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PharmaMar Annual Report 2002

Annual Report 2002





*PharmaMar is a biopharmaceutical leader in oncology, advancing cancer care through the discovery and development of innovative marine-derived medicines.*



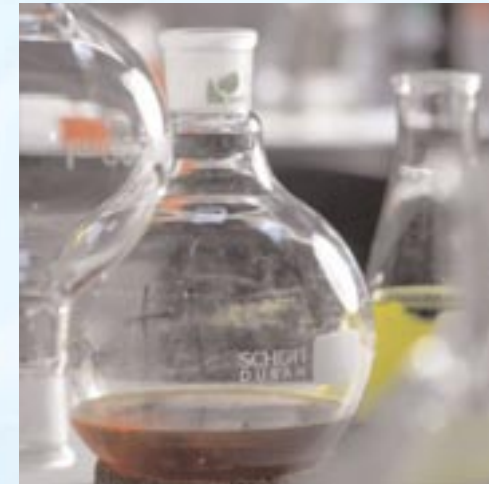


*Founded in 1986, PharmaMar, a subsidiary of Zeltia, was built on the vision of a scientist and entrepreneur, José María Fernández Sousa-Faro, today the chairman of PharmaMar and of the Zeltia Group.*



During 2002 PharmaMar has continued to strengthen its position as a pioneer biopharmaceutical company, and to advance cancer care through the discovery and development of innovative marine-derived medicines. This year we have made significant progress in the clinical development of our most advanced compounds and have reinforced our pipeline with the discovery of further novel marine-derived molecules.

We are expecting European approval of our first compound, Yondelis™ (ET-743), for the indication of advanced soft tissue sarcoma (STS) in 2003. In expectation of this, we have established our own marketing and sales structure in Europe. These initiatives now place PharmaMar in an optimal position to complete the transition from a successful research organization to a commercial company with the capability to commercialize an oncology franchise in the future.



## Letter from the Chairman

Dear Shareholders,

2002 has been a challenging year for PharmaMar. While we continued to develop a unique and increasingly enviable portfolio of compounds and intellectual property on which to base our future corporate direction, we concentrated in 2002 on creating and consolidating the platform to become a biopharmaceutical leader in oncology.

The company's vision, expressed in a new corporate identity, is to advance cancer care through the discovery and development of innovative marine-derived medicines, and the pending launch of Yondelis™ will be the first step towards realising this goal.

In terms of our research efforts, 2002 has seen important advances with our lead compound Yondelis™. Through PharmaMar's research co-operation with Ortho Biotech Products L.P., the clinical trial programme for this product has accelerated and expanded, and 11 new trials for different indications and treatment schedules have been started. Significantly, in 2002, we obtained the first convincing milestone results from Phase II studies of Yondelis™ in ovarian cancer, and from Phase I studies in children with advanced solid tumours, which point us to continue and expand studies in these indications.

*“The company's vision is to advance cancer care through the discovery and development of innovative marine-derived medicines”*



The development of Aplidin® and Kahalalide F has also proven to be a solid investment, with convincing clinical data for a broad spectrum of cancers emerging from clinical trials. ES-285, at the end-stages of preclinical evaluation, and six other pipeline compounds at advanced preclinical stage, continue to show strong promise and justify our decision to initiate clinical trials in 2003. In 2002, a further seven new families of compounds have been selected for advanced preclinical evaluation.

In the areas of new drug discovery, during 2002 alone we added 9,000 new marine samples to our library of 30,000, and we have identified and purified a further 29 completely new active marine-derived molecules. Implementing our prioritized planning and investment strategy, we will focus on the most promising compounds to provide significant additions to our future product portfolio.

It is this prolific and rich marine-derived portfolio that really distinguishes PharmaMar from competitors and other industry leaders.

We invested in R&D and infrastructure during 2002, culminating in the completion of new, bespoke headquarters in Colmenar Viejo, Madrid. This new facility houses state-of-the-art research and industrial facilities and will be the centre of our Europe-based research efforts. It is also the headquarters for our international commercial operations, thereby meeting our objective as an innovator in the biopharmaceutical sector to work in an ever-focused clinical-commercial manner.

Our research findings on all compounds were presented at the major oncology meetings or reported within prestigious journals throughout the year, thereby supporting our mission to establish PharmaMar as a biopharmaceutical leader in oncology. And reinforcing our continued commitment to cancer care, we sponsored two satellite symposia at the 2002 meetings of the European Association for Cancer Research (EACR) and the European Society for Medical Oncology (ESMO). These events were rewarded with unprecedented attention and attendance from the oncology community, not only demonstrating the need for innovative therapeutic advances in this sector, but also acknowledging the real interest and hope invested in our compounds.

PharmaMar continues to evolve into a company with significant innovative, commercial and operational capability, at headquarter level in Spain, as well as in the company's burgeoning presence in the key European territories. These changes would not have been possible without the continued commitment of our staff and the recruitment of further personnel of the very highest calibre; all of whom share our vision of providing new and improved therapies for cancer sufferers.

PharmaMar is an exciting company and we face many challenges in 2003 as we continue towards realising clinical hope and commercial success by building on our heritage. We, the staff at PharmaMar, and all our collaborators are committed to deliver to the very best of our ability and we thank you, the shareholders, for your continued and unstinting support of this worthwhile and rewarding mission.

José María Fernández Sousa-Faro  
Chairman

## Responsible Development, Exceptional Growth

PharmaMar is now recognized as the global leader in the discovery of innovative anti-cancer drugs of marine origin, having established a rationale-driven drug-discovery process for marine-derived therapeutic agents that extends to most of the oceans on the planet. More than a decade of marine 'bio-prospecting' in these oceans has yielded a broad and exciting pipeline of compounds with novel structures and mechanisms of action. However, while we are committed to our mission of developing marine-derived medicines that will significantly

advance the treatment of human cancers, PharmaMar has a strong commitment to good corporate practice and continues its own environmentally approved policies towards protecting the precious resource of the sea.

Our main objectives for 2002 were to advance the registration process of our flagship drug Yondelis (ET-743), an innovative treatment for cancer, and to implement the demanding development schedule. In support of this launch, PharmaMar has undertaken further significant investment in our people, research, commercial operations and facilities. For example, our R&D spending in 2002 increased by 35.5% to €42 million compared with the previous year.

PharmaMar is proud to report the key events and issues of 2002:

**Progress with our Lead Compound Yondelis**

**Other Compounds in Clinical Development**

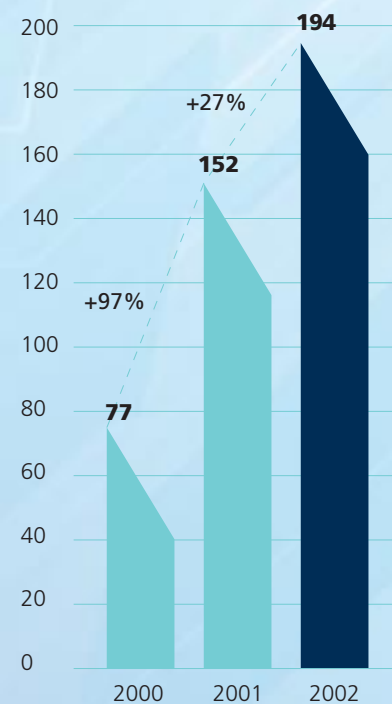
**Scientific Communications during 2002**

**Further Research at PharmaMar**

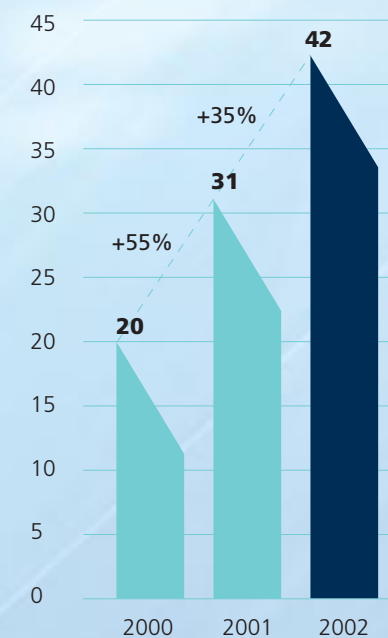
**PharmaMar — an International Organization**



**Total Assets**  
Million Euros



**Investment in Research and Development**  
Million Euros



## Progress with our Lead Compound Yondelis™

Yondelis is a new anti-tumour drug developed by PharmaMar, derived from the marine organism, *Ecteinascidia turbinata*, a 'sea squirt'. Since September 2001, the efficacy and safety of Yondelis has been further researched jointly by PharmaMar and Ortho Biotech Products L.P. Yondelis has shown activity against a number of advanced cancers, most significantly in soft tissue sarcoma (STS) in three multicentre Phase II clinical trials. A pooled analysis of these pivotal trials showed Yondelis to be generally well tolerated with a 6-month progression-free survival rate of 27.2%, a median survival time of 10.2 months and an overall 1-year survival rate of 40% in these pretreated patients.<sup>1</sup> Objective responses were seen in 9.4% of patients, and 38.9% achieved disease stabilization.<sup>1,2</sup> Yondelis is the first active drug to be developed for STS in the last 25 years.

*Yondelis "has shown promise as a new and effective treatment for soft-tissue sarcomas"*

*(Anticancer Drugs, May 2002)*

Studies of a 3-hour infusion schedule in sarcoma patients showed similar preliminary efficacy and safety data to the currently recommended infusion schedule of 24 hours, raising the possibility of using the 3-hour infusion for more convenient treatment in the future.<sup>3</sup> Weekly and low-dose sub-toxic treatment regimens are currently being investigated.

*STS is a malignant tumour of soft tissues, such as fat, muscle, nerve, joint, blood vessel, or deep skin tissue. Advanced sarcoma can spread (metastasize) to other tissues such as the lungs or liver. In Western Europe about 9,000 people develop STS each year, 8,000 in the United States. STS also has a relatively high incidence rate in the paediatric population, where it accounts for 10% of all cancers. There is an urgent need for new agents to treat STS.*

Phase II studies (four initiated in 2002) are underway, evaluating the efficacy of Yondelis in ovarian, endometrial and breast cancer, as well as in adult and paediatric patients with pretreated advanced or recurrent sarcomas. Excellent interim results in ovarian cancer, a milestone achievement for PharmaMar, suggest that this might become an important target indication for Yondelis.<sup>4</sup>

Yondelis is also actively being studied in clinical trials for other solid malignancies. The results of a Phase I trial in paediatric refractory solid tumours<sup>5</sup> were so encouraging that PharmaMar will file for Phase II studies in this indication to commence in 2003.

Preclinical studies have shown that Yondelis can help overcome cisplatin resistance in human ovarian cancer cells that had been grafted into mice.<sup>6,7</sup> This synergistic effect between Yondelis and cisplatin is likely to be linked to an important part of the mechanism of action of Yondelis, the transcription-coupled nucleotide excision pathway. An advanced Phase I study of Yondelis in combination with cisplatin is being conducted in Europe and is expected to proceed to Phase II trials. Phase I clinical trials of Yondelis in combination with other established chemotherapy agents (doxorubicin, docetaxel, paclitaxel, capecitabine, oxaliplatin, carboplatin and gemcitabine) also commenced in 2002. Studies of Yondelis in ovarian cancer are continuing,

including a trial as second-line treatment in patients who did not respond to platinum-taxanes, the most frequently used first-line treatment for ovarian cancer. Preliminary results from this ongoing study indicate an overall response rate of 26% in refractory and relapsing patients, with a response rate of 54% considering the subgroup of relapsing patients.<sup>4</sup>



*"Sarcoma cell lines are exquisitely sensitive to ET-743 [Yondelis]. The drug has a unique mechanism of action that makes it a novel anti-tumour agent."*

*(Anticancer Drugs, May 2002).*

At the end of 2002, our worldwide clinical programme for Yondelis comprised nine Phase I and 20 Phase II trials for Yondelis as a single agent, and nine Phase I studies of Yondelis in combination with other chemotherapies. About 1,600 patients have now been treated with Yondelis in Europe, the USA, Canada, South Africa and South America.

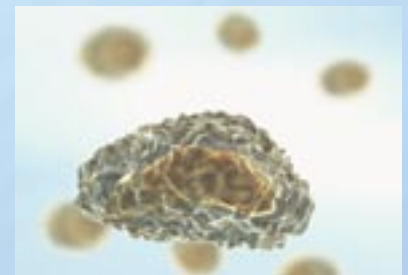
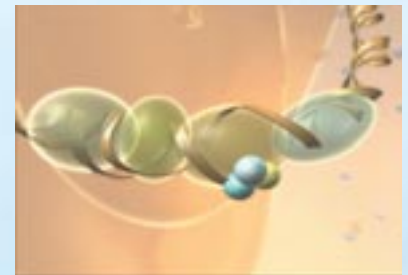
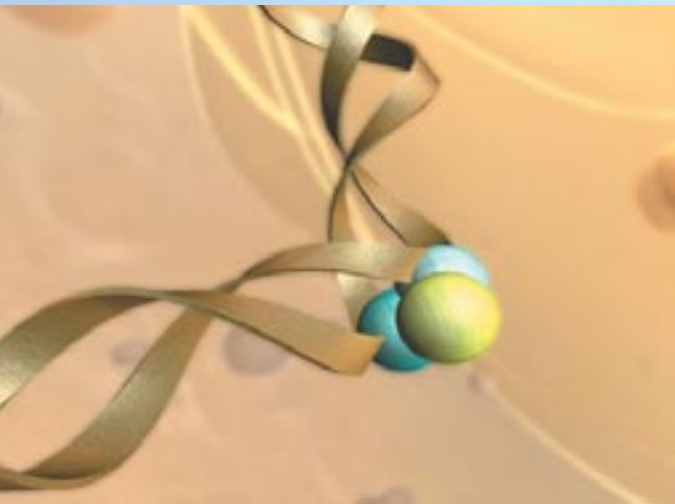
Other major landmarks for Yondelis in 2002 include: Yondelis was adopted as the global trademark name for ET-743, for both PharmaMar and Ortho Biotech Products L.P.

PharmaMar received a milestone payment (\$5 million) from Ortho Biotech Products L.P., for target achievement of Yondelis in development. Our co-development agreement with Ortho Biotech Products L.P. has significantly accelerated the pace of our clinical trials programme.

Yondelis is now in the final stages of review for marketing authorization. Once this is granted, PharmaMar will have a 10-year exclusive licence to market Yondelis for STS in the European Union. As Yondelis was developed for the treatment of STS, it was eligible for orphan drug designation and this was granted in 2001.

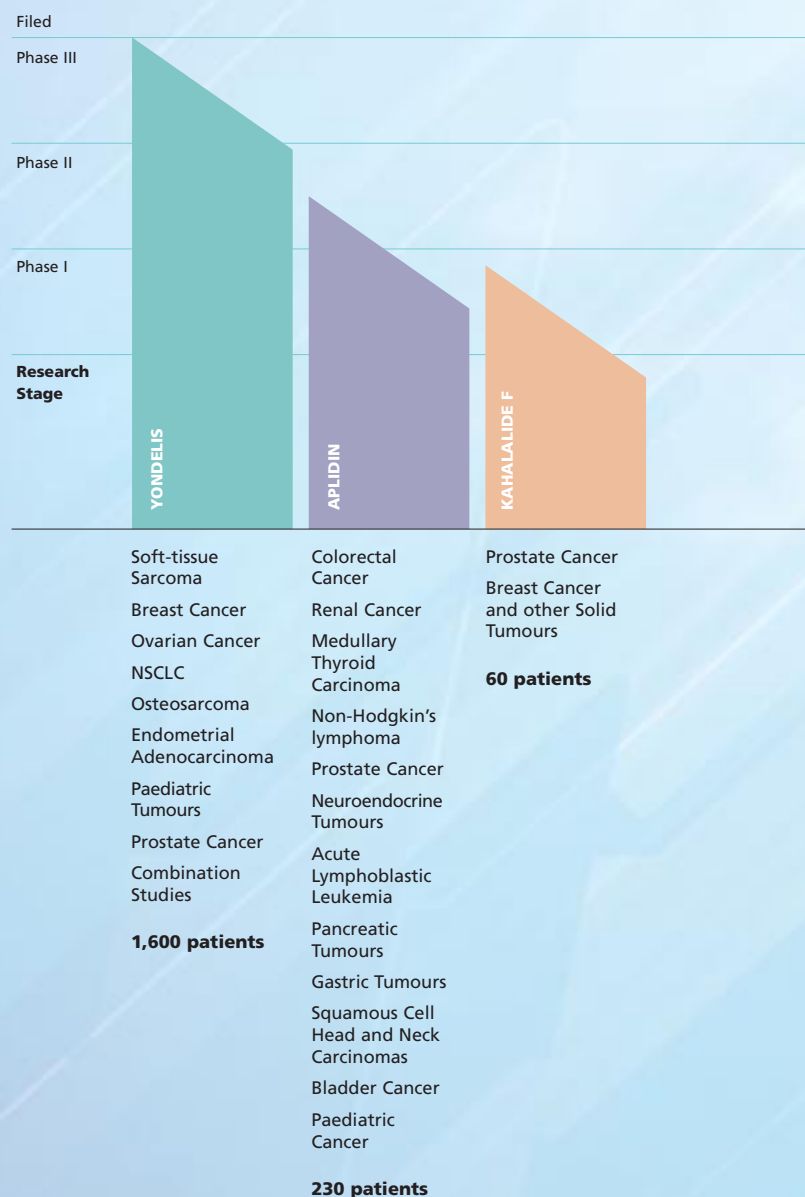
The company is overseeing the progression of Yondelis through the centralized European approval process. With the registration process for Yondelis progressing, pre-marketing activities are well underway, based on our developing local marketing presence in the key European countries.

*The broad activity spectrum of Yondelis is thought to be related to its unique mechanism of action. Unlike any other agent, Yondelis binds to the minor groove of DNA, bending the macromolecule towards the major groove. Yondelis has a multicomponent mechanism of action that affects different cancer cell cycle processes in a way that no other chemotherapy does. Yondelis inhibits the activation of transcription of genes, proliferation of tumour cells and the transcription-coupled nucleotide excision repair pathways. The net result is to prevent the tumour cell from replicating, or to induce apoptosis (death of the tumour cell). This multi-component mechanism of action of Yondelis, affecting different cell cycle processes, makes it a significant new agent for use as monotherapy or in combination with other agents.*



## Other Compounds in Clinical Development

### Clinical Development



As concerted efforts are now being dedicated to developing follow-up products for Yondelis, 2002 was a very busy and successful year for the clinical R&D department. This department oversees the design, management and data analysis of all phases of clinical trials.

### Aplidin®

PharmaMar's second compound in development, Aplidin, derived from the tunicate, *Aplidium albicans*, is currently undergoing Phase II clinical trials in colorectal and renal cancer and medullary thyroid carcinoma (MTC). To date, over 230 patients have been treated with this compound, in five Phase I and two Phase II trials.

Phase II clinical trials of Aplidin commenced in October 2001. Other studies planned to start in 2003 include Phase II trials in neuroendocrine tumours, non-Hodgkin's lymphoma, pancreatic carcinoma, head and neck tumours, gastric, bladder, small cell lung and non-small cell lung cancer and melanoma. Phase I studies particularly noted activity of Aplidin in neuroendocrine tumours and MTC.<sup>8</sup> In all studies conducted so far, no bone marrow toxicity has been reported.

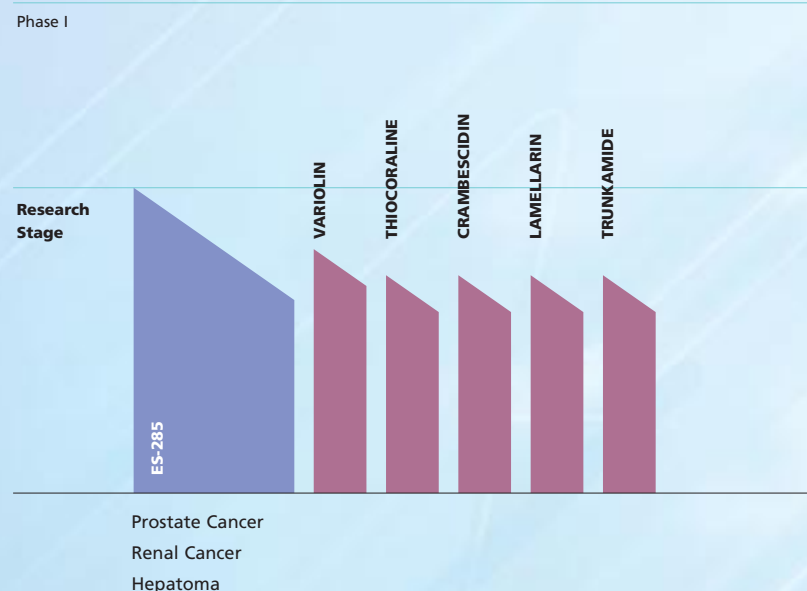
In preclinical trials, Aplidin showed potent anti-tumour activity against other tumour types including leukaemia and lymphoma.<sup>9,10</sup> In one study, high levels of Aplidin did not appear to induce significant haematotoxicity – a very reassuring and noteworthy finding regarding safety of the drug – indicating its potential in combination therapy. Aplidin has

also been found to display anti-angiogenic activity, which may be significant for its possible use against solid tumours that depend on blood vessel proliferation.<sup>11</sup> Overall, Aplidin has shown selectivity for certain cancer cell lines versus normal cells, suggesting a wide therapeutic window.

Phase I studies into childhood leukaemia are also planned for 2003.

*Aplidin induces a very rapid apoptosis, combined with blocking of cell division in the G1/G2 phase of the cell cycle in tumour cells. It also inhibits the secretion of vascular endothelial growth factor (VEGF), a crucial protein involved in the vascularization and growth of a number of tumours, and the expression of the VEGF receptor 1 (VEGFR1). The combination of these diverse mechanisms clearly differentiates Aplidin from other known anti-cancer agents.*

## Preclinical Development



## Kahalalide F

Kahalalide F is PharmaMar's third most advanced anti-tumour compound. An extract of the marine mollusc, *Elysia rufescens*, Kahalalide F displays a unique anti-tumour cytotoxicity pattern that differs from any other chemotherapeutic agent, and it is now clear that it possesses a broad activity spectrum. *In vitro* data suggest that Kahalalide F is active against breast, lung, ovarian and colon cancer cells as well as chondro- and osteo-sarcoma cells.

Kahalalide F is currently completing Phase I clinical trials and PharmaMar plans to initiate Phase II studies in 2003. Promising data in advanced solid tumour<sup>12</sup> and androgen-resistant prostate cancer<sup>13</sup> have been reported, suggesting a positive therapeutic index for Kahalalide F. The recommended doses for future studies have now been established.

Results of initial pharmacokinetic studies indicate rapid clearance of this compound, which is beneficial since it will permit serial dosing to enhance its efficacy in patients. Kahalalide F possesses a favourable safety profile: in contrast to many other chemotherapies, it exhibits no bone marrow or renal toxicity, mucositis, alopecia or cumulative toxicity. Improvements in symptoms, disease stabilization or minor partial responses were seen over a wide range of cancer types, making it an exciting agent for future development. At the end of 2002, more than 60 patients have been treated with Kahalalide F.

*Studies into the mechanism of action indicate that Kahalalide F alters the function of the lysosomal membrane, distinguishing it from all other known anti-tumour agents. In vivo studies have shown that Kahalalide F induces cell necrosis and shows in vitro selectivity for tumour compared to normal cells. The cytotoxic activity of Kahalalide F is mediated by neither mRNA and protein synthesis de novo, nor caspase activation.*

## ES-285

ES-285, the fourth clinical candidate in PharmaMar's pipeline, was originally isolated from the clam, *Mactromeris polynyma*. Preclinical studies have shown selective anti-tumour activity against hepatoma, prostate and renal cancer cells in human tumour models. *In vivo* activity has also been observed in human xenograft models of melanoma and prostate cancer. ES-285 is set to enter Phase I clinical trials in 2003 for advanced malignant solid tumours.

In line with PharmaMar's strategy to develop synthetic routes for its drugs in development, a synthetic process for the production of ES-285 has been developed.

*ES-285 is thought to inhibit the activity of the GTP-binding protein rho, leading to disruption of the intracellular actin fibres of the cytoskeleton. Rho plays a major role in the migration and adhesion processes that facilitate tumour metastasis.*

## Scientific Communications and Initiatives during 2002

As PharmaMar continues to develop into a biopharmaceutical leader in oncology, our presence at, and commitment to, international congresses has grown. PharmaMar has featured significantly at several major USA and EU cancer congresses during 2002, including the annual meeting of the American Society of Clinical Oncology (ASCO) – the most prestigious event in the oncologist calendar. Symposia, press conferences, and educational meetings were all used to communicate the decisive progress represented by Yondelis. In particular, there has been real interest in the latest Yondelis clinical trial results and the implications for patients, as reflected by the attendance at the PharmaMar symposia. However, we also communicated significant progress with our other compounds.



### **The American Association for Cancer Research (AACR) – 93rd annual meeting, San Francisco, California (USA)**

Data presented indicate that Yondelis has a low potential for cross-resistance to other commonly used chemotherapy. Other studies show that Yondelis inhibits the growth of model human bone cancer (osteosarcoma xenografts), shows synergistic or additive effects with cisplatin in cancer cell lines, and in some tumour models causes comparatively little damage to red blood-cell-forming (haematopoietic) stem cells, implying that the drug may not produce long-term bone marrow toxicity.

Two reports of the effects of Aplidin in *in vitro* studies of childhood leukaemia and evidence of anti-neoplastic and anti-angiogenic properties were presented. In these studies Aplidin demonstrated selectivity towards leukaemic cells over normal blood cells at concentrations that are safely reachable in human plasma. A lack of *in vitro* cross-resistance was noted between Aplidin and nine other cytostatic drugs frequently used in childhood leukaemia.

### **American Society of Clinical Oncology (ASCO) – 38th annual meeting, Orlando, Florida (USA)**

Six abstracts were presented on Yondelis including studies in ovarian cancer, paediatric and adult solid tumours, osteosarcoma and STS. In particular we highlighted the positive outcomes from the Phase II studies of Yondelis in ovarian cancer and in refractory or relapsed ovarian cancer using a 3-hour infusion schedule.

Promising results from Phase I studies of Aplidin in solid tumours and Kahalalide F in androgen-resistant prostate cancer were also reported.

### **European Association for Cancer Research (EACR), Granada (Spain)**

There was an enthusiastic audience at the PharmaMar symposium 'Exploring the potential of the sea: new drugs with new action mechanisms'.

Preclinical data on the novel mechanisms of action of Yondelis, Aplidin and Kahalalide F were presented at this key European oncology meeting.

### **International Society of Paediatric Oncology (SIOP) 24th Annual Meeting, Oporto (Portugal)**

Early positive results in paediatric oncology were presented for Yondelis and Aplidin. These included two reports on the effects of Aplidin in *in vitro* studies of childhood leukaemia and evidence of anti-neoplastic and anti-angiogenic properties. In these studies Aplidin demonstrated selectivity towards leukaemic cells over normal blood cells at concentrations that are safely reachable in human plasma. A lack of *in vitro* cross-resistance was reported between Aplidin and other cytostatic drugs frequently used in childhood leukaemia.





**European Society for Medical Oncology (ESMO) – 27th Congress, Nice (France)**

An overview of safety and efficacy of Yondelis in STS was presented at the PharmaMar-supported ESMO satellite symposium 'Managing Soft Tissue Sarcoma: Can we do more?' and the oncology community received this with huge interest.

Encouraging results for PharmaMar's second lead compound, Aplidin, in both medullary thyroid carcinoma and paediatric leukaemia, were also reported. The effects of Aplidin in *in vitro* studies of childhood leukaemia and evidence of anti-neoplastic and anti-angiogenic properties were the subjects of two reports presented. Aplidin demonstrated selectivity towards leukaemic cells over normal blood cells at concentrations that are safely tolerated in human plasma.

Positive outcomes from Phase II studies of Yondelis in ovarian cancer and in refractory or relapsed ovarian cancer using a 3-hour infusion schedule were also reported. Studies of Yondelis in ovarian cancer are continuing, including patients with failure of platinum-taxanes – the drugs most frequently used for treating ovarian cancer.

**Molecular Targets and Cancer Therapeutics – 14th EORTC-NCI-AACR, Frankfurt (Germany)**

Positive preclinical data were presented on the anti-tumour activity of Yondelis in combination with cisplatin; this poster elicited particular interest from the scientific community and international press.

Phase I data for Kahalalide F were also reported at the symposium 'Molecular Targets and Cancer Therapeutics'. The results were from dose-finding Phase I studies using Kahalalide F, administered as weekly 1-hour intravenous infusions at different dose levels, in advanced solid tumours.

Preclinical data on Variolin B (an early pipeline compound) were also presented at this symposium. Variolin B showed potent cytostatic and cytotoxic effects in a number of human leukaemic, ovarian and intestinal carcinoma cell lines, and was also effective in a multi-drug resistant intestinal carcinoma cell line at nanomolar concentrations.



“...we added 29 completely new, chemically unique molecules to our substantial library...”



## Further Research at PharmaMar

Despite the advancement of our lead compounds, our underlying drug discovery efforts continue to increase and we constantly strive to identify future candidates for development. In 2002 alone we added 29 completely new chemically unique molecules to our substantial library of marine compounds. As a result we have now identified more than 150 marine-derived compounds with potential anti-tumour activity as candidates for clinical testing. By synthetically modifying our most potent marine-derived anti-tumour agents, we have greatly expanded the pool of potential new medicines from which we can draw.

We have also added 9,000 new specimens to our collection of marine organisms, extending the library of marine organisms to more than 39,000 by the end of 2002. Our pioneering research endeavours resulted in the protection of nine entirely new inventions and applications for eight international and 94 Spanish patents in 2002. Our patent portfolio, overseen by the Technology and Intellectual Property department, now encompasses more than 900 patent applications, of which more than half have already been granted.

PharmaMar's extensive preclinical pipeline includes several promising candidate drugs in late-stage, preclinical evaluations, including Thiocoraline (from *micromonospora marina*) and the sponge-derived compound Variolin B as well as Crambescidin and members of the Lamellarin, Miriaporona, and Trunkamide families of molecules. In 2002, a further seven new families of compounds have been selected for *in vivo* testing.

In addition to compound discovery, PharmaMar has also developed a number of new biological *in vitro* assays and optimized screening facilities to significantly increase the throughput and thoroughness of first-stage testing for anti-tumour activity. Expansion of the preclinical facilities in PharmaMar Boston (USA) enables the more efficient assessment of further advanced anti-tumour compounds in an *in vivo* setting.



## **PharmaMar** — an International Organization

*PharmaMar utilizes an extensive international research collaboration to maximize the potential for its new compounds — currently more than 60 oncology centers participate worldwide.*



During 2002, PharmaMar has furthered its transition from a successful research company to an established biopharmaceutical company by investment in a European marketing structure – in preparation for the successful launch of Yondelis in 2003.

PharmaMar's Commercial Operations division ensures that we are optimally positioned to take maximum advantage at launch. We have appointed country managers and specialist sales forces in Germany, France, Italy, Spain and the UK who have performed a comprehensive market assessment and who have built a strong network with centres of excellence in oncology. To ensure continuity in our marketing strategy, a pre-marketing programme has already been developed for Aplidin and Kahalalide F.

Pricing and reimbursement strategies for Yondelis in the European key markets are already being established by our new pricing and health economics team.

The work of our Industrial Operations department has also been critical in ensuring an effective supply chain for PharmaMar's products, especially in the production and the quality control of the raw materials and active ingredients for Yondelis.

Our highly qualified workforce grew once again in 2002. Over the past year we have recruited more than 60 experienced staff, bringing our head count to a total of 261, a growth of more than 30% over 2001.

As an innovative and dynamic company, PharmaMar has recruited the brightest and the best staff, who mirror the company's philosophy of innovation with responsibility. Our staff share our vision of providing exciting new therapies for people living with cancer, and their ingenuity and enthusiasm will continue to make PharmaMar a success.

As we move into 2003 we are confident that, with the strength of our international staff, allied to our ongoing commitment to deliver commercial success and a developing pipeline, PharmaMar will continue to demonstrate its presence as a major new force in biopharmaceuticals via further significant and impressive achievements.

## References

1. Le Cesne A, *et al.* Consistent evidence of activity of ecteinascidin (ET-743) in pretreated, advanced, soft tissue sarcoma (ASTS): results from a pooled analysis of three pivotal phase II clinical trials (P2CT) and safety profile of a 24 h infusion schedule. *Eur J Cancer* 2001; **37,Suppl 6**: abstract 114.
2. Cvetkovic RS, *et al.* ET-743. *Drugs* 2002; **62**:1185–1192.
3. George S, *et al.* Phase II study of ecteinascidin-743 (ET-743) given by 3-hour IV infusion in patients (pts) with soft tissue sarcomas (STS) failing prior chemotherapies. Proceedings 2002 annual meeting ASCO, abstract 1630.
4. Sessa C, *et al.* Phase II study of salvage ET-743 given as 3-hr infusion in ovarian cancer (OC) patients. *Ann Oncol* 2002; **13**:109, abstract 397O.
5. Baruchel S, *et al.* A Phase I study of ET-743 in pediatric refractory solid tumors: a Children's Oncology Group Study. Proceedings 2002 annual meeting ASCO abstract 381.
6. D'Incalci M, *et al.* In human tumor xenografts the resistance to ET-743 or to cisplatin can be overcome by giving the two drugs in combination. *Eur J Cancer* 2002; **38,Suppl 7**:S34, abstract 97.
7. D'Incalci M, *et al.* The combination of ET-743 and cisplatin (DDP). From a molecular pharmacology study to a phase I clinical trial. Proceedings 2002 annual meeting AACR abstract 404.
8. Raymond E, *et al.* Activity of aplidine, a new marine compound, against medullary thyroid carcinoma (MTC): Phase I trials as screening tool for rare tumors. *Ann Oncol* 2002; **13,Suppl 5**: 22, abstract 79P.
9. Jimeno JM, *et al.* Translational studies supporting the clinical development of Aplidine (APL) in pediatric leukemia. *Ann Oncol* 2002; **13,Suppl 5**:19, abstract 65P.
10. Bresters D, *et al.* Different cytotoxic activity in vitro of Aplidin in pediatric and normal bone marrow and blood samples. Proceedings 2002 annual meeting AACR abstract 4579.
11. Taraboletti G, *et al.* Antineoplastic and antiangiogenic activity of aplidine, a new agent of marine origin. Proceedings 2002 annual meeting AACR abstract 886.
12. Ciruelos E, *et al.* A phase I clinical and pharmacokinetic study with Kahalalide F (KF) in patients (pts) with advanced solid tumours (AST) with a continuous weekly (W) 1-hour iv infusion schedule. *Eur J Cancer* 2002; **38,Suppl 7**:S33, abstract 95.
13. Schellens JH, *et al.* Phase I and pharmacokinetic study of Kahalalide F in patients with advanced androgen resistant prostate cancer. ASCO abstract 451.