Background

Target

- Patients with relapsed or refractory multiple myeloma (RRMM) who have progressed through multiple prior lines of therapy need novel, effective therapeutic options.
- Cell-based vaccination strategies (BCMA) or cell-based CAR T-cells may be used for novel therapy.
- BCMA vaccines may be used to target MM cells and improve outcomes for patients with RRMM.

Belantamab mafodotin

- Belantamab mafodotin is a monovalent ADC conjugated with MMAE (maytansine derivative) and a BCMA-directed antibody.

Study design

The DREAMM-5 platform trial (study NCT04126200) is a Phase 1/2 study that incorporates a design into one master protocol, wherein multiple belantamab mafodotin-containing combinations will be evaluated in separate sub-studies to identify effective and safe combinations versus a standard belantamab mafodotin monotherapy arm.

- The dose escalation phase (DE) will evaluate the safety, pharmacologic, and clinical activity, as well as selecting the recommended phase 2 dose (RP2D) for each investigational combination treatment.
- Following dose escalation, a cohort expansion phase (CE) will be performed to further assess the clinical activity of the combination regimen vs belantamab mafodotin monotherapy.

- For each sub-study, the DE phase will consist of multiple dosing cohorts up to 10 participants per dose level.
- For each sub-study, the CE phase will consist of multiple dosing cohorts up to 10 participants per dose level.

- No more than two consecutive cohorts will be dosed at the same dose level.
- No more than three dose-escalation or de-escalation cohorts will be included in the RP2D.

- The RP2D for the combination treatment will be selected based on findings from the DE phase.

- Following selection of the RP2D, a CE phase will be performed to further characterize the safety of the combination treatment arm.

- Patients will be enrolled in either DE or CE and disease evaluation will continue until disease progression, death, start of other anti-cancer treatment, withdrawal of consent or end of study.

Study objectives and endpoints

Dose Exploration (DE) phase:

- The primary objective is to assess the safety and tolerability of belantamab mafodotin in combination with other anti-cancer treatments in multiple sub-studies and to identify effective and safe combinations versus a standard belantamab mafodotin monotherapy arm.

- Secondary objectives include evaluating the clinical activity of belantamab mafodotin in combination with other anti-cancer treatments in multiple sub-studies and to identify effective and safe combinations versus a standard belantamab mafodotin monotherapy arm.

- Other secondary objectives include assessing the clinical activity of belantamab mafodotin in combination with other anti-cancer treatments in multiple sub-studies and to identify effective and safe combinations versus a standard belantamab mafodotin monotherapy arm.

- Secondary objectives include assessing the clinical activity of belantamab mafodotin in combination with other anti-cancer treatments in multiple sub-studies and to identify effective and safe combinations versus a standard belantamab mafodotin monotherapy arm.

Cohort Expansion (CE) phase:

- The primary objective is to assess the clinical activity of belantamab mafodotin in combination with other anti-cancer treatments in multiple sub-studies and to identify effective and safe combinations versus a standard belantamab mafodotin monotherapy arm.

- Secondary objectives include evaluating the clinical activity of belantamab mafodotin in combination with other anti-cancer treatments in multiple sub-studies and to identify effective and safe combinations versus a standard belantamab mafodotin monotherapy arm.

- Other secondary objectives include assessing the clinical activity of belantamab mafodotin in combination with other anti-cancer treatments in multiple sub-studies and to identify effective and safe combinations versus a standard belantamab mafodotin monotherapy arm.

Follow-up and analysis

- The primary analysis in CE will be performed after the last patient has completed the first follow-up visit.

- Final analysis in CE will be performed after all patients have completed the last scheduled follow-up visit.

- A combination treatment may be considered superior to belantamab mafodotin monotherapy if the 95% confidence interval for the primary endpoint does not overlap with the prespecified boundary.

Study population

- Inclusion criteria:
  - Age ≥18 years
  - Eastern Cooperative Oncology Group (ECOG) performance status 0–2
  - At least 1 prior anti-MM treatment and disease progression
  - Adequate organ and hematologic function
  - History of autologous SCT allowed if >100 days prior to screening and no active infections

- Exclusion criteria:
  - Active malignancy, excluding treated non-melanoma skin cancer
  - Human immunodeficiency virus (HIV) infection
  - Central nervous system (CNS) disease
  - History of acute diverticulitis, inflammatory bowel disease, or uncontrolled ulcerative colitis
  - History of autoimmune disease
  - History of myasthenia gravis

Endpoints for the DE and CE phases of DREAMM-5

- The primary endpoint is the overall response rate (ORR) in patients with RRMM.

Study key inclusion criteria

- History of autologous SCT allowed if >100 days prior to screening and no active infections
- Adequate organ and hematologic function
- History of autologous SCT allowed if >100 days prior to screening and no active infections
- History of autologous SCT allowed if >100 days prior to screening and no active infections

Key exclusion criteria

- Active malignancy, excluding treated non-melanoma skin cancer
- Human immunodeficiency virus (HIV) infection
- Central nervous system (CNS) disease
- History of acute diverticulitis, inflammatory bowel disease, or uncontrolled ulcerative colitis
- History of autoimmune disease
- History of myasthenia gravis

Study key objectives

- The primary objective is to assess the safety and tolerability of belantamab mafodotin in combination with other anti-cancer treatments in multiple sub-studies and to identify effective and safe combinations versus a standard belantamab mafodotin monotherapy arm.

- Secondary objectives include evaluating the clinical activity of belantamab mafodotin in combination with other anti-cancer treatments in multiple sub-studies and to identify effective and safe combinations versus a standard belantamab mafodotin monotherapy arm.

- Other secondary objectives include assessing the clinical activity of belantamab mafodotin in combination with other anti-cancer treatments in multiple sub-studies and to identify effective and safe combinations versus a standard belantamab mafodotin monotherapy arm.

- Follow-up and analysis objectives include performing the primary analysis in CE after the last patient has completed the first follow-up visit.

- Final analysis in CE will be performed after all patients have completed the last scheduled follow-up visit.

- A combination treatment may be considered superior to belantamab mafodotin monotherapy if the 95% confidence interval for the primary endpoint does not overlap with the prespecified boundary.

Sub-study 1

- OX40 signaling promotes effector T-cell proliferation and survival, while blocking the negative regulation function of OX40. This results in a T-cell mediated immune response against tumor cells (Figure 3).

- The DREAMM-5 platform trial incorporates a design into one master protocol, wherein multiple belantamab mafodotin-containing combinations will be evaluated in separate sub-studies to identify effective and safe combinations versus a standard belantamab mafodotin monotherapy arm.

- Patients will be stratified by numbers of prior lines of therapy (≤6 months) of acute diverticulitis, inflammatory bowel disease, or uncontrolled ulcerative colitis

Sub-study 2

- The principle of the immune system is that the immune system is kept in balance.

- Patients will be stratified by numbers of prior lines of therapy (≤6 months) of acute diverticulitis, inflammatory bowel disease, or uncontrolled ulcerative colitis

Sub-study 3

- A combination treatment may be considered superior to belantamab mafodotin monotherapy if the 95% confidence interval for the primary endpoint does not overlap with the prespecified boundary.

- Follow-up and analysis objectives include performing the primary analysis in CE after the last patient has completed the first follow-up visit.

- Final analysis in CE will be performed after all patients have completed the last scheduled follow-up visit.

- A combination treatment may be considered superior to belantamab mafodotin monotherapy if the 95% confidence interval for the primary endpoint does not overlap with the prespecified boundary.

Study key inclusion criteria

- History of autologous SCT allowed if >100 days prior to screening and no active infections
- Adequate organ and hematologic function
- History of autologous SCT allowed if >100 days prior to screening and no active infections
- History of autologous SCT allowed if >100 days prior to screening and no active infections

Key exclusion criteria

- Active malignancy, excluding treated non-melanoma skin cancer
- Human immunodeficiency virus (HIV) infection
- Central nervous system (CNS) disease
- History of acute diverticulitis, inflammatory bowel disease, or uncontrolled ulcerative colitis
- History of autoimmune disease
- History of myasthenia gravis

Study key objectives

- The primary objective is to assess the safety and tolerability of belantamab mafodotin in combination with other anti-cancer treatments in multiple sub-studies and to identify effective and safe combinations versus a standard belantamab mafodotin monotherapy arm.

- Secondary objectives include evaluating the clinical activity of belantamab mafodotin in combination with other anti-cancer treatments in multiple sub-studies and to identify effective and safe combinations versus a standard belantamab mafodotin monotherapy arm.

- Other secondary objectives include assessing the clinical activity of belantamab mafodotin in combination with other anti-cancer treatments in multiple sub-studies and to identify effective and safe combinations versus a standard belantamab mafodotin monotherapy arm.

Follow-up and analysis objectives include performing the primary analysis in CE after the last patient has completed the first follow-up visit.

- Final analysis in CE will be performed after all patients have completed the last scheduled follow-up visit.

- A combination treatment may be considered superior to belantamab mafodotin monotherapy if the 95% confidence interval for the primary endpoint does not overlap with the prespecified boundary.

Cancer and Blood Disease Drug Development Summit

This study is open to accrual.

References