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The first-in-human trial of MDX-124 in patients with advanced cancer

Submission date 23/09/2022	**Recruitment status** Recruiting	[X] Prospectively registered [_] Protocol
Registration date 25/10/2022	**Overall study status** Ongoing	[_] Statistical analysis plan [X] Results
Last Edited 17/11/2026	**Condition category** Cancer	[_] Individual participant data

Plain English summary of protocol

Background and study aims
This study aims to find an effective dose of the study drug (MDX-124) for future studies. The research will look at how safe and well the body copes with the drug before any severe side effects appear (tolerability) and examine how this drug may work with existing forms of treatment available.
The study drug is a molecule involved within the immune system that can specifically bind to a target and activate an immune response (antibody). These antibodies are based on human antibodies (humanised) and have been changed to specifically target a protein called annexin-A1 (ANXA1). All antibodies used will be exactly the same (monoclonal). These are referred to as humanised monoclonal antibodies. The study drug binds to a protein produced by humans and animals called ANXA1.
ANXA1 is a protein produced by various organs in the human body and has several normal functions, but when overproduced is known to play a critical role in how certain cancers behave.

Who can participate?
Adults with solid tumours

What does the study involve?
This is the first clinical trial to use the study drug in humans. There are 2 sections (or modules). In the first part of Module 1, a set dose of the study drug will be given to each participant every 14 days. Dosing will continue until cancer progresses as indicated by an increase in tumour size and /or the identification of new tumours. Dosing may stop if the participant does not feel well enough to continue or if the doctor decides the participant should stop the study. Depending on the information on how well that dose works it is possible that the dose will be increased in the next joining participant. It is expected that 24 participants will join Module 1 of the study to find the effective dose of MDX-124. The next part of Module 1 will involve 20 participants being given the effective dose every 21 days. Module 2 will involve using the information on safe and effective doses gained from Module 1 to determine how the study drug works in selected tumour types, either as monotherapy or in combination with approved chemotherapies. Module 2 will recruit between 20 and 29 participants for each tumour type. The results will be used to improve treatments for patients with advanced, unresectable, or metastatic cancers.

What are the possible benefits and risks of participating?
Participants may derive clinical benefits following treatment with the study drug (MDX-124), which is not currently available other than via participation in the trial. Participants will receive increased medical care (including blood tests and scans) as part of participation in the trial. Participation in the study will enable the potential benefits and side effects of MDX-124 to be assessed which will then inform future research.
To date, there is limited knowledge of MDX-124's safety profile in humans. The study has been designed to mirror the treatment and clinical assessments carried out as part of the standard of care in this group of patients. In addition, as this is a first-in-human study, additional cytokine (Module 1 dose escalation) and immunophenotyping lab tests have been included in the schedule of events.

There are 4 main areas where there may be an increase in the risk/burden on the trial subjects:
1. Administration of MDX-124
2. Taking part in sample collection
3. Informed consent
4. Radiation exposure when receiving scans

The following precautionary measures have been put in place:
1. Assessment of full blood count, renal function and liver function will be made prior to each administration of MDX-124
2. The occurrence of toxicity including haematological toxicity which requires dose adjustment will be specified in the protocol
3. The effect of exposure to MDX-124 in patients with renal impairment is not known. Therefore, trial entry is restricted to patients with an estimated glomerular filtration rate (eGFR) ≥50 ml/min /1.73m2.
4. MDX-124 should not be administered to pregnant women. A negative pregnancy test should be confirmed before the administration of MDX-124 for all women of childbearing age.
5. Subjects will be asked to remain at the site for 6 hours post-dose on Cycle 1 Day 1 in order for them to be observed by study staff.
6. There is no known antidote for MDX-124 and treatment of AEs associated with its use should be for the underlying adverse symptoms
7. Since MDX-124 will be prepared in specialist oncology pharmacies and administered by experienced chemotherapy-trained nurses via intravenous infusion, overdose is considered to be highly unlikely. There is no specific treatment for an overdose of MDX-124. In case of overdose, therapy may be interrupted and any adverse reactions treated symptomatically.

Risks of taking part in blood or biopsy sample collection:
Plasma and serum will be taken prior to the start of treatment and at every dosing visit of every cycle. In addition, blood samples will be collected for PK, annexin-A1, cytokine (Module 1 dose escalation), immunophenotyping, tumour marker and immunogenicity analysis.
When the needle is inserted to draw the blood the patients may feel moderate pain, or only a prick or stinging sensation and afterwards there may be some throbbing or slight bruising.
The total number of PK samples collected per participant will be 24 in Module 1 and 22 in Module 2. This will require subjects to remain at the site for 6 hours after receiving administration of MDX-124 on 2 separate days (Module 1 dose escalation) and having to return to the site on no treatment days for sample collection.
Tissue collection is not compulsory in Module 1 of the study but is part of the study for Module 2. Patients can either agree or disagree to take part. Complications with biopsies are uncommon. In a small number of cases, there may be some bleeding from the biopsy site. This is usually minor and soon stops. There is also a risk of inflammation at the site of the biopsy but again this is rare. There is a slight risk that the small wound will become infected by the biopsy.

In this study, scans will be used to determine efficacy but as this is a first-in-human study the scans are included primarily for patient safety as they will be used to identify disease progression. The study involves the use of CT scans which will expose the patients to radiation which is potentially harmful. Oncology patients undergo routine CT and MRI scans to monitor disease status. The oncology patients who will be enrolled in this study have unmet medical need which is taken into consideration when assessing the risk of radiation exposure. As a result, the scanning frequency of every 8 weeks has been selected for Module 1 Dose Escalation and Module 2 of this trial, and every 9 weeks for Module 1 Dose Expansion. This strikes an appropriate balance between standard of care and providing safety oversight of the patients.
Some CT scans may need special preparation beforehand, called contrast medium. Iodinated contrast is generally safe. At the time of administration patients may:
1. Feel hot and flushed for a minute or two
2. Have a metallic taste in the mouth
3. Feel like they are passing urine but they aren't – this feeling is common and passes quickly
Rarely people have an allergic reaction to the contrast medium. This most often starts with weakness, sweating and difficulty breathing. The radiographer will ask for any allergies before the contrast medium is administered.
Patients might get a small bruise around the area where they put the needle in.
There's a risk that the contrast medium will leak outside the vein. This can cause swelling and pain in the hand or arm but it's rare.
There is a small risk that the contrast medium can affect the kidneys. The radiographer will check the most recent blood test results before the scan to make sure the kidneys are working well.
The study is only to be conducted at hospitals with expertise in the treatment and diagnosis of advanced cancer to ensure the highest standard of care for the patients.

Where is the study run from?
Medannex Limited (UK)

When is the study starting and how long is it expected to run for?
September 2022 to September 2028

Who is funding the study?
Medannex Limited (UK)

Who is the main contact?
Prof Daniel Palmer (UK)
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https://www.cancerresearchuk.org/about-cancer/find-a-clinical-trial/a-trial-looking-at-mdx-124-for-solid-tumours-that-have-spread-attainment

Contact information

Type(s)
Scientific, Public

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None - Liverpool Clinical Trials Centre

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Additional identifiers

Integrated Research Application System (IRAS)
1005488

Central Portfolio Management System (CPMS)
54029

Protocol serial number
MDX-124-101

Study information

Scientific Title

A modular, multi-arm, first-in-human trial to evaluate the safety and tolerability of MDX-124 alone and in combination with anti-cancer treatments, in participants with locally advanced, unresectable or metastatic solid malignancies

Acronym
ATTAINMENT

Study objectives
Current study hypothesis as of 23/06/2025:

Primary Objectives:
Module 1: Determine the recommended phase II dose (RP2D) of MDX-124 when administered as a single agent (Single Agent RP2D).
Module 2: Assess the safety and tolerability of MDX-124 in selected tumour types when administered as a single agent or in combination with anti-cancer treatments.

Secondary Objectives:
Assess the safety and tolerability of MDX-124 when given as a single agent (Module 1 only).
Characterise the pharmacokinetics (PK) of MDX-124 following a single dose and at a steady state after multiple doses when given as a single agent and when given in combination with anti-cancer treatments.
Assess evidence of anti-tumour activity of MDX-124 when given as a single agent and when given in combination with anti-cancer treatments.

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Previous study hypothesis:

Determine the recommended phase II dose (RP2D) of MDX-124 as a single agent and in combination with anti-cancer treatments.

1. Assess the safety and tolerability of MDX-124 when given as a single agent and when given in combination with anti-cancer treatments
2. Characterise the pharmacokinetics (PK) of MDX-124 following a single dose and at a steady state after multiple doses when given as a single agent and when given in combination with anti-cancer treatments
3. Assess evidence of anti-tumour activity of MDX-124 when given as a single agent and when given in combination with anti-cancer treatments

Ethics approval required
Old ethics approval format

Ethics approval(s)
Approved 28/11/2022, London - Central Research Ethics Committee (3rd Floor, Barlow House 4 Minshull Street, Manchester, M13DZ, United Kingdom; 02071048225; londoncentral.rec@hra.nhs.uk), ref: 22/LO/0770

Primary study design
Interventional

Study design
Interventional modular multi-arm first-in-human trial

Study type(s)
Treatment

Health condition(s) or problem(s) studied
Locally advanced, unresectable or metastatic solid malignancies

Interventions
Current interventions:

The ATTAINMENT study is comprised of two modules: Module 1 and Module 2.
Module 1 includes dose escalation and dose expansion cohorts. In the dose escalation phase using a Bayesian Optimal Interval (BOIN) model, up to 24 participants will receive MDX-124 via intravenous infusion on day 1 of a 14-day cycle. The initial cohort will start at a dose of 1 mg/kg to be administered once every 14 days. Subsequent cohorts in the dose escalation cohort will receive 2.5, 5, 10, 20 or 30 mg/kg if dose-limiting toxicities (DLTs) are not observed. Participants who are enrolled at lower doses that are viewed to be sub-therapeutic will be given the option to be up-titrated to the next dose level if determined by the dose escalation committee (DEC) per the DEC Charter. This may be done once the first cohort of participants at the next dose level has all completed the 14-day DLT evaluation period and the criteria to enrol additional participants at the same dose or escalate the dose have been met. Dosing of MDX-124 should continue until there is evidence of disease progression, unacceptable toxicity or at the participant's request.
After the dose escalation cohort has been completed, a dose expansion cohort will commence at the recommended phase 2 dose (RP2D) selected from the dose escalation cohort, given every 21 days (20 participants).
Module 2 comprises participants with the selected tumour types. In Arm 1 (pancreatic cancer), participants will receive MDX-124 via intravenous infusion in combination with standard-of-care treatments, gemcitabine and nab-paclitaxel. Arm 1 will start with an initial cohort one dose level lower than the RP2D of MDX-124, administered every 14 days. The RP2D for Module 2 Arm 1 will be determined by dose escalation with sequential participants receiving increasing doses of MDX-124 in a modified 3 + 3 cohort design. Once the dose of MDX-124 in combination with standard-of-care treatment has been determined by the DEC, further participants will be enrolled in a Module 2 expansion cohort until 20 participants have been treated with the selected combination dose.
The dose of the standard-of-care combination treatment being studied in Module 2 will not be escalated. Participants who are enrolled at lower doses (considered sub-therapeutic) will be given the option to be up-titrated to the next dose level as determined by the DEC and in accordance with the DEC Charter.

In Module 2 Arm 2 (cholangiocarcinoma), participants will receive MDX-124 at the single agent RP2D via intravenous infusion every 14 days.

In Module 2, dosing of MDX-124 should continue until there is evidence of disease progression, unacceptable toxicity or at the participant's request. In Module 2 Arm 1, in the event the standard of care combination treatment is stopped due to toxicity, completion of regimen, participant request or Investigator decision, treatment with MDX-124 may continue until there is evidence of disease progression, unacceptable toxicity or at the participant's request.

Participants will be followed up to monitor for disease progression every 6 months ± 7 days until death, loss to follow-up, or trial discontinuation. Follow-up will be restricted to 12 weeks in Module 1 and 12 months in Module 2.
There is no randomisation of participants in either Module 1 or Module 2.

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Previous interventions:

The ATTAINMENT study is comprised of two modules: Module 1 and Module 2.
Module 1 includes dose escalation and dose expansion cohorts. In the dose escalation phase using a Bayesian Optimal Interval (BOIN) model, up to 24 participants will receive MDX-124 via intravenous infusion on day 1 of a 14-day cycle. The initial cohort will start at a dose of 1 mg/kg to be administered once every 14 days. Subsequent cohorts in the dose escalation cohort will receive 2.5, 5, 10, 20 or 30 mg/kg if dose-limiting toxicities (DLTs) are not observed. Participants who are enrolled at lower doses that are viewed to be sub-therapeutic will be given the option to be up-titrated to the next dose level if determined by the dose escalation committee (DEC) per the DEC Charter. This may be done once the first cohort of participants at the next dose level have all completed the 14-day DLT evaluation period and the criteria to enrol additional participants at the same dose or escalate the dose have been met. Dosing of MDX-124 should continue until there is evidence of disease progression, unacceptable toxicity or at the participant's request.
After the dose escalation cohort has been completed, a dose expansion cohort will commence at the recommended phase 2 dose (RP2D) selected from the dose escalation cohort. Up to 2 doses or 2 dose schedules may be explored in the expansion cohort (20 participants), as determined by the dose escalation committee.
Module 2 comprises participants with the selected tumour types. In Arm 1 (pancreatic cancer), participants will receive MDX-124 via intravenous infusion in combination with standard-of-care treatments gemcitabine and nab-paclitaxel. Arm 1 will start with an initial cohort one dose level lower than the RP2D of MDX-124, and the dosing schedule, determined in Module 1. The RP2D from Module 2 will be determined by dose escalation with sequential participants receiving increasing doses of MDX-124 in a modified '3 + 3' cohort design. The dose of the standard-of-care combination treatment being studied in Module 2 will not be escalated. Participants who are enrolled at lower doses (considered sub-therapeutic) will be given the option to be up-titrated to the next dose level as determined by the DEC and in accordance with the DEC Charter. Once the dose of MDX-124 in combination with standard-of-care treatment has been determined by the DEC, further participants will be enrolled in a Module 2 expansion cohort until 20 participants have been treated with the selected combination dose.
In Module 2 dosing of MDX-124 should continue until there is evidence of disease progression, unacceptable toxicity or at the participant's request. In the event the standard of care combination treatment is stopped due to toxicity, completion of regimen, participant request or Investigator decision, treatment with MDX-124 may continue until there is evidence of disease progression, unacceptable toxicity or at the participant's request.
Participants will be followed-up to monitor for disease progression every 12 weeks ± 7 days until death, loss to follow-up, or trial discontinuation. Follow-up will be restricted to 12 weeks in Module 1 and 12 months in Module 2.
There is no randomisation of participants in either Module 1 or Module 2.

Intervention Type
Biological/Vaccine

Phase

Phase I

Drug/device/biological/vaccine name(s)
MDX-124

Primary outcome(s)
Current primary outcome measure as of 23/06/2025:

Module 1: The occurrence of dose-limiting toxicities (DLTs) at each dosing level recorded by the Investigator and trial site staff during Cycle 1.
Module 2: Treatment-emergent adverse events (per NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5) during the study period

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Previous primary outcome measure:

The occurrence of dose-limiting toxicities (DLTs) at each dosing level recorded by the Investigator and trial site staff during Cycle 1

Key secondary outcome(s)
Current secondary outcome measure as of 23/06/2025:

1. Treatment-emergent adverse events (per NCI Common Terminology Criteria for Adverse Events (CTCAE) v5) recorded by the Investigator and trial site staff at the following study visits:
1.1. Module 1 dose escalation: screening, cycle 1 day 1, cycle 1 day 8, cycle 2 day 1, cycle 2 day 8, cycle 3 (and any subsequent cycles) day 1 onwards, end of treatment, and the 28-day follow-up visit (+/- 7 days)
1.2. Module 1 dose expansion: screening, cycle 1 day 1, cycle 1 day 8, cycle 1 day 15, cycle 2 (and subsequent cycles) day 1 onwards, end of treatment, and the 28-day follow-up visit (+/- 7 days)
1.3. Module 2 Arm 1: screening, cycle 1 (and subsequent cycles) day 1, day 8, day 15, day 22, end of treatment, and the 28-day follow-up visit (+/- 7 days)
1.4. Module 2 Arm 2: screening, cycle 1 day 1, cycle 1 day 8, cycle 2 (and subsequent cycles) day 1, end of treatment, and the 28-day follow-up visit (+/- 7 days)
2. Clinically significant laboratory changes (per NCI CTCAE v5) recorded by the Investigator and trial site staff and evaluated by the Trial Management Group at the following study visits:
2.1. Module 1 dose escalation: screening, cycle 1 day 1 (if more than 14 days since the screening visit have passed), cycle 1 day 8, cycle 2 day 1, cycle 2 day 8, cycle 3 (and any subsequent cycles) day 1 onwards, end of treatment, and the 28-day follow-up visit (+/- 7 days)
2.2. Module 1 dose expansion: screening, cycle 1 day 1 (if more than 14 days since the screening visit have passed), cycle 1 day 8, cycle 1 day 15, Cycle 2 and subsequent cycles day 1, onwards, end of treatment, and the 28-day follow-up visit (+/- 7 days)
2.3. Module 2 Arm 1: screening, cycle 1 day 1 (if more than 14 days since the screening visit have passed), day 8, day 15, day 22, subsequent cycles day 1, day 8, day 15, and day 22, end of treatment, and the 28-day follow-up visit (+/- 7 days)
2.4. Module 2 Arm 2: screening, cycle 1 day 1 (if more than 14 days since the screening visit have passed), cycle 1 day 8, cycle 2 (and subsequent cycles) day 1, end of treatment, and the 28-day follow-up visit (+/- 7 days)
3. Changes in physical exam, vital signs and serial electrocardiograms (ECGs) recorded by the Investigator and trial site staff at the following study visits:
3.1. Module 1 dose escalation: screening, Cycle 1 and 2 day 1, Cycle 2 (day 8 (vital signs only),

Cycle 3 (and any subsequent cycles) day 1, and end of treatment, when symptoms are evident
3.2. Module 1 dose expansion: screening, cycle 1 day 1, cycle 1 day 8 (vital signs and weight only), day 15 (vital signs and weight only), Cycle 2 and subsequent cycles day 1, onwards and end of treatment
3.3. Module 2 Arm 1: screening, cycle 1 day 1 (if more than 14 days since the screening visit have passed; and subsequent cycles), end of treatment. Vital signs and weight: also all cycles, day 8, day 15, day 22
3.4. Module 2 Arm 2: screening, cycle 1 day 1 (if more than 14 days since the screening visit have passed), cycle 1 day 8 (vital signs and weight only), cycle 2 (and subsequent cycles) day 1, end of treatment

Pharmacokinetics:
The PK of MDX-124 will be measured using serum analyses:
1. Maximum concentration (Cmax)
2. Area under the curve (AUC)
3. Half-life (T1/2)
4. Volume of distribution (Vd)
5. Clearance (CL)
At the following study visits:
Module 1 dose escalation:
Cycle 1 Day 1 pre-dose (T0), immediately post-infusion (T1), T1 +15min, +30min, +1hr, +2hr, +4hr, +6hr, +24hr, +48hr, +168hr (Cycle 1 day 8) and pre-dose on Cycle 2 Day 1. Cycle 4 day 1 pre-dose (T0), immediately post-infusion (T1), T1 +15min, +30min, +1hr, +2hr, +4hr, +6hr, +24hr, +48hr, +168hr (Day 8) and pre-dose on Cycle 5 Day 1.
Module 1 dose expansion:
Cycle 1 and Cycle 3 only. Cycle 1 Day 1 pre-dose (T0), immediately post-infusion (T1), T1 +15min, +30min, +1hr, +2hr, +4hr, +24hr, +168hr (Day 8), +336hr (Day 15) and pre-dose on Cycle 2 Day 1. Cycle 3 Day 1 Pre-Dose (T0), Immediately Post Infusion (T1), T1 +15min, +30min, +1hr, +2hr, +4hr, +24hr, +168hr (Day 8), +336hr (Day 15) and pre-dose on Cycle 4 Day 1.
Module 2 Arm 1: cycle 1 Day 1 pre-dose (T0), immediately post-infusion (T1), T1 +15min, +30min, +1hr, +2hr, +4hr, +24hr, +168hr (Day 8) and pre-dose on Cycle 1 Day 15; Cycle 3 Day 1 pre-dose (T0), immediately post-infusion (T1), T1 +15min, +30min, +1hr, +2hr, +4hr, +24hr, +168hr (Day 8) and pre-dose on Cycle 3 Day 15.
Module 2 Arm 2: Cycle 1 Day 1 pre-dose (T0), immediately post-infusion (T1), T1 +15min, +30min, +1hr, +2hr, +4hr, +24hr, +168hr (Day 8) and pre-dose on Cycle 2 Day 1. Cycle 4 Day 1 Pre-Dose (T0), Immediately Post Infusion (T1), T1 +15min, +30min, +1hr, +2hr, +4hr, +24hr, +168hr (Day 8) and pre-dose on Cycle 5 Day 1.

Efficacy:
1. Best overall response (per RECIST version 1.1) measured as an ordered categorical endpoint with results presented in terms of frequencies of counts with associated percentages for the duration of participant participation in the trial
2. Duration of objective response (per RECIST version 1.1) measured as the unit of time (in days) during which the patient was determined to have either partial response (PR) or complete response (CR) as determined by RECIST (1.1) for the duration of participant participation in the trial
3. Progression-free survival (per RECIST version 1.1) measured as the time from registration until disease progression or death by any cause. Rates of PFS will be estimated using the Kaplan-Meier approach for the duration of participant participation in the trial
4. Overall survival measured as the time from registration until death by any cause. Rates of PFS will be estimated using the Kaplan-Meier approach for the duration of participant participation in the trial

All secondary endpoints will be reviewed throughout the study. The Dose Escalation Committee will review data related to the endpoints at the DEC meetings, which are convened once all subjects in a cohort have completed the DLT evaluation period. The endpoints will also be reviewed prior to determining the RP2D.

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Previous secondary outcome measure:

Safety and tolerability:
1. Treatment-emergent adverse events (per NCI Common Terminology Criteria for Adverse Events (CTCAE) v5) recorded by the Investigator and trial site staff at the following study visits: screening, cycle 1 day 1, cycle 1 day 8, cycle 2 (and any subsequent cycles) day 1 onwards, end of treatment, and the 28-day follow-up visit (+/- 7 days)
2. Clinically significant laboratory changes (per NCI CTCAE v5) recorded by the Investigator and trial site staff and evaluated by the Trial Management Group at the following study visits: screening, cycle 1 day 1, cycle 1 day 8, cycle 2 (and any subsequent cycles) day 1 onwards, end of treatment, and the 28-day follow up visit (+/- 7 days)
3. Changes in physical exam, vital signs and serial electrocardiograms (ECGs) recorded by the Investigator and trial site staff at the following study visits: screening, Cycle 1 day 1, Cycle 2 (and any subsequent cycles) day 1, and end of treatment, when symptoms are evident

Pharmacokinetics:
The PK of MDX-124 will be measured using serum analyses:
1. Maximum concentration (Cmax)
2. Area under the curve (AUC)
3. Half-life (T1/2)
4. Volume of distribution (Vd)
5. Clearance (CL)
At the following study visits:
Module 1:
Cycle 1 Day 1 pre-dose (T0), immediately post-infusion (T1), T1 +15min, +30min, +1hr, +2hr, +4hr, +6hr, +24hr, +48hr, +168hr (Day 8) and pre-dose on Cycle 2 Day 1, Cycle 4 Day 1 pre dose (T0), immediately post-infusion (T1), T1 +15min, +30min, +1hr, +2hr, +4hr, +6hr, +24hr, +48hr, +168hr (Day 8) and pre dose on Cycle 5 Day 1.
Module 2:
Cycle 1 Day 1 pre-dose (T0), immediately post-infusion (T1), T1 +15min, +30min, +1hr, +2hr, +4hr, +6hr, +24hr, +48hr, +168hr (Day 8) and pre-dose on Cycle 1 Day 15; Cycle 3 Day 1 pre-dose (T0), immediately post-infusion (T1), T1 +15min, +30min, +1hr, +2hr, +4hr, +6hr, +24hr, +48hr, +168hr (Day 8) and pre-dose on Cycle 3 Day 15.

Efficacy:
1. Best overall response (per RECIST version 1.1) measured as an ordered categorical endpoint with results presented in terms of frequencies of counts with associated percentages for the duration of participant participation in the trial
2. Duration of objective response (per RECIST version 1.1) measured as the unit of time (in days) during which the patient was determined to have either partial response (PR) or complete response (CR) as determined by RECIST (1.1) for the duration of participant participation in the trial
3. Progression-free survival (per RECIST version 1.1) measured as the time from registration until disease progression or death by any cause. Rates of PFS will be estimated using the Kaplan-

Meier approach for the duration of participant participation in the trial
4. Overall survival measured as the time from registration until death by any cause. Rates of PFS will be estimated using the Kaplan Meier approach for the duration of participant participation in the trial

All secondary endpoints will be reviewed throughout the study. The Dose Escalation Committee will review data related to the endpoints at the TMG meetings which are convened once all subjects in a cohort have completed the DLT evaluation period. The endpoints will also be reviewed prior to determining the RP2D.

Completion date
30/09/2028

Eligibility

Key inclusion criteria
Current inclusion criteria as of 23/06/2025:

Core:
1. Provision of signed written informed consent
2. Age 18 years old and over
3. ECOG Performance status 0-1
4. Adequate bone marrow function as defined by:
4.1. Absolute neutrophil count (ANC) ≥1.5×10^9/l
4.2. Platelet count ≥100×10^9/l
4.3. Haemoglobin level ≥9.0 g/dl
5. Adequate liver function, as defined by:
5.1. Serum total bilirubin ≤1.5×upper limit of normal (ULN)
5.2. Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤2.5×ULN
6. Adequate renal function assessed as estimated glomerular filtration rate (eGFR) ≥50 ml/min/1.73m2
7. Ability to comply with protocol requirements
8. Female participants of child-bearing potential must have a negative serum pregnancy test

Module 1:
Participants being enrolled in Module 1 must meet all criteria listed below in addition to the Core Inclusion Criteria:
1. Histologically or cytologically confirmed diagnosis of a solid tumour believed to overexpress ANXA1 (e.g., cholangiocarcinoma, triple negative breast, bladder, ovarian, colorectal, kidney, liver, pancreatic, gastric, prostate and lung) which is not amenable to standard therapy, is refractory to standard therapy or for which no standard therapy exists. Tumours identified as not responding to ANXA1 inhibition (i.e. head and neck (oral, nasal and throat regions) and cervical) are excluded.
2. Participants must have measurable disease per RECIST version 1.1 criteria and/or evaluable disease (evaluable: cytologically or radiologically detectable disease such as ascites, peritoneal deposits, or lesions which do not fulfil RECIST version 1.1 criteria for measurable disease).

Module 2:
Participants being enrolled in Module 2 must meet the applicable inclusion criteria listed below in addition to the Core Inclusion Criteria:
Arm 1:

1. Participants with a histologically or cytologically confirmed diagnosis of locally advanced or metastatic pancreatic cancer.
2. Participants must be suitable for combination treatment.
3. Participants must have at least one measurable lesion as per RECIST version 1.1.
Arm 2:
1. Participants with a histologically or cytologically confirmed diagnosis of locally advanced or metastatic cholangiocarcinoma or gallbladder cancer.
2. Participants must have received and have documented evidence of progression following treatment with cisplatin and gemcitabine (with or without durvalumab).
3. Adequate biliary drainage, with no evidence of ongoing infection.
4. Participants must have at least one measurable lesion as per RECIST version 1.1.

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Previous inclusion criteria as of 28/06/2024:

Core:
1. Provision of signed written informed consent
2. Age 18 years old and over
3. ECOG Performance status 0-1
4. Adequate bone marrow function as defined by:
4.1. Absolute neutrophil count (ANC) ≥1.5×10^9/l
4.2. Platelet count ≥100×10^9/l
4.3. Haemoglobin level ≥10.0 g/dl
5. Adequate liver function, as defined by:
5.1. Serum total bilirubin ≤1.5×upper limit of normal (ULN)
5.2. Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤2.5×ULN
6. Adequate renal function assessed as estimated glomerular filtration rate (eGFR) ≥50 ml/min/1.73m2
7. Ability to comply with protocol requirements
8. Female participants of child-bearing potential must have a negative serum pregnancy test

Module 1:
Participants being enrolled in Module 1 must meet all criteria listed below in addition to the Core Inclusion Criteria:
1. Histologically or cytologically confirmed diagnosis of a solid tumour believed to overexpress ANXA1 (e.g., cholangiocarcinoma, triple negative breast, bladder, ovarian, colorectal, kidney, liver, pancreatic, gastric, prostate and lung) which is not amenable to standard therapy, is refractory to standard therapy or for which no standard therapy exists. Tumours identified as not responding to ANXA1 inhibition (i.e. head and neck (oral, nasal and throat regions) and cervical) are excluded.
2. Participants must have measurable disease per RECIST version 1.1 criteria and/or evaluable disease (evaluable: cytologically or radiologically detectable disease such as ascites, peritoneal deposits, or lesions which do not fulfil RECIST version 1.1 criteria for measurable disease).

Module 2:
Participants being enrolled in Module 2 must meet the applicable criteria listed below in addition to the Core Inclusion Criteria:
1. Arm 1: Participants with a histologically or cytologically confirmed diagnosis of locally advanced or metastatic pancreatic cancer.
2. Participants must be suitable for combination treatment.
3. Participants must have at least one measurable lesion as per RECIST version 1.1.

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Previous inclusion criteria:

Core:
1. Provision of signed written informed consent
2. Age 18 years old and over
3. ECOG Performance status 0-1
4. Adequate bone marrow function as defined by:
4.1. Absolute neutrophil count (ANC) ≥1.5×10^9/l
4.2. Platelet count ≥100×10^9/l
4.3. Haemoglobin level ≥10.0 g/dl
5. Adequate liver function, as defined by:
5.1. Serum total bilirubin ≤1.5×upper limit of normal (ULN)
5.2. Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤2.5×ULN
6. Adequate renal function assessed as estimated glomerular filtration rate (eGFR) ≥50 ml/min/1.73m2
7. Negative SARS-CoV-2 reverse transcription polymerase chain reaction (RT PCR) test within 48 hours prior to first receipt of IMP
8. Ability to comply with protocol requirements
9. Female participants of child-bearing potential must have a negative serum pregnancy test

Module 1:
Participants being enrolled in Module 1 must meet all criteria listed below in addition to the Core Inclusion Criteria:
1. Histologically or cytologically confirmed diagnosis of a solid tumour believed to overexpress ANXA1 (i.e., cholangiocarcinoma, triple negative breast, bladder, ovarian, colorectal, kidney, liver, pancreatic, gastric, prostate and lung) which is not amenable to standard therapy, is refractory to standard therapy or for which no standard therapy exists. Tumours identified as not responding to ANXA1 inhibition (i.e. head and neck (oral, nasal and throat regions) and cervical) are excluded.
2. Participants must have measurable disease per RECIST version 1.1 criteria and/or evaluable disease (evaluable: cytologically or radiologically detectable disease such as ascites, peritoneal deposits, or lesions which do not fulfil RECIST version 1.1 criteria for measurable disease).

Module 2:
Participants being enrolled in Module 2 must meet the applicable criteria listed below in addition to the Core Inclusion Criteria:
1. Arm 1: Participants with a histologically or cytologically confirmed diagnosis of locally advanced or metastatic pancreatic cancer.
2. Participants must be suitable for combination treatment.
3. Participants must have at least one measurable lesion as per RECIST version 1.1.

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Mixed

Lower age limit
18 Years

Upper age limit
120 Years

Sex
All

Total final enrolment
0

Key exclusion criteria
Current exclusion criteria as of 23/06/2025:

Core
1. Symptomatic central nervous system (CNS) or leptomeningeal metastases.
2. Residual toxicities from chemotherapy or radiotherapy, which have not regressed to Grade ≤1 severity (NCI CTCAE v5), except for neuropathy (Grade 2 allowed) or alopecia.
3. Participants receiving daily high-dose steroids (defined as >2 mg/day of dexamethasone or >15 mg/ day prednisolone) during the 14 days prior to the first dose of IMP. Participants who are receiving glucocorticoids as part of steroid replacement (e.g., after immunotherapy hypophysitis) remain eligible.
4. Participants who have a history of another malignancy diagnosed within the past 2 years, with the exception of adequately treated non-melanoma skin cancer, curatively treated carcinoma in situ of the cervix or ductal carcinoma in situ (DCIS) of the breast. Participants with previous invasive cancers are eligible if treatment was completed more than a year prior to initiating the trial, and the participant has had no evidence of recurrence since then.
5. Presence of an uncontrolled concomitant illness or active infection requiring intravenous (IV) antibiotics or a fever >38.5°C on the day of scheduled dosing.
6. Presence of any serious illnesses, medical conditions, or other medical history, including laboratory results, which, in the Investigator's opinion, would be likely to interfere with their participation in the trial, or with the interpretation of the results.
7. Known diagnosis of human immunodeficiency virus (HIV) or active hepatitis B or C. Participants who are HBV carriers and receiving anti-viral prophylaxis are excluded.
8. Any condition (e.g., known or suspected poor compliance, psychological instability, geographical location etc.) that, in the judgment of the Investigator, may affect the participant's ability to sign the informed consent and undergo trial procedures.
9. Known allergy to any of the excipients of the MDX-124 drug product (histidine, sucrose and polysorbate 20).
10. Currently pregnant, lactating or breastfeeding.
11. All men or women of reproductive potential, unless using at least two highly effective contraceptive measures, or abstaining from sexual intercourse, until six months after the last dose of IMP.
12. History or presence of alcoholism or drug abuse within the past 2 years.

13. Participants who have received a live vaccine 4 weeks or fewer prior to enrolment.
14. Drugs that have anti-cancer characteristics or other compounds such as herbal, "alternative" or traditional Chinese medicine, which may have anti-cancer properties.

Module 1:
In addition to the core exclusion criteria, if participants being considered for enrolment in Module 1 meet any criteria listed below, they will be ineligible for the trial:
1. Prior chemotherapy, radiotherapy (other than a short cycle of palliative radiotherapy for bone pain) or other targeted therapy administered within 28 days of first receipt of IMP.
- For immunotherapy, within 42 days of the first administration of IMP.
- For targeted hormone therapy within 14 days of the first administration of IMP. Patients on standard-of-care hormonal therapies may continue that therapy.
- For nitrosoureas and mitomycin C therapy within 42 days of the first administration of IMP.

Module 2:
In addition to the core exclusion criteria, if participants being considered for enrolment in Module 2 meet any criteria listed below, they will be ineligible for the trial:
Arm 1:
1. Patient has received previous systemic anticancer therapy for advanced pancreatic adenocarcinoma. Patients receiving adjuvant or neoadjuvant treatment and completed ≥ 6 months prior to registration are eligible.
2. History of allergic reactions attributed to previous gemcitabine or nab-paclitaxel treatment.
3. Known contraindication to any of the excipients of gemcitabine or nab-paclitaxel.
4. History of posterior reversible encephalopathy syndrome (PRES).
5. Participants with a high cardiovascular risk including but not limited to a history of myocardial infarction within the last 5 years or with significant cardiac arrhythmias requiring medication or pacemaker.
6. Participants who take drugs that inhibit or induce CYP3A4.
7. History of (non-infectious) pneumonitis or has current pneumonitis.
8. Previous radiotherapy for measurable lesions.

Arm 2:
1. Participant has received more than 1 line of prior systemic therapy with chemotherapy.
- Prior adjuvant and/or neoadjuvant treatment is not exclusionary.
- Treatment with a targeted therapy (e.g. IDH1 and/or FGFR2 inhibitors) is not exclusionary.
2. Ampullary carcinoma is excluded.
3. Prior chemotherapy, radiotherapy (other than a short cycle of palliative radiotherapy for bone pain) or other targeted therapy administered within 28 days of first receipt of IMP. Prior immunotherapy within 42 days of the first administration of IMP.

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Previous exclusion criteria as of 28/06/2024:

Core
1. Symptomatic central nervous system (CNS) or leptomeningeal metastases.
2. Residual toxicities from chemotherapy or radiotherapy, which have not regressed to Grade ≤1 severity (NCI CTCAE v5), except for neuropathy (Grade 2 allowed) or alopecia.
3. Participants receiving daily high dose steroids (defined as >2 mg/day of dexamethasone or >15 mg/ day prednisolone) during the 14 days prior to first dose of IMP. Participants who are receiving glucocorticoids as part of steroid replacement (e.g., after immunotherapy hypophysitis) remain eligible.
4. Participants who have a history of another malignancy diagnosed within the past 2 years, with the exception of adequately treated non-melanoma skin cancer curatively treated carcinoma in situ of the cervix or ductal carcinoma in situ (DCIS) of the breast. Participants with previous invasive cancers are eligible if treatment was completed more than a year prior to initiating the

trial, and the participant has had no evidence of recurrence since then.
5. Presence of an uncontrolled concomitant illness or active infection requiring intravenous (IV) antibiotics or a fever >38.5°C on the day of scheduled dosing.
6. Presence of any serious illnesses, medical conditions, or other medical history, including laboratory results, which, in the Investigator's opinion, would be likely to interfere with their participation in the trial, or with the interpretation of the results.
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8. Any condition (e.g., known or suspected poor compliance, psychological instability, geographical location etc.) that, in the judgment of the Investigator, may affect the participant's ability to sign the informed consent and undergo trial procedures.
9. Known allergy to any of the excipients of the MDX-124 drug product (histidine, sucrose and polysorbate 20).
10. Currently pregnant, lactating or breastfeeding.
11. All men or women of reproductive potential, unless using at least two highly effective contraceptive measures, or abstaining from sexual intercourse, until six months after last dose of IMP.
12. History or presence of alcoholism or drug abuse within the past 2 years.

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1.1. For immunotherapy within 42 days of first administration of IMP.
1.2. For targeted hormone therapy within 14 days of first administration of IMP. Patients on standard-of-care hormonal therapies may continue that therapy.
1.3. For nitrosoureas and mitomycin C therapy within 42 days of first administration of IMP.

Module 2:
In addition to the core exclusion criteria, if participants being considered for enrolment in Module 2 meet any criteria listed below, they will be ineligible for the trial:
Arm 1:
1. Patient has received previous systemic anticancer therapy for advanced pancreatic adenocarcinoma. Patients receiving adjuvant or neoadjuvant treatment and completed ≥ 6 months prior to registration are eligible.
2. History of allergic reactions attributed to previous gemcitabine or nab-paclitaxel treatment.
3. Known contraindication to any of the excipients of gemcitabine or nab-paclitaxel.
4. History of posterior reversible encephalopathy syndrome (PRES).
5. Participants with a high cardiovascular risk including but not limited to a history of myocardial infarction within the last 5 years or with significant cardiac arrhythmias requiring medication or pacemaker.

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Previous exclusion criteria:

Core
1. Symptomatic central nervous system (CNS) or leptomeningeal metastases.
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>15 mg/ day prednisolone) during the 14 days prior to first dose of IMP. Participants who are receiving glucocorticoids as part of steroid replacement (e.g., after immunotherapy hypophysitis) remain eligible.
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6. Presence of any serious illnesses, medical conditions, or other medical history, including laboratory results, which, in the Investigator's opinion, would be likely to interfere with their participation in the trial, or with the interpretation of the results.
7. Known diagnosis of human immunodeficiency virus (HIV) or active hepatitis B or C. Participants who are HBV carriers and receiving anti-viral prophylaxis are excluded.
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1.1. For immunotherapy within 42 days of first administration of IMP.
1.2. For hormone therapy within 14 days of first administration of IMP.
1.3. For nitrosoureas and mitomycin C therapy within 42 days of first administration of IMP.

Module 2:
In addition to the core exclusion criteria, if participants being considered for enrolment in Module 2 meet any criteria listed below, they will be ineligible for the trial:
Arm 1:
1. Patient has received previous systemic anticancer therapy for advanced pancreatic adenocarcinoma. Patients receiving adjuvant or neoadjuvant treatment and completed ≥ 6 months prior to randomisation are eligible.
2. History of allergic reactions attributed to previous gemcitabine or nab-paclitaxel treatment.
3. Known contraindication to any of the excipients of gemcitabine or nab-paclitaxel.
4. History of posterior reversible encephalopathy syndrome (PRES).
5. Participants with a high cardiovascular risk including but not limited to a history of myocardial infarction within the last 5 years or with significant cardiac arrhythmias requiring medication or pacemaker.

Date of first enrolment
01/08/2023

Date of final enrolment

30/09/2027

Locations

Countries of recruitment
United Kingdom

England

Scotland

Study participating centre
Clatterbridge Hospital
Clatterbridge Road
Bebington
Birkenhead
Wirral
England
CH63 4JY

Study participating centre
Edinburgh Cancer Research Centre
The University of Edinburgh
Western General Hospital
Crewe Road South
Edinburgh
Scotland
EH4 2XR

Study participating centre
Churchill Hospital
Churchill Hospital
Old Road
Headington
Oxford
England
OX3 7LE

Study participating centre
Beatson West of Scotland Cancer Centre
1053 Great Western Road

Glasgow
Scotland
G12 0YN

Study participating centre
The Christie NHS Foundation Trust
550 Wilmslow Road
Withington
Manchester
England
M20 4BX

Study participating centre
Guys and St Thomas NHS Foundation Trust
15th Floor Tower Wing
Guys Hospital
London
England
SE1 9RT

Sponsor information

Organisation
Medannex Limited

Funder(s)

Funder type
Industry

Funder Name
Medannex Limited

Results and Publications

Individual participant data (IPD) sharing plan

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?
Abstract results		29/05/2024	17/11/2026	No	No