PRESS RELEASE

Fidia announces the FDA Orphan Drug designation for ONCOFID®-P for the treatment of malignant mesothelioma, the cancer caused by exposure to asbestos

- *ONCOFID®-P is an innovative conjugation of the anticancer drug paclitaxel (taxol) with hyaluronic acid (HA).*
- *Thanks to the HA component, ONCOFID®-P specifically binds cancer cells expressing CD44, the HA receptor, significantly increasing the intracellular concentration of paclitaxel and maintaining an excellent tolerability profile.*
- *The loco-regional administration makes ONCOFID®-P an ideal anticancer drug in combination with existing treatments for patients with malignant mesothelioma.*
- *Preclinical studies are underway to complete the pharmaco-toxicological profile of ONCOFID®-P, particularly in pleural mesothelioma, with the aim of submitting the authorisation dossier for human studies to the regulatory authorities by 2022.*
- *ONCOFID®-P is developed by the Italian multinational company Fidia Farmaceutici.*

Abano Terme (PD), July 26th, 2021 – Fidia Farmaceutici, an Italian company world leader in the research, development, formulation and commercialization of hyaluronic acid-based products, announced today that the U.S. Food and Drug Administration has granted Orphan Drug Designation for ONCOFID®-P for the treatment of malignant mesothelioma (MM), a rare and aggressive cancer with limited therapeutic options.

ONCOFID®-P is an anticancer drug in advanced clinical development for the loco-regional treatment of non-muscle invasive bladder cancer, on which it has already demonstrated potent efficacy and excellent tolerability.

Its characteristics make *ONCOFID®-P* ideal also for the loco-regional treatment of some forms of mesothelioma, especially pleural mesothelioma, which represents about 83% of all types of mesotheliomas, a group of highly lethal neoplasms with an average survival of 10.6% at 5 years and 49.8% at 1 year from diagnosis *.

The onset of mesothelioma is closely related to exposure to asbestos, used as an insulator in many industries, from constructions to naval-aircraft and heavy industries.

"*Patients are diagnosed in advanced-stage and experience high mortality rate after the first year. Patients have an essentially uniform prognosis across countries, and they did not benefit from significant therapeutic improvements in the last thirty years* - says **Prof. Antonio Rosato**, Professor at the University of Padua and Director of the Immunology and Molecular Oncology Diagnostics Unit and Deputy Scientific Director at the Istituto Oncologico Veneto IRCCS who conducted the

pre-clinical trials and developed the concept of loco-regional application for the drug - *Oncofid-P represents a very important step forward for the treatment of this serious disease*".

The Orphan Drug status has been granted according to strong preclinical data documenting the high anti-tumor activity of ONCOFID®-P on human mesothelioma lines, both in vitro and in murine models of the disease.

"*The FDA designation represents an opportunity for physicians and patients who, until now, did not benefit from any innovative therapy, and makes us proud* - underlines **Carlo Pizzocaro**, President and CEO of Fidia Farmaceutici - *This result demonstrates that the scientific research must not stop and that every step forward will add hope for patients, especially those who are victims of such serious rare diseases.*"

Background information

ONCOFID®-P

ONCOFID®-P is an innovative anti-cancer drug, a conjugate of paclitaxel (taxol) with hyaluronic acid (HA), resulting from the research of Fidia Farmaceutici. This conjugation brings several advantages, including the possibility of loco-regional administration. ONCOFID®-P, thanks to the HA component, specifically binds cancer cells expressing CD44, the HA receptor, significantly increasing the intracellular concentration of paclitaxel, and maintaining an excellent tolerability profile.
The muco-adhesive property derived from the HA component of Oncofid®-P, retains the drug on the mucosal surface and, consequently, concentrates it in the tumor tissue reducing the possibility of systemic diffusion.

Clinical Development

Oncofid®-P in non-muscle invasive bladder cancer

In recent years, the clinical efficacy of Oncofid®-P administered intravesically (loco-regionally) has been evaluated in a Phase 1 study in BCG-unresponsive carcinoma *in situ* (CIS) of the bladder, to identify the minimum effective dose; in a Phase 2 study in low-grade papillary bladder cancer and in a Phase 1/2 study in BCG-unresponsive CIS according to an innovative therapeutic scheme. The results, obtained in Europe on about 100 patients, confirm the high efficacy and excellent tolerability of Oncofid®-P in this indication. Phase 3 study is expected to start soon in the US and Europe.

Experimental Data on pleural mesothelioma

CD44 expression has been well documented on human pleural mesothelioma cell lines, which, as a result, are up to 70 times more susceptible to the anticancer activity of ONCOFID®-P as compared to paclitaxel alone. In murine models of human mesothelioma, ONCOFID®-P was significantly more effective than paclitaxel alone in terms of survival and tumor mass reduction. Moreover, intrapleural administration of ONCOFID®-P is associated with low systemic exposure, indicating that ONCOFID®-P localizes in the pleural cavity where, thanks to its muco-adhesive properties, it shows a prolonged residence time. The high pleural concentration coupled with the limited systemic exposure leads to high antitumor activity, with reduced likelihood of side effects.

Mesothelioma

Mesothelioma is a rare neoplasm that affects the mesothelium, the thin tissue that lines most internal organs. The form that affects the pleura (the mesothelium that lines the lungs and the inner wall of the chest) is the most common. Rarer are mesotheliomas of the peritoneum (mesothelium lining the abdominal organs), of the pericardium (mesothelium lining the heart muscle) and of the testicles. Typically, it is caused by genetic alterations in the mesothelium cells, leading to their uncontrolled growth.

The main cause of mesothelioma is exposure to asbestos, a mineral widely used in the past as an insulator in construction and in the transport sector. When its fragments are inhaled, like small hooks they get into the pulmonary alveoli causing an inflammatory reaction that, over time, generates the cancer.
Mesothelioma occurs in subjects exposed to this substance for work or proximity to sources of asbestos and after decades of exposure. The diagnosis is often difficult because the symptoms are similar to those of many other diseases. Most often, when diagnosed, the extent of the tumor is large, and for patients referred for surgical removal, a chemotherapeutic intervention is required to reduce the tumor mass.

Pleural Mesothelioma
Pleural mesothelioma represents about 83% of all forms of malignant mesotheliomas. At 5 years from first diagnosis, the average survival is 9.1%-10.6%, with a 1-year survival rate of 49.8%*. The unfavourable prognosis is partly due to the long incubation period of the disease, which leads to the diagnosis very often when the disease is already advanced, and a pharmacological approach is difficult.
Treatment options include surgery (when applicable), radiotherapy, and chemotherapy. Recently, innovative approaches for the treatment of pleural mesothelioma are being tested, including new immunotherapies, new chemotherapies and, above all, the combination of already known treatments with new chemotherapeutic drugs. The possibility of intrapleural administration of anticancer drugs with a prolonged local residence and a good tolerability profile, as well as the ability to easily penetrate the tumor tissue present on the surface of the pleural cavity are important properties for a new anticancer drug. These properties are present in ONCOFID®-P and are well suited for combination with other chemotherapeutic drugs administered systemically, thereby increasing the antineoplastic activity without impacting on the tolerability profile.

Fidia Farmaceutici
Privately held, fully integrated Italian multinational company, with R&D, manufacturing, marketing and sales capabilities. The company was founded in 1946 and is headquartered in Abano Terme (a short distance from Venice). Fidia's overall objective is establishing its leadership, through an extensive product portfolio mainly based on hyaluronic acid (HA) in joint care, wound care ophthalmology, aesthetic and regenerative medicine, thereby providing patients and healthcare professionals with a variety of treatment options, such as pharmaceutical products, medical devices and food supplements. Over 55 years of R&D have placed Fidia at the forefront in the production of natural and functionalized HA, with different ranges of molecular weight (1,100 patents). Manufacturing operations - located in Italy - are inspected and approved by major international health authorities, including the US and Korean FDA, the Brazilian ANVISA and G-MED Notified Body, and comply with the strictest international regulations and safety standards. Fidia extends its global reach through local partners in +100 countries worldwide, as well as wholly owned subsidiaries in USA, Germany, Austria, Spain, France, Russia, Czech Republic, Slovakia, Romania, Egypt, and Middle East.

*Fonte: https://seer.cancer.gov