To be presented on local headed paper

TebeMRD

A Phase II Non-Randomized, Open-label, Multi-centre Study of the Safety and Efficacy of Tebentafusp in Melanoma with Molecular Relapsed Disease

PARTICIPANT INFORMATION SHEET

Pre-screening for HLA type

1 You are invited to take part in our research

Before you decide whether to take part in this study, we would like you to understand why the research is being done, how your information will be used, what the trial will involve, including the possible benefits, risks and discomforts.

One of our team will go through the information sheet with you and answer any questions you may have.

This study involves three different stages. This information sheet is for the first stage of the study, called **pre-screening**. If you become eligible to take part in the later stages of the study, you will be given a new information sheet, relevant to that stage of the study. The different stages will be described in this information sheet.

You do not have to take part in this study, as this is a voluntary decision and whatever you decide there will be no effect on your standard of care.

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2 Why Have I Been Invited?

We have invited you to take part because you have received treatment for either cutaneous (skin) or uveal (eye) melanoma and are, or shortly will start to be, monitored in case it comes back. Your doctors feel this new, and as yet unproven approach, is an option you may wish to consider. The information we get from this trial may help us to improve the future treatment of patients with cutaneous and uveal melanoma.

3 What is the purpose of this trial?

We are trying to find ways to improve the management of people with intermediate or high risk resected cutaneous melanoma or with primary uveal melanoma and/or who have had metastases removed by an operation.

This research study is investigating using a new blood test (molecular screening) to decide when to give a drug called tebentafusp. Tebentafusp has been used in clinical trials in patients with advanced cutaneous and uveal melanoma. These trials have shown that treatment with tebentafusp resulted in longer overall survival than the control therapy, among previously untreated patients with metastatic uveal melanoma. The results of these trials have meant that tebentafusp has been granted a marketing authorisation for the treatment of advanced uveal melanoma. The TebeMRD study is designed to determine if tebentafusp can work at an earlier stage of the disease. We want to find out whether tebentafusp can help patients with cutaneous or uveal melanoma live longer and feel better, and if tebentafusp can make these melanoma tumours stop growing (or shrink).

To help decide whether or not you can take part in this research study we need to first test your blood to determine if your immune system (or tissue type) can 'see' tebentafusp. People have differences in their immune systems (a bit like blood groups) and the study treatment can only work with a particular tissue type called Human Leukocyte Antigen (HLA) A*0201. To be able to take part in the later stages of this study you need to be HLA A*0201 positive. Your study doctor does not already know your HLA type so we will need to do a blood test to find out. About half of the general population are HLA type A*0201 positive. Therefore it is anticipated that roughly half of the patients who enter this pre-screening stage will be eligible for the main study. If when your blood is tested and you are found to be negative to HLA type A*0201, you will not be eligible to take part in this study and your involvement will end. Your treatment will continue with standard care as discussed with your clinician.

For this pre-screening stage we aim to recruit approximately 850 participants like you from up to 50 centres across the UK.

4 Do I have to take part?

No, taking part in the **pre-screening** is entirely voluntary. It is up to you to decide whether to take part or not. We will describe the trial and go through this information sheet with you, but the decision is yours. If you agree to take part in the trial we will ask you to sign a consent form. Any current or future healthcare that you receive will not be affected by deciding whether or not to take part in the trial.

If you agree to have this blood test you will be given this patient information sheet to keep for future reference. Consenting to the blood test

does not mean you have to take part in molecular screening or the main study.

You can also withdraw from the trial at any time without giving a reason and this will not affect the standard of care that you receive.

5 What would taking part involve?

This stage of the trial involves only a blood test but we will also talk you through what will happen in the later stages of the trial to help with your decision about taking part. If you wish to know at this stage what the rest of the study involves in detail, you can ask your doctor for a copy of the main study information sheet. After you have had the opportunity to ask any questions you might have, and if you decide that you would like to take part, we will ask you to sign a consent form. You will then have the blood sample taken for HLA-A*0201 testing. The blood sample is about 10ml, approximately 2 teaspoons. If a suitable blood sample has already been taken and is available, a fresh blood sample may not need to be taken.

6 What does the treatment involve?

Participants who have the HLA type A*201 positive will then be invited for molecular screening. For the molecular screening you will have a blood test every three months for two years. If one of these tests shows traces of melanoma, then you may become eligible to join the main study to receive tebentafusp. Where possible, we will try and schedule your study tests at the same time as your normal standard of care clinic visits.

For the main study we are aiming to recruit approximately 50 participants who will receive tebentafusp in 1 (one) of up to 10 centres across the UK. This centre may be different from the one where you are having your pre-screening and your study doctor will discuss the likely centre(s) that you would be asked to attend.

During the main study you will have weekly assessments to assess the effect of tebentafusp on your body and monitor your health. Although many of the assessments are part your normal standard of care, some additional tests are performed, such as the research blood samples. The main study consists of weekly visits for up to 6 months, so this part of the trial can involve up to 24 clinic visits.
The study treatment, tebentafusp, is given weekly as an intravenous infusion (into your bloodstream), usually over 15 to 20 minutes. In addition to receiving tebentafusp you will receive all the other care that you would normally receive. You will need to stay in hospital overnight following the first three doses of the study treatment.

If you develop serious side effects, or are unable to follow trial procedures, you may be withdrawn from the trial.

Reasonable travel expenses for any visits additional to your normal care will be reimbursed on production of receipts or a mileage allowance provided as appropriate. The local arrangements will be explained to you during the informed consent discussions prior to trial entry. No other reimbursement will be provided.

If you have private medical insurance you should tell your insurers and check that your cover will not be affected before agreeing to take part in this trial.

7 Will any genetic tests be done?

For pre-screening there will be no genetic tests.

8 What will happen to any samples I give?

For pre-screening your blood sample will only be used to test your HLA type. Your blood sample will be either tested at your local centre or transferred out to the central laboratory at the Transplant Immunology Laboratory, Churchill Hospital, Oxford which is the designated laboratory for performing these tests where local resources are not available. The process uses all the sample collected but where there is any left-over sample, this will be destroyed according to the laboratory's local policy and in accordance with the requirements of the Human Tissue Act. The results will be provided to your study doctor as well as to the TebeMRD trial office.

9 What should I consider?

Regular medications

If you begin the trial treatment, it may be necessary to change or stop some of your regular medications. The doctor will discuss any changes with you in advance of starting the trial. If you are going to take other medications, please discuss this with the trial team before starting them. This includes complementary medicines e.g. cannabis oil/herbal medicines, vitamins etc.

Pregnancy and breast feeding

You will also be informed of all the precautions required for the main study if you or your partner is of child-bearing potential.
If you are pregnant or breastfeeding you cannot take part in this trial, as to protect the developing baby from the potential harm received from the study treatment.

Other considerations

You should not take part in any other trial at the same time as this trial without telling us first.
You should not have taken part in another clinical trial in the month before you start this trial.

Covid-19

Please let us know as soon as it is practical if you test positive for Covid-19 whilst taking part in this trial. We will discuss options with you, but you should be able to resume treatment as soon as you have recovered.

10 What are the possible benefits of taking part?

Whether or not you would benefit from the treatment in the main phase of this research trial is unknown. Most people who enter the trial are expected to show no signs of melanoma during the monitoring phase, and so will not receive tebentafusp. If there are signs that your melanoma is coming back we hope that by taking part in the trial tebentafusp may help slow down the reappearance of your cancer, but this cannot be guaranteed.

Tebentafusp has recently received a Marketing Authorisation for the treatment of advanced uveal melanoma. It is also a drug that we hope will improve the long term outcome for patients with cutaneous or uveal melanoma (at an earlier stage of the disease). However, these benefits have not yet been proven in these indications, and you may not have any direct health benefits from taking part in this trial. We will tell your doctor if the extra research tests give any information that might help your medical care.

By entering this trial you will be making a significant contribution to increase our

knowledge of cutaneous and uveal melanoma cancer, which may help us to improve the future treatment of patients with these cancer types.

11 What are the possible disadvantages of taking part?

For the HLA-*A201 testing, blood will be taken through a small needle placed in your vein. At the area where the blood is taken there may be mild pain, bruising and swelling. In addition, light-headedness, fainting or infection (rare) at the injection site is possible.

The treatments used on this trial can cause side effects. Some people may have very few side effects, while others may experience more. Your doctor will be able to advise on the potential side effects in much more detail if you were to go on to the main phase of the study.

Disadvantages associated with the assessments required for the main part of the trial may be discussed with your doctor at this time. However, these are all assessments that you will have previously experienced during your normal standard of care with the exception of the research blood samples.

12 What if there is a problem?

You will receive the best medical care available during and after the trial, but because this is a new treatment, unexpected side effects may occur. In the unlikely event of an injury arising from taking part in this trial, you will be provided with the all the necessary care.

Any complaints about the way you have been dealt with during the trial or any possible harm you might suffer will be addressed.

The University of Oxford, as Sponsor, has appropriate insurance in place in the unlikely event that you suffer any harm as a direct consequence of your participation in this trial. NHS indemnity operates in respect of the clinical treatment which is provided.

Complaints

If you have a concern about any aspect of this trial, you should ask to speak to the researchers. If you wish to complain about any aspect of the way in which you have been approached or treated or how your information was handled during the course of this trial, you should contact:

- The TebeMRD Trial Office by emailing *octo-tebemrd@oncology.ox.ac.uk*
- You may contact the University of Oxford Research Governance, Ethics & Assurance Team on 01865 616480, or the head of RGEA, email: RGEA.Sponsor@admin.ox.ac.uk .

The Patient Advisory Liaison Service (PALS) is a confidential NHS service (available only in England) that can provide you with support for any complaints or queries you may have regarding the care you receive as an NHS patient. PALS is unable to provide information about this research trial. If you wish to contact the PALS team please contact: PALS Office, *[Hospital Name, address & postcode] Tel: [insert contact phone number]*

13 What will happen if I don't want to carry on with the trial?

You are free to withdraw at any time and without giving a reason. A decision to withdraw

at any time, or a decision not to take part, will not affect the standard of care you receive. If you change your mind, we would kindly ask that you contact the research team to inform them of your decision at your earliest possible convenience. The research team will respect your decision and we will happily answer any questions you might have at the time.

14 Will my information be kept confidential?

Yes. Responsible members of the University of Oxford (and the relevant NHS Trust(s) may be given access to data for monitoring and/or audit of the study to ensure that the research is complying with applicable regulations. We will follow ethical and legal practice and all information about you will be handled in confidence. This means we will only tell those who have a right or need to know. Information collected about you during the trial will be kept at the TebeMRD Trial Office, which is part of the University of Oxford. This information is strictly confidential.

Your trial record will be identified by a unique trial number and your personal identity will not be identifiable from this number.

The local NHS Trust will use your name, NHS number and contact details, to contact you about the research study, and to oversee the quality of the study. They will keep identifiable information about you from this study in keeping with local policy for retention of medical notes.

Your anonymised information may also be shared with third parties working with Oxford University. This information will be identified only by the unique trial number and you will not be personally identifiable. Third parties include the pharmaceutical company Immunocore and regulatory authorities in the UK (MHRA). The Sponsor will make every effort to ensure your anonymised data is adequately protected.

15 What will happen to my data?

We will be using information from you and your medical records in order to undertake this study and will use the minimum personally-identifiable information possible. We will keep identifiable information about you for **12 months-3 years** after the study has finished. Data protection regulation requires that we state the legal basis for processing information about you. In the case of research, this is 'a task in the public interest.' The University of Oxford is the sponsor for this study, based in the United Kingdom, is the data controller and is responsible for looking after your information and using it properly.

We will store the de-identified research data, securely at the University of Oxford for at least 25 years after the end of the trial. After the trial ends the information held in your medical records will be stored according to local NHS trust policies.

The University of Oxford will collect information about you for this research trial from your medical records held by your hospital. Your hospital will not provide any identifying information about you to the University of Oxford. We will use this information to answer the questions we are trying to address in this research trial, as described in the Patient Information Sheet.

Your rights to access, change or move your personal information may be limited, as we need to manage your information in specific ways in order for the research to be reliable and

accurate. If you withdraw from the trial, we will keep the information about you that we have already obtained. To safeguard your rights, we will use the minimum personally-identifiable information possible.

Further information about your rights with respect to your personal data is available at

https://compliance.web.ox.ac.uk/individual-rights

You can find out more about how we use your information by contacting:

octo-tebemrd@oncology.ox.ac.uk

16 What will happen to the results of this trial?

The results of the trial may be presented at meetings and/or published in a medical journal. However, you would never be identified individually during these *presentations*, *reports* or *publications* that arise from this research trial. If you are interested in the results, please ask your research doctor who will be able to tell you about these when the trial is over.

The results of the trial may be used by the researchers to find new treatments for patients with cancer, which may be of commercial benefit to the manufacturers of the drugs used.

17 Who is organising and funding the research?

The University of Oxford is the research sponsor. This means that it is legally responsible for the trial organisation and for overseeing the work of the researchers.

This trial is being funded by Immunocore, a company who has researched and developed the new tebentafusp drug.

Your research doctor will not be paid by any pharmaceutical company for including you and looking after you in this trial.

18 Who has reviewed the trial?

All research in the NHS is looked at by an independent group of people, called a Research Ethics Committee, to protect participants' interests. This study has been reviewed and given favourable opinion by the South Central Oxford A Research Ethics Committee.

A representative from a Patient and Public Involvement (PPI) organisation has also reviewed the trial and this information sheet.

19 Who are the researchers?

The Chief Investigator responsible for leading and directing this trial is Professor Mark Middleton, Professor of Experimental Cancer Medicine at the University of Oxford. The trial is managed by the Oncology Clinical Trials Office at the University of Oxford.

Conflict of Interest Statement

Professor Mark Middleton has received personal fees and research funding from Immunocore, which is the company providing funding for this study.

Dr Joseph Sacco, who contributed to the set-up of this study, has received payment,

participated in paid advisory boards and received research funding from Immunocore.
While the above investigators and contributors therefore have a potential conflict of interest, the integrity of this clinical study is maintained by an independent trial steering committee

Contact details for further information
< *[insert Local site details]*
> Tel: *[insert number]* or by email on *[include email address]*

For any emergencies outside office hours please contact:
< *[insert Local site details]*
> Tel: *[insert number]*

For more information about clinical trials you can contact Macmillan Cancer Support which is *an independent* charity providing support and information to help people with cancer. They can be contacted on 0808 808 00 00 (freephone) or visit their website: http://www.macmillan.org.uk

Thank you for taking the time to read this information sheet.

If you decide to take part in the trial, you will be asked to sign the consent form. We will give you a copy of this Information Sheet and the signed copy of the consent form to keep. Thank you for taking the time to read this Information Sheet.

A diagram showing what will happen and when in the TebeMRD Trial

Timeline	Visits
Before entering the trial Pre-screening	**Step 1 - Are you HLA A*0201?** Positive blood test
Molecular Screening	**Step 2 - Do you show signs on blood testing of a molecular relapse?** • Tests to check your suitability for the trial • Eligibility confirmed • Blood tests for molecular relapse on Day 1 and every 3 months for 2 years
After entering the trial (Pre- trial screening)	**Diagnosis: HLA-A*0201 positive uveal or cutaneous melanoma with molecular relapse disease**
	Step 3 - Consent to trial
	Tests to check your suitability for the trial: including CT scan, blood samples, physical exam, performance status, blood pressure, heart and respiratory rate, temperature, ECG, research blood samples, MR Liver (uveal patients only)
	Eligibility confirmed and patient registered onto the main phase of the trial
All Cycles (28 Days) Before Treatment	• ECG (before and after tebentafusp treatment during the first three doses), Blood pressure, heart rate, respiratory rate and temperature • Routine blood test, urine test; pregnancy test (Day 1 only) • Physical examination, Performance Status and assessment of any side effects from previous treatment doses. • Weight and height (Day 1 only) • Research blood samples • Record of other medication you are taking
IMP Administration	• Cycle 1: First three doses (Days 1,8,15) with overnight stay and Day 22 with at least 30 minutes observation • Cycles 2 - 6: All visit days (Day 1,8,15 and 22) with at least 30 minutes observation according to study doctor's discretion
During Treatment	• Research blood samples: All visit days during cycle 1 (Day 1,8,15 and 22) and on day 1 only during cycles 2-6 • Blood pressure, heart rate, respiratory rate and temperature • Assessment of any side effects
End of Treatment	**Until 6 months or decision taken by clinician**
28 Day Post Treatment	Similar assessments as performed during Screening **except** consent, medical history, weight, ECG, research blood samples, CT scan
Follow-up (every 3 months for 12 months)	Research blood sample Assessment of any side effects
	Patient referred back to their oncologist