

ADVANCES IN LLM

Current Developments in the Management of Leukemia, Lymphoma, and Myeloma

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Carfilzomib in Multiple Myeloma



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H&O What is carfilzomib (Kyprolis, Onyx Pharmaceuticals), and how does it differ from bortezomib (Velcade, Millennium Pharmaceuticals)?

RV Carfilzomib is a novel potent, highly selective epoxyketone proteasome inhibitor that targets the chymotrypsin-like activity of the 20S proteasome. Carfilzomib is believed to be more specific for the proteasome than bortezomib, which is a boronate. Whereas bortezomib is a reversible proteasome inhibitor, carfilzomib is an irreversible proteasome inhibitor, and this may account for a better potential efficacy profile of the drug. Furthermore, in laboratory models, carfilzomib appears to overcome bortezomib resistance in bortezomib-resistant cell lines. Thus, carfilzomib does have several potential advantages over bortezomib in terms of its structure and mechanism of action.

H&O What study formed the basis for the submission of carfilzomib for approval by the US Food and Drug Administration (FDA)?

RV The submission for approval was based on the phase IIb PX-171-003A1 trial, which enrolled multiple myeloma patients who had been exposed to both bortezomib and an immunomodulatory drug, and who were relapsed and refractory to their most recent line of therapy. Carfilzomib was administered on days 1, 2, 8, 9, 15, and 16 of 28-day cycles (20 mg/m² in cycle 1; 27 mg/m² in cycles 2–12). Of the 266 patients enrolled, 257 were evaluable, with a median age of 63 years and a median time from diagnosis of 5.4 years. Patients received a median of 5 prior lines of therapy, with approximately 80% of patients having had

4 or more prior lines of therapy. Seventy-four percent of patients had progressive disease on therapy, and approximately 14% of patients were progressive within 60 days of their last therapy. Patients were deemed to be bortezomib-refractory in approximately 72% of cases. The response rate was 23.7%, with a clinical benefit rate of 37%, when including minimal responses in the study. The responses were brisk, with a median time-to-response of less than 2 months, and a response duration of 7.8 months. The duration of clinical benefit, including patients with minimal response, was 8.3 months. The median time-to-progression was 3.9 months, and the overall survival was 15.6 months. Carfilzomib showed very low rates of peripheral neuropathy. Carfilzomib was well tolerated in this study. Adverse events were clinically manageable, with no new, unexpected, or cumulative toxicities.

H&O What were the key events of the review process? Where does carfilzomib currently stand?

RV Carfilzomib was granted fast track designation by the FDA in January 2011. In September 2011, a New Drug Application (NDA) for potential accelerated approval of carfilzomib in the United States was submitted. The FDA granted a standard review designation for the NDA in December 2011. This past June, the Oncologic Drugs Advisory Committee (ODAC) voted 11 to 0 with 1 abstention that carfilzomib's risk-benefit profile is favorable for patients with relapsed and refractory multiple myeloma who have received at least 2 prior lines of therapy that included a proteasome inhibitor and an immunomodulatory drug. The original decision deadline was set at July 27, 2012, with the option of

additional review time, if deemed necessary by the FDA. However, approval of carfilzomib was announced sooner, on July 20, 2012. As a condition of accelerated approval, manufacturers are required to provide more clinical data confirming benefit, and if the follow-up studies fail to confirm benefit, the FDA can withdraw approval.

H&O What additional data exists for single-agent carfilzomib?

RV The phase II PX-171-004 study (Table 1) evaluated single-agent carfilzomib in 165 patients with relapsed and/or refractory multiple myeloma who had received 1–3 prior treatments. A total of 129 patients with refractory, measurable multiple myeloma without prior bortezomib therapy were allocated to successive cohorts. Patients enrolled earlier received 20 mg/m², while later-enrolled patients were dose escalated from 20 mg/m² to 27 mg/m².

Additional studies are looking at higher doses of carfilzomib, including PX-171-007, where patients received carfilzomib 20 mg/m² during cycle 1, days 1 and 2, followed by escalation to either 26, 45, 56, or 70 mg/m² during subsequent dosing. Dose-limiting toxicity was noted at 70 mg/m². Of the 24 relapsed/refractory patients who received 56 mg/m², the overall response rate was 60%. Even with these escalated doses, carfilzomib was relatively well tolerated, with the majority of adverse events related to grade 1/2 anemia and thrombocytopenia. Another phase II trial, PX-171-005, enrolled patients with varying degrees of renal impairment, including some on hemodialysis. There was no significant difference found in the pharmacokinetic properties and adverse events in patients with varying degrees of renal impairment. Of the patients on hemodialysis, 2 were able to discontinue this treatment due to improvement in renal function.

H&O What do we know about the safety profile of carfilzomib?

RV A combined analysis of PX-171-003 (A0 and A1), PX-171-004, and PX-171-005 assessed the safety of carfilzomib in patients with multiple myeloma. The most common adverse effects associated with carfilzomib included fatigue (55%), anemia (47%), nausea (45%), thrombocytopenia (36%), dyspnea (35%), diarrhea (33%), and pyrexia (30%). The most common grade 3 or greater adverse events included thrombocytopenia (23%), anemia (22%), lymphopenia (18%), pneumonia (11%), and neutropenia (10%). The incidence of any grade peripheral neuropathy was 14%, with only 1.3% experiencing grade 3 or higher toxicity. Among the 527 patients pooled through the study, there appeared to be 14 treatment-related deaths due to cardiac events, hepatic

Table 1. Summary of Key Conclusions: PX-171-004

Single-agent carfilzomib active in patients with bortezomib-naïve, relapsed/refractory multiple myeloma (RRMM)
Overall response rate (ORR) 42% for carfilzomib 20 mg/m ² for 12 cycles 52% for carfilzomib 20 mg/m ² for 1 cycle followed by carfilzomib 27 mg/m ² for cycles 2–12
ORR plus minimal response (MR) 59% for carfilzomib 20 mg/m ² for 12 cycles 64% for carfilzomib 20 mg/m ² for 1 cycle followed by carfilzomib 27 mg/m ² for cycles 2–12
Evidence of potential dose-response relationship
Carfilzomib well tolerated, with low risk of treatment discontinuation due to adverse events
Most common grade ≥ 3 adverse events: hematologic toxicities Low risk of peripheral neuropathy

failure, and infection. A small number of patients did experience tumor lysis syndrome, which was subsequently prevented with intravenous fluids and allopurinol.

H&O Are there data for use of carfilzomib in the frontline setting?

RV At the 2012 American Society of Clinical Oncology (ASCO) meeting, Jakubowiak and colleagues presented updated results of a phase I/II trial that evaluated a combination of carfilzomib, lenalidomide (Revlimid, Celgene), and dexamethasone in 53 newly diagnosed myeloma patients. After a median follow-up of 14 months, 98% of patients had responded to treatment (complete response, 62%; stringent complete response, 42%; very good partial response, 19%; partial response, 17%). Responses continued to improve with longer treatment, as evidenced by the 61% of patients who achieved a stringent complete response after completing 8 cycles of treatment. The most common adverse events for patients who received more than 8 cycles of treatment included low lymphocyte counts (30%), low leukocyte counts (26%), and fatigue (25%). Mild peripheral neuropathy was limited (11%). In addition, preliminary data on combination therapy with carfilzomib-melphalan-prednisone (CMP), cyclophosphamide-carfilzomib-thalidomide-dexamethasone (CYCLONE), and carfilzomib-thalidomide-dexamethasone (Carthadex) were presented at the ASCO 2012 meeting.

H&O What are some current phase III trials of carfilzomib?

RV The ASPIRE (Carfilzomib, Lenalidomide, and Dexamethasone versus Lenalidomide and Dexamethasone for

the treatment of Patients with Relapsed Multiple Myeloma [PX-171-009]) trial is an international study that is evaluating carfilzomib in combination with lenalidomide and low-dose dexamethasone in patients with relapsed myeloma. After recently reaching its target enrollment of 780 patients who had received 1–3 prior therapies, the study is comparing the effect of this 3-drug combination on time to disease progression with that observed with lenalidomide and low-dose dexamethasone.

The FOCUS (Carfilzomib for Advanced Refractory Multiple Myeloma European Study [PX-171-011]) trial is comparing carfilzomib to best supportive care in patients with relapsed and refractory myeloma who have received at least 3 prior therapies. The main goal of the study is to determine the effect of carfilzomib on overall survival. There is an expected enrollment of 300 patients across Europe, and the trial is designed to support registration filing with the European regulatory agency.

Enrollment recently began for the ENDEAVOR (Randomized, Open-Label, Phase III Study of Carfilzomib Plus Dexamethasone Vs Bortezomib Plus Dexamethasone in Patients With Relapsed Multiple Myeloma) trial, which is evaluating carfilzomib in combination with dexamethasone versus bortezomib with dexamethasone in 888 patients whose multiple myeloma has relapsed after 1–3 prior treatment regimens. In this first head-to-head study involving carfilzomib, patients will be randomized to receive carfilzomib intravenously (20 mg/m² on days 1 and 2 of cycle 1 only, then 56 mg/m² subsequently) with low-dose dexamethasone (20 mg) or bortezomib (1.3 mg/m²) with low-dose dexamethasone. Progression-free survival is the primary endpoint of the trial. Secondary endpoints include overall survival, overall response rate, duration of response, and safety.

H&O What does the future hold?

RV Carfilzomib will become a valuable addition to the armamentarium of drugs that are available for patients with relapsed and refractory multiple myeloma. The drug is likely to be used in a combination regimen. Combination therapy with carfilzomib, lenalidomide, and low-dose dexamethasone (CRd) in a phase I/II clinical trial (PX-171-006) in patients with relapsed/refractory myeloma has already shown an overall response rate of 78%, with a complete response/stringent complete response rate of 18%. Additionally, I think that the use of this drug will naturally evolve into earlier lines of therapy, including the frontline treatment setting. Until substantial head-to-head comparison data are available,

such as results from the ENDEAVOR trial, it is too early to judge whether or not carfilzomib will replace bortezomib. However, it is clear that in the coming years, multiple myeloma treatment options will continue to improve. Personalized treatment will become more common, as advances are made in predicting patient response and creating more targeted therapies. Ensuring that quality of life is improved and maintained in these patients is essential. The low rates of neuropathy and ability to tolerate carfilzomib for extended periods of time is another step forward in this arena.

Suggested Readings

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ClinicalTrials.gov. A study of carfilzomib vs best supportive care in subjects with relapsed and refractory multiple myeloma (FOCUS). <http://clinicaltrials.gov/show/NCT01302392>. Identifier: NCT01302392.

ClinicalTrials.gov. Phase 3 study with carfilzomib and dexamethasone versus velcade and dexamethasone for relapsed multiple myeloma patients (ENDEAVOR). <http://clinicaltrials.gov/ct2/show/NCT01568866>. Identifier: NCT01568866.