DREAMM 5 - (dernière mise à jour : 17/07/2020)

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Informations générales

Titre de l'étude : A Phase I/II, Randomized, Open-label Platform Study Utilizing a Master Protocol to Study Belantamab Mafodotin (GSK2857916) as Monotherapy and in Combination With Anti-Cancer Treatments in Participants With Relapsed/Refractory Multiple Myeloma (RRMM) - DREAMM 5

Traitement :

Type d'étude : Ciblage moléculaire / Innovation thérapeutique

Phase : I/II **Stade** : NA **Ligne(s)** :

Schéma : Study design:
B-cell maturation antigen (BCMA) is a target present on tumor cells in participants with multiple myeloma. Belantamab mafodotin (GSK2857916); also referred to as GSK'916; is an antibody-drug conjugate (ADC) containing humanized anti-BCMA monoclonal antibody (mAb).
This is a phase I/II, randomized, open-label, platform study designed to evaluate the effects of GSK'916 (belantamab mafodotin) in combination with other anti-cancer drugs in participants with relapsed/refractory multiple myeloma (RRMM). The Platform design incorporates a single master protocol, where multiple treatment combinations, as sub-studies, will be evaluated simultaneously.

This study will include two parts:
- dose exploration (DE): In the DE phase, the safety and tolerability profile of GSK'916 (belantamab mafodotin) will be evaluated when administered in combination with other anti-cancer agents. This may identify a recommended phase 2 dose (RP2D) for each partner, as well as efficacy of each combination.
- and cohort expansion (CE): The CE phase of the study will evaluate the clinical activity of the combinations in comparison to monotherapy in additional participants with RRMM.
Approximately 85 participants will be enrolled across both the DE and CE phases of each sub-study.

Study arms:
1) DOSE EXPLORATION
- Experimental: Belantamab mafodotin+GSK3174998 dose exploration (Sub-study 1)
This arm will involve the administration of the starting dose (SD) to 3 participants. If the safety profile in the first 3 participants is estimated to be favorable then up to an additional 7 participants will be recruited into the SD group.
Both GSK'916 (belantamab mafodotin) and GSK3174998 will be administered to participants via intravenous (IV) infusion on Day 1 of every 21 day cycle. GSK'916 (belantamab mafodotin) (calculated dose as milligram [mg] per kilogram [kg]) will be administered 1 hour before administration of GSK3174998 (fixed dose) at the study site.

- Experimental: Belantamab mafodotin+GSK3174998 dose escalation (Sub-study 1)
This arm will involve the administration of 1 or more escalating dose levels. Each dose escalation (DESC) cohort will consist of at least 3 participants, and up to 10 participants. If the safety profile in these first 3 participants in the dose escalation cohort is deemed to be favorable, then up to an additional 7 participants may be recruited.
Both belantamab mafodotin and GSK3174998 will be administered to participants via IV infusion on Day 1 of every 21 day cycle. Belantamab mafodotin (calculated dose as mg per kg) will be administered 1 hour before administration of GSK3174998 (fixed dose) at the study site. If the combination is not considered safe, then the dose of either belantamab mafodotin or GSK3174998 can be de-escalated.

- Experimental: Belantamab mafodotin+GSK3359609 dose exploration (Sub-study 2)
This arm will involve the administration of the SD to 3 participants. If the safety profile in the first 3 participants is estimated to be favorable, then up to an additional 7 participants will be recruited into the SD group.
Both GSK'916 (belantamab mafodotin) and GSK3359609 will be administered to participants via IV infusion on Day 1 of every 21 day cycle. GSK'916 (belantamab mafodotin) (calculated dose as mg per kg) will be administered 1 hour before administration of GSK3359609 (fixed dose) at the study site.

- Experimental: Belantamab mafodotin+GSK3359609 dose escalation (Sub-study 2)

This arm will involve the administration of 1 or more escalating dose levels. Each DESC cohort will consist of at least 3 participants, and up to 10 participants. If the safety profile in these first 3 participants in the DESC cohort is deemed to be favorable, then up to an additional 7 participants may be recruited.
Both GSK'916 (belantamab mafodotin) and GSK3359609 will be administered to participants via IV infusion on Day 1 of every 21 day cycle. GSK'916 (belantamab mafodotin) (calculated dose as mg per kg) will be administered 1 hour before administration of GSK3359609 (fixed dose) at the study site. If the combination is not considered safe, then the dose of either GSK'916 (belantamab mafodotin) or GSK3359609 can be de-escalated.

2) COHORT EXPANSION
- Active Comparator: Belantamab mafodotin monotherapy cohort expansion (Sub-study1)
In the CE phase, there is a 2 part randomization. Participants will be randomized into a sub-study and then within a sub-study to receive either the contemporaneous GSK'916 (belantamab mafodotin) monotherapy control or the RP2D of the combination treatment.
Within a sub-study, participants will be randomized to receive GSK'916 (belantamab mafodotin) monotherapy IV on day 1 of each 21-day cycle. GSK'916 (belantamab mafodotin) will be administered to participants intravenously (calculated dose as mg per kg) at the study site. The intended cycle time of GSK'916 (belantamab mafodotin) as a monotherapy is 21 days (-3 day window) and cannot occur more frequently than this.

- Experimental: Belantamab mafodotin+GSK3174998 cohort expansion (Sub-study 1)
Within a sub-study, participants will be randomized to receive the RP2D of the combination of GSK'916 (belantamab mafodotin) plus GSK3174998 to further assess the additional clinical benefit and safety.
Both GSK'916 (belantamab mafodotin) and GSK3174998 will be administered to participants via IV infusion on Day 1 of every 21 day cycle. GSK'916 (belantamab mafodotin) (calculated dose as mg per kg) will be administered 1 hour before administration of GSK3174998 (fixed dose) at the study site.

- Active Comparator: Belantamab mafodotin monotherapy cohort expansion (Sub-study2)
Within a sub-study, participants will be randomized to receive GSK'916 (belantamab mafodotin) monotherapy IV on day 1 of each 21-day cycle. GSK'916 (belantamab mafodotin) will be administered to participants intravenously (calculated dose as mg per kg) at the study site. The intended cycle time of GSK'916 (belantamab mafodotin) as a monotherapy is 21 days (-3 day window) and cannot occur more frequently than this.

- Experimental: Belantamab mafodotin+GSK3359609 cohort expansion (Sub-study 2)
Within a sub-study, participants will be randomized to receive the RP2D of the combination of GSK'916 (belantamab mafodotin) plus GSK3359609 to further assess the additional clinical benefit and safety.
Both GSK'916 (belantamab mafodotin) and GSK3359609 will be administered to participants via IV infusion on Day 1 of every 21 day cycle. GSK'916 (belantamab mafodotin) (calculated dose as mg per kg) will be administered 1 hour before administration of GSK3359609 (fixed dose) at the study site.

Current primary outcome:
1) DOSE EXPLORATION Phase:
- Number of participants achieving dose limiting toxicities (DLT) [Time Frame: Up to 36 months]
- Number of participants with adverse events (AEs) and serious adverse events (SAEs) [Time Frame: Up to 36 months]
- Number of participants with abnormality in vital signs [Time Frame: Up to 36 months]
- Number of participants with abnormality in hematology parameters [Time Frame: Up to 36 months]
- Number of participants with abnormality in clinical chemistry parameters [Time Frame: Up to 36 months]
- Number of participants with abnormality in routine urinalysis parameters [Time Frame: Up to 36 months]
2) COHORT EXPANSION Phase: Number of participants achieving Overall Response Rate (ORR) [Time Frame: Up to 36 months]

Current secondary outcomes:
1) DOSE EXPLORATION Phase:
- Number of participants achieving ORR [Time Frame: Up to 36 months]
- Concentration observed of GSK'916 (belantamab mafodotin) when administered in combination with GSK3174998 [Time Frame: Up to 36 months]
- Concentration observed of GSK'916 (belantamab mafodotin) when administered in combination with GSK3359609 [Time Frame: Up to 36 months]
- Concentration observed of GSK3174998 when administered in combination with GSK'916 (belantamab mafodotin) [Time Frame: Up to 36 months]
- Concentration observed of GSK3359609 when administered in combination with GSK'916 (belantamab mafodotin) [Time Frame: Up to 36 months]

- Concentration of anti-drug antibodies (ADAs) against GSK'916 (belantamab mafodotin) when administered in combination with GSK3174998 [Time Frame: Up to 36 months]
- Concentration of ADAs against GSK'916 (belantamab mafodotin) when administered in combination with GSK3359609 [Time Frame: Up to 36 months]
- Concentration of ADAs against GSK3174998 when administered in combination with GSK'916 (belantamab mafodotin) [Time Frame: Up to 36 months]
- Concentration of ADAs against GSK3359609 when administered in combination with GSK'916 (belantamab mafodotin) [Time Frame: Up to 36 months]
- Number of participants with adverse events of special interest (AESI) for GSK'916 (belantamab mafodotin) when given in combination with GSK3174998 [Time Frame: Up to 36 months]
- Number of participants with AESI for GSK'916 (belantamab mafodotin) when given in combination with GSK3359609 [Time Frame: Up to 36 months]
- Number of participants with AESI for GSK3174998 when administered in combination with GSK'916 (belantamab mafodotin) [Time Frame: Up to 36 months]
- Number of participants with AESI for GSK3359609 when administered in combination with GSK'916 (belantamab mafodotin) [Time Frame: Up to 36 months]
- Number of participants with abnormal ocular findings on ophthalmic examination [Time Frame: Up to 36 months]
A continuous every 21 days ophthalmic examination up to 36 months for all participants will include best corrected visual acuity (BCVA), documentation of manifest refraction used to obtain BCVA, current glasses prescription (if applicable), pupillary exam, intraocular pressure measurement and time checked, full anterior segment examination including fluorescein staining of the cornea, anterior segment exam (slit lamp) includes: orbit/lids/adnexa, conjunctiva, sclera, cornea, anterior chamber, iris, lens and anterior vitreous, anterior segment photography of a fluorescein stained cornea, and dilated funduscopic exam: fundus photography with interpretation.

2) COHORT EXPANSION Phase:
- Number of participants achieving Clinical Benefit Rate (CBR) [Time Frame: Up to 36 months]
- Number of participants achieving Progression-free survival (PFS) [Time Frame: Up to 36 months]
- Duration of response (DoR) after administration of GSK'916 (belantamab mafodotin) in combination with GSK3174998 [Time Frame: Up to 36 months]
- DoR after administration of GSK'916 (belantamab mafodotin) in combination with GSK3359609 [Time Frame: Up to 36 months]
- Time to response (TTR) after administration of GSK'916 (belantamab mafodotin) in combination with GSK3174998 [Time Frame: Up to 36 months]
- TTR after administration of GSK'916 (belantamab mafodotin) in combination with GSK3359609 [Time Frame: Up to 36 months]
- Number of participants achieving Overall survival (OS) [Time Frame: Up to 36 months]
- Number of participants with AEs and SAEs [Time Frame: Up to 36 months]
- Number of participants with AEs leading to discontinuation [Time Frame: Up to 36 months]
- Number of participants with dose reduction or delay [Time Frame: Up to 36 months]
- Number of participants with abnormality in vital signs [Time Frame: Up to 36 months]
- Number of participants with abnormality in hematology parameters [Time Frame: Up to 36 months]
- Number of participants with abnormality in clinical chemistry parameters [Time Frame: Up to 36 months]
- Number of participants with abnormality in routine urinalysis parameters [Time Frame: Up to 36 months]
- Number of participants with abnormality in electrocardiogram (ECG) parameters [Time Frame: Up to 36 months]
- Number of participants with AESI for GSK'916 (belantamab mafodotin) when given in combination with GSK3174998 [Time Frame: Up to 36 months]
- Number of participants with AESI for GSK'916 (belantamab mafodotin) when given in combination with GSK3359609 [Time Frame: Up to 36 months]
- Number of participants with AESI for GSK3174998 when administered in combination with GSK'916 (belantamab mafodotin) [Time Frame: Up to 36 months]
- Number of participants with AESI for GSK3359609 when administered in combination with GSK'916 (belantamab mafodotin) [Time Frame: Up to 36 months]
- Number of participants with abnormal ocular findings on ophthalmic examination [Time Frame: Up to 36 months]
- Concentration observed of GSK'916 (belantamab mafodotin) when administered in combination with GSK3174998 [Time Frame: Up to 36 months]
- Concentration observed of GSK'916 (belantamab mafodotin) when administered in combination with GSK3359609 [Time Frame: Up to 36 months]
- Concentration observed of GSK3174998 when administered in combination with GSK'916 (belantamab mafodotin) [Time Frame: Up to 36 months]
- Concentration observed of GSK3359609 when administered in combination with GSK'916 (belantamab mafodotin) [Time Frame: Up to 36 months]

- Concentration of ADAs against GSK'916 (belantamab mafodotin) when administered in combination with GSK3174998 [Time Frame: Up to 36 months]
- Concentration of ADAs against GSK'916 (belantamab mafodotin) when administered in combination with GSK3359609 [Time Frame: Up to 36 months]
- Concentration of ADAs against GSK3174998 when administered in combination with GSK'916 (belantamab mafodotin) [Time Frame: Up to 36 months]
- Concentration of ADAs against GSK3359609 when administered in combination with GSK'916 (belantamab mafodotin) [Time Frame: Up to 36 months]

Spécialités / Localisations

Spécialité n°1 : Tissus lymphoïde, hématopoïétique et apparentés

CIM10 - Localisation n°1 : **C90** - Myélome multiple et tumeurs malignes à plasmocytes

Critères

Critères d'inclusion : 1. Participant must be 18 years of age inclusiveor older, at the time of signing the informed consent.
2. Participants who have histologically or cytologically confirmed diagnosis of MM,as defined by the International Myeloma Working Group(IMWG, [Rajkumar, 2014]).
3. Participants who have been treated with at least 3 prior lines of prior anti-myeloma treatments including an IMID (eg. lenalidomide), a proteasome inhibitor (eg. bortezomib) and an anti-CD38 monoclonal antibody. Lines of therapy are defined by consensus panel of the International Myeloma Workshop [Rajkumar, 2011a].
4. Participants with a history of autologous stem cell transplant are eligible for study participation provided the following eligibility criteria are met:
a. transplant was >100 days prior to screening
b. no active infection(s)
5. Eastern Cooperative Oncology Group (ECOG) performance status of 0-2
6. Measurable disease defined as at least 1 of the following:
• Serum M-protein >=0.5 g/dL (>=5 g/L)
• Urine M-protein >=200 mg/24 hours
• Serum free light chain (FLC) assay: Involved FLC level >=10 mg/dL (>=100 mg/L) and an abnormal serum FLC ratio (<0.26 or >1.65)
7. Have organ system functions as defined by the laboratory assessments in Table 13.
8. All prior treatment-related toxicities (defined by National Cancer Institute- Common Toxicity Criteria for Adverse Events [NCI -CTCAE], version 5.0, 2017) must be Grade <=1 at the time of screening except for alopecia (any grade), neuropathy (Grade <=2), or endocrinopathy managed with replacement therapy (any grade).
9. Male or female
Contraceptive use by men or women should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies (see Appendix 7 for further details).
a. Male Participants:
Contraceptive use by men should be consistent with local regulations regarding the methods of contraception for those participating in the clinical studies.
Male participants are eligible to participate if they agree to the following during the intervention period and for at least 140 days after the last dose of study intervention to allow for clearance of any altered sperm:
Refrain from donating sperm
PLUS either:
• Be abstinent from heterosexual intercourse as their preferred and usual lifestyle (abstinent on a long term and persistent basis) and agree to remain abstinent
OR

• Must agree to use contraception/barrier as detailed below
• Agree to use a male condom and female partner to use an additional highly effective contraceptive method with a failure rate of <1% per year when having sexual intercourse with a woman of childbearing potential who is not currently pregnant
b. Female Participants:
• Contraceptive use by women should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies.
A female participant is eligible to participate if she is not pregnant or breastfeeding, and at least one of the following conditions applies:
• Is not a woman of childbearing potential (WOCBP)
OR
• Is a WOCBP and using a contraceptive method that is highly effective (with a failure rate of <1% per year), preferably with low user dependency, as described in Appendix 7 during the intervention period and for at least 120 days after the last dose of study intervention and agrees not to donate eggs (ova, oocytes) for the purpose of reproduction during this period. The investigator should evaluate the effectiveness of the contraceptive method in relationship to the first dose of study intervention.
• A WOCBP must have a negative highly sensitive pregnancy test ([urine or serum] as required by local regulations) within 72 hours before the first dose of study intervention.
• The investigator is responsible for review of medical history, menstrual history, and recent sexual activity to decrease the risk for inclusion of a woman with an early undetected pregnancy
10. Capable of giving signed written informed consent which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and in this protocol.

Critères de non-inclusion : Medical Conditions
1. Symptomatic amyloidosis, active 'polyneuropathy, organomegaly, endocrinopathy, myeloma protein, and skin changes' (POEMS) syndrome, active plasma cell leukemia at the time of screening.
2. Any serious and/or unstable pre-existing medical, psychiatric disorder, or other conditions (including lab abnormalities) that could interfere with participant's safety, obtaining informed consent, or compliance with study procedures.
3. Current corneal epithelial disease except mild punctate keratopathy
4. Current unstable liver or biliary disease per investigator assessment defined by the presence of ascites, encephalopathy, coagulopathy, hypoalbuminemia, esophageal or gastric varices, persistent jaundice, or cirrhosis. Note: Stable chronic liver disease (including Gilbert's syndrome or asymptomatic gallstones) or hepatobiliary involvement of malignancy is acceptable if participant otherwise meets entry criteria.
5. Malignancies other than disease under study are excluded, except for any other malignancy from which the participant has been disease-free for more than 2 years and, in the opinion of the principal investigators and GSK Medical Monitor, will not affect the evaluation of the effects of this clinical trial treatment on the currently targeted malignancy (MM).
Participants with curatively treated non-melanoma skin cancer are not excluded.
6. Evidence of cardiovascular risk including any of the following:
a. QTcF interval >=480 msecs (the QT interval values must be corrected for heart rate by Fridericia's formula [QTcF])
b. Evidence of current clinically significant untreated arrhythmias, including clinically significant ECG abnormalities such as 2nd degree (Mobiz Type II) or 3rd degree atrioventricular (AV) block.
c. History of myocardial infarction, acute coronary syndromes (including unstable angina), coronary angioplasty, stenting or bypass grafting, all within three months of Screening.
d.Class III or IV heart failure as defined by the New York Heart Association (NYHA) functional classification system
e. Uncontrolled hypertension
f. Recent (within the past 6 months) history of symptomatic pericarditis.
7. Known immediate or delayed hypersensitivity reaction or idiosyncrasy to drugs chemically related to GSK'916 (belantamab mafodotin) or any of the components of the study treatment. History of severe hypersensitivity to other mAbs.
8. Active infection requiring antibiotic, antiviral, or antifungal treatment.
9. Known HIV infection.
10. Recent history (within the past 6 months) of acute diverticulitis, inflammatory bowel disease, intra-abdominal abscess, or gastrointestinal obstruction.
11. Presence of hepatitis B surface antigen (HBsAg), or hepatitis B core antibody (HBcAb) at screening or within 3 months prior to first dose of study treatment
12. Positive hepatitis C antibody test result or positive hepatitis C RNA test result at screening or within 3 months prior to first dose of study treatment.
Note: Participants with positive Hepatitis C antibody due to prior resolved disease can be enrolled, only if a confirmatory negative Hepatitis C RNA test is obtained. Hepatitis RNA testing is optional and participants with negative Hepatitis C antibody test are not required to also undergo Hepatitis C RNA testing

Prior/Concomitant Therapy
13. Patients who have received prior therapy with GSK'916 (belantamab mafodotin).
14. Other monoclonal antibodies within 30 days orsystemic anti-myeloma therapy within <14 days of first dose of study drug.

15. Prior radiotherapy within 2 weeks of start of study therapy. Participants must have recovered from all radiation-related toxicities, not require corticosteroids, and not have had radiation pneumonitis. A 1-week washout is permitted for palliative radiation (<=2 weeks of radiotherapy) to non-central nervous system (CNS) disease.
16. Plasmapheresis within 7 days prior to the first dose of study drug
17. Prior allogeneic transplant is prohibited
18. Patients who have received prior CAR-T therapy with lymphodepletion with chemotherapy within 3 months of screening.
19. Any major surgery (other than bone-stabilizing surgery) within 30 days of screening.
20. Prior treatment with a monoclonal antibody within 30 days of receiving the first dose of study drugs, or treatment with an investigational agent or approved systemic anti-myeloma therapy (including systemic steroids) within 14 days or 5 half-lives of receiving the first dose of study drugs, whichever is shorter.

For 'Other Exclusions' please refer to the protocol.

Informations promoteur

Nom du promoteur : GlaxoSmithKline GSK

Type de promoteur : Industriel

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Statut de l'essai : CLOS

Liens utiles

ClinicalTrials (anglais) : https://clinicaltrials.gov/ct2/show/record/NCT04126200

EU clinical trial register (anglais) : https://www.clinicaltrialsregister.eu/ctr-search/trial/2019-001138-32/SE