HYBRIGENICS

Press Release

Hybrigenics' inecalcitol receives positive opinion from EMA for orphan drug designation in acute myeloid leukemia

Paris, 22 June 2015 – Hybrigenics (ALHYG), a bio-pharmaceutical company listed on the Alternext market of Euronext Paris, with a focus on research and development of new treatments against proliferative diseases, today announces the issuance by the Committee for Orphan Medicinal Products of the European Medicines Agency (EMA) of a positive opinion for the orphan drug designation of inecalcitol in acute myeloid leukemia (AML), during its meeting held on June 16-18, 2015. The complete EMA Public Summary of Opinion will be available during the Summer.

This favourable opinion is based on *in vitro* and *in vivo* preclinical evidence showing the synergy between inecalcitol and azacytidine or decitabine, two hypo-methylating anticancer drugs, to inhibit the growth of human AML cell lines *in vitro* and, *in vivo*, to prolong the survival of mice in two different experimental models of AML (cf. Hybrigenics' press releases of March 05 and June 20, 2014).

The molecular basis of their synergy with inecalcitol, a vitamin D receptor agonist, has been elucidated: azacytidine or decitabine "unmask" the gene coding for vitamin D receptors (by reducing the methylation of its promoter region). As a consequence, more vitamin D receptors are expressed and available to be activated by inecalcitol, resulting in an improved efficacy to limit leukemia progression over the hypo-methylating agents alone.

Azacytidine (Vidaza®, Celgene) and decitabine (Dacogen®, Janssen-Cilag) are two hypo-methylating agents already used for AML in older (>65 years old) or frail patients not eligible to standard induction chemotherapy. Inecalcitol alone has already been studied in a Phase II clinical trial in chronic lymphocytic leukemia: an inhibitory effect has been shown in half of the treated patients. Another Phase II clinical study has recently been launched in combination with imatinib (Gleevec®, Novartis) in chronic myeloid leukemia: enrolment is ongoing.

"*We are actively preparing an additional clinical Phase II study of inecalcitol in combination with either azacytidine or decitabine in older or frail Acute Myeloid Leukemia patients, in France as well as in the United States,*" said Jean-François Dufour-Lamartinie, Hybrigenics' Head of Clinical R&D.

About Acute Myeloid Leukemia

World-wide, acute myeloid leukemia (AML) is the second most frequent form of leukemia (behind chronic lymphocytic leukemia) and accounts for about 30% of all leukemic patients. In the United States, it has recently become the most frequent one with 36% of all newly diagnosed leukemia cases. Annual estimates of new AML cases amount to 18,900 in the United States (American Leukemia Lymphoma Society, Facts 2015), 18,500 in Europe (RARECARE Working Group, 2012), 2,800 in France (Francim, 2013) and 110,000 world-wide (Globocan, 2012). AML is designated as an orphan disease in the United States, Europe and Japan.

Acute myeloid leukemia is a type of cancer that affects the blood and bone marrow. AML is characterized by a fast-increasing overproduction of immature white blood cells, called myeloblasts. These cells rapidly crowd the bone marrow, soon preventing it from making normal blood cells. They can also spill out into the blood stream and circulate around the body. Due to their immaturity, they are unable to function properly to prevent or fight infection. Inadequate numbers of red cells and platelets being made by the marrow cause anemia, and easy bleeding and/or bruising. AML is sometimes called acute myelocytic, myelogenous or granulocytic leukemia.

AML can occur at any age but is more common in adults over the age of 60 years. Treatment needs to begin soon after AML is diagnosed, as it progresses very quickly. Chemotherapy is the main form of treatment for AML; occasionally, a stem cell transplant may be used. Despite available treatments, AML shows the lowest 5-year survival rate of all leukemias: 25% in the US and 19% in Europe.

About Hybrigenics

Hybrigenics (www.hybrigenics.com) is a bio-pharmaceutical group listed (ALHYG) on the Alternext market of Euronext Paris, focusing its internal R&D programs on innovative targets and therapies for the treatment of proliferative diseases and providing cutting-edge proteomic and genomic scientific services.
Hybrigenics' current development program is based on inecalcitol, a vitamin D receptor agonist active by oral administration. Oral inecalcitol has shown excellent tolerance and strong presumption of efficacy for the first-line treatment of metastatic castrate-resistant prostate cancer in combination with Taxotere®, which is the current gold-standard chemotherapeutic treatment for this indication. Inecalcitol has also been tested in chronic lymphocytic leukemia patients, an indication for which inecalcitol has received orphan drug status in Europe and the United States. A clinical Phase II study of inecalcitol is currently ongoing in chronic myeloid leukemia patients.
Hybrigenics has a research collaboration with Servier on deubiquitinating enzymes (DUBs) and their inhibitors in oncology, neurology, psychiatry, rheumatology, ophthalmology, diabetes and cardiovascular diseases. A first milestone has been achieved in a drug discovery program targeting one DUB in oncology.
Hybrigenics Services (www.hybrigenics-services.com) is the market leader in Yeast Two-Hybrid (Y2H) and related services to identify, validate and inhibit protein interactions for researchers in all areas of life sciences, using its ISO 9001-certified high-throughput Y2H screening platform.
Helixio (www.helixio.com), Hybrigenics' genomic branch, provides state-of-the-art services specialized in DNA chips, DNA or RNA target enrichment and next generation sequencing with an Illumina NextSeq500.
Hybrigenics Corp., based in Cambridge, Mass., is the American subsidiary of Hybrigenics.

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