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Platform study Kalidescope: A Phase 1/2 Open-label Platform Study to Evaluate the Safety and Efficacy of Multiple Amivantamab-based Therapeutic Combinations in Participants with Advanced, Unresectable Lung Cancer (LC) ISA1 METalmark (now closed in UK): A phase I/II open-label platform study to evaluate the safety and efficacy of multiple amivantamab-based therapeutic combinations in participants with advanced, unresectable lung cancer ISA2 Polydamas: A Phase 1/2 Study Evaluating the Safety and Efficacy of Amivantamab and Cetrelimab Combination Therapy in Metastatic Non-small Cell Lung Cancer ISA3 SwalloWTail: A Phase 1/2 Study Evaluating the Safety and Efficacy of Amivantamab and Docetaxel Combination Therapy in Metastatic Non-small Cell Lung Cancer

Submission date
20/09/2022

Recruitment status
No longer recruiting

Registration date
28/02/2023

Overall study status
Ongoing

Last Edited
28/11/2024

Condition category
Cancer

[ ] Prospectively registered
[ ] Protocol
[ ] Statistical analysis plan
[ ] Results
[ ] Individual participant data
[ ] Record updated in last year

Plain English summary of protocol

ISA1 METalmark (now closed in the UK)
Background and study aims
NSCLC is the most common type of lung cancer and may have MET exon 14 skipping mutations (changes) and MET gene amplification (additions). Amivantamab and capmatinib target the MET gene and downregulate signals sent by the MET protein within cells, which may prevent the growth of cancer cells. This study is designed to assess if amivantamab and capmatinib can be safely administered as a combination therapy in Phase I and to see how effective it is in the treatment of lung cancer in participants with NSCLC with MET exon 14 skipping mutation or MET amplification in Phase II.

Who can participate?
Male and female participants 18 years or older who have been previously diagnosed with metastatic NSCLC

What does the study involve?
There are 2 parts (phases) of this study:
1. Phase I (Combination Dose Selection): Capmatinib 400 milligrams (mg) given orally twice daily from Cycle 1 Day 1, in combination with amivantamab 700 mg (body weight [BW] less than 80 kilograms [kg]) or 1050 mg (BW greater than or equal to 80 kg) as an infusion in the vein once weekly from Cycle 1 Day 1 for 4 weeks and then every 2 weeks of each 28-day cycle starting with Cycle 2. Doses may be gradually increased/decreased based on side effects.
2. Phase II (Dose Expansion): Participants with MET mutation who have not received any previous treatment (Cohort 1A), have advanced disease and are on at least 1 but no more than 3 lines of previous anti-cancer therapy (Cohort 1B), or participants with MET amplification, following the advancement of disease on at least 1 but no more than 3 lines of the previous standard of care therapy (Cohort 1C), will receive capmatinib along with amivantamab at RP2(C) D.

During the study, various tests such as blood tests, vital signs, electrocardiogram, Eastern Cooperative Oncology Group status and pregnancy tests will be performed. All side effects will be recorded until 30 days after the last dose of the study treatment.
The overall duration of the study will be approximately 2 years.

What are the possible benefits and risks of participating?
There may be risks to using amivantamab and capmatinib that are not yet known. Participants will be informed in a timely manner if new information is discovered about the study drug or its side effects. The participant information sheet(s) will contain full information on the potential side effects of study interventions.
Amivantamab:
The possible discomforts, side effects, and risks related to amivantamab treatment are not all known.
As of January 17, 2022, safety data is available for approximately 518 patients who have received amivantamab alone. Patients have been treated with amivantamab for an average of 5 months. Therefore, the safety information regarding amivantamab is still developing and there may be risks that are not yet known.
The following side effects have been observed in patients who have already received amivantamab alone:
Very Common (may affect more than 1 in 10 patients):
1. Rash
2. Infection or inflammation of the skin around the fingernail and other nail problems
3. Itching
4. Dry or cracked skin

5. Infusion-related reactions
6. Inflammation of the mouth or mouth sores
7. Nausea
8. Vomiting
9. Constipation
10. Diarrhoea
11. Abdominal pain
12. Low levels of albumin in the blood
13. Decreased appetite
14. Low levels of calcium in the blood
15. Low levels of potassium in the blood
16. Low levels of magnesium in the blood
17. Tiredness
18. Swelling in the hands, feet, or limbs
19. Increased levels of liver enzymes in the blood
20. Dizziness
21. Muscle pain

Common (may affect up to 1 in 10 patients):
1. Eye problems
2. Inflammation of the lung

Infusion-Related Reactions:
Infusion-related reactions have been reported in a little more than half of all patients treated with amivantamab. Infusion reactions are most common during the first infusion and are far less likely to occur during the following infusions. The most common symptoms of infusion-related reactions are chills, shortness of breath, nausea, flushing, and chest discomfort. Less common symptoms include vomiting, fever, cough, itching, rash, changes in blood pressure, fast heart rate and breathing rate, and decreased oxygen level in the blood.
Participants will receive medications, including paracetamol/acetaminophen, an antihistamine, and a corticosteroid before the infusion to help prevent or decrease any symptoms. If a participant experiences any symptoms, the infusion may be temporarily paused, they may be given additional medications, and the infusion rate may be changed.
Participants may also get medications after the infusion if this is determined as necessary by their clinician.
Rash:
Participants will be provided with instructions on how to prevent and treat rash. This will include not being in the sun unnecessarily and using high-factor sun protector when they need to be in the sun. It will also include using topical creams on areas of dry or sun-exposed skin.
Contraception:
Male participants will be instructed to use a condom when engaging in any activity that allows for the passage of ejaculate to another person when they start taking the study drug, until 6 months after their last dose.

Capmatinib:
The possible discomforts, side effects, and risks related to capmatinib treatment are not all known.

The following side effects have been observed in patients who have received capmatinib:

Very Common (may affect more than 1 in 10 patients):
1. Peripheral edema

2. Fatigue
3. Non-cardiac chest pain
4. Back pain
5. Pyrexia
6. Weight decrease
7. Nausea
8. Vomiting
9. Constipation
10. Diarrhoea
11. Dyspnea
12. Cough
13. Decreased appetite

May affect less than 1 in 10 participants:
1. Pruritus (allergic and generalised)
2. Interstitial Lung Disease (ILD)/Pneumonitis
3. Cellulitis
4. Acute kidney injury
5. Urticaria
6. Acute pancreatitis

The participant information sheet provides full details of potential laboratory abnormalities and other potential adverse events that may occur in patients.

Risks/side effects from study tests

Blood draw risk: Taking blood may cause bruising irritation at the place where the needle goes into the skin. Fainting, and in rare cases, an infection may occur.

ECG risk: There is generally no risk with having an ECG. The sticky patches may pull the skin or cause redness or itching.

CT Risk: CT scans do create low levels of radiation, which has a small potential to cause cancer and other defects. Risk information will be provided to participants.

MRI risk: Because radiation is not used, there is no risk of exposure to radiation during MRI procedure. If a contrast material is used during MRI, participants will be informed about possible side effects or allergic reactions.

Intravenous (IV) line risk: Use of an intravenous line for study treatment administration, imaging and other tests may cause discomfort, irritation, minor bruising, bleeding, or injection leakage, and in rare cases nausea, light dizziness and air embolism.

Where is the study run from?
Institute of Cancer Research (UK)

When is the study starting and how long is it expected to run for?
August 2022 to August 2026

Who is funding the study?
Janssen-Cilag (Belgium)

Who is the main contact?
Caitlin Young cyoung18@its.jnj.com

ISA2 PolyDamas
Background and study aims
NSCLC is the most common type of lung cancer. Metastatic NSCLC is when this disease spreads to other parts of the body. NSCLC may occur due to mutations (changes) in many genes including mesenchymal-epithelial transition (MET) and epidermal growth factor receptor (EGFR). Some metastatic NSCLC cells also show PD-L1 expression. Amivantamab is a bispecific antibody* that binds to the EGFR and MET receptor proteins and turns them off, which may kill or slow down the growth of cancer cells. Cetrelimab (JNJ-63723283) is a monoclonal antibody** that binds to programmed cell death protein 1 (PD-1), which may kill or slow down the growth of cancer cells.
*Type of protein that binds to 2 different targets at the same time.
**Type of protein that recognizes and attaches to a specific target.
In this study, researchers want to find a recommended dose of amivantamab in combination with cetrelimab that is safe and works well to fight against cancer in participants with metastatic NSCLC.

Who can participate?
Participants 18 years or older diagnosed with metastatic NSCLC.

What does the study involve?
There are two parts of this study:
Phase 1 (Combination Dose Selection): Amivantamab administered as an infusion in the vein based on body weight once weekly for the first Cycle & then every 2 weeks (q2w) starting Cycle 2.
Cetrelimab will be administered as an infusion in the vein q2w after the initial dose given on Day 2 of Cycle 1 (after the Day 2 infusion of amivantamab). Doses may be gradually increased /decreased based on side effects.
Phase 2 (Expansion): Participants will receive amivantamab along with cetrelimab at RP2CD in 2 cohorts:
• Cohort A- EGFR exon19del or L858R mutations, with progression of disease after standard-of-care therapy
• Cohort B- Treatment naïve NSCLC with PD-L1 high expression
Safety assessments include monitoring of adverse events (AEs), treatment-emergent AEs, vital signs, accompanying medications used & clinical laboratory parameters. All side effects will be recorded until the study ends (approximately 3 years).

What are the possible benefits and risks of participating?
There is no established benefit to participants of this study. Based on scientific theory, taking amivantamab and cetrelimab may improve the treatment of NSCLC. However, this cannot be guaranteed because amivantamab and cetrelimab are still under investigation as a treatment combination and it is not known whether they will work.
Participants may experience some benefit from participation in the study that is not due to receiving study drug, but due to regular visits and assessments monitoring overall health. Participation may also help other people with NSCLC in the future.
Participants may have side effects from the drugs or procedures used in this study that may be mild to severe and even life-threatening, and they can vary from person to person. The most common, known risks are getting symptoms such as infusion-related reactions (IRRs), respiratory system related toxicities, skin-related toxicities, risk of photosensitivity, liver toxicity, gastrointestinal AEs (including diarrhea and colitis), other EGFR-related AEs, immune-related AEs

and embryo-fetal
toxicity after getting the study drugs. There are other, less frequent risks. The participant information sheet and informed consent form, which will be signed by every participant agreeing to participate in the study, includes a detailed section outlining the known risks to participating in the study.
Not all possible side effects and risks related to amivantamab and cetrelimab are known at this moment. During the study, the sponsor may learn new information about amivantamab and cetrelimab. The study doctor will tell participants as soon as possible about any new information that might make them change their mind about being in the study, such as new risks.
To minimise the risk associated with taking part in the study, participants are frequently reviewed for any side effects and other medical events. Participants are educated to report any such events to their study doctor who will provide appropriate medical care. Any serious side effects that are reported to the sponsor are thoroughly reviewed by a specialist drug safety team.
There are no costs to participants to be in the study. The sponsor will pay for the study drug and tests that are part of the study. The participant will receive reasonable reimbursement for study-related costs (e.g., travel/parking costs).

Where is the study run from?
1. Royal Marsden Hospital
2. Freeman Hospital
3. Charing Cross Hospital

When is the study starting and how long is it expected to run for?
May 2023 to March 2026

Who is funding the study?
Janssen-Cilag (Belgium)

Who is the main contact?
Eleanor Cawthorne ecawthor@its.jnj.com

ISA3 SwalloWTail:
Background and study aims
NSCLC is the most common type of lung cancer. Metastatic NSCLC is when this disease spreads to other parts of the body. NSCLC may occur due to mutations (changes) in many genes including mesenchymal-epithelial transition (MET) and epidermal growth factor receptor (EGFR).
The study is evaluating a combination of amivantamab (JNJ-61186372) and docetaxel. Amivantamab binds to EGFR & MET and turns them off, which may slow the growth of cancer cells. Docetaxel is an approved anti-cancer treatment, used for metastatic NSCLC when other treatments did not work.
In this study, researchers want to find a recommended dose of amivantamab in combination with docetaxel that is safe (Combination dose selection phase) and works well to fight against cancer (Expansion) in participants with metastatic NSCLC.

Who can participate?
Participants aged 18 years or older diagnosed with metastatic NSCLC.

What does the study involve?
There are two parts of this study:
Phase 1 (Combination Dose Selection): Amivantamab will be administered as an infusion in the vein based on body weight from Cycle 1 Day 1, Day 2, & subsequent doses on Days 8 and 15, and

then every 3 weeks on Day 1 of each 21-day cycle. Docetaxel will be administered as an infusion in the vein on Day 2 of Cycle 1 & then on Day 1 of each 21-day cycle. Doses may be gradually increased/decreased based on side effects.
Phase 2 (Expansion): Participants will receive amivantamab in combination with docetaxel at RP2CD selected in Phase 1 of the study in 2 cohorts, after disease progression on platinum-doublet chemotherapy and immune checkpoint inhibitor:
•Cohort 1- NSCLC, Adenocarcinoma
•Cohort 2- NSCLC, Squamous cell carcinoma
During the study, various tests such as blood tests, vital signs, electrocardiogram, & pregnancy tests will be performed. Blood samples will be taken at multiple timepoints to understand how the body responds to treatment.
All side effects will be recorded 30 days after the last dose of study treatment. The overall duration of the study will be approximately 1 year and 4 months.

What are the possible benefits and risks of participating?
There is no established benefit to participants of this study. Although amivantamab and docetaxel have approved indications in certain countries, any potential benefits of taking both drugs as a combination are not known or guaranteed. Participants may experience some benefit from participation in the study that is not due to receiving the study drugs but may be due to regular visits and assessments monitoring overall health. Participation in the study may help other people with lung cancer in the future.
Participants may experience side effects from the study drugs or procedures used in this study. The severity of these side effects may vary from person to person and may even be life-threatening. The most common, known risks of the study treatment are peripheral edema (accumulation of fluid in the body tissues), liver toxicities, skin toxicity, nail disorders, pulmonary toxicity, low white blood cell count, low platelet count, low red blood cells count, tiredness or weakness, headache, nausea/vomiting and significant changes in male fertility.
The informed consent form, which will be signed by every participant agreeing to participate in the study, includes a detailed section outlining the known risks from participating in the study. Not all possible side effects and risks related to the combination of amivantamab and docetaxel or each separate study drug are known at this moment.
During the study, the sponsor may learn new information about amivantamab, docetaxel or a combination of both. The study doctor will tell participants as soon as possible if any new information is discovered about the study drugs or its side effects that might make them change their mind about being in the study, such as new risks. To minimize the risk associated with taking part in the study, participants are frequently monitored for any side effects and other medical events. Participants are educated to report any such events to the study doctor or study staff for care. Any serious side effects that are reported to the sponsor are thoroughly reviewed by the safety team. There are no costs to participants to be in the study. The sponsor will pay for the study drug and tests that are part of the study. The participant will receive reasonable reimbursement for study-related costs (e.g., travel/parking costs).

Where is the study run from?
1. Institute of Cancer Research (UK) at the Royal Marsden Hospital
2. St James's University Hospital

When is the study starting and how long is it expected to run for?
August 2024 to October 2025

Who is funding the study?
Janssen-Cilag (Belgium)

Who is the main contact?
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Additional identifiers

Clinical Trials Information System (CTIS)
ISA1: 2022-000485-18, ISA2: 2022-501452-29

Integrated Research Application System (IRAS)
1006057

ClinicalTrials.gov (NCT)
ISA1: NCT05488314, ISA2: NCT05908734

Protocol serial number

ISA1: 61186372PANSC2001, ISA2: 61186372PANSC2002

Study information

Scientific Title
Platform study Kalidescope: A Phase 1/2 Open-label Platform Study to Evaluate the Safety and Efficacy of Multiple Amivantamab-based Therapeutic Combinations in Participants with Advanced,
Unresectable Lung Cancer (LC)

ISA1 METalmark (now closed in UK): A phase I/II open-label platform study to evaluate the safety and efficacy of multiple amivantamab-based therapeutic combinations in participants with advanced, unresectable lung cancer

ISA2 Polydamas: A Phase 1/2 Study Evaluating the Safety and Efficacy of Amivantamab and Cetrelimab Combination Therapy in Metastatic Non-small Cell Lung Cancer

ISA3 SwalloWTail: A Phase 1/2 Study Evaluating the Safety and Efficacy of Amivantamab and Docetaxel Combination Therapy in Metastatic Non-small Cell Lung Cancer

Acronym
ISA1: METalmark, ISA2: Polydamas, ISA3: SwalloWTail

Study objectives
Current study hypothesis:

ISA1 METalmark (now closed in the UK): The primary objective of the phase I combination dose selection is to identify the recommended phase II dose combination dose(s) (RP2CD[s]) of amivantamab and capmatinib in participants with non-small cell lung cancer (NSCLC). The primary objective of the phase II Expansion is to evaluate the anti-tumour effect of amivantamab and capmatinib combination therapy in MET exon 14 skipping mutation and MET amplified NSCLC, when administered at the selected RP2CD(s)

The secondary objectives of this study are:
Phase I and Phase II:
1. To further evaluate safety and tolerability of the amivantamab and capmatinib combination therapy.

Phase II:
2. To further assess the clinical benefit achieved by the amivantamab and capmatinib combination therapy.
3. To assess Health-related Quality of Life (Cohort 1A only).

The exploratory objectives of this study are:
- To evaluate pharmacokinetics and immunogenicity for amivantamab and PK for capmatinib and assess their relationship to selected endpoints (including but not limited to efficacy, safety, and /or patient-reported outcomes [PRO]).
-To explore biomarkers predictive of improved outcome of amivantamab with capmatinib.
- To explore mechanisms of resistance to amivantamab with capmatinib.
- To explore the effect of amivantamab and capmatinib combination therapy on the formation of new brain metastasis.

Added 25/09/2024:
ISA2 Polydamas:
The primary hypothesis of Phase 1 is that amivantamab and cetrelimab can be safely administered as a
combination therapy, with a tolerable safety profile.
For Phase 2 the primary hypotheses are that the combination of amivantamab and cetrelimab will demonstrate clinically significant antitumor activity for:
1) patients with NSCLC, characterized by EGFR exon19del or L858R mutations, who have progressed on or after platinum-based chemotherapy (Cohort A)
AND
2) treatment naïve patients with NSCLC with no known oncogenic driver mutations and with PD-L1 ≥50% (Cohort B). Note: Sponsor will open Cohort B based on evolving safety and efficacy data and global regulatory approvals for new targeted therapies.

Added 28/11/2024:
ISA3 SwalloWTail:
Main objectives
Phase 1 Combination Dose Selection
• To find the recommended dose (recommended Phase 2 combination dose [RP2CD]) of the amivantamab in combination with docetaxel in participants with non-small cell lung cancer (NSCLC) that has spread to other parts of body.
Phase 2 Expansion
• To evaluate how well amivantamab in combination with docetaxel can fight against cancer (antitumor effect) in participants with NSCLC which got worse after platinum-based chemotherapy (anti-cancer therapy) and immune checkpoint inhibitor at RP2CD.

Secondary objectives
Phase 1 and 2:
•To evaluate safety and tolerability of amivantamab in combination with docetaxel.
Phase 2
•To evaluate the potential clinical benefit achieved by amivantamab in combination with docetaxel in participants with NSCLC which got worse after platinum-based chemotherapy and immune checkpoint inhibitor at RP2CD.

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Previous study hypothesis:

The primary objective of the phase I combination dose selection is to identify the recommended phase II dose combination dose(s) (RP2CD[s]) of amivantamab and capmatinib in participants with non-small cell lung cancer (NSCLC). The primary objective of the phase II Expansion is to evaluate the anti-tumour effect of amivantamab and capmatinib combination therapyin MET exon 14 skipping mutation and MET amplified NSCLC, when administered at the selected RP2CD (s)

The secondary objectives of this study are:

Phase I and Phase II:
1. To further evaluate safety and tolerability of the amivantamab and capmatinib combination therapy.

Phase II:
2. To further assess the clinical benefit achieved by the amivantamab and capmatinib combination therapy.
3. To assess Health-related Quality of Life (Cohort 1A only).

The exploratory objectives of this study are:

- To evaluate pharmacokinetics and immunogenicity for amivantamab and PK for capmatinib and assess their relationship to selected endpoints (including but not limited to efficacy, safety, and /or patient-reported outcomes [PRO]).
-To explore biomarkers predictive of improved outcome of amivantamab with capmatinib.
- To explore mechanisms of resistance to amivantamab with capmatinib.
- To explore the effect of amivantamab and capmatinib combination therapy on the formation of new brain metastasis.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Approval 19/01/2023, London - Westminster Research Ethics Committee (Equinox House, City Link, Nottingham, NG2 4LA, UK; +44 (0)207 104 8066; westminster.rec@hra.nhs.uk), ref: 22/WS /0131

Study design
Interventional open-label combination dose-selection study

Primary study design
Interventional

Study type(s)
Treatment

Health condition(s) or problem(s) studied
Unresectable metastatic non-small cell lung cancer

Interventions
Current interventions:

ISA1 METalmark (now closed in UK): Phase 1 (Combination Dose Selection) – Participants will receive capmatinib 400 milligrams (mg) orally twice daily from Cycle 1 Day 1, in combination with amivantamab 700 mg intravenous (IV) infusion (for body weight less than 80 kilograms [kg]) or 1050 mg IV infusion (for body weight greater than or equal to 80 kg) once weekly from Cycle 1 Day 1 for 4 weeks and then every 2 weeks from Week 5 (Cycle 2; each cycle of 28 days). Doses will be escalated or de-escalated based on the dose-limiting toxicities (DLTs) and the recommended Phase 2 combination dose (RP2CD) will be determined by the study evaluation team (SET). – Not open in the UK

Phase 2 (Dose Expansion) – Participants with mesenchymal-epithelial transition (MET) exon 14 skipping mutation who are treatment naïve (Cohort 1A), who have received prior therapy

(Cohort 1B), or participants with MET amplification who have received prior therapy (Cohort 1C) will receive capmatinib in combination with amivantamab at the RP2CD determined by the SET in Phase 1. – Opening in the UK

Added 25/09/2024:
ISA2 Polydamas: Phase 1 (combination dose selection) - Participants will receive amivantamab low dose or high dose intravenous (IV) infusion based on body weight from Cycle 1 Day 1, Day 2, and subsequently Day 8, Day 15, and Day 22 and then every 2 weeks from Cycle 2 in combination with cetrelimab IV infusion from Cycle 1 Day 2 (after the Day 2 infusion of amivantamab). Doses will be escalated or de-escalated based on the dose limiting toxicities (DLTs) and the recommended Phase 2 combination dose (RP2CD) will be determined by the study evaluation team (SET).
Phase 2 (dose expansion) Participants will receive amivantamab in combination with cetrelimab in Cohorts A and B at the RP2CD determined by the SET in Phase 1.

Added 28/11/2024:
ISA3 SwalloWTail:
Phase 1 (Combination Dose Selection): Amivantamab will be administered as an infusion in the vein based on body weight from Cycle 1 Day 1, Day 2, & subsequent doses on Days 8 and 15, and then every 3 weeks on Day 1 of each 21-day cycle. Docetaxel will be administered as an infusion in the vein on Day 2 of Cycle 1 & then on Day 1 of each 21-day cycle. Doses may be gradually increased/decreased based on side effects.
Phase 2 (Expansion): Participants will receive amivantamab in combination with docetaxel at RP2CD selected in Phase 1 of study in 2 cohorts, after disease progression on platinum-doublet chemotherapy and immune checkpoint inhibitor:
• Cohort 1- NSCLC, Adenocarcinoma
• Cohort 2- NSCLC, Squamous cell carcinoma

Participants will continue study treatment until disease progression, unacceptable toxicity, or until another criterion for discontinuation of study treatment is met.

This is an open-label, non-randomised study; therefore, no randomisation is applied

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Previous interventions:

Phase 1 (Combination Dose Selection) – Participants will receive capmatinib 400 milligrams (mg) orally twice daily from Cycle 1 Day 1, in combination with amivantamab 700 mg intravenous (IV) infusion (for body weight less than 80 kilograms [kg]) or 1050 mg IV infusion (for body weight greater than or equal to 80 kg) once weekly from Cycle 1 Day 1 for 4 weeks and then every 2 weeks from Week 5 (Cycle 2; each cycle of 28 days). Doses will be escalated or de-escalated based on the dose-limiting toxicities (DLTs) and the recommended Phase 2 combination dose (RP2CD) will be determined by the study evaluation team (SET). – Not open in the UK

Phase 2 (Dose Expansion) – Participants with mesenchymal-epithelial transition (MET) exon 14 skipping mutation who are treatment naïve (Cohort 1A), who have received prior therapy (Cohort 1B), or participants with MET amplification who have received prior therapy (Cohort 1C) will receive capmatinib in combination with amivantamab at the RP2CD determined by the SET in Phase 1. – Opening in the UK

This is an open-label, non-randomised study; therefore, no randomisation is applied

Intervention Type
Drug

Phase
Phase I/II

Drug/device/biological/vaccine name(s)
ISA1 METalmark ((now closed in UK)) amivantamab, capmatinib; ISA2 Polydamas: amivantamab, cetrelimab; ISA3 SwalloWTail: aminvantamab, docetaxel

Primary outcome(s)
Current primary outcome measure:

ISA1 METalmark (now closed in UK): Phase I:
1. Number of participants with adverse events (AEs) by severity for up to 2 years and 1 month. Severity will be graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 5.0. Severity scale ranges from Grade 1 (Mild) to Grade 5 (Death). Grade 1= Mild, Grade 2= Moderate, Grade 3= Severe, Grade 4= Life-threatening and Grade 5= Death related to an adverse event.
2. Number of participants with dose-limiting toxicities (DLTs), defined as any of the following: high-grade non-hematologic toxicity, hematologic toxicity, pulmonary toxicity, liver enzyme elevation, or treatment delay greater than (>) 28 days due to unresolved toxicity, and monitored from Cycle 1 (Day 1 through to day 28)

Phase II:
Objective Responsive Rate (OOR), for up to 2 years and 1 month. ORR is defined as the percentage of participants who achieve either a confirmed partial response (PR) or complete response (CR), using Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1

Added 25/09/2024:
ISA2 Polydamas:
Phase 1: Number of Participants with Adverse events (AEs) by Severity for up to 2 years and 3 months. Severity will be graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 5.0. Severity scale ranges from Grade 1 (Mild) to Grade 5 (Death). Grade 1= Mild, Grade 2= Moderate, Grade 3= Severe, Grade 4= Life-threatening and Grade 5= Death related to adverse event.
Phase 1: Number of Participants with Dose Limiting Toxicities (DLTs) up to C1D28. The DLTs are specific adverse events and are defined as any of the following: high grade non-hematologic toxicity, hematological toxicity, pulmonary toxicity, liver enzyme elevation, treatment delay greater than (>) 28 days due to unresolved toxicity, or immune-related toxicity requiring the use of therapies in excess of corticosteroids.
Phase 2: Objective Response Rate up to 2 years 3 months. ORR is defined as the percentage of participants who achieve either a confirmed partial response (PR) or complete response (CR), using Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 as per investigator assessment.

Added 28/11/2024:
ISA3 SwalloWTail:
Phase 1: Number of participants with Adverse Events (AEs) by Severity up to 1 year and 4 months. An AE is any untoward medical occurrence in a clinical study participant administered a pharmaceutical (investigational or non-investigational) product. An adverse event does not

necessarily have a causal relationship with the intervention. Severity will be graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCICTCAE) version 5.0. Severity scale ranges from Grade 1 (Mild) to Grade 5 (Death). Grade 1= Mild, Grade 2= Moderate, Grade 3= Severe, Grade 4= Life-threatening and Grade 5= Death related to adverse event.
Phase 1: Number of participants with Dose Limiting Toxicities (DLTs) up to 21 days. DLTs are specific adverse events and are defined as any of following: Any high grade (Grade 3, 4 or 5) non-hematologic toxicity with exceptions such as: Grade 3 fever resolved in <=48 hours, anorexia; Grade 3 nausea, vomiting or diarrhea, or constipation Grade 3 fatigue; rash that improves to Grade <; transient electrolyte abnormalities; symptoms of IRRs that are attributable to amivantamab or docetaxel; Tumor flare; hematologic toxicity (Grade 4 anemia or neutropenia, Febrile neutropenia; Grade 3 or 4 thrombocytopenia associated with bleeding or requiring transfusion); pulmonary toxicity (confirmed any grade pulmonary toxicity, including pneumonitis or interstitial lung disease [ILD]), liver enzyme elevation (ALT or AST elevation>=Grade 3 persisting >=7 days); or treatment delay greater than (>) 28 days due to unresolved toxicity.
Phase 2: Objective Response Rate (ORR) up to 1 year and 4 months. ORR is defined as the percentage of participants who achieve either a confirmed partial response (PR) or complete response (CR), using Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1.

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Previous primary outcome measure:

Phase I:
1. Number of participants with adverse events (AEs) by severity for up to 2 years and 1 month. Severity will be graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 5.0. Severity scale ranges from Grade 1 (Mild) to Grade 5 (Death). Grade 1= Mild, Grade 2= Moderate, Grade 3= Severe, Grade 4= Life-threatening and Grade 5= Death related to an adverse event.
2. Number of participants with dose-limiting toxicities (DLTs), defined as any of the following: high-grade non-hematologic toxicity, hematologic toxicity, pulmonary toxicity, liver enzyme elevation, or treatment delay greater than (>) 28 days due to unresolved toxicity, and monitored from Cycle 1 (Day 1 through to day 28)

Phase II:
Objective Responsive Rate (OOR), for up to 2 years and 1 month. ORR is defined as the percentage of participants who achieve either a confirmed partial response (PR) or complete response (CR), using Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1

Key secondary outcome(s))

Current secondary outcome measures:

ISA1 METalmark (now closed in UK): Phase I:
1. Number of participants with adverse events (AEs) by severity for up to 2 years and 1 month. Severity will be graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 5.0. Severity scale ranges from Grade 1 (Mild) to Grade 5 (Death). Grade 1= Mild, Grade 2= Moderate, Grade 3= Severe, Grade 4= Life-threatening and Grade 5= Death related to an adverse event.
2. Number of participants with abnormalities in clinical laboratory parameters for up to 2 years and 1 month

Phase II:
1. Duration of Response (DoR) for up to 2 years and 1 month from the date of first documented

response (PR or CR) until the date of documented progression or death from any case, whichever comes first, for participants who have PR or CR
2. Disease Control Rate (DCR) for up to 2 years and 1 month. Where DCR is the percentage of participants who achieve a PR, CR or stable disease using RECISIT v1.1
3. Progression Free Survival (PFS) for up to 2 years and 1 month. Where PFS is the time from the first dose date until the date of disease progression or death, whichever comes first, based on investigator assessment using RECIST version 1.1
4. Overall Survival (OS) for up to 2 years and 1 month. Where OS is the time from the date of administration of the first study treatment until the date of death due to any cause.
5. Time to Subsequent Therapy (TTST) for up to 2 years and 1 month. Where TTST is the time from the date of administration of the first study treatment to the start date of the subsequent anticancer therapy following study treatment discontinuation, or death, whichever comes first
6. Only Cohort 1A: Change from baseline in Health-related Quality of Life in (HRQoL) as assessed by European Organization of Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC-QLQ-C30) scale score, from baseline till up to 2 years and 1 month
7. Only Cohort 1A: HRQoL as assessed by Non-Small Cell Lung Cancer - Symptom Assessment Questionnaire (NSCLC-SAQ) scale score from baseline till up to 2 years and 1 month
8. Only Cohort 1A: HRQoL as assessed by EuroQol 5-Dimension 5-Level (EQ-5D-5L) scale score from baseline till up to 2 years and 1 month
9. Only Cohort 1A: HRQoL as assessed by Patient-reported Outcomes Measurement Information System Short Form Version 2.0 - Physical Function 8c (PROMIS PF 8c) scale score from baseline till up to 2 years and 1 month

Added 25/09/2024:
ISA2 Polydamas:
Phase 1 and Phase 2: Number of Participants with AEs by Severity up to 2 years 3 months.
Phase 1 and Phase 2: Number of Participants with Abnormalities in Clinical Laboratory Parameters up to 2 years 3 months. Number of participants with abnormalities in clinical laboratory parameters (serum chemistry, hematology, coagulation, serology, and urinalysis) will be reported.
Phase 2 : Duration of Response (DoR) up to 2 years 3 months. DoR is defined as the time from the date of first documented response (PR or CR) until the date of documented progression or death from any case, whichever comes first, for participants who have PR or CR. If a participant does not progress following a response, then his/her duration of response will be censored at the date of last evaluable disease assessment. Participants who started a subsequent anticancer therapy in the absence of progression will be censored at the last disease assessment before or on the start of subsequent therapy.
Phase 2: Disease Control Rate (DCR) up to 2 years 3 months. DCR is defined as the percentage of participants who achieve a PR, CR, or stable disease using RECIST version 1.1 by investigator review.
Phase 2: Progression Free Survival (PFS) up to 2 years 3 months. PFS is defined as the time from first dose date until the date of disease progression or death, whichever comes first, based on investigator assessment using RECIST version 1.1. Participants who have not progressed or have not died at the time of analysis will be censored at the time of their last evaluable RECIST v1.1 assessment.
Phase 2: Overall Survival (OS) up to 2 years 3 months. OS is defined as the time from the date of administration of the first study treatment until the date of death due to any cause. Any participant not known to have died at the time of analysis will be censored based on the last recorded date on which the participant was known to be alive.

Added 28/11/2024:
ISA3 SwalloWTail:

Phase 1 and Phase 2: Number of participants with AEs by Severity up to 1 year 4 months. An AE is any untoward medical occurrence in a clinical study participant administered a pharmaceutical (investigational or non-investigational) product. An adverse event does not necessarily have a causal relationship with the intervention. Severity will be graded according to the NCI-CTCAE version 5.0. Severity scale ranges from Grade 1 (Mild) to Grade 5 (Death). Grade 1= Mild, Grade 2= Moderate, Grade 3= Severe, Grade 4= Life-threatening and Grade 5= Death related to adverse event.
Phase 1 and Phase 2: Number of participants with Abnormalities in Clinical Laboratory Parameters up to 1 year 4 months. Number of participants with abnormalities in clinical laboratory parameters (serum chemistry, hematology, coagulation, serology, and urinalysis) will be reported.
Phase 2 : Duration of Response (DoR) up to 1 year 4 months. DoR is defined as the time from the date of first documented response (PR or CR) until the date of documented progression or death from any case, whichever comes first, for participants who have PR or CR.
Phase 2: Disease Control Rate (DCR) up to 1 year 4 months. DCR is defined as the percentage of participants who achieve a PR, CR, or stable disease using RECIST version 1.1.
Phase 2: Progression Free Survival (PFS) up to 1 year 4 months. PFS is defined as the time from first dose date until the date of disease progression or death, whichever comes first, based on investigator assessment using RECIST version 1.1.
Phase 2: Overall Survival (OS) up to 1 year 4 months. OS is defined as the time from the date of administration of the first study treatment until the date of death due to any cause.

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Previous secondary outcome measures:

Phase I:
1. Number of participants with adverse events (AEs) by severity for up to 2 years and 1 month. Severity will be graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 5.0. Severity scale ranges from Grade 1 (Mild) to Grade 5 (Death). Grade 1= Mild, Grade 2= Moderate, Grade 3= Severe, Grade 4= Life-threatening and Grade 5= Death related to an adverse event.
2. Number of participants with abnormalities in clinical laboratory parameters for up to 2 years and 1 month

Phase II:
1. Duration of Response (DoR) for up to 2 years and 1 month from the date of first documented response (PR or CR) until the date of documented progression or death from any case, whichever comes first, for participants who have PR or CR
2. Disease Control Rate (DCR) for up to 2 years and 1 month. Where DCR is the percentage of participants who achieve a PR, CR or stable disease using RECISIT v1.1
3. Progression Free Survival (PFS) for up to 2 years and 1 month. Where PFS is the time from the first dose date until the date of disease progression or death, whichever comes first, based on investigator assessment using RECIST version 1.1
4. Overall Survival (OS) for up to 2 years and 1 month. Where OS is the time from the date of administration of the first study treatment until the date of death due to any cause.
5. Time to Subsequent Therapy (TTST) for up to 2 years and 1 month. Where TTST is the time from the date of administration of the first study treatment to the start date of the subsequent anticancer therapy following study treatment discontinuation, or death, whichever comes first
6. Only Cohort 1A: Change from baseline in Health-related Quality of Life in (HRQoL) as assessed by European Organization of Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC-QLQ-C30) scale score, from baseline till up to 2 years and 1 month

7. Only Cohort 1A: HRQoL as assessed by Non-Small Cell Lung Cancer - Symptom Assessment Questionnaire (NSCLC-SAQ) scale score from baseline till up to 2 years and 1 month
8. Only Cohort 1A: HRQoL as assessed by EuroQol 5-Dimension 5-Level (EQ-5D-5L) scale score from baseline till up to 2 years and 1 month
9. Only Cohort 1A: HRQoL as assessed by Patient-reported Outcomes Measurement Information System Short Form Version 2.0 - Physical Function 8c (PROMIS PF 8c) scale score from baseline till up to 2 years and 1 month

Completion date
22/08/2026

Eligibility

Key inclusion criteria
Current inclusion criteria:

ISA1 METalmark (now closed in UK):
1. Aged 18 years old and over (or the legal age of consent in the jurisdiction in which the study is taking place) at the time of informed consent
2. Previously diagnosed with histologically or cytologically confirmed unresectable Stage IV (metastatic) NSCLC (any histology)

For Phase I – Combination Dose Finding Confirmation:
Metastatic NSCLC progressed on or after standard of care systemic anti-cancer therapy and is declining other systemic treatment options, if any.

For Phase II – Dose Expansion:
1. Cohort 1A: MET exon 11 skipping mutation (without prior therapy for metastatic disease)
1.1. Metastatic NSCLC previously characterized as MET exon 11 skipping mutation positive AND lacking EGFR and ALK mutation, by a local test using a CLIA certified laboratory or an accredited laboratory
1.2. Participant must not have received systemic anti-cancer therapy for metastatic NSCLC. Neo-adjuvant and adjuvant therapies for earlier stage disease are allowed if relapse occurred >12 months from end of neoadjuvant or adjuvant systemic therapy
1.3. Adequate tumor tissue sample must be submitted to the sponsor
2. Cohort 1B: MET exon 11 skipping mutation (prior therapy)
2.1. Metastatic NSCLC previously characterized as MET exon 11 skipping mutation positive AND lacking EGFR and ALK mutation, by a local test using a CLIA certified laboratory or an accredited laboratory
2.2. Progression of metastatic disease on at least 1 but no more than 3 lines of prior systemic anti-cancer therapy, which may include MET TKI or chemotherapy as per local standard of care
2.3. Adequate tumor tissue sample must be submitted to the sponsor before enrollment
3. Cohort 1C: MET amplification (prior therapy)
3.1. Metastatic NSCLC previously characterized as having MET amplification (≥2 copy number of MET) AND lacking EGFR and ALK mutation, by a local test using a CLIA certified laboratory or an accredited laboratorya
3.2. Progression of metastatic disease on at least 1 but no more than 3 prior lines of standard of care therapy for metastatic disease
3.3. Submission of adequate archival or fresh tumor tissue, obtained following metastatic NSCLC diagnosis and after disease progression on the last systemic therapy is required

1. At least 1 measurable lesion, according to RECIST v1.1. Must not have been previously irradiated. May be used for the screening biopsy provided baseline tumor assessment scans are performed ≥7 days after the biopsy.

2. A female participant of childbearing potential must have a negative serum pregnancy test at screening and within 72 hours of the first dose of study treatment and must agree to further serum or urine pregnancy tests during the study.

3. A female participant must be either of the following: Not of childbearing potential, or of childbearing potential and practicing at least 1 highly effective method of contraception.

Added 25/09/2024:
ISA2 Polydamas:
1. Participant must have histologically or cytologically confirmed non-small cell lung cancer (NSCLC) (any histology), and must have metastatic NSCLC at the time of enrollment: Phase 1 (Combination Dose Selection) Cohort; Metastatic NSCLC progressed on or after standard of care systemic anti-cancer therapy and participant is declining other systemic treatment options, if any;1. Participants without known mutations must have had disease progression on, or have intolerance to, prior platinum-based chemotherapy and PD-(L)1-targeted immunotherapy given concurrently or sequentially, OR 2. Participants with NSCLC characterized by known driver mutations must have had disease progression on, or have intolerance to, appropriate targeted therapies as per local standard of care. Participants may have received prior therapy with amivantamab as long as discontinuation was not due to toxicity. Participants with EGFR mutation must not have had an anti-PD-1/PD-L1 therapy, Phase 2 Expansion Cohorts; Cohort A: Participant's tumor must have an EGFR exon19del or L858R mutation, as determined by local molecular testing, Cohort B: Participants must have tumors lacking known primary driver mutations and must have PD-L1 expression of greater than or equal to (>=)50 percentage (%), per local testing, and are treatment-naïve in the metastatic setting
2. Participant must have at least 1 measurable lesion, according to Response Evaluation Criteria in Solid Tumors (RECIST) v1.1, that has not been previously irradiated
3. Have an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1

Added 28/11/2024:
ISA3 SwalloWTail:

1. Be 18 years of age or older at the time of enrolment.
2. Have histologically or cytologically confirmed non-small cell lung cancer (NSCLC) and must have metastatic NSCLC at the time of enrolment.

Phase 1 (Combination Dose Selection) Cohort:
Metastatic NSCLC (any histology) progressed on or after systemic anti-cancer therapy:
- Participants with metastatic NSCLC without known mutations must have had disease progression on, or have intolerance to, prior platinum-based chemotherapy and immunotherapy given concurrently or sequentially; or,
- Participants with metastatic NSCLC characterised by known driver mutations must have had disease progression on, or have intolerance to, appropriate targeted therapies as per local standard of care (SoC).

Phase 2 Expansion Cohorts:
Cohort A: Participant must have histologically confirmed adenocarcinoma NSCLC lacking known primary driver mutations, as determined by local genomic testing followed by central confirmation. Participant must have had disease progression on or after platinum-based

chemotherapy and immune checkpoint inhibitor and must have had no more than 3 prior lines of therapy.
Cohort B: Participant must have histologically confirmed squamous NSCLC tumours lacking known primary driver mutations, as determined by local genomic testing (when available) followed by central confirmation. Participant must have had disease progression on or after platinum-based chemotherapy and immune checkpoint inhibitor and must have had no more than 3 prior
lines of therapy.

3. Must have at least 1 measurable lesion, according to RECIST v1.1, that has not been previously irradiated. Measurable lesions should not have been biopsied during screening, but if only 1 non-irradiated measurable lesion exists, it may undergo the diagnostic biopsy and be acceptable as a target lesion, provided the baseline tumour assessment scans are performed at least 7 days after the
biopsy.
4. Participant may have brain metastases only if previously definitively treated, and participant is clinically stable and asymptomatic for more than 2 weeks and is off or receiving low-dose corticosteroid treatment (less than or equal to 10 mg prednisone or equivalent) for at least 2 weeks prior to start of study treatment.
5. Participant may have a prior malignancy (other than the disease under study) if the natural history or treatment is unlikely to interfere with any study endpoints of safety or the efficacy of the study treatment(s).
6. Have an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1.

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Previous inclusion criteria:

1. Aged 18 years old and over (or the legal age of consent in the jurisdiction in which the study is taking place) at the time of informed consent
2. Previously diagnosed with histologically or cytologically confirmed unresectable Stage IV (metastatic) NSCLC (any histology)

For Phase I – Combination Dose Finding Confirmation:
Metastatic NSCLC progressed on or after standard of care systemic anti-cancer therapy and is declining other systemic treatment options, if any.

For Phase II – Dose Expansion:
1. Cohort 1A: MET exon 11 skipping mutation (without prior therapy for metastatic disease)
1.1. Metastatic NSCLC previously characterized as MET exon 11 skipping mutation positive AND lacking EGFR and ALK mutation, by a local test using a CLIA certified laboratory or an accredited laboratory
1.2. Participant must not have received systemic anti-cancer therapy for metastatic NSCLC. Neo-adjuvant and adjuvant therapies for earlier stage disease are allowed if relapse occurred >12 months from end of neoadjuvant or adjuvant systemic therapy
1.3. Adequate tumor tissue sample must be submitted to the sponsor
2. Cohort 1B: MET exon 11 skipping mutation (prior therapy)
2.1. Metastatic NSCLC previously characterized as MET exon 11 skipping mutation positive AND lacking EGFR and ALK mutation, by a local test using a CLIA certified laboratory or an accredited laboratory
2.2. Progression of metastatic disease on at least 1 but no more than 3 lines of prior systemic anti-cancer therapy, which may include MET TKI or chemotherapy as per local standard of care

2.3. Adequate tumor tissue sample must be submitted to the sponsor before enrollment
3. Cohort 1C: MET amplification (prior therapy)
3.1. Metastatic NSCLC previously characterized as having MET amplification (≥2 copy number of MET) AND lacking EGFR and ALK mutation, by a local test using a CLIA certified laboratory or an accredited laboratorya
3.2. Progression of metastatic disease on at least 1 but no more than 3 prior lines of standard of care therapy for metastatic disease
3.3. Submission of adequate archival or fresh tumor tissue, obtained following metastatic NSCLC diagnosis and after disease progression on the last systemic therapy is required

1. At least 1 measurable lesion, according to RECIST v1.1. Must not have been previously irradiated. May be used for the screening biopsy provided baseline tumor assessment scans are performed ≥7 days after the biopsy.

2. A female participant of childbearing potential must have a negative serum pregnancy test at screening and within 72 hours of the first dose of study treatment and must agree to further serum or urine pregnancy tests during the study.

3. A female participant must be either of the following: Not of childbearing potential, or of childbearing potential and practicing at least 1 highly effective method of contraception.

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Adult

Lower age limit
18 years

Sex
All

Key exclusion criteria
Current exclusion criteria:

ISA1 METalmark (now closed in UK):
1. History of uncontrolled illness, including but not limited to:
1.1. Uncontrolled diabetes
1.2. Ongoing or active infection (includes infection requiring treatment with antimicrobial therapy [participants will be required to complete antibiotics 1 week prior to starting study treatment] or diagnosed or suspected viral infection). See also inclusion criterion 1013 and exclusion criterion 14 for considerations with respect to HIV and hepatitis infection, respectively.
1.3. Active bleeding diathesis
1.4. Impaired oxygenation requiring continuous oxygen supplementation
1.5. Psychiatric illness or any other circumstances (including social circumstances) that would limit compliance with study requirements
2. Medical history of (non-infectious) ILD/pneumonitis, or has current ILD/pneumonitis, or where

suspected ILD/pneumonitis cannot be ruled out by imaging at screening.
3. Known allergies, hypersensitivity, or intolerance to:
3.1. Amivantamab excipients
3.2. Capmatinib or its excipients
4. Participant has, or will have, any of the following:
4.1. An invasive operative procedure with entry into a body cavity, within 4 weeks or without complete recovery before administration of the first study treatment. Thoracentesis, if needed, and percutaneous biopsy for baseline tumor tissue sample may be done less than 4 weeks prior to administration of the first study treatment, as long as the participant has adequately recovered from the procedure prior to the first dose of study treatment in the clinical judgement of the investigator.
4.2. Significant traumatic injury within 3 weeks before the start of administration of the first study treatment (all wounds must be fully healed prior to Day 1).
5. Expected major surgery while the investigational agent is being administered or within 6 months after the last dose of study treatment.
6. The participant has impairment of the gastrointestinal function that could affect absorption of capmatinib or is unable or unwilling to swallow tablets.
7. Participant has a history of clinically significant cardiovascular disease including, but not limited to the following:
7.1 Diagnosis of deep vein thrombosis or pulmonary embolism within 1 month prior to administration of the first dose of study treatment, or any of the following within 6 months prior to administration of the first dose of study treatment: myocardial infarction, unstable angina, stroke, transient ischemic attack, coronary/peripheral artery bypass graft, or any acute coronary syndrome. Clinically non-significant thrombosis, such as non-obstructive catheter-associated clots, are not exclusionary.
7.2. Prolonged QTc interval >480 msec or clinically significant cardiac arrhythmia or electrophysiologic disease (eg, placement of implantable cardioverter defibrillator or atrial fibrillation with uncontrolled rate)
7.3. Note: Participants with cardiac pacemakers who are clinically stable are eligible.
7.4. Uncontrolled (persistent) hypertension: systolic blood pressure >160 mmHg; diastolic blood pressure >100 mmHg
7.5. Congestive heart failure (CHF) defined as New York Heart Association (NYHA) class III-IV or hospitalization for CHF (any NYHA class) within 6 months of administration of the first study treatment
7.6. Pericarditis/clinically significant pericardial effusion within 1 month prior to administration of the first dose of study treatment
7.7. Myocarditis
8. Participant received thoracic radiotherapy to lung fields ≤4 weeks prior to Cycle 1 Day 1 or patients who have not recovered from radiotherapy-related toxicities. For all other anatomic sites (including radiotherapy to thoracic vertebrae and ribs), radiotherapy ≤2 weeks prior to Cycle 1 Day 1 or patients who have not recovered from radiotherapy-related toxicities.
9. Participant has symptomatic central nervous system (CNS) metastases which are neurologically unstable or have required increasing doses of steroids >10 mg prednisone or equivalent within the 2 weeks prior to study entry to manage CNS symptoms.

Added 25/09/2024:
ISA2 Polydamas:
1. Participant has an uncontrolled illness, including but not limited to:
1.1. Uncontrolled diabetes,
1.2. Ongoing or active infection (includes infection requiring treatment with antimicrobial therapy [participants will be required to complete antibiotics 1 week prior to starting study treatment] or diagnosed or suspected viral infection),

1.3. Active bleeding diathesis,
1.4. Impaired oxygenation requiring continuous oxygen supplementation,
1.5. Psychiatric illness or any other circumstances (including social circumstances) that would limit compliance with study requirements
2. Medical history of (non-infectious) interstitial lung disease (ILD)/pneumonitis, or has current ILD/pneumonitis, or where suspected ILD/pneumonitis cannot be ruled out by imaging at screening - Has an active autoimmune disease or a documented history of autoimmune disease that requires systemic steroids or immunosuppressive agents
3. Participant has received radiotherapy for palliative purposes less than 14 days prior to the first dose of study treatment
4. Participant has a. (or has a history of) leptomeningeal disease (carcinomatous meningitis), b. spinal cord compression not definitively treated with surgery or radiation

Added 28/11/2024:
ISA3 SwalloWTail:
1. Phase 2 only: Participant has known oncogenic driver mutations as detected by local testing or by central circulating tumour deoxyribonucleic acid (ctDNA) testing.
2. Participant has received radiotherapy for palliative purposes less than 14 days prior to the first dose of study treatment.
3. Participant has:
a. (Or has a history of) leptomeningeal disease (carcinomatous meningitis).
b. Spinal cord compression not definitively treated with surgery or radiation.
4. Participant has an uncontrolled illness.
5. Participant has history of any significant drug allergy or has known allergies, hypersensitivity, or intolerance to either of the study drugs or their excipients.
6. Medical history of (non-infectious) interstitial lung disease (ILD)/pneumonitis, or has current ILD/pneumonitis, or where suspected ILD/pneumonitis cannot be ruled out by imaging at screening.
4. Participant has, or will have, any of the following:
4.1. An invasive operative procedure with entry into a body cavity, within 4 weeks or without complete recovery before administration of the first study treatment.
4.2. Significant traumatic injury within 3 weeks before the start of administration of the first study treatment (all wounds must be fully healed prior to Day 1).
4.3. Expected major surgery while the investigational agent is being administered or within 6 months after the last dose of study treatment.
8. Participant has a history of clinically significant cardiovascular disease.
9. Phase 2 only: Participant received prior amivantamab or docetaxel.
10. Participant received live or live attenuated vaccine(s) within 3 months prior to screening or plans to receive such vaccines during the study.
11. Participant has had prior chemotherapy, targeted cancer therapy, or treatment with an investigational anticancer agent within 2 weeks or 4 half-lives (whichever is longer) before administration of the first study treatment. For agents with long half-lives the maximum required time since last dose is 28 days.
12. Toxicities from previous anticancer therapies should have resolved to baseline levels or to Grade 1 or less prior to the first dose of study treatment (except as per the protocol).
13. Has taken immunosuppressive doses of systemic medications, such as corticosteroids within 2 weeks before the planned first dose of study treatment.
14. Active hepatitis of infectious origin.
15. Other clinically active liver disease of infectious origin.
16. Any condition for which, in the opinion of the investigator, participation would not be in the best interest of the participant or that could prevent, limit, or confound the protocol-specified assessments.

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Previous exclusion criteria:

1. History of uncontrolled illness, including but not limited to:
1.1. Uncontrolled diabetes
1.2. Ongoing or active infection (includes infection requiring treatment with antimicrobial therapy [participants will be required to complete antibiotics 1 week prior to starting study treatment] or diagnosed or suspected viral infection). See also inclusion criterion 1013 and exclusion criterion 14 for considerations with respect to HIV and hepatitis infection, respectively.
1.3. Active bleeding diathesis
1.4. Impaired oxygenation requiring continuous oxygen supplementation
1.5. Psychiatric illness or any other circumstances (including social circumstances) that would limit compliance with study requirements

2. Medical history of (non-infectious) ILD/pneumonitis, or has current ILD/pneumonitis, or where suspected ILD/pneumonitis cannot be ruled out by imaging at screening.

3. Known allergies, hypersensitivity, or intolerance to:
3.1. Amivantamab excipients
3.2. Capmatinib or its excipients

4. Participant has, or will have, any of the following:
4.1. An invasive operative procedure with entry into a body cavity, within 4 weeks or without complete recovery before administration of the first study treatment. Thoracentesis, if needed, and percutaneous biopsy for baseline tumor tissue sample may be done less than 4 weeks prior to administration of the first study treatment, as long as the participant has adequately recovered from the procedure prior to the first dose of study treatment in the clinical judgement of the investigator.
4.2. Significant traumatic injury within 3 weeks before the start of administration of the first study treatment (all wounds must be fully healed prior to Day 1).

5. Expected major surgery while the investigational agent is being administered or within 6 months after the last dose of study treatment.

6. The participant has impairment of the gastrointestinal function that could affect absorption of capmatinib or is unable or unwilling to swallow tablets.

7. Participant has a history of clinically significant cardiovascular disease including, but not limited to the following:
7.1 Diagnosis of deep vein thrombosis or pulmonary embolism within 1 month prior to administration of the first dose of study treatment, or any of the following within 6 months prior to administration of the first dose of study treatment: myocardial infarction, unstable angina, stroke, transient ischemic attack, coronary/peripheral artery bypass graft, or any acute coronary syndrome. Clinically non-significant thrombosis, such as non-obstructive catheter-associated clots, are not exclusionary.
7.2. Prolonged QTc interval >480 msec or clinically significant cardiac arrhythmia or electrophysiologic disease (eg, placement of implantable cardioverter defibrillator or atrial fibrillation with uncontrolled rate)
7.3. Note: Participants with cardiac pacemakers who are clinically stable are eligible.
7.4. Uncontrolled (persistent) hypertension: systolic blood pressure >160 mmHg; diastolic blood

pressure >100 mmHg
7.5. Congestive heart failure (CHF) defined as New York Heart Association (NYHA) class III-IV or hospitalization for CHF (any NYHA class) within 6 months of administration of the first study treatment
7.6. Pericarditis/clinically significant pericardial effusion within 1 month prior to administration of the first dose of study treatment
7.7. Myocarditis

8. Participant received thoracic radiotherapy to lung fields ≤4 weeks prior to Cycle 1 Day 1 or patients who have not recovered from radiotherapy-related toxicities. For all other anatomic sites (including radiotherapy to thoracic vertebrae and ribs), radiotherapy ≤2 weeks prior to Cycle 1 Day 1 or patients who have not recovered from radiotherapy-related toxicities.

9. Participant has symptomatic central nervous system (CNS) metastases which are neurologically unstable or have required increasing doses of steroids >10 mg prednisone or equivalent within the 2 weeks prior to study entry to manage CNS symptoms.

Date of first enrolment
28/11/2022

Date of final enrolment
25/04/2025

Locations

Countries of recruitment
United Kingdom

England

Brazil

Italy

Korea, South

Malaysia

Poland

Spain

Türkiye

United States of America

Study participating centre
Royal Marsden Hospital
Downs Road
Sutton

United Kingdom
SM2 5PT

Study participating centre
Freeman Road Hospital
Freeman Road
High Heaton
Newcastle upon Tyne
United Kingdom
NE7 7DN

Study participating centre
Imperial College London and Imperial College Healthcare NHS Trust
St Marys Hospital
Praed Street
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W2 1NY

Study participating centre
St James Hospital
Locksway Road
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Study participating centre
St James' S University Hospital
Beckett Street
Leeds
United Kingdom
LS9 7TF

Sponsor information

Organisation
Janssen-Cilag International NV

Funder(s)

Funder type
Industry

Funder Name
Cilag

Alternative Name(s)
Janssen-Cilag, Cilag AG

Funding Body Type
Private sector organisation

Funding Body Subtype
For-profit companies (industry)

Location
Switzerland

Results and Publications

Individual participant data (IPD) sharing plan
The datasets generated during and/or analysed during the current study are/will be available upon request. The data sharing policy of the Janssen Pharmaceutical Companies of Johnson & Johnson is available at https://www.janssen.com/clinical-trials/transparency. As noted on that site, requests for access to the study data can be submitted through the Yale Open Data Access (YODA) Project site at yoda.yale.edu.

IPD sharing plan summary
Available on request