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# Melflufen: a potential new treatment backbone for multiple myeloma

**Oncopeptides is developing melflufen, a first-in-class peptide-conjugated alkylator for the treatment of relapsed and refractory multiple myeloma. Oncopeptides has attained orphan drug designations in the United States and Europe for melflufen and is preparing it for rapid marketing approval upon completion of an ongoing phase 3 clinical trial. The company is open to potential commercialization partnerships.**

Oncopeptides, a pharmaceutical company based in Stockholm, Sweden, and Mountain View, California, has been developing cancer therapeutics since 2000. The company's lead product is melflufen, a peptide-conjugated alkylator for the treatment of relapsed and refractory multiple myeloma (RRMM). Melflufen is in a pivotal phase 3 study under the umbrella of a Special Protocol Assessment from the US Food and Drug Administration. Successful achievement of the trial's primary endpoint may lead to rapid regulatory approval in the United States and Europe and regulatory filings in other regions.

Melflufen belongs to a novel class of peptidase-enhanced compounds that elicit increased cytotoxicity in target multiple myeloma (MM) cells and substantially reduced off-target cell toxicity. Melflufen is intended for use as a first choice for patients with RRMM.

"Side effects from anticancer treatments that significantly reduce a patient's quality of life are a serious problem within oncology," stated Jakob Lindberg, CEO at Oncopeptides. "Based on recent melflufen clinical data we presented at ASH 2018 [the annual meeting of the American Society of Hematology], we are addressing the need for efficacious drugs with new mechanisms of action in RRMM, while preserving a seemingly favorable quality-of-life profile for patients."

## The need for new MM treatments

MM is a cancer of the bone marrow that results in the production of abnormal blood plasma cells. Treatments for MM, which include alkylators, steroids, immunomodulatory drugs, proteasome inhibitors, and anti-CD38 antibodies, used individually or in combination, have helped increase the five-year median survival rate to more than 50%. Despite recent therapeutic advances, all MM patients experience relapses as they become resistant to various classes and combinations of treatment. At this stage of the disease, generally classified as RRMM, the focus of treatment is to optimize outcomes with as good a quality of life as possible.

Melflufen is initially intended to improve the care of patients with RRMM. These patients may suffer from symptoms such as skeletal fractures with associated bone pain, infections due to a weakened immune system, and side effects from their multiple treatments.

## Melflufen: a novel mechanism of action

Melflufen is a peptide-conjugated alkylator that belongs to a novel class of compounds potentiated by aminopeptidases. Aminopeptidases are present in all human cells but are heavily overexpressed in several cancers including in MM cells. Upon entering a cell, the conjugated peptide is cleaved by aminopeptidases, releasing the alkylating payload and eliciting further inflow and cleavage of melflufen until all extracellular melflufen has been consumed. In vitro, this aminopeptidase-driven accumulation effects a 50-fold increase in the enrichment of the alkylator in MM cells compared with free alkylator, resulting in selective cytotoxicity—increased on-target cell potency and decreased off-target cell toxicity—and overcoming resistance pathways triggered by previous myeloma treatments, including alkylators.

Based on ongoing preclinical studies, the company is also exploring the potential for the use of melflufen, or other peptide-conjugated drugs, to treat various cancers beyond MM, including other hematological cancers and solid tumors.

## On the fast track to the clinic

Oncopeptides is developing melflufen as a first choice therapy for the treatment of patients with RRMM (**Fig. 1**). In an ongoing pivotal phase 3 trial (OCEAN; study identifier OP-103) with an expected primary completion date in H2 of 2019, the combination of melflufen plus dexamethasone is being compared directly with pomalidomide plus dexamethasone, a current standard of care for RRMM.

Because RRMM is a rare disease, melflufen has been granted orphan drug designation by both the United States and European regulatory authorities, which will translate into benefits such as extended exclusive marketing rights—of seven and ten years, respectively—upon regulatory approval.

Melflufen is protected by more than 50 granted patents and pending patent applications covering the composition of matter, formulations, manufacturing processes, and medical applications. The patents cover major markets across the world, including the United States, Europe, Canada, and Japan, with the potential for some patent extensions following marketing approval.

So far, Oncopeptides has been the sole driver of all melflufen research and development efforts, but with the global RRMM market expected to reach more than $8 billion in 2019, the company is adopting a flexible approach to commercialization that could include one or more interested partners.

According to Lindberg, "we are making great progress in our broad clinical development program with melflufen in RRMM. Based on growing clinical evidence, melflufen might be not only a good addition in the fight against treatment-resistant myeloma, but also a drug with a very favorable tolerability profile for patients. Personally, it has been an honor to contribute to the improvement of patients' lives through our clinical studies."

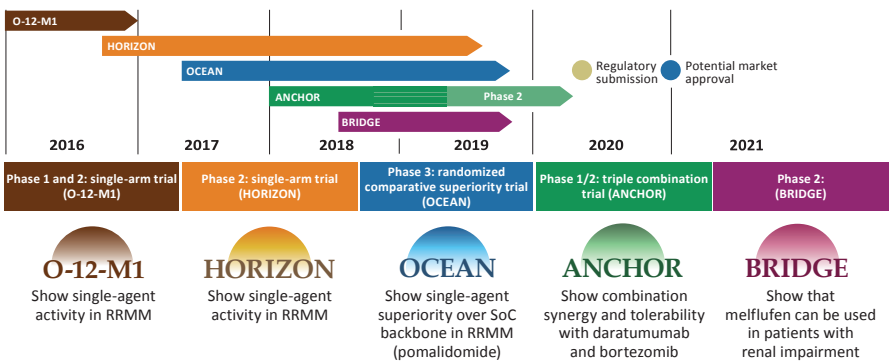


**Fig. 1 | Oncopeptides clinical development program of melflufen.** SoC, standard of care; RRMM, relapsed and refractory multiple myeloma.

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