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 malignancy\(^1\), affecting more than 138,000\(^2\) 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.

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diseases and the millions with long-term chronic conditions.

With more than 100,000 people in 100 countries, Sanofi is transforming scientific innovation into healthcare solutions around the globe.

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Sanofi Forward-Looking Statements

This press release contains forward-looking statements as defined in the Private Securities Litigation Reform Act of 1995, as amended. Forward-looking statements are statements that are not historical facts. These statements include projections and estimates and their underlying assumptions, statements regarding plans, objectives, intentions and expectations with respect to future financial results, events, operations, services, product development and potential, and statements regarding future performance. Forward-looking statements are generally identified by the words “expects”, “anticipates”, “believes”, “intends”, “estimates”, “plans” and similar expressions. Although Sanofi's management believes that the expectations reflected in such forward-looking statements are reasonable, investors are cautioned that forward-looking information and statements are subject to various risks and uncertainties, many of which are difficult to predict and generally beyond the control of Sanofi, that could cause actual results and developments to differ materially from those expressed in, or implied or projected by, the forward-looking information and statements. These risks and uncertainties include among other things, the uncertainties inherent in research and development, future clinical data and analysis, including post marketing, decisions by regulatory authorities, such as the FDA or the EMA, regarding whether and when to approve any drug, device or biological application that may be filed for any such product candidates as well as their decisions regarding labelling and other matters that could affect the availability or commercial potential of such product candidates, the absence of guarantee that the product candidates if approved will be commercially successful, the future approval and commercial success of therapeutic alternatives, Sanofi's ability to benefit from external growth opportunities and/or obtain regulatory clearances, risks associated with intellectual property and any related pending or future litigation and the ultimate outcome of such litigation, trends in exchange rates and prevailing interest rates, volatile economic conditions, the impact of cost containment initiatives and subsequent changes thereto, the average number of shares outstanding as well as those discussed or identified in the public filings with the SEC and the AMF made by Sanofi, including those listed under "Risk Factors" and "Cautionary Statement Regarding Forward-Looking Statements" in Sanofi's annual report on Form 20-F for the year ended December 31, 2018. Other than as required by applicable law, Sanofi does not undertake any obligation to update or revise any forward-looking information or statements.