

Phase 3 trial of isatuximab combination therapy showed 40% reduction in the risk of disease progression or death for patients with relapsed/refractory multiple myeloma

News Summary:

- * *Isatuximab, an investigational anti-CD38 monoclonal antibody, added to pomalidomide and dexamethasone prolonged progression free survival by 5 months compared to pomalidomide and dexamethasone alone (11.53 vs. 6.47 months, $p=0.001$, HR 0.596)*
- * *Overall response rate significantly greater with isatuximab combination therapy compared to pomalidomide and dexamethasone (60% vs. 35%, $p<0.0001$)*
- * *First positive randomized Phase 3 trial to evaluate an antibody in combination with pomalidomide and dexamethasone presented at this year's ASCO annual meeting*
- * *European Medicines Agency accepted for review the Marketing Authorization Application for isatuximab*

Paris – June 2, 2019 – Pivotal Phase 3 ICARIA-MM trial results demonstrated that isatuximab added to pomalidomide and dexamethasone (isatuximab combination therapy) showed statistically significant improvements compared to pomalidomide and dexamethasone (pom-dex) alone in patients with relapsed/refractory multiple myeloma (RRMM).

These findings were presented today at the 2019 American Society of Clinical Oncology (ASCO) Annual Meeting in Chicago. Isatuximab is an investigational monoclonal antibody that targets a specific epitope on the CD38 receptor of a plasma cell.

“Isatuximab in combination with pomalidomide and dexamethasone resulted in an impressive 40% reduction in the risk of progression or death compared to pomalidomide and dexamethasone alone,” said Paul Richardson, MD, principal investigator and clinical program leader and director of clinical research at the Jerome Lipper Multiple Myeloma Center at Dana-Farber Cancer Institute. *“This outcome is noteworthy because this trial included a particularly difficult-to-treat, relapsed and refractory patient population that was, in my view, highly reflective of real-world practice.”*

Isatuximab combination therapy showed a statistically significant improvement in progression free survival (HR 0.596, 95% CI 0.44-0.81, $p=0.001$), and the median progression free survival was longer in the isatuximab combination therapy arm (11.53

months, 95% CI: 8.936 to 13.897) than pom-dex alone (6.47 months, 95% CI: 4.468 to 8.279).

Also of note, isatuximab combination therapy demonstrated a significantly greater overall response rate, compared to pom-dex alone (60% vs. 35%, $p < 0.0001$). In additional analyses, isatuximab combination therapy compared to pom-dex alone showed a treatment benefit consistent across multiple subgroups, including patients 75 years and older, patients with renal insufficiency, and patients who were refractory to lenalidomide. The results presented above were based on an independent review committee assessment.

In addition, the following results favored isatuximab combination therapy:

- Isatuximab combination therapy demonstrated significantly higher very good partial response (VGPR) rate compared to pom-dex (31.8% vs. 8.5%, respectively, $p < 0.0001$) and a longer duration of response compared to pom-dex alone (median 13.27 months vs. 11.07 months, respectively). Among patients who achieved a response, isatuximab combination therapy demonstrated faster median time to first response compared to pom-dex alone (35 days vs. 58 days, respectively).
- Time to next treatment was longer with isatuximab combination therapy compared to pom-dex alone (median not reached vs. 9.1 months, HR=0.538).
- Data at the time of analysis showed a trend towards an overall survival benefit associated with isatuximab combination therapy. Final data on overall survival will be reported when available.

Adverse events (AEs) of Grade ≥ 3 were observed in 86.8% of isatuximab combination therapy patients vs. 70.5% of pom-dex patients. Additionally, isatuximab combination therapy compared to pom-dex showed: 7.2% vs. 12.8% of patients discontinued due to AEs, respectively; 7.9% vs. 9.4% patients died due to AEs, respectively; infections of Grade ≥ 3 were seen in 42.8% vs. 30.2% of patients, respectively; and Grade ≥ 3 neutropenia was seen in 84.9% (febrile 11.8%) vs. 70.1% (febrile 2.0%) of patients, respectively. Infusion reactions were reported in 38.2% (2.6% grade 3-4) of isatuximab combination therapy patients.

First Positive Phase 3 Trial of a Monoclonal Antibody in Combination with Pom-Dex

ICARIA-MM is a pivotal Phase 3 randomized, open-label, multi-center trial evaluating isatuximab in combination with pom-dex versus pom-dex alone in patients with RRMM. The study enrolled 307 patients with RRMM across 96 centers spanning 24 countries. Overall, patients had received a median of three prior lines of anti-myeloma therapies, including at least two consecutive cycles of lenalidomide and a proteasome inhibitor given alone or in combination.

During the trial, isatuximab was administered through an intravenous infusion at a dose of 10mg/kg once weekly for four weeks, then every other week for 28-day cycles in combination with standard doses of pom-dex for the duration of treatment.

Topline results from ICARIA-MM were previously announced in February 2019.

Developing Isatuximab, a Monoclonal Antibody

Isatuximab is an investigational monoclonal antibody (mAb) targeting a specific epitope on the CD38 receptor. It is designed to trigger multiple, distinct mechanisms of action that are believed to directly promote programmed tumor cell death (apoptosis) and immunomodulatory activity. CD38 is highly and uniformly expressed on multiple myeloma cells and is a cell surface receptor target for antibody-based therapeutics in multiple myeloma and other malignancies. The clinical significance of these findings is under investigation.

Isatuximab is being developed by Sanofi and is currently being evaluated in multiple ongoing Phase 3 clinical trials in combination with currently available treatments across the multiple myeloma treatment continuum.

In the second quarter of 2019, the European Medicines Agency (EMA) accepted for review the Marketing Authorization Application and Sanofi filed a Biologics License Application with the U.S. Food and Drug Administration (FDA), both for use of isatuximab in combination with pom-dex for the treatment of certain patients with RRMM.

Isatuximab is also under investigation for the treatment of other hematologic malignancies and solid tumors. Isatuximab is an investigational agent and its safety and efficacy have not been evaluated by the U.S. FDA, the EMA, or any other regulatory authority.

Multiple Myeloma Leads to Significant Disease Burden

Multiple myeloma is the second most common hematologic malignancy¹, affecting more than 138,000² people worldwide. Multiple myeloma results in significant disease burden. Patients with multiple myeloma continue to relapse over time making it a difficult to treat and incurable malignancy.

About Sanofi

Sanofi is dedicated to supporting people through their health challenges. We are a global biopharmaceutical company focused on human health. We prevent illness with vaccines, provide innovative treatments to fight pain and ease suffering. We stand by the few who suffer from rare

¹ Kazandjian. Multiple myeloma epidemiology and survival: A unique malignancy. *Semin Oncol.* 2016;43(6):676-681. doi:10.1053/j.seminoncol.2016.11.004

² Cowan AJ, Allen C, Barac A, et al. Global Burden of Multiple Myeloma: A Systematic Analysis for the Global Burden of Disease Study 2016. *JAMA Oncol.* 2018;4(9):1221–1227. doi:10.1001/jamaoncol.2018.2128

diseases and the millions with long-term chronic conditions.

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Sanofi, Empowering Life

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