Yondelis® (trabectedin) in the spotlight at the 18th Annual Meeting of the Connective Tissue Oncology Society (CTOS) with twenty-one trials

- A selection of recent trials with trabectedin (Yondelis®), the marine-based drug developed by PharmaMar, the GrupoZeltia (MC:ZEL) biotechnology subsidiary, was the central focus of the scientific programme at one of the leading international oncology events.
- The combination of trabectedin+doxorubicin offers significant clinical benefits in patients with metastatic uterine leiomyosarcoma and soft tissue leiomyosarcoma, with an acceptable safety profile.
- Trabectedin can be considered as an option for first-line treatment in translocation-related sarcomas.

Madrid, 04 November 2013.—A selection of recent trials with trabectedin (Yondelis®), the marine-based drug developed by PharmaMar, the GrupoZeltia (MC:ZEL) biotechnology subsidiary, was the central focus of the scientific programme at one of the leading international oncology events, the 18th Annual Meeting of the Connective Tissue Oncology Society (CTOS), held in New York from 30 October to 2 November. The results of twenty-one trials with trabectedin were presented in a range of formats (oral presentations, posters and abstracts).

One of the most important trials is "LMS-02: A phase II single-arm multicenter study of trabectedin in combination with doxorubicin as first line treatment of metastatic and/or locally advanced leiomyosarcoma of uterine (U-LMS) or soft tissue (ST-LMS) origin: results from both cohorts,"
This trial reveals the benefits of the combination in leiomyosarcoma, a tremendously aggressive soft tissue sarcoma with moderate chemo-sensitivity to drugs like doxorubicin. The French Sarcoma Group found that the combination of doxorubicin and trabectedin is a valid first-line treatment for these tumours.

A total of 105 patients, with a median age of 60, were enrolled for this trial (44 with U-LMS and 61 with ST-LMS). After evaluating the patients that received at least two cycles of the combined treatment, 25 partial responses and 13 disease stabilisations were observed in the U-LMS (n=44) cohort, yielding a disease control rate of over 86%.

In the sub-group with ST-LMS, of which 36 cases have been analysed to date, there has been one complete response, 13 partial responses and 20 cases of disease stabilisation, yielding a disease control rate of 94%. At 12 weeks, the progression-free survival rate was 86% in U-LMS and 95% in ST-LMS.

The authors of this trial, Florence Duffaud et al, concluded: “The combination of trabectedin plus doxorubicin is an active first-line regimen with meaningful clinical benefits in patients with U-LMS and ST-LMS and manageable safety profile, which did not affect efficacy outcomes”.

The results from the "Randomized phase III trial of trabectedin (T) versus doxorubicin-based chemotherapy (DXCT) as first-line therapy in patients (pts) with translocation-related sarcoma (TRS)”, a prospective trial which included 121 patients with various TRS sub-types, were also presented. The primary and secondary endpoints were to determine the efficacy of both treatments by comparing progression free survival and overall survival, respectively.

The conclusions of this prospective trial suggest that the PFS and OS results with trabectedin are comparable with those obtained in the standard approach with Doxorubicin as first-line treatment, with a safety profile that is in line with expectations. Sant P. Chawla et al. concluded that “Trabectedin may be considered as a treatment option for first line therapy of TRS.

Together with the 3 above-mentioned studies, “The antitumor and antimetastatic activity of trabectedin is potentiated by PARP-1 inhibition in preclinical models of bone and soft tissue sarcomas” was also discussed in an oral presentation. This experiment using preclinical models of soft tissue and bone sarcoma observed that trabectedin's anti-tumour effect is significantly enhanced in association with olaparib, which inhibits PARP-1 (a key enzyme in DNA repair). The authors concluded that PARP-1 inhibition potentiates the effect of trabectedin against mesenchymal tumours, suggesting that this effect merits assessment in clinical trials.
Other studies of interest

“Exploratory analysis for the evaluation of response (RECIST VS.CHOI CRITERIA) in the phase III trial of trabectedin vs. doxorubicin-based chemotherapy as first-line treatment of patients with translocation-related sarcoma (TRS)”. This trial compares two evaluations methods. The analysis according to RECIST, based exclusively on dimensional measurements, ignores a considerable fraction of responses to treatment with trabectedin; however, this is largely remedied by using Choi criteria. It is assumed that trabectedin's mechanism of action differs from conventional cytotoxic drugs, and that combining size and density criteria is more appropriate for evaluating its benefits (as in the case of target therapies). According to the researchers, this may be due to the unique mechanism of action of Yondelis® in the tumour microenvironment. This project has been financed in part by Spain's Centre for Industrial Technological Development (CDTI) and the European Regional Development Fund (ERDF), through the Technology Fund Operating Programme.

“Trabectedin in patients with advanced soft tissue sarcoma (STS): importance of maintenance therapy in responding patients”. Retrospective analysis by the French Sarcoma Group of data from 885 patients treated with trabectedin between January 2008 and December 2011 in 26 French referral sarcoma centres. This study, conducted in actual clinical practice conditions, evidenced that patients with advanced STS treated with trabectedin had progression-free survival (PFS) and overall survival (OS) levels that are comparable to, or even better than, those observed in clinical trials. Trabectedin given as maintenance treatment to patients with non-progression after 6 cycles of initial treatment is associated with statistically superior PFS and OS levels.

“Non-progression rate in patients with advanced soft tissue sarcoma receiving 6 cycles of trabectedin: first results of T-DIS TRIAL”. In this prospective trial with a cohort of patients with advanced soft tissue sarcoma, the rate of non-progression after six cycles of trabectedin was much higher than expected in the initial statistical plan (42% vs. 23%) based on the current literature.

“Thermo-sensitization of trabectedin in human soft tissue sarcoma (STS) cells: hyperthermia-mediated BRCA2-degradation is involved in enhanced cytotoxicity”. In line with the above-mentioned trial, the same group of researchers conducted this trial with STS cell lines which showed a dose-dependent reduction of clonogenic survival after treatment with trabectedin. Concomitant treatment with Yondelis® and hyperthermia increases cytotoxicity. Heat-mediated BRCA2-degradation and impairment of HR dependent DSB-repair
seem to be related mechanisms for the thermosensitisation of trabectedin-induced lethality.

"Trabectedin-related liver enzyme elevation in patients with soft tissue sarcoma: not a good reason to discontinue the treatment". Although treatment with trabectedin may raise liver enzyme (transaminase) levels in some patients, this event does not always justify cessation of treatment. That, at least, is the main conclusion of the trial conducted by Vincenzi et al., which noted that a transient increase in transaminase levels is a common undesired side effect of treatment with trabectedin that can be managed, is not cumulative and does not affect efficacy. The authors note that the "increase in liver enzymes only, should not be a prompt for a premature discontinuation of trabectedin".

"MiRNA signature characterization in round cell myxoidliposarcomas treated with trabectedin". This study sought to identify a microRNA signature associated with trabectedin administration in treating round cell myxoidliposarcoma, one of the most aggressive subtypes of this disease. An exhaustive analysis of a cohort of FFPE biopsy samples of myxoidliposarcoma raises the possibility that, following treatment with trabectedin, the molecular profile of round cell myxoidliposarcoma is more similar to the standard subtype than to the parental RCML.

Other studies published at this meeting were:

1. "Relationship between CSF1 gene signature and response to trabectedin in patients with advanced leiomyosarcoma”

2. “Predictive value of BRCA1 haplotype for trabectedin efficacy in patients with advanced soft tissue sarcoma”

3. “Toxicity profile and outcomes of older patients ≥ 65 (op) treated with trabectedin for advanced sarcoma as compared with younger patients (yp)”

4. "Efficacy of trabectedin in patients with pretreated advanced soft tissue sarcomas (STSS): a retrospective analysis”

5. “Trabectedin with regional hyperthermia: experiences in patients with high-risk liposarcoma”

6. "The Danish experience with trabectedin treatment for metastatic soft tissue sarcoma: Importance of hyponatremia”

8. “A retrospective analysis of trabectedin infusion in an outpatient setting by peripherally inserted central venous catheters (PICC): a multicentric Italian experience”.

9. “A retrospective tumor response assessment in locally unresectable or metastatic soft tissue sarcoma (aSTS) patients (pts): A three–years Regina Elena Cancer Institute (IRE) experience with trabectedin therapy”.

10. “The real time data of trabectedin as maintenance therapy in patients with advanced soft tissue sarcoma: the Swedish experience from Karolinska University Hospital”

11. “Trabectedin in pretreated metastatic L-sarcomas: a single institution study”

12. “Retrospective analysis of efficacy of trabectedin (t) in palliative treatment of advanced soft tissue sarcomas (STS) and its relation to gemcitabine-based treatment (GBT). Spanish Group of Research on Sarcomas (GEIS)”

About PharmaMar

PharmaMar is a biopharmaceutical subsidiary of GrupoZeltia; it is a world leader in discovering, developing and marketing marine-based drugs to treat cancer. Yondelis® is the first marine-based antitumour drug. 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. GrupoZeltia 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 company in molecular diagnostics based on DNA analysis; and Sylentis, dedicated to researching therapeutic applications of gene silencing (RNAi).

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
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**For more information +34 91 444 4500**

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