OP201: A Phase 1/2 Study of Melflufen and Dexamethasone in Patients With Immunoglobulin Light Chain Amyloidosis

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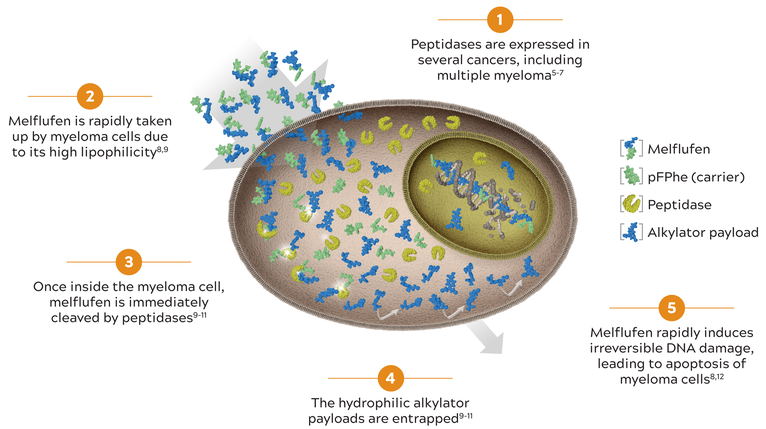
BACKGROUND

- Immunoglobulin light chain (AL) amyloidosis is a rare, life-threatening disease arising from a neoplasia of plasma cells resulting in excessive immunoglobulin free light chains (FLCs) that are misfolded, aggregate, and form toxic deposits in vital organs, including the heart, kidneys, and liver[1]
- The primary goal of AL amyloidosis therapy is to reduce or eliminate the amyloidogenic light chains, halt the progression of organ damage, and improve function[1,2]
- Measures that can improve AL amyloidosis hematologic response may improve organ response and impact survival[2]
- Treatments used in other plasma cell disorders such as multiple myeloma (MM) are commonly used to treat AL amyloidosis, including autologous stem cell transplantation (ASCT)[3,4]
- However, there are no approved therapies for AL amyloidosis, and effective treatment, especially for patients with advanced cardiac involvement, remains a high unmet medical need[1,2]
- Melflufen is a novel peptide-drug conjugate that rapidly delivers a cytotoxic payload into tumor cells (**Figure 1**)[5-12]

Figure 1. Melflufen Mechanism of Action

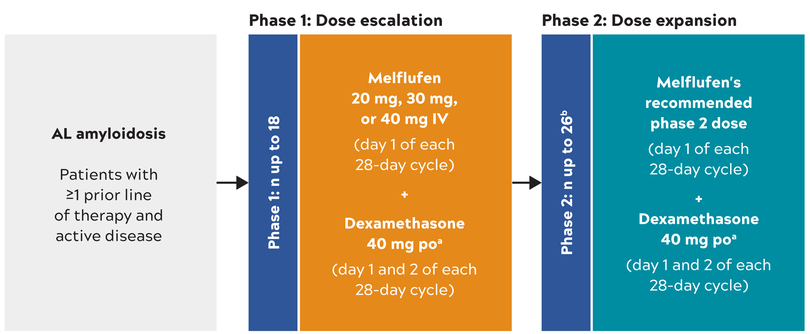


pFPhe, p-Fluorophenylalanine.

- Melflufen is currently under investigation for the treatment of relapsed/refractory multiple myeloma (RRMM)[13]
- In the phase 1/2 study O-12-M1, melflufen and dexamethasone (dex) showed promising activity in patients with RRMM and a median of 4 prior lines of therapy, including prior lenalidomide and bortezomib[13]
  - Overall response rate (ORR): 31%
  - Median progression-free survival (PFS): 5.7 months
  - Median overall survival (OS): 20.7 months
  - Treatment with melflufen-dex was well tolerated, with an acceptable safety profile
- The activity of melflufen in RRMM suggests that it may have potential therapeutic applications for patients with AL amyloidosis
- OP201 is a planned, phase 1/2, open-label study evaluating the safety and efficacy of melflufen-dex in patients who have AL amyloidosis and have received ≥1 prior therapy

METHODS

Figure 2. OP201: Phase 1/2, Open-Label, Dose Escalation Study (NCT04115956)



[a]Dexamethasone dose may be 20 mg at investigator's discretion.
[b]The phase 2 dose expansion will include 26 patients (20 from phase 2 and 6 from phase 1) treated at the recommended phase 2 dose.
AL, immunoglobulin light chain; IV, intravenous; po, orally.

- The phase 1 dose escalation will follow a standard 3+3 design, with 3-6 patients evaluable for dose-limiting toxicity at each melflufen dose level (**Figure 2**)
- Treatment will continue until any of the stopping events is reached:
  - Completion of 8 cycles or stable hematologic partial response (PR) or better after cycle 4
  - Less than hematologic PR after cycle 2
  - Nonhematologic or hematologic disease progression
  - Unacceptable toxicity or physician's determination that it is not in patient's best interest to continue treatment

PRIMARY OBJECTIVES

- **Phase 1:** The primary objective of phase 1 is to explore the safety and tolerability of treatment with melflufen and to identify the recommended phase 2 dose (RP2D)
- **Phase 2:** The primary objective of phase 2 is to evaluate the hematologic ORR after 4 cycles at the RP2D determined in phase 1

PRIMARY ENDPOINTS

- **Phase 1:** The primary endpoints of phase 1 are evaluating frequency and grade of adverse events (AEs) and laboratory values and determining dose-limiting toxicities (DLTs) during cycle 1 up to a maximum dose of melflufen 40 mg
- **Phase 2:** The primary endpoint of phase 2 is determining the proportion of patients who achieve a hematologic complete response (CR), very good PR (VGPR), or PR

KEY SECONDARY ENDPOINTS

- Proportion of patients with hematologic CR, VGPR, and PR (phase 1)
- Best hematologic response
- Duration of hematologic response
- Organ response
- Duration of organ response
- Time to next AL amyloidosis treatment (TTNT)
- OS
- Pharmacokinetics (phase 1)

KEY ELIGIBILITY CRITERIA

Key Inclusion Criteria	Key Exclusion Criteria
• Diagnosis of AL amyloidosis and serum differential FLC ≥20 mg/L • ≥1 prior line of therapy • Measurable hematologic disease and organ involvement (cardiac and/or renal and/or liver) • <30% bone marrow plasma cells • Echocardiogram with left ventricular ejection fraction ≥45% and electrocardiogram with QTcF interval of ≤470 ms • Age ≥18 years • ECOG PS ≤2 • Adequate baseline hematologic and organ function	• Concurrent symptomatic MM • Evidence of gastrointestinal bleeding • Cardiac risk stage 3 with N-terminal pro-brain natriuretic peptide >5000 pg/mL • An active infection requiring treatment ≤14 days before treatment initiation • Significant ventricular arrhythmias • Prior ASCT or alloSCT ≤12 weeks before treatment initiation, with active GVHD • Intolerant to steroid therapy

AL, immunoglobulin light chain; alloSCT, allogeneic stem cell transplantation; ASCT, autologous stem cell transplantation; ECOG PS, Eastern Cooperative Oncology Group performance status; FLC, free light chain; GVHD, graft-versus-host disease; QTcF, Q to T wave with Fridericia's correction; MM, multiple myeloma.

STATISTICAL ANALYSES

- **Efficacy**
  - Recommended melflufen dose for phase 2 will be the highest of 20, 30, or 40 mg that results in ≤1 of 6 patients with DLT or a lower dose at the discretion of the data safety monitoring committee
  - Hematologic ORR (≥ PR) and the proportion of patients with kidney, cardiac, or liver response will be analyzed as a proportion and exact binomial 95% confidence interval for patients treated at the RP2D
  - Kaplan-Meier estimates will be calculated and plotted for duration of hematologic response, duration of organ response (separately for kidney, cardiac, and liver), TTNT, and OS
  - Best hematologic response will be analyzed and described as the proportion of patients with each outcome
  - Minimal residual disease will be analyzed descriptively
- **Safety**
  - Frequency and grade of AEs and defined DLTs will be recorded and summarized in frequency tables in terms of treatment-emergent AEs that start on or worsen after the first day of study treatment for up to 30 days after last administration of melflufen or before start of subsequent anticancer treatment (whichever occurs first)

STUDY STATUS

This study is open, with enrollment expected to begin in or after December 2019.

FUNDING SOURCE

This study is funded by Oncopeptides.

REGISTRATION

This study is sponsored by Oncopeptides and is registered at ClinicalTrials.gov (NCT04115956).

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