A randomised phase III trial with a PET response adapted design ABVD +/- ISRT and A2VD +/- ISRT in patients with previously untreated stage IA/IIA Hodgkin lymphoma

Sponsor: University College London (UK, Europe, Australia, New Zealand);
Canadian Cancer Trials Group (USA/Canada parallel study)

Funder: Takeda Pharmaceutical Company Ltd (Investigator-initiated study award)

Coordinating Centre: Cancer Research UK & UCL Cancer Trials Centre; ctc.radar@ucl.ac.uk

Chief Investigator: Professor John Radford, Christie Hospital/University of Manchester

Recruitment target: 1042 patients in 5 years worldwide (642 from UK/Europe/ANZ)

Recruitment period: April 2022-April 2027

Treatment duration: 3-5 months

Follow-up duration: Minimum 5 years from end of treatment

Overall aim:

To assess whether substituting A^2VD for ABVD as part of a PET-response adapted design in early stage HL can:

- Improve PFS (primary endpoint)
- Improve complete metabolic remission (CMR) rate
- Improve OS
- Decrease late toxicity by reducing the proportion of patients receiving RT and thereby the incidence of second cancers and cardiovascular disease
- Eliminate pulmonary toxicity

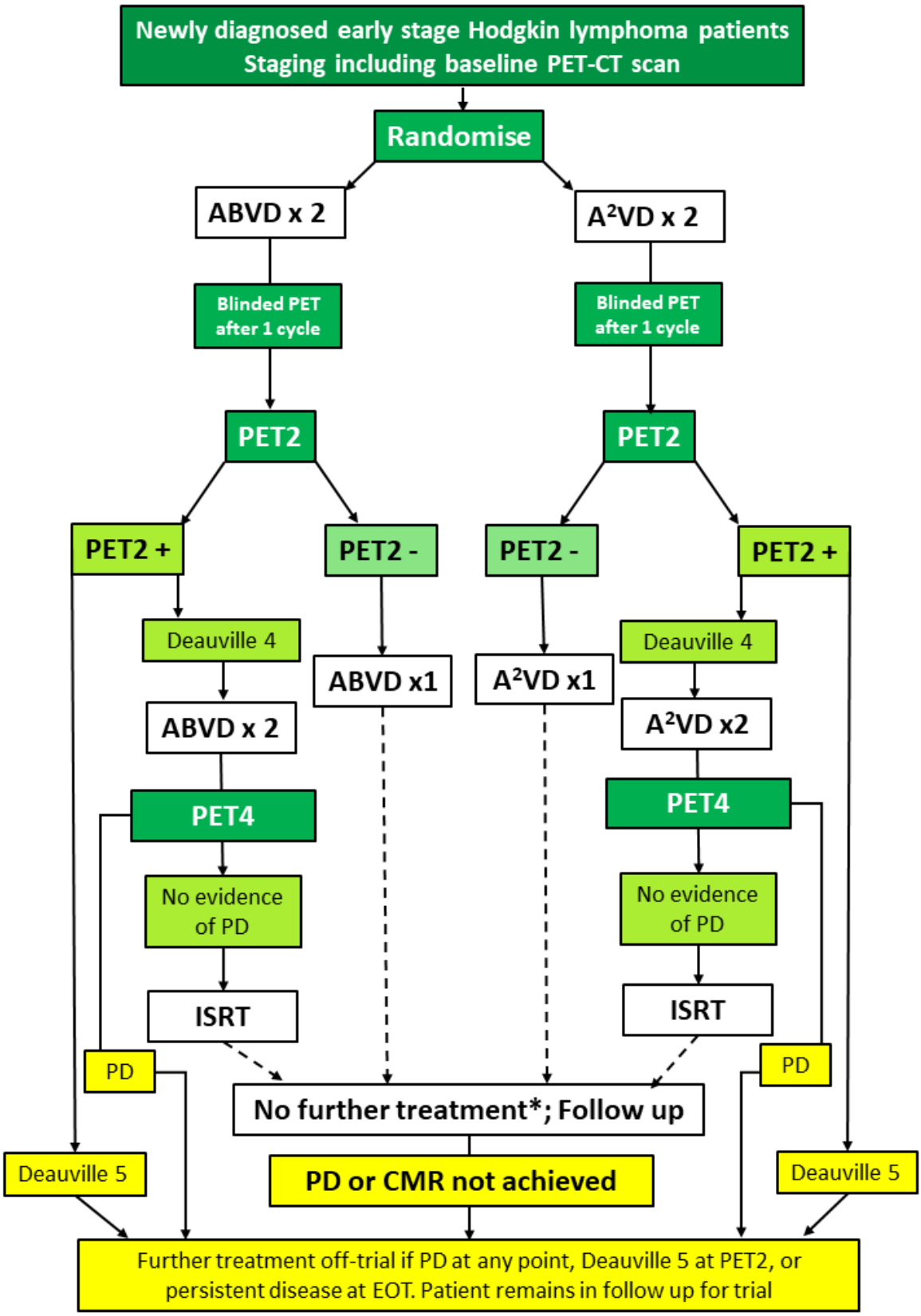
IMPs: Doxorubicin (hospital stock)
Bleomycin (hospital stock)
Vinblastine (hospital stock)
Dacarbazine (hospital stock)
Brentuximab vedotin (supplied free of charge)

NIMP: Filgrastim (hospital stock)

Trial treatments: Eligible patients will be randomised (1:1) to one of the following:

ABVD (standard arm; 3-4 x 28 day cycles)	**A^2VD (experimental arm; 3-4 x 28 day cycles)**
• Doxorubicin 25mg/m^2 IV, day 1 & 15 • Bleomycin 10,000 IU/m^2 IV, day 1 & 15 • Vinblastine 6mg/m^2 IV, day 1 & 15 • Dacarbazine 375mg/m^2 IV, day 1 & 15	• Doxorubicin 25mg/m^2 IV, day 1 & 15 • Brentuximab vedotin 1.2mg/kg (max 120mg) IV, day 1 & 15 • Vinblastine 6mg/m^2 IV, day 1 & 15 • Dacarbazine 375mg/m^2 IV, day 1 & 15 • Filgrastim for 5-7 days from days 2 & 16

Schema



*unless intention to give RT stated pre-treatment

Radiotherapy: Involved site radiotherapy (planned as per the International Lymphoma Radiation Oncology Group guidelines, recommended dose 30Gy) will be given to:

- Patients with Deauville score 4 on PET2, following completion of chemotherapy.
- Patients who have CMR (score 1-3) on PET2 where the treating clinician has indicated prior to study entry that they intend to give the patient radiotherapy regardless of PET2 result)

PET QA:

- In the UK, PET QA will be undertaken by the UK PET Core Laboratory at St Thomas' Hospital, London.
- Scanning cannot start at participating PET scanning facilities until written confirmation of compliance with trial requirements has been received from the PET Core Laboratory
- Scans must be performed in line with the trial PET imaging manual

PET central review: The following scans will be centrally reviewed as part of the trial:

- Baseline scan (to be sent to the core laboratory for comparison with later scans)
- PET1 (cycle 1 day 24-27); Optional exploratory scan (Deauville Score will not be reported)
- PET2 (cycle 2 day 24-27): PET score will be reported; determines subsequent treatment

Scans will be submitted for review via the WIDEN web-based platform (http://www.dixitsolutions.com/widen)

Samples for translational research: Patients will be asked to consent for the following samples to be sent for translational research:

- Diagnostic tumour block (including retention of tissue microarrays and sections for use in future research; remaining material will be returned)
- Peripheral blood in silica serum and streck tubes (up to 4 sequential samples)

Kits will be provided for collection and shipping of samples.

No processing is required at site.

Inclusion criteria:

1. Males and females aged 16-69 years (inclusive)
2. Histologically confirmed classical Hodgkin lymphoma
3. Stage I or II with no mediastinal bulk disease or B-symptoms. Bulky disease at other sites is acceptable. Extranodal disease (single extranodal site (stage I) or contiguous extranodal extension (stage II)) is acceptable
4. ECOG performance status 0-2
5. No previous treatment for Hodgkin lymphoma
6. Fit to receive anthracycline based chemotherapy
7. Creatinine clearance (measured or calculated) >40ml/min
8. Total bilirubin <1.5xULN unless attributable to disease or known Gilbert's syndrome
9. ALT or AST <2xULN
10. Adequate bone marrow function: Neutrophils ≥1.0 x 10^9/l, platelets ≥100 x 10^9/l
11. Haemoglobin ≥8g/dl
12. Willing and able to comply with the requirements of the protocol, including contraceptive advice where applicable

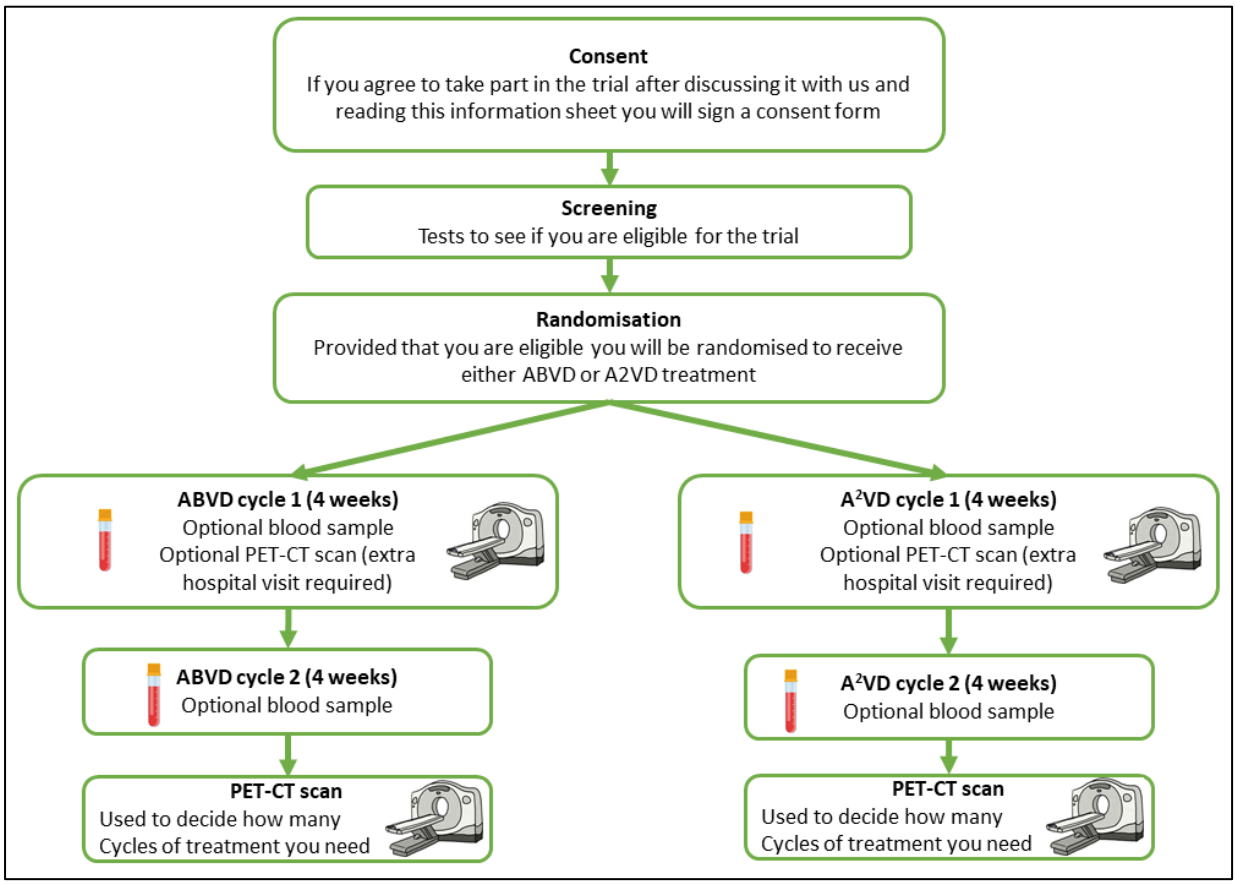
13. Written informed consent

Exclusion criteria:

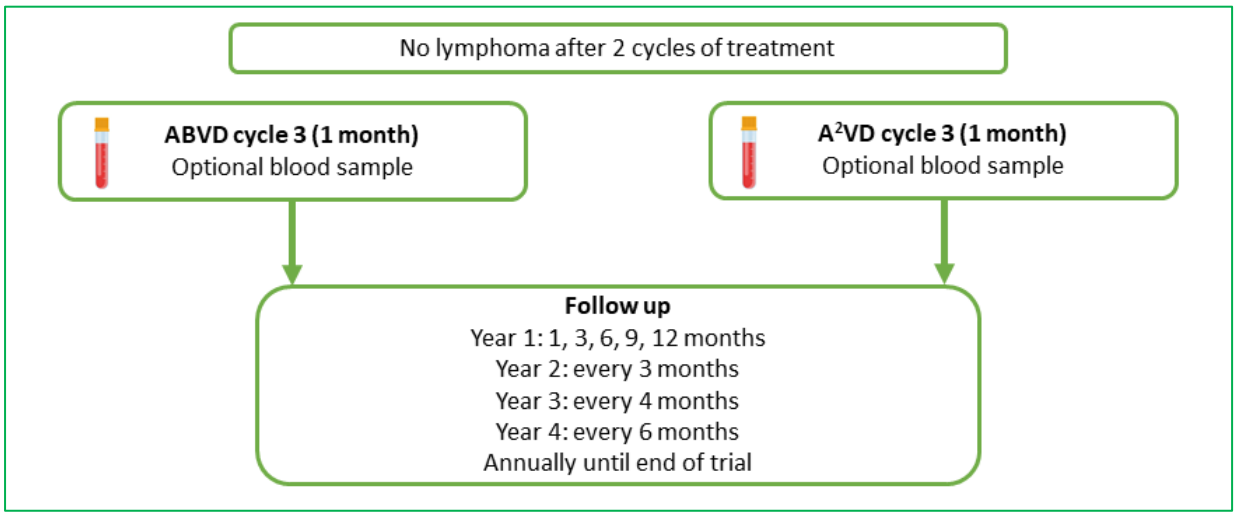
1. Previous treatment for Hodgkin lymphoma
2. Infradiaphragmatic disease
3. Nodular lymphocyte predominant Hodgkin lymphoma
4. Absence of FDG-avid lymphoma lesions on baseline PET scan
5. Age 70 years or over, or 15 years and under
6. Other cancer diagnosed within the past 5 years apart from completely excised carcinoma in situ of any type and basal or squamous cell carcinoma of the skin
7. Recurrent or persistent other cancer within the last 5 years irrespective of date of initial diagnosis
8. Pre-existing sensory or motor peripheral neuropathy from any cause, grade ≥1
9. History of, or current progressive multi-focal leukoencephalopathy or other chronic condition of the brain
10. Symptomatic neurologic disease compromising normal activities of daily living or requiring medications
11. Infection with HIV, hepatitis C or active hepatitis B infection (surface antigen or DNA positive)
12. Any active systemic viral, bacterial, or fungal infection requiring systemic antibiotics, antivirals or antifungals within 2 weeks prior to first study drug dose
13. Receiving or recently treated with any other investigational agent (within 4 weeks of trial entry)
14. Pregnant or breastfeeding women
15. Known hypersensitivity to recombinant proteins, murine proteins, or to any excipient contained in the drug formulation of brentuximab vedotin or any component of ABVD
16. Known history of any cardiovascular or respiratory conditions that would preclude anthracycline or bleomycin administration
17. Other significant medical or psychiatric comorbidity that in the opinion of the investigator would make administration of ABVD or A^2VD hazardous

SUMMARY OF PATIENT PARTICIPATION IN RADAR

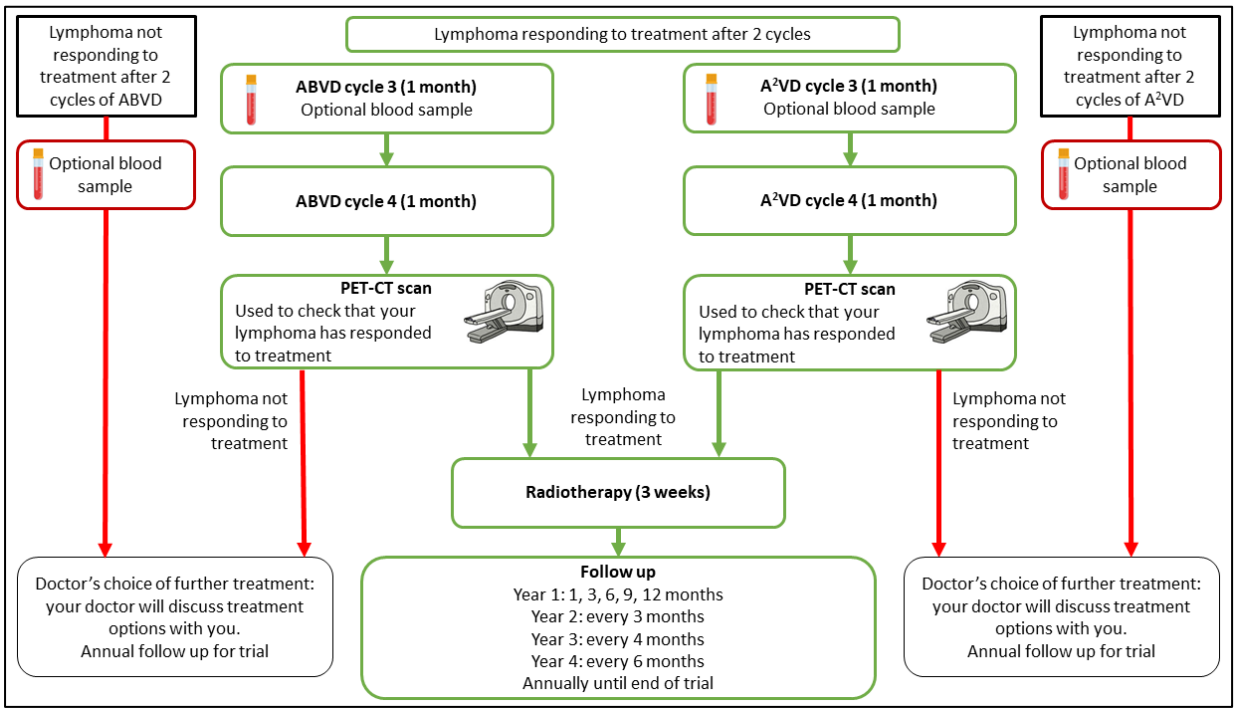
Initially everyone will have the same tests and treatment:



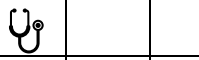
If the PET-CT scan after two cycles of treatment is 'negative' (the lymphoma has gone away), this is what will happen next:



If the PET-CT scan after two cycles of treatment is ‘positive’ (the patient still has some lymphoma in their body), this is what will happen next:



The table on the next page summarises what will be done at each follow up visit.

Follow up: summary of study activities												
Months after treatment	1	2	3	4	5	6	7	8	9	10	11	12
Activities												
Months after treatment	13	14	15	16	17	18	19	20	21	22	23	24
Activities												
Months after treatment	25	26	27	28	29	30	31	32	33	34	35	36
Activities												
Months after treatment	37	38	39	40	41	42	43	44	45	46	47	48
Activities												
Months after treatment	49	50	51	52	53	54	55	56	57	58	59	60
Activities												

Key:

 Clinic visit (includes routine blood tests)	 Research blood sample (optional)	 Scan (CT or PET-CT)
 Pregnancy test (women who could become pregnant)	 Lung function test (not standard care; may require an extra clinic visit)	