

ZELTIA NEWS:

PharmaMar presents five new trials with its marine-based drugs at the Annual Meeting of the American Association for Cancer Research (AACR)

- **The five trials provided new data on marine antitumour drugs Aplidin® and PM01183.**
- **Aplidin® is PharmaMar's second most advanced compound. It is currently in Phase III trials for multiple myeloma.**
- **PM01183 is currently undergoing Phase II clinical trials in relapsed ovarian, lung and breast cancers. It is also undergoing Phase I development in combination with other chemotherapies and in haematological tumours.**
- **Dr Paola Allavena, from Instituto Humanitas in Milan (Italy), was invited by the organising committee to speak in one of the closing symposia on the data showing the specific activity of Yondelis® in the tumour's microenvironment. That data was recently published in "Cancer Cell" journal.**

Washington (USA), 11 April 2013: PharmaMar, a biopharmaceutical company owned by Grupo Zeltia (ZEL.MC), presented five new trials with marine-based antitumour drugs Aplidin® and PM01183 at the 104th Annual Meeting of the American Association for Cancer Research (AACR), held in Washington, D.C. from 6 to 10 April.

The AACR meeting is the leading convention on cancer research, bringing together more than 17,000 attendees each year and covering breakthroughs in oncology and basic, clinical and epidemiological research.

Aplidin[®] is PharmaMar's second most-advanced compound, and its mechanism of action includes rapid oxidative imbalance in tumour cells by activating intracellular signalling pathways leading to cell death by apoptosis. It is currently in Phase III trials for multiple myeloma.

The paper "Aplidin triggers the activation of molecular components of the UPR as part of its pro-apoptotic program in tumour cells" is a continuation of a previous trial which showed that Aplidin[®] induces the expression of certain molecular markers that are compatible with non-canonical reticulum stress leading to cell death by apoptosis. That trial showed that this particular response is observed only in tumour cells that are sensitive to the drug, and not in resistant cells. The paper presented this year studied whether the stress produced in the reticulum is essential in the compound's mechanism of action. It was confirmed that this effect of Aplidin[®] is comparable in tumour cell lines of different tissue origin and the ER stress response induced by Aplidin[®] in tumour cells appears to contribute to the compound's cytotoxicity.

PM01183 is currently undergoing Phase II clinical trials in relapsed ovarian, lung and breast cancers. It is also undergoing Phase I development in combination with other chemotherapies and in haematological tumours. The results obtained with PM01183 were presented in 4 papers. The first, "Lurbinectedin (PM01183) specifically targets RNA Pol II for degradation via the proteasome pathway in a TC-NER dependent fashion", examined the effects of PM01183 in the activity and stability of RNA Pol II (RNA polymerase II), as well as in other factors in the transcriptional machinery, including TBP (TFIID), p62 (TFIIH), XPG and XPF. Different human tumour cell lines were used, and the conclusion was that lurbinectedin induces a specific time- and concentration-dependent degradation of RNA polymerase II in tumour cells. Moreover, degradation of RNA polymerase II by lurbinectedin depends on whether the transcription process is active and it is mediated by the proteasome machinery. It also depends on the presence of an active functional transcription-coupled nucleotide excision repair mechanism for DNA.

The second paper, "Lurbinectedin (PM01183) in vivo synergizes the antitumor activity of taxanes", demonstrates PM01183's synergy with the taxanes used in clinical practice (paclitaxel and docetaxel). These experiments used athymic mice in which various tumours (gastric, ovarian, non-small cell lung, prostate and breast) were induced and which were treated with PM01183 in combination with one of the

evaluated taxanes. The results showed that the combination treatment provided a greater antitumour response than when each compound was administered as monotherapy. This evidences the *in vivo* synergistic antitumour activity of PM00183 and the taxanes. The third paper, "Lurbinectedin (PM01183) synergizes with topoisomerase I inhibitors *in vitro* and *in vivo*", evaluated the synergies between PM01183 and the topoisomerase inhibitors Topotecan and Irinotecan. First, the *in vivo* antitumour activity of PM01183 in combination with Topotecan was evaluated against several tumour cell lines: stomach, pancreas, colon, glioma, melanoma and hepatocarcinoma. The results confirmed the synergistic antitumour activity of the combination of compounds. These results were subsequently complemented with *in vivo* experiments where mice with colon, pancreatic and non-small cell lung cancers were treated with PM01183 in combination with Irinotecan. The *in vivo* results confirmed the synergistic antitumour effect of administering PM01183 with topoisomerase inhibitors. The fourth paper, "Synergism of lurbinectedin (PM01183) combined with 5-Fluorouracil (5-FU): *in vitro* and *in vivo* studies", also addresses the synergistic antitumour activity of PM01183, in this case with the anti-metabolic compound Fluorouracil (5-FU). As in the previous paper, the combination of PM01183+5-FU showed an *in vitro* synergistic effect in various stomach and colon cancer cell lines. This synergistic effect was confirmed with *in vivo* trials in mice with stomach, colon and pancreatic tumours treated with the PM01183 and 5-FU combination.

Dr Paola Allavena, from Instituto Humanitas in Milan (Italy), was invited by the organising committee to speak in one of the closing symposia on the data showing the specific activity of Yondelis[®] in the tumour's microenvironment. In addition to inducing tumour cell death, Yondelis[®] depletes tumour-associated macrophages. Those cells, normally part of the immune system, exhibit protumoural activity by releasing a number of factors that stimulate tumour cell division and neovascularisation.

By inducing these cells' death, Yondelis[®] inhibits their protumoural activity and reduces the secretion of tumour growth stimulation factors. This action mechanism is specific to Yondelis[®] and has not been observed with any other antitumour agent to date. That data was recently published in "Cancer Cell" journal.

About PharmaMar

PharmaMar is a biopharmaceutical subsidiary of Grupo Zeltia; it is a world leader in discovering, developing and selling marine-based drugs to treat cancer. Yondelis® is Spain's first antitumour drug. Yondelis® is currently approved for soft tissue sarcoma (STS) in 42 countries outside the EEA, and for platinum-sensitive relapsed ovarian cancer (ROC) in 31 of those countries plus Brazil. Yondelis® is approved for STS and platinum-sensitive ROC in all 30 countries of the EEA. Yondelis® is also undergoing Phase II trials on breast and paediatric cancers. PharmaMar has four other compounds in clinical development: Aplidin®, Zalypsis®, PM01183 and PM060184. PharmaMar also has a rich pipeline of pre-clinical candidates and a major R&D programme.

About Zeltia

Zeltia S.A. is a world-leading biopharmaceutical company specialised in the development of marine-based drugs for use in oncology and central nervous system illnesses. Grupo Zeltia consists mainly of the following companies: PharmaMar, the world-leading biotechnology company in advancing cancer care through the discovery and development of innovative marine-derived medicines; Genómica, Spain's leading molecular diagnostics company; Sylentis, dedicated to researching therapeutic applications of gene silencing (RNAi); and a chemical division comprising Zelnova and Xylazel, two highly profitable companies that are leaders in their respective market segments.

Important note

PharmaMar, which is headquartered in Madrid (Spain), is a subsidiary of Zeltia, S.A. (Spanish stock exchange: ZEL), which has been listed on the Spanish Stock Exchange since 1963 and on Spain's Electronic Market since 1998. This document is a press release, not a prospectus. This document does not constitute or form part of an offering or invitation to sell or a solicitation to purchase, offer or subscribe shares of the company. Moreover, no reliance should be placed upon this document for any investment decision or contract and it does not constitute a recommendation of any type with regard to the shares of the company.

For more information:

Grupo Zeltia Communication Manager +34 91 444 4500

This note is also available on the PharmaMar web site: www.pharmamar.com and at Zeltia's website: www.zeltia.com