CLINICAL TRIAL PROTOCOL

ATTAINMENT STUDY

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

IMP:	MDX-124; gemcitabine; nab-paclitaxel
Protocol #:	MDX-124-101
Protocol Version, Date:	FINAL version 7.0, 9th April 2025
Development Phase:	I/Ib
IRAS Number:	**1005488**
ISRCTN:	**78740398**
Sponsor:	Medannex Limited
Chief Investigator:	Professor Daniel Palmer
Clinical Trials Unit:	Liverpool Clinical Trial Centre (LCTC)

1 STUDY PROTOCOL APPROVAL

I, the undersigned, hereby approve this clinical study protocol:

Signature: DocuSigned by: Dan Palmer A4123CCFD018434... Date: 4/11/2025

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I, the undersigned hereby approve this clinical study protocol:

Signature: DocuSigned by: Ian Abercrombie EC2D24B9248C48C... Date: 4/11/2025

Signed on behalf of Medannex Limited
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Trial 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**
Protocol #:	MDX-124-101
Phase:	1/1b
Objectives:	**Primary Objectives** **Module 1** - Determine the recommended phase 2 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 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 single agent and when given in combination with anti-cancer treatments. **Exploratory Objectives** - Explore the relationship between dose, blood borne and tissue biomarkers. - Assess host immune response to MDX-124 (immunogenicity and immunophenotyping). - Assess circulating levels of annexin-A1 (ANXA1) at baseline and after dosing in participants to correlate with response and outcome to MDX-124. - Assess the impact of MDX-124 on immunohistochemistry (IHC) biomarkers (e.g., tumour expression of ANXA1 and immune cell infiltration). If additional tumour molecular profiling is required to understand further any response to MDX-124, a tumour biopsy for additional research may be requested (Module 1 only).

Trial Design:	A phase 1 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. This trial is comprised of 2 modules: - Module 1: Dose escalation to determine the RP2D for single agent MDX-124 (Single Agent RP2D). A dose expansion cohort will explore an alternative dosing schedule using the Single Agent RP2D. - Module 2: Assess the safety and tolerability of MDX-124 Single Agent RP2D in selected tumour types when administered as a single agent or in combination with anti-cancer treatments. The Module 1 dose expansion and Module 2 will open for enrolment when the Single Agent RP2D has been determined by the Dose Escalation Committee (DEC) in Module 1. The Single Agent RP2D reduced by one dose level will be the starting dose in Module 2 when MDX-124 is administered in combination with other anti-cancer treatments. **<u>Module 1</u>** The Single Agent RP2D will be determined by a dose escalation utilising a Bayesian optimal interval (BOIN) model. The initial cohort will start with a dose of 1 mg/kg to be administered on Day 1 of a 14-day cycle. A DEC will be assigned to review safety and dose escalations. Full role and responsibilities of the DEC will be outlined in a charter. Up to 24 evaluable participants with tumours which are believed to overexpress ANXA1 (e.g., cholangiocarcinoma, triple negative breast, bladder, ovarian, colorectal, kidney, liver, pancreatic, gastric, prostate and lung) will be enrolled in Module 1. A starting dose of 1 mg/kg was identified with set planned dose escalations to 2.5, 5, 10, 20 and 30 mg/kg if dose limiting toxicities (DLTs) are not observed. Participant cohorts of 1 will be used for the initial doses but will increase to 3 in the event of a DLT or if determined by the DEC per the DEC Charter. Upon completion of the 21-day DLT period, the DEC will agree on the next dose. The minimum number of participants in subsequent cohorts will be 3 however this may be increased at the discretion of the DEC following a review of the verified safety data. Upon cohort expansion, the DEC will meet after at least 3 participants have been followed for the 21-day DLT period. To ensure safety data from a minimum of 3 evaluable patients is available for the DEC to make any decisions with regards to future doses the DEC may allocate 4 slots in a cohort. In addition, efficacy/PK data may also be considered when deciding on dose and cohort size for the next cohort of participants. The DEC will have the option to enrol additional participants at lower dose levels which the DEC have previously determined to be safe. If it is determined that the dose should be de-escalated the DEC will have the option to reduce the dose to the prior

dose level or to a dose determined by the DEC following their review of the data.

The trial will stop for safety if after 4 participants have been enrolled and dosed at dose level 1 the DLT rate is greater than the target toxicity level of 30%. The trial may re start following a review by the DEC and approval of a substantial amendment which should include a rationale for amendments to the proposed dosing.

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 DEC per the DEC Charter. This may be done once the first cohort of participants at the next dose level have all completed the 21-day DLT evaluation period and the criteria to enrol additional participants at the same dose or escalate the dose have been met.

Once the Single Agent RP2D has been determined an additional 20 participants will be enrolled in the Module 1 expansion cohort where the selected Single Agent RP2D will be administered every 21 days. The DEC will review the data once the 6th participant enrolled in the expansion cohort has completed 1 cycle to determine if the dose is appropriate and amend the dose if required. Additional reviews can be conducted at the DECs discretion.

Module 2

Module 2 will comprise participants with the selected tumour types being enrolled in the following arms:

- Arm 1: MDX-124 in combination with gemcitabine and nab-paclitaxel in participants with pancreatic cancer. MDX-124 administered on Days 1 and 14 and gemcitabine and nab-paclitaxel administered on days 1, 8 and 15 of a 28-day cycle.
- Arm 2: MDX-124 as a single agent in participants with cholangiocarcinoma. MDX-124 administered on day 1 of a 14-day cycle.

These arms were selected based on emerging clinical and non-clinical data.

Arm 1 will start with an initial cohort at one dose level below the Single Agent RP2D determined by the DEC.

Arm 2 will start at the Single Agent RP2D.

When administered as a single agent, MDX-124 will be administered at the Single Agent RP2D. As the dose has been determined in Module 1 the 3+3 design will not be required, and 20 participants will be enrolled. In the event the DEC determine that a dose reduction is required the dose can be reduced by 25% of the Single Agent RP2D with a further reduction to 50% of the Single Agent RP2D if required.

For each arm that includes MDX-124 being administered in combination with standard of care anti-cancer treatment a Combination RP2D will be determined. This will be done by dose escalation with participants receiving increasing doses of MDX-124 in a modified ‘3 + 3’ cohort

	design. The dose of the standard of care anti-cancer treatments will not be escalated. In Arm 1 once enrolment in a cohort has been completed and the participants have completed the DLT evaluation period (28 days) the DEC will review the available verified safety data and decide if further dose escalation is appropriate. An arm may be closed to further enrolment by the DEC based on the available safety and PK data. Once the Combination RP2D for a particular arm has been determined by the DEC further participants will be enrolled in an expansion cohort until 20 participants have been treated with the Combination RP2D and selected combination standard of care anti-cancer treatment. If at the -2-dose level at least 2 of 3 participants or at least 2 of 6 participants have a DLT, enrolment in the arm will be stopped for safety. The trial may re-start following a review by the DEC and approval of a substantial amendment which will include a rationale for amendments to the proposed dosing. Participants who are enrolled at a lower dose (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. This may be done once the cohort of participants at the next dose level have all completed the DLT evaluation period and the criteria to enrol additional participants at the same dose or escalate the dose have been met. Based on emerging clinical and non-clinical data, additional arms exploring the safety and tolerability of MDX-124 may be added by substantial amendment. A maximum of 2 additional arms will be added. **<u>All Modules</u>** MDX-124 will be administered until disease progression, unacceptable toxicity or withdrawal of consent. In Module 2 Arm 1, treatment with gemcitabine and nab-paclitaxel should continue until disease progression, unacceptable toxicity or withdrawal of consent. Participants will attend an end of treatment visit approximately 7 days (±1 day) following the last IMP dose. Participants will also be asked to attend a follow up visit approximately 28 days (±7 days) following the last IMP dose. In the Module 1 Dose Escalation or Module 2 Arm 2 (when the cycle duration is 14 days) tumour assessment scans will be performed at the screening visit, at the end of Cycle 4, Cycle 8, and every subsequent 4th cycle (±7 days) until disease progression. In the Module 1 Dose Expansion (when cycle duration is 21 days) tumour assessment scans will be performed at the screening visit, at the end of Cycle 3, Cycle 6, and every subsequent 3rd cycle (±7 days) until disease progression. In Module 2 Arm 1 (when the cycle duration is 28 days) tumour assessment scans should be conducted at the screening visit then at the end of Cycle 2, Cycle 4, and every subsequent 2nd cycle (±7 days) until disease progression.

	Participants who discontinue MDX-124 with no radiological evidence of disease progression will receive scans every 8 weeks (±7 days) from the prior scan. This will continue for a maximum duration of 6 months or until disease progression, initiation of a new treatment, or death in order to determine duration of overall response and progression free survival (PFS). Primary care givers of participants with evidence of disease progression as defined by RECIST version 1.1 criteria will be contacted at regular intervals (every 6 months ±7 days) until death, loss to follow-up, or trial discontinuation in order to determine duration of overall survival. Follow-up will be restricted to 12 weeks in Module 1 and 12 months in Module 2.
Trial Centres:	This trial will be conducted at sites in the United Kingdom.
Endpoints:	**Primary Endpoint** **Module 1** - The occurrence (number) of DLTs at each dosing level. **Module 2** - Treatment-emergent adverse events (per NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5). **Secondary Endpoints** **Safety** - Treatment-emergent adverse events (per NCI CTCAE version 5) (Module 1 only). - Clinically significant laboratory changes (per NCI CTCAE version 5). - Changes in physical exam, vital signs and serial electrocardiograms (ECG). **Pharmacokinetics** The PK of MDX-124 will be characterised for the trial population at limited timepoints: - Maximum concentration (C_{max}). - Area under the curve (AUC). - Half-life ($T_{1/2}$). - Volume of distribution (V_d). - Clearance (CL). **Efficacy** - Best overall response (per RECIST version 1.1). - Duration of objective response (per RECIST version 1.1). - Progression-free survival (per RECIST version 1.1). - Overall survival.

	Exploratory Endpoints - Correlation between dose and changes from baseline of blood borne and tissue biomarkers. - Changes in white blood cell (WBC) markers from baseline measured by flow cytometry. - Development of an assay to detect and characterise anti-drug antibodies (ADAs) following dosing with MDX-124, if required. - Changes in levels of circulating ANXA1 as measured by ELISA before and after dosing with MDX-124. - Correlation between post-dose levels of circulating ANXA1 and clinical outcome as defined by RECIST version 1.1. - Evaluation of participant specific tumour tissue before and after dosing with MDX-124 for impact on ANXA1 and expression of pathway-related proteins and mRNA by multiplex IHC and RNA scope.
Trial Population:	Participants with locally advanced, unresectable or metastatic solid malignancies.
Statistical Analysis	**<u>Sample Size</u>** **Module 1** Module 1 will utilise a BOIN design where the decision to escalate or de-escalate the dose is determined by the DLT rate observed at the current dose. The estimated MTD is the highest dose level with observed toxicity rate less than 30%. It is anticipated that a sample size of 24 participants will be required to determine the Single Agent RP2D. An additional 20 participants will then be enrolled at the Single Agent RP2D in the expansion cohort. **Module 2** Each arm which combines MDX-124 with a standard of care combination will utilise a modified '3+3' design with the DLT assessed and the maximum tolerated dose (MTD) declared on 6 participants. Since the number of dose levels is not fixed prior the start of the trial, it is not possible to provide a definitive sample size. However, it is anticipated that around 9 participants (range of 6 to 12) will be required to determine the Combination RP2D in each arm. Further participants will be enrolled in an expansion cohort until 20 participants have been treated with the selected dose. When administered as a single agent MDX-124 will be administered at the Single Agent RP2D. As the dose has been determined in Module 1 the 3+3 design will not be required, and the arm will enrol 20 participants as a dose expansion cohort. **<u>Safety Analysis</u>** The safety analysis set will comprise all participants who receive at least 1 dose of IMP. In the Module 1 and 2 dose escalation, for a participant to be considered evaluable for the analysis of a DLT, they must either have: • had a DLT within the defined DLT review period **or**

	• received at least 90% of the prescribed dose of IMP in Cycle 1 and completed all safety evaluations within the defined DLT review period after the first administration of IMP without experiencing a DLT. A participant without a DLT will be replaced if they did not adequately complete the defined DLT review period (i.e., discontinued prematurely due to a reason unrelated to MDX-124), or if that participant received <90% of the prescribed dose. In the dose expansion arms of Modules 1 and 2, all participants who receive an IMP will be evaluable for safety. Participants who are not evaluable for safety may be replaced. **Efficacy Analysis** The efficacy analysis set will comprise all participants who have received one dose of MDX-124 and a post baseline scan. **Pharmacokinetic Analysis** The PK analysis set will include all participants who have PK samples collected. Summary statistics will be tabulated for the PK parameters of MDX-124 by dose and trial cycle.
Investigational Medicinal Products:	Module 1: MDX-124. Module 2: Arm 1: MDX-124 in combination with 1000mg/m^2 gemcitabine and 125mg/m^2 nab-paclitaxel. MDX-124 administered on Days 1 and 14 and gemcitabine and nab-paclitaxel administered on days 1, 8 and 15 of a 28-day cycle. Arm 2: MDX-124. MDX-124 administered on day 1 of a 14-day cycle. MDX-124 is a humanised monoclonal antibody that binds specifically and with high affinity to ANXA1.

Key Inclusion Criteria:	**Core** 1. Provision of signed written informed consent. 2. Age ≥18 years. 3. ECOG performance status 0-1. 4. Adequate bone marrow function as defined by: - absolute neutrophil count (ANC) ≥1.5×10^9/l, - platelet count ≥100×10^9/l, - haemoglobin level ≥9.0 g/dl. 5. Adequate liver function, as defined by: - serum total bilirubin ≤1.5×upper limit of normal (ULN), - aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤2.5×ULN. 6. Adequate renal function assessed as estimated glomerular filtration rate (eGFR) ≥50 ml/min/1.73m^2. 7. Ability to comply with protocol requirements. 8. Female participants of child-bearing potential must have a negative serum pregnancy test. **Module 1** Participants 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 (e.g., head and neck (oral, nasal and throat regions) and cervical) are excluded. 2. Participants must have measurable disease per RECIST version 1.1 criteria 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 for which FOLFIRINOX treatment is not indicated and gemcitabine with nab-paclitaxel is the standard of care. 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.

Key Exclusion Criteria:	**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 >2mg/day of dexamethasone or >15mg/ 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. 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[*4], unless using at least 2 highly effective contraceptive measures, 1 of which must be from the list below, the other must be a condom[*1] or abstaining from sexual intercourse, until 6 months after last dose of MDX-124, gemcitabine and/ or nab-paclitaxel: 1. Combined (oestrogen and progesterone containing) hormonal contraception associated with inhibition of ovulation: either oral, intravaginal or transdermal 2. Progesterone-only hormonal contraception associated with inhibition of ovulation: either oral, injectable or implantable 3. Intra-uterine device (IUD) 4. Intra-uterine hormone-releasing system (IUS) 5. Bilateral tubal occlusion 6. Vasectomised partner[*2] 7. Sexual abstinence[*3] [*1] Male or female condom with or without spermicide is not an acceptable method of contraception alone.

*2 Vasectomised partner is a highly effective birth control method provided that partner is the sole sexual partner of the woman of childbearing potential trial participant and that the vasectomised partner has received medical assessment of the surgical success.
*3 In the context of this guidance sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the IMPs. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the participant.
*4 A woman is considered of childbearing potential (WOCBP), i.e., fertile, following menarche and until becoming post-menopausal unless permanently sterile. Permanent sterilisation methods include hysterectomy, bilateral salpingectomy and bilateral oophorectomy.
A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy. However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.
For the purpose of this document, a man is considered fertile after puberty unless permanently sterile by bilateral orchidectomy.

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 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 first administration of IMP.
    - For targeted hormone therapy within 14 days of 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 first administration of IMP.

Module 2
In addition to the core exclusion criteria if participants being considered for enrolment in Module 2 meet any of the applicable exclusion criteria listed below, they will be ineligible for the trial:

Arm 1

1. 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 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 first administration of IMP.
Trial Duration Per Participant:	IMP(s) will be administered until disease progression, unacceptable toxicity or withdrawal of consent. In Module 2, in the event the combination treatment is stopped due to toxicity, completion of regimen, participant request or PI decision, treatment with MDX-124 may continue until there is evidence of disease progression, unacceptable toxicity or at the participant's request. Participants discontinuing MDX-124 with no radiological evidence of disease progression will receive scans every 8 weeks (±7 days) from their prior scan. This will continue for a maximum duration of 6 months or until disease progression, initiation of a new treatment, withdrawal of consent, lost to follow up or death in order to determine duration of overall response and PFS. After disease progression primary care givers of participants with evidence of disease progression as defined by RECIST version 1.1 criteria will be contacted at regular intervals (every 6 months ±7 days) until death, loss to follow-up, or trial discontinuation in order to determine median overall survival. Follow-up will be restricted to 12 weeks in Module 1 and 12 months in Module 2.

5 SUMMARY SCHEDULE OF EVENTS

5.1 Module 1 Dose Escalation: MDX-124 dosing (14-day cycle)

Trial Assessments[1]	Screening	MDX-124 (Cycle Duration 14 days)				End of Treatment[2]	28 Day Follow-up Visit (±7 days)	Survival Follow-up Q6 months. (±7 days)
		Cycle 1 and 2		Cycle 3 Onwards				
	Days -28 to 0	D1 (Baseline)	D8 (±1)	D1 (±1)	D8 (±1)			
Informed consent (Including pregnancy counselling)	X							
Inclusion/exclusion criteria	X							
Registration	X							
Demographic data	X							
Previous medical history	X							
Concomitant medication	X	X	X	X		X	X	
Physical examination[3]	X	X		X		X		
ECOG performance status	X	X		X		X		
Vital signs and weight[4]	X	X	X	X		X		
ECG [5]	X	X		X		X		
Pregnancy test[6]	X	X		X		X		
Haematology[7]	X[22]	X[22]	X	X		X	X	
Serum chemistry[8]	X[22]	X[22]	X	X		X	X	
Coagulation profile[9]	X[22]	X[22]		X		X		
Urinalysis[10]	X	X		X		X		
Viral serology sample[11]	X							
Serum tumour marker sample[12]		X		X		X		
Serum for cytokine/pro-inflammatory panel[13]		X		X		X	X	
PK serum samples[14]		X	X[23]	X[21]	X[24]			
Immunophenotype/ TBNK and WBC sample[15]		X	X[23]	X		X	X	
Serum immunogenicity/ ADA sample[16]		X		X		X	X	
Serum annexin-A1 sample[17]	X	X	X[23]	X		X	X	
Radiologic tumour assessment (CT / MRI)[18]	X	Scans performed at Screening then end of cycle 4, 8, and every subsequent 4th cycle (±7 days) until disease progression, regardless of cycle. CRs and PRs must be confirmed by repeated images at least 4 weeks after initial documentation.						
MDX-124 administration		X		X				
AEs/SAEs	X	X	X	X		X	X	
Survival phone call[19]								X
Archived sample[20]	X							

1. Assessments scheduled on days of dosing should be done prior to MDX-124 administration, unless otherwise specified. Safety lab assessments may be performed up to 24 hours prior to MDX-124 administration.
2. End of treatment visit to be approximately 7 days (± 1 days) following last MDX-124 dose.
3. A full physical exam should be performed at screening. For all subsequent visits the physical exam should be symptom driven.
4. Vital signs include height (baseline only) respiration rate, pulse, temperature and resting supine blood pressure. Weight should be recorded at baseline, Day 1 of every cycle and at end of treatment visit.
5. Additional ECGs post baseline should be performed during the trial only if clinically indicated.
6. Female participants of childbearing potential must have a negative serum pregnancy test at screening and a negative urine pregnancy test within 24 hours prior to MDX-124 administration. A urine pregnancy test should be performed within 24 hours prior to MDX-124 administration on Day 1 of each subsequent Cycle. A serum pregnancy test should be performed at the End of Treatment visit. A woman is considered of childbearing potential (WOCBP), i.e. fertile, following menarche and until becoming post-menopausal unless permanently sterile. Permanent sterilisation methods include hysterectomy, bilateral salpingectomy and bilateral oophorectomy. A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy. However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.
7. Haematology includes white blood cell (WBC) count, lymphocyte count, absolute neutrophil count (ANC), red blood cell count (RBC), haemoglobin, haematocrit and platelet count.
8. Serum chemistry incudes sodium, potassium, magnesium, urea or blood urea nitrogen, creatinine, glucose, phosphate, total protein, albumin, adjusted calcium, total bilirubin, bicarbonate, chloride, uric acid, alkaline phosphatase, AST, ALT and LDH.
9. Either prothrombin time (PT) or international normalised ratio (INR) may be measured, depending on institutional standards.
10. Urinalysis includes pH, specific gravity, ketones, leukocytes, protein, glucose, bilirubin, urobilinogen and occult blood. Dipstick testing is acceptable.
11. Sample for HIV, Hepatitis B and C to confirm eligibility. Anti-HIV antibody, Hepatitis B surface antigen and anti-hepatitis C antibody tests to be performed.
12. Serum Tumour Marker Sample to be collected pre dose if applicable.
13. Cytokine (pro-inflammatory) sample to be collected on Cycle 1 Day 1 pre dose, T1 +1hr and T1 +4hr. Pre dose sample to be collected on Cycle 2 Day 1 and pre dose on Day 1 of all subsequent cycles. Sample also collected at end of treatment and follow-up visits.

14. Timepoints for population PK on 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. Participants are not required to stay overnight in hospital. PK samples collected on the day of infusion should have a +/- 5 minutes window and for samples collected at 24 hrs onwards a +/- 1 hour window can be applied.

15. Immunophenotyping (TBNK and WBC) sample to be collected on Cycle 1 Day 1 pre dose, T1 +4hr and T1 +168hr (Day 8). Pre dose sample to be collected on Cycle 2 Day 1 and pre dose on Day 1 of all subsequent cycles. Sample also collected at end of treatment and follow-up visits.

16. Serum immunogenicity (ADA) sample to be collected pre dose on Day 1 of all cycles. Sample also collected at end of treatment and follow-up visits.

17. Serum ANXA1 sample to be collected on Cycle 1 Day 1 pre dose, T1 +1hr, T1 +4hr, T1+24hr and T1 +168hr (Day 8). Pre dose sample to be collected on Cycle 2 Day 1 and pre dose on Day 1 of all subsequent cycles. Sample also collected at end of treatment and follow-up visits.

18. Baseline imaging of the thorax, abdomen and pelvis is required within 28 days prior to registration. CT and MRI scans are acceptable. In selected situations, combination of CT/MRI is acceptable (i.e., CT of chest, MRI of abdomen). The same imaging modalities for each anatomic component must be continued throughout the duration of the trial. Objective responses using RECIST version 1.1 must be confirmed by repeat assessment performed ≥4 weeks after initial documentation of response. Progressive disease should be confirmed by scan prior to stopping MDX-124.

19. The primary physicians of participants with evidence of disease progression as defined by RECIST version 1.1 criteria may receive a phone call at regular intervals (every 6 months ±7 days) until death, loss to follow-up or consent withdrawal. Status can be confirmed through the participant's GP or the appropriate sources of medical records. Capped at 12 weeks for participants in Module 1.

20. Original diagnostic block may be requested by sponsor if molecular profiling is required to understand further any response to MDX-124.

21. Timepoints for population PK on 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. PK samples collected on the day of infusion should have a +/- 5 minutes window and for samples collected at 24 hrs onwards a +/- 1 hour window can be applied.

22. If screening samples are collected within 14 days of Cycle 1 Day 1 haematology, serum chemistry and coagulation do not need to be collected at Cycle 1 Day 1. If not, these should be repeated prior to dosing on Cycle 1 Day 1.

23. Cycle 1 Day 8 only. Not required at Cycle 2 Day 8.

24. Cycle 4 Day 8 only. PK sample Post Infusion (T1) +168hr (Day 8) collected.

5.2 Module 1 Dose Expansion: MDX-124 dosing (21-day cycle)

Trial Assessments[1]	Screening	MDX-124 (Cycle Duration 21 days) All Cycles			End of Treatment[2]	28 Day Follow-up Visit (±7 days)	Survival Follow-up Q6 months. (±7 days)
	Days -28 to 0	D1 ((C1D1 - Baseline)	D8 (±1)[22,23]	D15 (±1)[22,23]			
Informed consent (Including pregnancy counselling)	X						
Inclusion/exclusion criteria	X						
Registration	X						
Demographic data	X						
Previous medical history	X						
Concomitant medication	X	X	X[22]	X[22]	X	X	
Physical examination[3]	X	X			X		
ECOG performance status	X	X			X		
Vital signs and weight[4]	X	X	X[22]	X[22]	X		
ECG [5]	X	X			X		
Pregnancy test[6]	X	X			X		
Haematology[7]	X[21]	X[21]	X[22]	X[23]	X	X	
Serum chemistry[8]	X[21]	X[21]	X[22]	X[22]	X	X	
Coagulation profile[9]	X[21]	X[21]			X		
Urinalysis[10]	X	X			X		
Viral serology sample[11]	X						
Serum tumour marker sample[12]		X			X		
PK serum samples[13,20]		X[13,20,23]	X[23]	X[23]			
Immunophenotype/ TBNK and WBC sample[14]		X[14]	X[22]		X	X	
Serum immunogenicity/ ADA sample[15]		X			X	X	
Serum annexin-A1 sample[16]	X	X			X	X	
Radiologic tumour assessment (CT / MRI) [17]	X	Scans performed at Screening then end of cycle 3, 6, and every subsequent 3rd cycle (±7 days) until disease progression, regardless of cycle. CRs and PRs must be confirmed by repeated images at least 4 weeks after initial documentation.					
MDX-124 administration		X					
AEs/SAEs	X	X	X[22]	X[22]	X	X	
Survival phone call[18]							X
Archived sample[19]	X						

1. Assessments scheduled on days of dosing should be done prior to MDX-124 administration, unless otherwise specified. Safety lab assessments may be performed up to 24 hours prior to MDX-124 administration.
2. End of treatment visit to be approximately 7 days (± 1 days) following last MDX-124 dose.
3. A full physical exam should be performed at screening. For all subsequent visits the physical exam should be symptom driven.
4. Vital signs include height (baseline only) respiration rate, pulse, temperature and resting supine blood pressure. Weight should be recorded at baseline, Day 1 of every cycle and at end of treatment visit.
5. Additional ECGs post baseline should be performed during the trial only if clinically indicated.
6. Female participants of childbearing potential must have a negative serum pregnancy test at screening and a negative urine pregnancy test within 24 hours prior to MDX-124 administration. A urine pregnancy test should be performed within 24 hours prior to MDX-124 administration on Day 1 of each subsequent Cycle. A serum pregnancy test should be performed at the End of Treatment visit. A woman is considered of childbearing potential (WOCBP), i.e. fertile, following menarche and until becoming post-menopausal unless permanently sterile. Permanent sterilisation methods include hysterectomy, bilateral salpingectomy and bilateral oophorectomy. A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy. However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.
7. Haematology includes white blood cell (WBC) count, lymphocyte count, absolute neutrophil count (ANC), red blood cell count (RBC), haemoglobin, haematocrit and platelet count.
8. Serum chemistry incudes sodium, potassium, magnesium, urea or blood urea nitrogen, creatinine, glucose, phosphate, total protein, albumin, adjusted calcium, total bilirubin, bicarbonate, chloride, uric acid, alkaline phosphatase, AST, ALT and LDH.
9. Either prothrombin time (PT) or international normalised ratio (INR) may be measured, depending on institutional standards.
10. Urinalysis includes pH, specific gravity, ketones, leukocytes, protein, glucose, bilirubin, urobilinogen and occult blood. Dipstick testing is acceptable.
11. Sample for HIV, Hepatitis B and C to confirm eligibility. Anti-HIV antibody, Hepatitis B surface antigen and anti-hepatitis C antibody tests to be performed.
12. Serum Tumour Marker Sample to be collected pre dose if applicable.
13. Timepoints for population PK on 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. Participants are not required to stay overnight in hospital. PK samples collected on the day of infusion should

have a +/- 5 minutes window and for samples collected at 24 hrs onwards a +/- 1 hour window can be applied.

14. Immunophenotyping (TBNK and WBC) sample to be collected on Cycle 1 Day 1 pre dose, T1 +4hr, T1 +24hr and T1 +168hr (Day 8). Pre dose sample to be collected on Cycle 2 Day 1 and pre dose on Day 1 of all subsequent cycles. Sample also collected at end of treatment and follow-up visits.

15. Serum immunogenicity (ADA) sample to be collected pre dose on Day 1 of all cycles. Sample also collected at end of treatment and follow-up visits.

16. Serum ANXA1 sample to be collected pre dose on Day 1 of each Cycle, at end of treatment visit and follow-up visit.

17. Baseline imaging of the thorax, abdomen and pelvis is required within 28 days prior to registration. CT and MRI scans are acceptable. In selected situations, combination of CT/MRI is acceptable (i.e., CT of chest, MRI of abdomen). The same imaging modalities for each anatomic component must be continued throughout the duration of the trial. Objective responses using RECIST version 1.1 must be confirmed by repeat assessment performed ≥4 weeks after initial documentation of response. Progressive disease should be confirmed by scan prior to stopping MDX-124.

18. The primary physicians of participants with evidence of disease progression as defined by RECIST version 1.1 criteria may receive a phone call at regular intervals (every 6 months ±7 days) until death, loss to follow-up or consent withdrawal. Status can be confirmed through the participant's GP or the appropriate sources of medical records. Capped at 12 weeks for participants in Module 1.

19. Original diagnostic block may be requested by sponsor if molecular profiling is required to understand further any response to MDX-124.

20. Timepoints for population PK on 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. PK samples collected on the day of infusion should have a +/- 5 minutes window and for samples collected at 24 hrs onwards a +/- 1 hour window can be applied.

21. If screening samples are collected within 14 days of Cycle 1 Day 1 haematology, serum chemistry and coagulation do not need to be collected at Cycle 1 Day 1. If not, these should be repeated prior to dosing on Cycle 1 Day 1.

22. Cycle 1 only. Not required at any other cycles.

23. Cycle 1 and 3 only. Not required at any other cycles

5.3 Module 2 Arm 1: MDX-124 dosing with gemcitabine and nab-paclitaxel (28-day cycle)

Trial Assessments[1]	Screening	All Cycles (Cycle Duration 28 days)				End of Treatment[2]	28 Day Follow-up Visit (±7 days)	Survival Follow-up Q6 months. (±7 days)
	Days -28 to 0	D1 (Baseline)	D8 (±1)	D15 (±1)	D22 (±1)[3]			
Informed consent (Including pregnancy counselling)	X							
Inclusion/exclusion criteria	X							
Registration	X							
Demographic data	X							
Previous medical history	X							
Concomitant medication	X	X	X	X	X	X	X	
Physical examination[4]	X	X				X		
ECOG performance status	X	X				X		
Vital signs and weight[5]	X	X	X	X	X	X		
ECG[6]	X	X				X		
Pregnancy test[7]	X	X				X		
Haematology[8]	X[24]	X[24]	X	X	X	X	X	
Serum chemistry[9]	X[24]	X[24]	X	X	X	X	X	
Coagulation profile[10]	X[24]	X[24]				X		
Urinalysis[11]	X	X				X		
Viral serology sample[12]	X							
Serum tumour marker sample[13]		X				X		
PK serum samples[14 21]		X[23]	X[23]	X[23]				
Immunophenotype/ TBNK and WBC sample[15]		X[15]	X[22]			X	X	
Serum immunogenicity/ ADA sample[16]		X				X	X	
Serum annexin-A1 sample[17]	X	X				X	X	
Radiologic tumour assessment (CT / MRI)[18]	X	Scans performed at Screening then end of cycle 2, 4, and every subsequent 2nd cycle (±7 days) until disease progression, regardless of cycle. CRs and PRs must be confirmed by repeated images at least 4 weeks after initial documentation.						
MDX-124 administration		X		X				
Gemcitabine and Nab-paclitaxel administration		X	X	X				
AEs/SAEs	X	X	X	X	X	X	X	
Survival phone call[19]								X
Archived sample[20]	X							
Tumour biopsy	X[26]			X[26]				

1. Assessments scheduled on days of dosing should be done prior to IMP administration, unless otherwise specified. Safety lab assessments may be performed up to 24 hours prior to IMP administration.
2. End of treatment visit to be approximately 7 days (± 1 days) following last IMP dose.
3. Day 22 is only required for Cycle 1.
4. A full physical exam should be performed at screening. For all subsequent visits the physical exam should be symptom driven.
5. Vital signs include height (baseline only) respiration rate, pulse, temperature and resting supine blood pressure. Weight should be recorded at baseline, Day 1 of every cycle and at end of treatment visit.
6. Additional ECGs post baseline should be performed during the trial only if clinically indicated.
7. Female participants of childbearing potential must have a negative serum pregnancy test at screening and a negative urine pregnancy test within 24 hours prior to IMP administration. A urine pregnancy test should be performed within 24 hours prior to IMP administration on Day 1 of each subsequent Cycle. A serum pregnancy test should be performed at the End of Treatment visit. A woman is considered of childbearing potential (WOCBP), i.e. fertile, following menarche and until becoming post-menopausal unless permanently sterile. Permanent sterilisation methods include hysterectomy, bilateral salpingectomy and bilateral oophorectomy. A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy. However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.
8. Haematology includes white blood cell (WBC) count, absolute neutrophil count (ANC), lymphocyte count, red blood cell count (RBC), haemoglobin, haematocrit and platelet count.
9. Serum chemistry incudes sodium, potassium, magnesium, urea or blood urea nitrogen, creatinine, glucose, phosphate, total protein, albumin, adjusted calcium, total bilirubin, bicarbonate, chloride, uric acid, alkaline phosphatase, AST, ALT and LDH.
10. Either prothrombin time (PT) or international normalised ratio (INR) may be measured, depending on institutional standards.
11. Urinalysis includes pH, specific gravity, ketones, leukocytes, protein, glucose, bilirubin, urobilinogen and occult blood. Dipstick testing is acceptable.
12. Sample for HIV, hepatitis B and C to confirm eligibility. Anti-HIV antibody, hepatitis B surface antigen and anti-hepatitis C antibody tests to be performed.
13. Sample to be collected pre dose if applicable.
14. Timepoints for population PK on 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. Participants are not required to stay overnight in hospital. PK samples collected on the day of infusion should have a +/- 5

minutes window and for samples collected at 24 hrs onwards a +/- 1 hour window can be applied.

15. Immunophenotyping (TBNK and WBC) sample to be collected on Cycle 1 Day 1 pre dose, T1 +4hr and T1 +24hr. Pre dose sample to be collected on Cycle 1 Day 8 and pre dose on Day 1 of all subsequent cycles. Sample also collected at end of treatment and follow-up visits.

16. Serum immunogenicity (ADA) sample to be collected pre-dose on Day 1 of all cycles. Sample also collected at Cycle 1 Day 15, Cycle 3 day 15, end of treatment and follow-up visits.

17. Serum ANXA1 sample to be collected pre dose on Day 1 of each Cycle, at end of treatment visit and follow-up visit.

18. Baseline imaging of the thorax, abdomen and pelvis is required within 28 days prior to registration. CT and MRI scans are acceptable. In selected situations, combination of CT/MRI is acceptable (i.e., CT of chest, MRI of abdomen). The same imaging modalities for each anatomic component must be continued throughout the duration of the trial. Objective responses using RECIST version 1.1 must be confirmed by repeat assessment performed ≥4 weeks after initial documentation of response. Progressive disease should be confirmed by scan prior to stopping IMP.

19. The primary physicians of participants with evidence of disease progression as defined by RECIST version 1.1 criteria may receive a phone call at regular intervals (every 6 months ±7 days) until death, loss to follow-up or consent withdrawal. Status can be confirmed through the participant's GP or the appropriate sources of medical records. Capped at 12 months in Module 2.

20. Original diagnostic block may be recalled if this is collected prior to the fresh tissue biopsy that is performed as part of the study.

21. Timepoints for population PK on 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. PK samples collected on the day of infusion should have a +/- 5 minutes window and for samples collected at 24 hrs onwards a +/- 1 hour window can be applied.

22. Cycle 1 only

23. Cycle 1 and Cycle 3 only. Samples collected pre dose.

24. If screening samples are collected within 14 days of Cycle 1 Day 1 haematology, serum chemistry and coagulation do not need to be collected at Cycle 1 Day 1. If not, these should be repeated prior to dosing on Cycle 1 Day 1.

25. The fresh tissue biopsy may be obtained when the diagnostic sample is collected. Therefore, this can be collected prior to the 28-day screening window starting.

26. Biopsy to be collected at the end of Cycle 2 only.

5.4 Module 2 Arm 2: MDX-124 dosing (14-day cycle)

Trial Assessments[1]	Screening	MDX-124 (Cycle Duration 14 days)				End of Treatment[2]	28 Day Follow-up Visit (±7 days)	Survival Follow-up Q6 months. (±7 days)
		Cycle 1		Cycle 2 Onwards				
	Days -28 to 0	D1 (Baseline)	D8 (±1)	D1 (±1)	D8 (±1)			
Informed consent (Including pregnancy counselling)	X							
Inclusion/exclusion criteria	X							
Registration	X							
Demographic data	X							
Previous medical history	X							
Concomitant medication	X	X	X	X		X	X	
Physical examination[3]	X	X		X		X		
ECOG performance status	X	X		X		X		
Vital signs and weight[4]	X	X	X	X		X		
ECG[5]	X	X		X		X		
Pregnancy test[6]	X	X		X		X		
Haematology[7]	X[21]	X[21]	X	X		X	X	
Serum chemistry[8]	X[21]	X[21]	X	X		X	X	
Coagulation profile[9]	X[21]	X[21]		X		X		
Urinalysis[10]	X	X		X		X		
Viral serology sample[11]	X							
Serum tumour marker sample[12]		X		X		X		
PK serum samples[13]		X	X[22]	X[20]	X[23]			
Immunophenotype/ TBNK and WBC sample[14]		X[14]	X[22]	X		X	X	
Serum immunogenicity/ ADA sample[15]		X		X		X	X	
Serum annexin-A1 sample[16]	X	X		X		X	X	
Radiologic tumour assessment (CT / MRI)[17]	X	Scans performed at Screening then end of cycle 4, 8, and every subsequent 4th cycle (±7 days) until disease progression, regardless of cycle. CRs and PRs must be confirmed by repeated images at least 4 weeks after initial documentation.						
MDX-124 administration		X		X				
AEs/SAEs	X	X	X	X		X	X	
Survival phone call[18]								X
Archived sample[19]	X							
Tumour Biopsy	X[24]			X[25]				

1. Assessments scheduled on days of dosing should be done prior to MDX-124 administration, unless otherwise specified. Safety lab assessments may be performed up to 24 hours prior to MDX-124 administration.
2. End of treatment visit to be approximately 7 days (± 1 days) following last MDX-124 dose.
3. A full physical exam should be performed at screening. For all subsequent visits the physical exam should be symptom driven.
4. Vital signs include height (baseline only) respiration rate, pulse, temperature and resting supine blood pressure. Weight should be recorded at baseline, Day 1 of every cycle and at end of treatment visit.
5. Additional ECGs post baseline should be performed during the trial only if clinically indicated.
6. Female participants of childbearing potential must have a negative serum pregnancy test at screening and a negative urine pregnancy test within 24 hours prior to MDX-124 administration. A urine pregnancy test should be performed within 24 hours prior to MDX-124 administration on Day 1 of each subsequent Cycle. A serum pregnancy test should be performed at the End of Treatment visit. A woman is considered of childbearing potential (WOCBP), i.e. fertile, following menarche and until becoming post-menopausal unless permanently sterile. Permanent sterilisation methods include hysterectomy, bilateral salpingectomy and bilateral oophorectomy. A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy. However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.
7. Haematology includes white blood cell (WBC) count, lymphocyte count, absolute neutrophil count (ANC), red blood cell count (RBC), haemoglobin, haematocrit and platelet count.
8. Serum chemistry incudes sodium, potassium, magnesium, urea or blood urea nitrogen, creatinine, glucose, phosphate, total protein, albumin, adjusted calcium, total bilirubin, bicarbonate, chloride, uric acid, alkaline phosphatase, AST, ALT and LDH.
9. Either prothrombin time (PT) or international normalised ratio (INR) may be measured, depending on institutional standards.
10. Urinalysis includes pH, specific gravity, ketones, leukocytes, protein, glucose, bilirubin, urobilinogen and occult blood. Dipstick testing is acceptable.
11. Sample for HIV, Hepatitis B and C to confirm eligibility. Anti-HIV antibody, Hepatitis B surface antigen and anti-hepatitis C antibody tests to be performed.
12. Serum Tumour Marker Sample to be collected pre dose if applicable.
13. Timepoints for population PK on 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. Participants are not required to stay overnight in hospital. PK samples collected on the day of infusion should have a +/- 5

minutes window and for samples collected at 24 hrs onwards a +/- 1 hour window can be applied.

14. Immunophenotyping (TBNK and WBC) sample to be collected on Cycle 1 Day 1 pre dose, T1 +4hr, T1 +24hr and T1 +168hr (Day 8). Pre dose sample to be collected on Cycle 2 Day 1 and pre dose on Day 1 of all subsequent cycles. Sample also collected at end of treatment and follow-up visits.

15. Serum immunogenicity (ADA) sample to be collected pre dose on Day 1 of all cycles. Sample also collected at end of treatment and follow-up visits.

16. Serum ANXA1 sample to be collected pre dose on Day 1 of each cycle, end of treatment visit and follow-up visit.

17. Baseline imaging of the thorax, abdomen and pelvis is required within 28 days prior to registration. CT and MRI scans are acceptable. In selected situations, combination of CT/MRI is acceptable (i.e., CT of chest, MRI of abdomen). The same imaging modalities for each anatomic component must be continued throughout the duration of the trial. Objective responses using RECIST version 1.1 must be confirmed by repeat assessment performed ≥4 weeks after initial documentation of response. Progressive disease should be confirmed by scan prior to stopping MDX-124.

18. The primary physicians of participants with evidence of disease progression as defined by RECIST version 1.1 criteria may receive a phone call at regular intervals (every 6 months ±7 days) until death, loss to follow-up or consent withdrawal. Status can be confirmed through the participant's GP or the appropriate sources of medical records. Capped at 12 months for participants in Module 2.

19. Original diagnostic block may be requested by sponsor if molecular profiling is required to understand further any response to MDX-124.

20. Timepoints for population PK on 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. PK samples collected on the day of infusion should have a +/- 5 minutes window and for samples collected at 24 hrs onwards a +/- 1 hour window can be applied.

21. If screening samples are collected within 14 days of Cycle 1 Day 1 haematology, serum chemistry and coagulation do not need to be collected at Cycle 1 Day 1. If not, these should be repeated prior to dosing on Cycle 1 Day 1.

22. Cycle 1 Day 8 only.

23. Cycle 4 Day 8 only. PK sample Post Infusion (T1) +168hr (Day 8) collected.

24. The fresh tissue biopsy may be obtained when the diagnostic sample is collected. Therefore, this can be collected prior to the 28-day screening window starting.

25. Biopsy should be collected at the end of Cycle 4 only.

6 TRIAL SCHEMA

Figure 1: Overall Trial Schema

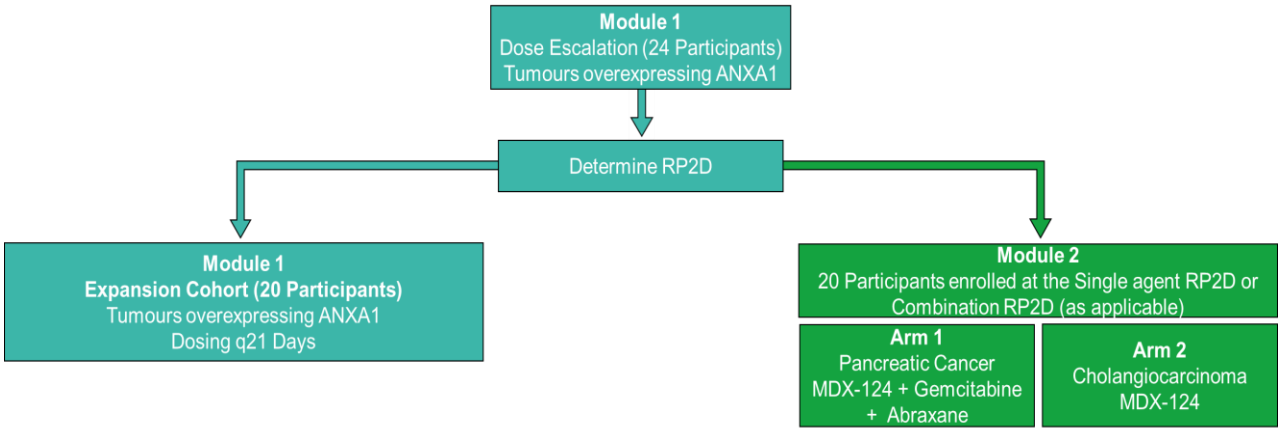
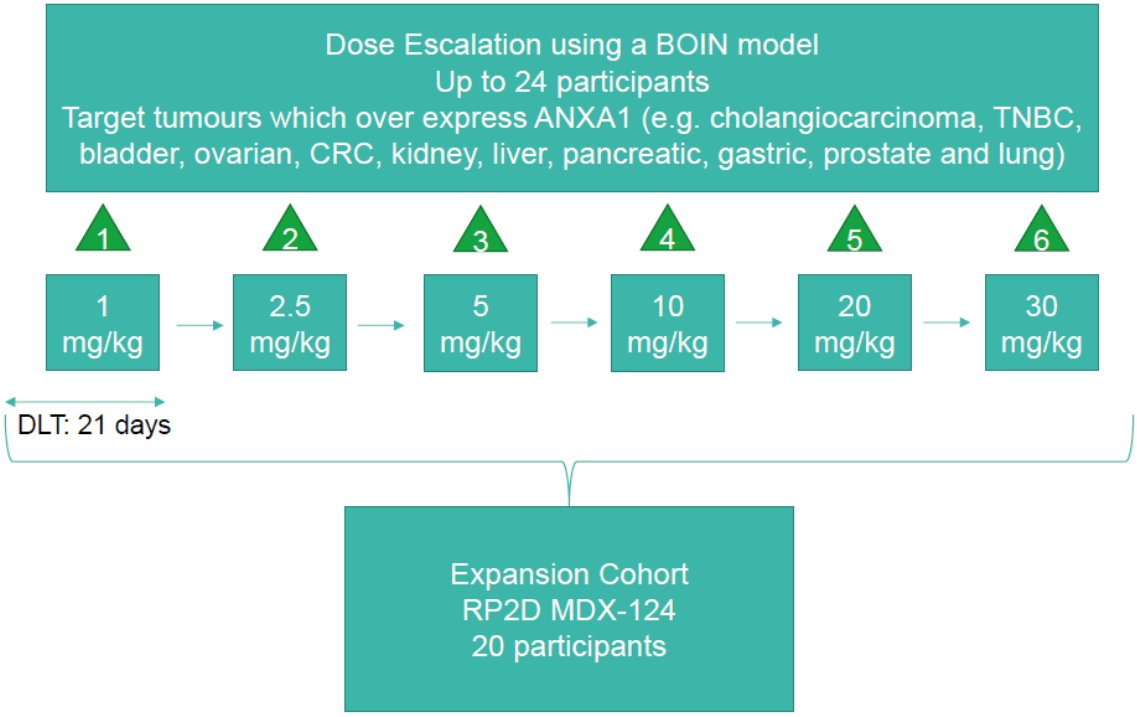


Figure 2: Module 1 Dose Escalation



7 ABBREVIATIONS

°C	Degrees Centigrade
ADA	Anti-Drug Antibodies
ADCC	Antibody-Dependent Cell-Mediated Cytotoxicity
AE	Adverse Event
ALT	Alanine Aminotransferase
ANC	Absolute Neutrophil Count
ANXA1	Annexin A1
aPTT	Activated Partial Thromboplastin Time
AST	Aspartate Aminotransferase
AUC	Area Under the Curve
BOIN	Bayesian Optimal Interval design
BP	Blood Pressure
CA125	Cancer Antigen 125
CI	Chief Investigator
CL	Clearance
C_{max}	Peak Serum Concentration
CNS	Central Nervous System
COG	Clinical Oversight Group
CR	Complete Response
CRC	Colorectal Cancer
eCRF	electronic Case Report Form
CSR	Clinical Study Report
CT	Computed Tomography
CTA	Clinical Trial Authorisation
CTCAE	Common Terminology Criteria for Adverse Events
CVAD	Central Venous Access Device
DCIS	Ductal Carcinoma in Situ
DEC	Dose Escalation Committee
DLT	Dose Limiting Toxicity
DSUR	Drug Safety Update Report
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
ELISA	Enzyme Linked Immunoassay
FFPE	Formalin Fixed Paraffin Embedded
FPR	Formyl Peptide Receptors
GCIG	Gynaecologic Cancer Inter Group
GCP	Good Clinical Practice
GFR	Glomerular Filtration Rate
GLP	Good Laboratory Practice
GP	General Practitioner
HIV	Human Immunodeficiency Virus
HTA	Human Tissue Act
IB	Investigator’s Brochure
ICH	International Conference on Harmonisation
ICH GCP	International Conference on Harmonisation for Good Clinical Practice
IHC	Immunohistochemistry
INR	International normalised ratio
IMP	Investigational Medicinal Product
IUD	Intra-uterine device

IUS	Intra-uterine hormone-releasing system
IV	Intravenous
LCTC	Liverpool Clinical Trials Centre
LDH	Lactate Dehydrogenase
LPLV	Last Participant Last Visit
MHRA	Medicines and Healthcare products Regulatory Agency
MRI	Magnetic Resonance Imaging
MTD	Maximum Tolerated Dose
mTPI	Modified Toxicity Probability Interval
NCI	National Cancer Institute
NHS	National Health Service
NICE	National Institute for Health and Clinical Excellence
NOEL	No Observed Effect Level
PAD	Pharmacological Active Dose
PD-L1	Programmed Death-Ligand 1
PFS	Progression-Free Survival
PI	Principal Investigator
PISC	Patient Information Sheet and Consent
PK	Pharmacokinetic
PR	Partial Response
PT	Prothrombin Time
RBC	Red Blood Cell
REC	Research Ethics Committee
RECIST	Response Evaluation Criteria in Solid Tumours
RP2D	Recommended Phase 2 Dose
RSI	Reference Safety Information
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SAP	Statistical Analysis Plan
SOP	Standard Operating Procedure
SPC	Summary of Product Characteristics
SUSAR	Suspected Unexpected Serious Adverse Reaction
$T_{½}$	Half Life
TNBC	Triple Negative Breast Cancer
UK	United Kingdom
ULN	Upper Limit of Normal
USM	Urgent Safety Measure
V_d	Volume of Distribution
WBC	White Blood Cell

8 BACKGROUND INFORMATION

8.1 Annexin-A1

Annexin-A1 (ANXA1) is a member of the annexin protein superfamily of calcium regulated, phospholipid-dependent membrane binding proteins with 40 to 60% structural homology[1]. Annexins are divided into 5 evolutionarily conserved groups: A to E, found in vertebrates, fungi, moulds, plants and protists, respectively. Group A contains 12 members, A1 to A13 (A12 unassigned). Annexins are involved in a diverse array of cellular activities including growth, proliferation, differentiation, endo- and exocytosis, signal transduction and cell division[2,3].

The human ANXA1 gene is located on chromosome 9q12-q21.2 and codes for a 346 amino acid protein of 37 kDa with a conserved C-terminus domain composed of 4 similar repeating motifs, each approximately 70 amino acids long. The repeats fold into a curved disc, with a slightly convex surface on which multiple calcium- and membrane-binding sites are located. On the concave side, in the absence of calcium, the N-terminus docks near the third repeat. In the presence of calcium, ANXA1 is activated and undergoes a conformational change that releases the N-terminus and enables both phospholipid binding and interactions with formyl peptide receptors 1 and 2 (FPR1/2)[4,5].

ANXA1 is widely expressed in various tissues and cell types including leukocytes, lymphocytes, epithelial and endothelial cells[6]. Experiments in mice have found the highest levels of expression in organs with mucosal tissues (stomach, lungs and uterus) and in hormone releasing organs (ovary, thyroid, pancreas and testes)[7]. ANXA1 is present intracellularly and at the membrane surface but can also be secreted into circulation thereby signalling in both an autocrine, paracrine and juxtacrine manner[8].

ANXA1 is known to modulate the immune system by affecting the function of several types of immune cells including neutrophils[5,9], T-cells[10,11] and macrophages[12]. In addition to its immunomodulatory role, accumulating evidence show that ANXA1 is a key factor in the development and spread of a variety of cancers[1].

8.2 Role of ANXA1 in Cancer

ANXA1, a potent endogenous immunomodulatory protein, is known to play a critical role in the development and progression of certain cancers, although ANXA1 expression varies depending on tumour type, and there are contradictory reports on its role in the regulation of proliferation and tumour growth.

The overexpression of ANXA1 by cancer cells has been demonstrated to increase cell proliferation[13], angiogenesis[14], and migration and invasion[15]. ANXA1 overexpression also enhances metastasis, drug resistance[16] and the development of multiple cancer types including triple-negative breast, colorectal, gastric, hepatocellular, lung, pancreatic[1] and cholangiocarcinoma[43].

ANXA1 expression has been found to be upregulated in tumour tissue versus adjacent or matched non-cancerous tissue in several indications including pancreatic[17], colorectal[18], liver[19], lung[20] and gastric cancer[21]. Furthermore, high levels of ANXA1 expression are often associated with poor patient prognosis and lower overall survival[17,19,21,22]. The consistently high expression of ANXA1 in TNBC and basal-like breast cancer, compared with other breast cancer subtypes, not only serves as a potential diagnostic marker, but also a prognostic marker for poor survival[23].

ANXA1 has also been observed to influence immune cells and the tumour microenvironment by enhancing regulatory T-cell function[24], promoting the activation of tumour-associated macrophages[12], suppressing dendritic cell activation and impairing $CD8^+$ T-cell anti-tumour immunity[25]. Furthermore, ANXA1 is a key component of tumour-derived extracellular vesicles promoting migration, invasion and angiogenesis[26] and is secreted by cancer associated fibroblasts increasing cancer stem cell generation[27].

8.3 MDX-124

MDX-124 is a humanised monoclonal antibody that binds specifically to ANXA1. Studies on ANXA1 activity support a mechanism of action for MDX-124 whereby the antibody blocks the interaction of extracellular and membrane bound forms of ANXA1 with formyl peptide receptors 1 and 2 (FPR1/2), and thus prevent the activation of downstream oncogenic processes that promote cancer cell proliferation and migration (Figure 3). In addition, MDX-124 has been shown to induce antibody-dependent cell-mediated cytotoxicity (ADCC) through binding to ANXA1 present on the surface of cancer cells and triggering effector cells to lyse target cancer cells via Fc gamma receptor (FcγR) mediated activity (Figure 3).

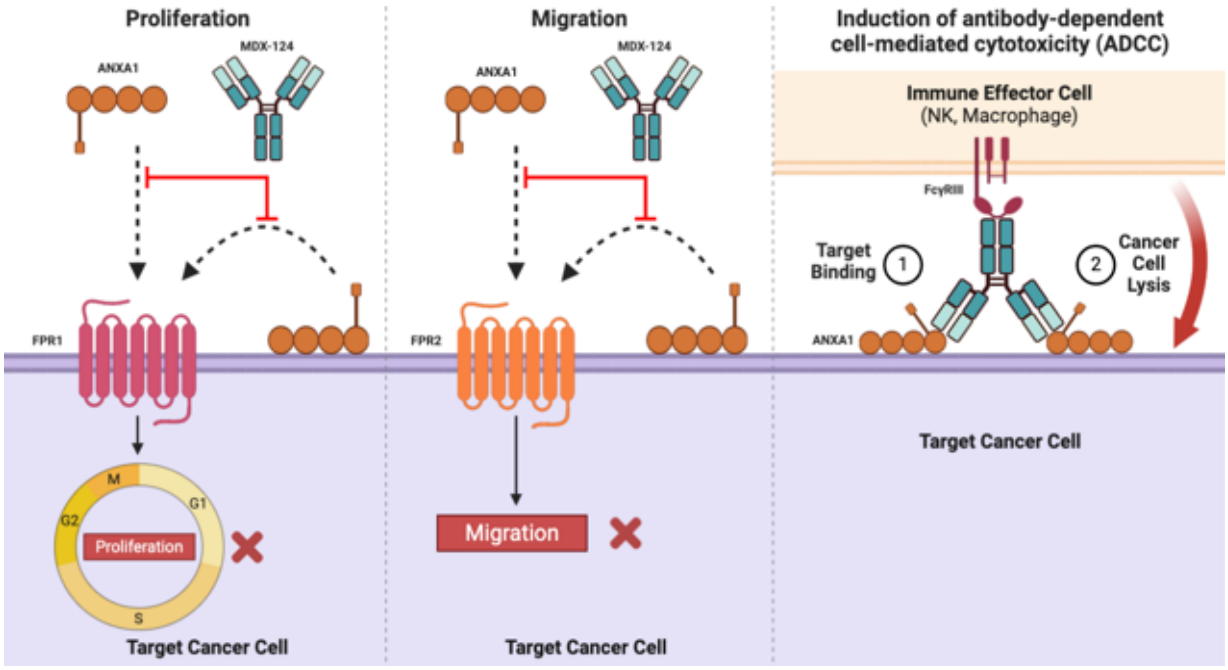


Figure 3: MDX-124 Mechanism of Action

8.4 MDX-124 Non-Clinical Summary

8.4.1 In vivo

MDX-124 (1 mg/kg) was evaluated in the syngeneic, orthotopic, 4T1-luc mouse model BALB/c model of breast cancer (Study 191024-P1650). MDX-124 showed a statistically significant inhibition of tumour growth in mice when compared with vehicle group.

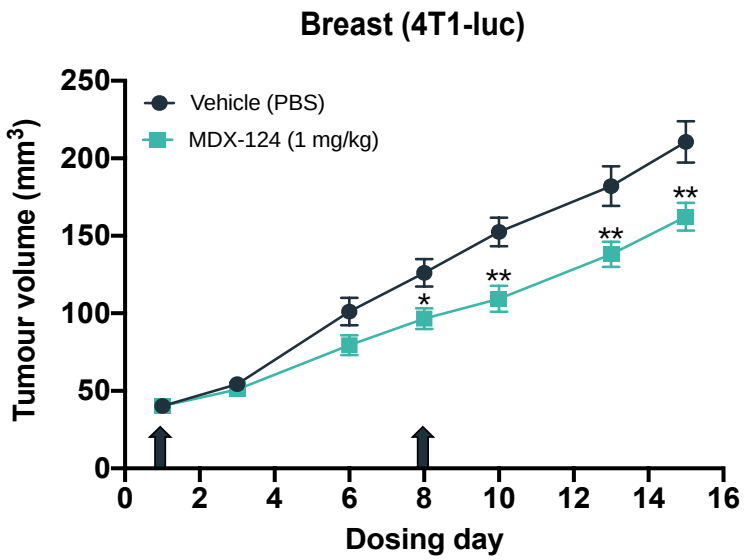


Figure 4: Tumour Growth Significantly Inhibited in Mice Treated with MDX-124

*Arrows indicate day of dosing. Data shown as the mean tumour volume +/- standard error of mean. Statistical significance calculated via 2-tailed unpaired T-test and indicated by *p<0.05 and **p<0.01.*

Whilst MDX-124 had no adverse effects in healthy mice, clinical signs were observed 15 minutes after antibody injection in tumour-bearing mice from the second dose onward, indicating a potential hypersensitivity reaction against the humanised antibody. Similar observations have previously been made in this syngeneic animal model with immuno-oncology therapies e.g., anti-PD1[28, 29].

The Investigator Brochure for MDX-124 provides a detailed summary of MDX-124 in vivo data.

8.4.2 Toxicology

A 4-week dose range finding study with weekly dosing was conducted in male Sprague Dawley rats at doses of 5, 10 and 50 mg/kg (Study E3722-U1902). Each dosing group comprised one male and one female. No study drug effects, nor mortality were observed in the study.

A Good Laboratory Practice (GLP) 4-week repeat dose toxicity study was performed in Han Wistar Rats (Study 515238). The study was split in two phases. A Maximum Tolerated Dose (MTD) phase comprised two males and two females receiving 100 mg/kg for two weeks. The main phase included a control arm and doses of 9.4, 50 and 100 mg/kg with ten males and ten females in each group. Five animals of each sex (in each of the control and 100 mg/kg groups) entered the recovery phase of the study. No study drug effects, nor mortality were observed in the study.

A 4-week dose range finding study was conducted in cynomolgus monkeys at doses of 9.4, 50 and 100 mg/kg (Study 514318). Each dose group comprised one male and one female. No study drug effects nor mortality were observed in the study. Toxicokinetic data demonstrated that exposure in terms of both maximum concentration (C_{max}) and area under the curve ($AUC_{(0-24)}$) increased with dose, and the increase was generally proportional to dose. No strong indication of a significant difference in exposure between male and female animals was observed. No evidence of accumulation was observed, with C_{max} and $AUC_{(0-24)}$ both decreasing on Day 22.

A GLP 4-week repeat dose toxicity study with a 4-week recovery period was performed in male and female cynomolgus monkeys (Study 514339). The study comprised three males and three females at each dose group receiving study drug for four weeks (Days 1, 8, 15, and 22). The dose groups were control and 9.4, 50 and 100 mg/kg MDX-124. In addition, two males and two females (in each of the control and 100 mg/kg groups) entered the recovery phase of the study. No study drug effects, nor mortality were observed in the study.

8.5 Trial Rationale

ANXA1 overexpression has been demonstrated to play a key role in cancer development through enhancing metastasis, drug resistance and the development of multiple cancer types and is therefore a valid target for further investigation.

The non-clinical safety and efficacy data generated on MDX-124 justify a first in human trial:

- GLP toxicology studies in 2 different species demonstrate that MDX-124 can be safely administered at doses up to 100 mg/kg without drug related adverse effects or mortality.
- *In vitro* models have demonstrated anti-proliferative, anti-migratory and ADCC effects.
- MDX-124 inhibits cell viability across a range of cancer cell lines.
- Single agent *in vivo* models have resulted in statistically significant reduction in tumour volume compared to the vehicle control.
- Addition of MDX-124 to gemcitabine and nab-paclitaxel increased tumour growth inhibition. MDX-124 significantly inhibited tumour growth versus capecitabine or vehicle control during maintenance phase post gemcitabine and nab-paclitaxel treatment.

The DEC will have safety oversight of the trial and will be responsible for participant safety oversight, cohort size and dose escalation decisions.

8.6 Risk/Benefit Assessment

8.6.1 Potential Risks

8.6.1.1 MDX-124

MDX-124 has not been used in clinical trials previously. Non-clinical toxicology studies did not demonstrate any study related adverse effects or mortality. The non-clinical pharmacology package has demonstrated activity as a single agent and in combination with anti-cancer treatments in *in vitro* and *in vivo* models. As a result, this first in human clinical trial has been designed to mirror the treatment and clinical assessments carried out as part of standard of care in eligible patients, with additional laboratory assessments to enable further oversight of safety.

The following risk mitigations have been put in place:

- In Module 1 the initial participant dosed at a new dose level will be dosed at a site which is supported by a MHRA accredited Phase 1 unit. This support will include additional governance activities, risk assessments, dose escalation processes and contingency planning. For cohorts of 3 or more participants at a

new increased dose level once the initial participant has been dosed, Liverpool Clinical Trials Centre (LCTC) will inform the other participating sites who have been allocated a slot that they are authorised to dose their participant. The LCTC will coordinate schedules to ensure there is a minimum of a 24-hour gap between the dosing of the initial participant in a cohort and the remaining participants in the cohort in order to observe any reactions and adverse events (AEs).

- The trial will be overseen by a Dose Escalation Committee (DEC) which will be responsible for all dose escalation decisions as outlined in the DEC Charter.
- The upper threshold in the BOIN model used in Module 1 of this study has been lowered to ensure a toxicity level of less than 30%.
- In addition to samples for PK analysis, samples will be collected for cytokine (pro-inflammatory) and immunophenotyping (TBNK and WBC) analysis by a central laboratory.
- 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.
- Participants will be asked to remain at the site for 6 hours post dose on Cycle 1 Day 1 to be observed by study staff.
- Each participant must meet pre-specified dosing criteria for full blood count, renal function and liver function prior to each administration of MDX-124.
- MDX-124 should not be administered to pregnant women. A negative pregnancy test should be confirmed before administration of MDX-124 for all women of childbearing potential.
- Since MDX-124 will be prepared in specialist oncology pharmacies and administered by experienced chemotherapy-trained nurses via IV 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.

8.6.2 Potential Benefits

The participants being enrolled in Module 1 of the study have significant tumour burden and co-morbidities and have exhausted all approved lines of treatment.

ANXA1 overexpression has been demonstrated to increase cell proliferation[14], angiogenesis[15] migration and invasion[16] and enhances metastasis and drug resistance in multiple tumours. If overexpression of ANXA1 can be inhibited considerable therapeutic benefit may be derived.

To date there is limited knowledge of the safety profile of MDX-124 in humans. This study has been designed to reflect the treatment and clinical assessments carried out as part of standard of care in eligible patients. In addition, as this is a first in human clinical trial, additional cytokine (pro-inflammatory) and immunophenotyping (TBNK and WBC) lab tests have been added.

8.6.3 Overall Risk Benefit Assessment

The use of monoclonal antibodies in oncology is well established. In addition, no toxicity signals resulting from MDX-124 administration have been detected in the non-clinical studies performed to date. As such the Chief Investigator has determined that

the proposed mitigations are appropriate for a first in human study in this patient population.

The risk benefit assessment will be reviewed prior to the finalisation of any future substantial amendments.

In relation to Module 2 of the study the above risk benefit analysis remains valid. Based on non-clinical data an increase in toxicity is not expected upon administration of MDX-124 in combination with standard of care chemotherapy. This has been informed by emerging data from Module 1.

Patients derive limited benefit from the current standard of care, but this may be enhanced when used in combination with MDX-124.

8.6.4 Tumour Selection Rationale

8.6.4.1 Module 1

Patients with tumours which are believed to overexpress ANXA1 (e.g., cholangiocarcinoma, TNBC, bladder, ovarian, CRC, kidney, liver, pancreatic, gastric, prostate and lung) will be included in Module 1. No specific testing is required, enrolment is focussed on tumour types with a high probability of overexpressing ANXA1.

Patients with head and neck[31, 32] or cervical[33] cancer will be excluded because there is a low likelihood that MDX-124 is effective in these cancers.

8.6.4.2 Module 2

Evidence demonstrates that ANXA1 expression plays a critical role in chemotherapy/immunotherapy resistance in some tumours[34, 35, 36, 37] with ANXA1 overexpression shown to correlate with 5-FU resistance in colon cancer cells[17]. ANXA1 has also been linked to DNA repair mechanisms with ANXA1-null mouse cells accumulating greater DNA damage and recovering more slowly than cells expressing some ANXA1[38, 39].

One hypothesis for overcoming resistance is to modulate ANXA1 expression back to homeostatic or healthy control levels and re-sensitise the cancer cells to therapy. The Module 2 arm 1 with approved standard of care anti-cancer treatments have been identified as they provide a synergistic or additive activity which complements MDX-124.

Further study of MDX-124 as a single agent in homogenous patient populations is also justified by the fact that MDX-124 has been shown to induce ADCC through binding to ANXA1 present on the surface of cancer cells and triggering effector cells to lyse target cancer cells via FcγR mediated activity (Study MEDN-1330). This activity is supported by preliminary data from Module 1 in patients with cholangiocarcinoma which is outlined in Section 8.6.4.2.2 and the MDX-124 Investigator Brochure.

8.6.4.2.1 Pancreatic Cancer

MDX-124 has shown *in vitro* activity in models of pancreatic cancer:

- Proliferation is reduced in BxPC-3, MIA PaCa-2 and PANC-1 pancreatic cancer cells.

- Localisation via imaging flow cytometry indicates ANXA1 expression in all cell lines tested (BxPC-3, MIA PaCa-2), with a greater extent in BxPC-3.
- MDX-124 reduced cell viability of BxPC-3 pancreatic cancer cells by 82% versus non-treated cells.
- Some impact on cell cycle of MIA PaCa-2 pancreatic cancer cells after MDX-124 treatment versus untreated control cells.
- MDX-124 has also been observed to have synergistic activity when combined with several SOC cancer therapies including, 5-fluorouracil (5-FU) and gemcitabine.

Per NICE guidelines gemcitabine in combination with nab-paclitaxel is established as first line treatment for metastatic pancreatic cancer as an alternative to FOLFIRINOX[42]. In second line treatment gemcitabine-based chemotherapy is recommended for patients whose cancer has progressed after first line FOLFIRINOX. As MDX-124 has demonstrated that it can prevent cancer cell growth and migration, it is feasible to combine it with a combination such as FOLFIRINOX or gemcitabine and nab-paclitaxel which is a well-established inducer of apoptosis.

8.6.4.2.2 Cholangiocarcinoma

MDX-124 has demonstrated clinical activity in patients with cholangiocarcinoma enrolled in the Module 1 dose escalation. As of 1st December 2024, 4 patients diagnosed with cholangiocarcinoma received doses of 10, 20 or 30 mg/kg MDX-124 every 2 weeks. Treatment-related AEs (TRAEs) were reported in all patients, however no grade 3-4 TRAEs or DLTs have been observed. At cut-off, 1 patient had achieved a confirmed partial response, 2 patients had stable disease and 1 patient had progressive disease as Best Overall Response. All 4 patients had received at least 2 prior lines of treatment including a gemcitabine/cisplatin combination and a 5-FU containing regimen and therefore had exhausted all lines of approved therapy.

Per NICE guidelines gemcitabine in combination with cisplatin and durvalumab is the recommended 1st line of treatment for locally advanced, unresectable, or metastatic biliary tract cancer in adults. In the 2nd line, treatments are approved for patients with FGFR2 and IDH1 mutations. However, for patients without a targetable mutation or who progress following treatment with a targeted agent there are limited therapeutic options. FOLFOX is generally accepted as the best 2nd line option, but response rate is limited to 5%, and PFS and OS respectively of 4 and 6.2 months is only slightly better than active symptom control[44].

This clinical data along with the limited treatment options provides justification to further explore the activity of MDX-124 as a single agent in advanced cholangiocarcinoma in the 2nd line setting.

8.6.4.3 Proposed Arms Added By Substantial Amendment

Based on emerging clinical and non-clinical data, additional arms exploring the safety and tolerability of MDX-124 as a single agent or in combination with standard of care treatments may be added by substantial amendment.

A maximum of 2 additional arms will be added. These arms will be consistent with the Module 2 hypothesis stated in 8.6.4.2 and the primary and secondary study objectives. If the arm combines MDX-124 with a standard of care combination treatment, the treatment will be based on the current standard of care at the time of the amendment.

The risk-benefit ratio for each new arm and overall for the trial will be evaluated based on the emerging non-clinical and clinical data.

9 TRIAL OBJECTIVES AND ENDPOINTS

Primary Objective	Endpoints/ Outcome Measures
Module 1 Determine the recommended phase 2 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 and in combination with anti-cancer treatments.	**Module 1** The occurrence (number) of DLTs at each dosing level. **Module 2** Treatment-emergent AEs (per NCI CTCAE v5)
Secondary Objectives	**Endpoints/ Outcome Measures**
Assess the safety and tolerability of MDX-124 when given as a single agent and when given (Module 1).	- Treatment-emergent AEs (per NCI CTCAE v5) (Module 1 only). - Clinically significant laboratory changes (per NCI CTCAE v5). - Changes in physical exam, vital signs and serial ECGs.
Characterise the PK of MDX-124 following single dose and at steady state after multiple doses when given as a single agent and when given in combination with anti-cancer treatments.	- Maximum concentration (C_{max}). - Area under the curve (AUC). - Half-life ($T_{1/2}$). - Volume of distribution (V_d). - Clearance (CL).
Assess evidence of anti-tumour activity of MDX-124 when given as a single agent and when given in combination with anti-cancer treatments.	- Best overall response (per RECIST version 1.1). - Duration of objective response (per RECIST version 1.1). - Progression-free survival (per RECIST version 1.1). - Overall survival.

Exploratory Objectives	Endpoints/ Outcome Measures
Explore the relationship between dose, blood borne and tissue biomarkers.	- Correlation between dose and changes from baseline of blood borne and tissue biomarkers.
Assess host immune response to MDX-124 (immunogenicity and immunophenotyping).	- Changes in white blood cell (WBC) markers from baseline measured by flow cytometry. - Development of an assay to detect and characterise anti-drug antibodies (ADAs) following dosing with MDX-124, if required.
Assess circulating levels of ANXA1 at baseline and after dosing to correlate with response and outcome to MDX-124.	- Changes in levels of circulating ANXA1 as measured by ELISA before and after dosing with MDX-124. - Correlation between post-dose levels of circulating ANXA1 and clinical outcome as defined by RECIST version 1.1.
Assess the impact of MDX-124 on IHC biomarkers (e.g., tumour expression of ANXA1 and immune cell infiltration).	- Evaluation of participant specific tumour tissue before and after dosing with MDX-124 for impact on ANXA1 and expression of pathway-related proteins and mRNA by multiplex IHC and RNAscope.

10 TRIAL DESIGN

This is a modular, multi-arm, first-in-human trial to evaluate the safety, tolerability and efficacy of MDX-124 administered as an IV infusion.

The RP2D is the most appropriate dose that will optimise the risk/benefit. RP2D determination will take into consideration the PK assessments, the nature of the PK relationship, any efficacy signals and any AEs observed during the conduct of the dose-escalation.

In Module 1 a Bayesian optimal interval (BOIN) model will be used to identify the Single Agent RP2D. Dose limiting toxicities (DLTs) will be reported, tracked and reviewed by the DEC to ensure participant safety. Once the Single Agent RP2D has been determined, MDX-124 will be administered every 21 days in the Module 1 expansion cohort.

The Single Agent RP2D will be used in Module 2. Module 2 cannot be opened until the Single Agent RP2D has been determined from Module 1 by the DEC.

Module 2 will evaluate the safety, tolerability and efficacy in selected tumour types. In the arms where MDX-124 is administered in combination with standard of care anti-cancer treatments a Combination RP2D will be determined. DLTs will be reported, tracked and reviewed by the DEC to ensure participant safety. It is anticipated that in each arm approximately 9 participants will be enrolled to determine the Combination RP2D. Further participants will be enrolled in an expansion cohort in each arm until 20 participants have been treated with the selected dose.

In Module 2 when MDX-124 is administered as a single agent it will be administered at the Single Agent RP2D. As the dose has been determined in Module 1 the 3+3 design will not be required, and 20 participants will be enrolled.

10.1 Duration of Participation

Participants will be in the trial treatment until disease progression, unacceptable toxicity occurs or withdrawal of consent. This is estimated at approximately 8 months from start of screening to last protocol visit. Reasons why participants may need to be withdrawn prior to disease progression or unacceptable toxicity occurs are described in Section 13 Participant Withdrawal.

Following the end of treatment visit, participants will be referred to their original oncologist for continuation of care.

After the completion of treatment, if applicable, participants will be followed up every 3 months. The follow-up period will be restricted to 12 weeks in Module 1 and 12 months in Module 2.

10.2 Dosing and Schedule

10.2.1 Dose Rationale

Toxicology studies in non-human primates and rats demonstrated a no observed effect level (NOEL) of 100 mg/kg when MDX-124 was administered weekly via intravenous injection. The observed NOEL (100 mg/kg) was divided by a correction factor of 10 to adjust for species difference and then divided by a further safety factor of 10. The resulting figure equated to a starting human dose of 1 mg/kg.

The pharmacological active dose (PAD) was identified as 1 mg/kg when MDX-124 was administered weekly in mice. The reduction of tumour burden (Figure 5) after 2 doses was statistically significant.

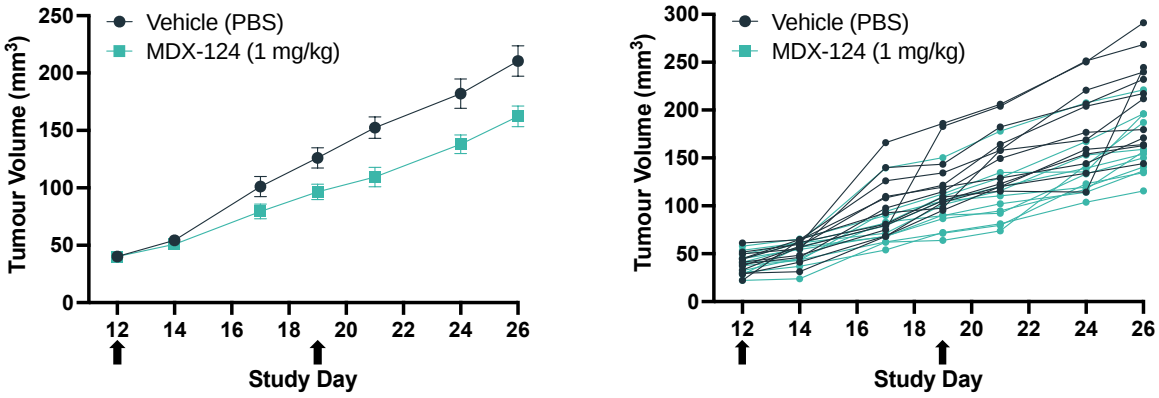


Figure 5: Comparison Tumour Volume after Treatment with MDX-124 at a Dose Level of 1mg/kg Compared with Vehicle Control

When translated to a human dose with a 14-day dosing regimen this equated to 2 mg/kg[41]. With a safety factor of 0.08 for mice the starting dose level would be 0.16 mg/kg administered every 14 days.

However, as the first in human clinical trial is conducted in cancer patients with advanced disease that have exhausted all approved lines of therapy, it is appropriate for the starting dose to be a presumed effective but the lowest pharmacologically active dose. Therefore, a starting dose of 1 mg/kg administered every 14 days has been identified for MDX-124.

A substantial amendment will be submitted for approval if additional higher doses (or steeper dose escalations) than stated in the protocol will be required.

10.2.2 Trial Regimens

10.2.2.1 Module 1

Module 1 will use a BOIN model and will enrol up to 24 evaluable participants. A starting dose of 1 mg/kg with escalations to 2.5, 5, 10, 20 and 30 mg/kg will be performed unless DLTs preclude further escalation. A list of DLTs can be found in Section 10.2.3. Participant cohorts of 1 will be used for the initial doses but will increase to 3, in the event of a DLT or if determined by the DEC per the DEC Charter. The minimum number of participants in subsequent cohorts will be 3 however this may be increased at the discretion of the DEC following a review of the verified safety data. The DEC will have final approval of all dosing decisions.

Upon completion of the 21-day DLT period of at least 3 patients (or 1 patient in a single patient cohort) in each cohort, the DEC will review the verified safety data for all participants in the cohort and agree on the next participant cohort size and dose. To ensure safety data from a minimum of 3 evaluable patients is available for the DEC to make any decisions with regards to future doses the DEC may allocate 4 slots in a cohort. Efficacy and/or PK data may be considered when deciding on dose escalation and cohort size. If the dose should be de-escalated the DEC will have the option to reduce the dose to the prior dose level or to a dose determined by the DEC following their review of the data.

Figure 6: Module 1: Summary of Dose Cohorts

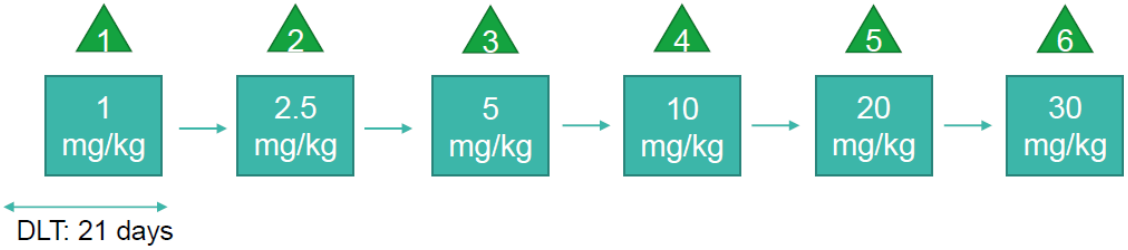
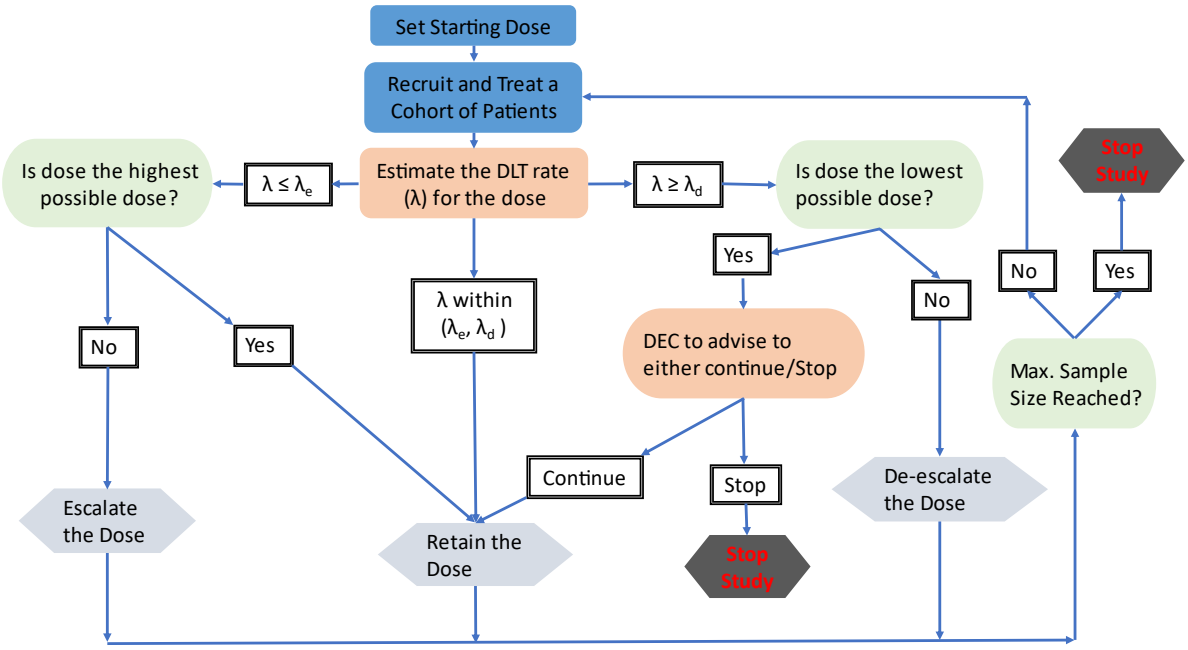


Figure 7: Dose Decision Tree for BOIN Model in Module 1 of the Trial



λe: prespecified dose escalation boundary (λe = 0.236)
λd: prespecified dose de-escalation boundary (λd = 0.333)

The DEC will meet in person, teleconference or via correspondence, and either approve the dose allocation recommendation by the model (Table 1) or select a different dose on the basis of a clinical review of the data.

The trial will stop for safety if after 4 participants have been enrolled and dosed at dose level 1 the DLT rate is greater than the target toxicity level of 30%. The trial may re start following a review by the DEC and approval of a substantial amendment which should include a rationale for amendments to the proposed dosing. The estimated MTD is the highest dose level with observed toxicity rate less than 30%.

Table 1: Module 1 Dose Escalation and De-Escalation Boundaries for Target Toxicity Rate = 30%

	Number of patients treated at the current dose																	
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18
Escalate if # of DLTs ≤	0	0	0	0	1	1	1	1	2	2	2	2	3	3	3	3	4	4
De-escalate if # of DLTs ≥	1	1	1	2	2	2	3	3	3	4	4	4	5	5	5	6	6	6

Participants who are enrolled at lower doses which are viewed to be sub-therapeutic will be given the option to be up titrated to the next dose level if determined by the DEC per the DEC Charter. This may be done once the first cohort of participants at the next dose level have all completed the 21-day DLT evaluation period, and the criteria to enrol additional participants at the same dose or escalate the dose, have been met.

The first cohort of participants enrolled at a new dose level will be dosed at least 1 day apart. If the first cohort at a new dose level comprises only 1 participant and needs to be expanded as the result of a DLT the 2 additional participants should be dosed at least one day apart.

Once up to 24 evaluable participants have competed their DLT period or the DEC has determined that there is adequate data to assess the risk/benefit ratio on MDX-124, the DEC will meet to determine the Single Agent RP2D.

An expansion cohort comprised of an additional 20 participants will be enrolled at the Single Agent RP2D. These participants will be dosed every 21 days. This is justified by the dose proportional increase in the concentration MDX-124 observed in Figure 8. This figure uses patient data from the Module 1 Dose Escalation and demonstrates the presence of MDX-124 prior to dosing at Cycle 2 Day 1, Cycle 4 Day 1 and Cycle 5 Day 1, this combined with a terminal half-life in the order of days for each dose provides a strong rationale for MDX-124 to be dosed effectively every 21 days.

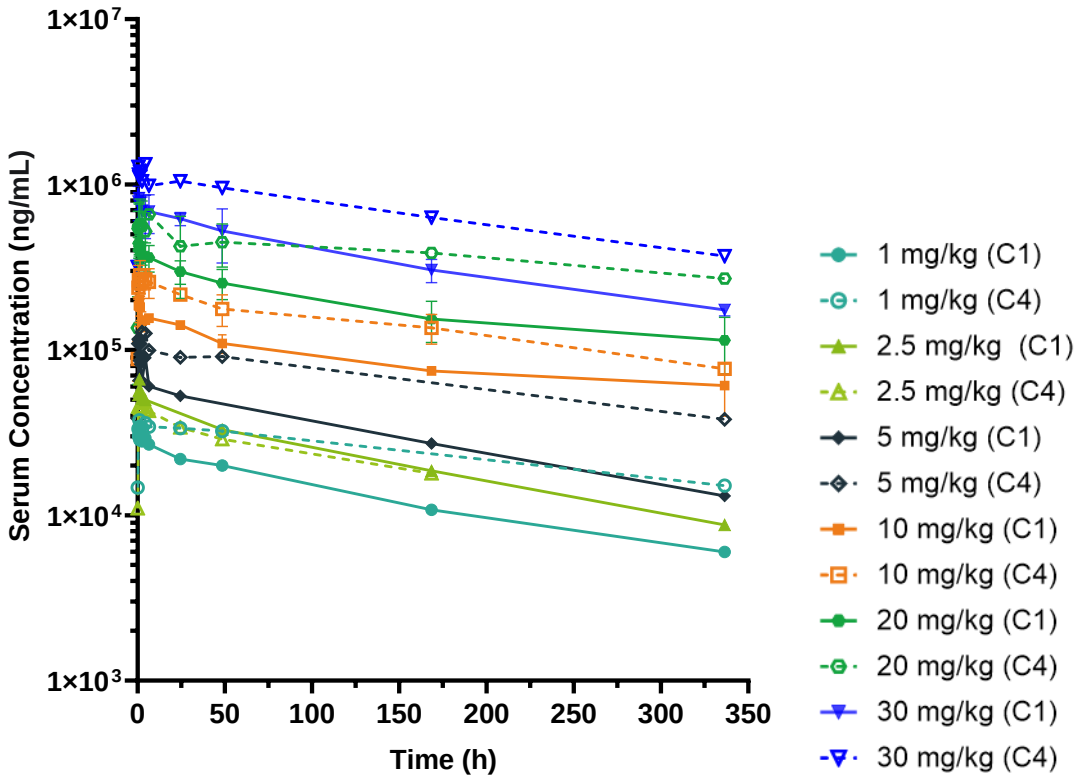


Figure 8: Mean Concentration of MDX-124 Observed in Module 1 Dose Escalation

The DEC will review the data once the 6th participant enrolled in the expansion cohort has completed 1 cycle to determine if the Single Agent RP2D and schedule are appropriate. An additional review later may be conducted by the DEC. All participants who receive a dose will be evaluable for safety. All participants who receive a dose and a post screening scan will be evaluable for efficacy. Participants who are not evaluable for safety may be replaced.

Additional information on the dose escalation process can be found in the DEC charter.

10.2.2.2 Module 2

In Module 2 when MDX-124 is administered in combination with anti-cancer treatments the starting dose will be one dose level below the Single Agent RP2D determined by the DEC (Cohort level '0' in Table 2). The dose of each combination treatment investigated will not exceed their current recommended dose.

When administered as a single agent MDX-124 will be administered at the Single Agent RP2D. As the dose has been determined in Module 1 the 3+3 design will not be required, and 20 participant expansion cohort will be enrolled. In the event the DEC determine that a dose reduction is required the dose can be reduced by 25% of the Single Agent RP2D with a further reduction to 50% of the Single Agent RP2D if required.

Table 2: Module 2: Summary of Dose Cohorts when Dosing in Combination

Cohort Level	Number of Participants	Dose Levels
-2	3-6	- MDX-124: 50% of 2 dose levels below Single Agent RP2D - 1000mg/m^2 gemcitabine - 125mg/m^2 nab-paclitaxel
-1	3-6	- MDX-124: 2 dose levels below Single Agent RP2D - 1000mg/m^2 gemcitabine - 125mg/m^2 nab-paclitaxel
0 (Starting Dose)	3-6	- MDX-124: 1 dose level below Single Agent RP2D - 1000mg/m^2 gemcitabine - 125mg/m^2 nab-paclitaxel
1	3-6	- MDX-124 at Single Agent RP2D - 1000mg/m^2 gemcitabine - 125mg/m^2 nab-paclitaxel
Module 2 Expansion	14	- MDX-124 at Combination RP2D determined by DEC - 1000mg/m^2 gemcitabine - 125mg/m^2 nab-paclitaxel

Figure 9 outlines the standard decision-making algorithm for dose level expansion or dose escalation used in the 3+3 design used in Module 2, Arm 1.

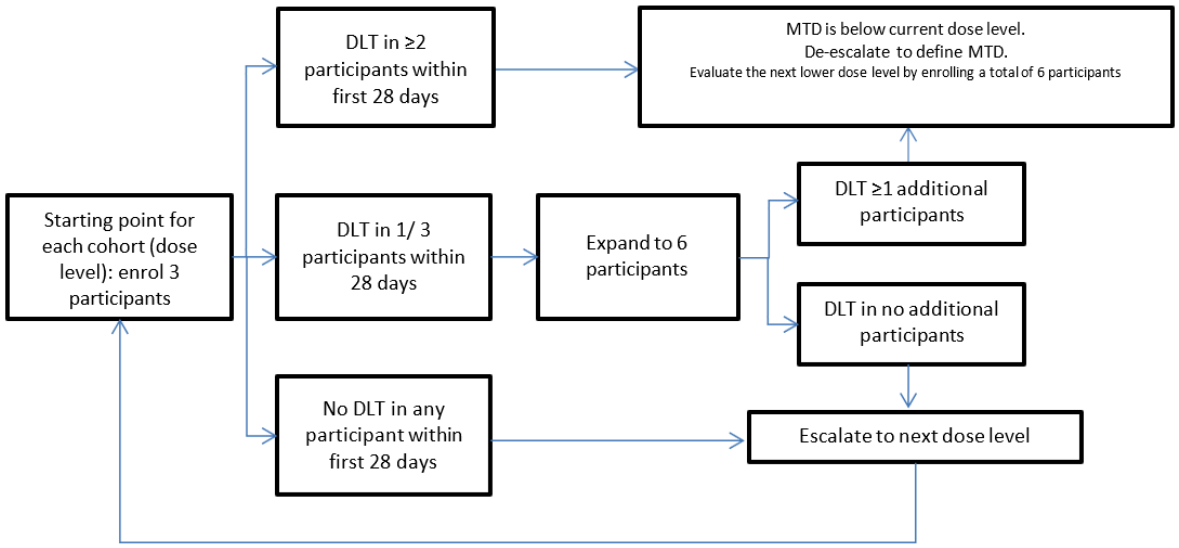


Figure 9: Modified '3+3' Dose Escalation Schema for Module 2 Arm 1 of the Trial

A minimum of 3 evaluable participants will be enrolled into each cohort. The DEC may determine that a cohort should be expanded/repeated if no DLTs are observed but additional data is required to evaluate the dose.

The DEC will review verified safety data once all participants in the cohort have completed the DLT evaluation period (28 days in Arm 1) to determine if the dose can be escalated. Please refer to Table 2 for specific dose escalation details. Subsequent safety reviews by the DEC will be for each cohort and to establish the Combination RP2D.

When assessing DLTs the DEC will consider if the event is a result of the combination or if the event is solely induced by the approved anti-cancer treatment. If the DEC assess that the DLT is solely the result of the approved treatment and MDX-124 has not increased the severity of the event, then the DLT will not be assessed on the combination.

In Module 2 Arm 1 to account for participants who may become unevaluable for the DLT evaluation, the DEC can approve recruitment of a 4th participant to each cohort whilst the first 3 participants are being recruited to or proceeding through Cycle 1 (see Section 21.1.2). The 4th participant's data can then be ready to be used to replace an unevaluable participant if required. If the 4th participant is not required to replace an unevaluable participant, the participant's data would be used for DLT evaluation in the event that the cohort is expanded to 6 or if the dose level is returned to after escalation.

As outlined in Figure 9, if 1/3 evaluable participants exhibit a DLT at a dose level the dose level will be expanded to a total of 6 participants. If no further DLT events are seen, dose-escalation to the next dose level may begin in a new cohort of participants. If 1 or more further DLT events are seen (i.e., 2 or more in the total of 6 participants), this dose level will be considered to have exceeded the MTD. The estimated MTD is the highest dose level with observed toxicity rate less than 33%. If dose escalation is still indicated at the highest dose level of the MDX-124, then the MTD is at or above the last dose level. In this situation additional dose escalation cohorts will not be introduced by the DEC and recruitment to the expansion cohort will start at that dose.

If at -2 dose level at least 2 of 3 participants or at least 2 of 6 participants have DLTs the trial will be stopped for safety. The trial may re-start following a review by the DEC and approval of a substantial amendment which should include a rationale for amendments to the proposed dosing.

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 DEC per the DEC Charter. This may be done once the first cohort of participants at the next dose level have all completed the DLT evaluation period and the criteria to enrol additional participants at the same dose or escalate the dose have been met.

Additional information on the dose escalation process can be found in the DEC charter.

10.2.3 Dose Limiting Toxicities (DLTs) in Modules 1 and 2

Toxicities that occur in the first 21 days in the Module 1 Dose Escalation or 28 days in Module 2 Arm 1 will be considered when determining DLTs. A DLT is defined as one or more of the following events occurring at any time up to and including the last scheduled day of the DLT evaluation period which, following case causality assessment, is deemed to be related to any IMP:

- Grade 4 non-haematologic toxicity (not laboratory)
- Neutropenia lasting > 7 days ≥ Grade 4
- Thrombocytopenia ≥ Grade 4
- Anaemia ≥ Grade 4
- Anaemia requiring transfusion ≥ Grade 3
- Grade 3 non-haematologic toxicity (not laboratory) lasting >3 days despite optimal supportive care.
- Any Grade 3 non-haematologic laboratory value if:
  - Medical intervention is required to treat the participant, or
  - The abnormality leads to hospitalisation, or
  - The abnormality persists for >1 week.
- Febrile neutropenia Grade 3 or Grade 4:
  - Grade 3 is defined as ANC <1000/mm^3 with a single temperature of >38.3°C or a sustained temperature of ≥38°C for more than one hour.
  - Grade 4 is defined as ANC <1000/mm^3 with a single temperature of >38.3°C or a sustained temperature of ≥38°C for more than one hour, with life-threatening consequences and urgent intervention indicated.
- Thrombocytopenia:
  - Thrombocytopenia with clinically significant bleeding ≥ Grade 3
  - Thrombocytopenia requiring a platelet transfusion ≥ Grade 3
- Grade 5 toxicity (i.e., death).
- Any clinically relevant event that causes concern to the investigator for patient's safety, including Hy's Law.

All suspected DLTs should be reported promptly (within 1 working day) to the LCTC and the Sponsor. The LCTC will then notify the other participating sites.

10.2.4 Criteria for Dosing in all Modules

10.2.4.1 Cycle 1

If screening samples for haematology, serum chemistry and coagulation are collected within 14 days of Cycle 1 Day 1 they do not need to be collected at Cycle 1 Day 1. If not, these should be repeated prior to dosing on Cycle 1 Day 1. If lab tests are being

repeated, they may be assessed within 24 hours of the scheduled dose. Dosing must take place within 10 days of registration.

In Module 2 Arm 1 when the Cycle duration is greater than 14 days (i.e., 28 days) and the participant is due to receive 2 doses of MDX-124 within that period then the criteria in Section 10.2.4.2 must be met prior to administration of MDX-124 (lab tests may be assessed within 24 hours of the scheduled dose). The criteria for dose modification in Section 10.2.4.3 and dose discontinuation (Section 10.2.4.4) should also be followed.

10.2.4.2 Subsequent Cycles

Participants must meet the following criteria prior to administration of MDX-124 on commencement of subsequent cycles (lab tests may be assessed within 24 hours of the scheduled dose). This is the minimum criteria required for dosing, however if all criteria below are met, at the PI discretion they may delay dosing for up to 14 days if it is deemed to be in the participants best interests.

- Absolute neutrophil count (ANC) ≥ 1.0 X 10^9/L. (In Modules 1 and 2 growth factor support is only permitted after Cycle 1.)
- Haemoglobin ≥ 9 g/dL. (Transfusions or growth factor support may be permitted.)
- Platelet count ≥ 75 X 10^9/L (WITHOUT platelet transfusions or growth factor support).
- Toxicities deemed clinically significant by the PI must recover to ≤ Grade 2.
- No evidence of disease progression (based on clinical or radiographic assessment) unless the participant is receiving clinical benefit in the opinion of the PI.

In Module 2 the standard of care combinations must meet the dosing criteria outlined in the approved Summary of Product Characteristics (SPC).
If the dose of the standard of care combination is to be delayed, then the MDX-124 dose should also be delayed to avoid additional participant visits to site due to dosing no longer being synchronised. However, if the full cycle of standard of care combination dose is omitted MDX-124 can still be dosed.

10.2.4.3 Dose Modifications

The initiation of dosing in Cycle 2 or beyond, can be delayed for up to 14 days for participants to meet the dosing criteria. Participants who fail this requirement after the additional time will not be allowed to receive further cycles and will be withdrawn from the trial, unless they are determined to be receiving a clinical benefit (i.e., stable disease, reduction in tumour markers) and agreed to by the Sponsor. A dosing delay of more than 14 days in starting the next cycle for reasons other than toxicity will result in the participant discontinuing treatment, unless otherwise agreed by the Sponsor.

If a participant experiences multiple toxicities, dose adjustments will be based on the most severe toxicity. A participant who experiences a toxicity meeting the definition of DLT (see Section 10.2.3) during any cycle but whose toxicity recovers within 14 days will be dose reduced to the previously tested next lower dose level, or to a dose level determined by the DEC if the participant is at the first dose cohort.

In Module 2 in the event of toxicity the dose of the standard of care combinations should be amended according to the approved SPC. This can occur at the start of a cycle or during a cycle.

Table 3: MDX-124 Dose Modifications for Cycle 2 Onwards

Toxicity Grade	Recommended Action	Recommendation for dose modification at start of next cycle
Grade 1	No immediate action	Continue current MDX-124 dose level
Grade 2	No immediate action	Continue current MDX-124 dose level
Grade 3/4	Hold MDX-124	If resolved to ≤ Grade 2 within 14 days reduce MDX-124 by 25%. If not resolved to ≤ Grade 2 within 14 days, withdraw participant from trial. A further reduction to 50% of the initial dose is permitted if event recurs or additional Grade 3/4 toxicities occur.

10.2.4.4 Dosing Discontinuation Criteria

A participant may continue to receive the MDX-124 until one of the following occurs:

- Unmanageable toxicity defined as an AE that is considered by the PI or delegate to warrant permanent discontinuation of MDX-124 including the following:
  - AE resulting in a dosing delay of more than 14 days in starting the next cycle.
  - Clinically significant related AE (grade 3 and above) that recurs despite separate dose reductions in 2 cycles.
- Progressive disease as defined by RECIST version 1.1 unless the participant is receiving clinical benefit in the opinion of the PI.
- Lack of further clinical benefit or unfavourable benefit-risk profile as judged by the PI and/or DEC.
- Intercurrent illness that prevents further administration of MDX-124.
- Participant withdraws consent from further dosing and for further data collection.
  - If the participant withdraws consent for further dosing, follow up visits should continue.
  - If the participant withdraws consent for further dosing and data collection, then no additional trial visits nor data collection should occur (see also Section 13).
- Pregnancy.

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 PI decision, treatment with MDX-124 may continue until there is evidence of disease progression, unacceptable toxicity or at the participant's request.

11 PARTICIPANT SELECTION

The trial aims to recruit up to 44 participants in Module 1 and up to 29 participants in each arm of Module 2 based on sample size calculations described in Section 21. All participants must provide written informed consent before any study procedures occur (see Section 12.1 for more information regarding informed consent processes) and must meet all eligibility criteria as described below prior to registration.

11.1 Inclusion Criteria

11.1.1 Core Inclusion Criteria

Participants eligible for the trial must comply with the following at enrolment:

1. Provision of signed written informed consent.
2. Age ≥18 years.
3. ECOG performance status 0-1.
4. Adequate bone marrow function as defined by:
   - absolute neutrophil count (ANC) ≥1.5×10^9/l,
   - platelet count ≥100×10^9/l
   - haemoglobin level ≥9.0 g/dl.
5. Adequate liver function, as defined by:
   - serum total bilirubin ≤1.5×upper limit of normal (ULN),
   - AST and ALT ≤2.5×ULN.
6. Adequate renal function assessed as estimated Glomerular Filtration Rate (eGFR) ≥50 ml/min/1.73m^2.
7. Ability to comply with protocol requirements.
8. Female participants of child-bearing potential must have a negative serum pregnancy test.

11.1.2 Module 1 Inclusion Criteria

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 (e.g., head and neck (oral, nasal and throat regions) and cervical) are excluded.
2. Participants must have measurable disease per RECIST version 1.1 criteria 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).

11.1.3 Module 2 Inclusion Criteria

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 for which FOLFIRINOX treatment is not indicated and gemcitabine with nab-paclitaxel is the standard of care.
2. Participant 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.

11.2 Exclusion Criteria

11.2.1 Core Exclusion Criteria

Any participant meeting any of the criteria listed below at enrolment will be excluded from study participation:

1. Symptomatic 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 trial, and the participant has had no evidence of recurrence since then.
5. Presence of an uncontrolled concomitant illness or active infection requiring 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 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[*4], unless using at least two highly effective contraceptive measures, one of which must be from the list below, the

other must be a condom*[1] or abstaining from sexual intercourse, until six months after last dose of MDX-124, gemcitabine and/or nab-paclitaxel:

- Combined (oestrogen and progesterone containing) hormonal contraception associated with inhibition of ovulation: either oral, intravaginal or transdermal
- Progesterone-only hormonal contraception associated with inhibition of ovulation: either oral, injectable or implantable
- Intra-uterine device (IUD)
- Intra-uterine hormone-releasing system (IUS)
- Bilateral tubal occlusion
- Vasectomised partner*[2]
- Sexual abstinence*[3]

*[1] Male or female condom with or without spermicide is not an acceptable method of contraception alone.
*[2] Vasectomised partner is a highly effective birth control method provided that partner is the sole sexual partner of the woman of childbearing potential trial participant and that the vasectomised partner has received medical assessment of the surgical success.
*[3] In the context of this guidance sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the IMPs. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the participant.
*[4] A woman is considered of childbearing potential (WOCBP), i.e. fertile, following menarche and until becoming post-menopausal unless permanently sterile. Permanent sterilisation methods include hysterectomy, bilateral salpingectomy and bilateral oophorectomy.
A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy. However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.
For the purpose of this document, a man is considered fertile after puberty unless permanently sterile by bilateral orchidectomy.

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.

11.2.2 Module 1 Exclusion Criteria

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 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 first administration of IMP.
    - For targeted hormone therapy within 14 days of 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 first administration of IMP.

11.2.3 Module 2 Exclusion Criteria

In addition to the Core Exclusion Criteria if participants being considered for enrolment in Module 2 meet any applicable exclusion criteria listed below, they will be ineligible for the trial:

Arm 1

1. 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 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 first administration of IMP.

11.3 Protocol Deviations and Waivers to Entry Criteria

Waivers will not be granted for a participant who does not satisfy the eligibility criteria. The Investigator must document and explain any deviations from the approved protocol and report any deviations impacting participant safety, data integrity or may be a possible serious breach.

11.4 Participant Re-screening

Participants who do not meet the eligibility criteria can be re-screened. All assessments need to be completed within 28 days of Cycle 1 Day 1. Participants who fail at re-screening are ineligible and will not be re-screened.

11.5 Participant Registration Procedure

A screening log must be kept of all participants considered for the trial i.e., all those that are included for screening and any that are subsequently excluded; the reason for exclusion must be recorded on this form. A copy of the screening log must be sent to the LCTC on request, but without participant identifiers. The original must be retained on site.

Prior to commencing screening, confirmation of available cohort slot must be obtained from LCTC. Slots will be held for 14 days unless the patient is no longer eligible. Sites will be made aware of available slots during the regular (i.e., weekly) trial management call or associated minutes. The frequency of the call may increase or decrease based on recruitment and the number of active participants.

Before registering a participant onto the trial, the PI or designee will confirm eligibility. If in any doubt, the Sponsor must be consulted via the LCTC before registering the participant. Details of the query and outcome of the decision must be documented on the registration/eligibility checklist.

To enrol a participant to the trial, the site must complete the registration form in the electronic Case Report Form (eCRF). The participant will then be enrolled to the trial, and the site will receive an email confirming registration has been recorded and the dosing cohort. **Dosing must not start until this registration process is complete and must start no later than 10 days after the day of registration.**

12 TRIAL ASSESSMENTS AND PROCEDURES

Please refer to the Schedule of Events at the front of this protocol. Details of all protocol evaluations and investigations must be recorded in the participant's medical record for transcription onto the eCRF.

12.1 Informed Consent

Potential participants will be given a module specific current, approved version of the participant information sheet and consent form. They will also receive clear verbal information about the trial detailing no less than: the nature of the trial; the implications and constraints of the protocol; the known side effects and any risks involved in taking part. It will be explained that they will be free to withdraw from the trial at any time, for any reason, without prejudice to future care, and with no obligation to give a reason for withdrawal. They will have at least 24 hours to consider the information provided and the opportunity to question the Investigator, their general practitioner (GP) or other independent parties before deciding whether to participate.

The Investigator who obtains consent must be suitably qualified and experienced. All delegates must be authorised by the PI to obtain consent. The Investigator is responsible for ensuring that the trial consent procedures comply with current applicable Good Clinical Practice (GCP), Regulatory and ethical requirements. Informed consent discussions and outcomes must be well documented in the medical record. The Investigator must be satisfied that the participant has made an informed decision before taking consent. The participant and the Investigator must personally sign and date the current approved version of the informed consent form in each other's presence. A copy of the information and signed consent form will be given to the participant. The original signed form will be retained at the trial site in the Investigator Site File, a copy will be sent to LCTC, and a copy will be stored in the participant's medical records.

Contraceptive/ Pregnancy counselling

All participants must be advised on the need to use highly effective methods of contraception during the trial. The advice should include:

(1) The acceptable methods, including male or female sterilisation, implants, injectables, combined oral contraceptives, some intrauterine devices (IUDs), and abstinence.

(2) The recommendation that a barrier method should be used in addition to another form of contraception.

(3) Males and females should continue to take these precautions a minimum of 6 months after the last dose of IMP.

(4) That any pregnancy (also applies to female partners of male trial participants) occurring within 6 months of the last administration of IMP, gemcitabine or nab-paclitaxel will be followed up and the outcome of all pregnancies (spontaneous miscarriage, elective termination, normal birth or congenital abnormality) will be reported and followed up even if participant is discontinued from the trial.

Cryoconservation of sperm

Participants should seek further advice regarding cryoconservation of sperm prior to initiating treatment as there is a risk of infertility due to treatment with gemcitabine or nab-paclitaxel.

12.2 Informed Consent for Translational Sub-Studies (Module 2)

Potential participants who are being requested to provide a fresh tissue biopsy will be provided a separate biopsy specific current, approved version of the participant information sheet and consent form.

12.3 Laboratory Evaluations

Blood samples for haematology and clinical chemistry will be taken at scheduled visits and analysed at the local laboratory using standard methods for routine tests. Safety labs required for dosing being analysed at the local laboratory can be performed up to 24 hours prior to IMP administration.

The following variables will be measured at the local laboratory:

- Clinical chemistry: albumin, ALT, AST, alkaline phosphatase, bilirubin (total), calcium (total), creatinine (total), random glucose, magnesium, phosphate, potassium, sodium, urea nitrogen, protein (total), urate, bicarbonate and chloride.
- Blood coagulation: Activated Partial Thromboplastin Time (aPTT) or INR.
- Haematology: complete blood count, including haemoglobin, haematocrit, white blood cells, ANC, neutrophils, lymphocytes and platelets.
- Viral serology: anti-HIV antibody, hepatitis B surface antigen and anti-hepatitis C antibody.

Samples will be collected at scheduled visits for the following and will be sent to a central laboratory for analysis. Please refer to the Lab Manual for more information.

The following variables will be measured at the central laboratory:

- Cytokines (pro-inflammatory panel) (Module 1 Dose Escalation only)
- Immunophenotyping (TBNK and WBC)
- Immunogenicity (anti-drug antibodies (ADA))
- PK

- Serum ANXA1 sample

Laboratory values that have changed significantly from baseline and are of clinical concern must be recorded as an AE and followed up as appropriate.

12.4 Screening Evaluations

Participants will undergo the following procedures:

- Evaluation against inclusion and exclusion criteria.
- Recording of demographic data.
- Previous medical history.
- ECOG performance status.
- Complete physical examination.
- Recording of concomitant medications.
- Vital signs: resting supine blood pressure (BP) and pulse measurement, respiratory rate, temperature, height and weight.
- ECG.
- If screening samples for haematology, serum chemistry and coagulation are collected within 14 days of Cycle 1 Day 1 they do not need to be collected at Cycle 1 Day 1. If not, haematology, chemistry and coagulation should be repeated prior to dosing on Cycle 1 Day 1.
- Urinalysis.
- Blood sample for viral serology – HIV, hepatitis B and C.
- Serum pregnancy test (if applicable in women of reproductive potential). A woman is considered of childbearing potential (WOCBP), i.e. fertile, following menarche and until becoming post-menopausal unless permanently sterile. Permanent sterilisation methods include hysterectomy, bilateral salpingectomy and bilateral oophorectomy. A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy. However in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.
- Tumour markers (if clinically indicated).
- Serum ANXA1 sample.
- Baseline tumour assessment according to the Response Evaluation Criteria in Solid Tumours (RECIST) criteria version 1.1 in combination with tumour specific evaluation criteria which incorporates the relevant tumour markers (e.g., GCIG criteria utilising the Cancer Antigen 125 [CA125]).
- Formalin fixed paraffin-embedded (FFPE) archival tumour tissue sample (if available) may be requested by sponsor:
    - Module 1: if molecular profiling is required to understand further any response to MDX-124.

  - Module 2: if this has been collected prior to the fresh tissue biopsy that is performed as part of the study.

- Fresh tumour tissue biopsy. This may be obtained when the diagnostic sample is collected. Therefore, this can be collected prior to the 28-day screening window starting (Module 2 only).

12.5 Evaluations During the Trial

During dosing, participants in Modules 1 and 2 will be reviewed on a weekly basis during the first cycle and on the day of dosing. Additional visits may be arranged at the Investigator's discretion.

12.5.1 Module 1 Dose Escalation (14-day cycle)

Cycle 1 Day 1

(All assessments will be pre-dose, unless otherwise indicated below.)

- Confirm participant still meets inclusion and exclusion criteria.
- Symptom driven physical examination.
- Recording of concomitant medications.
- Recording of AEs and aetiology.
- Vital signs: resting supine BP and pulse measurement, respiratory rate, temperature and weight.
- ECOG performance status.
- ECG (if clinically indicated).
- If screening samples for haematology, serum chemistry and coagulation are collected within 14 days of Cycle 1 Day 1 they do not need to be collected at Cycle 1 Day 1. If not, haematology, chemistry and coagulation should be repeated prior to dosing on Cycle 1 Day 1.
- Urinalysis.
- Urine pregnancy test (if applicable in women of reproductive potential) within 24 hours prior to MDX-124 administration.
- Tumour markers (if clinically indicated).
- Blood samples for PK: timepoints for population PK on Cycle 1 Day 1 pre dose (T0), immediately post infusion (T1), T1 +15min, +30min, +1hr, +2hr, +4hr, +6hr, +24hr and +48h.
- Immunophenotyping serum (TBNK and WBC) sample collected on Cycle 1 Day 1 pre dose and T1 +4hr.
- Cytokine (pro-inflammatory) serum sample collected on Cycle 1 Day 1 pre dose, T1+1hr and T1 +4hr.
- Immunogenicity (ADA) sample to be collected pre dose.
- Serum ANXA1 sample collected on Cycle 1 Day 1 pre dose and T1 +4hr and T1+24hr.

- MDX-124 administration. The T0 PK sample must be collected within 2 minutes of the infusion commencement.

The first participant enrolled at a new dose level will be admitted ensuring they can be monitored for the first 24 hours following their first dose of MDX-124.

All other participants will be asked to remain at the hospital until their final PK sample (T1 + 6 hours) is collected. This observation period is deemed to be suitable based on the half-life observed in the GLP toxicology studies. In addition MDX-124 does not have a cascading mechanism of action and no apparent risk of cytokine storm has been reported so far from *in vitro* human neutrophil or animal studies. It is expected that any immediate or longer term infusion related reactions would be observed within this 6 hour period. Any participants who request to be admitted for the first 24 hours following their first dose of MDX-124 will be accommodated.

Participants will also be reviewed by a member of the study team when they return for the 24 and 48 hour PK samples. Prior to leaving the site the participant will be provided with the contact details for the study team and advised what to do in the event of an emergency. Participants are not required to stay in hospital overnight. If the Investigator determines that it is in the participant's best interests to stay overnight, they should contact the LCTC. Possible reasons include but are not limited to long travel to site, late infusion time slot, late PK collection time slot and patient choice.

The LCTC will coordinate schedules to ensure that at a new increased dose level there is a minimum of a 24-hour gap between the dosing of the initial participant in a cohort and the remaining participants in the cohort to observe any reactions and AEs.

Cycle 1 Day 8 (+/- 1 day window)

- Recording of AEs and aetiology.
- Vital signs: resting supine BP and pulse measurement, respiratory rate and temperature.
- Blood samples for haematology and chemistry.
- Recording of concomitant medications.
- Blood sample for PK +168hr (Day 8) timepoint.
- Immunophenotyping serum sample for T1 +168hr (Day 8) timepoint.
- Serum ANXA1 sample T1 +168hr (Day 8) timepoint.

Cycle 2 Day 1

(All assessments will be pre-dose, unless otherwise indicated below. Participant must meet Criteria in Section 10.2.4.2.)

- Symptom driven physical examination.
- Recording of concomitant medications.
- Recording of AEs and aetiology.
- Vital signs: resting supine BP and pulse measurement, respiratory rate, temperature and weight.

- ECOG performance status.
- ECG (if clinically indicated)
- Blood samples for haematology, chemistry & coagulation.
- Urinalysis.
- Urine pregnancy test (if applicable in women of reproductive potential) within 24 hours prior to MDX-124 administration.
- Tumour markers (if clinically indicated).
- Pre dose PK sample (Cycle 2 only).
- Pre dose immunophenotyping (TBNK and WBC) serum sample.
- Immunogenicity (ADA) sample to be collected pre dose.
- Pre dose cytokine (pro-inflammatory) serum sample.
- Pre dose serum ANXA1 sample.
- MDX-124 administration.

Cycle 2 Day 8 (+/- 1 day window)

- Recording of AEs and aetiology.
- Vital signs: resting supine BP and pulse measurement, respiratory rate and temperature.
- Blood samples for haematology and chemistry.
- Recording of concomitant medications.

Day 1 for Cycle 3 and subsequent cycles (+/- 1 day window)

(All assessments will be pre-dose, unless otherwise indicated. Participant must meet Criteria in Section 10.2.4.2.)

- Symptom driven physical examination.
- Recording of concomitant medications.
- Recording of AEs and aetiology.
- Vital signs: resting supine BP and pulse measurement, respiratory rate, temperature and weight.
- ECG (if clinically indicated).
- ECOG performance status.
- Blood samples for haematology, chemistry & coagulation.
- Urinalysis.
- Urine pregnancy test (if applicable in women of reproductive potential) within 24 hours prior to MDX-124 administration.
- Tumour markers (if clinically indicated).
- Pre dose immunophenotyping (TBNK and WBC) serum sample.

- Pre dose cytokine (pro-inflammatory) serum sample.
- Pre dose serum ANXA1 sample.
- Blood samples for PK: timepoints: 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.
- Immunogenicity (ADA) sample to be collected pre dose on Day 1 of all cycles.
- MDX-124 administration. In Cycle 4 the T0 PK sample must be collected within 2 minutes of the infusion commencement.

12.5.2 Module 1 Dose Expansion (21-day Cycle)

Cycle 1 Day 1

(All assessments will be pre-dose, unless otherwise indicated below.)

- Confirm participant still meets inclusion and exclusion criteria.
- Symptom driven physical examination.
- Recording of concomitant medications.
- Recording of AEs and aetiology.
- Vital signs: resting supine BP and pulse measurement, respiratory rate, temperature and weight.
- ECOG performance status.
- ECG (if clinically indicated)
- If screening samples for haematology, serum chemistry and coagulation are collected within 14 days of Cycle 1 Day 1 they do not need to be collected at Cycle 1 Day 1. If not, haematology, chemistry and coagulation should be repeated prior to dosing on Cycle 1 Day 1.
- Urinalysis.
- Urine pregnancy test (if applicable in women of reproductive potential) within 24 hours prior to MDX-124 administration.
- Tumour markers (if clinically indicated).
- Blood samples for PK: timepoints for population PK on Cycle 1 Day 1 pre dose (T0), immediately post infusion (T1), T1 +15min, +30min, +1hr, +2hr, +4hr and +24hr.
- Immunophenotyping serum (TBNK and WBC) sample collected on Cycle 1 Day 1 pre dose, T1 +4hr and T1+24hr.
- Immunogenicity (ADA) sample to be collected pre dose.
- Serum ANXA1 sample collected on Cycle 1 Day 1 pre dose and T1 +4hr and T1+24hr.
- MDX-124 administration. The T0 PK sample must be collected within 2 minutes of the infusion commencement.

Participants will be reviewed by a member of the study team when they return for the 24 hour PK samples. Prior to leaving the site the participant will be provided

with the contact details for the study team and advised what to do in the event of an emergency. Participants are not required to stay in hospital overnight. If the Investigator determines that it is in the participant's best interests to stay overnight, they should contact the LCTC. Possible reasons include but are not limited to long travel to site, late infusion time slot, late PK collection time slot and patient choice.

Cycle 1 Day 8 (+/- 1 day window)

- Recording of AEs and aetiology.
- Vital signs: resting supine BP and pulse measurement, respiratory rate and temperature.
- Blood samples for haematology and chemistry.
- Recording of concomitant medications.
- Blood sample for PK +168hr (Day 8) timepoint.
- Immunophenotyping serum (TBNK and WBC) sample for +168hr (Day 8) timepoint.

Cycle 1 Day 15 (+/- 1 day window)

- Recording of AEs and aetiology.
- Vital signs: resting supine BP and pulse measurement, respiratory rate and temperature.
- Blood samples for haematology and chemistry.
- Recording of concomitant medications.
- Blood sample for PK +336hr (Day 15) timepoint.

Day 1 for Cycle 2 and subsequent cycles (+/- 1 day window)

(All assessments will be pre-dose unless otherwise indicated below. Participant must meet Criteria in section 10.2.4.2.)

- Symptom driven physical examination (if clinically indicated).
- Recording of concomitant medications.
- Recording of AEs and aetiology.
- Vital signs: resting supine BP and pulse measurement, respiratory rate, temperature and weight.
- ECOG performance status.
- ECG (if clinically indicated)
- Blood samples for haematology, chemistry & coagulation.
- Urinalysis.
- Urine pregnancy test (if applicable in women of reproductive potential) within 24 hours prior to MDX-124 administration.
- Tumour markers (if clinically indicated).

- Pre dose PK sample (Cycle 2 and 4 only).
- Pre dose immunogenicity (ADA) sample.
- Pre dose immunophenotyping (TBNK and WBC) sample.
- Pre dose serum ANXA1 sample.
- Blood samples for PK timepoints:
    - Pre dose on Cycle 2 day 1
    - Cycle 3 Day 1 pre-dose (T0), immediately post infusion (T1), T1 +15min, +30min, +1hr, +2hr, +4hr, +6hr and +24hr.
    - Pre dose on Cycle 4 Day 1.
- MDX-124 administration. In Cycle 3 the T0 PK sample must be collected within 2 minutes of the infusion commencement.

Cycle 3 Day 8 (+/- 1 day window)

- Blood sample for PK +168hr (Day 8) timepoint.

Cycle 3 Day 15 (+/- 1 day window)

- Blood sample for PK +336hr (Day 15) timepoint.

12.5.3 Module 2 Arm 1 (28-day Cycle)

All assessments will be pre-dose, unless otherwise indicated. From Cycle 2 onwards participants must meet criteria in Section 10.2.4.2 to receive MDX-124. Please refer to Summary of Product Characteristics for combination treatment dosing guidance.

All Cycles Day 1

- Confirm participant still meets inclusion and exclusion criteria (Cycle 1 Day 1 only).
- Symptom driven physical examination (post Cycle 1 Day 1 only if clinically indicated).
- Recording of AEs and aetiology
- Recording of concomitant medications.
- Vital signs: resting supine BP and pulse measurement, respiratory rate, temperature and weight.
- ECG (if clinically indicated).
- ECOG performance status.
- Blood samples for haematology, chemistry & coagulation. If screening samples for haematology, serum chemistry and coagulation are collected within 14 days of Cycle 1 Day 1 they do not need to be collected at Cycle 1 Day 1. If not, haematology, chemistry and coagulation should be repeated prior to dosing on Cycle 1 Day 1.
- Urinalysis.

- Urine pregnancy test (if applicable in women of reproductive potential) within 24 hours prior to IMP administration.
- Tumour markers (if clinically indicated).
- MDX-124 administration. The T0 PK sample must be collected within 2 minutes of the infusion commencement.
- 1000mg/m^2 gemcitabine and 125mg/m^2 nab-paclitaxel administration.
- Blood samples for PK:
    - Cycle 1: timepoints for population PK on Cycle 1 Day 1 pre-dose (T0), immediately post infusion (T1), T1 +15min, +30min, +1hr, +2hr, +4hr, and +24hr.
    - Cycle 3: timepoints for population PK on Cycle 3 Day 1 pre-dose (T0), immediately post infusion (T1), T1 +15min, +30min, +1hr, +2hr, +4hr, and +24hr.
- Immunophenotyping (TBNK and WBC) sample
    - Cycle 1: collected on Cycle 1 Day 1 pre dose, T1 +4hr and +24hr.
    - Cycle 2 onwards: collected pre dose on Day 1
- Immunogenicity (ADA) sample
    - All cycles: collected pre dose.
- Serum ANXA1 sample
    - Cycle 1: collected on Cycle 1 Day 1 pre dose.
    - Cycle 2 onwards: collected pre dose on Day 1

To ensure participants can be monitored following their first dose of IMP all participants will be asked to remain at the hospital until their final PK sample (T1 + 6 hours) is collected. Participants will be reviewed by a member of the study team the following day when they return for the 24 hour PK samples. Prior to leaving the site the participant will be provided with the contact details for the study team and advised what to do in the event of an emergency. Participants are not required to stay in hospital overnight.

The LCTC will coordinate schedules to ensure that at a new increased dose level there is a minimum of a 24-hour gap between the dosing of the initial participant in a cohort and the remaining participants in the cohort to observe any reactions and AEs.

All Cycles Day 8 (+/- 1 day window)

- Recording of AEs and aetiology.
- Vital signs: resting supine BP and pulse measurement, respiratory rate and temperature.
- Blood samples for haematology and chemistry.
- Recording of concomitant medications.
- Pre dose blood sample for PK (Cycle 1 and 3 only).

- Pre dose immunophenotyping (TBNK and WBC) sample (Cycle 1 only).
- 1000mg/m^2 gemcitabine and 125mg/m^2 nab-paclitaxel administration (Arm 1 only).

All Cycles Day 15 (+/- 1 day window)

- Recording of AEs and aetiology.
- Vital signs: resting supine BP and pulse measurement, respiratory rate and temperature.
- Blood samples for haematology and chemistry.
- Recording of concomitant medications.
- Pre dose blood sample for PK (Cycle 1 and 3 only).
- MDX-124 administration.
- 1000mg/m^2 gemcitabine and 125mg/m^2 nab-paclitaxel administration (Arm 1 only).
- Fresh tissue biopsy at the end of Cycle 2.

Cycle 1 Day 22 (Cycle 1 only) (+/- 1 day window)

- Recording of AEs and aetiology.
- Vital signs: resting supine BP and pulse measurement, respiratory rate and temperature.
- Blood samples for haematology and chemistry.
- Recording of concomitant medications.

12.5.4 Module 2 Arm 2 (14-day Cycle)

All assessments will be pre-dose, unless otherwise indicated. From Cycle 2 onwards participants must meet criteria in Section 10.2.4.2 to receive MDX-124. Please refer to Summary of Product Characteristics for combination treatment dosing guidance.

Cycle 1 Day 1

- Confirm participant still meets inclusion and exclusion criteria.
- Symptom driven physical examination.
- Recording of concomitant medications.
- Recording of AEs and aetiology.
- Vital signs: resting supine BP and pulse measurement, respiratory rate, temperature and weight.
- ECOG performance status.
- ECG (if clinically indicated).
- If screening samples for haematology, serum chemistry and coagulation are collected within 14 days of Cycle 1 Day 1 they do not need to be collected at

Cycle 1 Day 1. If not, haematology, chemistry and coagulation should be repeated prior to dosing on Cycle 1 Day 1.

- Urinalysis.
- Urine pregnancy test (if applicable in women of reproductive potential) within 24 hours prior to IMP administration.
- Tumour markers (if clinically indicated).
- Blood samples for PK: timepoints for population PK on Cycle 1 Day 1 pre dose (T0), immediately post infusion (T1), T1 +15min, +30min, +1hr, +2hr, +4hr and +24hr.
- Immunophenotyping serum (TBNK and WBC) sample collected on Cycle 1 Day 1 pre dose, T1 +4hr and T1+24hr.
- Immunogenicity (ADA) sample to be collected pre dose.
- Serum ANXA1 sample collected on Cycle 1 Day 1 pre dose and T1 +4hr and T1+24hr.
- MDX-124 administration. The T0 PK sample must be collected within 2 minutes of the infusion commencement.

Participants will also be reviewed by a member of the study team when they return for the 24 hour PK samples. Prior to leaving the site the participant will be provided with the contact details for the study team and advised what to do in the event of an emergency. Participants are not required to stay in hospital overnight. If the Investigator determines that it is in the participant's best interests to stay overnight, they should contact the LCTC. Possible reasons include but are not limited to long travel to site, late infusion time slot, late PK collection time slot and patient choice.

Cycle 1 Day 8 (+/- 1 day window)

- Recording of AEs and aetiology.
- Vital signs: resting supine BP and pulse measurement, respiratory rate and temperature.
- Blood samples for haematology and chemistry.
- Recording of concomitant medications.
- Blood sample for PK +168hr (Day 8) timepoint.
- Immunophenotyping (TBNK and WBC) serum sample.

Cycle 2 Day 1

- Symptom driven physical examination.
- Recording of concomitant medications (if clinically indicated).
- Recording of AEs and aetiology.
- Vital signs: resting supine BP and pulse measurement, respiratory rate, temperature and weight.
- ECOG performance status.
- ECG (if clinically indicated).

- Blood samples for haematology, chemistry & coagulation.
- Urinalysis.
- Urine pregnancy test (if applicable in women of reproductive potential) within 24 hours prior to IMP administration.
- Tumour markers (if clinically indicated).
- Pre dose PK sample (Cycle 2 only).
- Pre dose immunophenotyping (TBNK and WBC) sample.
- Pre dose serum ANXA1 sample.
- Immunogenicity (ADA) sample to be collected pre dose.
- MDX-124 administration.

Cycle 3 Day 1 and all subsequent cycles (+/- 1 day window)

- Symptom driven physical examination (if clinically indicated).
- Recording of concomitant medications.
- Recording of AEs and aetiology.
- Vital signs: resting supine BP and pulse measurement, respiratory rate, temperature and weight.
- ECG (if clinically indicated).
- ECOG performance status.
- Blood samples for haematology, chemistry & coagulation.
- Urinalysis.
- Urine pregnancy test (if applicable in women of reproductive potential) within 24 hours prior to IMP administration.
- Tumour markers (if clinically indicated).
- Pre dose immunophenotyping (TBNK and WBC) sample.
- Pre dose serum ANXA1 sample.
- Blood samples for PK: timepoints: 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.
- Immunogenicity (ADA) sample to be collected pre dose on Day 1 of all cycles.
- MDX-124 administration. In Cycle 4 the T0 PK sample must be collected within 2 minutes of the infusion commencement.
- Fresh tissue biopsy collection at the end of Cycle 4.

12.5.5 Tumour Assessment for all participants

Tumour assessment (CT scan/MRI scan) will be performed according to the RECIST criteria version 1.1 for participants with measurable disease. Iodinated contrast may be used when performing CT scans. If iodinated contrast is contraindicated, then non-

contrast CT chest with magnetic resonance imaging (MRI) of the abdomen and pelvis may be used.

Module 1 dose escalation and Module 2 (when cycle duration is 14 days) scans should be conducted at screening then at the end of Cycle 4, Cycle 8, and every subsequent 4th cycle (±7 days) until disease progression.

Module 1 dose expansion (when cycle duration is 21 days) tumour assessment scans will be performed at the screening visit, at the end of Cycle 3, Cycle 6, and every subsequent 3rd cycle (±7 days) until disease progression.

Module 2 (when cycle duration is 28 days) scans should be conducted at Screening then end of Cycle 2, Cycle 4, and every subsequent 2nd cycle (±7 days) until disease progression. Complete responses (CRs) and partial responses (PRs) must be confirmed by repeated images at least 4 weeks after initial documentation. Tumour response will also be assessed using tumour markers and the related tumour specific evaluation criteria.

12.5.6 End of Treatment Visit

The end of treatment visit is to be done 7 days (±1 day) after the last dose of IMP for all participants. The following assessments should be completed:

- Symptom driven standard physical examination.
- Recording of concomitant medications.
- Recording of AEs and aetiology.
- Vital signs: resting supine BP and pulse measurement, respiratory rate, temperature and weight.
- ECG (if clinically indicated).
- ECOG performance status.
- Blood samples for haematology, chemistry & coagulation.
- Urinalysis.
- Serum pregnancy test (if applicable in women of reproductive potential).
- Tumour markers (if clinically indicated).
- Cytokine (pro-inflammatory) serum sample (Module 1 Dose Escalation only).
- Immunogenicity (ADA) sample.
- Immunophenotyping (TBNK and WBC) sample.
- Serum ANXA1 sample.

12.5.7 Day 28 Follow Up Visit

The end of trial visit is to be done 28 days (±7 days) after the last dose of IMP for all participants. The following assessments should be completed:

- Recording of concomitant medications.
- Recording of AEs and aetiology.
- Blood samples for haematology & chemistry.
- Immunophenotyping (TBNK and WBC) sample.
- Serum ANXA1 sample.
- Cytokine (pro-inflammatory) serum sample (Module 1 Dose Escalation only).
- Immunogenicity (ADA) sample.

12.5.8 Survival Follow Up Call

Survival follow up call to the participants primary care physician is to be done every 6 months (±7 days) after the last dose of IMP for all participants. This can be conducted

by a member of the site staff delegated by the PI. If appropriate survival status can be confirmed through the participant's GP or the appropriate sources of medical records. Survival follow up will be capped at 12 weeks for Module 1 and 12 months for Module 2.

13 PARTICIPANT WITHDRAWAL

During the course of the trial, a participant may withdraw from treatment at any time. This may happen for several reasons, including but not limited to:

- Unacceptable toxicity (see Section10.2.4.4).
- AEs/ SAEs requiring discontinuation (see Section 10.2.4.4).
- Loss to follow-up.
- Significant protocol deviation or inability to comply with trial procedures.
- Clinical decision.
- Participant decision.
- Pregnancy.

When the participant stops dosing, the end of treatment visit and the Day 28 follow-up visit should be conducted. The Withdrawal from Study eCRF needs to be completed, and any other relevant eCRFs (e.g., SAE Form). The reason for withdrawing from dosing early should be clearly documented in the medical and trial records.

13.1 Consent Withdrawal

Consent withdrawal means that a participant has expressed a wish to withdraw from the trial altogether. Under these circumstances, the site needs to document all relevant discussions in the medical records.

Under these conditions, Investigators are still responsible to follow up any SAEs until resolution.

14 SAMPLES FOR LABORATORY ANALYSIS

14.1 Samples to be Analysed by Local Laboratories

Diagnostic Laboratories

Samples for haematology and biochemistry analysis will be labelled with standard participant identifiers and sent to the local hospital diagnostic laboratory. Results will be processed in the standard way and entered into the routine hospital reporting system. Samples will be stored, held, reported, and subsequently destroyed in accordance with standard local laboratory practice.

Pathology

The routine diagnostic pathology samples will also be labelled, processed and reported according to local hospital protocols.

14.2 Pharmacokinetic (PK) Samples

The PK samples will be processed and analysed at Alderley Analytical. The analysis will be carried out using validated methods and standard operating procedures (SOPs).

PK Sampling Schedule

PK studies will be carried out in the participants in the dose escalation phases of Module 1 and Module 2 Arm 1. Depending on these PK results, the number of PK samples may be reduced for the dose expansion phases of Module 1 and Module 2. This change must be approved by the DEC and documented in the TMF but will not constitute an amendment.

Approximately 2.5ml of blood will be collected at each sample timepoint stated in the PK sampling schedules (Table 4, Table 5, Table 6, Table 7, Table 8 and Table 9). The site of venepuncture (i.e., peripheral line or via central access port, etc.) and the amount of blood collected should be recorded on the appropriate log for all PK samples. The sample should not be drawn from the same line as was used for the administration of the IMP.

If the MDX-124 infusion is shortened or lengthened the timepoints may be adjusted appropriately. The infusion must start within 2 minutes of the T0 sample being collected.

PK samples collected on the day of infusion should have a ± 5 minutes window and for samples collected at 24 hrs onwards a ± 1 hour window can be applied.

Please refer to the Lab Manual for further information.

Table 4: PK Sampling Schedule for Cycle 1 Day 1 in Module 1 Dose Escalation

Sample 1: T0 Pre-dose (before the start of the infusion)
Sample 2: Immediately Post Infusion (T1)
Sample 3: T1 plus 15 minutes
Sample 4: T1 plus 30 minutes
Sample 5: T1 plus 1 hours
Sample 6: T1 plus 2 hours
Sample 7: T1 plus 4 hours
Sample 8: T1 plus 6 hours
Sample 9: T1 plus 24 hours
Sample 10: T1 plus 48 hours
Sample 11: T1 plus 168 hours (Day 8)
Sample 12: Pre dose on Cycle 2 Day 1

Table 5: PK Sampling Schedule for Cycle 4 Day 1 in Module 1 Dose Escalation

Sample 1: T0 Pre-dose (before the start of the infusion)
Sample 2: Immediately Post Infusion (T1)
Sample 3: T1 plus 15 minutes
Sample 4: T1 plus 30 minutes
Sample 5: T1 plus 1 hours
Sample 6: T1 plus 2 hours
Sample 7: T1 plus 4 hours
Sample 8: T1 plus 6 hours
Sample 9: T1 plus 24 hours
Sample 10: T1 plus 48 hours
Sample 11: T1 plus 168 hours (Day 8)
Sample 12: Pre dose on Cycle 5 Day 1

Table 6: PK Sampling Schedule for Cycle 1 Day 1 in Module 1 Dose Expansion

Sample 1: T0 Pre-dose (before the start of the infusion)
Sample 2: Immediately Post Infusion (T1)
Sample 3: T1 plus 15 minutes
Sample 4: T1 plus 30 minutes
Sample 5: T1 plus 1 hours
Sample 6: T1 plus 2 hours
Sample 7: T1 plus 4 hours
Sample 9: T1 plus 24 hours
Sample 11: T1 plus 168 hours (Day 8)
Sample 11: T1 plus 336 hours (Day 15)
Sample 12: Pre dose on Cycle 2 Day 1

Table 7: PK Sampling Schedule for Cycle 3 Day 1 in Module 1 Dose Expansion

Sample 1: T0 Pre-dose (before the start of the infusion)
Sample 2: Immediately Post Infusion (T1)
Sample 3: T1 plus 15 minutes
Sample 4: T1 plus 30 minutes
Sample 5: T1 plus 1 hours
Sample 6: T1 plus 2 hours
Sample 7: T1 plus 4 hours
Sample 8: T1 plus 6 hours
Sample 9: T1 plus 24 hours
Sample 10: T1 plus 168 hours (Day 8)
Sample 11: T1 plus 336 hours (Day 15)
Sample 12: Pre dose on Cycle 4 Day 1

Table 8: PK Sampling Schedule for Cycle 1 Day 1 in Module 2 (Arms 1 and 2)

Sample 1: T0 Pre-dose (before the start of the infusion)
Sample 2: Immediately Post Infusion (T1)
Sample 3: T1 plus 15 minutes
Sample 4: T1 plus 30 minutes
Sample 5: T1 plus 1 hours
Sample 6: T1 plus 2 hours
Sample 7: T1 plus 4 hours
Sample 8: T1 plus 24 hours
Sample 9: T1 plus 168 hours (Day 8)
Sample 10: Pre dose on Cycle 1 Day 15 (Module 2 Arm 1)/ Pre Dose Cycle 2 Day 1 (Module 2 Arm 2)

Table 9: PK Sampling Schedule for Cycle 3 Day 1 (Module 2 Arm 1) and Cycle 4 Day 1 (Module 2 Arm 2)

Sample 1: T0 Pre-dose (before the start of the infusion)
Sample 2: Immediately Post Infusion (T1)
Sample 3: T1 plus 15 minutes
Sample 4: T1 plus 30 minutes
Sample 5: T1 plus 1 hours
Sample 6: T1 plus 2 hours
Sample 7: T1 plus 4 hours
Sample 9: T1 plus 24 hours
Sample 11: T1 plus 168 hours (Day 8)
Sample 12: Pre dose on Cycle 4 Day 1 (Module 2 Arm 1) / Pre Dose Cycle 5 Day 1 (Module 2 Arm 2)

14.3 ANXA1 Samples

Please refer to the Lab Manual for further information.

14.4 Immunogenicity (ADA) Sample

Immunogenicity samples may be analysed by Alderley Analytical as required using the validated PK analysis method to determine the drug concentration in those samples. If the drug concentrations measured in these samples indicate the possibility of ADA presence (for example if the concentrations are unexpectedly low), an ADA assay may be developed to determine if ADAs are present.

Please refer to the Lab Manual for further information.

14.5 Immunophenotyping (TBNK and WBC) Analysis Samples

Please refer to the Lab Manual for further information.

14.6 Cytokine (Pro-Inflammatory) Analysis Samples

Please refer to the Lab Manual for further information.

14.7 Samples for Biobanking

Participants in this trial will be invited to permit the collection and long-term retention of samples for use in possible additional future research linked to trial data. Consent to participate in the Biobank is optional and not a requirement of participation in the main trial.

It is likely that new techniques and analytical methods will emerge during the trial, which enables further translational work and exploration of molecular diagnostics. No

additional samples will be obtained to support this research but excess tissue or blood following completion of all protocol required analysis will be sent to a licenced Biobank for storage.

Please refer to the Lab Manual for further information.

14.8 Sample Retention at End of Trial

The Sponsor has overall responsibility for custodianship of the trial samples. Laboratories are instructed to retain any surplus samples pending instruction from the Sponsor on use, storage or destruction. It is possible that new or alternative assays may be of future scientific interest. At the end of the research trial any surplus samples may be retained for use in other projects that have received ethical approval. Hence, any surplus trial samples may be transferred to a licensed tissue bank where they will be managed in accordance with applicable host institution policies and the Human Tissue Act (HTA) requirements.

14.9 Withdrawal of Consent for Sample Collection and/or Retention

A participant may withdraw consent to provide samples for research at any time without giving a reason. The Investigator must ensure that their wishes are recorded in the medical record and will inform the LCTC and Sponsor accordingly. The Investigator should discuss with participants the valuable use of samples that have already been provided and under circumstances where these samples have already been processed and anonymised, it would not be possible to destroy such samples.

15 INVESTIGATIONAL MEDICINAL PRODUCTS (IMPs)

15.1 Name of IMPs

MDX-124 for IV infusion is formulated at 30 mg/mL in 20 mM histidine, 8% (w/v) sucrose, 0.01% (v/v) polysorbate-20 and water for injection, at pH 6.3.

In Module 2 Arm 1 the following IMPs will be used**:** 1000mg/m^2 gemcitabine and 125mg/m^2nab-paclitaxel.

15.2 Module 2 IMP Treatment Provision, Storage, Dosing and Management

In Module 2 Arm 1 the combination treatments are standard of care and will be sourced from the site pharmacy. The site pharmacy will follow their applicable SOPs and policies for labelling and accountability of the IMPs.

For the storage, administration, dosing, dose reductions and management of the combination treatments please refer to the relevant Summary of Product Characteristics (www.medicines.org.uk).

15.3 MDX-124 Dose

Please refer to Section 10.2.

15.4 Duration of Treatment

Dosing should continue until there is evidence of disease progression, unacceptable toxicity or at the participant's request.

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

Reasons why participants may need to be withdrawn prior to disease progression or unacceptable toxicity are described in Section 13 Participant Withdrawal.

15.5 Management of MDX-124 Administration

Please refer to the administration guidance in the current version of the Pharmacy Manual for further information on the preparation and administration of MDX-124.

Participants will be administered MDX-124 through a central venous access device (CVAD) or through peripheral venous administration. The Investigator will decide which method is appropriate for the individual trial participant. The infusion should be administered over 30 minutes but can be adjusted following discussion with the Sponsor and/or DEC. The start and stop of the infusion along with the dose and volume administered must be documented in the medical records and eCRF.

MDX-124 is not known to be a vesicant.

15.6 MDX-124 Dose Modification

Please refer to Section 10.2.4.3.

15.7 MDX-124 Calculating and Recalculating Dose

The participant's weight at baseline will be used to determine the dose of MDX-124 for the duration of the trial. If a participant's weight changes by ≥10% during the trial, the dose of MDX-124 should be recalculated. If a participant's weight changes by <10% the dose may be adjusted according to local policy/clinician's discretion, but this is not an absolute requirement.

15.8 MDX-124 Management of Overdose

MDX-124 is contraindicated for all conditions other than those mentioned in this protocol.

Should an overdose occur, there is no known antidote. Symptoms and signs attributed to the overdose should be treated symptomatically. Any participant, who inadvertently receives a higher dose than intended should be monitored closely, managed with appropriate supportive care until recovery and followed up expectantly.

Such overdoses should be recorded as follows:

- An overdose will be recorded on the dosing eCRF, and any associated AEs/serious AEs (SAEs) will be recorded as the AE diagnosis/symptoms on the relevant AE/SAE eCRF in REDCap.
- An overdose with no associated symptoms is only reported on the dosing eCRF.

If an overdose occurs during the trial, site personnel must inform LCTC and Sponsor within one working day, i.e., immediately but no later than the end of the next business day of when they become aware of it. The LCTC will be responsible for informing the DEC immediately.

15.9 MDX-124 Supply

MDX-124 will be provided to the local hospital pharmacies in clear glass vials that are filled, sealed with a stopper and flip off overseal. The vials are then packaged in a cardboard outer box.

Please refer to the current version of the Pharmacy Manual for detailed guidance on dose preparation and administration.

All supportive medications are to be sourced and funded locally.

All combination medications are to be sourced locally.

15.10 MDX-124 Ordering

The PI and Pharmacy are responsible for monitoring stock levels and placing a re-order when required. The LCTC will provide oversight on behalf of the Sponsor and accountability logs should be provided to the Sponsor and LCTC at least monthly. Please refer to the current version of the Pharmacy Manual for further information.

15.11 Receipt of MDX-124

Upon receipt, complete details on the Acknowledgement of Receipt Form and return to vendor. If supplies are damaged on arrival, quarantine the supplies and contact the Sponsor and LCTC.

15.12 MDX-124 Handling and Storage

MDX-124 must be stored in accordance with the guidance on the vial and carton labels. No one, other than adequately trained pharmacy staff, is permitted to handle MDX-124. MDX-124 product must never be removed except for the purposes of dispensing.

15.13 MDX-124 Labelling

The responsible Pharmacy will ensure that MDX-124 supplies dispensed for trial use are appropriately labelled in accordance with all applicable regulatory requirements.

15.14 MDX-124 Accountability

Full drug accountability records must be maintained for MDX-124 and the combination treatments using the Drug Accountability Logs provided. Hospitals may amend the Drug Accountability Logs provided or use their own accountability logs if it captures all the information requested on the Drug Accountability Logs and is prior approved by the Sponsor.

The drug dispensing and inventory logs should be kept up to date and must contain the following information: participant identifier, date and quantity received at site, date and quantity dispensed, date and quantity returned/destroyed at site.

Copies of the Drug Accountability Logs must be sent to the Sponsor and LCTC at least monthly by email.

The inventory must be available for inspection by the monitor.

At the conclusion of the trial the overall numbers of drug shipped to the centre, the number dispensed, and the number destroyed or returned will be provided by the pharmacy. An account must be given of any discrepancy.

15.15 MDX-124 Returns from Participants

Not applicable.

15.16 MDX-124 Destruction

Used and partially used vials should be destroyed per local policy and a log should be maintained.

A copy of the certificates of disposal should be filed in the trial file.

Authorisation from the Sponsor must be gained prior to destroying expired, damaged, or excess undispensed stock and this must be documented in the destruction log.

16 OTHER MEDICATIONS

16.1 Support Medication

During the dose escalation stage in Modules 1 and 2, during Cycle 1 the participants may only receive standard prophylactic medical treatment for nausea, vomiting, allergy and/or diarrhoea. Following the completion of Cycle 1, participants may then receive additional support medication.

There are no restrictions on supportive medication in the Module 1 or Module 2 expansion cohorts.

16.2 Concomitant Medication and Non-Drug Therapies

Concomitant medication may be given as medically indicated. All participants will be asked to provide a complete list of prescription and over-the-counter medications that have been taken within the previous 4 weeks prior to the first dosing visit. They must also inform the Investigator about any new medication started while in the trial.

The following are prohibited in Module 1 and 2:

- Glucocorticoids induce ANXA1, therefore high doses of agents with high glucocorticoid potency (defined as >2mg/day dexamethasone or >15mg/day prednisolone) are prohibited. Agents with high mineralocorticoid potency (*e.g*. aldosterone) have less anti-inflammatory properties, therefore, this is allowed as an alternative.
- Live vaccines are prohibited during the study and for 3 months after the last dose of study therapy.
- Drugs that have anti-cancer characteristics or other compounds such as herbal, “alternative” or traditional Chinese medicine which may have anti-cancer properties.

The following are prohibited in Module 2:

- Arm 1:
    - Drugs that inhibit or induce CYP3A4 as these alter the metabolism of nab-paclitaxel to cause excessive toxicity or loss of efficacy.

17 EVALUATION OF RESPONSE

17.1 Measurement of Disease for Solid Tumour

Disease will be measured according to the RECIST version 1.1 criteria in combination with tumour specific evaluation criteria, which incorporates the relevant tumour markers (e.g., GCIG criteria utilising CA125).

17.2 Tumour Assessment

A clinical and radiological evaluation of malignancy, as judged appropriate by the Investigator, and in line with the protocol, must be performed before starting dosing where applicable. The same methods that detect lesions at baseline will be used to follow these lesions throughout the trial. To ensure compatibility, the radiological assessments used to assess response must be performed using identical techniques. Imaging based evaluation is preferred to evaluation by clinical examination when both methods have been used to assess the anti-tumour effect of a treatment. Disease must be measured according to the RECIST version 1.1 (Appendix 2: Measurement of disease - recist criteria).

Baseline evaluations

These will include radiological measurements of the extent of disease by CT scan. All areas of disease present must be mentioned (even if specific lesions are not going to be followed for response) and the measurements of all measurable lesions must be recorded on the scan reports. Any non-measurable lesions must be stated as being present. For clinical measurements, documentation by colour photography including a ruler to estimate the size of the lesion is recommended to aid external independent review of responses.

Baseline tumour markers (if appropriate) should be collected to enable evaluation using tumour specific evaluation criteria.

Evaluations during dosing and off-trial

Tumour assessment will be repeated as per the schedule of events given or more frequently if clinically indicated. All lesions measured at baseline must be measured at subsequent disease assessments and recorded on the scan reports. All non-measurable lesions noted at baseline must be reported as present or absent.

Investigators must ensure that their radiologists are aware of the requirement to follow up and measure every target lesion mentioned at baseline and comment on the non-target lesions in accordance with RECIST version 1.1 criteria.

Baseline tumour markers will be collected on Day 1 of each cycle.

18 SAFETY REPORTING

Adverse event monitoring starts at time of consent until 28 days after the final dose of IMP has been administered. The Investigator will monitor each participant for clinical and laboratory evidence of AEs on a routine basis throughout the trial.

Should an Investigator become aware of any IMP related SAEs following this period these must also be reported as stated below. All reportable AEs will be followed to a satisfactory conclusion. Any reportable drug-related AEs that are unresolved at the end of treatment visit are to be followed up by the Investigator until resolution or stabilisation.

All AEs reported to the LCTC will be processed according to internal SOPs. LCTC may request additional information for any AE as judged necessary.

18.1 Adverse Event Definition

An AE is any untoward medical occurrence in a trial participant temporarily associated with the administration of an IMP, whether or not considered related to the IMP. An AE can therefore be any unfavourable and unintended sign, symptom, disease (new or exacerbated) and/or significant abnormal laboratory or physiological observation temporally associated with the use of a medicinal product. For authorised medicinal products, this also includes failure to produce expected benefits (i.e., lack of efficacy), abuse or misuse. All AEs regardless if they are related to study drug or not should be reported.

The assessment of seriousness of safety events should be performed by an appropriately delegated, medically qualified member of the site research team.

Progression of underlying disease which is **deemed to be related to IMP** by the investigator should be reported as an AE/ SAE. Progression of underlying disease which is **deemed not to be related to IMP** by the investigator should not be reported as an AE/ SAE.

A **Serious Adverse Event (SAE)** is any AE, regardless of dose, causality or expectedness, that:

Results in death	
Is life-threatening	This refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event which hypothetically might have caused death if it were more severe.
Requires inpatient hospitalisation	In general, hospitalisation signifies that the participant has been admitted (usually involving at least an

or prolongs existing inpatient hospitalisation	overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalisation are AEs. If a complication prolongs hospitalisation or fulfils any other serious criteria, the event is serious. When in doubt as to whether hospitalisation occurred or was necessary, the AE should be considered serious. Hospitalisation for disease progression is not considered a SAE, unless the event is deemed related to IMP by the PI.
Results in persistent or significant incapacity or disability	This means a substantial disruption of a person's ability to conduct normal life functions. It does not include experiences of relatively minor medical significance or accidental trauma (e.g., sprained ankle), which do not constitute a substantial disruption.
Is a congenital anomaly or birth defect	Congenital anomalies can be defined as structural or functional anomalies that occur during intrauterine life. **Also called birth defects, congenital disorders, or congenital malformations**, these conditions develop prenatally and may be identified before or at birth, or later in life.
Is any other medically important event	Defined as an event that may jeopardise the participant or may require intervention to prevent one of the outcomes listed above. Any new primary cancer must be reported as an SAE.

An Adverse Reaction (AR) is any untoward and unintended response to an IMP related to any dose administered.

A Serious Adverse Reaction (SAR) is any SAE with any untoward and unintended response to an IMP related to any dose administered.

An Unexpected Adverse Reaction is an AR the nature and severity of which is not consistent with the information about the medicinal product in question set out in the Investigator's brochure (IB) or the Summary of Product Characteristics (SPC), which may be referenced where the IMP in question is a product with a marketing authorisation.

A Suspected Unexpected Serious Adverse Drug Reaction (SUSAR) is a SAR, the nature or severity of which is not consistent with the applicable product information (e.g., IB for an unapproved IMP or SPC for an approved product). The IB for MDX-124 will be used as the RSI. The SPC of the approved combination medications will be used as the RSI.

18.2 Clinical Laboratory Abnormalities and Other Abnormal Assessments as AEs and SAEs

Abnormal laboratory findings (e.g., clinical chemistry, haematology, urinalysis) or other abnormal assessments (e.g., ECGs, X-rays and scans) that are judged by the

Investigator as clinically significant will be recorded as AEs or SAEs if they meet the definitions given above.

Clinically significant abnormal laboratory findings or other abnormal assessments that are detected during the trial or are present at baseline and significantly worsen following the start of the trial will be reported as AEs or SAEs. However, clinically significant abnormal laboratory findings or other abnormal assessments that are associated with the disease being studied, unless judged by the Investigator as more severe than expected for the participant's condition, or that are present or detected at the start of the trial and do not worsen, will not be reported as AEs or SAEs.

The Investigator will exercise their medical and scientific judgment in deciding whether an abnormal laboratory finding, or other abnormal assessment is clinically significant.

18.3 Determining Adverse Event Causality

The assessment of "relatedness" of an AE or a SAE must be determined by a medically qualified individual and is primarily the responsibility of the PI at site or agreed designee. The assessment of relatedness is made using the following:

Classification	Definition
Related	• Starts within a time related to the IMP administration *and* • A causal relationship between the IMP and the AE is at least a reasonable possibility.
Not related	• The time association or the participant's clinical state is such that the IMP has not had an association with the observed effect. • The AE is not associated with the IMP administered.

The Investigator must endeavour to obtain sufficient information to confirm the causality of the AE (i.e., relation to surgery, IMP, background treatment, other illness, progressive malignancy etc) and give their opinion of the causal relationship between each AE and IMP. This may require instituting supplementary investigations of significant AEs based on their clinical judgement of the likely causative factors and/or include seeking a further specialist opinion.

In the case of discrepant views on causality between the treating investigator and The Sponsor, the opinion of the treating investigator will never be downgraded, and the MHRA/REC will be informed of both causality assessments.

18.4 Reference Safety Information (RSI) for Assessment of Expectedness

The Reference Safety Information (RSI) for the assessment of expectedness is Section 6.6 of the current approved IB for MDX-124.

In Module 2 Arm 1 when MDX-124 is administered in combination with an anti-cancer treatment, Section 4.8 of the summary of product characteristics for that anti-cancer treatment will be used to assess expectedness.

18.4.1 Substantial Changes to the Reference Safety Information

If there is a change to the RSI, an update that impacts on participant safety, or if the risk-benefit assessment or clinical management of trial participants is affected the updated IB will be submitted as a substantial amendment to the Regulatory Authority and Research Ethics Committee (REC).

All IB updates will be notified to clinical sites for their information.

Changes that impact on participant safety or alter the risk-benefit assessment may require changes to the trial documentation such as the participant information sheet.

18.4.2 Non-Substantial Changes to the Reference Safety Information

If changes to the RSI are minor and do not include new expected reactions, do not impact on participant safety or alter the risk-benefit assessment or the clinical management of the trial participants, the RSI will not require approval by the MHRA and REC and should be sent to sites promptly for information.

18.5 Suspected Unexpected Serious Adverse Drug Reactions (SUSARs)

All SUSARs must be reported to the MHRA and REC by the LCTC within the required timelines:

- Fatal or life threatening SUSARs will be reported within 7 days of the LCTC receiving the minimum information (Section 18.6). Any additional information will be reported within eight days of sending the first report.
- All other SUSARs will be reported within 15 days of the LCTC receiving the legally defined minimum information (Section 18.6).

In addition, other safety issues qualify for expedited reporting where they might materially alter the overall risk benefit assessment of an IMP or impact IMP administration or the overall conduct of the trial.

18.6 Expedited Reporting of SAEs

Events which are assessed as “serious” must be recorded in more detail on a SAE eCRF by the clinical site; a single form is used for each individual event (i.e. a single diagnosis), though multiple symptoms can be recorded. SAE eCRFs collect additional data regarding the nature of event, date of onset, severity, any treatment given, outcome and causality.

A SAE eCRF must be entered and submitted within the REDCap eCRF immediately and within 24 hours from becoming aware. If the eCRF is not available, then a paper copy of the SAE can be completed and sent to LCTC (lctcsafe@liverpool.ac.uk) immediately and in no circumstances later than 24 hours from becoming aware.

The SAE eCRF should be completed by an appropriately delegated member of the site research team; the assessments of seriousness and causality must be performed by an appropriately authorised medically qualified doctor. The following is considered the minimum reporting information and must be provided in SAE reports:

- Participant study number
- Study site identifier and name of reporting site staff member

- Description of the event, including date of onset
- Suspect IMP
- Seriousness assessment
- Causality assessment

If the SAE has not been reported within 24 hours of awareness, a reason for lateness must be provided when sending the SAE Report Form.

Investigators should also adhere to their local trust policy for incident and SAE reporting in research.

18.7 Follow-up of Serious Adverse Events

The initial SAE report shall be followed by detailed follow-up reports as additional information becomes available and to report the outcome of the event. Follow up information must be provided as requested by the LCTC.

A follow-up report must be completed when the SAE resolves or is unlikely to change. If new or amended information on a reported SAE becomes available, the Investigator should report this on a new SAE form using the completion guidelines.

18.8 Reporting Adverse Events on the eCRF

All AEs, including SAEs, must be recorded on the eCRF for that participant. The information provided will include date of onset, event diagnosis (if known) or sign/symptom, severity, outcome, resolution date, and relationship of the AE to IMP. Any concomitant medications or any other treatment for the event must be listed. The Investigator must provide the cause for SAEs considered to be unrelated to the IMP. Sites should ensure data entered into the eCRF is consistent with the SAE report information where applicable.

Each separate AE episode must be recorded. For example, if an AE resolves completely or resolves to baseline and then recurs or worsens again, this must be recorded as a separate AE.

AEs may be spontaneously reported by the participant and/or in response to an open question from trial personnel or revealed by observation, physical examination or other diagnostic procedures. Any clinically relevant deterioration in laboratory assessments or other clinical finding is considered an AE.

AEs and SAEs must be reported from the first date of consent up to and including 28 days after administration of the last dose of trial medication. Any SAE that occurs at any time after completion of IMP administration or after the designated follow-up period that the Sponsor-Investigator and/or Sub-Investigator consider to be related to any IMP must be reported.

Terms and Grading of Events
All AEs and toxicities must be graded according to the NCI-CTCAE version 5.0.

18.9 Events Exempt from Being Reported as AE/SAEs

Progression of underlying disease assessed as unrelated to IMP

Progression of underlying disease which is deemed to be related to IMP by the investigator should be reported as an AE/SAE.

Disease progression and resultant death will be captured on the eCRF. AEs including hospitalisation that are clearly consistent with disease progressions will not be reported as individual AE/SAEs. Clinical symptoms of progressions will only be reported as AEs if the symptom cannot be determined as exclusively due to the progression of the underlying malignancy or does not fit the expected pattern of progressions for the disease under study.

Every effort should be made to document the objective progression of underlying malignancy. In some cases, the determination of clinical progression may be based on symptomatic deterioration. For example, progression may be evident from clinical symptoms but not supported by tumour measurements. Or the disease progression may be so evident that the Investigator may elect not to perform further disease assessments.

Elective admissions and supportive care

Elective admissions to hospital for participant convenience or for planned procedures or investigations or treatment as specified in this protocol and standard supportive care are not SAEs, and do not require SAE reporting.

18.10 Death on Trial

Death is to be recorded on the Death and SAE eCRF and submitted. The Investigator must clearly state whether the death was due to disease under study and whether a causal relationship to the trial IMP or other protocol treatment intervention is suspected.

19 PREGNANCY

Pregnancies (in a participant or partner) occurring while participating in this trial require expedited reporting. A pregnancy form should be completed and emailed to the LCTC within the same timelines as an SAE. All reported pregnancies should be followed, and the outcome reported using the same form. If the outcome of the pregnancy meets any of the criteria for seriousness, it must also be reported as an SAE and followed up. Examples of pregnancy outcomes that are SAEs include reports of:

- Congenital anomalies or developmental delay, in the foetus or the child.
- Foetal death and spontaneous abortion.
- Suspected ARs in the neonate that are classified as serious.

Women who become pregnant should be withdrawn from trial treatment immediately.

20 END OF TRIAL

The end of the trial is defined to be the date on which data for all participants is frozen and data entry privileges are withdrawn from the trial database. The trial may be closed prematurely by the DEC.

Site and closure activities will be centrally coordinated and conducted in accordance with LCTC processes regardless of whether the trial closes as planned or prematurely. This includes activities such as:

- End of Trial notification to REC and competent authority (MHRA).
- Trial-related materials reconciled and returned/disposed of as appropriate
- All site data entered onto the study database, discrepancies raised and satisfactory responses received.
- Quality Control checks of the Investigator Site Files, Pharmacy Files and Trial Master File as appropriate.

The Sponsor reserves the right to terminate the trial earlier at any time. In terminating the trial, they must ensure that adequate consideration is given to the protection of the participant's best interests.

21 STATISTICAL CONSIDERATIONS

An overview of all statistical principles for the trial are included and a full Statistical Analysis Plan (SAP) will be finalised prior to first patient being recruited.

21.1 Sample Size

21.1.1 Module 1

Module 1 dose escalation will utilise a BOIN design where the decision to escalate or de-escalate the dose is determined by the DLT rate observed at the current dose. This utilises an accelerated titration design, which is more likely than the modified 3+3 design to correctly select the MTD and has a substantially lower risk of overdosing participants and generally a higher probability of correctly selecting the MTD compared to the modified toxicity probability interval (mTPI) design[30].

It is anticipated that a sample size of 24 evaluable participants will be required to determine the Single Agent RP2D. An additional 20 participants will then be enrolled at the Single Agent RP2D in the expansion cohort. The estimated MTD is the highest dose level with observed toxicity rate less than 30%.

During dose escalation an evaluable participant is defined as a participant who has received at least 90% of the intended dose of MDX-124 in Cycle 1 and completed the 21-day DLT evaluation period. Participants who experience a DLT which prevents them from completing the 21-day DLT evaluation period will also be evaluable. Participants who do not experience a DLT and withdraw from the trial prior to completion of the 21-day evaluation period will not be evaluable for dose escalation decisions.

During the Module 1 dose expansion all participants who receive a dose will be evaluable for safety. All participants who receive a dose and a post baseline scan will

be evaluable for efficacy. Participants who are not evaluable for safety may be replaced.

21.1.2 Module 2

When administered as a single agent (Arm 2) MDX-124 will be administered at the Single Agent RP2D. As the dose has been determined in Module 1 the 3+3 design will not be required, and a 20-participant expansion cohort will be enrolled.

Arm 1 which combines MDX-124 with a standard of care combination treatment will utilise a modified ‘3+3’ design with the DLT assessed and the MTD declared on 6 participants. Since the number of dose levels is not fixed prior the start of the trial, it is not possible to provide a definitive sample size. However, it is anticipated that around 12 participants (range of 6 to 15) will be required to determine the Combination RP2D in each arm. Further participants will be enrolled in an expansion cohort at the Combination RP2D until 20 participants have been treated with the selected dose.

During the Arm 1 dose escalation an evaluable participant is defined as having received at least 90% of the intended dose of MDX-124 and the combination treatment in Cycle 1 and completed the 28-day DLT evaluation period. Participants who experience a DLT which prevents them from completing the 28-day DLT evaluation period will also be evaluable. Participants who do not experience a DLT and withdraw from the trial prior to completion of the 28-day evaluation period will not be evaluable for dose escalation decisions and will be replaced.

During the dose expansion all participants who receive a dose will be evaluable for safety. All participants who receive a dose and a post baseline scan will be evaluable for efficacy. Participants who are not evaluable for safety may be replaced.

21.2 Trial Analysis Populations

The analysis populations defined for the trial analyses are:

21.2.1 All Participants Analysis Set

The ‘all participants’ analysis set comprises all participants who signed informed consent and will be used for the summary of disposition.

21.2.2 Efficacy Analysis Set

The efficacy analysis set will comprise all participants who have received 1 dose of MDX-124 and a post baseline scan. All efficacy data will be presented by IMP received. If a participant has a dose reduction, they will still be summarised in the cohort they initially started dosing in.

21.2.3 Safety Analysis Set

The safety analysis set will include all participants who receive at least 1 dose of IMP. Safety and tolerability data will be presented by IMP received.

21.2.4 PK Analysis Set

The PK analysis set will include all participants who have PK samples collected.

21.3 Planned Analysis

21.3.1 Safety Analysis

The Safety Analysis Set will be used for the safety data analysis.

In Modules 1 and 2 in order for a participant to be considered evaluable for the analysis of a DLT, they must either have;

- had a DLT within the defined DLT review period **or**
- received at least 90% of the prescribed dose of IMP in Cycle 1 and completed all safety evaluations within the defined DLT review period after the first administration of IMP without experiencing a DLT.

A participant without a DLT will be replaced if they did not adequately complete the defined DLT review period (i.e., discontinue prematurely due to a reason unrelated to IMP) or if that participant received <90% of the prescribed dose.

21.3.2 Data Monitoring

Accumulating data will be assessed by the DEC who will have access to the study data and will provide recommendations with respect to doses to be administered and cohort size.

21.3.3 Efficacy Analysis

Efficacy analysis will be performed on the best overall response rate, the duration of objective response, progression free survival (PFS) and overall survival.

Full details on all data manipulation and analytical approaches are included in the SAP. The planned efficacy analyses are:

- **Best Overall Response Rate:** is measured as an ordered categorical endpoint with results presented in terms of frequencies of counts with associated percentages.
- **Duration of Objective Response**: rate is measured as the unit of time (in days) during which the patient was determined to have either a partial response (PR) or complete response (CR) as determined by RECIST (1.1).
- **Progression Free Survival (PFS):** is 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.
- **Overall Survival (OS)**: is measured as the time from registration until death by any cause. Rates of OS will be estimated using the Kaplan Meier approach.

21.3.4 Pharmacokinetic (PK) Analysis

The PK analysis set will be used for the PK data analysis.

Data obtained from the analysis of ADA samples may be incorporated in the PK analysis.

Summary statistics will be tabulated for the PK parameters of MDX-124 by dose and trial cycle.

21.4 Subgroup Analysis

21.4.1 Module 1

Dose cohorts will be described separately.

21.4.2 Module 2

Arms will be described separately. The dose cohorts within each arm will also be described separately.

21.5 Interim Analysis

Interim analysis inherent in the BOIN and 3+3 design will be carried out for dose escalation as described in Section 10.2.2.

21.6 Procedure for Reporting and Deviation from the Original Statistical Analysis Plan

Any deviation(s) from the original SAP will be described and justified in the final report and in any dissemination.

21.7 Final Analysis

Based upon projected accrual rates, this trial is expected to complete recruitment within 48 months of opening to recruitment. Final analysis will be after all participants have been followed up for at least 12 months or until Last Participant Last Visit (LPLV) and database has been locked.

22 TRIAL COMMITTEES

22.1 Dose Escalation Committee (DEC)

The Chief Investigator will chair a DEC with responsibility for overseeing the successful conduct and publication of the trial in accordance with the protocol. The DEC will review safety and dose escalations. The full roles, responsibilities and operations of the DEC will be outlined in the DEC Charter.

Members of the DEC will include:

- Chief Investigator
- LCTC trial management staff (non-voting)
- Trial Statistician(s) (non-voting)
- PI from participating sites
- Independent Investigator
- Trial management staff from Medannex (non-voting)

22.2 Clinical Oversight Group (COG) and Trial Communication

The Clinical Oversight Group will comprise:

- Chief Investigator
- LCTC trial management staff (including operations, statistics, programmers)
- Trial management staff from Medannex
- PI and staff (i.e., sub investigators, research nurses, trial coordinators) from participating sites

A regular (e.g., weekly or fortnightly) trial management call comprising Sponsor and LCTC staff and staff from the participating sites will be held once enrolment has been opened. Minutes of the call will be distributed to all applicable trial management and participating site staff (i.e., PI, sub investigators, trial nurse and trial coordinator). The frequency of the call may increase, or decrease based on recruitment and the number of active participants.

The purpose of the call is to facilitate communication between the trial management team and the site staff and communication between the participating sites. Items for discussion on this call may include the following (if applicable):

- Review of current recruitment including availability of participant slots and pre-screening activities at the participating sites.
- Review of ongoing participants.
- Review of safety information including DLTs and AE and/or SAEs deemed pertinent by the participating site.
- IMP supply.
- Communication of trial administrational tasks. For example, upcoming substantial amendments, expected dates of upcoming data cuts, etc.
- General questions and discussion.

As a result of discussions on this call it may be determined to convene a meeting of the DEC to enable a more detailed review to take place.

All suspected DLTs should be reported promptly (within 24 hours) to the LCTC and the Sponsor. The LCTC will then notify the other participating sites immediately.

22.3 Sponsor/LCTC Operational Group

The Sponsor LCTC operational group will comprise:

- Sponsor Representative(s)
- LCTC Trial Management team members

This group will meet regularly (i.e., weekly) and the remit is the day-to-day management and Sponsor oversight of the trial to deliver all aspects of the Clinical Trial Agreement. The CI may attend if issues requiring their input are being discussed. The meeting will not have a standard agenda but summary notes and actions will be circulated by Medannex prior to the next meeting.

Sponsor and LCTC will also hold their own internal meetings on a regular basis.

23 DATA MANAGEMENT

23.1 Database

Data management will be performed via a web-based, bespoke trial database which is dedicated to and validated for electronic data capture. The LCTC will provide sites with instructions and a link for training purposes.

The participants will be identified by a unique trial specific number and/or code in any database. The participant's name and any other identifying detail will NOT be included in any trial data electronic file.

23.2 Electronic Case Report Forms (eCRF)

The Investigator and trial site staff will ensure that data collected on each participant is recorded in the eCRF as accurately and completely as possible. All appropriate laboratory data, summary reports and Investigator observations will be transcribed into the eCRF from the relevant source data held in the site medical record(s). eCRF entries will not contain any source data. It is important to ensure that:

- the relevant eCRFs are completed.
- all eCRF data are verifiable in the source documentation, or the discrepancies must be explained.
- eCRF sections are completed in a timely fashion, as close to the visit or event being recorded as possible.
- Data queries are resolved and documented by authorised trial staff in a timely fashion. The reason for the change or correction should be given where appropriate.
- As much data as possible is entered and cleaned in preparation for each trial database lock point.

Note: 'in a timely fashion' means within no more than 3 working days of the initial event and within 3 days of receipt of a data query unless otherwise specified.

The above considerations also apply to participants who are withdrawn early. If a participant withdraws from the trial, the reason must be noted on the appropriate form and must be followed up as per protocol Section 13.

23.3 Accounting for Missing, Unused or Spurious Data

Missing data will be chased up and supplemented where possible after consultation with the Investigator. Unused data will be retained as for used data. The completeness and correctness of the data will be monitored as per the monitoring plan.

24 CLINICAL STUDY REPORT

All clinical data will be presented at the end of the trial as data listings. These will be checked to confirm the lists accurately represent the data collected during the trial. The trial data will then be locked, and a final data listing produced. The clinical trial

report will be based on the final data listings. The locked trial data may then be used for analysis and publication.

Within 12 months of the “end of trial” (Section 20) the Clinical Study Report (CSR) will be prepared and submitted to the MHRA and REC.

25 TRIAL SITE MANAGEMENT

25.1 Trial Site Responsibilities

The PI (or lead clinician for the trial site) has overall responsibility for conduct of the trial but may delegate responsibility where appropriate to suitably experienced and trained members of the trial site team. All members of the trial site team must complete the site Staff Delegation of duties log provided prior to undertaking any trial duties. The PI must countersign and date each entry in a timely manner, authorising staff to take on the delegated responsibilities.

25.2 Trial Site Set Up and Activation

The PI leading the investigational trial site is responsible for providing all required core documentation. The investigator(s)/institution(s) will permit trial-related monitoring, audits, REC review, and regulatory inspection(s), providing direct access to source data/documents. Mandatory Site Training organised by the LCTC must be completed before the site can be activated. The LCTC will check to confirm that the site has all the required trial information/documentation and is ready to recruit. The site will then be notified once they are activated and able to enter participants.

25.3 Trial Documentation

The LCTC will provide an Investigator File and Pharmacy File to each investigational site containing the documents needed to initiate and conduct the trial. The LCTC must review and approve any local changes made to any trial documentation including participant information and consent forms prior to use. Additional documentation generated during the trial, including relevant communications, must be retained in the site files as necessary to reconstruct the conduct of the trial.

26 REGULATORY AND ETHICAL CONSIDERATIONS

The Sponsor, LCTC and Investigators will ensure that this protocol will be conducted in compliance with the UK Medicines for Human Use (Clinical Trials) Regulations[40] and the applicable policies of the sponsoring organisation. Together, these implement the ethical principles of the Declaration of Helsinki (1996).

26.1 Ethical Conduct of the Trial and Ethics Approval

The protocol, participant information sheet and consent form, and any other information that will be presented to potential trial participants will be reviewed and approved by an appropriately constituted, independent REC.

26.2 Regulatory Authority Approval

This trial will be conducted under a HRA Combined Review Clinical Trials Authorisation (CTA) which will be jointly reviewed by the MHRA and REC. Approval to conduct the trial will be obtained from the MHRA as part of a combined review prior to initiating the trial.

26.3 NHS Research Governance

Investigators are responsible for ensuring they obtain local trust management agreement to conduct the trial in accordance with local arrangements and policies.

26.4 Amendments to the Clinical Trial Authorisation

Amendments are changes made to the trial following initial clinical trial authorisation. The Sponsor will determine if the amendments are substantial or non-substantial.

Confirmation of all applicable REC, regulatory and local approvals must be in place prior to implementation by Investigators. The only exceptions are for changes necessary to eliminate an immediate hazard to trial participants (see below).

The Sponsor will determine the Investigator's need to update participants (or their authorised representatives, if applicable) whenever new information (in nature or severity) becomes available that might affect the participant's willingness to continue in the trial. The Investigator must ensure this is documented in the participant's medical notes and the participant is re-consented if appropriate.

26.5 Urgent Safety Measures

An urgent safety measure (USM) is a procedure to protect clinical trial participants from any immediate hazard to their health and safety that has not previously been defined by the protocol. It can be put in place prior to authorisation by the REC and the MHRA.

The Sponsor will notify the MHRA and REC immediately and, in any event, within 3 days that such a measure has been taken and the reasons why it has been taken. The initial notification to the REC and MHRA will be by telephone (ideally within 24 hours) and a notice in writing will be sent within 3 days, setting out the reasons for the USM and the plan for further action. After discussion with the REC and MHRA, further action will be agreed, which may include submission of a substantial amendment, a temporary halt, or permanent termination of the trial.

Following notification, if a substantial amendment is required this must be submitted as soon as possible to the REC and ideally within 2 weeks to the MHRA. If the study is temporarily halted it may not recommence until authorised to do so by the REC and MHRA. If the study is permanently terminated before the date specified for its conclusion (in the original applications to REC and MHRA), the Sponsor should notify the REC and MHRA within 15 days of the date of termination by submitting the formal end of trial notification.

26.6 Temporary Halt

The Sponsor reserves the right to place recruitment to this protocol on hold for short periods for administrative reasons or to declare a temporary halt. A temporary halt is defined as a formal decision to:

- interrupt the dosing of participants already in the trial for safety reasons;
- stop recruitment on safety grounds; or
- stop recruitment for any other reason(s) considered to meet the substantial amendment criteria, including possible impact on the feasibility of completing the trial in a timely manner.

The temporary halt will be reported via substantial amendment procedure. The trial may not restart after a temporary halt until a further substantial amendment to re-open is in place. If it is decided not to restart the trial this will be reported as an early termination.

26.7 Protocol Deviations and Serious Breaches

Deviations from, breaches or violations of, or non-compliance to either the protocol, the conditions or principles of GCP, and MHRA and REC requirements will be handled based on their nature and severity.

Non-Serious Breaches

Protocol deviations and other non-serious breaches of GCP will be managed according to local site and LCTC procedures as appropriate. They will be reported to trial oversight committees.

Serious Breaches

A breach of the protocol or GCP is ‘serious’ if it meets the definition of being “likely to affect to a significant degree the safety or physical or mental integrity of the trial participants, or the scientific value of the trial”. This assessment can only be determined by the Sponsor.

If any persons involved in the conduct of the trial become aware of a potential serious breach, they must immediately report this to the LCTC who will in turn notify the Sponsor within 1 working day. The Sponsor will assess the breach and determine if it meets the criteria of a ‘serious’ breach.

The Sponsor may seek advice from medical expert members of the DEC in determining whether or not the breach is likely to affect to a significant degree the safety, physical or mental integrity of participants.

The Sponsor may seek advice from the Trial Statistician in determining whether or not the breach is likely to significantly affect the scientific value of the trial. However, the Sponsor retains responsibility for the assessment of whether or not a breach meets the definition of ‘serious’ and is subject to expedited reporting to MHRA and REC.

Breaches confirmed as reportable will be reported to the MHRA within 7 days by the Sponsor and notified to the COG and DEC at their next meeting.

Open communication will be maintained to ensure appropriate corrective actions are taken and documented.

Incidents of protocol non-compliance will be recorded as protocol deviations, the incidence of which are monitored and reported to the COG.

26.8 Trial Reports

This protocol will comply with all current applicable MHRA and REC reporting requirements.

The LCTC will determine which documents need to be circulated to PI and other interested parties. Trial sites are responsible for forwarding trial documents they receive to their local trust as required.

26.9 Statement of Compliance

This document describes the trial including detailed information about procedures and recruitment. The protocol should not be used as an aide-memoir or guide for the treatment of other patients. Every care was taken in its drafting, but corrections or amendments may be necessary. Any amendments will be circulated to the Investigators participating in the trial, but sites entering patients for the first time are advised to contact the LCTC to confirm they have the most up to date version. Clinical problems relating to this trial should be referred to the Sponsor, via the LCTC.

This protocol defines the participant characteristics required for study entry and the schedule of treatment and follow-up. Participant recruitment will be undertaken in compliance with this document and applicable regulatory and governance requirements. Waivers to authorise non-compliance are not permitted.

Incidence of protocol non-compliance whether reported prospectively (e.g., where a treatment cannot be administered on a scheduled date as a result of public holidays) or retrospectively noted (e.g., as a result of central monitoring) are recorded as protocol deviations. These are monitored and reported to trial oversight committees.

The template content structure is consistent with the SPIRIT (Standard Protocol Item: Recommendations for Interventional Trials 2013) and has regard for the Health Research Authority guidance. Regulatory and ethical compliance information is located in Section 26.

The LCTC has achieved full registration by the UK Clinical Research Collaboration (www.ukcrc.org) as their standards and systems were assessed by an international review panel as reaching the highest quality. The LCTC has a diverse trial portfolio underpinned by methodological rigour, a GCP compliant data management system, and quality management system.

27 EXPENSES AND BENEFITS

Each participating centre will follow local regulations and policy on reimbursement of travel expenses. Reasonable travel costs will be covered by Medannex Limited.

28 QUALITY ASSURANCE

28.1 Risk Assessment

In accordance with the LCTC SOPs, a complete risk assessment has been completed in partnership with:

- Sponsor
- CI
- Trial Co-ordinator
- Trial Statistician
- LCTC Director

The contributors of this risk assessment have considered the participants, organisational and study hazards, the likelihood of their occurrence, and resulting impact should they occur.

The outcome of the risk assessment for a Clinical Trial of an Investigational Medicinal Product (CTIMP) has been considered as an overall risk level according to the classifications below:

CTIMP Type A = Comparable to the risk of standard medical care
CTIMP Type B = somewhat higher than the risk of standard medical care
CTIMP Type C = markedly higher than the risk of standard medical care

As this is a Phase 1b clinical trial of a previously unauthorised IMP it has been classified as a CTIMP Type C = markedly higher than the risk of standard medical care.

28.2 Monitoring

Regular monitoring will be performed according to the monitoring plan. Data will be evaluated for compliance with the protocol, completeness, and accuracy. The Investigator and institutions involved in the trial will permit trial-related monitoring and provide direct on-site access to all trial records and facilities if required. They will provide adequate time and space for the completion of monitoring activities.

Trial sites will be monitored centrally by checking incoming data for compliance with the protocol, consistency, completeness, and timing. The eCRF data will be validated using appropriate set criteria, range, and verification checks. The trial site must resolve all data queries in a timely manner. All queries relating to key outcome and safety data and any requiring further clarification will be referred back to the trial site for resolution.

Trial sites will also be monitored by site visit as necessary to ensure their proper conduct of the trial. Monitoring staff will be in regular contact with site personnel to check on progress and deal with any queries that they may have. Monitoring reports will be sent to the site in a timely fashion. The Investigator is expected to action any points highlighted through monitoring and must ensure that corrective and preventative measures are put into place as necessary to achieve satisfactory compliance.

Where sites need to provide copies of participant information to the LCTC for remote monitoring purposes, all participant personal identifiers must be obliterated.

Monitoring is conducted to ensure protection of patients participating in the trial and all aspects of the trial (procedures, laboratory, trial intervention administration and data

collection) are of high quality and conducted in accordance with Sponsor and regulatory requirements.

A detailed Trial Monitoring Plan has been developed and agreed by the Sponsor to describe the responsibilities, frequency, and level of detail for monitoring. This will be dependent on the documented risk assessment of the trial which determines the level and type of monitoring required for specific hazards. All processes may be subject to monitoring, e.g., enrolment, consent, adherence to trial interventions, accuracy and timeliness of data collection.

Trial Oversight Committees related to the monitoring of the trial are detailed in Section 22.

Monitoring will involve a combination of central, remote and on-site monitoring. The monitoring features in place at the LCTC ensure reliability and validity of the trial data. Metrics will be reviewed based on the data collected in REDCap, as well as other metrics such as informed consent, missing eCRFs, protocol deviations, and SAE reporting.

In some cases, remote monitoring will be used. This involves source data verification of data completed remotely via anonymised copies of source data requested from site.

28.3 Audit and Regulatory Inspection

All aspects of the trial conduct may be participant to internal or external quality assurance audit to ensure compliance with the protocol, GCP requirements and other applicable regulations and standards. Audits or inspections may occur at any time during or after the completion of the trial. Investigators and their host Institution(s) should understand that it is necessary to allow auditors/inspectors direct access to all relevant documents, trial facilities and to allocate their time and the time of their staff to facilitate the audit or inspection visit. Anyone receiving notification of a Regulatory Inspection that will (or is likely to) involve this trial must inform the Sponsor and LCTC without delay.

To assure protocol compliance, ethical standards, regulatory compliance and data quality, as a minimum, the following will occur:

- The PI and other key staff from each centre will attend initiation training, which will incorporate elements of trial-specific training necessary to fulfil the requirements of the protocol.
- The Sponsor and LCTC will determine the minimum key staff required to be recorded on the delegation log for the clinical site to be initiated.
- The Trial Manager (or delegate) at the LCTC will verify that appropriate approvals are in place prior to initiation of a clinical site and that the relevant personnel have attended the trial specific training. A greenlight checklist will verify all approvals are in place prior to trial initiation at LCTC and the individual clinical site.
- The trial will be conducted in accordance with procedures identified in the protocol.

- The DEC will provide oversight of the trial.
- The Sponsor and LCTC will monitor screening and consent rates between centres and compliance with the protocol.
- Data quality checks and monitoring procedures will be undertaken in line with the trial Data Management Plan.

29 RECORDS RETENTION AND ARCHIVING

During the clinical trial and after trial closure the Investigator must maintain adequate and accurate records to enable the conduct of a clinical trial and the quality of the research data to be evaluated and verified. All essential documents must be stored in such a way as to ensure that they are readily available upon request for the minimum period required by national legislation or for longer if needed. The medical files of trial participants must be retained in accordance with applicable national legislation and the host institution policy.

Retention and storage of laboratory records for clinical trial samples must also follow these guidelines.

Retention and storage of central laboratory records supporting PK endpoints and the disposition of samples donated via the trial must also comply with applicable legislation and Sponsor requirements.

It is policy to store data for a minimum of 25 years. Investigators may not archive or destroy trial essential documents or samples without written instruction from the Sponsor.

The retention period for the ATTAINMENT data and information is 25 years from the official end of trial date (defined in Section 20).

The PI at each investigational site must make arrangements to store the essential trial documents (as defined by ICH GCP guidelines) including the Investigator Site File, the applicable participant medical records and Pharmacy Site File, for the full length of the trial's retention period and will arrange for confidential destruction at the end of this period as instructed by the Sponsor.

The PI is also responsible for archiving all relevant source documents so that the trial data can be compared against source data after completion of the trial (e.g., in case of inspection from authorities). They must ensure the continued storage of the documents, even if they, for example, leave the clinic/practice or retire before the end of required storage period. Delegation of responsibility for this must be documented in writing.

All other persons and organisations involved in the trial will be responsible for storing and archiving the parts of the TMF relevant to their delegated duties (e.g., laboratories, IMP manufacturers and distributors, third-party vendors providing randomisation and IMP allocation systems, etc.).

The LCTC undertakes to archive as per their contractual requirements; documents will be archived in compliance with the principles of GCP. All eCRFs and trial data will be archived onto an appropriate medium for long term accessible storage. Hard copies of data will be boxed and transferred to secure premises where unique reference numbers are applied to enable confidentiality, tracking and retrieval.

30 PARTICIPANT CONFIDENTIALITY

Personal data recorded on all documents will be regarded as confidential, and to preserve each participant's confidentiality, only their participant trial number, initials and year of birth (or other identifier as appropriate to country regulations and agreed with the Sponsor) will be recorded on the eCRFs.

The Investigator site must maintain the participant's confidentiality in all communications and reports related to the research. The Investigator site team must keep a separate log of enrolled participants' personal identification details as necessary to enable them to be tracked. These documents must be retained securely, in strict confidence. They form part of the Investigator Site File and are not to be released externally.

This trial will collect personal data (e.g., participant names), including special category personal data (i.e., participant medical information) and this will be handled in accordance with all applicable data protection legislation. Data (including special category) will only be collected, used and stored if necessary for the trial (e.g., evidencing provision of consent, for data management and central monitoring, statistical analysis, regulatory reporting, etc.). At all times, this data will be handled confidentially and securely.

eCRFs will be labelled with a unique trial number. Verification that appropriate informed consent is obtained will be enabled by the provision of copies of participant's signed informed consent forms being supplied to the LCTC by recruiting sites. This transfer of identifiable data is disclosed in the Patient Information Sheet and Consent (PISC). N.B. Consent forms must be transferred separately to any other trial documentation to ensure the pseudonymisation of special category data is maintained.

Site-specific study-related information will be stored securely and confidentially at sites and all local relevant data protection policies will be adhered to.

The Sponsor and LCTC will each act as data controllers for this study. The LCTC as part of The University of Liverpool will preserve the confidentiality of participants taking part in the study. The University of Liverpool is registered as a Data Controller with the Information Commissioner's Office.

Breaches of data protection principles or regulations identified by LCTC will be notified promptly to the trial Sponsor and The University of Liverpool's Data Protection Officer and appropriate processes followed.

31 TRIAL FUNDING

The trial will be funded by the Sponsor.

32 SPONSORSHIP AND INDEMNITY

32.1 Sponsorship

Medannex is the Sponsor assuming overall responsibility for the initiation, management, and financing of the trial.

32.2 Indemnity

The Sponsor holds insurance against claims from participants for harm caused by their participation in this clinical study. However, the treating hospital continues to have a duty of care to the participant and the Sponsor does not accept liability for any breach in the hospital's duty of care, or any negligence of the part of hospital employees. In these cases, clinical negligence indemnification will rest with the participating NHS Trust or Trusts under standard NHS arrangements.

32.3 Contracts/Agreements

A service agreement is in place between the Sponsor and the LCTC which defines the roles and responsibilities for each party regarding the conduct of the trial.

A Clinical Trial Agreement (CTA) will be put in place between the Sponsor, LCTC and participating sites prior to site activation.

The Sponsor will also set up written agreements with any other external third parties involved in the conduct of the trial as appropriate.

33 PUBLICATION POLICY

The Sponsor will retain ownership of all data arising from the trial.

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APPENDIX 1: ECOG PERFORMANCE SCALE

Activity Performance Description	Score
Fully active, able to carry on all pre-disease performance without restriction.	0
Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light housework, office work.	1
Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.	2
Capable of only limited self-care. Confined to bed or chair more than 50% of waking hours.	3
Completely disabled. Cannot carry out any self-care. Totally confined to bed or chair.	4

APPENDIX 2: MEASUREMENT OF DISEASE - RECIST CRITERIA

RESPONSE EVALUATION CRITERIA IN SOLID TUMOURS

Objective tumour response and time of progression will be measured according to the RECIST (Response Evaluation Criteria in Solid Tumours) criteria (version 1.1). Response criteria are essentially based on a set of measurable lesions identified at baseline as target lesions, and – together with other lesions that are denoted as non-target lesions – followed until disease progression.

The complete criteria are included in the published RECIST document:

Eisenhauer, EA, Therasse, P, Bogaerts, J, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer 2009; 45:228-247

And also available at: http://www.eortc.be/RECIST

APPENDIX 3: AMENDMENT HISTORY

Protocol Version No.	Date Issued	Author	Details of Changes Made
7.0	9 April 2025	Medannex	The following sections have been amended as a result of the changes which allow the Module 1 Dose Expansion to focus on dosing every 21 days and the addition of 1 arm in Module 2. In addition, for clarity the Module 1 and Module 2 primary objectives and endpoints are now stated individually. Synopsis, study schema and schedule of events have been revised in line with changes stated above and below. Section 8 has been updated to include cholangiocarcinoma as a tumour that overexpresses ANXA1 with a rationale for its inclusion in Module 2. Section 9 has been updated so that the primary objectives and related endpoints for Module 1 and Module 2 are stated separately for clarity. However, the primary focus of identifying safe and tolerable dose of MDX-124 is unchanged. Minor edit was made to the secondary endpoints. Section 10 has been updated to clarify design of Module 1 and 2 and to state that the Module 1 expansion cohort will explore dosing every 21 days along with the applicable rationale. Dosing in subsequent cycles and dose modification have been amended for clarity. Section 11 has been updated to include new Module 2 inclusion and exclusion criteria. Haemoglobin value in Core inclusion criteria has been revised so it is now appropriate for the patient population. Eligibility assessment and labs requirement amended for clarity. Section 12 has been updated to include Module 1 dose expansion cohort and Module 2 arm 2 assessments. Eligibility assessment and labs requirement amended for clarity.

			Section 14 has been updated to include Module 1 dose expansion cohort and Module 2 arm 2 sample collection. Section 18, 22, 26 and 28 have been revised in line with changes to the management of the study. Section 21 has been updated in line with the changes to Module 2. Section 34 has been updated with 2 new references. Throughout the protocol administrative updates have been made for accuracy and clarity.
6.0	10 October 2024	Medannex	Synopsis and Sections 8.6.1.1, 10.2.2.1, 12.5.1 and 12.5.2 amended to clarify that cohort size can be increased by the DEC following a review of verified safety data, that in the event of a dose reduction the DEC will determine the dose and that additional participants can be enrolled at dose levels deemed to be safe by the DEC.
5.0	17 May 2024	Medannex	Protocol signatories revised. In Section 8.6.4.4 list of tumour types removed to allow emerging nonclinical or clinical data to determine which tumour types may be added in Module 2. Section 10.2.4.2 updated to clarify minimum dosing criteria. Section 11 Inclusion criteria updated to clarify that the tumours listed are an example and not a finite list. Requirement for COVID-19 test has been removed, Exclusion criteria 15 clarified in regard to permission of standard of care hormonal therapy, where applicable. Section 14 updated to include PK collection windows and to clarify process for identifying ADAs. Section 16.2 has been revised for clarification and to ensure consistency with exclusion criteria.

			Section 22 has been updated to clarify the oversight of the study. General updates and edits have been made throughout for clarification.
4.0	1st March 2023	Medannex and University of Liverpool	Change to IMP storage guidance in section 15.12. Section 18.7 revised to clarify process for SAE reporting in eCRF. General updates of typos for clarification.
3.0	10th November 2022	Medannex and University of Liverpool	Updates made following initial review by ethics and regulatory.
2.0	8th September 2022	Medannex and University of Liverpool	Initial version submitted to ethics and regulatory for review.
1.0	12th April 2021	Medannex	Submitted to MHRA for scientific advice