Dana-Farber Cancer Institute drives deep remissions in Waldenström's with targeted, time limited therapies

Posted date: **December 7, 2025**

Early phase results from Dana Farber suggest chemo free, time limited strategies may reduce the need for lifelong treatment in Waldenström's

Building on decades of leadership in Waldenström's macroglobulinemia research, Dana Farber Cancer Institute investigators have designed and led two early phase, institute initiated clinical trials that aim to overcome treatment resistance and reduce the need for indefinite therapy. These studies, one testing a fixed duration, chemotherapy free oral regimen and the other evaluating a precision antibody-drug conjugate, are reporting strong responses.

The research teams presented their findings at the *67th American Society of Hematology (ASH) Annual Meeting & Exposition* in Orlando, Florida, December 6 to 9.

Waldenström's macroglobulinemia (WM) is a rare blood cancer of the lymphatic system. Standard treatment often relies on Bruton tyrosine kinase (BTK) inhibitors given without a defined stop date. While effective, indefinite therapy can lead to cumulative toxicities and, over time, resistance. To address these challenges, researchers at Dana-Farber are testing targeted, time limited approaches designed to achieve deep remissions without lifelong treatment. Both studies show strong results, including deep remissions, and with further testing could offer new options for patients with WM.

Oral fixed-duration pill as targeted therapy for Waldenström's macroglobulinemia

Dr. Jorge Castillo, clinical director for the Bing Center for Waldenström's Macroglobulinemia and clinical investigator at Dana-Farber, presented findings from an investigator-initiated, multicenter, prospective phase II chemotherapy-free study that combines the BTK inhibitor pirtobrutinib and the BCL-2 antagonist venetoclax as a fixed-duration targeted therapy for symptomatic patients who received at least one previous line of therapy.

BTK therapies are impressive in their ability to control WM, however, certain mutations, such as CXCR4, TP53 or BTK mutations, may impede their effectiveness. Castillo highlights in his study that the combination of venetoclax and pirtobrutinib can lead to deep hematologic responses and deliver time-limited treatment to minimize potential long-term adverse effects caused by continuous therapy.

Within the trial, 36 patients with MYD88 mutation were included. Of the 36 patients, 27 completed 6 months on the study and are assessable for response. After a median of 11 months of follow-up, 100% of patients had shown a response to the regimen, with 56% experiencing deep responses, attaining either a complete response or a very good partial response. Most common Grade 3 or higher events included neutropenia, anemia and thrombocytopenia.

Pirtobrutinib and venetoclax has been approved by the Food and Drug Administration (FDA) for certain cancers such as lymphoma and leukemia, but not specifically for WM. Based on the current success of this clinical trial, this may be a valuable option for future patients whose disease is resistant to existing therapies. Additional follow-up is needed to assess the durability of the response after therapy completion.

"The combination of the two powerful medicines induces rapid and profound responses with manageable side effects," Castillo says. "The depth of response is beyond what was expected for each of the medications separately. This combination could become a new standard of care for patients with WM."

Antibody-drug conjugate shows responses in relapsed/refractory Waldenström's macroglobulinemia

Dr. Shayna Sarosiek, a senior physician at the Bing Center for Waldenström's Macroglobulinemia and a clinical investigator at Dana-Farber, shared results from the multicenter investigator-initiated, prospective phase II study in patients with relapsed/refractory WM. Patients on the trial received loncastuximab tesirine, an antibody-drug conjugate (a form of targeted or "smart" chemotherapy that links a potent chemotherapy drug to a disease-specific antibody). This study is being run in collaboration with the Mayo Clinic and the Fred Hutch Cancer Center within the context of the WM-NET, a partnership of 25 academic centers in the United States that aims to improve the lives of patients with WM through clinical research.

Patients with WM typically have a good prognosis with a long-life expectancy, according to Sarosiek, but when a patient has high-risk disease, such as a mutation in CXCR4 or TP53, their disease is more likely to be resistant to therapies and have a shorter response time after therapy. Between 30 and 40% of patients have the CXCR4 mutation, and approximately 10% of patients have a TP53 alteration, although the number of patients with TP53 alterations increases significantly in patients who have been previously treated. This study aims to fight the resistance that these mutations cause, weakening the current standard of treatment for WM.

Patients on this trial received six cycles of loncastuximab tesirine monotherapy over the course of six months. The 14 patients who completed this study were between the ages of 53 and 81 and were heavily treated, with a median of four prior therapies. Of these patients, 12 had disease with the MYD88 mutation, 8 with a CXCR4 mutation, and 8 with a TP53 alteration. Sarosiek reports 71% of patients experienced a complete response or very good partial response. Notably, all patients with a TP53 alteration responded to treatment and 89% of patients with a TP53 alteration had a complete response or very good partial response. Additional follow-up is needed to assess the durability of the response after therapy completion.

"We need new therapies for patients with high-risk WM. This phase 2 trial of loncastuximab tesirine is showing response rates that are higher than expected but also deeper and better than expected in this high-risk population," Sarosiek says. "Hopefully, with continued treatment of patients, this trial will lead to the adoption of loncastuximab tesirine as a standard therapy for relapsed WM."

Funding: The pirtobrutinib and venetoclax study is funded by Loxo Oncology, and the loncastuximab tesirine study by ADC Therapeutics.

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Jorge Castillo, MD

Shayna Sarosiek, MD

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Jorge J. Castillo, MD

Shayna Sarosiek, MD