

# The TOURMALINE Clinical Development Program:


## An in-depth investigation of ixazomib in multiple myeloma and AL amyloidosis


Multiple myeloma is a rare form of cancer that starts in plasma cells, which are found in the bone marrow.<sup>1</sup> It is the second most common blood cancer and represents approximately 1 percent of all diagnosed cancers worldwide.<sup>2</sup> Despite treatment advances in the past decade, multiple myeloma remains a devastating, relapsing and incurable cancer.


Long-term treatment is emerging as a standard of care in multiple myeloma because it has demonstrated the potential to improve clinical outcomes.<sup>3</sup> In addition, proteasome inhibition is an established standard of care in the treatment of multiple myeloma. Ixazomib's TOURMALINE program is designed to evaluate whether sustained therapy with an oral proteasome inhibitor improves the outcomes for patients living with multiple myeloma and AL amyloidosis. TOURMALINE investigates ixazomib in treatment settings and in combinations that have not previously been studied in Phase 3 clinical trials of proteasome inhibitors.


The TOURMALINE program is the result of Takeda's long standing history of patient-centric innovation in multiple myeloma and the company's continuing commitment to individual patient needs in populations across the continuum of multiple myeloma care.


Takeda would like to express its appreciation for the patients, their families and trial investigators participating in the TOURMALINE program, without whom this would not be possible.

TRIAL	DESCRIPTION
 <p>(NCT01564537)</p>	<p>A Phase 3 Study of Oral Ixazomib Plus Lenalidomide and Dexamethasone in Adult Patients With Relapsed and/or Refractory Multiple Myeloma</p> <ul style="list-style-type: none"> <li>» <b>Initiated:</b> August 2012</li> <li>» <b>Design:</b> Global, randomized, double-blind, placebo-controlled, multi-center</li> <li>» <b>Eligibility:</b> Patients with relapsed/refractory multiple myeloma who have received 1 to 3 prior therapies</li> <li>» <b>Primary Endpoints:</b> Progression-free survival (PFS)</li> <li>» <b>Enrollment:</b> 722 patients worldwide; Completed</li> <li>» <b>Status:</b> This study met its endpoint at the first pre-specified interim analysis. Data are expected to be presented by the end of 2015.</li> </ul> <p><a href="https://clinicaltrials.gov/ct2/show/NCT01564537">https://clinicaltrials.gov/ct2/show/NCT01564537</a></p>

TRIAL	DESCRIPTION
 <p>(NCT01850524)</p>	<p>A Phase 3 Study of Oral Ixazomib Plus Lenalidomide and Dexamethasone in Adult Patients With Newly Diagnosed Multiple Myeloma</p> <ul style="list-style-type: none"> <li>» <b>Initiated:</b> May 2013</li> <li>» <b>Design:</b> Global, randomized, controlled, open-label, multi-center</li> <li>» <b>Eligibility:</b> Patients with newly diagnosed multiple myeloma ineligible for stem cell transplant</li> <li>» <b>Primary Endpoints:</b> PFS</li> <li>» <b>Enrollment:</b> Approximately 700 patients worldwide; Open for enrollment</li> </ul> <p><a href="https://clinicaltrials.gov/ct2/show/NCT01850524">https://clinicaltrials.gov/ct2/show/NCT01850524</a></p>

TRIAL	DESCRIPTION
 <p data-bbox="272 390 423 411">(NCT02181413)</p>	<p data-bbox="662 195 1458 247">A Phase 3 Study of Oral Ixazomib Maintenance Therapy in Patients With Multiple Myeloma Following Autologous Stem Cell Transplant</p> <ul style="list-style-type: none"> <li data-bbox="643 264 854 285">» <b>Initiated:</b> July 2014</li> <li data-bbox="643 302 1398 323">» <b>Design:</b> Global, randomized, placebo-controlled, double-blind, multi-center</li> <li data-bbox="643 340 1409 392">» <b>Eligibility:</b> Patients with symptomatic multiple myeloma with prior induction therapy and ASCT and no post-ASCT consolidation therapy</li> <li data-bbox="643 409 911 430">» <b>Primary Endpoints:</b> PFS</li> <li data-bbox="643 447 1382 468">» <b>Enrollment:</b> Approximately 650 patients worldwide; Open for enrollment</li> </ul> <p data-bbox="662 485 1049 506"><a href="https://clinicaltrials.gov/ct2/show/NCT02181413">https://clinicaltrials.gov/ct2/show/NCT02181413</a></p>

TRIAL	DESCRIPTION
 <p data-bbox="272 871 423 892">(NCT02312258)</p>	<p data-bbox="662 676 1446 728">A Phase 3 Study of Oral Ixazomib Maintenance Therapy in Patients With Newly Diagnosed Multiple Myeloma Not Treated With Stem Cell Transplantation</p> <ul style="list-style-type: none"> <li data-bbox="643 745 862 766">» <b>Initiated:</b> April 2015</li> <li data-bbox="643 783 1398 804">» <b>Design:</b> Global, randomized, placebo-controlled, double-blind, multi-center</li> <li data-bbox="643 821 1479 873">» <b>Eligibility:</b> Patients with newly diagnosed multiple myeloma with response to prior induction therapy and not receiving stem-cell transplantation</li> <li data-bbox="643 890 911 911">» <b>Primary Endpoints:</b> PFS</li> <li data-bbox="643 928 1382 949">» <b>Enrollment:</b> Approximately 700 patients worldwide; Open for enrollment</li> </ul> <p data-bbox="662 966 1049 987"><a href="https://clinicaltrials.gov/ct2/show/NCT02312258">https://clinicaltrials.gov/ct2/show/NCT02312258</a></p>

TRIAL	DESCRIPTION
 <p data-bbox="272 1365 423 1386">(NCT01659658)</p>	<p data-bbox="662 1171 1474 1224">A Phase 3 Study of Oral Ixazomib Plus Dexamethasone in Relapsed or Refractory Systemic Light Chain (AL) Amyloidosis</p> <ul style="list-style-type: none"> <li data-bbox="643 1241 911 1262">» <b>Initiated:</b> December 2012</li> <li data-bbox="643 1278 1292 1299">» <b>Design:</b> Global, randomized, controlled, open-label, multi-center</li> <li data-bbox="643 1316 1382 1369">» <b>Eligibility:</b> Biopsy-proven diagnosis of AL amyloidosis that is relapsed or refractory after 1 or 2 prior therapies</li> <li data-bbox="643 1386 1398 1407">» <b>Primary Endpoints:</b> Number of patients with overall hematologic response</li> <li data-bbox="643 1423 1382 1444">» <b>Enrollment:</b> Approximately 250 patients worldwide; Open for enrollment</li> </ul> <p data-bbox="662 1461 1049 1482"><a href="https://clinicaltrials.gov/ct2/show/NCT01659658">https://clinicaltrials.gov/ct2/show/NCT01659658</a></p>

For more information, please visit <https://www.clinicaltrials.gov/>.

1 Palumbo A, Anderson K. Multiple Myeloma. *New England Journal of Medicine*. 2011;364:1046-60.

2 Mateos MV, San Miguel JF. How should we treat newly diagnosed multiple myeloma patients? *Hematology Am Soc Hematol Educ Program*. 2013;2013:488-495.

3 Palumbo A, Gay F, Cavallo F et al. Continuous Therapy Versus Fixed Duration of Therapy in Patients With Newly Diagnosed Multiple Myeloma. *Journal of Clinical Oncology*. 2015;60:2466

4 US National Institutes of Health Clinical Trials Registry. A phase 3 study comparing oral ixazomib plus lenalidomide and dexamethasone versus placebo plus lenalidomide and dexamethasone in adult patients with relapsed and/or refractory multiple myeloma. <https://clinicaltrials.gov/ct2/show/NCT01564537>. Updated August 4, 2015. Accessed September 1, 2015.

5 US National Institutes of Health Clinical Trials Registry. IXAZOMIB plus lenalidomide and dexamethasone versus placebo plus lenalidomide and dexamethasone in adult patients with newly diagnosed multiple myeloma. <https://clinicaltrials.gov/ct2/show/NCT01850524>. Updated February 23, 2015. Accessed September 1, 2015.

6 US National Institutes of Health Clinical Trials Registry. A study of oral ixazomib citrate (MLN9708) maintenance therapy in patients with multiple myeloma following autologous stem cell transplant. <https://clinicaltrials.gov/ct2/show/NCT02181413>. Updated March 31, 2015. Accessed September 1, 2015.

7 US National Institutes of Health Clinical Trials Registry. A study of oral ixazomib maintenance therapy in patients with newly diagnosed multiple myeloma not treated with stem cell transplantation. <https://clinicaltrials.gov/ct2/show/NCT02312258>. Updated July 26, 2015. Accessed September 1, 2015.

8 US National Institutes of Health Clinical Trials Registry. Study of dexamethasone plus ixazomib or physicians choice of treatment in relapsed or refractory systemic light chain (AL) amyloidosis. <https://clinicaltrials.gov/ct2/show/NCT01659658>. Updated February 24, 2015. Accessed September 1, 2015.