

PharmaMar Announces Presentations at American Association for Cancer Research (AACR) Annual Meeting 2016

- *The RNA polymerase II inhibitor, PM1183, acts also on macrophages, cells that are essential in the inflammatory tumor microenvironment, rendering tumor growth unfeasible*
- *Plitidepsin directly interacts with the eEF1A2 protein, a new molecular target in Multiple Myeloma and other tumors*
- *The molecule of marine origin, PM184, provokes the disruption of the blood vessels that supply the tumor*

Madrid, April XX, 2016. PharmaMar (MSE:PHM) today announced four poster presentations at the American Association of Cancer Research (AACR) annual meeting, taking place in New Orleans, April 16-20th 2016. The presentations are based on the latest data obtained on the company's compounds of marine origin, lurbinectedin, plitidepsin and PM184. Under the heading "*Delivering Cures Through Cancer Science*", oncologists and investigators from around the world will interchange knowhow and reinforce the links between research and the advancements in patient care.

PharmaMar will present results from three molecules that are presently under clinical investigation in different types of solid and hematological tumors. Each one of these compounds has a very different mechanism of action. Apart from its direct activity on tumor cells, lurbinectedin (PM1183) also attacks the microenvironment, rendering tumor growth unfeasible. Plitidepsin (Aplidin), targets the eEF1A2 protein, and finally PM184 disrupts the tumor's blood vessels, causing a reduction in the supply of both nutrients and oxygen to the tumor cells.

"At PharmaMar we have a commitment to the identification of new and novel mechanisms of action from marine compounds that can provide a step forward in the treatment of patients with cancer," explains Carmen Cuevas, Ph.D., R&D Director from the Oncology Business Unit at PharmaMar. *"The results that we will present at scientific congresses such as the AACR show that we are on right path and that we can count on a robust pipeline that will provide new methods for attacking tumor cells."*

Presentation details are as follows:

PM1183 (lurbinectedin)

PM1183 is compound under clinical investigation, inhibitor of the RNA polymerase II enzyme. It is essential for the transcription process, inhibiting tumor growth, and resulting in tumor death. The antitumor efficacy of PM1183 is being investigated in various types of solid tumors.

- *Lurbinectedin reduces tumor-associated macrophages and the production of inflammatory cytokines, chemokines and angiogenic factors in preclinical models* (abstract No 1284). Paola Allavena et al. Poster presentation, section 18, Monday April 18th, 8:00 am - 12:00 am.

This proves that part of lurbinectedin's antitumor activity is due to its antiproliferative activity in monocytes and tumor associated macrophages, cells that are essential in the inflammatory microenvironment. Lurbinectedin inhibits transcription, therefore, the production of cytokines and angiogenic factors by these cells. Tumor growth is unfeasible, even when the tumor cells are resistant to the compound.

- *Lurbinectedin specifically targets transcription in cancer cells, triggering DNA breaks and degradation of phosphorylated Pol II* (Abstract No 3039). Gema Santamaría-Nuñez et al. Poster presentation, section 17, Tuesday April 19th, 8:00 am-12:00 am.

Lurbinectedin (PM1183) binds to the DNA in the CG rich regions surrounding the promoter of genes, inhibiting transcription activity. The mechanism involves the ubiquitination and degradation by proteasome of the RNA polymerase II (pol II). The degradation of pol II is directly related to the appearance of DNA damage and the induction of cell death through apoptosis.

Plitidepsin (Aplidin®)

Plitidepsin is an antitumor drug of marine origin, at the investigational phase for hematological tumors, including a phase Ib study in relapsed and refractory Multiple Myeloma, in triple combination with bortezomib and dexamethasone, along with a phase II study in Relapsed and Refractory Angioimmunoblastic T-cell Lymphoma. Recently, positive results have been seen in pivotal study in combination with dexamethasone in patients with Multiple Myeloma.

- *Plitidepsin targets the GTP-bound form of eEF1A2 in cancer cells* (Abstract No 3015). Alejandro Losada et al. Poster presentation, section 17, Tuesday April 19th, 8:00am-12:00am.

This confirms that the protein eEF1A2 is Aplidin's pharmacological target. This protein has numerous functions within the tumor cell, some of which have a marked oncogenic character. This assay delves into the peculiarities of the direct interaction of Aplidin with purified GTP bound eEF1A2.

PM184

PM184 is an inhibitor of tubulin polymerization. It is at the clinical development stage for solid tumors, including a Phase II trial in hormone-receptor positive, HER2-negative, locally advanced and/or metastatic breast cancer.

- *Anti-angiogenic properties of PM184* (Abstract No 3066). Carlos M. Galmarini et al. Poster presentation, section 25, Tuesday April 19th, 8:00am-12:00am.

The tumor cells rapidly growth, needing the supply of a large quantity of nutrients. One of the paths for the treatment of cancer at the moment is to disrupt the blood cells within the tumor, or to stop the development of new cells, cutting the supply of nutrients and oxygen to the tumor cells. Adding to its capacity to specifically eliminate tumor cells, PM184 has shown itself to have a strong intratumor vascular disrupting activity, inhibiting in this extraordinarily effective way, human transplanted tumors in mice.

About PharmaMar

Headquartered in Madrid, PharmaMar is a world-leading biopharmaceutical company in the discovery and development of innovative marine-derived anticancer drugs. The company has an important pipeline of drug candidates and a robust R&D oncology program. PharmaMar develops and commercializes YONDELIS® in Europe and has other three clinical-stage programs under development for several types of solid and hematological cancers, PM1183, plitidepsin, and PM184. PharmaMar is a global biopharmaceutical company with subsidiaries in Germany, Italy, France, Switzerland, United Kingdom, Belgium and the United States. PharmaMar fully owns other companies: GENOMICA, Spain's leading molecular diagnostics company; Sylentis, dedicated to researching therapeutic applications of gene silencing (RNAi); and two other chemical enterprises, Zelnova Zeltia and Xylazel. To learn more about PharmaMar, please visit us at www.pharmamar.com.

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