Research Square

Preprints are preliminary reports that have not undergone peer review.
They should not be considered conclusive, used to inform clinical practice,
or referenced by the media as validated information.

Alirocumab offers superior benefits to usual care in treating high-risk patients with type 2 diabetes

Meletios A. Dimopoulos
Jacob P. Laubach
Maria Asunción Echeveste Gutierrez
Norbert Grzasko
Craig C. Hofmeister
Jesus F. San-Miguel
Shaji Kumar
Richard Labotka
Vickie Lu
Deborah Berg
Catriona Byrne
Zhaoyang Teng
Guohui Liu
Helgi van de Velde
Paul G. Richardson

Video Abstract

Keywords: ixazomib, multiple myeloma, phase I/II, proteasome inhibitor, proteasome, NDMM, induction therapy, lenalidomide, dexamethasone, melphalan, prednisone, cyclophosphamide, disease progression, toxicity, maintenance, clinical trial, patients, PFS, European Journal of Haematology, National and Kapodistrian University of Athens

Posted Date: February 19th, 2020

DOI: https://doi.org/10.21203/rs.2.24077/v1

License: This work is licensed under a Creative Commons Attribution 4.0 International License.
Read Full License

Abstract

A recent analysis suggests that ixazomib, an oral proteasome inhibitor (or PI), is tolerable and enhances therapeutic responses in patients with multiple myeloma. Ixazomib is approved for use in combination with lenalidomide and dexamethasone for patients who have already received 1 or more prior therapy. The promising results obtained for non-transplant patients taking ixazomib alone, if their disease has responded to primary induction therapy, point to a new possible treatment option for multiple myeloma. Multiple myeloma is a form of cancer that develops in bone marrow. Here, the body normally generates white blood cells that help fight off infection. But in multiple myeloma, malignant cells gradually crowd out these disease-fighting cells, compromising the body's immune response, while also damaging the bones. The malignant cells also secrete large amounts of a non-functional protein which leads to kidney failure and other harms. Proteasome inhibitors are a mainstay treatment for patients with multiple myeloma. These drugs block the internal garbage disposal for cells—called the proteasome, which is essential for cell survival. Despite their promise, long-term treatment with existing PIs may be limited due to toxicity and the need for regular parenteral administration, which can increase treatment burden. Ixazomib can be dosed orally, thus making the possibility of extended dosing more feasible. The current analysis provides evidence that ixazomib maintenance following ixazomib-based induction is associated with deepening of responses and a positive safety profile with no cumulative toxicity in patients with newly diagnosed multiple myeloma not undergoing transplantation. Clinical data were pooled from 4 phase I and II clinical trials, with study participants receiving initial ixazomib therapy once or twice per week in combination with one of the following: lenalidomide and dexamethasone, melphalan and prednisone, or cyclophosphamide and dexamethasone. For patients whose disease responded to initial treatment, this was then followed by maintenance therapy with ixazomib alone until disease progression, death, or unacceptable toxicity. Among 215 initial patients, 121 achieved stable disease and entered ixazomib maintenance therapy. Regarding efficacy, 23% of patients improved their responses during maintenance, with an improvement in the rate of complete response from 22% at initial treatment to 35% following ixazomib maintenance therapy. Promising long-term outcomes from the start of maintenance were also observed, with a median progression-free survival of 21.4 months, and 3-year overall survival rate of 82%. Results showed that 94 patients stopped maintenance therapy completely, due mostly to disease progression, followed by adverse events and patient withdrawal. The most common adverse events were rash, peripheral neuropathy, hematological toxicities, and GI symptoms. Those findings should be interpreted with some caution. The clinical studies examined were limited by the small number of patients analyzed and the lack of comparison to a control group with no ixazomib maintenance. Still, the results are encouraging. They suggest that for patients with multiple myeloma who have not undergone transplantation, ixazomib may be a beneficial maintenance treatment option. The PFS results reported in this analysis are also consistent with the PFS outcomes observed with single-agent ixazomib maintenance in the phase III TOURMALINE-MM3 study, although differences in patient populations exist between the two studies.