REQUEST FOR AUTHORISATION OF A CLINICAL TRIAL ON A MEDICINAL PRODUCT FOR HUMAN USE TO THE COMPETENT AUTHORITIES AND FOR OPINION OF THE ETHICS COMMITTEES IN THE COMMUNITY

For official use:

Date of receiving the request:	Date of request for additional information:	Grounds for non acceptance / negative opinion :
Date of request for information to make it valid:		Give date:
Date of valid application :	Date of receipt of additional / amended information :	Authorisation / positive opinion:
Date of start of procedure :		Give date:
Competent authority registration number :		Withdrawal of application :
Ethics Committee registration number :		Give date :

A: Trial identification

A1. National Competent Authority:

UK - MHRA

A2. European Clinical Trials Database (EudraCT) number:

2017-002544-32

A3. Full title of the trial:

A phase II study of nivolumab monotherapy in patients with relapsed/refractory Hodgkin lymphoma, fit for autologous stem cell transplant, who fail to reach complete metabolic remission after first or second line salvage therapy

A3-1. Title of the trial for lay people, in easily understood, i.e. non-technical, language

A phase II study of nivolumab monotherapy in patients with relapsed/refractory Hodgkin lymphoma fit for autologous stem cell transplant who fail to reach complete metabolic remission after first or second line salvage therapy

A3-2. Name or abbreviated title of the trial where available:

ANIMATE

A4. Sponsor's protocol:

Number: UCL/15/0515
Version: 1.0
Date:

A5-1. ISRCTN number, if available :

A5-2. US NCT number:

NCT03337919

A5-3. Who Universal Trial Reference Number (UTRN)

A5-4. Other Identifiers:

Name	Identifier
Funder Reference	CA-209-445

A6. Is this a resubmission?

◯ Yes ◉ No

A7. Is the trial part of a Paediatric Investigation Plan?

◯ Yes ◉ No ◯ Not Answered

B: Identification of the sponsor responsible for the request

B1. Sponsor

SP1
Contact person

Name of organisation	University College London
Given name	Nick
Family name	McNally
Address	Joint Research Office, UCL, Gower Street
Town/city	London
Post code	WC1E 6BT
Country	UNITED KINGDOM
Telephone	020 7380 9995
Fax	020 7380 9937
E-mail	ctc.sponsor@ucl.ac.uk

B2.Legal representative in the European Economic Area for the purpose of this trial
A legal representative must be appointed for a clinical trial of an investigational medicinal product if the sponsor is not established within the European Economic Area (EEA) (see article 19 of Directive 2001/20/EC). If this applies, please enclose evidence that the legal representative is established within the EEA and has accepted the role of legal representative.

Legal Representative 1

Contact person

Name of organisation
Given name
Family name
Address
Town/city
Post code
Country
Telephone
Fax
E-mail

B3. Status of the sponsor: Non-Commercial

B.4 Source(s) of Monetary or Material Support for the clinical trial (repeat as necessary):

Name of organisation	Bristol-Myers Squibb Pharmaceuticals Ltd
Country	UNITED KINGDOM

B.5 Contact point designated by the sponsor for further information on the trial:

Name of organisation	CRUK & UCL Cancer Trials Centre
Functional name of contact point	Oliver Schofield
Street Address	90 Tottenham Court Road
Town/city	London
Post code	W1T 4TJ
Country	UNITED KINGDOM
Telephone	020 7679 9860
Fax	020 7679 9861
E-mail	ctc.animate@ucl.ac.uk

C: Applicant identification

C1. Request for the competent authority

C1-1. Who is responsible for the Clinical Trial Authorisation Application?

Person or organisation authorised by the Sponsor

C1-4. Complete the details of the applicant below even if they are provided elsewhere on the form:

Contact person

Person or organisation name:	CRUK & UCL Cancer Trials Centre
Contact person Given name	Oliver
Contact person Family name	Schofield
Address	90 Tottenham Court Road
Town/city	London
Post code	W1T 4TJ
Country	UNITED KINGDOM
Telephone	020 7679 9860
Fax	020 7679 9861
E-mail	ctc.animate@ucl.ac.uk

C1-5. Do you want a xml file copy of the CTA form data saved on EudraCT?

○ Yes ◉ No ○ Not Answered

C2.Request for ethics commitee

C2-1. Who is responsible for the Clinical Trial Authorisation Application?

.....

C2-5. Complete the details of the applicant below even if they are provided elsewhere on the form

Person or organisation name:	.....
Title:	.....
Forename/Initials:	.....
Surname:	.....
Middlename:	.....
Address:	.....
Town/city:	.....
Post code:	.....
Country:	.....
Telephone:	.....
Fax:	.....
E-mail:	.....

Part D: Investigational Medicinal Products

D: Information on the IMPs

Information on each "bulk product" before trial-specific operations (blinding, trial specific packaging and labelling) should be provided in this section for each investigational medicinal product (IMP) being tested including each comparator, if applicable. If the trial is performed with several products please create a separate set of the following questions for each product. If the product is a combination product please give separate information for each active substance.

Click on the first row and enter details of the product in the following screens. When you have completed the details, click on the navigate button or the "See All" link and return to this section to enter details of the next product. When you have completed details of all products please move to question D7 using the navigation screen.

D. Investigational medicinal products

PR1 Opdivo

D1. Indicate which of the following is described below then repeat as necessary for each:

This refers to the IMP number: **PR1**
Investigational medicinal product category:
Test IMP

D2. Status of the IMP ***If the IMP has a marketing authorisation in the Member State concerned by this application but the trade name and marketing authorisation holder are not fixed in the protocol, go to section D.2.2***

D2-1. Does the IMP to be used in the trial have a marketing authorisation?

◉ Yes ○ No ○ Not Answered

Trade name:
Opdivo
EV Product Code
Name of the MA holder:
Bristol-Myers Squibb Pharma EEIG
MA number (if MA granted by a Member State):
EU/1/15/1014/001-002
Is the IMP modified in relation to its MA?

◉ Yes ○ No ○ Not Answered

Please specify:
Clinical Trial Material as per IMPD
Which country granted the MA?
EUROPEAN UNION
Is this the Member State concerned with this application?

◉ Yes ○ No ○ Not Answered

D2-2. Situations where an IMP to be used in the CT has a MA in the MS concerned, but the protocol allows that any brand of the IMP with a MA in that MS be administered to the trial subjects and it is not possible to clearly identify the IMP(s) in advance of the trial start

In the protocol, is treatment defined only by active substance?

○ Yes ○ No ◉ Not Answered

In the protocol, do treatment regimens allow different combinations of marketed products used according to local clinical practice at some or all investigator sites in the MS?

◯ Yes ◯ No ◉ Not Answered

The products to be administered as IMPs are defined as belonging to an ATC group

◯ Yes ◯ No ◉ Not Answered

Other :

◯ Yes ◯ No ◉ Not Answered

D2-3. IMPD submitted:

Full IMPD

◉ Yes ◯ No ◯ Not Answered

Simplified IMPD

◯ Yes ◉ No ◯ Not Answered

Provide justification for using simplified dossier in the covering letter

Summary of product characteristics (SmPC) only

◯ Yes ◉ No ◯ Not Answered

D2-4. Has the use of the IMP been previously authorised in a clinical trial conducted by the sponsor in the Community?

◉ Yes ◯ No ◯ Not Answered

Specify which Member States:

AUSTRIA	☐	BELGIUM	☐	BULGARIA	☐	CYPRUS	☐
CZECH REPUBLIC	☐	DENMARK	☐	ESTONIA	☐	FINLAND	☐
FRANCE	☐	GERMANY	☐	GREECE	☐	HUNGARY	☐
ICELAND	☐	IRELAND	☐	ITALY	☐	LATVIA	☐
LIECHTENSTEIN	☐	LITHUANIA	☐	LUXEMBOURG	☐	MALTA	☐
NETHERLANDS	☐	NORWAY	☐	POLAND	☐	PORTUGAL	☐
ROMANIA	☐	SLOVAKIA	☐	SLOVENIA	☐	SPAIN	☐
SWEDEN	☐	UNITED KINGDOM	☑				

D2-5. Has the IMP been designated in this indication as an orphan drug in the Community?

◯ Yes ◉ No ◯ Not Answered

D2-6. Has the IMP been the subject of scientific advice related to this clinical trial?

◯ Yes ◉ No ◯ Not Answered

Please indicate source of advice and provide a copy in the CTA request:

From the CHMP?

◯ Yes ◉ No ◯ Not Answered

CHMP = Committee for Medicinal Products for Human Use

From a MS competent authority?

◯ Yes ◉ No ◯ Not Answered

This is a sub-set of questions about each IMP. To return to the list of IMPs select "See all" at the top of the page or select "Navigate". To complete further questions about this IMP select "Next".

D3. Description of IMP

D3-1.

D.3.1 Product name where applicable	Opdivo
D.3.2 Product code where applicable	BMS-936558
D.3.3 ATC codes, if officially registered	L01XC17
D.3.4 Pharmaceutical form (use standard terms)	Concentrate For Solution For Infusion
D.3.4.1 Is this a specific paediatric formulation?	◯ Yes ◉ No ◯ Not Answered
D.3.5 Maximum duration of treatment of a subject according to the protocol	Nivolumab is given on day 1 of each 14 day cycle. Patients will undergo up to 8 cycles of treatment (total duration of treatment approximately 4 months)

D.3.6 Dose allowed

D.3.6.1 First dose for first-in-human clinical trial	
D.3.6.1 Specify per day or total:	◯ per day ◯ total ◉ Not Answered
D.3.6.1 Specify total dose (number and unit)	
D.3.6.1 Route of administration (relevant to the first dose):	
D.3.6.2 Maximum dose allowed	240mg
D.3.6.2 Specify per day or total	◉ per day ◯ total ◯ Not Answered
D.3.6.2 Specify total dose (number and unit)	1920 mg milligram(s)
D.3.6.2 Route of administration (relevant to the maximum dose):	Intravenous Use

D.3.7 Routes of administration for this IMP

Intravenous Use

This is a sub-set of questions about each IMP. To return to the list of IMPs select "See all" at the top of the page or select "Navigate". To complete further questions about this IMP select "Next".

D3-8. Active substances

Complete all fields that currently apply to this Active Substance in this Product. If you have IMPs with different concentrations of the Active Substance complete a new Sub-section D for each.

Active Substance 1

Name of active substance (INN or proposed INN if available):	Nivolumab
CAS number:	946414-94-4
Current sponsor code:	
Other descriptive name:	
Full Molecular formula	C6362H9862N1712O1995S42
Chemical/biological description of the Active Substance	Nivolumab is a monoclonal antibody, a type of protein designed to recognise and attach to a specific target substance in the body. Nivolumab attaches to a target protein called programmed death-1 receptor (PD-1) that can switch off the activity of T cells (a type of white blood cell that forms part of the immune system, the body's natural defences). By attaching to PD-1, nivolumab blocks its action and prevents it from switching off your T cells. This helps increase their activity against the cancerous cells.
Strength	
Concentration unit:	mg/ml milligram(s)/millilitre
Concentration type:	equal
Concentration number (only use both fields for range):	10

D3-11. Type of IMP

Does the IMP contain an active substance:

Of chemical origin?	○ Yes	◉ No	○ Not Answered
Of biological / biotechnological origin?(other than Advanced Therapy IMP (ATIMP))	◉ Yes	○ No	○ Not Answered
Is this a:			
Advanced Therapy IMP (ATIMP) [1]	○ Yes	◉ No	○ Not Answered
Combination product that includes a device, but does not involve an Advanced Therapy	○ Yes	◉ No	○ Not Answered
Radiopharmaceutical medicinal product?	○ Yes	◉ No	○ Not Answered
Immunological medicinal product (e.g. vaccine, allergen, immune serum)?	○ Yes	◉ No	○ Not Answered
Plasma derived medicinal product?	○ Yes	◉ No	○ Not Answered
Extractive medicinal product?	○ Yes	◉ No	○ Not Answered
Recombinant medicinal product?	◉ Yes	○ No	○ Not Answered
Medicinal product containing genetically modified organisms?	○ Yes	◉ No	○ Not Answered
Herbal medicinal product?	○ Yes	◉ No	○ Not Answered
Homeopathic medicinal product?	○ Yes	◉ No	○ Not Answered
Another type of medicinal product?	○ Yes	◉ No	○ Not Answered

Specify the mode of action for the active substance in this medicinal product
The mode of action should briefly describe the chemical, biochemical, immunological or biological means that the IMP uses to effect its pharmaceutical action. Nivolumab is a human monoclonal antibody that targets the programmed death-1 (PD-1) CD279 cell surface membrane receptor. PD-1 is a negative regulatory molecule expressed by activated T and B lymphocytes.1 Binding of PD-1 to its ligands, PDL1) and PD-L2, results in the down-regulation of lymphocyte activation. Inhibition of the interaction between PD-1 and its ligands promotes immune responses and antigenspecific
T-cell responses to both foreign antigens as well as self-antigens.

Is it an IMP to be used in a first-in-human clinical trial? ◯ Yes ◉ No ◯ Not Answered

(1,2,3,4,5) Complete sections D.4, D.5, D.6. and D.7, as applicable
(2,3) As defined in Annex 1 part IV of Directive 2001/83/EC as amended
(4) As defined in Article 2(1)(b) of Regulation 1394/2007/EC
(6) Guideline on strategies to identify and mitigate risks for first-in-human clinical trials with investigational medicinal products. EMEA/CHMP/SWP/28367/2007

D8. Information on placebo *(if relevant; repeat as necessary)*

D8. Is there a placebo:

◯ Yes ◉ No ◯ Not Answered

D9. Sites responsible for final QP release for distribution to investigators.

D9-1. IMPs and placebos for which no responsible site needs to be identified.

This section is used to identify IMPs and placebos which:

- Have an MA in the EU **and**
- Are sourced from the EU market **and**
- Are used in the trial without modification (eg not overencapsulated) **and**
- The packaging and labeling is carried out for local use only as per article 9.2 of the Directive 2005/28/EC (GCP Directive).

If all the conditions above are met, then select below the IMPs and placebos to which this applies.

Index of Sites where the qualified person certifies batch release

In accordance with paragraph 38 of Annex 13 of Volume 4 of the Rules Governing Medicinal Products in the European Union

D9-2. Who is responsible in the Community for the certification of the finished IMP or placebo?
This section is dedicated to finished IMPs, i.e. medicinal products randomised, packaged, labelled and certified for use in the clinical trial. If there is more than one site or more than one IMP is certified, use extra pages and give each IMP its number from section D1 or D7 In the case of multiple sites indicate the product certified by each site.

RS1

Both

Name of the organisation:	Bristol-Myers Squibb International Corporation
Address	Parc de l'Alliance, Avenue de Finlande 4
Town/city	Braine-l'Alleud
Post code	B-1420
Country	BELGIUM

Give the manufacturing authorisation number

1595IMP

If no authorisation, give the reasons:

Select the relevant IMP(s) and Placebo(s) from the drop down lists.

IMP

PR1

RS2

Importer

Name of the organisation:	Clinical Supplies Management Europe sa
Address	Watson & Crick Hill, Rue Granbonpre 11
Town/city	Mont-Saint-Guibert
Post code	1435
Country	BELGIUM

Give the manufacturing authorisation number

1573IMP

If no authorisation, give the reasons:

Select the relevant IMP(s) and Placebo(s) from the drop down lists.

IMP

PR1

E: Design of the Trial.

E.1 Medical Condition or Disease under Investigation

E1-1. Medical condition or disease under investigation (1)

Specify the medical condition(s) to be investigated (free text) :
Relapsed/refractory Hodgkin lymphoma

Medical condition in easily understood language
Hodgkin lymphoma is a cancer of the lymphatic system due to abnormal lymphocytes. Refractory means not responding to initial treatment. Relapse is where disease returns after initial response.

Identify the therapeutic area

Diseases [C] - Cancer [C04]

(1) In the case of healthy volunteer trials, the intended indication for the product under development should be provided.

E1-2. MedDRA information (2)

MR2

Version	14.0
Level	LLT
Classification Code	10020266
Term	Hodgkin's disease recurrent
SOC	10029104 - Neoplasms benign, malignant and unspecified (incl cysts and polyps)

MR3

Version	14.0

Level	LLT
Classification Code	10020267
Term	Hodgkin's disease refractory
SOC	10029104 - Neoplasms benign, malignant and unspecified (incl cysts and polyps)

(2) Applicants are encouraged to provide the MedDRA lower level term (LLT) if applicable and classification code.

E1-3. Is any of the conditions being studied a rare disease? (3)

○ Yes ◉ No ○ Not Answered

(3) Refer to "Points to consider on the calculation and reporting of the prevalence of a condition for Orphan drug designation": COM/436/01 (http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2009/09/WC500003773.pd

E2. Objective of the trial

E2-1. What is the principal research question/objective? *Please put this in language comprehensible to a lay person.*

To assess whether nivolumab, given on its own, can be used effectively to treat patients with Hodgkin lymphoma that has either failed to respond to initial treatment or which has returned after initially responding to treatment, and has not responded fully to salvage chemotherapy. The trial aims to find out how many patients have a negative PET-CT scan after 4-8 cycles of nivolumab treatment.

E2-2. What are the secondary research questions/objectives if applicable? *Please put this in language comprehensible to a lay person.*

To investigate whether patients' disease relapses after nivolumab treatment, and if so, how long this takes to happen.

To find out how long patients live after nivolumab treatment.

To find out if patients who have a negative PET-CT scan after nivolumab take longer to relapse than those who have a positive PET-CT scan after nivolumab

To investigate what side effects patients experience from nivolumab treatment.

To find out whether it is safe for patients to have a stem cell transplant after nivolumab treatment

To investigate whether PET scanning is an effective way of checking response to nivolumab treatment

To look at whether there are blood tests that can be used to monitor response to treatment for Hodgkin lymphoma

To understand more about the biology of Hodgkin lymphoma, and whether it is possible to predict response to salvage treatment

E2-3. Is there a sub-study?

○ Yes ◉ No ○ Not Answered

E3. Please list the principal inclusion criteria (list the most important, max 5000 characters).

Inclusion criteria for registration
• Age 16 or over
• Primary refractory classical Hodgkin lymphoma or classical Hodgkin lymphoma in first relapse
• About to receive, receiving or within 14 days of first 2 cycles of first or second line salvage therapy (4 cycles if receiving treatment with brentuximab vedotin)

• Fit for autologous stem cell transplantation
• Written informed consent
• Willing to comply with the contraceptive requirements of the trial

Inclusion criteria – trial treatment
• Has received 2 cycles of first line or second line salvage chemotherapy (4 cycles if being treated with brentuximab vedotin)
• PET positive (Deauville score 4 or 5) after 2 cycles of first or second line salvage chemotherapy (4 cycles if being treated with brentuximab vedotin)
• Fit for further salvage chemotherapy
• ECOG performance status 0-1
• Creatinine clearance >30ml/min calculated by Cockroft-Gault formula
• Bilirubin <1.5 x ULN, ALT/AST <2.5 x ULN
• Adequate bone marrow function (Hb >80g/l, Platelets >50 x 10^9/l, neutrophils >1.0 x 10^9/l

E4. Please list the principal exclusion criteria (list the most important, max 5000 characters).

Exclusion criteria for registration
• Nodular lymphocyte predominant Hodgkin lymphoma
• Women who are pregnant or breastfeeding
• History of colitis, inflammatory bowel disease or pneumonitis
• Patients with autoimmune disorders excluding patients with vitiligo, diabetes mellitus type 1, hypo- and hyperthyroidism not requiring immunosuppressive therapy
• Known history of hepatitis B or C infection
• Known HIV infection
• History of allergy (including severe/life threatening skin reaction) to monoclonal antibodies, anaphylaxis or uncontrolled allergy
• Major surgery within 4 weeks prior to registration
• Myocardial infarction, unstable angina, coronary artery bypass graft, cerebrovascular accident or transient ischaemic attack within the past 6 months
• Non-haematological malignancy within the past 3 years (some exceptions apply – listed in trial protocol)

Exclusion criteria for trial treatment
• Deauville score 1-3 after 2 cycles of first or second line salvage chemotherapy (4 cycles if being treated with brentuximab vedotin)
• Positive serology for hepatitis B or C (unless due to vaccination)
• Active infection requiring systemic therapy
• Ongoing immunosuppressive therapy, apart from inhaled, intranasal, topical corticosteroids or systemic corticosteroids at low doses (≤10mg prednisolone or equivalent per day).
• Chemo- or radiotherapy or corticosteroids at a dose of more than 10mg/day prednisolone or equivalent within 14 days prior to response PET-CT. NOTE: corticosteroids can be used AFTER a positive PET-CT scan for symptomatic disease but must be weaned to a dose of prednisolone ≤10mg/day or less (or equivalent) at least 7 days prior to starting nivolumab.
• Treatment with any investigational agent within 28 days prior to planned start of nivolumab
• Ongoing grade 2-4 non-haematological toxicities related to prior Hodgkin lymphoma treatments, with the exception of alopecia and grade 2 fatigue
• Pregnant or breastfeeding women

E5-1. What is the primary outcome measure for the study?(max 5000 characters)

Overall response rate (ORR) by PET-CT scan following 4-8 cycles of nivolumab

Timepoint(s) of evaluation of this end point (max 800 characters)
Response assessed by centrally reviewed PET CT scan after 4 and 8 cycles of nivolumab (approximately 2 & 4 months of treatment).

Scans are to be performed 11-13 days after trial treatment administration during cycles 4 and 8, as per trial requirements on an approved scanner, and images sent to the UK PET Core Lab at St Thomas' Hospital for expert central review.

The protocol will usually identify a single primary end point but there may be a co-primary end point in some cases and/or a

number of secondary end points.

E5-2. Secondary end point(s) (max 5000 characters)

(1)Progression-free survival at 1 year
(2)Overall survival at 1 year
(3)Proportion of patients proceeding to SCT (auto-SCT or allo-SCT)
(4)Safety & toxicity of nivolumab, particularly autoimmune toxicity
(5)OS and PFS stratified by partial metabolic response (PMR) versus complete metabolic response (CMR) on FDG-PET
(6)Transplant-related mortality and rate of serious complications of allogeneic transplant (grade 3-4 graft-vs-host disease, hyperacute graft-vs-host disease and steroid-responsive febrile syndrome)
(7)Correlate PET positive disease with histological evidence of disease on biopsy to establish biopsy negative PMR rate (subject to patient consent; exploratory)
(8) Correlate disease response, as assessed by FDG-PET and histology, with serological markers, including serum TARC (exploratory)
(9) Evaluate the correlation betweem response to nivolumab and biological parameters e.g. PD-1 expression on Reed-Sternberg cells (exploratory)

Timepoint(s) of evaluation of this end point (max 800 characters)
(1), (2), (3), (5): assessed at 1 year after completion of trial treatment. Longer term survival follow up will also be presented.
(4): from start of nivolumab until 5 month post last trial treatment administration; late toxicity during follow up will also be reported.
(6): from transplant day 0 until day 100 post transplant (patients undergoing allogeneic transplant only)
(7): following cycle 8 of nivolumab (patients who remain PET positive and consent to repeat biopsy only)
(8): from start of treatment until end of treatment; based on sequential blood samples.
(9): exploratory analysis based on archival biopsy material collected after study entry

E6. What is the scope of the trial?

Diagnosis	○ Yes	◉ No	○ Not Answered
Prophylaxis	○ Yes	◉ No	○ Not Answered
Therapy	○ Yes	◉ No	○ Not Answered
Safety	◉ Yes	○ No	○ Not Answered
Efficacy	◉ Yes	○ No	○ Not Answered
Pharmacokinetic	○ Yes	◉ No	○ Not Answered
Pharmacodynamic	○ Yes	◉ No	○ Not Answered
Bioequivalence	○ Yes	◉ No	○ Not Answered
Dose Response	○ Yes	◉ No	○ Not Answered
Pharmacogenetic	○ Yes	◉ No	○ Not Answered
Pharmacogenomic	○ Yes	◉ No	○ Not Answered
Pharmacoeconomic	○ Yes	◉ No	○ Not Answered
Others	○ Yes	◉ No	○ Not Answered

Specify:

E7-1. Trial type and phase [(1)]

Human pharmacology (Phase I)	○ Yes ◉ No ○ Not Answered
Therapeutic exploratory (Phase II)	◉ Yes ○ No ○ Not Answered
Therapeutic confirmatory (Phase III)	○ Yes ◉ No ○ Not Answered
Therapeutic use (Phase IV)	○ Yes ◉ No ○ Not Answered

(1) The descriptions of the trial types provided are those recommended in preference to Phases. See page 5 of Community guideline CPMP/ICH/291/95. The development of a new indication after initial approval of a medicine should be considered as a new development plan.

E8. Design of the Trial.

E8-1. Is the trial design controlled?

◉ Yes ○ No ○ Not Answered

Specify:

Randomised	○ Yes ◉ No ○ Not Answered
Open	◉ Yes ○ No ○ Not Answered
Single blind	○ Yes ◉ No ○ Not Answered
Double blind	○ Yes ◉ No ○ Not Answered
Parallel group	○ Yes ◉ No ○ Not Answered
Cross over	○ Yes ◉ No ○ Not Answered
Other	○ Yes ◉ No ○ Not Answered

E8-2. If controlled, specify the comparator:

Other medicinal product(s)	○ Yes ◉ No ○ Not Answered
Placebo	○ Yes ◉ No ○ Not Answered
Other	○ Yes ◉ No ○ Not Answered

Number of treatment arms in the trial

E8-3. Single site in the Member State concerned (see also section G):

○ Yes ◉ No ○ Not Answered

E8-4. Multiple sites in the Member State concerned (see also section G):

◉ Yes ○ No ○ Not Answered

Number of sites anticipated in Member State concerned
30

E8-5. Multiple Member States

◯ Yes ◉ No ◯ Not Answered

Number of sites anticipated in the Community.

E8-6. Trial being conducted both within and outside the EEA

◯ Yes ◉ No ◯ Not Answered

Trial conducted completely outside EEA

◯ Yes ◉ No ◯ Not Answered

E8-7. Will a data monitoring committee (DMC) be convened?

◯ Yes ◉ No ◯ Not Answered

E8-8.

Definition of the end of trial, and justification in the case where it is not the last visit of the last subject undergoing the trial.
If it is the last visit of the last subject, please enter "LVLS". If it is not LVLS provide the definition.
End of trial will be declared when the last patient treated with nivolumab has completed three years of follow up.

E8-9. How long do you expect the study to last? (1)

In all countries concerned by the trial
Years: 6 Months: 6 Days: 1

In the MS concerned
Years: 6 Months: 6 Days: 1

(1) *From the first inclusion until the last visit of the last subject.*

E8-10. Recruitment start date

Recruitment start date in MS
01/05/2018
In any country
01/05/2018

(1) *If not provided in the protocol.*

F: Population of Trial Subjects

F1. What is the age span of the trial subjects?

Less than 18 years	(●) Yes ( ) No ( ) Not Answered	Approx no of participants: 10

Please specify the estimated number of participants planned in each age range for the whole trial:

In Utero	( ) Yes (●) No ( ) Not Answered	Approx no of participants: 0
Preterm newborn infants (up to gestational age less than 37 weeks)	( ) Yes (●) No ( ) Not Answered	Approx no of participants: 0
Newborn (0-27 days)	( ) Yes (●) No ( ) Not Answered	Approx no of participants: 0
Infant and toddler (28 days - 23 months)	( ) Yes (●) No ( ) Not Answered	Approx no of participants: 0
Children (2-11 years)	( ) Yes (●) No ( ) Not Answered	Approx no of participants: 0
Adolescent (12-17 years)	(●) Yes ( ) No ( ) Not Answered	Approx no of participants: 10
Adult (18-64 years)	(●) Yes ( ) No ( ) Not Answered	Approx no of participants: 110
Elderly (geater than 65 years)	( ) Yes (●) No ( ) Not Answered	Approx no of participants: 0

The number of participants will be initial estimates. Applicants will not be required to update this information nor do they constitute an authorisation or restriction on the inclusion of these numbers of patients in the trial.

F2. What is the gender of the trial subjects?

Female	(●) Yes ( ) No ( ) Not Answered	
Male	(●) Yes ( ) No ( ) Not Answered	

F3. Please select the categories of the trial subjects:

Healthy volunteers	( ) Yes (●) No ( ) Not Answered	
Patients	(●) Yes ( ) No ( ) Not Answered	
Specific vulnerable populations	(●) Yes ( ) No ( ) Not Answered	
Women of childbearing potential not using contraception	( ) Yes (●) No ( ) Not Answered	
Women of child bearing potential using contraception	(●) Yes ( ) No ( ) Not Answered	
Pregnant women	( ) Yes (●) No ( ) Not Answered	
Nursing women	( ) Yes (●) No ( ) Not Answered	
Emergency situations	( ) Yes (●) No ( ) Not Answered	
Subjects incapable of giving consent personally	( ) Yes (●) No ( ) Not Answered	
Others	( ) Yes (●) No ( ) Not Answered	

F4. Planned number of subjects to be included:

In the member state 120

For a multinational trial:

In the European community: 120

In the whole clinical trial: 120

F5. Plans for treatment or care after a subject has ended his/her participation in the trial. ***If it is different from the expected normal treatment, please specify:***

Trial treatment is of a limited duration (up to 8 cycles) and BMS have committed to supply nivolumab for the duration of the trial. Therefore ANIMATE patients will not require treatment with the study drug beyond the end of the research.

Patients will receive the local standard of care for their disease as required after the trial ends.

G1. and G2. Investigator Details

G1. National coordinating investigator (for a multicentre trial) **or principal investigator** (for a single centre trial)

- (●) National coordinating investigator
- ( ) Principal investigator

Given name	Graham
Family name	Collins
Qualification (MD...)	MBBS, DPhil, FRCPath, MRCP (UK)
Institution name	Churchill Hospital
Institution department name	Department of Haematology
Street address	Old Road, Headington
Town/city	Oxford
Post Code	OX3 7LE
Country	UNITED KINGDOM
Telephone	01865235252
Fax	
E-mail	graham.collins@ouh.nhs.uk

G2. Other principal Investigators *(for a multicentre trial)*

IN1

Given name	Graham
Family name	Collins
Qualification (MD...)	MBBS, MRCP (UK), FRCPath, DPhil
Institution name	Oxford University Hospitals NHS Foundation Trust
Institution department name	Department of Haematology
Street address	Churchill Hospital, Old Way, Headington
Town/city	Oxford
Post Code	OX3 7LE
Country	UNITED KINGDOM
Telephone	
Fax	
E-mail	Graham.collins@ouh.nhs.uk

IN2

Given name	Kirit
Family name	Ardeshna
Qualification (MD...)	
Institution name	University College London Hospitals NHS Foundation Trust
Institution department name	Department of Haematology
Street address	University College Hospital, 235 Euston Road
Town/city	London
Post Code	NW1 2BU
Country	UNITED KINGDOM
Telephone	

Fax	
E-mail	kiritardeshna@nhs.net

IN3

Given name	Eve
Family name	Gallop-Evans
Qualification (MD...)	BSc. MBBS, FRCR (UK), PhD, FRCR (UK)
Institution name	Cardiff and Vale UHB - University Hospital of Wales
Institution department name	Oncology Department
Street address	Oncology Department
Town/city	University Hospital of Wales, Heath Park
Post Code	CF14 4XW
Country	UNITED KINGDOM
Telephone	
Fax	
E-mail	eve.gallop-evans@wales.nhs.uk

IN4

Given name	Pam
Family name	McKay
Qualification (MD...)	MBChB, MRCP (UK), FRCP, MRCPath, FRCPath
Institution name	Greater Glasgow & Clyde Health Board - Beatson West of Scotland Cancer Centre
Institution department name	Department of Haematology
Street address	Department of Haematology
Town/city	Beatson West of Scotland Cancer Centre, 1053 Great Western Road
Post Code	G12 0YN
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Telephone	
Fax	
E-mail	pam.mckay@ggc.scot.nhs.uk

IN5

Given name	Kim
Family name	Linton
Qualification (MD...)	MBChB, MRCP, PhD
Institution name	The Christie NHS Foundation Trust
Institution department name	Department of Haematology
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Town/city	Withington, Manchester
Post Code	M20 4BX
Country	UNITED KINGDOM
Telephone	
Fax	
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IN6

Given name	Wendy
Family name	Osborne
Qualification (MD...)	

Institution name	Newcastle upon Tyne Hospitals NHS Foundation Trust
Institution department name	Department of Haematology
Street address	Freeman Hospital, Freeman Road
Town/city	Newcastle upon Tyne
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Country	UNITED KINGDOM
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Fax	
E-mail	Wendy.Osborne@nuth.nhs.uk

IN7

Given name	Shankara
Family name	Paneesha
Qualification (MD...)	FRCP. FRCPath, MRCP (UK), MD (General Medecine), Diplomate of National Board (India), MBBS
Institution name	Heart of England NHS Foundation Trust
Institution department name	Department of Haematology
Street address	Birmingham Heartlands Hospital, Bordesley Green East
Town/city	Birmingham
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Country	UNITED KINGDOM
Telephone	
Fax	
E-mail	shankara.paneesha@nhs.net

IN8

Given name	Andrea
Family name	Kuhnl
Qualification (MD...)	MD
Institution name	King's College Hospital NHS Foundation Trust
Institution department name	Department of Haematology
Street address	King's College Hospital, Denmark Hill
Town/city	London
Post Code	SE5 9RS
Country	UNITED KINGDOM
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Fax	
E-mail	Andrea.Kuhnl@nhs.net

IN9

Given name	Fiona
Family name	Miall
Qualification (MD...)	BMedSci, BMBS, MRCPath, FCRPath
Institution name	University Hospitals of Leicester NHS Trust
Institution department name	Department of Haematology
Street address	Leicester Royal Infirmary, Infirmary Square
Town/city	Leicester
Post Code	LE1 5WW
Country	UNITED KINGDOM

Telephone	
Fax	
E-mail	fiona.miall@uhl-tr.nhs.uk

IN10

Given name	Charalampia
Family name	Kyriakou
Qualification (MD...)	MD, PhD
Institution name	London North West Healthcare NHS Trust
Institution department name	Department of Haematology
Street address	Northwick Park Hospital, Watford Road
Town/city	Harrow
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Country	UNITED KINGDOM
Telephone	
Fax	
E-mail	c.kyriakou@nhs.net

IN11

Given name	Nimish
Family name	Shah
Qualification (MD...)	MbbCH BAO, MRCP, FRCPath, MD
Institution name	Norfolk & Norwich University Hospitals NHS Foundation Trust
Institution department name	Department of Haematology
Street address	Colney Lane, Colney
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Post Code	NR4 7UY
Country	UNITED KINGDOM
Telephone	
Fax	
E-mail	NIMISH.SHAH@nnuh.nhs.uk

IN12

Given name	Bryson
Family name	Pottinger
Qualification (MD...)	MBChB, MRCP, FRCPath
Institution name	Royal Cornwall Hospitals NHS Trust
Institution department name	Department of Haematology
Street address	Royal Cornwall Hospital, Treliske
Town/city	Truro
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Country	UNITED KINGDOM
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Fax	
E-mail	bryson.pottinger@nhs.net

IN13

Given name	Nick

Family name	Morley
Qualification (MD...)	MRCPath, MRCP, MB.BS. BA
Institution name	SHEFFIELD TEACHING HOSPITALS NHS FOUNDATION TRUST
Institution department name	Department of Haematology
Street address	Royal Hallamshire Hospital, Glossop Road
Town/city	Sheffield
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Fax	
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IN14

Given name	Rifca
Family name	Le Dieu
Qualification (MD...)	
Institution name	Bart's Health NHS Trust
Institution department name	Department of Haematology
Street address	St Bartholomew's Hospital, West Smithfield
Town/city	London
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Country	UNITED KINGDOM
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Fax	
E-mail	Rifca.LeDieu@bartshealth.nhs.uk

IN15

Given name	Ruth
Family name	Pettengell
Qualification (MD...)	
Institution name	St George's University Hospitals NHS Foundation Trust
Institution department name	Department of Haematology
Street address	St George's Hospital, Blackshaw Road
Town/city	London
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Telephone	
Fax	
E-mail	rpetteng@sgul.ac.uk

IN16

Given name	Cathy
Family name	Burton
Qualification (MD...)	BA(Hons), MBBChir, MRCP, FRCPath, MD
Institution name	Leeds Teaching Hospitals NHS Trust
Institution department name	Department of Haematology
Street address	St James' University Hospital, Beckett Street
Town/city	Leeds
Post Code	LS9 7TF

Country	UNITED KINGDOM
Telephone	
Fax	
E-mail	cathy.burton1@nhs.net

IN17

Given name	Deborah
Family name	Turner
Qualification (MD...)	BSc, MBBS, MRCP, MRCPath, FRCPath, PCGE
Institution name	Torbay and South Devon NHS Foundation Trust
Institution department name	Department of Haematology
Street address	Torbay Hospital, Lowes Bridge
Town/city	Torquay, Devon
Post Code	TQ2 7AA
Country	UNITED KINGDOM
Telephone	
Fax	
E-mail	deborah.turner2@nhs.net

IN18

Given name	Paul
Family name	Fields
Qualification (MD...)	
Institution name	GUY'S AND ST THOMAS' NHS FOUNDATION TRUST
Institution department name	
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Town/city	GUY'S HOSPITAL
Post Code	SE1 9RT
Country	UNITED KINGDOM
Telephone	
Fax	
E-mail	paul.fields@gstt.nhs.uk

IN19

Given name	Andrew
Family name	McMillan
Qualification (MD...)	FRCPath, FRCP(UK), PhD, MRCPath, MRCP(UK), MA
Institution name	NOTTINGHAM UNIVERSITY HOSPITALS NHS TRUST
Institution department name	
Street address	TRUST HEADQUARTERS
Town/city	QUEENS MEDICAL CENTRE
Post Code	NG7 2UH
Country	UNITED KINGDOM
Telephone	01159691169
Fax	01159627742
E-mail	andrew.mcmillan@nhs.net

IN20

Given name	Peter
Family name	Johnson
Qualification (MD...)	FRCP(UK), MRCP(UK), MD, MA, M.B.B.Chir., BA
Institution name	UNIVERSITY HOSPITAL SOUTHAMPTON NHS FOUNDATION TRUST
Institution department name	
Street address	MAILPOINT 18
Town/city	SOUTHAMPTON GENERAL HOSPITAL
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Country	UNITED KINGDOM
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Fax	02381205152
E-mail	johnsonp@soton.ac.uk

IN21

Given name	David
Family name	Cunningham
Qualification (MD...)	FRCP(UK), MD, FMedSci
Institution name	THE ROYAL MARSDEN NHS FOUNDATION TRUST
Institution department name	
Street address	FULHAM ROAD
Town/city	
Post Code	SW3 6JJ
Country	UNITED KINGDOM
Telephone	020 8661 3157
Fax	
E-mail	David.Cunningham@rmh.nhs.uk

For multi-centre trials where the CI is also a local PI, please list the CI as a PI at G2 (single-centre).

G3. Central Technical Facility Details

G3. Central technical facilities to be used in the conduct of the trial. *Laboratory or other technical facility, in which the measurement or assessment of the main evaluation criteria are centralised.*

Organisation

Central technical facility organisation name	Kings College London
Central technical facility organisation department	Kings College London & Guy's and St Thomas' NHS Foundation Trust PET Centre
Contact person Given name	Sally
Contact person Family name	Barrington
Street address	4th Floor, Lambeth Wing, St Thomas' Hospital, Westminster Bridge Road
Town/city	London
Post code	SE1 7EH
Country	UNITED KINGDOM
Work Telephone	02071884988
Fax	

E-mail	sally.barrington@kcl.ac.uk

Enter the details of any duties subcontracted to this central technical facility in this trial:

Routine clinical pathology testing	○ Yes ◉ No ○ Not Answered
Clinical chemistry	○ Yes ◉ No ○ Not Answered
Clinical haematology	○ Yes ◉ No ○ Not Answered
Clinical microbiology	○ Yes ◉ No ○ Not Answered
Histopathology	○ Yes ◉ No ○ Not Answered
Serology / endocrinology	○ Yes ◉ No ○ Not Answered
Analytical chemistry	○ Yes ◉ No ○ Not Answered
ECG analysis / review	○ Yes ◉ No ○ Not Answered
Medical image analysis/ review - X-ray, MRI, ultrasound, etc.	◉ Yes ○ No ○ Not Answered
Primary/ surrogate endpoint test	○ Yes ◉ No ○ Not Answered
Other	○ Yes ◉ No ○ Not Answered

Organisation

Central technical facility organisation name	St James' University Hospital
Central technical facility organisation department	Haematoligcal Malignancy Diagnostic Service (HMDS)
Contact person Given name	Cathy
Contact person Family name	Burton
Street address	Beckett Street
Town/city	Leeds
Post code	LS9 7TF
Country	UNITED KINGDOM
Work Telephone	
Fax	
E-mail	cathy.burton1@nhs.net

Enter the details of any duties subcontracted to this central technical facility in this trial:

Routine clinical pathology testing	○ Yes ◉ No ○ Not Answered
Clinical chemistry	○ Yes ◉ No ○ Not Answered
Clinical haematology	○ Yes ◉ No ○ Not Answered
Clinical microbiology	○ Yes ◉ No ○ Not Answered
Histopathology	○ Yes ◉ No ○ Not Answered
Serology / endocrinology	○ Yes ◉ No ○ Not Answered

Analytical chemistry	○ Yes	◉ No	○ Not Answered
ECG analysis / review	○ Yes	◉ No	○ Not Answered
Medical image analysis/ review - X-ray, MRI, ultrasound, etc.	○ Yes	◉ No	○ Not Answered
Primary/ surrogate endpoint test	○ Yes	◉ No	○ Not Answered
Other	◉ Yes	○ No	○ Not Answered

If "Other", specify the other duties

Gene expression profiling, fluorescent in-situ hybridisation, immunohistochemistry

Organisation

Central technical facility organisation name	MRC Weatherall Institute of Molecular Medicine
Central technical facility organisation department	MRC Molecular Haematology Unit - Lab 326
Contact person Given name	Paresh
Contact person Family name	Vyas
Street address	University of Oxford, John Radcliffe Hospital
Town/city	Oxford
Post code	OX3 9DS
Country	UNITED KINGDOM
Work Telephone	01865222410
Fax	
E-mail	paresh.vyas@imm.ox.ac.uk

Enter the details of any duties subcontracted to this central technical facility in this trial:

Routine clinical pathology testing	○ Yes	◉ No	○ Not Answered
Clinical chemistry	○ Yes	◉ No	○ Not Answered
Clinical haematology	○ Yes	◉ No	○ Not Answered
Clinical microbiology	○ Yes	◉ No	○ Not Answered
Histopathology	○ Yes	◉ No	○ Not Answered
Serology / endocrinology	○ Yes	◉ No	○ Not Answered
Analytical chemistry	○ Yes	◉ No	○ Not Answered
ECG analysis / review	○ Yes	◉ No	○ Not Answered
Medical image analysis/ review - X-ray, MRI, ultrasound, etc.	○ Yes	◉ No	○ Not Answered
Primary/ surrogate endpoint test	○ Yes	◉ No	○ Not Answered
Other	◉ Yes	○ No	○ Not Answered

If "Other", specify the other duties

Immunohistochemistry, flow cytometry

Network organisation details

G4. Network organisation details

Organisation
Contact person Given name
Contact person Middle name
Contact person Family name
Street address
Town/city
PostCode
Country
Telephone number
Fax number
E-mail

Activities carried out by the network

G5. Organisations to whom the sponsor has transferred trial related duties and functions

G5. Subcontractor organisations.
Enter details of central CRO facilities supplying services for at least this Member State.

Organisation	Cancer Research UK & UCL Cancer Trials Centre (UCL CTC)
Department	Haematology Trials Group
Contact person Given name	Oliver
Contact person Family name	Schofield
Street address	5th Floor, 90 Tottenham Court Road
Town/city	London
PostCode	W1T 4TJ
Country	UNITED KINGDOM
Telephone number	02076799860
Fax	02076799861
E-mail	ctc.animate@ucl.ac.uk

Enter the details of any duties/ functions subcontracted to this sponsor's subcontractor facility in this trial

All tasks of the sponsor:	○ Yes ◉ No ○ Not Answered
Monitoring:	◉ Yes ○ No ○ Not Answered
Regulatory (e.g. preparation of applications to CA and Ethics Committee):	◉ Yes ○ No ○ Not Answered
Investigator recruitment:	◉ Yes ○ No ○ Not Answered
IVRS(1) - treatment randomisation:	○ Yes ◉ No ○ Not Answered
Data management:	◉ Yes ○ No ○ Not Answered
E-data capture:	○ Yes ◉ No ○ Not Answered
SUSAR reporting:	◉ Yes ○ No ○ Not Answered

Quality assurance auditing:	○ Yes ◉ No ○ Not Answered
Statistical analysis:	◉ Yes ○ No ○ Not Answered
Medical writing:	○ Yes ◉ No ○ Not Answered
Other duties subcontracted:	○ Yes ◉ No ○ Not Answered

H: Ethics Committee

H1-1. Type of application
Please tick the Ethics Committee box and give information of the Ethics committee concerned.

Ethics committee ☑

H2-1. Name and address of ethics committee:

Organisation	London - South East REC
Work Address	HRA, 3rd Floor, Barlow House, 4 Minshull Street Manchester
PostCode	M1 3DZ
Country	UNITED KINGDOM
Fax	

H2-2. Date of submission:

11/01/2018

H2-3. Current status of Ethics Committee Opinion at the time of submission to the National Competent Authority:

○ To be requested ◉ Pending ○ Given

I: Signature Of The Applicant In The Member State

I1. I hereby confirm that /confirm on behalf of the sponsor (tick which is applicable) that:

☐ The information provided is complete;

☐ The attached documents contain an accurate account of the information available;

☐ the clinical trial will be conducted in accordance with the protocol;

☐ The clinical trial will be conducted, and SUSARs and result-related information will be reported, in accordance with the applicable legislation.

I2. Applicant of the request for the competent authority (as stated in section C.1):

Date .....

Signature .....

Print name .....

J: Checklist

J3. ***For details of the documents required for applications to the MHRA in the UK please see*** ***http://www.mhra.gov.uk/Howweregulate/Medicines/Licensingofmedicines/Clinicaltrials/Applyingforaclinicaltrialauthorisation/Whattosend/index.htm***