TAP
From Leukaemia & Lymphoma Research

BREVITY

Cancer Research UK Clinical Trials Unit @CRCTU

A phase II study of brentuximab vedotin using a response adapted design in patients with Hodgkin lymphoma unsuitable for chemotherapy due to age, frailty or co-morbidity

Trial Design

An early phase II, single arm, two stage study, to investigate the level of activity, duration of response and tolerability of brentuximab vedotin (SGN-35), as a single agent, utilising a response adapted approach, in older, frailer or co-morbid patients with previously untreated Hodgkin lymphoma.

Objectives

To investigate the level of activity, duration of response and tolerability of brentuximab vedotin (SGN-35), in older, frailer or co-morbid patients with previously untreated Hodgkin lymphoma.

Trial Duration

Opened Feb 2014 and will recruit over 18 months. Duration of treatment will be dependent on the patients' response (see schema below) with a maximum of 16 cycles over 48 weeks.
At the end of treatment patients will be assessed clinically at 3 months intervals and by CT scan at 15, 18, 24 and 36 months. For those still alive and disease free after 2 years, follow-up will be according to local practice.

Inclusion Criteria

- Histologically confirmed CD30 positive Classical Hodgkin lymphoma
- No previous treatment for Classical Hodgkin lymphoma
- Stages II (unfavourable as determined by B symptoms, extranodal disease, bulky disease, ≥3 sites of nodal involvement, ESR ≥50 mm/h.), III and IV
- Standard chemotherapy considered inappropriate at any age and with ECOG score of 0, 1, 2 or 3, because any of the below:
    - Impaired cardiac function defined either by an ejection fraction of <50% assessed by echocardiogram or nuclear medicine scan (MUGA)
    - Left ventricular ejection fraction ≥50% measured by echocardiography or MUGA but in the presence of significant co-morbidities or cardiac risk factors such as diabetes mellitus, hypertension, peripheral vascular disease, ischaemic heart disease, previous myocardial infarction, obesity, stroke or transient ischaemic attacks (TIA) that make anthracycline-containing chemotherapy inadvisable as determined by the treating physician.
    - Heart failure clinically determined by the presence of New York Heart Association (NYHA) heart failure grade II and III due to a cause other than Hodgkin Lymphoma
    - Impaired respiratory function with DLCO and/or FVC/FEV1 ratio <75% of predicted due to a cause other than Hodgkin Lymphoma

  Standard chemotherapy considered for patients aged 60 years or older,
    - an ECOG score of 1, 2 or 3 for any reason, before the start of permitted steroids and considered unsuitable for treatment with standard chemotherapy by the Investigator.
- FDG avid disease - proven by PET scan
- Measurable disease with at least one lesion measuring >1.5 cm in long axis diameter (for nodal lesions) or >1.0cm in long axis diameter (for extra-nodal lesions)
- Written informed consent
- Able to comply with requirements of the protocol (including PET scans)
- Agree and be able to use adequate contraception if required

Exclusion Criteria

- Grade 2 or worse peripheral neuropathy
- Haemoglobin < 9 g/dl (transfusion allowed)
- Unsupported neutrophil count < 1.0 x 10^9/l and platelet count < 100 x 10^9/l unless due to bone marrow infiltration demonstrated by trephine biopsy
- Serum bilirubin ≥1.5 times upper limit normal unless due to Hodgkin lymphoma or Gilbert's syndrome
- Creatinine clearance <30 ml/min (calculated by the modified Cockroft-Gault formula, see appendix) unless due to Hodgkin lymphoma. Patients with a calculated GFR <30 ml/min but a GFR by EDTA clearance of ≥30 ml/min would be eligible
- Pregnant or lactating women
- Any other cancer diagnosis within the last 24 months – except for:
    - Appropriately treated superficial melanoma, basal cell carcinoma and squamous cell carcinoma of the skin
    - Appropriately treated cervical intra-epithelial neoplasia
    - *In situ* or organ confined prostate cancer not currently requiring therapy

  Previous cancers treated with curative intent and with no evidence of recurrence following a minimum of at least 2 years of follow-up are permitted.
- The use of other investigational or anti-neoplastic agents within the previous 6 weeks or during the trial.
- Known to be HIV, Hep B or C positive
- Known hypersensitivity to recombinant proteins, murine proteins, or to any excipient contained in the drug formulation of brentuximab vedotin.
- Known cerebral or meningeal involvement by Hodgkin Lymphoma
- Symptoms or signs of Progressive Multifocal Leukoencephalopathy (PML)
- Any active systemic viral, bacterial, or fungal infection requiring intravenous antimicrobials within 2 weeks prior to registration
- Evidence of current uncontrolled cardiovascular conditions, including unstable angina and NYHA grade IV heart failure
- ECOG score 4 at time of registration

Sample Size

Stage 1 will recruit 20 patients. If at least patients 8 respond after the initial 4 cycles of SGN-35 a further 10 patients will be recruited to stage 2.

Primary Endpoints

- Overall objective response rate (ORR) defined as complete metabolic response (CMR) and partial metabolic response (PMR) after 4 cycles of brentuximab vedotin with PET-CT according to the Deauville criteria.

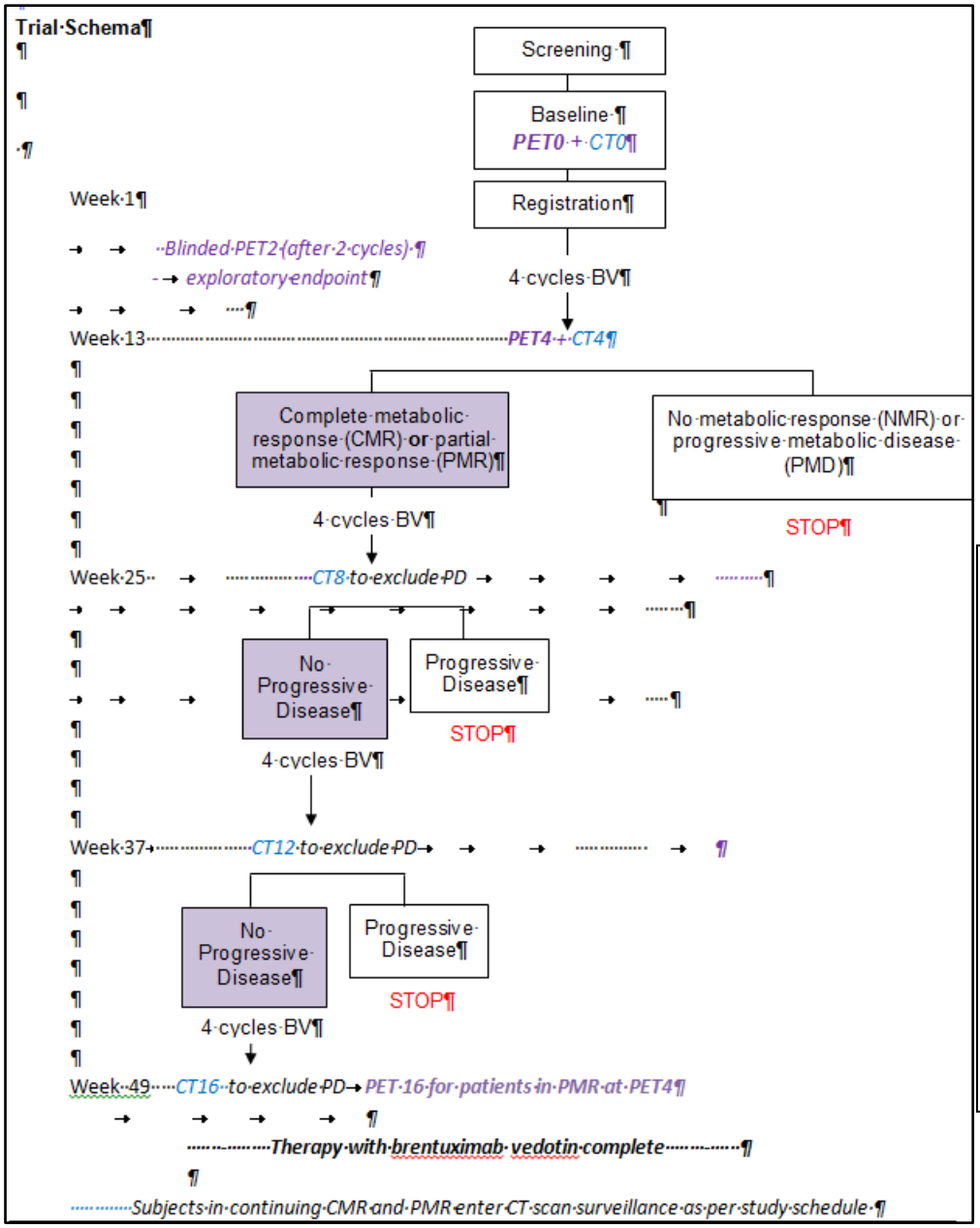
Secondary Endpoints

- ORR (CMR and PMR) after 8 cycles of brentuximab vedotin according to Deauville criteria
- ORR (CR and PR) after 4 and 8 cycles of brentuximab vedotin according to the Revised Response Criteria for malignant lymphoma
- ORR after 2 cycles (blinded PET 2)
- Correlation of response rates after 2 cycles (blinded PET) to the response rates after 4 (PET 4) and 8 (PET 8) and to Progression Free and overall survival
- Duration of response
- Tolerability in terms of toxicity, number of doses of brentuximab vedotin administered and dose intensity
- Progression free survival
- Overall survival and cause of death
- Second primary cancers at 2 years
- Physician reported performance status at 6 months and 1 year
- Alternative and additional treatments administered following treatment with brentuximab vedotin

Protocol Updates:

Updates In progress:

Extension of treatment to a maximum of 16 cycles for patients with PMR at PET 4
Reduced AE reporting



BV= Brentuximab Vedotin

DS = Deauville Score

STOP = Stop brentuximab vedotin and receive subsequent treatment at investigator discretion

CMR is DS 1,2,3,

PMR is DS 4,5 with uptake less than baseline

NMR is DS 4,5 with no change from baseline

PMD is DS 4,5 with increased intensity of uptake compared to baseline and/or new lesions consistent with lymphoma

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