SUMMARY OF DRUG ARRANGEMENTS
ANIMATE

United Kingdom - EudraCT Number: 2017-002544-32
BMS reference: CA209-445

CONTACT DETAILS

For further information on trial drugs, trial protocol, dosing, drug supply and distribution, please contact:

Trial Coordinator
Name: Trial Coordinator
Phone: 020 7679 9860
Email: ctc.animate@ucl.ac.uk

Chief Investigator
Name: Dr Graham Collins
Email: Graham.Collins@ouh.nhs.uk

Drug Distributer
Name: Clinical Supplies Management (CSM)
Email: ca209@csmondemand.com

VERSION HISTORY

Version number	Date	Summary of changes from previous version	Changes made by
1.0	18.10.2018	N/A – initial version	Oliver Schofield & Pip Patrick

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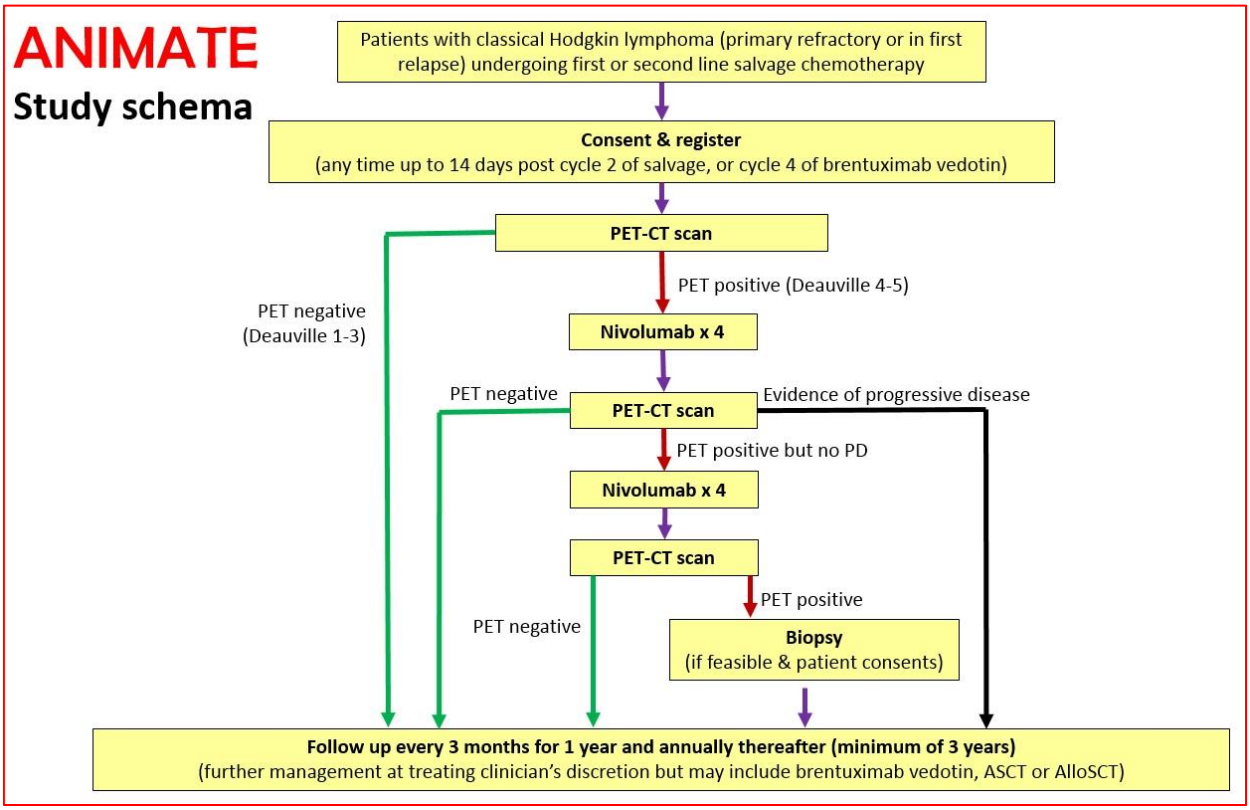
1. OVERVIEW

1.1 APPLICABILITY

This Summary of Drug Arrangements is applicable to the Pharmacy Lead and all other members of site staff who have responsibilities in conducting the ANIMATE trial.

2. TRIAL INFORMATION



For detailed information on the ANIMATE trial, please refer to the current version of the protocol.

Patients for whom eligibility for treatment has been confirmed will receive 4-8 x 14-day cycles of nivolumab. Nivolumab 240mg will be administered intravenously on day 1 of each 14 day cycle.

An interim PET-CT scan will be performed after 4 cycles. Patients who are PET negative or who have progressive disease after 4 cycles will stop trial treatment.

	1	2	3	4	5	6	7	8	9	10	11	12	13	14
Nivolumab 240mg IV	X													

An interim PET-CT scan (referred to in the protocol as PET4) will be performed after 4 cycles of nivolumab. Patients who are PET negative or who have progressive disease will stop trial treatment.

3. PHARMACY REGISTRATION & SET-UP

The Principal Investigator must ensure pharmacy is informed about the trial and pharmacy related duties delegated appropriately.

A designated member of the pharmacy staff, who takes overall responsibility for all pharmacy aspects of the clinical trial, must be identified and will be assigned the title of Pharmacy Lead. This person will be listed on the **Site Delegation Log**.

The Pharmacy Lead is responsible for ensuring all members of staff undertaking trial pharmacy related activities have completed the Delegation Log.

The Pharmacy Lead (or appropriate delegate) must be present at the site initiation teleconference, which will take place prior to site activation. If the Pharmacy Lead (or appropriate delegate) is not available for the general site initiation, a separate teleconference conducted by UCL CTC trial staff must be held.

Prior to site initiation, Pharmacy Site File documentation for a file will be sent electronically to the Pharmacy Lead (or appropriate delegate) from UCL CTC. Pharmacy staff are responsible for printing and filing Pharmacy Site File documentation.

The contents of the file will include copies of forms for drug ordering/reordering and accountability logs for ANIMATE. All trial related documentation should be retained in the Pharmacy Site File (or a statement of its location).

Where it is Pharmacy practice to require the use local forms in place of those provided by the Sponsor, the Pharmacy Lead must ensure these collect the same information as the Sponsor's template as a minimum and provide copies to UCL CTC prior to site activation.

Bristol-Myers Squibb, who are providing nivolumab for use in the ANIMATE trial, and their nominated distributor, CSM, require contact details for the lead pharmacist and up to two additional pharmacy staff in for correspondence regarding the trial (e.g. receipt of orders,

confirmation of shipping etc.). A **supplementary site contacts form** will be provided to sites for this purpose. If there are staff changes at site, sites should review and update the supplementary site contacts form and forward to UCL CTC.

3.1 PHARMACY ACTIVATION

The following must be completed and/or in place prior to site activation:

- Clinical Trial Authorisation
- REC Approval
- HRA Approval
- R&D and other local approvals as applicable
- Signed Clinical Trial Site Agreement
- Site files complete – including site contacts form and delegation log
- Site (Principal Investigator & Research Team) & Pharmacy Initiation
- Copies of trial prescriptions sent to UCL CTC for approval
- Copies of local site labels added to Investigational Medicinal Products (IMPs) sent to UCL CTC for approval
- Copies of accountability logs sent to UCL CTC for approval (where site wish to use their own templates)
  ARSAC certificate/license for the trial (PET centres)

Once the above are completed and/or are in place a Site Activation letter will be sent from UCL CTC, confirming site is open to recruit patients. UCL CTC will also notify BMS and CSM that the site has been activated and is permitted to order study drug.

4. PATIENT REGISTRATION

Please note the ANIMATE trial has a two-stage patient registration process.

Registration for trial

Once the site is activated, patients may be recruited into the trial. Once an eligible patient has been identified, the site research team will contact UCL CTC to register the patient.

UCL CTC will provide confirmation of registration by email to the investigator, research team and to the Pharmacy Lead.

Confirmation of eligibility for trial treatment

Eligibility for trial treatment will be confirmed centrally at UCL CTC after two cycles of first or second line salvage chemotherapy (four cycles if receiving treatment with brentuximab vedotin).

Evaluations should be carried out at sites and the results of these investigations will be used alongside the outcome of the central review of the patient's post-salvage PET-CT scan (referred to in the protocol as PET0) to confirm eligibility for trial treatment. UCL CTC will provide confirmation that the patient is eligible to proceed with trial treatment by email to the investigator, research team and to the Pharmacy Lead (or appropriate delegate).

Patients should begin nivolumab treatment within 4 weeks following the PET-CT scan to confirm eligibility for trial treatment.

It is the responsibility of the Pharmacy Lead to ensure that the trial site has sufficient trial stock of nivolumab present to treat the patient.

5. TRIAL DRUGS

In accordance with the Clinical Trial Authorisation (CTA) granted by the MHRA on 27.02.2018, the following drug is classed as an Investigational Medicinal Product (IMP):

- Nivolumab (Opdivo®) 10mg/ml concentrate for solution for infusion

6. SUPPLY OF TRIAL DRUGS

For ANIMATE, the following drug will be provided free of charge to sites for the duration of the trial:

- Nivolumab (Opdivo®) 10mg/ml concentrate for solution for infusion (IMP) – boxes of 5 x 10ml vials provided by Bristol-Myers Squibb Pharmaceuticals Ltd.

ANIMATE trial stock is not specific to an individual patient and may be used to treat any ANIMATE patient, even if they were not the intended recipient at the time of ordering.

6.1. ORDERING NIVOLUMAB

Nivolumab is supplied in boxes of 5 x 100mg (10ml) vials for the ANIMATE trial. A flat dose of 240mg will be administered on day 1 of each 14 day cycle. Therefore, 3 vials of drug will be required for each dose. When a patient is registered, please order 2 boxes to cover the first dose and continue to monitor supply to ensure there is enough to cover subsequent treatment cycles. Sites are advised to include some overage when placing an order to allow for re-making doses.

Clinical Supplies Management (CSM) will act as distributor for the ANIMATE trial. Sites should email a completed **CA209-455 Drug Request Form** to:
ca209@csmondemand.com (and send a copy to ctc.animate@ucl.ac.uk)

Sections A and B of the Drug Request Form should be completed electronically if possible, or if handwritten, capital letters must be used.

The Drug Request Form must be sent a minimum of 5-7 working days prior to the required delivery date. **Please note that CSM do not deliver drug on Mondays**.

The CA209-445 Drug Request Form is used for both initial supplies and subsequent resupplies and ensuring adequate supply at site is the responsibility of the Pharmacy Lead. Completed Drug Order forms must be retained in the relevant section of Pharmacy Site File.

CSM will acknowledge receipt of the order by email to UCL CTC and the pharmacy contact(s) nominated on the Supplementary Contacts Form.
A QP certificate will be provided by CSM with the product in the shipment.

6.2 RECEIPT OF NIVOLUMAB

Once the order has been approved by CSM, shipments will arrive within 5-7 working days from shipment approval, unless otherwise instructed. CSM will give notice of shipping by email to UCL CTC and the pharmacy contact(s) nominated on the Supplementary Contacts Form.

Nivolumab will be delivered labelled and packed via courier. If the nivolumab has not arrived within 5-7 days of placing the order, pharmacy should contact the ANIMATE Trial Coordinator in the first instance.

It is important to log receipt of each batch of nivolumab on the **Nivolumab Balance Log** in a timely manner and store the drug appropriately (see section 6.5). Following delivery of nivolumab, please inspect and verify the contents and conditions of the shipment.

Pharmacy must confirm receipt of nivolumab, and confirm the contents and condition of the shipment, by completing the Acknowledgement of Receipt form (T_CS_070.00) which will arrive with the shipment, and returning it directly to CSM and UCL CTC via email to:
ca209@csmondemand.com and ctc.animate@ucl.ac.uk.

All trial stock will be shipped with a Libero temperature monitor. Upon receipt, immediately place the medication into the storage area at +2°C to +8°C and retrieve the temperature monitor. If the device is showing a warning, quarantine the product and report to CSM and UCL CTC immediately by completing the Acknowledgement of Receipt form (T_CS_070.00) which will arrive with the shipment, and emailing the form and the temperature monitoring profile to:
ca209@csmondemand.com and to ctc.animate@ucl.ac.uk.

If the nivolumab arrives damaged, pharmacy quarantine the product and report to CSM and UCL CTC immediately by completing the Acknowledgement of Receipt form (T_CS_070.00) which will arrive with the shipment, and emailing the form to:
ca209@csmondemand.com and to ctc.animate@ucl.ac.uk.

Copies of completed Drug Request Forms, and any correspondence relating to delivery problems or any other problem with respect to nivolumab must be filed the Pharmacy Site File.

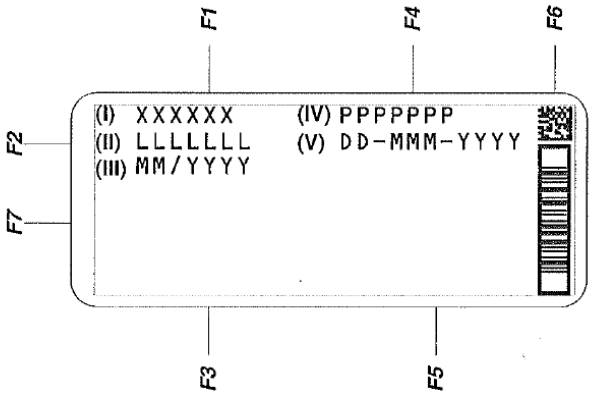
A QP certificate will be provided by CSM in the shipment. A copy of this must be filed in the Pharmacy Site File.

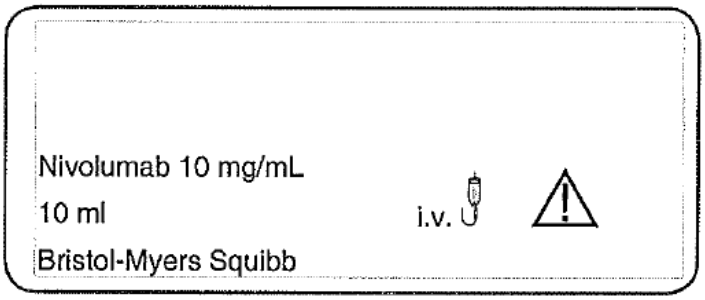
6.3 LABELLING OF NIVOLUMAB

Nivolumab will be supplied as labelled clinical trial stock with separate labels on both the vials and boxes, with a trial-specific auxiliary label on both. The label wording is shown below.

Primary label – Nivolumab vial label

Coding Specifications	
Coding Spec ID	**Drug Name/Strength**
BMS3153CS1.1	Nivolumab 10 mg/mL
Variable Field Requirements	
F # Placeholder	**Placeholder Description**
F1 XXXXXX	I. (Container Number Range)
F2 LLLLLLL	II. (Batch No.)
F3 MM/YYYY	III. (Use Date)
F4 PPPPPPP	IV. (Protocol)
F5 DD-MMM-YYYY	V. (Manufacture Date)
F6 XXXXXX	(Barcode\DataMatrix)
F7 123456	(Barcode\Interleaved 2 of 5)





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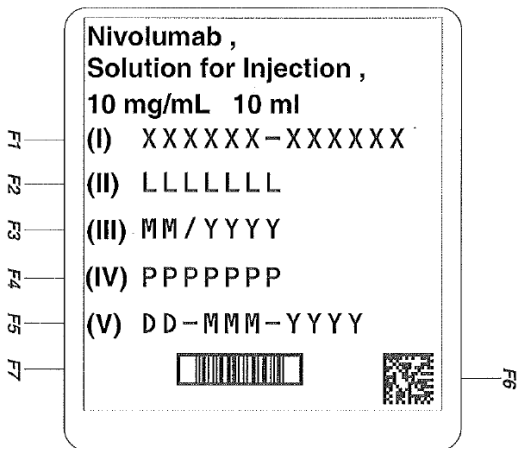
Auxiliary label text:
University College London
90 Tottenham Court Road, London W1T 4TJ
UCL/15/0515 ANIMATE
2017-002544-32
Patient trial number: _____
Cycle: _____
Site: _____

Secondary label – Nivolumab box label

Investigator _____
Subject No. _____
Contents: 5 Vials
Nivolumab , Solution for Injection , 10 mg/mL 10 ml
For Intravenous Use.
Use as directed..Store at 2° C - 8° C. Protect from light. Protect from freezing.
For Clinical Trial Use Only. For Clinical Trial Use Only -
This product shall be only used under strict medical surveillance.
Caution New Drug - Limited by United States Law to Investigational Use. ⚠
To be used by qualified investigators only.
Clinical Trial Material Not For Sale. Sample Use Only.
Investigational drug - To be used by qualified investigators only.
Keep out of reach and sight of children.
Return this package and any unused medicine.

Coding Specifications				
Coding Spec ID	Drug Name/Strength			Client Part
BMS3152CS1.1	Nivolumab , Solution for Injection , 10 mg/mL (12 pt.)			8222-V-3-N
Variable Field Requirements				
F #	Placeholder	Placeholder Description	Placements	
F1	XXXXXX-XXXXXX	Container Number Range	F1: CP	(13pt)
F2	LLLLLLL	Batch No.	F2: CP	(13pt)
F3	MM/YYYY	Use Date	F3: CP	(13pt)
F4	PPPPPPP	Protocol	F4: CP	(13pt)
F5	DD-MMM-YYYY	Manufacture Date	F5: CP	(13pt)
F6	XXXXXX-XXXXXX	(Barcode\DataMatrix)	F6: CP	(20pt)
F7	123456	(Barcode\Interleaved 2 of 5)	F7: CP	(10pt)



Auxiliary label text:

University College London
90 Tottenham Court Road, London W1T 4TJ
UCL/15/0515 ANIMATE
2017-002544-32
Patient trial number: _____
Cycle: _____
Site: _____

Pharmacy staff at trial sites should complete all blank fields on the above labels accordingly. The protocol number (F4 on the box/label) will be CA209-445. The container number (F1) is a unique kit number and will change throughout the trial. The distributor will amend all other fields that are not blank as necessary.

6.4 HANDLING OF NIVOLUMAB

For details of IMP handling and incompatibilities please refer to the current version of the supplied IB.

6.5 STORAGE CONDITIONS FOR NIVOLUMAB

Nivolumab must be stored in a designated clinical trial area segregated clearly as clinical trial stock, to be stored at 2°C to 8°C (36°F to 46°F) and protected from light and freezing. Vials should be kept in the outer box until dispensed.

Pharmacies must keep a record of temperature in the drug storage area(s) using their own logs. Pharmacies should insert a file note in the Pharmacy Site File with details of temperature monitor systems and location of temperature logs if held elsewhere.

6.6 TEMPERATURE EXCURSIONS FOR NIVOLUMAB

Temperature excursions outside of the acceptable ranges 2°C to 8°C (36°F to 46°F) must be reported to CSM and UCL CTC as soon as possible. Affected trial stock must be quarantined until notice is received from CSM as to whether it can be used for the trial.

Procedures are outlined in the "ANIMATE Procedures for Reporting Temperature Excursions" document, which is held in the Pharmacy Site File. UCL CTC and CSM should be notified of temperature excursions using the ANIMATE Notification of Temperature Excursions form.

Sites will be notified by CSM whether quarantined drug should be destroyed, or can be used for the trial.

6.7 PRESCRIBING IMPs

The Investigator is responsible for ensuring that nivolumab is prescribed appropriately for each patient on the trial. Please refer to the trial protocol for dosing schedules of nivolumab.

Sites should develop their own trial specific prescriptions. A copy must be forwarded to UCL CTC for approval prior site activation.

Prescriptions must be signed by the PI or appropriate member of staff (as identified on the site delegation log) and a copy must be retained in the Pharmacy Site File.

Nivolumab will be administered at a flat dose of 240mg for all patients. There will be no dose reductions, and dose banding is not permitted.

6.8 DISPENSING & RECORDING OF NIVOLUMAB

The **Nivolumab Balance Log** must be completed to record each dose of nivolumab dispensed for each trial participant. This must be retained in the relevant section of the Pharmacy Site File, and a copy must be submitted to UCL CTC upon request (see section 6.9).

Trial specific nivolumab must not be dispensed to patients who are not enrolled in the ANIMATE trial.

Please see the current IB (in particular the sections on 'Drug Product Preparation' and 'Recommended Storage and Use Conditions') for details of how to reconstitute nivolumab (including details of appropriate giving sets and filters) and for details of storage conditions and drug stability following reconstitution. Nivolumab must be reconstituted in aseptic conditions.

When a prescription of nivolumab is made, Pharmacy are advised to label the reconstituted solution with the following details in addition to the standard dispensing label:

- For Clinical Trial Use Only *and*
- Name of the Trial or EudraCT number
- Name of the Sponsor or Local Investigator

Nivolumab 240mg will be administered on day 1 of each 14 day cycle.

In the event of an overdose or trial treatment error relating to nivolumab, patients should receive supportive care in accordance with local policies. As per protocol section 8.5, UCL CTC must be informed immediately.

6.9 COMPLAINTS CONCERNING NIVOLUMAB TRIAL STOCK

If you have any concerns regarding the quality of nivolumab trial stock received, please inform UCL CTC via email to ctc.animate@ucl.ac.uk as soon as possible, this will then be reported to CSM and BMS. Please include as much detail as possible when raising your complaint. Affected trial stock must be quarantined until notice is received from UCL CTC as to whether it can be used for the trial. A response to a complaint will be due within 30 days, so if more stock is required in order to treat patients then please place a new order with CSM to ensure an adequate supply is maintained at site.

6.10 ACCOUNTABILITY LOGS FOR NIVOLUMAB

It is the responsibility of the Pharmacy Lead to maintain drug accountability records for nivolumab. The Pharmacy Lead (or appropriate delegate) must record the receipt and dispensing of nivolumab accurately, and in a timely fashion, on the appropriate **Accountability Logs** found in the Pharmacy Site File. It is not anticipated that there will be any drug returns for this trial.

The following template accountability Log(s) will be provided for the trial:

- Nivolumab Balance Log
- Nivolumab Patient Accountability Log

However, sites can use their own logs providing they capture the same information as the UCL CTC supplied logs and a copy is sent to UCL CTC for approval prior to site activation.

Completed Accountability Log(s) must be retained in the relevant section of the Pharmacy Site File.

During the course of the trial UCL CTC will request copies of the following for central monitoring purposes:

- Drug Request Forms
- Nivolumab Balance Log
- Nivolumab Patient Accountability Log

Patient Accountability Logs should be emailed to ctc.animate@ucl.ac.uk when a patient stops trial treatment, either once they have completed the full 8 cycles of nivolumab or when they have stopped treatment early for any reason.

Nivolumab Balance Logs should be emailed to ctc.animate@ucl.ac.uk upon request.

6.11 DISPOSAL/DESTRUCTION OF NIVOLUMAB

Details of the local drug destruction policy should be filed in the Pharmacy Site File.

Used and partially used vials can be disposed of at time of aseptic preparation.

If the site has unopened/unexpired nivolumab left at the end of the trial, please contact UCL CTC prior to any action. Notify UCL CTC who will liaise with CSM and Bristol-Myers Squibb Pharmaceuticals Ltd for advice on its use.

Once authorisation has been received from UCL CTC, stock of trial-specific nivolumab should be disposed at the site according to local procedures. Disposal/destruction must be recorded on the nivolumab drug balance log. Records of destruction must be filed in the PSF and sent to UCL CTC on request.

6.12 SHELF LIFE EXTENSION

The Lead Pharmacist (or appropriate delegate) should regularly check clinical trial stock held at site to ensure it is within its expiry date.

Expired trial-specific nivolumab should be quarantined and not used after the expiry date, which is stated on the carton and on the vial label after EXP. The expiry date refers to the last day of that month. UCL CTC should be contacted for advice.

UCL CTC will advise whether expired stock should be destroyed or if there will be a shelf life extension. If drug is to be destroyed, please follow the instructions in section 6.10 above. If shelf life is extended, UCL CTC will advise on arrangements for relabelling.

6.13 RECALL OF NIVOLUMAB

In the event of nivolumab recall, UCL CTC will notify the Pharmacy Lead with arrangements for recall and liaise with CSM to ensure replacement product is supplied where necessary.

7. NON INVESTIGATIONAL MEDICINAL PRODUCTS (NIMPS)

There are no drugs defined as NIMPs for this trial.