



Carfilzomib

Carfilzomib is a selective, next generation proteasome inhibitor currently undergoing evaluation in multiple clinical settings, including a Phase 3 combination trial in patients with relapsed multiple myeloma, as well as an advanced Phase 2b clinical trial in patients with relapsed and refractory multiple myeloma. Inhibition of the cellular proteasome is a validated and well-characterized approach to treating certain hematological malignancies.

Carfilzomib was designed to have higher selectivity and specificity, thereby potentially increasing therapeutic efficacy and reducing the affinity for off-target proteases. Through unique chemistry, the binding for carfilzomib is engineered to be selective for the unique N-terminal threonine active sites within the proteasome. This mechanism prolongs proteasome inhibition and increases levels of inhibition resulting in greater cell death and anti-tumor activity, with minimal effects on normal cells. Additionally, the higher selectivity is thought to reduce neurotoxicity and provide a decreased incidence of neutropenia, or low white blood cell count, both of which are major concerns with existing agents.

To date, carfilzomib has generated a positive signal in numerous early-stage studies with an encouraging safety profile, including low rates of neuropathy and neutropenia.

Clinical Trials

Onyx is committed to exploring the full potential of carfilzomib and is conducting a comprehensive development program. Enrollment has been completed in an ongoing 250-patient Phase 2b trial, known as the 003-A1 trial, in patients with relapsed and refractory multiple myeloma. Data is anticipated in mid-2010 to support a potential new drug application (NDA) filing by year-end 2010.

Onyx has initiated a Phase 3 international, randomized trial, known as the ASPIRE trial, evaluating the safety and efficacy of carfilzomib in combination with lenalidomide and low-dose dexamethasone versus lenalidomide and dexamethasone alone as a potential treatment option for patients with relapsed multiple myeloma.

In addition, carfilzomib is being evaluated in a Phase 2 trial, known as the 004 trial, in patients with relapsed and/or refractory multiple myeloma who have relapsed after one to three prior therapies. For this trial, patients are divided into two populations: patients with relapsed and/or refractory multiple myeloma who had not received prior bortezomib (Velcade[®]) treatment, or patients with relapsed and/or refractory disease following bortezomib treatment.

Carfilzomib is also being evaluated in a Phase 1b/2 trial, known as the 007 trial, evaluating the safety and efficacy as a single agent for advanced solid tumor cancers.