ISRCTN80472712 https://doi.org/10.1186/ISRCTN80472712

Testing IMM60 in combination with pembrolizumab in melanoma and non-small cell lung cancer

Submission date 10/12/2020	**Recruitment status** No longer recruiting	[X] Prospectively registered [_] Protocol [_] Statistical analysis plan [_] Results [_] Individual participant data [_] Record updated in last year
Registration date 22/01/2021	**Overall study status** Completed	
Last Edited 18/12/2023	**Condition category** Cancer	

Plain English summary of protocol

05/12/2023: This record contains out-of-date information and will not be updated further. Please see https://clinicaltrials.gov/study/NCT05709821 for the most up-to-date trial record.

Background and study aims
Melanoma is a type of skin cancer that can spread to other organs in the body. Non-small-cell lung cancer is the most common form of lung cancer, accounting for more than 87% of cases. The trial is a first-in-human study called the IMP-MEL trial and is sponsored by the University of Oxford; the information we get from this trial may help us to improve the future treatment of patients with melanoma and non-small cell lung cancer. The experimental drug, called IMM60, has not been given to patients before.
This trial will aim to:
• Establish the safe dose of IMM60
• Establish that the safe dose of IMM60 can be safely given with an existing drug already used in the treatment of melanoma and non-small cell lung cancer called pembrolizumab, which is the standard of care treatment
• Explore if IMM60 in combination with pembrolizumab (a commonly used drug for cancer treatment) is more effective than pembrolizumab alone
• Explore if IMM60 can sensitise non-small cell lung cancer tumours to pembrolizumab in settings where pembrolizumab has been considered ineffective

Who can participate?
Patients diagnosed with either advanced melanoma or non-small cell lung cancer. Patients must be over 18 and meet the trial's specific eligibility criteria to participate in the study. For more information, please contact your GP or oncologist.

What does the study involve?
Patients will be allocated to a) the IMM60 dose cohort if you are one if the initial participants or b) a cohort where IMM60 will be given with pembrolizumab, if recruited later on in the trial. Once enrolled, the trial is then divided into the treatment phase and follow-up phase.

For those patients in the dose escalation phase, they will receive a maximum of 6 cycles of IMM60, with each cycle dose given once every 3 weeks. For those in the IMM60 and pembrolizumab combined phase, they will receive the combination treatment once every 3 weeks up to a maximum of 6 cycles of IMM60. After these 6 cycles of trial treatment, if patients are benefitting from treatment, they will be eligible to continue pembrolizumab treatment after the initial 6 cycles, as determined by current standard of care practice.

After the patient's 6th and final cycle of trial treatment, they will be asked to return for a follow-up visit 30 days after the last dose of IMM60 when patients will have similar assessments as those performed during the screening visit.

Once patients come off the trial treatment, they will receive a CT scan every 12 weeks after their last dose of trial treatment. During this 12-weekly follow-up visit, patients will be asked for a patient status update, where the research team will see how they are doing. These follow-up visits will continue for 1 year from patient's first dose of trial treatment.

What are the possible benefits and risks of participating?
No benefit can be guaranteed from receiving the trial treatment in this research trial, and whether or not patients will benefit from the treatment is unknown. It is hoped that by taking part the trial treatments may help and may slow down the growth of patients' cancer, or shrink it. We hope that for some patients the trial drugs may control their cancer better than standard treatment. This cannot, however be guaranteed for all or for any of the patients on trial, as this has not been definitely demonstrated in patients with advanced melanoma or non-small cell lung cancer.

By entering this trial, patients will be making a significant contribution to a trial which will provide information to increase our knowledge of the treatment of melanoma and non-small cell lung cancer, which may help us to improve the future treatment of patients with these conditions.

As IMM60 and IMM60 & pembrolizumab in combination have never been given to patients before, the risks of both treatments are unknown. The treatments used on this trial could cause side effects. Some people may have very few side effects, while others may experience more.

This is a first in human study; IMM60 has not yet been given to patients and subsequently side effects related to IMM60 are unknown. Based on the chemical formula of IMM60 potential side effects may include but are not limited to a low blood count which could lead to bleeding, infection or fever (especially low white cells), chills, headache, dizziness, heart problems including chest pains (angina), rhythm abnormalities (arrhythmias), redness, swelling, numbness, digestive symptoms such as abdominal pain, mouth ulcers, diarrhoea, loss of appetite, nausea and vomiting, fatigue, enlarged spleen, impaired liver function and impaired kidney function.

It is also possible that unexpected side effects could occur. The combination treatment of IMM60 & pembrolizumab has never been given to patients and subsequently side effects related to this combination are unknown.

Where is the study run from?
John Radcliffe Hospital (UK)

When is the study starting and how long is it expected to run for?
February 2020 to December 2023

Who is funding the study?
1. iOx Therapeutics (UK)
2. NIHR Biomedical Research Centre (UK)

Who is the main contact?
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Contact information

Type(s)
Scientific

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Public

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Additional identifiers

ClinicalTrials.gov (NCT)
NCT05709821

Clinical Trials Information System (CTIS)
2020-001351-41

Integrated Research Application System (IRAS)
286317

Central Portfolio Management System (CPMS)
46501

Study information

Scientific Title
A phase 1 first-in-human dose finding/randomised phase 2 study of IMM60 and pembrolizumab in advanced melanoma and NSCLC

Study objectives
The aims of the IMP-MEL trial are to:
> Establish the safe dose of the experimental drug, called IMM60
> Establish that the safe dose of IMM60 can be safely given with an existing drug already used in the treatment of melanoma and non-small cell lung cancer (NSCLC) called pembrolizumab
> Explore if IMM60 in combination with pembrolizumab is more effective than pembrolizumab alone
> Explore if IMM60 can promote anti-tumour activity in non-small cell lung cancer tumours and melanoma in settings where pembrolizumab has been considered ineffective

Ethics approval required
Old ethics approval format

Ethics approval(s)
Approved 25/11/2020, RES Committee South Central – Oxford B (Barlow House, 3rd Floor, 4 Minshull Street, Manchester, M1 3DZ, UK; +44 (0)207 104 8235; oxfordb.rec@hra.nhs.uk), ref: 20 /SC/0367

Primary study design
Interventional

Study design
Interventional randomized controlled trial

Study type(s)
Treatment

Health condition(s) or problem(s) studied
Malignant neoplasms of respiratory and intrathoracic organs, Melanoma and other malignant neoplasms of skin

Interventions
IMM60 has not been combined with pembrolizumab before to treat patients. This trial will investigate whether adding IMM60 to pembrolizumab is tolerated by patients, and identify the best dose of IMM60 to combine safely with pembrolizumab. Up to 18 patients will be recruited in the first part of the study and 82 into the second, phase 2 component. We will initially test a low dose of IMM60 in the first patient cohort and then escalate using a standard "3+3" trial design model. The starting dose selected has been informed by toxicology information from animal studies.
If this dose is well tolerated (as defined in the protocol) the dose of IMM60 will escalate up to a pre-defined maximum dose. Once this dose is determined, an IMM60 dose one level lower than the maximum tolerated dose will be combined with the standard dose of pembrolizumab and

given to 3 patients to establish that the combination is safe. If so, the maximum tolerated IMM60 dose level will be combined with the standard of dose of pembrolizumab and given to 3 further patients to confirm safety of the combination at this dose level.

In the phase 2 component of the trial, IMM60 in combination with pembrolizumab will be compared to pembrolizumab alone to assess early signs of clinical efficacy. If the combination is more effective, then a larger trial is planned to prove if the combination of IMM60 and pembrolizumab should become a new standard treatment option for patients.

This is a phase 1a and randomised phase 2 trial. Initial safety will be assessed in a multiple ascending dose cohort for IMM60, then for IMM60 + pembrolizumab. The Trial Management Group (TMG) will review the Phase 1 data and guide dose escalation decisions. The TMG will also review safety data and permit proceeding to the phase 2 component if safe to do so. Planned arms in the Phase 2 component include: pembrolizumab alone & IMM60+pembrolizumab for NSCLC patients; and pembrolizumab alone, IMM60+pembrolizumab, and additional IMM60 alone cohort for melanoma patients.

The Phase 1 trial will be a modified 3 + 3 trial design. In the IMM60 ascending dose safety arm, three dose levels of IMM60 will be assessed (1/3/9 mg/m2). If one of the first 3 patients experiences a pre-defined dose limiting toxicity (DLT), that cohort will be expanded to a total of 6 patients. If a further patient in this cohort experiences a DLT, this dose level will be defined as the MTD. If more than 2 DLTs occur in the 6 patients in the expanded cohort then MTD will be defined as the dose level below that cohort. Should more than 2 DLTs occur in the lowest IMM60 dose level cohort, the TMG will consider de-escalating this dose level. If no patient in the highest dose cohort (9mg/m2) experiences a DLT, this cohort will still be expanded to 6 patients. To decide if the next cohort can be opened at a higher dose level in Phase 1 of the study, the Trial Management Group (TMG) will review available data (e.g. safety profile) once all participants in the preceding cohort have completed the first cycle through to Day 21. Subsequent safety reviews by the TMG will be conducted prior to enrolment of patients in a new cohort.

For the IMM60 + pembrolizumab safety arm, pembrolizumab will be administered in combination with IMM60. The dose of pembrolizumab will be that administered as per standard of care; the IMM60 dose will be dependent on the IMM60 dose escalation arm. This combination safety arm will also use the modified 3+3 design - the IMM60 starting dose level will be one below IMM60 MTD (referred to as MTD-1), and will dose escalate to a cohort with IMM60 at MTD. For example, if the IMM60 MTD is 9mg/m2, the first combination cohort will be with IMM60 at 3mg/m2 and will escalate to a combination cohort with IMM60 at 9mg/m2. Should the IMM60 MTD be 1mg/m2 (lowest dose level in the
ascending dose cohort), then the TMG will consider whether to begin the combination safety arm at MTD, or a deescalated dose. The DLT rules applied to the IMM60 dose escalation arms will also apply to the combination safety arms.

For Phase 2 of the trial, patients with melanoma will be randomised 1:2 between treatment arms: either pembrolizumab as per its licensed indication or the combination of pembrolizumab+IMM60. A potential cohort of IMM60 at the MTD given every 3 weeks for patients who have progressed through pembrolizumab is also planned to explore a secondary objective. Eligible patients with PDL1 positive NSCLC will be randomised 1:2 to either pembrolizumab as per its licensed indication or the combination of pembrolizumab and IMM60. Depending on review of IMM60 monotherapy activity, both melanoma and NSCLC patients in the pembrolizumab alone cohort who show no
response at their 3-month CT scan can then receive pembrolizumab and IMM60.

A potential additional cohort of PDL1 negative (PD-L1 expression less than 50%) NSCLC will be treated with one cycle of IMM60 with a tumour biopsy before and after, to determine any changes in PDL1 expression. After this one cycle, these patients will receive the combination of IMM60 + pembrolizumab and a second biopsy will be taken. Depending on review IMM60 monotherapy activity a potential group of patients who are receiving pembrolizumab monotherapy will be allowed to receive IMM60 at progression in combination with pembrolizumab to see if sensitivity can be restored. The purpose of this arm is to see if IMM60 enhances PDL1 expression, which is hypothesised to increase sensitivity to pembrolizumab in a patient group which typically do not benefit from treatment with this drug. Patients registered to the trial will receive their treatment on a 3-weekly cycle; IMM60 will be administered every three weeks (1 cycle) for a maximum of 6 cycles, or disease progression, whichever occurs first. Pembrolizumab infusions will be repeated every three weeks for 6 cycles or until disease progression, whichever is sooner.

Patients will undergo safety assessments, vital signs and physical examination before each dose is administered. Additional blood samples will be taken for research tests on the first cycle of the study. A number of additional blood samples (approximately 15ml, equivalent to 3 teaspoons) will be taken. The first sample will be taken immediately before starting the infusion and then at set time points after the start of the infusion: 1 hour, 2 hours, 4 hours, 6 hours and 24 hours. These PK samples and are taken in order to measure the levels of IMM60 in the bloodstream. Additional blood samples will also be taken for research purposes at the following time points: before the start of infusion, 4 hours, 24 hours after first infusion and then at C1D8, one week after first infusion.

All patients participating in this study are required to give two tumour biopsies - at baseline and at 3 weeks. These will be obtained by either CT or ultrasound guidance, bronchoscopy or percutaneously in the case of superficial lesions.

Intervention Type
Drug

Phase
Phase I

Drug/device/biological/vaccine name(s)
IMM60, pembrolizumab

Primary outcome(s)
1. Frequency of grade 3 or higher treatment-related AEs measured using case report forms during the Dose Escalation period and at Completion of Phase 1 safety cohort
2. Maximum tolerated dose measured using case report forms during the Dose Escalation period and at Completion of Phase 1 safety cohort
3. Progression free survival at 12 onths measured using patient records

Key secondary outcome(s)
1. IMM60 Cmax and AUC IFN-g measured by blood samples taken 0, 1, 2, 4, 6, 24 hours post first dose
2. Frequency of grade 3 or higher treatment-related AEs measured using case report forms at 6 months
3. Objective response rate in melanoma patients who have progressed on PD1, and have added IMM60 measured using CT Scan RECIST 1.1 at 6 months

4. ORR in PDL1-ve NSCLC patients who receive IMM60 + Pembrolizumab measured using CT Scan RECIST 1.1 at 6 months

Completion date
04/01/2024

Eligibility

Key inclusion criteria
1. Aged >=18 years
2. Melanoma arms:
2.1. Unresectable stage 3 or 4, histologically proven cutaneous or unknown primary melanoma
2.2. Result of BRAF mutation status (ie BRAF mutant or wildtype)
2.3. Phase 1:
2.3.1. IMM60 dose escalation arm: Patients progressing through at least one line of immunotherapy. For those patients with BRAF mutant tumours, progression through BRAF/MEK inhibitor treatment and at least one line of immunotherapy
2.3.2. IMM60 + pembrolizumab dose safety arm: Patients not previously exposed to a PD-1 inhibitor who fulfil NHS criteria for the funding of Pembrolizumab as determined by the Cancer Drugs Fund (CDF) (explained in separate appendix within the protocol) with the exception that pembrolizumab will not be administered as monotherapy.
2.4. Phase 2:
2.4.1. Melanoma Cohort 1: Patients with metastatic disease not previously exposed a PD-1 inhibitor
2.4.2. Melanoma Cohort 2: Patients with metastatic disease previously exposed to a PD-1 inhibitor
2.5. Patients in Melanoma Cohort 1 must meet CDF criteria for funding for pembrolizumab, Melanoma Cohort 2 patients do not need to meet these criteria.
3. NSCLC arms:
3.1. Histologically confirmed stage 4 non-small cell lung cancer
3.2. Patients with adenocarcinoma histology must not have sensitizing EGFR or ROS1 mutations or ALK translocations
3.3. No prior systemic therapy for advanced disease. Previous chemotherapy in the context of adjuvant treatment is permissible as long as the treatments were completed at least 6 months prior to consent
3.4. Patients in non-small cell lung cancer arms must have a PD-L1 assessment prior to randomization. PDL1 assessment must be performed in an approved laboratory
3.5. Phase 1:
3.5.1. IMM60 dose escalation arm: Progression through systemic therapy consisting of at least platinum based chemotherapy and immunotherapy (either sequentially or in combination)
3.5.2. IMM60 + pembrolizumab dose safety arm: First line treatment for patients who fulfil NHS criteria for the funding of Pembrolizumab as determined by the Cancer Drugs Fund (CDF) (detailed in separate appendix) with the exception that pembrolizumab will not be administered as monotherapy
3.6. Phase 2:
3.6.1. NSCLC Cohort 1: Metastatic NSLC, PDL1 +ve (PDL1 TPS greater than or equal to 50%) not previously exposed to a PD-1 inhibitor
3.6.2. NSCLC Cohort 2: Metastatic NSLC, PDL1 –ve (PDL1 < 50%) not previously exposed to a PD-1 inhibitor but pre-treated with at least one line of systemic treatment
3.7. Patients in NSCLC Cohorts 1 must meet CDF criteria for funding for pembrolizumab, with the exception of pembrolizumab administration as monotherapy

4. At least 1 lesion, not previously irradiated, that can be accurately measured on CT or MRI as defined by RECIST 1.1 criteria. Cutaneous lesions and other superficial lesions detectable only by physical examination are not measurable lesions however may be considered non-target lesions.
5. ECOG performance score of 0 or 1.
6. Life expectancy of at least 12 weeks.
7. The patient is willing to give consent to the main study and able to comply with the protocol for the duration of the study, including scheduled follow-up visits and examinations.
8. Prior systemic treatments must have been completed at least 4 weeks prior to enrolment and all toxicities have either returned to baseline or resolved to less than or equal to grade 1 with the exception of alopecia. For patients with melanoma previously treated with a target tyrosine kinase inhibitor, prior treatment within 2 weeks is acceptable
9. Haematological and biochemical indices within the ranges shown below:
Lab Test Value required
Haemoglobin (Hb) >10g/dL
White Blood Count (WBC) >3 x 10(9)/L
Platelet count >100 x 10(9)/L
Absolute Neutrophil count >1.5 x 10(9)/L
Serum bilirubin <=1.5 x ULN
Or direct bilirubin <=ULN for patients with total bilirubin concentration >1.5 x ULN
AST (SGOT) or ALT <=2.5 x ULN <=5 x ULN for patients with liver metastases
Creatinine clearance (Cockcroft-Gault) >50 ml/min
International Normalized Ratio (INR) or Prothrombin Time (PT):
Activated Partial Thromboplastin Time (aPTT) <=1.5 x ULN unless patient is receiving anticoagulant therapy as long as PT or PTT is within therapeutic range of intended use of anticoagulants
<=1.5 x ULN unless patient is receiving anticoagulant therapy as long as PT or PTT is within therapeutic range of intended use of anticoagulants

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Adult

Lower age limit
18 Years

Sex
All

Total final enrolment
15

Key exclusion criteria
1. Any anti-cancer therapy (including radiotherapy and participation in other clinical trials) within 28 days except tyrosine kinase inhibitors in which case 2 weeks prior to Day 1
2. Any unresolved toxicity from prior anti-cancer therapy that is greater than CTCAE grade 2
3. Pregnant or breastfeeding women. Female patients must have a negative urinary or serum

pregnancy test or have evidence of post-menopausal status (defined as absence of menstruation for > 12 months, bilateral oophrectomy or hysterectomy)
4. Patients with non-small cell lung cancer with large volume tumour burden, who, at the investigator's discretion are considered more appropriate for systemic chemotherapy
5. Patients of reproductive potential who are not willing to use adequate contraceptive measures for the duration of the study (both male and female patients)
6. Known severe hypersensitivity reactions to anti-PD1 agents or has received prior therapy with an agent directed towards PD1/PDL1 or to another stimulatory or co-inhibitory T-cell receptor (e. g., CTLA-4, OX 40, CD137) and was discontinued from that treatment due to a Grade 3 or higher irAE (except IMM60 monotherapy cohort who can have received prior PD1)
7. Ocular or mucosal malignant melanoma
8. Another active malignancy within the past two years (Note: Participants with basal cell carcinoma of the skin, squamous cell carcinoma of the skin, superficial bladder, or carcinoma in situ (e.g., breast carcinoma, cervical cancer in situ) that have undergone potentially curative therapy are not excluded. Also, prostate, breast and neuroendocrine tumours that are stable on hormonal treatment for a period of 1 year or more without the need to adjust dose are not excluded.)
9. Evidence of brain metastases, unless surgically resected/stereotactic radiosurgery treated brain metastasis and stable off treatment, including steroids, for 8 weeks
10. Clinically significant and uncontrolled major medical condition(s): such as active infection, bleeding diathesis
11. Patients who are known to be serologically positive for Hepatitis B, Hepatitis C or HIV. Testing is not required unless clinically indicated
12. Cardiac conditions, defined by uncontrolled hypertension (BP> 160/100 despite treatment), heart failure NYHA class 2 or above, myocardial infarction within 6 months or angina requiring nitrate therapy more than once a week
13. Previous treatment with anti -PD1 antibodies for experimental arms: (cohort 3 for melanoma in the phase 2 trial) or all cohorts in NSCLC.
14. Severe hypersensitivity (> = Grade 3) to pembrolizumab and/or any of its excipients
15. History of (non-infectious) pneumonitis that required steroids or has current pneumonitis
16. Has an active infection requiring systemic therapy
17. Prior treatment with IMM60
18. Patients with an active autoimmune disease or a documented history of autoimmune disease or syndrome that requires systemic steroids (in dosing exceeding 10 mg daily of prednisone equivalent) or immunosuppressive agents. Patients with vitiligo or resolved childhood asthma /atopy would be an exception to this rule. Patients that require intermittent use of bronchodilators or local steroid injections would not be excluded from the study. Patients with hypothyroidism stable on hormone replacement will not be excluded from the study
19. Has received a live vaccine within 30 days prior to the first dose of study drug. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, varicella /zoster (chicken pox), yellow fever, rabies, Bacillus Calmette–Guérin (BCG), and typhoid vaccine. Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed; however, intranasal influenza vaccines (e.g., FluMist®) are live attenuated vaccines and are not allowed

Date of first enrolment
01/06/2021

Date of final enrolment
31/10/2023

Locations

Countries of recruitment
United Kingdom

England

Study participating centre
John Radcliffe Hopsital
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Study participating centre
Hammersmith Hospital
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Sponsor information

Organisation
University of Oxford

ROR
https://ror.org/052gg0110

Funder(s)

Funder type
Government

Funder Name
NIHR Oxford Biomedical Research Centre

Alternative Name(s)
NIHR Biomedical Research Centre, Oxford, OxfordBRC, OxBRC

Funding Body Type
Private sector organisation

Funding Body Subtype
Research institutes and centers

Location
United Kingdom

Funder Name
iOx Therapeutics

Results and Publications

Individual participant data (IPD) sharing plan
The current data sharing plans for this study are unknown and will be 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?
HRA research summary			26/07/2023	No	No