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A modular, multi-part, multi-arm, open-label, phase I/II study to evaluate the safety and tolerability of GRWD5769 alone and in combination with anticancer treatments in patients with solid malignancies

Submission date
07/06/2023

Recruitment status
No longer recruiting

Registration date
18/03/2024

Overall study status
Ongoing

Last Edited
02/09/2025

Condition category
Cancer

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

Plain English summary of protocol

Background and study aims
Cancer is one of the leading causes of death, responsible for 16% of deaths worldwide in 2018. Immunotherapy is a type of cancer treatment that helps the immune system to fight cancer. Immunotherapy with drugs called checkpoint inhibitors have begun to transform cancer treatment, bringing about significant improvements. However, they have only been proven effective for a small subset of cancers and specific patient groups. Hence, an urgent and significant healthcare need remains to support cancer patients who do not respond to first-generation checkpoint inhibitors.
GRWD5769 is a potential new treatment for advanced or metastatic solid malignancies. GRWD5769 works by stopping an enzyme in the body, called endoplasmic reticulum aminopeptidase 1 (ERAP1), from working. ERAP1 is part of how the body recognizes the presence of a cancer tumour and helps trigger the immune system to fight the cancer. However, in patients with cancer, the immune system cells can become exhausted and no longer work effectively. By blocking ERAP1 it makes the tumour look different to the immune system and so the immune system starts fighting the cancer again. Giving the study drug intermittently may also help prevent the immune system cells from becoming exhausted. Studies have been conducted in animals which support the use of GRWD5769 in humans for the treatment of advanced solid tumours in a broad range of cancer types. GRWD5769 has the potential of producing clinically meaningful improvements in monotherapy and in combination with therapy like cemiplimab (Libtayo®) by enhancing the antitumour immune response.

Who can participate?
Patients with advanced or metastatic solid malignancy aged 18 years or older.

What does the study involve?
This study consists of Module 1 (Parts A to D), which will look at the effects of GRWD5769 when

given alone and Module 2 (Parts A to C) which will look at the effects of GRWD5769 when given in combination with another anticancer drug called Libtayo® (cemiplimab).

What are the possible benefits and risks of participating? Benefits:
GRWD5769 is an experimental drug, and this is the first time it is being tested in humans and it is not known whether GRWD5769 alone or in combination with cemiplimab will improve a participant's cancer. It is hoped that the information learned from this study may help future patients with cancer. This research may lead to new or improved drug treatments in the future.
Risks:
This is the first time GRWD5769 is given to humans. Whilst, based on animal data, GRWD5769 has not been linked to significant safety issues, the safety in humans is not known. The dose levels to be used in this study will not exceed the dose levels that were tolerated in animals. Each time a new dose of GRWD5769 is given to a participant, a minimum of 48 hours will be allowed to check for safety before any other participants receive that dose. A safety review committee will also oversee the dose escalation phases and decide whether it is safe to test a higher dose. GRWD5769 is potentially phototoxic. Participants are provided with instructions to minimise this risk. GRWD5769 may also interact with other drugs, so participants are not allowed to take certain medications. The effects of GRWD5769 on the unborn child or newborn baby is unknown so all precautions are taken to exclude pregnant or breast-feeding women and to ensure appropriate contraception is used.
Cemiplimab is a licenced medication, but in this study may be used in unlicenced indications and it has not been given with GRWD5769 before. Cemiplimab can cause potentially serious side effects associated with inflammation. It can also be associated with infusion reactions. Administration of cemiplimab will be managed by experienced hospital staff, according to established guidelines and patients will be informed about the risks. There is the possibility of additional or worse side effects by giving both GRWD5769 and cemiplimab together. This will be monitored and overseen by the safety review committee.
The study requires a number of blood draws to be made and a significant amount of blood to be collected as part of assessing levels of GRWD5769 in the blood and the potential effects of GRWD5769. Patients may also need to stay in hospital overnight on a few occasions where late night and/or early morning samples are needed. This will be made clear to patients when they consider if they want to take part in the study. There can be pain or bruising at the site where blood is drawn from, which Study staff will monitor and manage. There are potential risks associated with some of the other study interventions, such as pain and bleeding after a biopsy procedure. CT, MRI and bone scans needed to monitor disease use ionizing radiation, which can cause cell damage that may, after many years or decades, turn cancerous, though the chance of this happening is extremely small.

Where is the study run from?
Precision for Medicine (UK)

When is the study starting and how long is it expected to run for?
February 2023 to April 2027

Who is funding the study?
Grey Wolf Therapeutics (UK)

Who is the main contact?
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Additional identifiers

Clinical Trials Information System (CTIS)
2023-504845-30-00

Integrated Research Application System (IRAS)
1007712

ClinicalTrials.gov (NCT)
Nil known

Protocol serial number
GRWD5769-ST-01, IRAS 1007712, CPMS 56048

Study information

Scientific Title
ERAP Mediated Immunopeptidome Targeting Trial – 1

Acronym
EMITT-1

Study objectives

Current study hypothesis as of 02/12/2024:

Primary objectives:
Module 1: To determine the safety and tolerability of GRWD5769 monotherapy in participants with advanced malignancies.
Module 2: To determine the safety and tolerability of GRWD5769 when administered in combination with cemiplimab (Libtayo®) 350 mg

Secondary objectives:
Module 1
1. To determine the MTD (if any) and/or RP2D of GRWD5769 monotherapy.
2. To characterise the plasma PK of GRWD5769 monotherapy, following single and multiple dose administration.
3. To assess the preliminary efficacy of GRWD5769 when administered as a monotherapy.
4. To identify the MBAD of GRWD5769 when administered as a monotherapy. Module 2
5. To determine the MTD (if any) and/or RP2D of GRWD5769 when administered in combination with cemiplimab 350 mg.
6. To evaluate plasma accumulation of GRWD5769 when administered in combination with cemiplimab 350 mg.
7. To assess the preliminary efficacy of GRWD5769 when administered in combination with cemiplimab 350 mg.
8. To identify the MBAD of GRWD5769 when administered in combination with cemiplimab 350 mg.

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Previous study hypothesis:

Primary objectives:
Module 1: To determine the safety and tolerability of GRWD5769 monotherapy in participants with advanced malignancies.
Module 2: To determine the safety and tolerability of GRWD5769 when administered in combination with cemiplimab 350 mg in participants with advanced malignancies

Secondary objectives:
Module 1
1. To determine the MTD (if any) and/or RP2D of GRWD5769 monotherapy.
2. To characterise the plasma PK of GRWD5769 monotherapy, following single and multiple dose administration.
3. To assess the preliminary efficacy of GRWD5769 when administered as a monotherapy.
4. To identify the MBAD of GRWD5769 when administered as a monotherapy.
Module 2
5. To determine the MTD (if any) and/or RP2D of GRWD5769 when administered in combination with cemiplimab 350 mg.
6. To evaluate plasma accumulation of GRWD5769 when administered in combination with cemiplimab 350 mg.
7. To assess the preliminary efficacy of GRWD5769 when administered in combination with cemiplimab 350 mg.
8. To identify the MBAD of GRWD5769 when administered in combination with cemiplimab 350 mg.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Approval pending, ref: 23/LO/0547

Study design
Interventional non randomized

Primary study design
Interventional

Study type(s)
Safety, Efficacy

Health condition(s) or problem(s) studied
Advanced or metastatic solid malignancy

Interventions
Current interventions as of 02/12/2024:

This is a Phase I/II, open-label, first-in human study of GRWD5769 alone (administered orally 2 times a day), and in combination with another anti-cancer agent in advanced solid cancers. The study design consists of two modules: Module 1 (GRWD5769 on its own as monotherapy) and Module 2 (GRWD5769 in combination with cemiplimab, administered IV). Additional modules and study parts may be added to this protocol as part of the overall GRWD5769 development plan.

Module 1 will initially be conducted in 4 study parts:
Part A: Monotherapy dose escalation (where the safety of increasing doses of GRWD5769 will initially be assessed in a small group of patients, overseen by a safety review committee). Patients in this arm will be given the option to crossover to combination therapy if they are still active on the study when their dose of GRWD5769 has been shown to be safe in Module 2 Part A below.
Part B: (Optional) Monotherapy dose expansion part (to look at the effect of GRWD5769 on the body, and of the body on GRWD5769, at particular dose levels to include evaluation of biopsies of tumour tissue)
Part C: (Optional) Intra-patient dose escalation (where a patient may receive three different GRWD5769 doses so that blood levels at each dose can be measured in an individual).

Part D (Optional): Monotherapy dose expansion group(s) (where a dose of GRWD5769 may be chosen to be evaluated in specific types of cancer)
In Module 1, GRWD5769 will be given to patients in alternating, 3-week cycles of treatment until the participant withdraws/is withdrawn from the study. GRWD5769 is taken orally (by mouth) twice a day 3 weeks at a time. Each 3-week period of taking GRWD5769 is followed by a break of 3 weeks when it is not taken. The dosing frequency of GRWD5769 administered may be modified.

Module 2 will initially be conducted as 3 study parts, similar to those above, but looking at GRWD5769 when given in combination with cemiplimab:
Part A: Combination therapy dose escalation (like Module 1 Part A)
Part B: (Optional) Combination therapy dose expansion part (like Module 1 Part B) Part C:

Combination therapy dose expansion group(s) (where a dose of GRWD5769 given with cemiplimab will be evaluated in specific types of cancer)

In Module 2 combination therapy, patients will be treated with GRWD5769 as for Module 1 but with the addition of cemiplimab 350 mg, which will be given every 3 weeks as an IV infusion, on Day 1 of Cycle 1 and all subsequent cycles (except for Module 2 Part B, where cemiplimab is commenced Day 1 of Cycle 2). As for Module 1, each cycle of treatment is over 3 weeks.

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Previous interventions:

This is a Phase I/II, open-label, first-in human study of GRWD5769 alone (administered orally 2 times a day), and in combination with another anti-cancer agent in advanced solid cancers. The study design consists of two modules: Module 1 (GRWD5769 on its own as monotherapy) and Module 2 (GRWD5769 in combination with cemiplimab, administered IV). Additional modules and study parts may be added to this protocol as part of the overall GRWD5769 development plan.

Module 1 will initially be conducted in 4 study parts:
Part A: Monotherapy dose escalation (where the safety of increasing doses of GRWD5769 will initially be assessed in a small group of patients, overseen by a safety review committee)
Part B: (Optional) Monotherapy dose expansion part (to look at the effect of GRWD5769 on the body, and of the body on GRWD5769, at particular dose levels and in patients who have previously had clinical benefit from their most recent checkpoint inhibitor therapy but subsequently progressed on this treatment)
Part C: (Optional) Intra-patient dose escalation (where a patient may receive three different GRWD5769 doses so that blood levels at each dose can be measured in an individual)
Part D: Monotherapy dose expansion group(s) (where a dose of GRWD5769 may be chosen to be evaluated in specific types of cancer)

In Module 1, GRWD5769 will be given to patients in repeating cycles of treatment until the participant withdraws/is withdrawn from the study. GRWD5769 is taken orally (by mouth) twice a day for the first 14 days of each 21-day cycle. The only exception to this is the (optional) Module 1 Part C, where cycle 1 will last 28 days, to allow three different doses of GRWD5769 to be assessed. The dosing frequency of GRWD5769 administered may be modified.

Module 2 will initially be conducted as 3 study parts, similar to those above, but looking at GRWD5769 when given in combination with cemiplimab:
Part A: Combination therapy dose escalation (like Module 1 Part A)
Part B: (Optional) Combination therapy dose expansion part (like Module 1 Part B)
Part C: Combination therapy dose expansion group(s) (like Module 1 Part D)

In Module 2 combination therapy, patients will be treated with GRWD5769 as for Module 1 but with the addition of cemiplimab 350 mg, which will be given every 3 weeks as an IV infusion, on Day 1 of Cycle 1 and all subsequent cycles. As for Module 1, each cycle of treatment is over 21 days.

Intervention Type
Drug

Phase

Phase I

Drug/device/biological/vaccine name(s)
GRWD5769, cemiplimab (Libtayo)

Primary outcome(s)
Current primary outcome measure as of 02/12/2024:

Safety and tolerability of GRWD5769 will be determined by:
1. Incidence of treatment emergent and treatment related AEs assessed from start of study drug to 30 days post last dose of GRWD5769 (Module 1) or to 90 days post last dose of cemiplimab (Module 2)
2. Incidence of Dose limiting toxicities (DLT) during the DLT period which commences Cycle 0 Day 1 and continues to 21 days after Cycle 1 Day 1

Note the timepoint information above is for the dose escalation cohorts (Module 1 Part A and Module 2 Part A) and may differ for other Modules/Parts.

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Previous primary outcome measure:

Safety and tolerability of GRWD5769 will be determined by:
1. Incidence of treatment emergent and treatment related AEs assessed from start of study drug to 30 days post last dose of GRWD5769 (Module 1) or to 90 days post last dose of cemiplimab (Module 2)
2. Incidence of Dose limiting toxicities (DLT) during the DLT period which commences Cycle 0 Day 1 and continues to 21 days after Cycle 1 Day 1
3. Clinical laboratory safety assessments performed pre-treatment, on Cycle 0 Day 1, Cycle 1 Days 1, 8 and 14, Cycle 2 (and all subsequent cycles) Days 1 and 14, at each 6-weekly safety extension visit and at end of study visit and at follow up visit 30 days post last dose of GRWD5769 and 90 days post last dose of cemiplimab (Module 2)
4. Vital signs performed pre-treatment, on Cycle 0 Day 1, Cycle 1 Days 1, 2, 8, 14 and 15, Cycle 2 (and all subsequent cycles) Day 1, at each 6-weekly safety extension visit and at end of study visit and at follow up visit 30 days post last dose of GRWD5769 and 90 days post last dose of cemiplimab (Module 2)
5. ECG performed pre-treatment, Cycle 0 Days 1 and 2, Cycle 1 Days 1, 2, 8, and 14, Cycle 2 (and all subsequent cycles) Day 1, at each 6-weekly safety extension visit and at end of study visit and at follow up visit 90 days post last dose of cemiplimab (Module 2)
6. ECOG performance status scores assessed pre-treatment, Cycle 0 Day 1, Cycle 2 (and all subsequent cycles) Day 1, at each 6-weekly safety extension visit and at end of study visit and at follow up visit 30 days post last dose post last dose of GRWD5769.

Note the timepoint information above is for the dose escalation cohorts (Module 1 Part A and Module 2 Part A) and may differ for other Modules/Parts.

Key secondary outcome(s))
1. The pharmacokinetics of GRWD5769 will be assessed to include but not limited to Cmax, Tmax, AUC0-t, t½, CL/F and Vss/F measured at Cycle 0 Day 1 and Cycle 1 Days 1 and 14 and trough concentrations measured prior to dose administration including Day 8 of Cycle 1 and Days 1 and 14 of each cycle from Cycle 2 onwards.

2. Preliminary efficacy of GRWD5769 will be assessed by:
2.1.Tumour response (ORR, TTR, DOR, DCR, and PFS) by RECIST 1.1 or iRECIST as determined by CT/MRI scans performed every 8 weeks until participant disease progression or withdrawal
2.2. Changes in any applicable disease-specific tumour markers assessed pre-treatment, Day 1 of each cycle from Cycle 2 onwards, at each 6-weekly safety extension visit, at the end of study visit and at follow up visit 30 days post last dose of GRWD5769

Note the timepoint information above is for the dose escalation cohorts (Module 1 Part A and Module 2 Part A) and may differ for other Modules/Parts.

Completion date
30/04/2027

Eligibility

Key inclusion criteria
Current inclusion criteria as of 02/12/2024:

1. Provision of written informed consent
2. Male or female, ≥ 18 years of age.
3. An ECOG performance status of 0 or 1
4. Willing to permit access to stored historical tumour tissue and prior tumour radiological assessments and tumour biomarker data (if available).
5. Able to take oral medications and be willing to record daily adherence to the study drug.
6. Female participants must be of non-child-bearing potential, or, if of childbearing potential must have a negative pregnancy tests (as required by protocol), must use a highly effective method of contraception combined with a condom and not donate ova (for the protocol specified period of time).
7. Male participants must use a condom and their female participant must also use a highly effective method of contraception (for the protocol specified period of time). If engaging in sexual intercourse with a female partner who could become pregnant and not donate sperm.
8. Estimated life expectancy of at least 3 months, in the opinion of the PI.
9. Willing and able to comply with all scheduled visits, treatment plans, laboratory tests, and other study procedures.
Module 1 (Parts A, B and C) and Module 2 (Parts A and B)
10. Participant has cytologically or histologically confirmed locally advanced or metastatic solid malignancy not considered appropriate for which no standard of care (SoC) therapy is available, (or no SoC therapy exists), or who have been offered and declined SoC therapy, or are intolerant of SoC therapy..
11. Participant has measurable disease per RECIST 1.1/iRECIST.

Module 1 (Part B) and Module 2 (Part B) Only
12. Participant has at least one tumour lesion amenable to serial biopsies and is willing to provide consent for biopsies and has measurable disease per RECIST 1.1/iRECIST, excluding the lesion(s) identified for biopsy.

Module 1 (Part D)
Additional selection criteria for Module 1 Part D will be described in a future protocol amendment.

Module 2 (Part C)
Cohort 1
13. Participants with histologically confirmed persistent, recurrent or metastatic cervical cancer who are not amenable to curative therapy.
14. Participants should have received at least 3 months first line anti-PD(L)-1 maintenance therapy (± bevacizumab) following combination with chemotherapy (± bevacizumab) with initial clinical benefit but who have now progressed.
15. Participants may enrol in the study immediately following progression on the first line CPI or may have received 1 further line of systemic cancer therapy after progression on CPI.

Cohort 2
16. Participants with histologically confirmed hepatocellular carcinoma who are not amenable to curative therapy and ineligible for loco-regional therapy.
17. Participants should have received at least 3 months first line anti-PD(L)-1 containing with initial clinical benefit but who have now progressed.
18. Participants may enrol in the study immediately following progression on the first line CPI or may have received 1 further line of systemic cancer therapy after progression on CPI.
19. Participant has Child-Pugh score class A liver function.

Cohort 3
20. Participants with cytologically or histologically confirmed advanced, recurrent or metastatic disease, which is not amenable to curative therapy, in up to 5 types of solid tumour with moderate to high median TMB.
21. Participants should have received at least 3 months first line anti-PD(L)-1 either initiated as monotherapy or as maintenance therapy with initial clinical benefit, but who have now progressed.
Participants may enrol in the study immediately following progression on the first line CPI or may have received 1 further line of systemic cancer therapy after progression on CPI.

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Previous inclusion criteria:

1. Must have given written informed consent before any study-related activities are carried out and must be able to understand the full nature and purpose of the trial, including possible risks and adverse effects.
2. Male or female, ≥ 18 years of age.
3. An ECOG performance status of 0 or 1 with no deterioration over the previous 2 weeks, as determined on the day of first dose administration of IMP (prior to dose administration).
4. Willing to permit access to stored historical tumour tissue and prior tumour radiological assessments and tumour biomarker data (if available).
5. Able to take oral medications and be willing to record daily adherence to the study drug.
6. Female participants must be of non-child-bearing potential i.e., surgically sterilised (hysterectomy, bilateral salpingectomy, bilateral oophorectomy at least 6 weeks before the screening visit) or postmenopausal (where postmenopausal is defined as no menses for 12 months without an alternative medical cause and a follicle-stimulating hormone (FSH) level consistent with postmenopausal status, per local laboratory guidelines), or, if of child-bearing potential: a. Must have a negative serum pregnancy test at the screening visit and a negative urine pregnancy test within 24 hours prior to the start of study drug b. Must agree not to attempt to become pregnant c. Must not donate ova from signing consent until at least 33 days (30 days + minimum of 5 x half-lives of GRWD5769) after the last dose of study drug d. If not exclusively in a same-sex relationship, must agree to use adequate contraception (which is

defined as use of a condom by the male partner combined with use of a highly effective method of contraception from signing the consent form until at least 33 days after the last dose of study drug.
7. Male participants must: a. Agree not to donate sperm from the time of signing consent until at least 93 days (90 days + minimum of 5 x half-lives of GRWD5769) after the last dose of study drug b. If engaging in sexual intercourse with a female partner who could become pregnant, must agree to use a condom plus a highly effective method of contraception (Section 23.1) from the time of signing consent until at least 93 days after the last dose of study drug. c. If engaging in sexual intercourse with a female partner who is not of childbearing potential or a same-sex partner, must agree to use a condom from the time of signing consent until at least 93 days after the last dose of study drug.
8. Estimated life expectancy of at least 3 months, in the opinion of the PI.
9. Willing and able to comply with all scheduled visits, treatment plans, laboratory tests, and other study procedures.

Module 1 (Parts A and C) and Module 2 (Part A) Only
10. Participant has cytologically or histologically confirmed locally advanced or metastatic solid malignancy not considered appropriate for further standard treatment.
11. Participant has measurable disease per RECIST 1.1/iRECIST.

Module 1 (Part B) and Module 2 (Part B) Only
12. Participant has cytologically or histologically confirmed locally advanced or metastatic solid malignancy.
13. Participant has confirmed progressive disease (as determined by the Investigator) after having received at least 12 weeks of prior anti-PD-1 or anti-PD-L1 mAb therapy, without evidence of primary resistant disease (defined as progression during the initial 12 weeks of treatment, or at the time of the first tumour assessment, without subsequent response to the therapy, as determined by the Investigator).
14. Participant has at least one tumour lesion amenable to serial biopsies and is willing to provide consent for biopsies and has measurable disease per RECIST 1.1/iRECIST, excluding the lesion(s) identified for biopsy.

Module 1 (Part D) and Module 2 (Part C) Only
Additional selection criteria for Module 1 Part D and Module 2 Part C will be described in a future protocol amendment.

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Adult

Lower age limit
18 years

Sex
All

Key exclusion criteria

Current exclusion criteria as of 02/12/2024:

1. Prior therapy with an ERAP1 inhibitor.
2. Any other malignancy within the past 3 years, with the exception of cervical intraepithelial neoplasia and nonmelanoma skin cancer.
3. Any unresolved toxicity (except alopecia) from prior therapy of ≥ CTCAE Grade 1. Participants with Grade 2 toxicity that is not clinically significant (e.g., alopecia, vitiligo), or that is deemed stable or irreversible (e.g., peripheral neuropathy) can be enrolled.
4. Active or documented history of autoimmune disease (within 2 years) requiring systemic immunosuppressive therapy, or participant is immunocompromised for any other reason (as determined by the Investigator).
5. Spinal cord compression or brain metastases, unless asymptomatic, stable, and not requiring steroids for at least 4 weeks (if stable and requiring no intervention, the participant can be enrolled in the study).
6. Uncontrolled seizures
7. Active infection requiring systemic antibiotic, antifungal, or antiviral medication within 14 days.
8. Severe or uncontrolled medical condition (e.g., severe chronic obstructive pulmonary disease, severe Parkinson's disease, active inflammatory bowel disease) or psychiatric condition.
9. Active bleeding diatheses.
10. Participant has received an organ transplant.
11. Known active hepatitis B, hepatitis C, or human immunodeficiency virus infection (HIV). Note: participants with prior hepatitis B or C infection which has been adequately treated (and/or is controlled) are eligible for study participation.
12. Participant is breastfeeding or pregnant.
13. Receipt of licenced or unlicenced cytotoxic, noncytotoxic or small molecule treatment for the malignancy within 28 days or 5 half-lives, whichever is shorter. Note: CPI therapy is permitted within any timeframe.
14. Receipt of oral corticosteroids (at a dose > 10 mg prednisone/day or equivalent) within 14 days (except for subjects receiving corticosteroids for adrenal insufficiency).
15. Receipt of St John's Wort or of another concomitant medication, herbal supplement, or food that is a strong inhibitor or inducer of CYP3A4 enzymes within 14 days.
16. Receipt of a blood transfusion (blood or blood products) within 7 days.
17. Impaired hepatic or renal function.
18. Liver function deteriorating in a manner that would likely make the participant ineligible per protocol specified requirements.
19. Other evidence of impaired hepatic synthesis function.
20. Inadequate bone marrow reserve or organ function.
21. Any prior history of persistent (> 4 weeks) severe pancytopenia due to previous therapy rather than to disease (ANC < 0.5 × 10^9/L or platelets < 50 x 10^9/L).
22. Cardiac dysfunction or other clinically significant cardiac pathology likely to impair the participants ability to participate in the study.
23. Mean QTcF > 450 ms for males or > 470 ms for females.
24. Any clinically important abnormalities in rhythm, conduction, or morphology on resting ECG. Controlled atrial fibrillation is permitted.
25. Any factor that in the Investigator's opinion increases the risk of QTc prolongation or arrythmic events.
26. In the opinion of the Investigator, unlikely to comply with study procedures, restrictions, or requirements.
27. A history of haemolytic anaemia or marrow aplasia.

28. Has received a live-virus vaccination within 28 days. Note: seasonal flu or COVID vaccines that do not contain live virus are permitted.
29. History of Grade 3 or 4 pneumonitis or interstitial lung disease within the last 5 years, or other clinically significant pulmonary pathology likely to impair ability to participate in the study.

Module 2 all Parts and Module 1A Crossover Participants Only Only
30. Has discontinued a prior checkpoint inhibitor due to toxicity.
31. Hypersensitivity to cemiplimab or any of its excipients, or contraindicated to cemiplimab per approved local labelling.
32. Has experienced ≥ Grade 2 immune-mediated AE on this study (applies to crossover participants only).
Module 2 Only
33. Participant previously discontinued treatment with anti-PD-L1 mAb due to immune related toxicity.

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Previous exclusion criteria:

1. Prior therapy with an ERAP1 inhibitor, within any timeframe prior to the first dose of IMP.
2. Any other malignancy not meeting inclusion criterion #1 which has been active or treated within the past 3 years, with the exception of cervical intraepithelial neoplasia and nonmelanoma skin cancer
3. Any unresolved toxicity (except alopecia) from prior therapy of ≥ CTCAE Grade 3, prior to the day of the first dose of IMP.
4. Active or documented history of autoimmune disease
5. Spinal cord compression or brain metastases, unless asymptomatic, stable, and not requiring steroids for at least 4 weeks before the day of the first dose of IMP (if stable and requiring no intervention, the participant can be enrolled in the study).
6. Uncontrolled seizures
7. Active infection requiring systemic antibiotic, antifungal, or antiviral medication within 14 days prior to the day of first dose of IMP.
8. Severe or uncontrolled medical condition (e.g., severe chronic obstructive pulmonary disease, severe Parkinson's disease, active inflammatory bowel disease) or psychiatric condition
9. Active bleeding diatheses
10. Participant has received a renal transplant
11. Active hepatitis B, hepatitis C, Epstein-Barr virus (EBV) or human immunodeficiency virus infection (HIV).
12. Participant is breastfeeding or pregnant.
13. Receipt of cytotoxic treatment for the malignancy within 28 days or 5 half-lives, whichever is longer, prior to the day of first dose of IMP.
14. Receipt of noncytotoxic treatment for the malignancy (including biologics such as ICIs, antibodies, nanoparticles etc.) within 5 half-lives of the drug or 42 days (whichever is longer) prior to the day of first dose of study drug (exception: anti-PD-1 or anti-PD-L1 mAb therapy)
15. Receipt of corticosteroids (at a dose > 10 mg prednisone/day or equivalent) within 14 days prior to the day of the first dose of IMP
16. Receipt of any small-molecule IMP within 28 days or 5 half-lives, whichever is longer, prior to the day of the first dose of IMP
17. Receipt of St John's Wort within 21 days prior to the day of the first dose of IMP or of another concomitant medication, herbal supplement, or food that is a strong inhibitor or inducer of CYP3A4 enzymes (Section 23.5) within 14 days prior to the day of the first dose of IMP
18. Receipt of a blood transfusion (blood or blood products) within 14 days prior to the day of

the first dose of IMP
19. Impaired hepatic or renal function as demonstrated by any of the following laboratory values:
19.1. Albumin < 30 g/L
19.2. Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) > 2.5 × the upper limit of normal (ULN) (> 5.0 × ULN for participants with liver metastases)
19.3. Total bilirubin > 1.5 × ULN
19.4. Serum creatinine > 1.5 × ULN.
20. Liver function deteriorating in a manner that would likely make the participant meet the AST, ALT, or bilirubin levels specified above prior to the day of the first dose of IMP.
21. Other evidence of impaired hepatic synthesis function.
22. Inadequate bone marrow reserve or organ function as demonstrated by any of the following laboratory values:
22.1. Absolute neutrophil count (ANC) < 1.5 × 10^9/L.
22.2.. Platelet count < 100 × 10^9/L.
22.3. Haemoglobin < 90 g/L.
23. Any prior history of persistent (> 4 weeks) severe pancytopenia due to previous therapy rather than to disease (ANC < 0.5 × 10^9/L or platelets < 50 x 10^9/L).
24. Cardiac dysfunction (defined as myocardial infarction within the last 6 months, New York Heart Association Class II/III/IV heart failure, unstable angina, unstable cardiac arrhythmias, or left ventricular ejection fraction < 55%).
25. Mean QTcF > 450 ms for males or > 470 ms for females at both Screening and prior to the first dose of IMP (on the day of first dose administration) (the mean of triplicate measurements [within 10 minutes with each reading separated by 1-5 minutes] will be used to determine eligibility).
26. Any clinically important abnormalities in rhythm, conduction, or morphology on resting ECG (e.g., complete left bundle branch block, third degree heart block). Controlled atrial fibrillation is permitted.
27. Any factor that increases the risk of QTc prolongation or of arrhythmic events (e.g., heart failure, hypokalemia, congenital long QT syndrome, immediate family history of long QT syndrome or unexplained sudden death under40 years of age).
28. In the opinion of the Investigator, unlikely to comply with study procedures, restrictions, or requirements.
29. A history of haemolytic anaemia or marrow aplasia.
30. Has received a live-virus vaccination within 28 days or less of planned treatment start.
Note: seasonal flu or COVID vaccines that do not contain live virus are permitted.

Module 2 Only
31. Participant previously discontinued treatment with anti-PD-L1 mAb due to immune related toxicity.

Date of first enrolment
21/02/2023

Date of final enrolment
30/09/2025

Locations

Countries of recruitment
United Kingdom

England

Scotland

Australia

Spain

Study participating centre
Western General Hospital
Crewe Road South
Edinburgh
Lothian
United Kingdom
EH4 2XU

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

Study participating centre
Royal Free Hospital
Pond Street
London
United Kingdom
NW3 2QG

Study participating centre
Hammersmith Hospitals NHS Trust
Hammersmith Hospital
Du Cane Road
London
United Kingdom
W12 0HS

Study participating centre

"START Madrid" - Hospital Universitario Fundacion Jimenez Diaz
Avda. Reyes Catolicos 2
Madrid
Spain
28040

Study participating centre
"START Madrid" - Centro Integral Oncológico Clara Campal (HM CIOCC)
Calle Oña, 10
Madrid
Spain
28050

Study participating centre
"START Barcelona" - Hospital HM Nou Delfos
Avenida de Vallcarca, 151
Barcelona
Spain
08023

Study participating centre
Hospital Universitario Vall d'Hebrón (VHIO)
Passeig Vall d'Hebrón 119 – 129
Barcelona
Spain
08035

Study participating centre
Southern Oncology Clinical Research Unit (SOCRU)
Level 3, Mark Oliphant Building, 5 Laffer D
Bedford
Australia
SA 5042

Study participating centre
Alfred Hospital
The Alfred Medical Oncology Unit, Second Floor, William Buckland Radiotherapy Centre, 55 Commercial Rd
Melbourne
Australia
VIC 3004

Study participating centre
Austin Health
Olivia Newton John Cancer Wellness & Research Centre, Level 4, 145 Studley Rd
Heidelberg
Australia
VIC 3084

Study participating centre
Kinghorn Cancer Centre (KCC)
Level 6, 370 Victoria St
Darlinghurst
Australia
NSW 2010

Sponsor information

Organisation
Grey Wolf Therapeutics

Funder(s)

Funder type
Industry

Funder Name
Grey Wolf Therapeutics

Results and Publications

Individual participant data (IPD) sharing plan
The current data sharing plans for this study are unknown and will be available at a later date

IPD sharing plan summary
Data sharing statement to be made available at a later date