
Only one dose reduction is permitted.	

Toxicity	Gemcitabine dose
Non-haematological toxicity	
Grade 1-2	No dose reduction of Gemcitabine, unless this toxicity significantly affects the patient's quality of life in the opinion of the investigator.
Grade 3-4	Omit until recovery then restart therapy at 500 mg/m^2/dose. **This is a permanent dose reduction.**
Dose reductions should not be performed for alopecia or nausea and/or vomiting that are not treated with aggressive anti-emetic support.	
Only one dose reduction is permitted.	

Treatment delays within Cycles

Day 1 dose May be delayed due to treatment related toxicities other than outlined in 6.2 (record in CRF).

1-14 days delay: reduce dose to 500mg/m^2

>14 days delay: withdraw from study

Treatment interruptions for non-medical reasons (for any reason, at the discretion of the patient and/or physician) are at times unavoidable and are permissible under this protocol. If the delay is more than 16 days, the patient should be discontinued from the study. However, every attempt should be made to avoid any non-medical treatment delays. Patients who require frequent or prolonged treatment interruptions should be taken off study.

Day 8 dose If the Day 8 dose cannot be given due to toxicity then skip the Day 8 dose and resume treatment on Day 21 (i.e. Day 1 of the next cycle). Record the Day 8 study drug interruption on the study drug administration page of the CRF.

A maximum of 2 working days' delay due to non-medical reasons will be allowed for the Day 8 dose.

6.3 Bexarotene Specific Instructions

Lipid abnormalities, particularly increased serum triglycerides, are the most common adverse events seen on initiation of oral Bexarotene therapy. Abnormalities in thyroid function (particularly primary hypothyroidism) also occur relatively frequently. These are generally manageable with proper laboratory monitoring, lipid-lowering drugs, thyroid hormone replacement and if needed, adjustment or interruption of Bexarotene dose. The hyperlipaemia and hypothyroidism are reversible with cessation of Bexarotene capsules and anti-lipid lowering agents and thyroxine replacement may be stopped at the same time.

In the Phase II-III clinical trials of Bexarotene capsules, hyperlipaemia (hyperlipidemia and elevated triglycerides) occurred in 79% (66/84) of CTCL patients who received an initial Bexarotene dose of 300 mg/m^2/day. About 68% (57/84) of patients in this dose group had fasting triglyceride levels greater than 2.5 times the upper limit of normal. Cholesterol elevations above 7.8 mmol/l occurred in approximately 61% of patients in this dose group, with decreases in high density lipoprotein (HDL) cholesterol to less than 0.65 mmol/l occurring in 54%.[14]

Significantly elevated serum triglycerides increase the risk for development of acute pancreatitis.[15] Acute pancreatitis in association with serum triglyceride levels exceeding 8.7 mmol/l was reported in the Bexarotene capsules clinical trials.[14] Patients with CTCL who have other risk factors for pancreatitis such as excessive alcohol consumption, uncontrolled diabetes mellitus, biliary tract disease, history of pancreatitis or concomitant drug therapy with other medications that can elevate triglycerides or cause pancreatic toxicity should generally not be treated with Bexarotene capsules.[16]

Management of Hyperlipaemia

Baseline fasting blood lipid levels should be normal or normalized on lipid-lowering therapy, prior to starting patients on Bexarotene therapy. After initiating therapy, fasting lipid levels should be determined weekly for the first four weeks or until a lipid response to Bexarotene capsules is established. Continued monitoring of fasting lipid levels should occur every four weeks, with the goal of maintaining serum triglyceride levels below 4.5 mmol/l.[16] Lipid levels may need to be repeated more frequently if the dose of Bexarotene or of the lipid-lowering agents is being adjusted.

Both atorvastatin (Lipitor®) (10-80 mg/day) and fenofibrate (Lapantil Micro®) (145mg -200 mg/day) have been used effectively in controlling hypertriglyceridemia associated with Bexarotene.

In this study it is recommended that lipid-lowering therapy with fenofibrate is started one week prior to the initiation of Bexarotene capsule therapy, at a dose of 160mg – 200mg. Following this thyroxine therapy should be initiated at a dose of 25mcg on the same day that the patient receives their first dose of Bexarotene. If triglycerides become elevated further, the dose of fenofibrate should be increased to 267mg. Gemcitabine can be administered even if the patient is receiving lipid-lowering therapy. If the level of hyperlipidaemia cannot be normalized, then the patient should be withdrawn from the study. If you require further information, please contact UCL CTC.

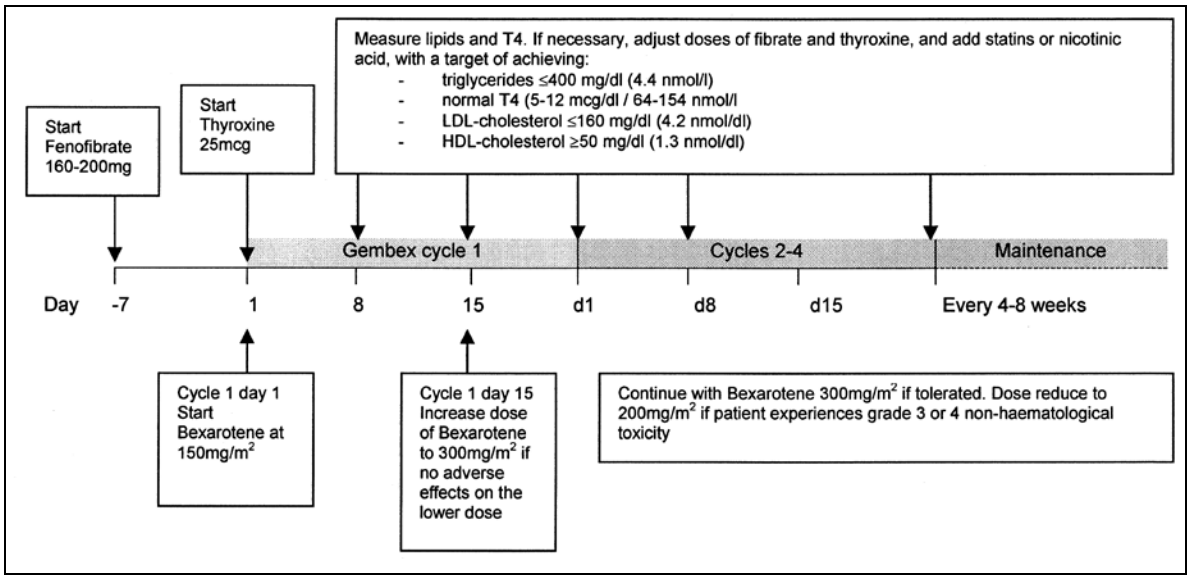
Fenofibrate lowers both triglyceride and cholesterol levels and is therefore the preferred agent.[12] In the Phase II-III clinical trials in CTCL, Atorvastatin was administered to 48% (73/152) of the patients.[14] Fenofibrate was used in the Bexarotene breast cancer trial and was initiated in 67% (52/90) of patients.

If the patient's cholesterol is raised in addition to the triglycerides, atorvastatin may be added, initially at a dose of 20mg, and titrated to a dose of 40-80mg. Caution should be exercised in the concomitant use of fibric acid derivatives (e.g. fenofibrate) and Atorvastatin due to an increased risk for severe myopathy, rhabdomyolysis, and acute renal failure. Elderly patients and patients with impaired renal function are especially at risk of these complications. [15] **Gemfibrozil (Lopid®) should not be used with Bexarotene capsules based on a documented drug-drug interaction that results in exacerbating hypertriglyceridemia and unpredictable elevations in Bexarotene levels.** [16,17]

A Bexarotene capsule dose reduction should be instituted for triglyceride levels that are not controlled with lipid-lowering drugs. Concurrently, the dose of lipid-lowering agent should be increased if the patient is not already at the maximum daily dose.[12] It may take up to four weeks to obtain the maximum benefit from lipid-lowering drugs. [18] Patients should be counselled on the importance of avoiding heavy alcohol consumption and/or dehydration, factors that can lead to pancreatitis. Furthermore, they should be advised to self-monitor for any symptoms of pancreatitis (abdominal pain, nausea, and vomiting) or myopathy (muscle pain or weakness).

A flow diagram outlining the management of thyroid and lipid abnormalities during Bexarotene treatment is shown in Figure 1 below.

Figure 1: Thyroid/lipid abnormalities during Bexarotene therapy



Dose Modification and Treatment Delays for Bexarotene

Toxicity	Bexarotene dose
Non-haematological toxicity	
Grade 1-2	No dose reduction of Bexarotene, unless this toxicity significantly affects the patient's quality of life in the opinion of the investigator
Grade 3	Restart therapy at 200 mg/m^2/dose. If grade 3 toxicity recurs, then stop Bexarotene therapy and patient is discontinued from the clinical trial protocol.
Grade 4	Withhold treatment until toxicity returns to ≤ grade 1 or baseline then restart therapy at 200 mg/m^2/dose. **<u>This is a permanent dose reduction</u>**. If toxicity recurs then stop Bexarotene therapy and patient is discontinued from the clinical trial protocol.

Only one dose reduction is permitted.

6.4 Data on concomitant medication

All medications taken during the trial must be documented in the CRF. Changes in these medications must also be documented.

Treatment for Cancer

A one-month "washout" period is required prior to trial entry for patients who have received chemotherapy or psoralen plus ultraviolet A (PUVA) therapy. Local radiotherapy may be given up to 2 weeks before trial entry. No other systemic anti-cancer treatment or radiotherapy may be used during the trial. If cytotoxic, cytostatic, or immunomodulating agents must be administered; the patient will go off study. If palliative radiation in defined areas becomes necessary, the further evaluability of each case will be decided individually based on a discussion between the Chief Investigator and the Trial Management Group. If individual plaque radiation becomes necessary in an otherwise responding patient, the irradiated lesion will no longer be assessable for response. These patients will NOT be eligible for assessment as CCR or CR and shall be assessed as PR, assuming other criteria for this designation are met. After a patient is taken off study, further treatment with chemotherapy or radiotherapy may be used at the discretion of the primary physician.

Steroids

The use of topical or systemic steroids (including as anti-emetic treatment) should be avoided where possible during the study, as steroids may be regarded as anti-cancer treatment. If possible, patients should stop any steroid treatment prior to study entry. If, however, this is not possible, patients will be permitted to enter the trial if the dose of steroids is at a low dose (≤20mg) which has been stable for at least 3 months. The initiation of steroid treatment during the study, or the necessity to increase the dose of any ongoing steroid treatment, should lead to withdrawal of the patient from the study.

Other Concomitant Treatment

- Patients must not receive concomitant warfarin. Patients on long-term warfarin therapy should be switched to heparin for the duration of study treatment.
- Supportive care measures should only be by the use of emollients; anti-histamines are not to be used. Symptomatic treatment for any drug-related toxicity may be instituted if clinically indicated.
- The prophylactic use of anti-emetics (e.g. 5HT3 antagonists) before the patient's first dose of trial medication is allowed at the investigator's discretion. Prophylactic anti-emetics may be administered as needed to patients who experience nausea and/or vomiting.

- The use of erythropoietin is allowed to maintain haemoglobin/haematocrit at acceptable levels for patient comfort. Blood transfusions may also be administered as needed per the investigator's judgment.
- Neutropenic patients may be given G-CSF at the treating clinician's discretion.

7. ASSESSMENTS AND PROCEDURES

7.1 Schedule of Study Activities

Please refer to Appendix 9 for a schedule of activities.

7.2 On-study Disease Assessments

Disease assessments should be made on day 1 of each cycle of Gemcitabine (weeks 4, 7, & 10), at the end of Gemcitabine-Bexarotene (week 13) then 4-weekly during Bexarotene maintenance.

Tumour measurement

In those patients with lymphadenopathy, the RECIST algorithm (see Appendix 6) will be used to determine the extent and date of response and date of progression. Palpable lymph nodes that were identified at baseline should be evaluated on Day 1 of each cycle. Evaluation on Day 1 of Cycle 1 is required only if the screening/baseline assessment is >1 week prior to the start of Cycle 1. Patients with abnormal lymph nodes on CT scan at baseline should have a repeat CT scan at the end of Gemcitabine + Bexarotene therapy (week 13) and at their end of treatment visit.

At the end of the study, the investigator will determine the patient's best response according to RECIST v1.0 and OPDREC criteria during the study. During the course of the study, abnormal lymph nodes must be recorded on the CRFs in the same order as that used at baseline. Details of any new abnormal lymph nodes and/or non-cutaneous tumours will also be collected.

Standardised photography

Standardised photography of skin lesions during study will be used to document skin response and improvement (see Appendix 8). This is required at baseline, end of gemcitabine+bexarotene combination therapy (week 13), the 'end of treatment' visit (week 24 or 4 weeks after last protocol treatment if sooner) and disease progression.

Assessment of skin lesion severity

This will be assessed through SWAT analysis. See section 2.6

Pruritus

Pruritus will be measured using a visual analogue scale (See Appendix 5).

Biopsy specimens

Blood Patients with Sézary cells at baseline will be followed for clearing of these cells. The clearing of Sézary cells in blood will be used as a measure of disease response.

Skin In patients who consent to providing 2 biopsies the second biopsy should be performed for confirmation of CR (if applicable).

All histological specimens (skin lesions of all types – plaque/patch/tumour and lymph node biopsies) must be reviewed and confirmed by Dr Alistair Robson (St. Thomas' Hospital, London).

Objective Primary Disease Response Evaluation Criteria (OPDREC)

The response to treatment by OPDREC (see table below) will be evaluated on day 1 of each cycle of Gemcitabine (weeks 4, 7, & 10), at the end of Gemcitabine-Bexarotene (week 13) then 4-weekly during Bexarotene maintenance.At the end of treatment, in addition to an overall OPDREC response, the investigator will determine the patient's best response during the study.

In order to claim a CCR or PR as the best response, the response must be confirmed at least 1 month later by

i. Repeating the assessments and observing the same or a better OPDREC outcome,

ii. Excluding any progression of visceral disease by CT scan. In order to claim an outcome of CR, the initial and confirmatory assessment must meet the criteria of CCR, and a skin biopsy must be performed at the confirmatory assessment to histologically verify resolution of skin disease. If the skin biopsy shows complete resolution of skin disease, a confirmed CR may be claimed in place of CCR.

Table 2: OPDREC Criteria

Response Definition*	Description	
	Patients without Erythroderma	**Patients with Erythroderma**
Complete Response (CR)	Complete resolution of skin patches, skin plaques, and skin tumours. No evidence of abnormal lymph nodes. Absence of circulating Sézary cells. No evidence of new tumour (cutaneous or non-cutaneous). **PLUS** confirmation by skin biopsy.	Complete resolution of erythroderma. No evidence of abnormal lymph nodes. Absence of circulating Sézary cells. No evidence of new tumour (cutaneous or non-cutaneous). **PLUS** confirmation by skin biopsy.
Clinical Complete Response (CCR)	Complete resolution of skin patches, skin plaques, and skin tumours. No evidence of abnormal lymph nodes. Absence of circulating Sézary cells. No evidence of new tumour (cutaneous or non-cutaneous).	Complete resolution of erythroderma. No evidence of abnormal lymph nodes. Absence of circulating Sézary cells. No evidence of new tumour (cutaneous or non-cutaneous).
Partial Response (PR)	$\geq$ 50% improvement in the summation of (Δ Skin + Δ Lymph Node + Δ Peripheral Blood) with at least $\geq$ 30% improvement in Δ Skin and no worsening in Lymph Node or Sézary cells. No evidence of new tumours (cutaneous or non-cutaneous).	$\geq$ 50% improvement in the summation of (Δ Skin + Δ Lymph Node + Δ Peripheral Blood) with at least $\geq$ 30% improvement in Δ Skin and no worsening in Lymph Node or Sézary cells. No evidence of new tumours (cutaneous or non-cutaneous).
Stable Disease (SD)	Patients who do not have enough improvement or worsening improvement in the summation of (Δ Skin + Δ Lymph Node + Δ Peripheral Blood) to qualify as PR or PD, respectively. No evidence of new tumour (cutaneous or non-cutaneous).	Patients who do not have enough improvement or worsening improvement in the summation of (Δ Skin + Δ Lymph Node + Δ Peripheral Blood) to qualify as PR or PD, respectively. No evidence of new tumour (cutaneous or non-cutaneous).
Progressive Disease (PD)	Evidence of new tumour (cutaneous or non-cutaneous), OR >25% worsening in the summation of (ΔSkin + Δ Lymph Node + Δ Peripheral Blood) with >15% worsening in Δ Skin.	Evidence of new tumour (cutaneous or non-cutaneous), OR >25% worsening in the summation of (Δ Skin + Δ Lymph Node + Δ Peripheral Blood) with >15% worsening in Δ Skin.

Footnotes to table 2

* A confirmed assessment is one that is repeated at least 1 month after the initial assessment. To be classified as CR, CCR, or, PR the response must be a confirmed assessment.
Note: If individual plaque radiation becomes necessary in an otherwise responding patient, the irradiated lesion will no longer be assessable for response. These patients will NOT be eligible for assessment as CCR or CR and shall be assessed as PR, assuming other criteria for this designation are met.

Δ Skin (patients without erythroderma), = % change in the total score from baseline of the SWAT Score, (see Section 2.6).

Δ Skin (patients with erythroderma), = % change in the total score from baseline SWAT Score, (see Section 2.6).

Δ Lymph Node = % change in the size of abnormal lymph nodes (sum of longest diameter) from baseline based on physical examination and/or CT/MRI scan.

Δ Peripheral Blood = % change in the absolute number of circulating Sézary cells from baseline.

Quality of Life should be assessed using Skindex 29 and EORTC QLQ-C30. Following the initial baseline Quality of Life assessment, further assessments should be made prior to each cycle of Gemcitabine (i.e. weeks 1, 4, 7 and 10), 4-weekly during Bexarotene maintenance (i.e. weeks 13 and 17) and at the end of treatment visit (week 24 or 4 weeks post last study treatment if sooner). This would equate to 8 Quality of Life assessments in total whilst on therapy. Quality of Life assessments should be conducted at subsequent follow-up visits until disease progression or 2 years post baseline visit.

7.3 Tolerability

All patients who receive at least one dose of Gemcitabine and Bexarotene will be assessed for toxicity. Patients will be monitored for adverse events during trial treatment and until 30 days after the last dose of trial treatment or until all toxicities have resolved. Any abnormal haematology or biochemistry laboratory value, which the investigator considers may have a significant clinical impact on the welfare of the patient, should also be recorded as an adverse event. Adverse events will be graded according to the NCI CTCAE v.3.0 (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/ctcaev3.pdf) and recorded on CRFs.

Complete details of reporting adverse events, including the definition of drug-related adverse events, are given in Section 10.1

7.4 Laboratory Assessments

Laboratory parameters will be assessed for the duration of the treatment period, at the final visit, and at the follow-up visits. The schedule for blood tests during the treatment period is as shown below:

Gemcitabine + Bexarotene			
Cycle 1	Week 1	Day 1	FBC, U&E, LFT, TFT, fasting lipids, CPK, CD4 count (NB only required if >1 week from screening tests)
	Week 2	Day 1	FBC, U&E, LFT, TFT, fasting lipids, CPK
	Week 3	Day 1	TFT, fasting lipids, CPK
Cycle 2	Week 4	Day 1	FBC, U&E, LFT, TFT, fasting lipids, CPK, CD4 count
	Week 5	Day 1	FBC, U&E, LFT
	Week 6		No tests required
Cycle 3	Week 7	Day 1	FBC, U&E, LFT, TFT, fasting lipids, CPK, CD4 count
	Week 8	Day 1	FBC, U&E, LFT
	Week 9		No tests required
Cycle 4	Week 10	Day 1	FBC, U&E, LFT, TFT, fasting lipids, CPK, CD4 count
	Week 11	Day 1	FBC, U&E, LFT
	Week 12		No tests required
o Further samples may be taken if clinically indicated o **Repeat FBC at least twice weekly if patient has grade IV neutropenia or thrombocytopenia** o **Measurement of lipids and thyroid function may need to be performed more frequently if results are out of range**			

Bexarotene maintenance and follow up		
Week 13	D1	FBC, U&E, LFT, TFT, fasting lipids, CPK, CD4 count
Week 17	D1	FBC, U&E, LFT, TFT, fasting lipids, CPK, CD4 count
Week 24	D1	FBC, U&E, LFT, TFT, fasting lipids, CPK, CD4 count
Every 8 weeks thereafter	FBC, U&E, LFT, TFT, fasting lipids, CPK, CD4 count	
Further samples may be taken if clinically indicated. **Repeat FBC at least twice weekly if grade IV neutropenia or thrombocytopenia** **Measurement of lipids and thyroid function may need to be performed more frequently if results out of range**		

7.5 Other Safety Aspects

Physical Examination

Physical examination should be performed on day 1 of each cycle of Gemcitabine, at the end of Gemcitabine-Bexarotene (week 13), 4-weekly for the first 8 weeks of maintenance, at the 'end of treatment visit' (week 24 or 4 weeks after last study treatment if sooner), then every 8 weeks until disease progression. Further examinations may be performed as clinically indicated.

Body Weight

Body weight should be assessed on day 1 of each cycle of Gemcitabine, at the end of Gemcitabine-Bexarotene (week 13), 4-weekly for the first 8 weeks of maintenance, at the 'end of treatment visit' (week 24 or 4 weeks after last study treatment if sooner), then every 8 weeks until disease progression

Vital Signs

Vital signs assessments should include sitting pulse, temperature, and blood pressure. These assessments should be performed on days 1 & 8 of each cycle of Gemcitabine, at the end of Gemcitabine-Bexarotene (week 13), 4-weekly for the first 8 weeks of maintenance, at the 'end of treatment visit' (week 24 or 4 weeks after last study treatment if sooner), then every 8 weeks until disease progression.

Performance Status

Performance status will be assessed using the ECOG scale (see Appendix 7), and will be assessed on days 1 & 8 of each cycle of Gemcitabine, at the end of Gemcitabine-Bexarotene (week 13), 4-weekly for the first 8 weeks of maintenance, at the 'end of treatment visit' (week 24 or 4 weeks after last study treatment if sooner), then every 8 weeks until disease progression.

Follow-up and Final Visits

A final visit for the primary part of the study ('end of treatment visit') will be performed at week 24 or 4 weeks after the patient's last study treatment if sooner . Thereafter patients will be followed up 8-weekly until disease progression or until 2 years after study entry. After this time patients will be followed up for survival and remission status every 6 months until 5 years after study entry, and annually thereafter.

7.6 Loss to follow-up

Patients will be followed-up for five years in the first instance and then until death. If a patient fails to attend a clinic or cannot be followed up at site, efforts should be made to contact the patient's GP to assess their condition. Any patients "lost to follow-up" and who subsequently die will be "flagged" by the NHS Information Centre. This will be mentioned on the Patient Information Sheet.

7.7 Trial closure

The trial will be considered complete when the last patient has their last follow up visit required to address the primary endpoint (2 years after study entry). However, further observational follow-up of all patients enrolled in the trial will continue until all registered patients have died. This will initially be via the hospital, but in the longer term may employ national registers.

8. WITHDRAWAL OF PATIENTS

In consenting to the trial, patients are consenting to trial treatment, trial follow-up and data collection. If a patient wishes to withdraw from trial treatment, centres should nevertheless explain the importance of remaining on trial follow-up, or failing this of allowing routine follow-up data to be used for trial purposes.

If the patient explicitly states their wish not to contribute further data to the study, UCL CTC must be informed in writing. All data up to the date of withdrawal must still be submitted.

8.1 Withdrawal from trial intervention

Patients may be withdrawn from treatment for any of the following reasons: -

i. Disease progression whilst on therapy

ii. Patient withdraws consent

iii. Unacceptable toxicity

iv. Intercurrent illness, which prevents further treatment

v. Any change in the patient's condition which justifies the discontinuation of treatment in the clinician's opinion

When a patient is withdrawn from treatment for any reason, the end of treatment summary form must be completed and sent to UCL CTC.

Patients who withdraw from the trial for other reasons have previously consented to follow-up in the trial. All data up to the time of withdrawal must be submitted. Patients may need to reaffirm that they consent to follow-up through usual NHS mechanisms e.g. NHS Information Centre.

If the reason for patient withdrawal is death, then the withdrawal should be categorised as either (a) disease progression or (b) adverse event (more than one adverse event may be documented as causing withdrawal).

Patients with global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression should be reported as "symptomatic deterioration" at withdrawal. Every effort should be made to ensure "symptomatic deterioration" patients have objective disease assessments at withdrawal from trial treatment.

If patients do not complete the assessments scheduled for the 'end of treatment visit', the investigator will document the specific reason for the incomplete information (e.g., withdrawal of consent, lost to follow-up) on the appropriate page of the CRF. Reasonable efforts should be made to contact patients who are lost to follow up. These must be documented in the patient's file.

The reason for withdrawal and the date of withdrawal must be documented on the CRF provided. For database purposes, the date of withdrawal from trial treatment will be the date of the last dose of trial drug, not the day on which the decision is made to withdraw the patient from any further trial therapy.

When the decision is taken to permanently stop trial therapy, a full assessment should be carried out where possible. The patient should have an end of treatment visit 4 weeks after stopping therapy, and then be followed up regularly in accordance with section 7.5 above.

8.2 Patient transfers

For patients moving from the area, every effort should be made for the patient to be followed up at another participating trial centre and for this new centre to take over the responsibility for the patient. UCL CTC can provide details of participating centres in the area to which the patient is relocating. UCL CTC must be provided with written notification that the patient's care is being transferred and that the new trial site has agreed to undertake all future trial related duties for that patient. **Until written confirmation is received, the patient remains the responsibility of the original centre**. A copy of the patient CRFs will need to be provided to the new site. The patient will have to sign a new consent form at the new site, and until this occurs, the patient remains the **responsibility of the original centre.**

9. STATISTICAL CONSIDERATIONS

9.1 Data Management

All study data will be recorded on CRFs specific for the study. Data should be recorded directly and legibly onto the CRFs in black ball-point pen. If any data are not available, omissions will be indicated on the CRFs. Corrections should be made legibly and initialled and dated by approved personnel. Correction fluid or covering labels must not be used.

Any data queries following in-house validation will be documented. The distribution of copies will be as for the CRFs.

9.2 Study Population

Study Populations and Planned Analyses

Two study populations will be used to summarize study data, as treated population and evaluable population.

As-treated Population

The as-treated population includes all enrolled patients that received at least one dose of study treatment. This population will be used for the analysis of all patient characteristics, treatment administration and safety endpoints, and applicable efficacy endpoints.

Evaluable Population

The evaluable population includes all enrolled patients who received at least 2 cycles of Gemcitabine and Bexarotene treatment and patients who received less than 2 cycles of study treatment due to disease progression or toxicity. This population will be used for the analysis of all efficacy endpoints. In addition, a per-protocol subset of the evaluable population will be used to analyse some efficacy endpoints. The per-protocol set may exclude patients based on violation of eligibility criteria, concomitant therapy use, poor treatment compliance, protocol deviations, and/or other factors that may affect the evaluation of disease status. Determination of the per-protocol set will occur prior to the final analysis.

9.3 Outcome measures

Primary

The primary efficacy endpoint is the rate of objective response, defined as the proportion of patients with confirmed CR, CCR, or PR, as determined by the OPDREC (Table 2).

The number and percentage of patients with objective disease response will be presented. A two-sided 95% confidence interval will be constructed using exact methods based on the binomial distribution. The primary analysis will be performed using the evaluable population. A secondary efficacy analysis on the primary endpoint will be conducted using the per-protocol set.

Secondary

- Rate of objective disease control: Proportion of patients with confirmed CR, CCR, PR, or stable disease (SD, for SD with a duration of at least 6 months) as determined by the OPDREC.
- Duration of objective disease response. For patients with confirmed CR, CCR, or PR as determined by the OPDREC criteria, duration of response is defined as the time from the first date of treatment to the first date of diagnosis of progressive disease, or date of last study assessment if no disease progression.
- Durability of objective disease response: For patients with confirmed CR, CCR, or PR as determined by the OPDREC criteria, the time from the first date of a confirmed disease response to the first date of diagnosis of progressive disease, or date of last study assessment if no disease progression.
- Time to objective disease response: For patients with confirmed CR, CCR, or PR as determined by the OPDREC criteria, the time from the first date of treatment to the first date of confirmed disease response.
- Time to objective disease progression: The time from the first date of treatment to the first date of diagnosis of progressive disease, as determined by the OPDREC criteria.
- Time to treatment failure: The time from the first date of treatment to the date of permanent treatment withdrawal (due to objective disease progression, toxicity and/or other treatment-related withdrawal reasons).
- Change from baseline in Severity-Weighted Assessment Tool (SWAT) value: at each assessment during the study, the SWAT value minus the baseline SWAT value.
- Change from baseline in Erythroderma SWAT value: At each assessment during the study, the erythroderma SWAT value minus the baseline erythroderma SWAT value.
- Change from baseline in Pruritus VAS: At each assessment during the study, the pruritus VAS value minus the baseline pruritus VAS value.

- Change from baseline in ECOG performance status: At each assessment during the study, the ECOG performance status value minus the baseline ECOG performance status value.
- Proportion of disease control, response, and progression as determined by RECIST criteria
- Proportion of patients with clearing of Sézary cells from the peripheral blood

All continuous secondary endpoints, including change from baseline values, will be summarized with descriptive statistics (n, mean, median, standard deviation, minimum, maximum) overall and by objective disease control status, objective disease response status and the individual OPDREC categories. Change from baseline endpoints will be summarized at each study visit. For the pruritus assessment, summaries may also be performed by relevant concomitant medication status.

Time to objective disease response, time to objective disease progression, and time to treatment failure will be estimated using the Kaplan-Meier method. For time to objective disease response and time to objective disease progression, censoring will occur on the date of the last on-study visit with non-missing OPDREC assessments or date of the switch to an alternate therapy, if applicable. For time to withdrawal, censoring will occur on the last date of treatment.

The number and percentage of patients with clearing of Sézary cells from the blood will be summarized overall and by objective disease control status, objective disease response status and the individual OPDREC categories. Clearing of Sézary cells will be achieved if the Sézary cells comprise less than 5% of the total white blood cells in the peripheral blood.

The number and percentage of patients with disease control, disease response, and disease progression as determined by RECIST criteria will be summarized. Two-sided 95% confidence intervals will be constructed using exact methods based on the binomial distribution.

9.4 Sample Size

The primary objective of the study is to evaluate the efficacy of Gemcitabine and Bexarotene as a combination therapy in patients with CTCL in terms of the rate of objective disease response and to determine whether the combination has sufficient biological activity in CTCL

to warrant more extensive investigation. Response will be assessed at 24 weeks. We will use the "optimal two stage design" published by Simon [20]. Initially 35 patients will be treated and a further 49 to a total of 84 patients if the response criteria are met as outlined below.

In the sample size calculations we have assumed that we would not be interested in pursuing the Gemcitabine-Bexarotene combination if the response rate was less than 50% but would be interested in pursuing it further if the response rate was 65% or more. Assuming a statistical power of 90% we would first treat 35 patients and if fewer that 19 respond, stop. If 19 or more respond then a further 49 patients would be treated and if fewer than 48 patients respond we stop the study. If the criteria to proceed are met at both stages this indicates that the probability that the response rate is less than or equal to 50% is less than 10%. If the criteria for stopping are met at any stage, this indicates that that the probability that the response rate to the Gemcitabine-Bexarotene combination is greater than or equal to 65% is less than 10%.

9.5 Interim Monitoring and Analyses

Descriptive summaries of accumulating safety and patient disposition data will be prepared at least once a year for review by a data monitoring committee (DMC). The DMC may also review evaluability and the OPDREC classification on a by-patient basis. The sample size will be re-estimated when at least half of evaluable patients have completed the 24 weeks of treatment or discontinued study treatment early. The DMC will recommend whether the sample size should be increased or stay as planned, based on projections from the observed response rate. Details of the sample size re-estimation will be provided in an interim analysis plan. A DMC charter that describes the member composition, goals, meeting conduct, and content of the DMC review is in place. Since planned analyses will be descriptive and there is no a priori intent to stop the trial early for efficacy, no adjustment for multiple testing is required.

Analysis to address the feasibility endpoint will be performed when all patients have either completed 24 weeks of treatment or stopped treatment early.

9.6 Final Analysis

A final analysis is planned 2 years after the last patient is entered into the trial.

10. PHARMACOVIGILANCE

10.1 Definitions of Adverse Events

The following definitions have been adapted from Directive 2001/20/EC and ICH GCP E6:

Adverse Event (AE)

Any untoward medical occurrence or effect in a patient treated on a trial protocol, which does not necessarily have a causal relationship this treatment. An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom or disease temporally associated with the use of the trial treatment, whether or not related to the trial treatment.

Adverse Reaction

All untoward and unintended responses to a trial treatment related to any dose administered. A causal relationship between the trial treatment and an adverse event is at least a reasonable possibility, i.e. the relationship cannot be ruled out.

Serious Adverse Event (SAE) or Serious Adverse Reaction

An adverse event or adverse reaction that at any dose:

- Results in death
- Is life threatening (The term "life-threatening" refers to an event in which the subject was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death if it were more severe.)
- Results in persistent or significant or disability/incapacity
- Requires in-patient hospitalisation or prolongs existing hospitalisation
- Is a congenital anomaly or birth defect
- Is otherwise medically significant (i.e. withdrawal reactions, all accidental or intentional overdoses whether they result in an adverse event or not, or any event which the investigator considers significant but which is not covered by the above.)

Suspected Unexpected Serious Adverse Reaction (SUSAR)

A Serious Adverse Reaction, the nature or severity of which **is not consistent** with the applicable trial treatment information.

A serious event or reaction is not defined as a SUSAR when:

- it is serious but expected
- it does not fit the definition of an SAE, whether expected or not.

10.2 Reporting Procedures

All Adverse Events (AEs)

All adverse events that occur between informed consent and 28 days post last trial treatment administration must be recorded in the patient notes and the trial CRFs. Information regarding dates of event onset and resolution, outcome, severity and causality for the trial treatment must be recorded. Those meeting the definition of a Serious Adverse Event (SAE) must also be reported to the UCL Cancer Trials Centre using the trial specific SAE Report (see Serious Adverse Events section for details).

Pre-existing conditions do not qualify as an adverse event unless they worsen.

Adverse Event Term

An adverse event term needs to be provided for each adverse event, preferably using the Short Name as listed in the Common Terminology Criteria for Adverse Events v3.0 (CTCAE), available online at:
http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/ctcaev3.pdf.

Severity

Severity for each adverse event will be determined by using the Common Terminology Criteria for Adverse Events v3.0 (CTCAE) as a guideline, wherever possible. The criteria are available online at:
http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/ctcaev3.pdf. In those cases where the CTCAE criteria do not apply, severity should be coded according to the following criteria:

1 = Mild
2 = Moderate
3 = Severe
4 = Life threatening
5 = Fatal

Causality

Site investigators must perform an evaluation of causality for each adverse event.
Causality relationship to the trial treatment must be determined as follows:

- **None**

  There is no evidence of any causal relationship.

- **Unlikely**

There is little evidence to suggest a causal relationship (e.g. because the event did not occur within a reasonable time after administration of the trial treatment). There is another reasonable explanation of the event (e.g. the patient's clinical condition, other concomitant medications).

- **Possible**

There is some evidence to suggest a causal relationship (e.g. because the event occurs within a reasonable time after administration of the trial treatment). However, the influence of other factors may have contributed to the event (e.g. the patient's clinical condition, other concomitant medications).

- **Probable**

There is evidence to suggest a causal relationship and the influence of other factors is unlikely.

- **Definitely**

There is clear evidence to suggest a causal relationship and other possible contributing factors can be ruled out.

Serious Adverse Events (SAEs)

All SAEs that occur between informed consent and 30 days post the last trial treatment administration (or after this date if the site investigator feels the event is related to the trial treatment) must be submitted to the UCL Cancer Trials Centre by fax within **1 business day** of observing or learning of the event, using the trial specific SAE Report. All sections on the SAE Report must be completed.

Expectedness

Site investigators must perform an evaluation of expectedness for all SAEs regardless of causal relationship to the trial treatment. This evaluation must be performed using the list of expected adverse events in appendices 11 & 12, cross-referencing with the Summary of Product Characteristics (SmPC) for each trial treatment provided by the UCL CTC.

Expectedness of the event to the trial treatment must be determined as follows:

- **Expected**

The event is listed as an expected adverse event in the protocol appendix/SmPC.

- **Unexpected**

The event is not listed as an expected adverse event in the protocol appendix/SmPC, or, the severity of the event is greater than that listed in the protocol appendix/SmPC, for example:

- the event is life threatening or fatal (unless stated in the protocol appendix as expected).
- the patient presents with an event which is considered to be moderate or severe, but only mild is listed as expected in the protocol appendix/SmPC.

Events which do not require reporting as an SAE

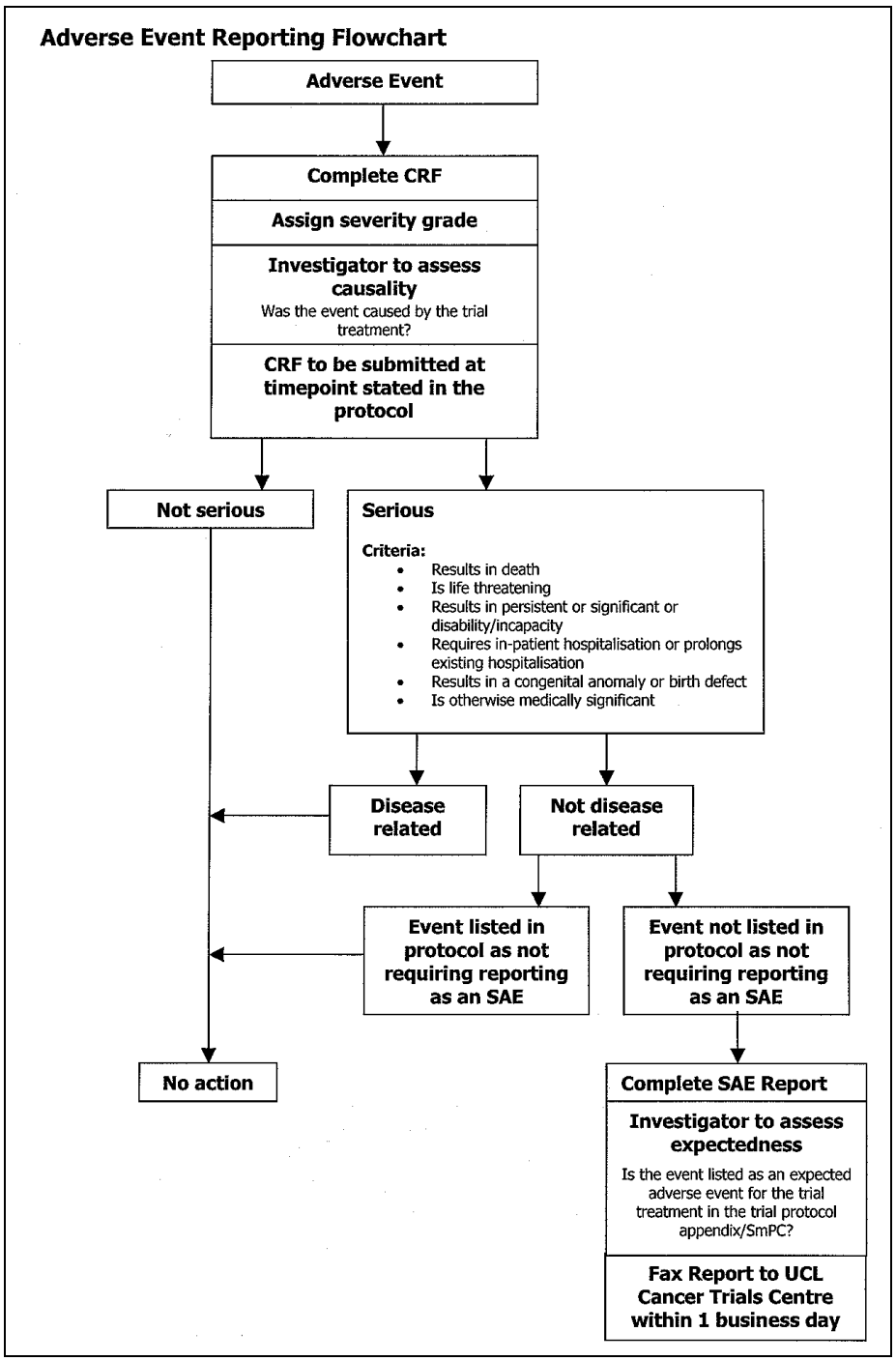
The following events do not require reporting as an SAE, but must be recorded in the relevant section(s) of the CRF:

- disease progression
- disease related deaths
- hospitalisation for elective treatment
- admissions for palliative care.

All SAEs must be reported by faxing a completed SAE Report within 1 business day of becoming aware of the event to the UCL Cancer Trials Centre.

Fax: 020 7679 9861

Figure 2 : Adverse Event Reporting Flowchart



SAE Follow-Up Reports

All SAEs must be followed up until resolution. Site investigators must provide follow up SAE reports if the SAE had not resolved at the time the initial report was submitted.

SAE processing at the UCL CTC

On receipt of the SAE report, the UCL CTC will evaluate the event for seriousness and expectedness to determine whether or not the case qualifies for expedited reporting. If this is difficult to determine, the Chief Investigator or Trial Management Group will be consulted for their opinion. In the case of discrepant views, both opinions will be reported.

The UCL CTC will periodically submit line listings of SARs related to Bexarotene to Cephalon as stated in the IMP supply agreement

SUSARs

If the event is evaluated by either the site or the UCL CTC as a Suspected Unexpected Serious Adverse Reaction (SUSAR), the UCL CTC will submit a report to the MHRA and MREC within 7 calendar days for fatal/life threatening events, with a follow-up report within a further 8 calendar days, and 15 calendar days for all other events.

The UCL CTC will inform all Principal Investigators of any SUSARs which occur on the trial. Site investigators will receive expedited SUSAR reports that must be processed according to local requirements.

Where the SUSAR is related to Bexarotene, the UCL CTC will fax the SUSAR report to Cephalon within 1 business day.

The UCL CTC will forward reports regarding SUSARs that have occurred on other trials using the same trial treatment to all Principal Investigators. These must be processed according to local requirements and filed with the SmPC for the drug concerned.

Clinical Review

The UCL CTC will provide safety information to the Chief Investigator, Trial Management Group and Independent Safety Monitoring Committee on a periodic basis for review. Should the outcome of the review result in upgrading/downgrading of SAEs and SUSARs and vice versa, the UCL CTC will provide relevant reports to the MHRA and MREC.

Additional Safety Monitoring at the UCL CTC

The UCL CTC will also monitor safety data for any trial related events that are not considered related to the trial treatment. In the event that any trial procedures appear to be

resulting in adverse events, the Chief Investigator and the Trial Management Group will be contacted for their opinion. If it is declared necessary to review the conduct of the trial, the UCL CTC will inform the MHRA and MREC as appropriate.

If the UCL CTC detect a higher incidence rate in rare events than is stated in the SmPC(s) for the trial treatment, a report detailing the findings will be sent to the MHRA and MREC.

10.3 Pregnancy

If a female patient or the female partner of a male patient becomes pregnant at any point during the trial, a completed trial specific Pregnancy Report must be faxed to the UCL Cancer Trials Centre within **1 business day** of learning of its occurrence.

All pregnancies must be reported by faxing a completed Pregnancy Report within 1 business day of becoming aware of the event to the UCL CTC

Fax: 0207 679 9861

Pregnancy Follow-Up Reports

All pregnancies must be followed up until an outcome is determined. Follow-Up Pregnancy Reports must be submitted to the UCL CTC by fax within **7 calendar days** of learning of the outcome. Reports must include an evaluation of the possible relationship of the trial treatment to the pregnancy outcome. Consent to report information regarding pregnancy outcomes must be obtained from the mother.

SAEs during pregnancy

Any SAE occurring in a pregnant patient must be reported using the trial specific SAE Report, according to SAE reporting procedures.

Pregnancy Report Processing at the UCL CTC

The UCL CTC will fax all pregnancy reports to Cephalon within 1 business day.

The UCL CTC will submit Pregnancy Reports to the MHRA and MREC should the pregnancy outcome meet the definition of a SUSAR.

10.4 Annual Safety Reports

The UCL CTC will submit Annual Safety Reports to the MHRA and MREC. This will commence one year from the date of CTA approval for the trial.

10.5 Serious Breaches of Safety

Systematic or persistent non-compliance by a site of the safety requirements set out in the protocol, including failure to report SAEs occurring on the trial within the specified timeframe, may be deemed a serious breach. In cases where a serious breach has been identified, the UCL CTC will inform the MHRA within 7 calendar days of becoming aware of the breach.

11. ETHICAL CONSIDERATIONS AND APPROVAL

11.1 Ethical considerations

GemBex is a Phase II open-label single arm study. Therefore neither the patients nor their physicians will be able to choose the patient's treatment. Treatment will be allocated upon registration and all patients will receive the same treatment.

The study will abide by the principles of the Declaration of Helsinki (Appendix 3).

11.2 Ethical approval

The study has been approved by the Leeds (East) Research Ethics Committee as designated by the Central Office for Research Ethics Committees (COREC) and in addition, Site Specific Approval and R&D Approval must be obtained at each institution before patients are entered at that site.

The patient's consent to participate in the trial should be obtained after a full explanation has been given of the treatment options, including the conventional and generally accepted methods of treatment. Patients should be given sufficient time after being given the trial patient information sheet to consider and discuss participation in the trial with friends and family. A contact number should be given to the patient should they wish to discuss any aspect of the trial. Following this, the investigator should determine that the patient is fully informed of the trial and their participation, in accordance with ICH GCP guidelines. Patients should always be asked to sign a consent form. One copy should be given to the patient, one copy should be kept with patient's hospital notes and one copy should be kept in the local investigator's file.

The right of the patient to refuse to participate in the trial without giving reasons must be respected. After the patient has entered the trial, the investigator must remain free to give alternative treatment to that specified in the protocol, at any stage, if he/she feels it to be in the best interest of the patient. However, the reason for doing so should be recorded and the patient will remain within the trial for the purpose of follow up and data analysis according to the treatment option to which he/she has been allocated. Similarly, the patient

must remain free to withdraw at any time from the protocol treatment without giving reasons and without prejudicing his/her further treatment.

12. REGULATORY APPROVAL

This trial will be conducted in accordance with Good Clinical Practice and Medicines for Human Use (Clinical Trials) Regulations 2004. The trial has a Clinical Trials Authorisation from the Medicines and Healthcare Regulatory Authority. The trial has also been reviewed by a Research Ethics Committee.

13. INDEMNITY

Non-negligent harm: University College London, as Sponsor, holds insurance cover that will provide compensation for injury caused by participation in this clinical trial without the need to prove negligence on the part of University College London. Participants who sustain injury and wishing to make a claim for compensation should do so in writing to the Chief Investigator in the first instance.

Negligent harm: Participants in this clinical trial are also able to seek compensation via the negligent harm route but this would involve proving negligence on the part of University College London. Insurance cover is held by University College London to cater for this but it is expected that any claim for compensation would be via the non-negligent route by virtue of compensation being paid without the need to prove negligence. However, as this clinical trial is being carried out in a hospital, the hospital continues to have a duty of care to the participant of the clinical trial. University College London does not accept liability for any breach of the hospital's duty of care, or any negligence on the part of employees of hospitals. This applies whether the hospital is an NHS trust or not. This does not affect the participant's right to seek compensation via the non-negligence route.

14. FINANCE

This study is funded by a grant from Cancer Research UK.
Cephalon Pharmaceuticals are providing Bexarotene at a 50% discount for the trial.

15. TRIAL COMMITTEES

15.1 Trial Management Group (TMG)

A Trial Management Group (TMG) will be formed comprising the Chief Investigator, other lead investigators (clinical and non-clinical) and members with specific interest (e.g. nurses; radiographers). The TMG will be responsible for the day-to-day running and management of the trial and will meet approximately every six months but may convene more often by other means to advise the CI and UCL CTC in the promotion and running of the trial.

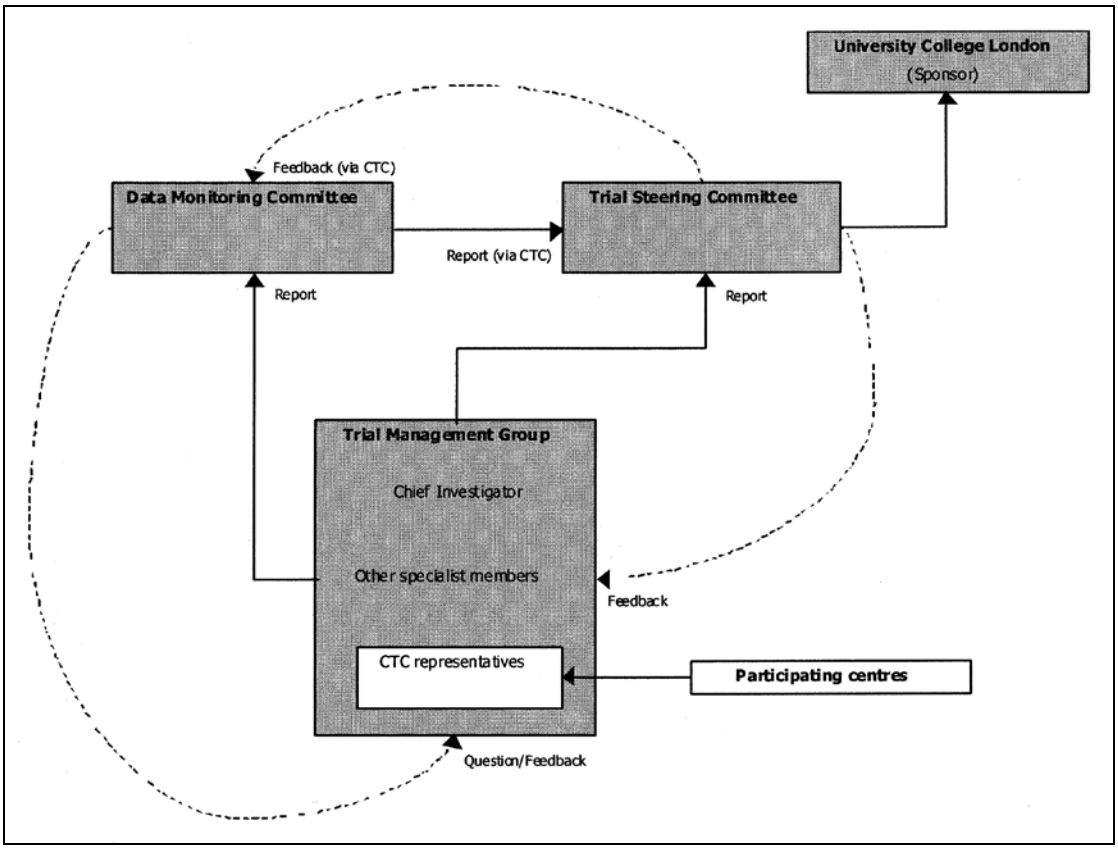
15.2 Trial Steering Committee (TSC)

The role of the TSC is to provide overall supervision for the trial and provide advice through its independent Chairman. The ultimate decision for the continuation of the trial lies with the TSC. It will meet at least annually and will receive reports from UCL CTC, the CI and IMDC

15.3 Independent Data Monitoring Committee (IDMC)

The Independent Data Monitoring Committee will meet at least annually, with interim analysis reports from UCL CTC, to give advice on continuing recruitment. A recommendation to discontinue recruitment (in all patients or in selected subgroups) will be made only if the result is likely to convince a broad range of investigators including participants in the trial and the general clinical community. If a decision is made to continue, the IDMC will advise on the frequency of future reviews of the data on the basis of accrual and event rates. The IDMC will make recommendations to the TSC as to the continuation of the trial. Details of the analysis and monitoring are provided in the IDMC charter and in section 9.5.

Figure 3: Relationships between trial committees



16. PUBLICATION

Publication will follow the rules of the NCRI lymphoma CSG. Authorship will include the Chief Investigator, trial statistician, a representative of UCL CTC, a member of the central histopathology review team and one additional author from each centre entering more than 5% of the total patients.

17. PROTOCOL AMENDMENTS

It may be necessary to amend the protocol during the course of the trial. In this event all registered collaborators will be notified of the changes.

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APPENDIX 1: EXPECTED ADVERSE EVENTS

Adverse events will be graded according to the NCI CTCAE 3.0 (see http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/ctcaev3.pdf) and recorded on CRFs.

Expected adverse events is listed below. A more comprehensive list of expected AEs can be found in appendices 11 and 12.

Gemcitabine

1. Leucopenia and thrombocytopenia are common. Mainly mild to moderate.
2. Shortness of breath frequently occurs during the infusion although is typically transient
3. Nausea, vomiting, sore mouth and diarrhoea are common
4. Elevation in ALT and ALP occurs frequently. Raised bilirubin is less common. Serious liver dysfunction is very rare.
5. Haematuria and proteinuria are common but rarely are of any significance
6. Oedema (limb and facial swelling) is common but reversible after stopping treatment and not associated with any organ dysfunction.
7. A flu like illness and skin rash may occur after Gemcitabine infusion although this is typically transient and treated with paracetemol or anti-histamines.

Bexarotene

1. Leucopenia is common following treatment. Anaemia occurs less frequently.
2. Hypothyroidism occurs frequently. All patients will have thyroid function assessed before and during treatment and receive thyroxine (thyroid hormone replacement) tablets if required
3. Hyperlipidaemia (high blood triglycerides and cholesterol) occurs in the majority of patients. All patients will have serum lipids assessed before and during treatment and all will receive lipid lowering medication.
4. Nausea, vomiting, diarrhoea, constipation, flatulence and dry mouth are common.
5. Acute pancreatitis occurs uncommonly as a consequence of hyperlipidaemia - see above and patients will also be advised to moderate alcohol intake.
6. Insomnia and dizziness occur frequently
7. Arthralgia, bone pains, myalgia and asthenia
8. Skin rashes, dry skin and pruritis.

APPENDIX 2: CTCL STAGING

Table 3: CTCL staging

T Skin	
T1	Limited plaques, papules or eczematous patches (<10% of skin surfaces)
T2	Generalised plaques, papules or eczematous patches (>10% of skin surfaces)
T3	Tumours
T4	Generalised erythroderma

N Lymph nodes	
N0	No clinically abnormal lymph nodes
N1	Palpable nodes with no histological involvement
N2	Non-palpable nodes with histological involvement
N3	Palpable nodes with histological involvement

B Peripheral blood	
B0	Atypical circulating cells (Sézary) not present (<5%)
B1	Atypical circulating cells present (>5%)

M Visceral organ involvement	
M0	No visceral organ involvement
M1	Visceral organ involvement

CLINICAL STAGING	
Ia	T1, N0, M0
Ib	T2, N0, M0
IIa	T1-2, N1, M0
IIb	T3, N0-1, M0
III	T4, N0-1, M0
IVa	T1-4, N2-3, M0
IVb	T1-4, N3, M1

APPENDIX 3: DECLARATION OF HELSINKI

Adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964, and amended by the:
29th WMA General Assembly, Tokyo, Japan, October 1975
35th WMA General Assembly, Venice, Italy, October 1983
41st WMA General Assembly, Hong Kong, September 1989
48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996
52nd WMA General Assembly, Edinburgh, Scotland, October 2000
53th WMA General Assembly, Washington 2002 (Note of Clarification on paragraph 29 added)
55th WMA General Assembly, Tokyo 2004 (Note of Clarification on Paragraph 30 added)
59th WMA General Assembly, Seoul, October 2008

A. INTRODUCTION

1. The World Medical Association (WMA) has developed the Declaration of Helsinki as a statement of ethical principles for medical research involving human subjects, including research on identifiable human material and data.

   The Declaration is intended to be read as a whole and each of its constituent paragraphs should not be applied without consideration of all other relevant paragraphs.

2. Although the Declaration is addressed primarily to physicians, the WMA encourages other participants in medical research involving human subjects to adopt these principles.

3. It is the duty of the physician to promote and safeguard the health of patients, including those who are involved in medical research. The physician's knowledge and conscience are dedicated to the fulfilment of this duty.

4. The Declaration of Geneva of the WMA binds the physician with the words, "The health of my patient will be my first consideration," and the International Code of Medical Ethics declares that, "A physician shall act in the patient's best interest when providing medical care."

5. Medical progress is based on research that ultimately must include studies involving human subjects. Populations that are underrepresented in medical research should be provided appropriate access to participation in research.

6. In medical research involving human subjects, the well-being of the individual research subject must take precedence over all other interests.

7. The primary purpose of medical research involving human subjects is to understand the causes, development and effects of diseases and improve preventive, diagnostic and therapeutic interventions (methods, procedures and treatments). Even the best current interventions must be evaluated continually through research for their safety, effectiveness, efficiency, accessibility and quality.

8. In medical practice and in medical research, most interventions involve risks and burdens.

9. Medical research is subject to ethical standards that promote respect for all human subjects and protect their health and rights. Some research populations are particularly vulnerable and need special protection. These include those who cannot give or refuse consent for themselves and those who may be vulnerable to coercion or undue influence.

10. Physicians should consider the ethical, legal and regulatory norms and standards for research involving human subjects in their own countries as well as applicable

international norms and standards. No national or international ethical, legal or regulatory requirement should reduce or eliminate any of the protections for research subjects set forth in this Declaration.

B. BASIC PRINCIPLES FOR ALL MEDICAL RESEARCH

11. It is the duty of physicians who participate in medical research to protect the life, health, dignity, integrity, right to self-determination, privacy, and confidentiality of personal information of research subjects.

12. Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and adequate laboratory and, as appropriate, animal experimentation. The welfare of animals used for research must be respected.

13. Appropriate caution must be exercised in the conduct of medical research that may harm the environment.

14. The design and performance of each research study involving human subjects must be clearly described in a research protocol. The protocol should contain a statement of the ethical considerations involved and should indicate how the principles in this Declaration have been addressed. The protocol should include information regarding funding, sponsors, institutional affiliations, other potential conflicts of interest, incentives for subjects and provisions for treating and/or compensating subjects who are harmed as a consequence of participation in the research study. The protocol should describe arrangements for post-study access by study subjects to interventions identified as beneficial in the study or access to other appropriate care or benefits.

15. The research protocol must be submitted for consideration, comment, guidance and approval to a research ethics committee before the study begins. This committee must be independent of the researcher, the sponsor and any other undue influence. It must take into consideration the laws and regulations of the country or countries in which the research is to be performed as well as applicable international norms and standards but these must not be allowed to reduce or eliminate any of the protections for research subjects set forth in this Declaration. The committee must have the right to monitor ongoing studies. The researcher must provide monitoring information to the committee, especially information about any serious adverse events. No change to the protocol may be made without consideration and approval by the committee.

16. Medical research involving human subjects must be conducted only by individuals with the appropriate scientific training and qualifications. Research on patients or healthy volunteers requires the supervision of a competent and appropriately qualified physician or other health care professional. The responsibility for the protection of research subjects must always rest with the physician or other health care professional and never the research subjects, even though they have given consent.

17. Medical research involving a disadvantaged or vulnerable population or community is only justified if the research is responsive to the health needs and priorities of this population or community and if there is a reasonable likelihood that this population or community stands to benefit from the results of the research.

18. Every medical research study involving human subjects must be preceded by careful assessment of predictable risks and burdens to the individuals and communities

involved in the research in comparison with foreseeable benefits to them and to other individuals or communities affected by the condition under investigation.

19. Every clinical trial must be registered in a publicly accessible database before recruitment of the first subject.

20. Physicians may not participate in a research study involving human subjects unless they are confident that the risks involved have been adequately assessed and can be satisfactorily managed. Physicians must immediately stop a study when the risks are found to outweigh the potential benefits or when there is conclusive proof of positive and beneficial results.

21. Medical research involving human subjects may only be conducted if the importance of the objective outweighs the inherent risks and burdens to the research subjects.

22. Participation by competent individuals as subjects in medical research must be voluntary. Although it may be appropriate to consult family members or community leaders, no competent individual may be enrolled in a research study unless he or she freely agrees.

23. Every precaution must be taken to protect the privacy of research subjects and the confidentiality of their personal information and to minimize the impact of the study on their physical, mental and social integrity.

24. In medical research involving competent human subjects, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail, and any other relevant aspects of the study. The potential subject must be informed of the right to refuse to participate in the study or to withdraw consent to participate at any time without reprisal. Special attention should be given to the specific information needs of individual potential subjects as well as to the methods used to deliver the information. After ensuring that the potential subject has understood the information, the physician or another appropriately qualified individual must then seek the potential subject's freely-given informed consent, preferably in writing. If the consent cannot be expressed in writing, the non-written consent must be formally documented and witnessed.

25. For medical research using identifiable human material or data, physicians must normally seek consent for the collection, analysis, storage and/or reuse. There may be situations where consent would be impossible or impractical to obtain for such research or would pose a threat to the validity of the research. In such situations the research may be done only after consideration and approval of a research ethics committee.

26. When seeking informed consent for participation in a research study the physician should be particularly cautious if the potential subject is in a dependent relationship with the physician or may consent under duress. In such situations the informed consent should be sought by an appropriately qualified individual who is completely independent of this relationship.

27. For a potential research subject who is incompetent, the physician must seek informed consent from the legally authorized representative. These individuals must not be included in a research study that has no likelihood of benefit for them unless it is intended to promote the health of the population represented by the potential subject, the research cannot instead be performed with competent persons, and the research entails only minimal risk and minimal burden.

28. When a potential research subject who is deemed incompetent is able to give assent to decisions about participation in research, the physician must seek that assent in addition to the consent of the legally authorized representative. The potential subject's dissent should be respected.

29. Research involving subjects who are physically or mentally incapable of giving consent, for example, unconscious patients, may be done only if the physical or mental condition that prevents giving informed consent is a necessary characteristic of the research population. In such circumstances the physician should seek informed consent from the legally authorized representative. If no such representative is available and if the research cannot be delayed, the study may proceed without informed consent provided that the specific reasons for involving subjects with a condition that renders them unable to give informed consent have been stated in the research protocol and the study has been approved by a research ethics committee. Consent to remain in the research should be obtained as soon as possible from the subject or a legally authorized representative.

30. Authors, editors and publishers all have ethical obligations with regard to the publication of the results of research. Authors have a duty to make publicly available the results of their research on human subjects and are accountable for the completeness and accuracy of their reports. They should adhere to accepted guidelines for ethical reporting. Negative and inconclusive as well as positive results should be published or otherwise made publicly available. Sources of funding, institutional affiliations and conflicts of interest should be declared in the publication. Reports of research not in accordance with the principles of this Declaration should not be accepted for publication.

C. ADDITIONAL PRINCIPLES FOR MEDICAL RESEARCH COMBINED WITH MEDICAL CARE

31. The physician may combine medical research with medical care only to the extent that the research is justified by its potential preventive, diagnostic or therapeutic value and if the physician has good reason to believe that participation in the research study will not adversely affect the health of the patients who serve as research subjects.

32. The benefits, risks, burdens and effectiveness of a new intervention must be tested against those of the best current proven intervention, except in the following circumstances:

- The use of placebo, or no treatment, is acceptable in studies where no current proven intervention exists; or

- Where for compelling and scientifically sound methodological reasons the use of placebo is necessary to determine the efficacy or safety of an intervention and the patients who receive placebo or no treatment will not be subject to any risk of serious or irreversible harm. Extreme care must be taken to avoid abuse of this option.

33. At the conclusion of the study, patients entered into the study are entitled to be informed about the outcome of the study and to share any benefits that result from it, for example, access to interventions identified as beneficial in the study or to other appropriate care or benefits.

34. The physician must fully inform the patient which aspects of the care are related to the research. The refusal of a patient to participate in a study or the patient's decision to withdraw from the study must never interfere with the patient-physician relationship.

35. In the treatment of a patient, where proven interventions do not exist or have been ineffective, the physician, after seeking expert advice, with informed consent from the patient or a legally authorized representative, may use an unproven intervention if in the physician's judgement it offers hope of saving life, re-establishing health or alleviating suffering. Where possible, this intervention should be made the object of research, designed to evaluate its safety and efficacy. In all cases, new information should be recorded and, where appropriate, made publicly available.

APPENDIX 4: SKINDEX 29 & EORTC QLQ-C30

DERMATOLOGY SURVEY

This survey concerns the skin condition which has bothered you the most during the past four weeks.

These questions concern your feelings over the past 4 weeks about **the skin condition that has bothered you the most**. Check (tick) the answer that comes closest to the way you have been feeling.

HOW OFTEN DURING THE PAST FOUR WEEKS DO THESE STATEMENTS DESCRIBE YOU?	NEVER	RARELY	SOME-TIMES	OFTEN	ALL THE TIME
1. My skin hurts	☐1	☐2	☐3	☐4	☐5
2. My skin condition affects how well I sleep	☐1	☐2	☐3	☐4	☐5
3. I worry that my skin condition may be serious	☐1	☐2	☐3	☐4	☐5
4. My skin condition makes it hard to work or do hobbies	☐1	☐2	☐3	☐4	☐5
5. My skin condition affects my social life	☐1	☐2	☐3	☐4	☐5
6. My skin condition makes me feel depressed	☐1	☐2	☐3	☐4	☐5
7. My skin condition burns or stings	☐1	☐2	☐3	☐4	☐5
8. I tend to stay at home because of my skin condition	☐1	☐2	☐3	☐4	☐5
9. I worry about getting scars from my skin condition	☐1	☐2	☐3	☐4	☐5
10. My skin itches	☐1	☐2	☐3	☐4	☐5
11. My skin condition affects how close I can be with those I love	☐1	☐2	☐3	☐4	☐5
12. I am ashamed of my skin condition	☐1	☐2	☐3	☐4	☐5
13. I worry that my skin condition may get worse	☐1	☐2	☐3	☐4	☐5
14. I tend to do things by myself because of my skin condition	☐1	☐2	☐3	☐4	☐5
15. I am angry about my skin condition	☐1	☐2	☐3	☐4	☐5
16. Water bothers my skin condition (bathing, washing hands)	☐1	☐2	☐3	☐4	☐5
17. My skin condition makes showing affection difficult	☐1	☐2	☐3	☐4	☐5
18. I worry about side-effects from skin medications / treatments	☐1	☐2	☐3	☐4	☐5
19. My skin is irritated	☐1	☐2	☐3	☐4	☐5
20. My skin condition affects my interactions with others	☐1	☐2	☐3	☐4	☐5

Skindex29

Please turn to next page

These questions concern your feelings over the past 4 weeks about **the skin condition that has bothered you the most**. Check (tick) the answer that comes closest to the way you have been feeling.

HOW OFTEN DURING THE PAST FOUR WEEKS DO THESE STATEMENTS DESCRIBE YOU?	NEVER	RARELY	SOME-TIMES	OFTEN	ALL THE TIME
21. I am embarrassed by my skin condition	☐1	☐2	☐3	☐4	☐5
22. My skin condition is a problem for the people I love	☐1	☐2	☐3	☐4	☐5
23. I am frustrated by my skin condition	☐1	☐2	☐3	☐4	☐5
24. My skin is sensitive	☐1	☐2	☐3	☐4	☐5
25. My skin condition affects my desire to be with people	☐1	☐2	☐3	☐4	☐5
26. I am humiliated by my skin condition	☐1	☐2	☐3	☐4	☐5
27. My skin condition bleeds	☐1	☐2	☐3	☐4	☐5
28. I am annoyed by my skin condition	☐1	☐2	☐3	☐4	☐5
29. My skin condition interferes with my sex life	☐1	☐2	☐3	☐4	☐5
30. My skin condition makes me tired	☐1	☐2	☐3	☐4	☐5

Skindex29

NCRI and Cancer Research UK GEMBEX Trial

ENGLISH

EORTC QLQ-C30 (version 3)

We are interested in some things about you and your health. Please answer all of the questions yourself by circling the number that best applies to you. There are no "right" or "wrong" answers. The information that you provide will remain strictly confidential.

Please fill in your initials:
Your birthdate (Day, Month, Year):
Today's date (Day, Month, Year): 31

		Not at All	A Little	Quite a Bit	Very Much
1.	Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?	1	2	3	4
2.	Do you have any trouble taking a long walk?	1	2	3	4
3.	Do you have any trouble taking a short walk outside of the house?	1	2	3	4
4.	Do you need to stay in bed or a chair during the day?	1	2	3	4
5.	Do you need help with eating, dressing, washing yourself or using the toilet?	1	2	3	4

During the past week:		Not at All	A Little	Quite a Bit	Very Much
6.	Were you limited in doing either your work or other daily activities?	1	2	3	4
7.	Were you limited in pursuing your hobbies or other leisure time activities?	1	2	3	4
8.	Were you short of breath?	1	2	3	4
9.	Have you had pain?	1	2	3	4
10.	Did you need to rest?	1	2	3	4
11.	Have you had trouble sleeping?	1	2	3	4
12.	Have you felt weak?	1	2	3	4
13.	Have you lacked appetite?	1	2	3	4
14.	Have you felt nauseated?	1	2	3	4
15.	Have you vomited?	1	2	3	4
16.	Have you been constipated?	1	2	3	4

Please go on to the next page

ENGLISH

During the past week:	Not at All	A Little	Quite a Bit	Very Much
17. Have you had diarrhea?	1	2	3	4
18. Were you tired?	1	2	3	4
19. Did pain interfere with your daily activities?	1	2	3	4
20. Have you had difficulty in concentrating on things, like reading a newspaper or watching television?	1	2	3	4
21. Did you feel tense?	1	2	3	4
22. Did you worry?	1	2	3	4
23. Did you feel irritable?	1	2	3	4
24. Did you feel depressed?	1	2	3	4
25. Have you had difficulty remembering things?	1	2	3	4
26. Has your physical condition or medical treatment interfered with your family life?	1	2	3	4
27. Has your physical condition or medical treatment interfered with your social activities?	1	2	3	4
28. Has your physical condition or medical treatment caused you financial difficulties?	1	2	3	4

For the following questions please circle the number between 1 and 7 that best applies to you

29. How would you rate your overall health during the past week?

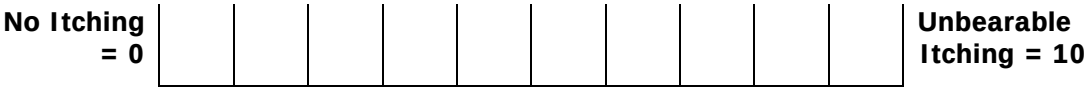
1	2	3	4	5	6	7
Very poor						Excellent

30. How would you rate your overall quality of life during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

APPENDIX 5: PRURITUS SCALE

VISUAL ANALOGUE SCALE - PRURITUS



PLEASE INDICATE THE LEVEL OF ITCHING BY MARKING THE LINE ABOVE APPROPRIATELY

APPENDIX 6: RECIST CRITERIA

Response Evaluation Criteria in Solid Tumours (RECIST) v1.0

Quick Reference:

Eligibility

- Only patients with measurable disease at baseline should be included in protocols where objective tumor response is the primary endpoint.
    - **Measurable disease** - the presence of at least one measurable lesion. If the measurable disease is restricted to a solitary lesion, its neoplastic nature should be confirmed by cytology/histology.
    - **Measurable lesions** - lesions that can be accurately measured in at least one dimension with longest diameter ≥20 mm using conventional techniques or ≥10 mm with spiral CT scan.
    - **Non-measurable lesions** - all other lesions, including small lesions (longest diameter <20 mm with conventional techniques or <10 mm with spiral CT scan), i.e., bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusion, inflammatory breast disease, lymphangitis cutis/pulmonis, cystic lesions, and also abdominal masses that are not confirmed and followed by imaging techniques; and.
- All measurements should be taken and recorded in metric notation, using a ruler or calipers. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 4 weeks before the beginning of the treatment.
- The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up.
- Clinical lesions will only be considered measurable when they are superficial (e.g., skin nodules and palpable lymph nodes). For the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.

Response Criteria

Table 4: Evaluation of target lesions

*** Complete Response (CR):**	Disappearance of all target lesions
*** Partial Response (PR):**	At least a 30% decrease in the sum of the LD of target lesions, taking as reference the baseline sum LD
*** Progressive Disease (PD):**	At least a 20% increase in the sum of the LD of target lesions, taking as reference the smallest sum LD recorded since the treatment started or the appearance of one or more new lesions
*** Stable Disease (SD):**	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum LD since the treatment started

Table 5: Evaluation of non target lesions

*** Complete Response (CR):**	Disappearance of all non-target lesions and normalization of tumor marker level
*** Incomplete Response/ Stable Disease (SD):**	Persistence of one or more non-target lesion(s) or/and maintenance of tumor marker level above the normal limits
*** Progressive Disease (PD):**	Appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions (1)

Although a clear progression of “non target” lesions only is exceptional, in such circumstances, the opinion of the treating physician should prevail and the progression status should be confirmed later on by the review panel (or study chair).

Evaluation of best overall response

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for PD the smallest measurements recorded since the treatment started). In general, the patient's best response assignment will depend on the achievement of both measurement and confirmation criteria

Table 6: Evaluation of best overall response

Target lesions	Non-Target lesions	New Lesions	Overall response
CR	CR	No	CR
CR	Incomplete response/SD	No	PR
PR	Non-PD	No	PR
SD	Non-PD	No	SD
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be classified as having "symptomatic deterioration". Every effort should be made to document the objective progression even after discontinuation of treatment.

In some circumstances it may be difficult to distinguish residual disease from normal tissue. When the evaluation of complete response depends on this determination, it is recommended that the residual lesion be investigated (fine needle aspirate/biopsy) to confirm the complete response status

APPENDIX 7: ECOG PERFORMANCE STATUS

Table 7: ECOG Performance Status

Grade	ECOG
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
5	Dead

From: Oken, M.M., Creech, R.H., Tormey, D.C., Horton, J., Davis, T.E., McFadden, E.T., Carbone, P.P.: Toxicity And Response Criteria Of The Eastern Cooperative Oncology Group. Am J Clin Oncol 5:649-655, 1982.

APPENDIX 8: STANDARDISED PHOTOGRAPHY

Standardised conditions will be used for lighting, flash intensity and distance of camera from the patient.

- Photographs will be taken at **baseline**, at the **end of Gemcitamine + Bexarotene chemotherapy** (end of week 12), at **week 24** (or 4 weeks after last trial treatment if sooner), and at **disease progression**.
- All **photographs should include a ruler or other measuring device** for accurate assessment of lesion size, eyes should be blanked.
- Where possible use a camera with a 105mm lens
- Target areas are to be chosen at baseline, examples include: upper anterior body/ lower anterior body, palm left/ palm right, soles of feet/ dorsum feet.
- At each disease assessment, photography (photos should be repeated x3) for each patient will include:
    - Hemi body views (4 x 1/2 body views)
    - 1-15 shots for views commonly termed “PUVA views” (see below)
    - Shots of all target lesions at a 1- 4 ratio with further closer views as appropriate to individual patients.

Electronic copies of photographs should be sent to the trial team at UCL CTC, either by email to gembex@ctc.ucl.ac.uk, or on a CD-ROM to:

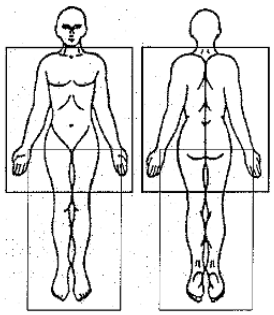
GemBex, Haematology Trials Group

CR-UK & UCL Cancer Trials Centre

90 Tottenham Court Road

London W1T 4TJ

- PUVA views 4 x ½ body views see
- (diagram below)



Examples include:

- upper anterior body / lower anterior body (see above)
- upper posterior body / lower posterior body (see above)

NOTES:

A **coded** patient label should be added to each photo for identification within the trial but to allow electronic storage **without divulging actual patient details**.

Shots of the face may be taken but the eyes should be blanked to however this will not necessarily ensure complete anonymity of the patient.

APPENDIX 9: SCHEDULE OF STUDY ACTIVITIES

Table 8a: Schedule of study activities during Screening & initial GemBex chemotherapy

EVALUATIONS	Screening[1]	Gemcitabine + Bexarotene Cycles 1-4 (weeks 1-12)	
		Day 1	Day 8
Informed consent	X[1]		
Medical history	X[1]		
Histology of skin, lymph node and peripheral blood	X[1]		
Physical examination	X[1]	X	
Disease assessment (including SWAT score)	X[1]	X	
Photography of lesions	X[1]		
Concomitant medications	X[1]	X	X
Body weight	X[1]	X	
Height	X[1]		
Vital signs[2]	X[1]	X	X
ECOG performance status	X[1]	X	X
FBC with differential & CD4 count (see below)[3]	X[1, 4]	X[3]	X[3]
Biochemistry (see below)[5]	X[1, 4]	X[5]	X[5]
Lipid profile, CPK & thyroid function	X[1]	X	X
Urinalysis	X[1]		
Urine pregnancy test	X[1]		
ECG	X[1]		
CT chest/abdomen/pelvis[6]	X[7]		
Gemcitabine dosing		X	X
Adverse events		X	X
Skindex 29 & EORTC QLQ-C30	X	X	

Bloods required during GemBex chemotherapy:

Gemcitabine + Bexarotene			
Cycle 1	Week 1	Day 1	FBC, U&E, LFT, TFT, fasting lipids, CPK, CD4 count
	Week 2	Day 1	FBC, U&E, LFT, TFT, fasting lipids, CPK
	Week 3	Day 1	TFT, fasting lipids, CPK
Cycle 2	Week 4	Day 1	FBC, U&E, LFT, TFT, fasting lipids, CPK, CD4 count
	Week 5	Day 1	FBC, U&E, LFT
	Week 6		No tests required
Cycle 3	Week 7	Day 1	FBC, U&E, LFT, TFT, fasting lipids, CPK, CD4 count
	Week 8	Day 1	FBC, U&E, LFT
	Week 9	Day 1	No tests required
Cycle 4	Week 10	Day 1	FBC, U&E, LFT, TFT, fasting lipids, CPK, CD4 count
	Week 11	Day 1	FBC, U&E LFT
	Week 12		No tests required

- Further samples may be taken if clinically indicated.
- **REPEAT FBC AT LEAST TWICE WEEKLY IF PATIENT HAS GRADE IV NEUTROPENIA OR THROMBOCYTOPENIA**
- **Measurement of lipids and thyroid function may need to be performed more frequently if results are out of range**

Footnotes to table 8a

[1] Screening tests must be performed within 2 weeks prior to study entry unless otherwise stated
[2] Vital signs to include pulse, blood pressure & temperature
[3] Performed prior to each dose of gemcitabine. In case of grade 4 neutropenia or thrombocytopenia, repeat at least twice weekly until resolution. Further testing may be performed if clinically indicated
[4] Haematology & biochemistry assessment on day 1 or cycle 1 is required only if the baseline/screening visit is >1 week prior to the start of cycle 1.
[5] Assessment of U&E and LFT prior to each dose of gemcitabine. In addition, LFT, CPK, fasting lipids, T4 & TSH to be performed weekly for 1st month and then at the start of each subsequent cycle. Further testing may be performed if clinically indicated.
[6] CT scan will be repeated at the end of week 12 and end of treatment if abnormal at baseline
[7] CT scan to be performed within 4 weeks prior to study entry (see section 4.4)

Table 8b: Schedule of study activities during Bexarotene maintenance

EVALUATIONS	Bexarotene maintenance (week 13until progression or withdrawal due to lack of toleration of bexarotene)[1]			
	Week 13, day 1	Week 17, day 1	Week 24	Every 8 weeks thereafter
Physical examination	X	X	X	X
Disease assessment (including SWAT score)	X	X	X	X
Photography of lesions	X		X	
Concomitant medications	X	X	X	X
Body weight	X		X	X
Vital signs[2]	X	X	X	X
ECOG performance status	X	X	X	X
FBC with differential & CD4 count (see below)[3]	X[3]	X[3]	X	X
Biochemistry (see below)[4]	X[4]	X[4]	X	X
Lipid profile, CPK & thyroid function[4]	X[4]	X[4]	X	X
CT chest/abdomen/pelvis	X[5]		X[5]	
Adverse events	X	X	X	X
Skindex 29 & EORTC QLQ-C30	X	X	X	X

Bloods required during Bexarotene maintenance

Bexarotene maintenance and follow up		
Week 13	D1	FBC, U&E, LFT, TFT, fasting lipids, CPK, CD4 count
Week 17	D1	FBC, U&E, LFT, TFT, fasting lipids, CPK, CD4 count
Week 24	D1	FBC, U&E, LFT, TFT, fasting lipids, CPK, CD4 count
Every 8 weeks thereafter	D1	FBC, U&E, LFT, TFT, fasting lipids, CPK, CD4 count
Further samples may be taken if clinically indicated. **Repeat FBC at least twice weekly if grade IV neutropenia or thrombocytopenia** **Measurement of lipids and thyroid function may need to be performed more frequently if results out of range**		

Footnotes to table 8b

[1] In patients showing adequate response to GemBex only
[2] Vital signs to include pulse, blood pressure & temperature
[3] Performed weekly during bexarotene maintenance. In case of grade 4 neutropenia or thrombocytopenia, repeat at least twice weekly until resolution. Further testing may be performed if clinically indicated
[4] U&E, LFT, CPK, fasting lipids, T4 & TSH to be performed 4-weekly during bexarotene maintenance. Further testing may be performed if clinically indicated.
[5] Only required if nodal or visceral involvement at baseline

Table 8c: Schedule of study activities during follow up for all patients withdrawn from treatment

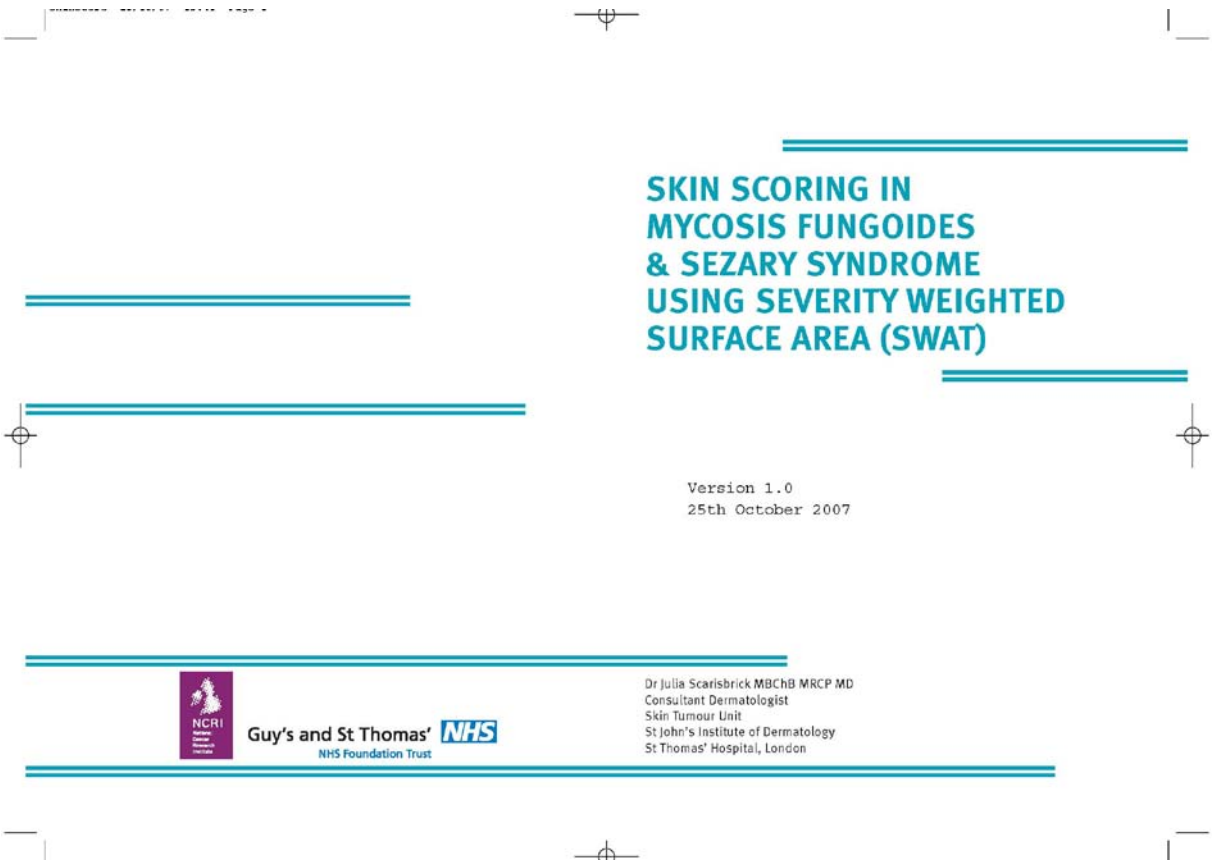
EVALUATIONS	End of treatment (4 weeks post treatment)	Follow up		Disease progression
		Until 2 years post study entry or until progression (8-weekly)	Post-progression or >2 years after study entry (6-monthly)	
Histology of skin, lymph node and peripheral blood	X[1]			
Physical examination	X	X		
Disease assessment (including SWAT score)	X	X	X	X
Photography of lesions	X			X
Concomitant medications	X	X	X	
Body weight	X	X		
Vital signs	X	X		
ECOG performance status	X	X		
FBC with differential & CD4 count	X	X		
Biochemistry	X	X		
Lipid profile, CPK & thyroid function	X	X		
CT chest/abdomen/pelvis	X[2]			
Adverse events (follow up of ongoing AEs from treatment phase until resolution)	X	X		
Skindex 29 & EORTC QLQ-C30	X	X		

Footnotes to table 8c

[1] Optional repeat biopsy to confirm CR

[2] Only required if nodal or visceral involvement at baseline

APPENDIX 10: SKIN SCORING IN MYCOSIS FUNGOIDES & SEZARY SYNDROME USING SEVERITY WEIGHTED SURFACE AREA (SWAT)



SKIN SCORING IN MYCOSIS FUNGOIDES & SEZARY SYNDROME USING SEVERITY WEIGHTED SURFACE AREA (SWAT)

Version 1.0
25th October 2007

NCRI

Guy's and St Thomas' NHS
NHS Foundation Trust

Dr Julia Scarisbrick MBChB MRCP MD
Consultant Dermatologist
Skin Tumour Unit
St John's Institute of Dermatology
St Thomas' Hospital, London

Skin Scoring

There are various methods of quantifying skin disease tumour burden in CTCL including:-

- Physician global assessment (PGA: no disease, mild, moderate, severe (0-3))
- Total body surface area (BSA) 0 - 100%
- Severity-weighted surface area (SWAT) 0 - 300
- Clinical photos

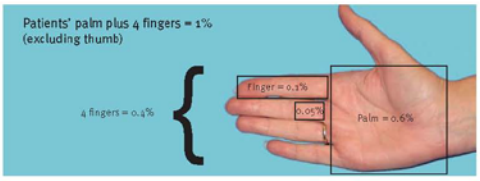
SWAT scores reflect skin surface area involved and the type of skin lesion. It is therefore a good method for measuring skin tumour burden in CTCL.
This pamphlet is aimed at teaching how to assess a patient's skin score using a SWAT assessment.

Calculating SWAT Score

The adult body may be divided and each structure given an approximate surface area. This approach has been used to assess psoriasis and burns as well as CTCL.

Anatomic structure	*Surface area*
Head	9%
Anterior torso	18%
Posterior torso	18%
Each leg	18%
Each arm	9%
Genital/perineum	1%

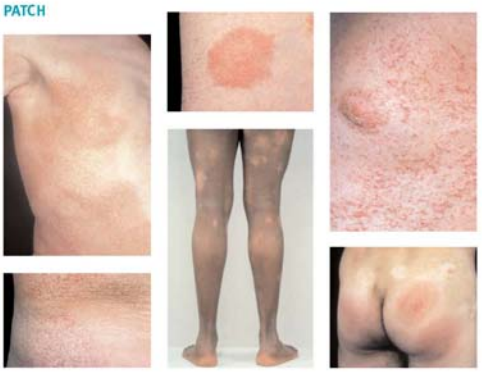
The palm method can be used to calculate the area of involvement with CTCL. The palm and 4 fingers of a patient excluding the thumb and measured from the wrist to the fingertips is equal to 1%. The palm corresponds to 0.6% and the index finger to 0.1% as depicted below.



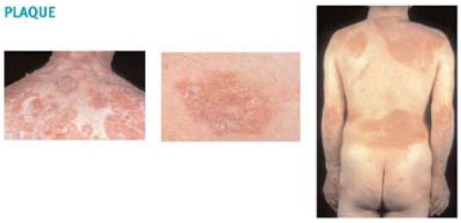
To perform a SWAT assessment body surface area for patch, plaque and tumour need to be calculated seperately

- Patch disease is defined as flat erythema, light scale
- Plaque disease is defined as an elevated area <5mm, palpable, scaley, may be excoriated and includes ketatodema of hands/feet
- Tumors are defined as dome-shaped, nodular lesions ≥5mm in vertical height
- Ulcerative lesions are those with significant loss of superficial skin, including the entire epidermis and some portion of the upper dermis and are scored as tumour stage disease

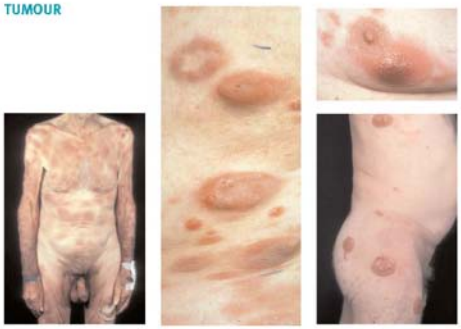
PATCH



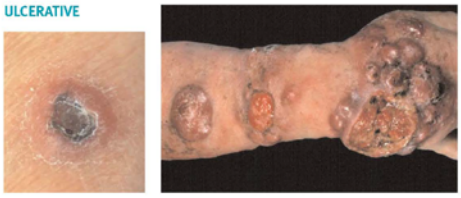
PLAQUE



TUMOUR



ULCERATIVE



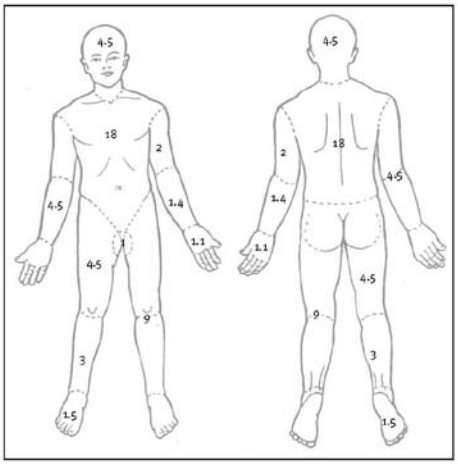
To calculate the severity weighted BSA or SWAT

- Firstly the surface area affected by patch, plaque and tumour is calculated and recorded in the table below
- The surface area affected is then multiplied by a severity weighting factor 1, 2, or 3 for patch, plaque and tumour respectively
- The sum of these 3 values is added and an overall SWAT score between 0-300 is achieved

Table for Calculating SWAT scores

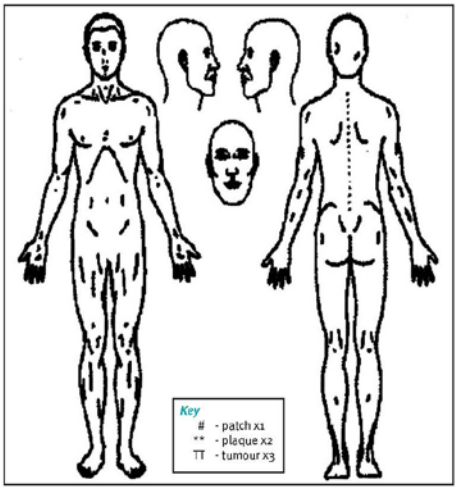
% Surface Area	Possible BSA	%BSA Patch	%BSA Plaque	%BSA Plaque x2	%BSA Tumour	%BSA Tumour x3	Total
Head	9						
Anterior Trunk	18						
Posterior Trunk	18						
Left Arm	9						
Right Arm	9						
Left Leg	18						
Right Leg	18						
Perineum/genitals	1						
Skin Score / 300							

Percentage body surface area may be further divided as shown below – this may aid skin scoring and allow 'double checking' of scores.



A diagramatic representation of skin involved should also be filled in to document the site of skin lesions.

Type and position of skin lesions



Erythrodermic CTCL

- The SWAT system needs to be modified for informative assessment of erythrodermic CTCL (mSWAT)
- In erythrodermic CTCL, the degree of oedema or infiltration may be used for mapping skin severity
- Erythroderma with mild infiltration is mapped as patch disease (x1) defined as erythema but no oedema or fissuring
- Erythroderma with moderate infiltration is mapped as plaques (x2) defined as erythema with oedema or exudation
- Erythroderma with severe infiltration is mapped as tumours (x3) defined as - erythema with tumourous lesions, fissuring or ulceration
- Modified SWAT (mSWAT) = (mild %TBSA x 1) + (moderate %TBSA x 2) + (tumorous or ulcererative %TBSA x 3).

ERYTHRODERMA

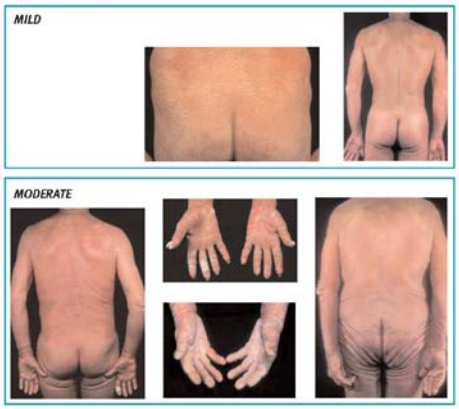


Table for calculating mSWAT scores

% Surface Area	Possible BSA	%BSA Mild	%BSA Moderate	%BSA Moderate x2	%BSA Severe	%BSA Severe x3	Total
Head	9						
Anterior Trunk	18						
Posterior Trunk	18						
Left Arm	9						
Right Arm	9						
Left Leg	18						
Right Leg	18						
Perineum/genitals	1						
Skin Score / 300							

SWAT	*mSWAT*
Patch/Plaque/Tumours	*Erythroderma*
0 = normal skin	0 = normal skin
x1 = patch stage disease	x1 = erythema with mild infiltration, no oedema
x2 = plaque stage disease	x2 = erythema with mod. infiltration, oedema or exudate
x3 = tumours or ulceration	x3 = erythema with tumorous infiltration or ulceration or fissuring

Pros & cons of SWAT

Pros

- The SWAT score is a useful clinical measurement for CTCL
- Captures overall physician impressions of disease status on a continuous dimensionless numerical scale
- Provides a defined, objective, and sensitive quantitative measure
- Relates to the %TBSA and nature of skin lesions
- Is a suitable tool for individual patient skin assessment & for use in clinical trials and outcome comparisons

Cons

- Does not assess all aspects of the disease
- No measure of internal involvement, psychosocial disability, or comorbidity

To ensure accurate recording of skin disease photographs should also be taken as a visual measure of skin tumour burden using a standardised method.

Standardised Photography

- Standardised conditions for lighting, flash intensity and distance from patient
- Photographs at baseline and monthly
- All photographs should include a ruler, eyes should be blanked
- Suggested hemi views 4x1/2 body views

Where possible use a camera with a 105mm lens

Target areas

To be chosen at baseline

examples include:

- upper anterior body / lower anterior body
- upper posterior body / lower posterior body
- palm left / palm right
- dorsum hand left / dorsum hand right
- soles of feet / dorsum feet
- head front / head back

APPENDIX 11: GEMCITABINE EXPECTED ADVERSE EVENTS

The following information has been supplied from the Summary of Product Characteristics (SmPC) for Gemcitabine (Gemzar®) last updated on 04.09.2007. Investigators should cross-reference the information in this appendix with the current SmPC.

The most commonly reported adverse drug reactions associated with Gemcitabine treatment include: nausea, with or without vomiting, raised liver transaminases (AST/ALT) and alkaline phosphatase, reported in approximately 60% of patients; proteinuria and haematuria, reported in approximately 50% patients; dyspnoea, reported in 10-40% of patients (highest incidence in lung cancer patients); allergic skin rashes occur in approximately 25% of patients and are associated with itching in 10% of patients. The frequency and severity of the adverse reactions are affected by the dose, infusion rate, and intervals between doses. Dose-limiting adverse reactions are reductions in thrombocyte, leucocyte, and granulocyte counts.

The following table of undesirable effects and frequencies is based on clinical trial and post-marketing spontaneous reports.

Condition	**Very Common** *(>1/10)*	**Common** *<>1/100, <1/10)*	**Uncommon** *(>1/1000, <1/100)*	**Rare** *(>1/10000, <1/1000)*	**Very Rare** *(<1/10000)*
Blood and Lymphatic System Disorders	Leucopenia	Febrile neutropenia			Thrombocythaemia
	Thrombocytopenia				
	Neutropenia (frequency of Grade 3 is 19.3%, and of Grade 4 6%. Bone-marrow suppression is usually mild to moderate and mostly affects the granulocyte count)				
	Anaemia				
Immune System Disorders					Anaphylactoid reaction
Nervous System Disorders		Somnolence			

Condition	Very Common *(>1/10)*	Common *(>1/100, <1/10)*	Uncommon *(>1/1000, <1/100)*	Rare *(<1/1000, >1/10000)*	Very Rare *(<1/10000)*
Cardiac Disorders					Myocardial infarct
					Congestive heart failure
					Arrhythmia (predominantly supraventricular in nature)
Vascular Disorders				Hypotension	Clinical signs of peripheral vasculitis and gangrene
Respiratory, Thoracic, and Mediastinal Disorders	Dyspnoea (usually mild and passes rapidly without treatment)		Bronchospasm (usually mild and transient but may require parenteral treatment)	Adult respiratory distress syndrome (ARDS)	
				Interstitial pneumonitis together with pulmonary infiltrates (symptoms may be relieved with steroid treatment)	
				Pulmonary oedema	
Gastro-intestinal Disorders	Nausea	Stomatitis and ulceration of mouth			
	Vomiting	Diarrhoea			
		Constipation			
Hepatobiliary Disorders	Elevation of liver transaminases (AST and ALT) and alkaline phosphatase	Increased bilirubin		Increased gamma-glutamyl transferase (GGT)	Serious hepatotoxicity, including liver failure and death (in patients receiving Gemcitabine alone or in combination with other potentially hepatotoxic drugs)
Skin and Subcutaneous Tissue Disorders	Allergic skin rash often associated with pruritus			Vesicle formation and ulceration	Severe desquamative and bullous skin eruptions

	Alopecia - usually mild with minimal hair loss		Scaling	
Renal and Urinary Disorders	Haematuria Protienuria		Renal failure Haemolytic uraemic syndrome	

Condition	Very Common *(>1/10)*	Common *(>1/100, <1/10)*	Uncommon *(>1/1000, <1/100)*	Rare *(>1/10000, <1/1000)*	Very Rare *(<1/10000)*
General Disorders and Administration Site Conditions	Oedema/peripheral oedema	Fever		Injection site reactions (mainly mild in nature)	
	Influenza-like symptoms - the most commonly reported symptoms include fever, headache, back pain, shivering, muscle pain, asthenia, and anorexia. Cough, rhinitis, malaise, perspiration, and sleeping difficulties have also been reported.	Asthenia			

Injury and Poisoning

• Radiation toxicity (see SmPC for Gemcitabine for further details)

Haemolytic uraemic syndrome (HUS) and/or thrombotic thrombocytopenic purpura and/or renal failure have been reported following one or more doses of Gemzar. Renal failure leading to death or requiring dialysis, despite discontinuation of therapy, has been rarely reported. The majority of the cases of renal failure leading to death were due to HUS.
Pulmonary effects, sometimes severe (such as pulmonary oedema, interstitial pneumonitis, or adult respiratory distress syndrome [ARDS]), have been reported rarely in association with Gemcitabine therapy. The aetiology of these effects is unknown. If such effects develop, consideration should be made to discontinuing Gemcitabine. Early use of supportive care measures may help ameliorate the condition.
A few cases of facial oedema have occurred.

APPENDIX 12: BEXAROTENE EXPECTED ADVERSE EVENTS

The following information has been supplied from the Summary of Product Characteristics for Bexarotene (Tagretin®)

The safety of Bexarotene has been examined in clinical studies of 193 patients with CTCL who received Bexarotene for up to 118 weeks and in 420 non-CTCL cancer patients in other studies.

In 109 patients with CTCL treated at the recommended initial dose of 300 mg/m^2/day, the most commonly reported adverse reactions to Targretin were hyperlipaemia ((primarily elevated triglycerides) 74%), hypothyroidism (29%), hypercholesterolaemia (28%), headache (27%), leucopenia (20%), pruritus (20%), asthenia (19%), rash (16%), exfoliative dermatitis (15%), and pain (12%).

The following Targretin-related adverse reactions were reported during clinical studies in patients with CTCL (N=109) treated at the recommended initial dose of 300 mg/m^2/day.

Condition	Very Common *(>1/10)*	Common *(>1/100, <1/10)*	Uncommon *(>1/1000, <1/100)*
Blood and lymphatic system disorders	Leucopenia	Lymphoma Like Reaction	Blood Dyscrasia
		Lymphadenopathy	Purpura
		Hypochromic Anaemia [1,2,3]	Coagulation Disorder
			Coagulation Time Increased[2,3]
			Anaemia[1]
			Thrombocytopenia[3]
			Thrombocythemia
			Eosinophilia[1]
			Leukocytosis[2]
			Lymphocytosis

Condition	Very Common *(>1/10)*	Common *(>1/100, <1/10)*	Uncommon *(>1/1000, <1/100)*
Endocrine disorders	Hypothyroidism	Thyroid Disorder	Hyperthyroidism
Metabolism and nutrition disorders	Hyperlipaemia,	Weight Gain,	Gout
	Hypercholesterolaemia	SGOT Increased,	BUN Increased[1]
		SGPT Increased,	High Density Lipoprotein Decreased
		Lactic Dehydrogenase	Bilirubinemia[1,3]
		Increased, Creatinine	
		Increased, Hypoproteinaemia	
Nervous system disorders		Dizziness	Ataxia
		Hypesthesia	Neuropathy
		Insomnia	Vertigo
			Hyperaesthesia
			Depression[1,2,3]
			Agitation

Condition	Very Common *(>1/10)*	Common *(>1/100, <1/10)*	Uncommon *(>1/1000, <1/100)*
Eye disorders		Dry Eyes	Conjunctivitis[3]
		Eye Disorder	Cataract Specified[1,2,3]
			Amblyopia[3]
			Visual Field Defect
			Corneal Lesion
			Abnormal Vision
			Blepharitis
Ear and labyrinth disorders		Deafness	Ear disorder
Cardiac disorders			Tachycardia
Vascular disorders		Peripheral Oedema	Haemorrhage
			Hypertension
			Oedema[3]
			Vasodilatation[1,2,3]
			Varicose Vein

Condition	Very Common *(>1/10)*	Common *(>1/100, <1/10)*	Uncommon *(>1/1000, <1/100)*
Gastrointestinal disorders		Vomiting	Pancreatitis[1,3]
		Diarrhoea[1,3]	Hepatic Failure
		Nausea[3]	Gastrointestinal Disorder[1]
		Anorexia[1]	
		Liver Function Tests Abnormal	
		Cheilitis[2]	
		Dry Mouth[2,3]	
		Constipation	
		Flatulence	
Skin and subcutaneous tissue disorders	Exfoliative Dermatitis,	Skin Ulcer,	Serous Drainage[1],
	Pruritus,	Alopecia[1],	Herpes Simplex,
	Rash	Skin Hypertrophy,	Pustular Rash,
		Skin Nodule,	Skin Discoloration[3]
		Acne,	Hair Disorder[1],
		Sweating,	Nail Disorder[1,3]
		Dry Skin[2,3],	
		Skin Disorder	

Condition	Very Common *(>1/10)*	Common *(>1/100, <1/10)*	Uncommon *(>1/1000, <1/100)*
Musculoskeletal and connective tissue disorders		Bone Pain,	Myasthaenia[1]
		Arthralgia,	
		Myalgia	
Renal and urinary disorders			Albuminuria[1,3],
			Kidney Function Abnormal
General Disorders and administration site conditions	Pain,	Allergic Reaction,	Neoplasm,
	Headache,	Infection,	Fever[1,2,3],
	Asthaenia	Chills[1],	Cellulitis,
		Abdominal Pain,	Infection Parasitic,
		Hormone Level Altered[1]	Mucous Membrane Disorder[3],
			Back Pain[1,2,3],
			Lab Test Abnormal

1: adverse reactions noted with increased frequency when Bexarotene was administered at a dose>300mg/m^2/day.
2: adverse reactions noted with increased frequency when Bexarotene was administered at a dose of 300 mg/m^2/day in non-CTCL cancer patients.
3: adverse reactions noted with increased frequency when Bexarotene was administered at a dose of>300 mg/m^2/day (compared to administration to CTCL patients at 300 mg/m^2/day) in non-CTCL cancer patients.