Scientific & Clinical

PHASE II STUDY OF CARFILZOMIB IN PATIENTS WITH RELAPSED MYELOMA

Myeloma Today in conversation with Dr. Sundar Jagannath

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At the 2009 annual meeting of the American Society of Clinical Oncology (ASCO), IMF spoke with Dr. Sundar Jagannath, the principal investigator of a Phase II study of carfilzomib in patients with relapsed and refractory multiple myeloma.

Dr. Jagannath, at the recent ASCO meeting you presented the final results of your study of carfilzomib, a new agent being investigated in myeloma. Would you please tell us more about this agent and your study findings?

Carfilzomib (CFZ) is a novel proteasome inhibitor of the epoxyketone class that exhibits a high level of proteasome selectivity and demonstrates anti-tumor activity in bortezomib-resistant myeloma patients in Phase I studies.

Our study, PX-171-003-A0, was an open-label, single-arm, multicenter study that enrolled myeloma patients who had relapsed from more than two prior therapies, failed on therapy with bortezomib (Velcade®), and failed at least one immunomodulatory agent (thalidomide or lenalidomide). The enrolled patients were refractory to last treatment while on, or within 60 days of last therapy, or had <25% response to last therapy. Patients received CFZ 20mg/m^2 intravenously two days per week for three weeks (on days 1, 2, 8, 9, 15, and 16) of a 28-day cycle, for up to 12 cycles. Again, let me stress that all study participants had exhausted all treatments currently available to them and their disease had progressed on their last therapy.

Forty-six patients were enrolled in the initial phase of the study, including 78% with progression on/within 60 days of last therapy and 22% with no response to last therapy.

Thirty-nine patients completed at least one cycle of CFZ, had measurable M-protein, and were evaluable for response. All patients had received prior bortezomib therapy, 91% had prior thalidomide and 89% prior lenalidomide, and 83% had prior stem cell transplant. All had failed combinations including anthracyclines (80%) and/or alkylating agents (94%).

What conclusions did you reach as a result of the initial phase of this carfilzomib study?

I feel that CFZ is a very active and very well-tolerated anti-myeloma agent. Eight out of ten patients achieved response during cycle one, and 72% of participants experienced either improvement or stabilization of their disease. Median time to progression (TTP) was 6.2 months. Close to one out of five patients responded to treatment.

Single-agent CFZ achieved a TTP of >6 months in relapsed and refractory myeloma patients who failed available therapies. We are quite excited that the drug seems to be tolerated very well. Patients stayed with this study for a median of eight months, which demonstrates that most study participants tolerated the treatment well and that most of the toxicities were manageable. The most common adverse events were fatigue, anemia, thrombocytopenia, nausea, upper respiratory infection, increased creatinine, and diarrhea. As with most of the other side effects, peripheral neuropathy (PN) occurred in less than 10% of participants. Importantly, exacerbation of pre-existing PN was rare, and 80% of study participants had pre-existing PN.

What is the next phase for this carfilzomib study?

The study has been expanded to enroll an additional 250 patients in this unmet medical need population at an escalated dose, and treatment has been extended beyond a year. If this compound continues to prove to be an effective treatment for myeloma in the next phase of the study (PX-171-004), we are hoping that the expanded trial will help expedite the drug approval process for the use of CFZ in myeloma.
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Editor's Note: For more information, please see below, visit www.myeloma.org, or call the IMF Hotline at 800-452-CURE (2873).

Open-label, Single-arm, Phase II Study of Carfilzomib in Patients with Relapsed Multiple Myeloma: Carfilzomib given at increasing doses with dexamethasone (PX-171-004)

Trial description: This is a single-arm study for patients who have relapsed, refractory or progressive disease after at least one but no more than 3 prior treatments for myeloma. The initial dose of carfilzomib will be increased if the drug is well tolerated. Both patients never treated with Velcade® and patients previously treated with Velcade® will be studied.

Trial Objectives: To evaluate the best Overall Response Rate after 6 cycles of carfilzomib.

Inclusion criteria:

- 18 years or older
- Adequate ability to perform acts of daily living
- Symptomatic myeloma with measurable disease
- Relapsed, refractory or progressive disease after at least one, but no more than three treatments or regimens for multiple myeloma

Exclusion Criteria:

- Non-secretory multiple myeloma or myeloma only measurable by serum free light chain (SFLC) assay
- Not responsive to standard front line therapy
- Systemic myeloma treatment within 3 weeks of study, radiation therapy or immunotherapy within 4 weeks of study or localized radiation therapy within 2 weeks of study
- Significant neuropathy (Grade 3, 4 or Grade 2 with pain)
- Acute active infection requiring systemic antibiotics, antivirals or antifungals within 2 weeks of study

Locations and Trial Coordinator Telephone Contacts:

Mayo Clinic, Scottsdale, AZ: 480-301-4890

Barnes-Jewish Hospital, St. Louis, MO: 314-454-8377

Hackensack University Medical Center, Hackensack, NJ: 210-336-8020

St. Vincent's Compr. Cancer Center, New York, NY: 212-604-6026

MD Anderson Cancer Center, Houston, TX: 713-792-9559

Princess Margaret Hosp, Toronto, Ontario, Canada: 416-946-4501, x 5931

This study continues to expand, adding new locations weekly, so please visit **www.myeloma.org** or call the IMF Hotline at **800-452-CURE (2873)** for the most up-to-date list of trial sites.
