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A study on patients with melanoma who are receiving cancer immunotherapy to identify specific features related to the immune system and gut bacteria that may indicate a higher risk of negative side effects from a type of cancer treatment called checkpoint inhibitors, comparing patients who experience immune-related side effects to those who do not

Submission date 30/03/2023	**Recruitment status** No longer recruiting	[_] Prospectively registered [X] Protocol
Registration date 18/09/2023	**Overall study status** Ongoing	[_] Statistical analysis plan [_] Results
Last Edited 02/07/2025	**Condition category** Cancer	[_] Individual participant data [X] Record updated in last year

Plain English summary of protocol

Background and study aims

Normal healthy cells emit signals, to prevent the immune system attacking them. Unfortunately, some cancer cells also emit signals, tricking the immune system into thinking they are harmless and healthy. Checkpoint inhibitor (CPI) drugs can interfere with signals from cancer cells, called checkpoint proteins, resulting in the immune system recognising and destroying cancer cells. This can result in responses where tumours stop growing or shrink.

However, CPI therapy can sometimes result in normal healthy cells, in the rest of the body, being vulnerable to attack from the immune system as well. This can result in a variety of side effects, which will be explained in your standard of care treatment consent form.

The main aims of this study are to understand why and how some patients receiving CPIs develop side effects and others don't, so that we might be able to prevent them in the future. Some of the side effects from CPI's share characteristics with fairly common autoimmune diseases such as inflammatory bowel disease and rheumatoid arthritis, so this study might reveal knowledge useful in treating these other diseases too. We aim to recruit 80 patients with melanoma, non-small cell lung carcinoma or mesothelioma, to help answer these questions.

If you join the study it will not affect your cancer treatment in any way at all, either with regards to its effectiveness or the risk of you getting side effects from the CPI treatment.

Who can participate?
Any patients receiving checkpoint inhibitors for melanoma may be eligible to participate. Unfortunately, if you have a pre-existing autoimmune condition, chronic infection, have recently taken steroids or have been recently vaccinated (except for Covid-19 vaccines or boosters) you would not be able to participate in the study.

What does the study involve?
This research study is being undertaken by Newcastle University and is being run at the Northern Centre for Cancer Care at the Freeman Hospital. Your involvement in the study will last for a maximum of approximately 10 months, over which time you will have up to 6 appointments with the research team. These will coincide with your routine appointments with your melanoma team, as part of your cancer care, but may add up to approximately 55 minutes to your visit time.

If you agree to take part in this study, you will be invited to meet with one of the research team to discuss the study further and to ask any questions. We would then ask you to sign a consent form to state that you are happy to join the study. The first visit will be called a 'baseline' visit and will happen within 2 weeks before your first dose of CPI. You will have further research visits within 7 days (before or after) your 2nd, 3rd, 4th, 5th and 6th or 7th CPI dose. If the type of CPI you are given changes before you have completed 6 study visits, you will continue on the study with the new CPI treatment for a maximum of 6 study visits in total. You may have an End of Study Visit if you come off treatment before either your 6th or 7th CPI dose. The End of Study Visit will take place within 14 days of the decision to stop treatment if you have a standard of care visit during this time.

At these visits you may:
1. Have a physical examination as part of your standard of care, the results of which we will record as part of this study.
2. Be asked to complete a questionnaire about any symptoms you may have.
3. Have skin swabs taken from your forehead, upper chest, upper back, forearm and back of hand.
4. Have blood tests taken for research. A maximum of 64 mls of blood (equivalent to about 4 and a half tablespoons-full) will be taken at a study visit.
5. Be asked to provide an optional stool sample using a specially designed kit and complete a questionnaire. The stool sample should be collected ideally within 7 days of receiving the stool kit and returned by post within 24 hours of collecting.

At each study visit, you will be asked about any symptoms you may develop, to determine if you have developed a "significant or severe" side effect due to taking your CPI treatment. In addition, you will be asked to contact your oncology team in between visits if you have new symptoms so that your oncology team can arrange to see you if needed. An additional one or two "requested" visit(s) to hospital may follow for further assessment by an oncologist and for study assessments. This visit may include all or some of the study tests you had at the other visits. If your skin is affected a skin swab may be taken from the area. The area of skin affected may also be photographed by a medical photographer, or a member of the study team, if you are happy to consent to this. If you do develop a "severe" side effect then you will normally complete your participation in the study early following this.

What are the possible benefits and risks of participating?
You will not directly benefit from participating part in this study and payment is not offered for your participation to ensure participation is voluntary. Your study information however could help doctors to develop better strategies for treating patients with CPIs in the future,

particularly reducing the risk of side effects. This information may also help doctors to better understand and treat common autoimmune diseases that occur spontaneously in the general population, which are not related to CPI treatment.

In terms of risks, you may experience some mild discomfort and bruising as a result of the blood sample collection. There is also a risk of infection or haematoma (collection of blood under the skin) when taking blood, but these rarely happen. Research blood samples will be taken, wherever possible, at the same time as your routine blood tests, without the need for extra needles. The skin swabs taken are moistened with a solution containing salt and a mild detergent, and there is a small risk of localised skin irritation after the procedure. If you consent to optional biopsies within the study, there are risks associated with taking biopsies which your oncologist/the doctor performing these will discuss with you at the time if it should become necessary to do these as part of your standard of care. These risks could be slightly higher if additional biopsies were taken for this study.

Where is the study run from?
This research study is being undertaken by Newcastle University and is being run at the Northern Centre for Cancer Care at the Freeman Hospital (UK)

When is the study starting and how long is it expected to run for?
October 2018 to June 2027

Who is funding the study?
Cancer Research UK funds the clinical costs associated with the study and the microbiome laboratory work, the JGW Patterson Foundation fund the immunological laboratory work (UK)

Who is the main contact?
Professor Ruth Plummer, ruth.plummer@newcastle.ac.uk

Contact information

Type(s)
Public

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Additional identifiers

EudraCT/CTIS number
Nil known

IRAS number
252992

ClinicalTrials.gov number
Nil known

Secondary identifying numbers
NCCC-BH162398, IRAS 252992, CPMS 40680

Study information

Scientific Title
Monitoring immunE DysregulAtion foLLowing Immune checkpOint-inhibitioN (MEDALLION): an observational cancer immunotherapy cohort study

Acronym
MEDALLION

Study objectives
Our over-arching hypothesis is that a continuum of “latent auto-reactivity” exists within the general population, and immune and/or microbiome perturbation as a result of checkpoint inhibitor (CPI) therapy lowers the threshold above which transition to immune related adverse event (irAE) occurs.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Approved 17/01/2019, East of England - Essex Research Ethics Committee (Level 3, Block B, Whitefriars, Lewins Mead, Bristol, BS1 2NT, UK; +44(0)207 1048227; essex.rec@hra.nhs.uk), ref: 18/EE/0400.

Study design
Single centre prospective longitudinal observational cohort study

Primary study design
Observational

Secondary study design
Longitudinal study

Study setting(s)
Hospital

Study type(s)
Other

Participant information sheet
Not available in web format, please use contact details to request a participant information sheet.

Health condition(s) or problem(s) studied
Detection of immunological & microbiome features consistent with toxicity in patients with melanoma treated with checkpoint inhibitor drugs.

Interventions
MEDALLION aims to recruit up to 80 patients consented to therapy with checkpoint inhibition (CPI) in the form of either anti-PD1, anti-PDL1, anti-CTLA4 or combination of these therapies for cancer. Participants include those with malignant melanoma (any subtype), non-small cell lung

cancer or mesothelioma either treated in the adjuvant or metastatic setting. The study is not randomised and all patients initiate the study at the time of their first CPI dose, with those who fail to develop significant toxicity during follow-up acting as the control population for those who do. Comprehensive clinical evaluation of patients is done as standard of care, with additional sampling of blood, skin swabs and stool specimens at baseline, and following cycle 1, 2, 3 & 4 of therapy, with a further visit at approximately 9-10 months. Conservative estimates of toxicity of 27% were used, with those who develop toxicity undertaking an additional 'ad hoc' irAE visit and optionally consenting for affected tissue biopsy where appropriate. Following irAE, withdrawal from the study occurs, with decision regarding discontinuing CPI therapy due to toxicity made according to standard of care.
Blood samples will be analysed to investigate immune cell subsets, their activation status and cytokine profiles, with further material being stored for genetic analysis. Tissue biopsies will undergo in situ and single-cell evaluation by immunohistochemical/immunofluorescence analysis and/or single cell genomic sequencing. Stool samples and skin swabs will undergo DNA extraction for microbial sequencing to determine bacteria & fungal microbiome diversity and species associated with toxicity. As well as identifying individual predictors of irAEs, these workstreams will enable exploratory analyses to develop a predictive model for CPI toxicity using multivariate statistical approaches.

Intervention Type
Other

Primary outcome measure
CD4+ T cell phospho-STAT3 measurement by flow cytometric analysis at the pre-irAE time-point compared to that seen in non-irAE patients.

Secondary outcome measures
1. Baseline microbiome diversity as measured by whole genome sequencing between irAE and non-irAE groups at a single time point
2. Peripheral immune cell subsets as determined by multi-parameter flow cytometry between irAE and non-irAE groups at the pre-irAE event or matched timepoint for the non-irAE group.

Overall study start date
31/10/2018

Completion date
02/06/2027

Eligibility

Key inclusion criteria
1. Male or female patient >18 years of age.
2. Confirmed diagnosis of malignant melanoma.
3. Shared decision by oncologist and patient to proceed with CPI treatment, either with the combination of ipilimumab and nivolumab, or with single-agent nivolumab or pembrolizumab as standard of care.
4. Patient is judged as being capable of understanding the information sheet and of giving informed consent according to the Mental Capacity Act 2005.
5. Written informed consent to participate in the study.

Participant type(s)

Patient

Age group
Adult

Lower age limit
18 Years

Sex
Both

Target number of participants
80

Total final enrolment
66

Key exclusion criteria
1. Known pre-existing autoimmune or immune-mediated inflammatory disease requiring immunomodulatory treatment, including (but not limited to) inflammatory bowel disease (Crohn’s disease, ulcerative colitis) autoimmune endocrinopathy or hepatitis, vitiligo and inflammatory arthritis.
2. Received enteral or parenteral steroids within past month (topical, inhaled or intranasal permitted).
3. Previous treatment with CPI therapy.
4. Vaccination within the past 4 weeks, except COVID-19 vaccination permitted.
5. Known chronic infection.
6. Current pregnancy, or pregnancy planned within next 6 months
7. Inability to provide informed consent and/or undergo any of the procedures mandated by the study.

Date of first enrolment
04/04/2019

Date of final enrolment
02/12/2024

Locations

Countries of recruitment
England

United Kingdom

Study participating centre
Northern Centre for Cancer Care
Freeman Road
High Heaton
Newcastle upon Tyne

United Kingdom
NE7 7DN

Sponsor information

Organisation
Newcastle upon Tyne Hospitals NHS Foundation Trust

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England
United Kingdom
NE7 7DN
+44(0)191 2336161
nuth.communications@nhs.net

Sponsor type
Hospital/treatment centre

Website
http://www.newcastle-hospitals.org.uk/

ROR
https://ror.org/05p40t847

Funder(s)

Funder type
Charity

Funder Name
Cancer Research UK

Alternative Name(s)
CR_UK, Cancer Research UK - London, CRUK

Funding Body Type
Private sector organisation

Funding Body Subtype
Other non-profit organizations

Location

United Kingdom

Funder Name
JGW Patterson Foundation

Alternative Name(s)
John George William Patterson Foundation

Funding Body Type
Private sector organisation

Funding Body Subtype
Trusts, charities, foundations (both public and private)

Location
United Kingdom

Results and Publications

Publication and dissemination plan
Planned publication in a high-impact peer-reviewed journal.

Intention to publish date
31/12/2025

Individual participant data (IPD) sharing plan
The data-sharing plans for the current study are unknown and will be made available at a later date.

IPD sharing plan summary
Data sharing statement to be made available at a later date

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Protocol file	version 8.0	28/03/2023	03/04/2023	No	No
Protocol article		14/06/2024	17/06/2024	Yes	No