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Injection of IP-001 into thermally ablated solid tumors

Submission date 22/09/2022	**Recruitment status** No longer recruiting	[X] Prospectively registered [_] Protocol [_] Statistical analysis plan [_] Results [_] Individual participant data [_] Record updated in last year
Registration date 15/11/2022	**Overall study status** Completed	
Last Edited 11/12/2024	**Condition category** Cancer	

Plain English summary of protocol

Background and study aims
Treatment in patients with advanced colorectal cancer, (CRC) non-small cell lung cancer (NSCLC) and soft tissue sarcoma (STS) represent a significant unmet need. Local thermal ablation of tumor tissue using techniques such as radiofrequency ablation (RFA) or stereotactic radiotherapy is an established treatment option for different tumors, in particular, CRC and NSCLC. There is strong nonclinical and early clinical evidence that combining thermal ablation with the investigational product, 1.0% IP-001 for Injection might be able to turn 'cold' tumors into 'hot' tumors, inducing a long-term systemic immune response mediated by the patient's immunological defense system against any remaining tumor cells both at the site of the ablation treatment and those that are outside or distant from the treated area (known as the abscopal effect).

The 2 components of treatment play unique roles in inducing an antitumor immune response:
1. During thermal ablation, treated tumor undergoes immunogenic cell death via a well-defined heat gradient
2. Adding 1.0% IP-001 for Injection elicits a tumor-specific adaptive immune response

As a result, it is hypothesized that ablation + IP-001 can be deployed against a wide variety of tumor types to induce customized immune activation against a patient's own, unique cancer.

Who can participate?
Adult patients with confirmed CRC, NSCLC, or STS

What does the study involve?
In this study, a solid tumor will first be thermally ablated by a standard ablation modality, and then 1.0% IP-001 for Injection will be injected into the area of the ablated tumor. Patients can be treated every 6 weeks for up to 4 treatments with RFA + 1.0% IP-001 for Injection.

What are the possible benefits and risks of participating?
Risk of study drug (IP-001) with thermal ablation:

The safety data below are from previous clinical studies where a total of 38 patients took the study drug with one of two types of thermal ablation. The treatment was generally well tolerated and there were no severe side effects.

Side effects associated with the study drug:
1. Very common: fever
2. Common: fatigue, reddening of the skin, red eyes, eye and skin itching, rash, facial swelling, joint pain and swelling, and dizziness
3. Uncommon: blurred vision, pain, low blood pressure, nausea, coughing, and increase in C reactive protein (a marker of inflammation)

Side effects associated with the thermal ablation:
1. Very common: pain
2. Common: fever
3. Applied to the skin (not included in this study)
4. Very common: redness, blistering, burning, swelling and pain at treatment site
5. Common: fever, nausea, formation of a lump at the injection site
6. Uncommon: stinging

Known side effects associated with RFA alone are pain, burns, infection, low blood pressure, fainting, excessive sweating, bleeding, blood clots, a swollen area, diarrhoea, nausea, vomiting, muscle pain, cough, tumour getting worse and death.

Potential side effects are mitigated as follows:
1. Exclusion criteria for patients with allergies to shellfish due to one of the IMP starting materials
2. At the discretion of the treating physician/intervention radiologist the following premedication or supportive medication can be given:
2.1. A selection of pain premedication
2.2. A topical or local anesthetic (e.g., lidocaine), at the ablation site/site of administration of 1.0% IP 001 for Injection (depending on the location of ablation)
2.3. Anesthetics according to normal tumor ablation protocol and according to the standard operating procedures of the hospital
2.4. Oral sedation with benzodiazepines or similar drugs may be used
2.5. Monitored intravenous sedation (such as propofol). It is recommended that if IV sedation is used, an anesthesiologist, nurse anesthetist or similarly skilled individual monitor vital signs and administer intravenous sedatives (according to the standard operating procedures of the hospital).
2.6. Cool packs can be used to cool the skin above the treated area
3. The use of prophylactic antibiotics due to the risk of post-treatment infections or abscess can be given at the discretion of the treating Investigator
4. Warnings and precautions are provided for use of RFA devices, and the Investigator is instructed to refer to the RFA instructions for use
5. Treatment can be delayed due to unresolved toxicity related to previous ablation + IP-001 treatment

Radiation and The Ionising Radiation (Medical Exposure) Regulations – (IRMER)
Several CT (or MRI) scans will be taken of the body over a year. However as the very small risk of developing cancer later in life as a result of increased exposure to radiation is outweighed by potential benefit of treatment, the risk-benefit ratio should be acceptable as long as imaging kept to only what is necessary.

Harm to an unborn child
It is not known whether the study treatment can harm the unborn child or embryo.
To mitigate the risk of pregnancy:
1. The protocol instructs patients and partners to use double contraception for the duration of the study and for an additional 90 days after the last dose of an investigational medicinal product
2. The protocol instructs men to not donate sperm from the first dose of the investigational medicinal product to 90 days after the last treatment

Where is the study run from?
Department of Oncology - University of Oxford (UK)

When is the study starting and how long is it expected to run for?
June 2022 to March 2025

Who is funding the study?
Immunophotonics Inc (USA)

Who is the main contact?
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Contact information

Type(s)
Scientific

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Additional identifiers

Clinical Trials Information System (CTIS)
2022-000176-19

Integrated Research Application System (IRAS)
1005966

Central Portfolio Management System (CPMS)
52093

Protocol serial number
IP-IIO-622

Study information

Scientific Title
Intratumoral injection of IP-001 following thermal ablation in patients with advanced solid tumors. A multicenter phase Ib/IIa trial in colorectal cancer, non-small cell lung cancer, and soft tissue sarcoma patients

Study objectives
The primary objective is to determine safety and tolerability of 1.0% IP-001 for Injection administered intratumorally following thermal ablation of a solid tumor.

The secondary objective is to determine anti-tumor activity of 1.0% IP-001 for Injection administered intratumorally following thermal ablation of a solid tumor.The exploratory objectives of the trial are translational research to:

1. Determine the presence and nature of the immune response elicited by 1.0% IP-001 for Injection administered intratumorally following thermal ablation of a solid tumor
2. Determine the formation of anti-drug antibodies (ADA) by 1.0% IP-001 for Injection administered intratumorally following thermal ablation of a solid tumor
3. Determine the correlation between a tumor market and response to 1.0% IP-001 for Injection administered intratumorally following thermal ablation of a solid tumor
4. Determine the pharmacokinetics of 1.0% IP-001 for Injection

Ethics approval required
Old ethics approval format

Ethics approval(s)
Approved 29/09/2022, London - Surrey Borders Research Ethics Committee (Equinox House, City Link, Nottingham, NG2 4LA, UK; +44 (0)207 104 8104, (0)207 104 8143, (0)207 104 8057; surreyborders.rec@hra.nhs.uk), ref: 22/LO/0508

Primary study design
Interventional

Study design
Multicenter phase Ib/IIa study

Study type(s)
Treatment

Health condition(s) or problem(s) studied
Colorectal cancer, non-small cell lung cancer and soft tissue sarcoma

Interventions
IP-001 (1.0% IP-001 for Injection) for the treatment of solid tumor cancers (colorectal, non-small cell lung and soft tissue sarcoma) immediately following an approved thermal ablation of a solid tumor.

Intervention Type
Drug

Phase
Phase I/II

Drug/device/biological/vaccine name(s)
IP-001

Primary outcome(s)
Safety and tolerability of 1.0% IP-001 for Injection administered intratumorally following thermal ablation of a solid tumor measured using adverse events (AEs), vital sign measurements, physical examination findings, Eastern Cooperative Oncology Group (ECOG) performance status, pulmonary function, clinical laboratory assessments, and electrocardiogram (ECG) from start of trial treatment until 90 days after the last trial treatment

Key secondary outcome(s)
All secondary outcomes were measured for 12 weeks.
Anti-tumor activity of 1.0% IP-001 for Injection administered intratumorally following thermal ablation of a solid tumor measured using:
1. Disease control according to Response Evaluation Criteria in Solid Tumors for immune-based treatments (iRECIST) (iDC)
2. Disease control according to Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST 1.1) (DC)
3. Objective response according to iRECIST (iOR)
4. Duration of response according to iRECIST (iDOR)
5. Progression-free survival according to iRECIST (iPFS)
6. Objective response according to RECIST 1.1 (OR)
7. Duration of response according to RECIST 1.1 (DOR)
8. Progression-free survival according to RECIST 1.1 (PFS)
9. Time to response according to iRECIST 1.1 (iTTR)
10. Time to response according to RECIST 1.1 (TTR)
11. Disease-free survival (DFS)
12. Overall survival (OS)
12. OR of the injected lesions according to RECIST 1.1
13. OR of the non-injected lesions according to RECIST 1.1
14. iOR of the injected lesions according to iRECIST
15. iOR of the non-injected lesions according to iRECIST

Exploratory outcomes of the trial are translational research to:
1. Determine the presence and nature of the immune response elicited by 1.0% IP-001 for Injection administered intratumorally following thermal ablation of a solid tumor measured using H&E and GeoMx nanostring transcriptome analysis of tumor biopsies at baseline and C2D1 or follow up visit 1, whichever applies, and flow cytometry analysis of immune cell populations in peripheral blood at baseline, C1D1, C1D8, C1D15, C2D1 and Follow-up visit 1
2. Determine the formation of anti-drug antibodies (ADA) by 1.0% IP-001 for Injection administered intratumorally following thermal ablation of a solid tumor measured using ELISA at baseline, C1D1, C1D8, C1D15, C2D1 and Follow-up visit 1
3. Determine the correlation between a tumor marker and response to 1.0% IP 001 for Injection administered intratumorally following thermal ablation of a solid tumor measured using O-link proteomic analysis of serum at baseline, C1D1, C1D8, C1D15, C2D1 and Follow-up visit 1

4. Determine the pharmacokinetics of 1.0% IP-001 for Injection administered intratumorally following thermal ablation of a solid tumor using mass spectrometry with population statistics at baseline, C1D1:1hr, C1D1: 2hr, C1D1:6hr, C1D1:12hr, C1D1:24hr. Other bioanalytical methods under development

Completion date
03/03/2025

Eligibility

Key inclusion criteria
1. Signed and dated informed consent from patient or legal representative in accordance with local regulatory and/or national laws and ICH/GCP regulations before registration and before any study specific activity is performed.
2. Patients with either histologically or cytologically confirmed Stage 3 or Stage 4 CRC, NSCLC, or STS who have failed, are ineligible, refused, or become intolerant to at least first line (but no more than 4 lines) of systemic therapy, have a life expectancy of > 6 months, and only have lesions with the longest diameter of ≤ 5 cm.
3. Presence of at least one non-bone tumor lesion that is ablation-accessible, with a minimum size of 1.0 cm and located such that it can be treated without risk of skin necrosis or serious damage to other adjacent vital and healthy tissue.
4. Measurable or evaluable disease, determined with the most suitable imaging method, either computed tomography (CT) or magnetic resonance imaging (MRI), according to RECIST 1.1.
5. Age ≥ 18 years.
6. ECOG performance status 0-1.
7. Bone marrow function: neutrophil count ≥ 1.5 × 109/L, platelet count ≥ 100 × 109/L, hemoglobin ≥ 90 g/L.
8. Adequate hematological function defined by white blood cell count ≥ 2.5 × 109/L with absolute neutrophil count ≥ 1.5 × 109/L, and hemoglobin ≥ 9 g/dL (transfusions allowed on study).
9. Adequate hepatic function defined by a total bilirubin level ≤ 1.5 × the upper limit of normal (ULN) range and aspartate transaminase (AST) and alanine aminotransferase (ALT) levels ≤ 2.5 × ULN for all patients, or for patients with documented metastatic disease to the liver and AST and ALT levels ≤ 5 × ULN. Patients with documented Gilbert disease are allowed if total bilirubin is less than 3 × ULN.
10. Adequate renal function defined by an estimated creatinine clearance ≥ 50 mL/min according to the Cockcroft-Gault formula (or local institutional standard method).
11. Women with childbearing potential are using effective contraception, are not pregnant or lactating and agree not to become pregnant during trial treatment and for an additional 90 days after the last dose of investigational drug. Women of childbearing potential must have a negative serum human chorionic gonadotropin pregnancy test before inclusion.
12. Men agree not to donate sperm or to father a child during trial treatment and until 90 days after the last dose of investigational drug.

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group

Adult

Lower age limit
18 Years

Sex
All

Total final enrolment
42

Key exclusion criteria
1. Known allergic reaction to shellfish, crabs, crustaceans, or any trial components, used in trial treatment.
2. Malignant primary brain tumors or evidence of brain metastases or leptomeningeal disease as ascertained by clinical examination and brain imaging (MRI or CT).
3. Patients who have received chemotherapy, radiotherapy, immunotherapy, or concurrent or recent treatment with any other investigational agents within 21 days (7 days for single fraction of palliative radiotherapy, 42 days for nitrosoureas or mitomycin C) prior to treatment.
4. Patients who have not recovered to common terminology criteria for adverse events (CTCAE) Grade ≤ 1 from all side effects of prior therapies except for residual toxicities, such as alopecia or Grade 2 neuropathy, which do not pose an ongoing medical risk.
5. Patients with a history of malignancy, with the exception of non-melanoma skin cancers and in situ cancers such as the following: bladder, gastric, colon, cervical/dysplasia, melanoma, prostate, or breast, or has undergone potentially curative therapy with no evidence of disease recurrence for at least 3 years prior to the first trial treatment and no additional therapy is required or anticipated to be required during the trial period. Other exceptions may be considered with Sponsor consultation.
6. Concomitant treatment with systemic corticosteroids (daily dose not to exceed 10 mg prednisolone or equivalent) or other immunosuppressive therapy (e.g., methotrexate).
7. Oral anti-coagulation with vitamin K antagonists (e.g., phenprocoumon, warfarin) and heparin, including therapeutically dosed low molecular weight heparins, which cannot be stopped 24 hours prior to trial treatment (low-dose aspirin allowed) and bleeding diathesis.
8. Severe or uncontrolled cardiovascular disease (congestive heart failure New York Heart Association classification III or IV), unstable angina pectoris, history of myocardial infarction within the last 6 months, serious arrhythmias requiring medication (with exception of atrial fibrillation or paroxysmal supraventricular tachycardia), significant QT-prolongation, uncontrolled hypertension.
9. Known history of human immunodeficiency virus or active chronic Hepatitis C or Hepatitis B Viral infection or any uncontrolled active systemic infection requiring intravenous antimicrobial treatment.
10. Serious autoimmune disease (e.g., systemic lupus erythematosus) which is judged to reduce an anti-tumor immune response.
11. Any other serious underlying medical, psychological, familial or geographical condition, which in the judgment of the Investigator may limit compliance with the planned staging, treatment and follow-up, or place the patient at high risk from treatment-related complications.
12. Patient not eligible for general endotracheal anesthesia, if necessary, for thermal ablation treatment.

Date of first enrolment
15/12/2022

Date of final enrolment
01/10/2023

Locations

Countries of recruitment
United Kingdom

France

Germany

Switzerland

Study participating centre
-
United Kingdom
-

Sponsor information

Organisation
IQVIA RDS Ireland

Funder(s)

Funder type
Industry

Funder Name
Immunophotonics Inc

Results and Publications

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?
HRA research summary			28/06/2023	No	No