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Director: Professor JA Ledermann

Dr Anthony Fox
London - South East Research Ethics Committee
Barlow House
3rd Floor
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28/05/2020

Dear Anthony,

Trial Title: 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

Funders: Bristol-Myers Squibb
Sponsor Name: University College London
Sponsor's Trial ID Number: UCL/15/0515
EudraCT Number: 2017-002544-32

Amendment Number/Date: 6 – Protocol v4.0, 28/05/2020

Please find enclosed a request for authorisation for a substantial amendment to the above-named trial. The trial protocol, patient information sheet, informed consent form, pregnancy monitoring information sheet for patients and pregnancy monitoring informed consent form for patients have been amended.

The following documents are provided:

		Version	Date
1.	Notice of Substantial Amendment form	N/A	N/A
2.	ARSAC form	N/A	N/A
3.	Protocol (with tracked changes)	v4.0	28.05.2020
4.	Protocol (final clean copy)	v4.0	28.05.2020
5.	Patient Information Sheet (with tracked changes)	v5.0	28.05.2020
6.	Patient Information Sheet (final clean copy)	v5.0	28.05.2020
7.	Patient Information videos – YouTube link	N/A	N/A
8.	Pregnancy Monitoring Information Sheet for patients (clean and tracked)	v1.0	28.05.2020
9.	Pregnancy Monitoring Informed Consent Form for patients (clean and tracked)	v1.0	28.05.2020
10.	Informed Consent Form (with tracked changes)	v4.1	28.05.2020
11	Informed Consent Form (final clean copy)	v4.1	28.05.2020

ARSAC Form updated

The ARSAC form with highlighted changes has been included with this amendment, more as a reference and to provide confirmation of sign off by both the CRE and MPE for the trial. Changes in the following sections have been made:

- A1: effective dose or target tissue dose per administration has been amended to remove wording in brackets, dose itself not changed
- A2: total effective dose or target tissue dose per individual has been updated to reflect the inclusion of the CT guided biopsy (previously missed in error)
- B1: table of ionising radiation has been updated;
    - Additional row added for the CT guided biopsy procedure, which was previously missed in error. This is not an additional procedure
    - Contrast enhanced CT scan estimated procedure dose has been amended to reflect the inclusion of the neck within the scanned areas
- C1: Dose and risk assessment text updated to reflect the changes in section A & B1

Protocol Amendment Details

This amendment will change the version number of the protocol from 3.0 to 4.0; tracked and clean copies of the amended protocol have been submitted.

The main changes from protocol v3.0 are listed in the table below:

Protocol Section (no./title)	Summary of main changes from previous version.
TMG page 1	Amendment to Dr Beth Phillips' job title and location. Addition of new Trial Coordinator
4.2.2 Required documentation	Removal of 'Clinical Trial Site Agreement' as the trial uses the model Non-commercial agreement
8.2 Treatment Summary	Clarification that PET-CT scans should be conducted 'during' cycle 4
8.4 Treatment discontinuation criteria	Added back in G4 lipase abnormalities, as lipase testing has been added back into assessments.
8.5.1 Autoimmune complications	Removal of wording 'summary of product characteristics' and replaced with 'relevant appendix within the Investigator Brochure'
8.5.1.8 Management of myocarditis	Addition of section to manage myocarditis. Current Investigator Brochure v18 has new guidance for managing myocarditis. Section created based on information within IB.
8.5.1.9 Management of other immune-related adverse reactions	Removal of wording 'summary of product characteristics' and replaced with 'relevant appendix within the Investigator Brochure' Removed reference to myocarditis as this now has a separate standalone section for toxicity management
9.2 Assessment of eligibility for nivolumab treatment	• Clarification added for timing of eligibility assessment; 'Once registered on trial and after completion of…' • Added confirmation that the PET-CT scan is to include neck, chest, abdomen and pelvis. • Added clarification to stipulate the ceCT scan areas; neck, chest, abdomen and pelvis (NCAP). • Added in details to inform sites to contact UCL CTC if the timeframe of assessments is outside those stipulated.

	• Lipase testing has been added back in to assessments. This is due to some sites conducting lipase instead of amylase tests. • Hep C testing; amended from 'Hepatitis C DNA' & 'HCV DNA' to 'Hepatitis C RNA' & 'HCV RNA'. DNA wording used in error, Hep C is a RNA virus.
9.3 Assessments prior to cycle 1of Nivolumab	• Lipase testing has been added back in to assessments. This is due to some sites conducting lipase instead of amylase tests.
9.4 Assessments during nivolumab treatment	• Clarification added to heading; 'Assessments during **Nivolumab** Treatment'. • Lipase testing has been added back in to assessments. This is due to some sites conducting lipase instead of amylase tests. • ceCT4 scan times have been added to reflect the fact that these should be in keeping with the timings of the PET4 scan. • Various minor re-wording to provide clarity of assessment timing.
9.5 Assessments on completion of nivolumab treatment	• Clarification added to heading; 'Assessments during **Nivolumab** Treatment'. • Added details of the CT guided biopsy, which was previously missed • Added in wording to provide clarification that the ceCT scan should be conducted as well as PET-CT; 'Contract enhanced CT scan to be carried out at least 11-13 days after last trial treatment administration, and sent to the PET core lab for central review. This should be performed at the same imaging session as the PET-CT if feasible. If performed at the same session, the ceCT scan should be performed after the low dose PET-CT (see trial Imaging Manual and Sample Tracking Website Manual for details).'
9.6.2 Patients who receive nivolumab	Lipase testing has been added back in to assessments. This is due to some sites conducting lipase instead of amylase tests.
9.7 Assessments at time of disease progression	Added details of the CT guided biopsy, which was previously missed
11.3 Timelines for Data Return	Reference to section 14.2 has been amended to reflect the renamed title; 'For Cause On-Site Monitoring' has been renamed 'Triggered On-Site Monitoring'
12.4.1 Autoimmune events due to nivolumab	Duplication of paragraph, 'The following adverse events of special interest for Nivolumab must be reported on the appropriate AE of Special Interest form within **24 hours of confirmed diagnosis'** therefore removed
14.1 Centralised Monitoring	Reference to section 14.2 has been amended to reflect the renamed title; 'For Cause On-Site Monitoring' has been renamed 'Triggered On-Site Monitoring'
14.2 For Cause On-Site Monitoring	Section renamed. Was 'For Cause On-Site Monitoring' now reads 'Triggered On-Site Monitoring'
15 Withdrawal of patients	New paragraph added 15.1 – 'Patients who do not start treatment' There are now 6 sub-sections to section 15
16.4 Withdrawal from Trial Participation by a Site	Removal of 'CTSA' and replaced with 'site agreement (mNCA)' to reflect the correct type of contract used within the trial
19 Ethical and Regulatory considerations	Data protection Act updated from 1998 to 2018 to reflect the new update. And addition of the General Data Protection Regulation (EU)2016/679 (GDPR) (*changes previously missed in error from v2.1 protocol amendment*)
19.5 Patient Confidentiality & Data Protection	DP Act date updated to 2018, and addition of GDPR.

21 Funding	Removal of 'CTSA' and replaced with 'site agreement (mNCA)' to reflect the correct type of contract used within the trial
Appendix 1 Abbreviations	Addition of the following: GDPR - General Data Protection Regulation mNCA - Model Non-Commercial Agreement
Appendix 2.1 tables 'Patients who receive nivolumab' footnote 4 & 'Investigations during treatment' footnote 2	Lipase testing has been added back in to assessments. This is due to some sites conducting lipase instead of amylase tests. Hep C testing; amended from ''HCV DNA' to 'HCV RNA'. DNA wording used in error, Hep C is a RNA virus.
Appendix 2.2 table 'Patients who do not receive nivolumab' footnote 4	Lipase testing has been added back in to assessments. This is due to some sites conducting lipase instead of amylase tests. Hep C testing; amended from 'HCV DNA' to 'HCV RNA'. DNA wording used in error, Hep C is a RNA virus.

Other minor clarifications have been made to the protocol, as well as general administrative and typographical edits. Please see tracked changes version for full details.

New Sites

There will be 5 new sites participating in the trial:

- United Lincolnshire Hospitals NHS Trust (**Lincoln County Hospital, PI Dr Gamal Sidra**)
- University Hospitals Plymouth NHS Trust (**Derriford Hospital, PI Dr Patrick Medd**)
- Sandwell and West Birmingham Hospitals NHS Trust (**Sandwell General Hospital, PI Dr Syeda Yasmin Hasan**)
- Clatterbridge Cancer Centre NHS Foundation Trust (**Clatterbridge Cancer Centre,** based at Royal Liverpool Hospital, **PI Dr Nagesh Kalakonda**)
- NHS Grampian (**Aberdeen Royal Infirmary, PI Dr Dominic Culligan**)

Change in Principal Investigators

The Principal Investigators have changed at the following sites:

- The Christie NHS Foundation Trust (**The Christie Hospital**), was Dr Kim Linton and **transferring to Dr Elizabeth (Beth) Phillips**
- Nottingham University Hospital NHS Trust (**Nottingham University Hospital**), was Dr Andrew McMillan and **transferring to Dr Nicolas Martinez-Calle**

Other amended trial documents

The following trial documentation has also been amended and is submitted to REC for approval.

Patient Information Sheet version 5.0

The patient information sheet has been amended to reflect the current reference safety information as detailed in the Nivolumab Investigator Brochure v18 and several sections have been updated to clarify certain points. Once approved this will be released to sites to be provided to all new potential patients considering participation in the trial.

Site Investigators will be asked to re-consent patients already recruited to the trial to re-consent at their next visit to the site. During the COVID-19 pandemic the PIS may be posted to patients already on trial who are not due to be seen in clinic soon, and a phone will be made to discuss the changes. This phone call will be documented in the patient notes. These patients will be re-consented at their next visit to the site.

Tracked and clean copies of the amended patient information sheet is attached. The key changes are as follows:

- Section 3, on Page 7: added new wording 'The assessments and scans you have will be looking to see if your disease has progressed If it has you will then have another CT scan and then a biopsy will be taken

to confirm relapse. The biopsy will help us to know whether the PET scans are correctly identifying the presence of your disease.'

- Section 5, on page 9 added new wording 'The company also reports that some patients have experienced kidney failure after receiving nivolumab which has been life threatening in some instances, so it is important that you tell your doctor if you feel unwell. Your kidney function will be monitored closely with blood tests during the trial' and 'Another common complication of treatment with nivolumab is inflammation of the lungs In some instances, this has been life-threatening and even fatal. Other events experienced by a very small number of people (>1/10,000 to < 1/1,000) that have been fatal include; myocarditis (inflammation of the heart), muscle inflammation and the rapid breakdown of muscle tissue leading to a toxic build-up of chemicals.'
- Further Information, on page 17 added a website link to patient videos - https://tinyurl.com/yagrr934
- Appendix 2, on pages 19 & 20 added in added in new possible side effects and amended wording of some existing side effects to clarify in layman's terms.
- Appendix 4, on page 24 added extra tests for CT guided biopsy which was previously missed off in error.

Patient Video – YouTube link

The purpose behind the patient videos is not to replace the PIS but to provide an easy to digest recap of the information in small bite size video clips. There are 31 video clips in total ranging from 31 seconds long to 2 minutes 50 seconds long. The videos were put together following a PPI focus group. They provide not only a recap of information but provide answers to frequently asked questions.

The videos are uploaded on YouTube via a specific link which is documented in the PIS. This video link cannot be searched for and is only available to those people who have access to the specific patient video link.

The videos can be viewed via the following link: https://tinyurl.com/yagrr934

Pregnancy Monitoring Information Sheet

New document created, not previously included within trial documentation in error. Please note, to date there have not been any pregnancies on trial.

Pregnancy Monitoring Informed Consent Form

New document created, not previously included within trial documentation in error.

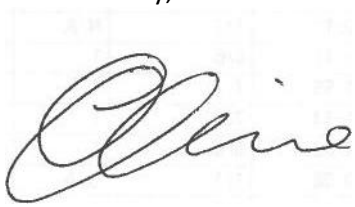
Informed Consent Form

The Informed consent form has been amended to correct a typo within section 11. The change made to this section is as follows:

> **'Women of childbearing potential only:**
> I understand that nivolumab may be harmful to an unborn ~~trial~~child, and I agree to use one of the forms of hormonal birth control listed in the Patient Information Sheet, and advise my partner to use condoms, during trial treatment until 6 months after last administration of nivolumab.'

If you have any questions, please do not hesitate to contact me.

Yours faithfully,



Mrs Emma Lawrie
ANIMATE Trial Coordinator