**OP201: A Phase 1/2 Study of Melflufen and Dexamethasone in Patients with Immunoglobulin Light Chain (AL) Amyloidosis**

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**Background:** AL amyloidosis is a rare life-threatening disease arising from a disorder of plasma cells resulting in excessive immunoglobulin free light chains (FLC) that are misfolded, aggregate, and form toxic deposits in vital organs including the heart, kidneys, and liver (Merlini G, et al. *Nat Rev Dis Primers*. 2018). The primary goal of therapy is to reduce or eliminate the FLC and halt the progression of organ damage and improve function. Measures that can improve hematologic responses may improve organ responses and impact survival. Treatments used in other plasma cell disorders, like multiple myeloma (MM), including autologous stem cell transplantation (ASCT), are commonly used to treat AL amyloidosis. However, there are no approved therapies for AL amyloidosis. Effective treatment, especially for patients with advanced cardiac involvement, remains a high unmet medical need (Merlini G, et al. *Nat Rev Dis Primers*. 2018; Milani P, et al. *Expert Rev Hematol*. 2018). Melflufen, a lipophilic peptide-conjugated alkylator that rapidly delivers a highly cytotoxic payload into cells through peptidase activity, is currently under investigation for the treatment of relapsed/refractory MM (RRMM). In the
Oncopeptides phase 1/2 study, O-12-M1, of patients with RRMM and ≥2 prior lines of therapy, including lenalidomide and bortezomib, melflufen plus dexamethasone showed an overall response rate of 31%, median progression-free survival of 5.7 months, and median overall survival of 20.7 months, with manageable hematologic toxicity (Richardson PG, et al. Blood. 2017; Abstract 3150). 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 and dexamethasone in patients who have AL amyloidosis and have received ≥1 prior therapy.

**Study Design:** The planned enrollment for OP201 is approximately 46 patients. Patients must have AL amyloidosis and ≥1 prior therapy, which can include 1 prior nontransplant regimen, a prior ASCT, or 1 prior induction regimen followed by a single ASCT (without hematologic progression between induction and ASCT). Other key inclusion criteria include measurable hematologic and organ involvement (cardiac and/or renal and/or liver), Eastern Cooperative Oncology Group performance status ≤2, adequate baseline hematologic and organ function, ≤30% bone marrow plasma cells, echocardiogram with left ventricular ejection fraction ≥45% and electrocardiogram with QTcF interval of ≤470 ms. Key exclusion criteria include evidence of gastrointestinal bleeding, cardiac risk stage 3 with N-terminal pro-brain natriuretic peptide >5000 pg/mL, active infection, concurrent symptomatic MM, significant ventricular arrhythmias, and severe orthostatic hypotension. Phase 1 dose escalation will follow a standard 3+3 design, with 3 to 6 patients evaluable for dose-limiting toxicity at each dose level. Patients will receive melflufen intravenously at 1 of 3 dose levels (20 mg, 30 mg, or 40 mg) on day 1 and oral dexamethasone 40 mg (20 mg at investigator's discretion) on days 1 and 2 of each 28-day cycle. Treatment will continue for up to 8 cycles until stable hematologic partial response or better after cycle 4, less than hematologic partial response 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. The primary endpoints for the phase 1 study are safety and identifying the recommended phase 2 dose (RP2D) of melflufen. Phase 2 will include 26 patients (20 phase 2 + 6 phase 1) treated at the RP2D. The primary endpoint for phase 2 is the hematologic overall response rate after 4 cycles of treatment. Key secondary endpoints include pharmacokinetics (phase 1), best hematologic response, duration of hematologic response, organ system-specific response, duration of organ system-specific responses, time to next AL amyloidosis treatment, and overall survival.