Drugs of the Future 2010, 35(4): 287-296
Copyright © 2010 Prous Science, S.A.U. or its licensors. All rights reserved.
CCC: 0377-8282/2010
DOI: 10.1358/dof.2010.35.4.1497635

MONOGRAPH

ELISIDEPSIN

Antineoplastic Agent

Rec INN

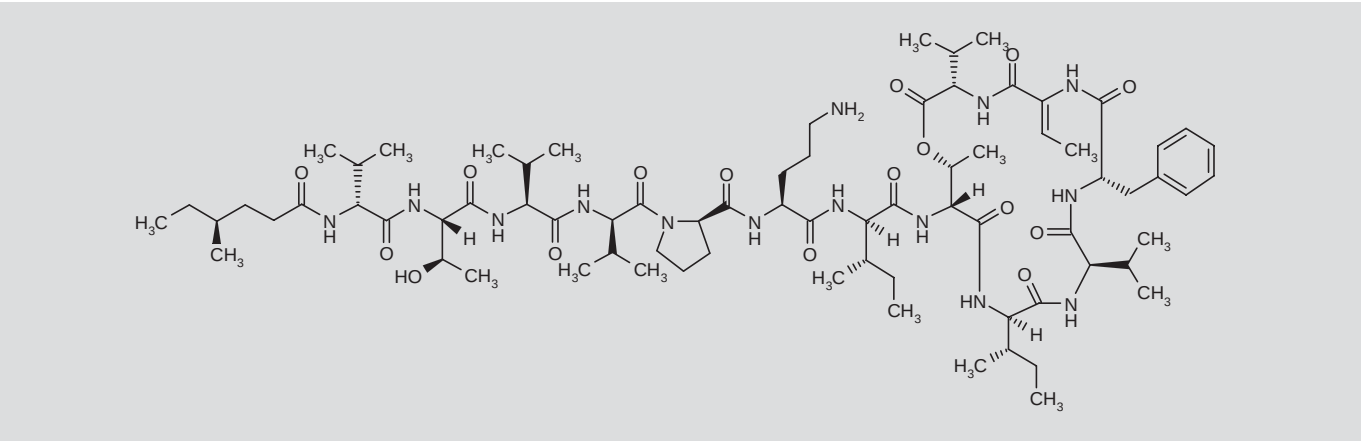
PM02734
Irvalec®

1-[*N*-[(4*S*)-4-Methyl-1-oxohexyl]-D-valine]kahalalide F

N-[4(S)-Methylhexanoyl]-D-valyl-L-threonyl-L-valyl-D-valyl-D-prolyl-L-ornithyl-D-*allo*-isoleucyl-D-*allo*-threonyl-D-*allo*-isoleucyl-D-valyl-L-phenylalanyl-[2-amino-2(*Z*)-butenoyl]-L-valine *C*-1.13-*O*-3.8-lactone

(4*S*)-5-[[(1*R*,2*S*)-1-[[(3*S*,6*Z*,9*S*,12*R*,15*R*,18*R*,19*R*)-9-Benzyl-6-ethylidene-3,12-diisopropyl-19-methyl-15-[(1*S*)-1-methylpropyl]-2,5,8,11,14,17-hexaoxo-1-oxa-4,7,10,13,16-pentaazacyclononadecan-18-yl]amino]carbonyl]-2-methylbutyl]amino]-4-[[[(2*R*)-1-[(2*R*,5*S*,8*S*,11*R*,16*S*)-8-[(1*R*)-1-hydroxyethyl]-2,5,11-triisopropyl-16-methyl-4,7,10,13-tetraoxo-3,6,9,12-tetraazaoctadec-1-anoyl]pyrrolidinyl]carbonyl]amino]-5-oxo-1-pentanamine

InChI: 1S/C75H124N14O16.C2HF3O2/c1-20-43(15)33-34-53(91)80-54(38(5)6)68(97)87-61(46(18)90)72(101)82-56(40(9)10)69(98)83-57(41(11)12)74(103)89-36-28-32-52(89)66(95)78-50(31-27-35-76)64(93)85-59(44(16)21-2)71(100)88-62-47(19)105-75(104)58(42(13)14)84-63(92)49(23-4)77-65(94)51(37-48-29-25-24-26-30-48)79-67(96)55(39(7)8)81-70(99)60(45(17)22-3)86-73(62)102;3-2(4,5)1(6)7/h23-26,29-30,38-47,50-52,54-62,90H,20-22,27-28,31-37,76H2,1-19H3,(H,77,94)(H,78,95)(H,79,96)(H,80,91)(H,81,99)(H,82,101)(H,83,98)(H,84,92)(H,85,93)(H,86,102)(H,87,97)(H,88,100);(H,6,7)/b49-23-;/t43-,44-,45-,46+,47+,50-,51-,52+,54+,55+,56-,57+,58-,59+,60+,61-,62+;/m0./s1



$C_{75}H_{124}N_{14}O_{16}$
Mol wt: 1477.8713
CAS: 681272-30-0
CAS: 915713-02-9 (trifluoroacetate)
EN: 408542

C. Coronado, C.M. Galmarini, V. Alfaro and A. Yovine. PharmaMar S.A., Avenida de los Reyes 1, Polígono Industrial La Mina-Norte, 28770 Colmenar Viejo, Madrid, Spain. E-mail: ayovine@pharmamar.com.
*Synthesis prepared by R. Pandian, J. Bolós and R. Castañer. Thomson Reuters, Provença 388, 08025 Barcelona, Spain.

SUMMARY

Elisidepsin (Irvalec®, PM02734) is a depsipeptide produced by chemical synthesis and chosen for development as an antineoplastic agent based on its in vitro activity against human solid tumor cell lines, in vivo activity in hollow fibers and xenografted human tumors, as well as its acceptable preclinical toxicology profile. Elisidepsin causes a typical necrotic cell death and induces profound alterations in tumor cell morphology. The compound is currently under clinical evaluation in four phase I trials: two as a single-agent i.v. infusion and evaluating three every-3-week (q3wk) schedules: 30 min, 3 h and 24 h; two in combination with erlotinib; and another in combination with carboplatin or gemcitabine. On the basis of the previous phase I/II experience with a

related compound, kahalalide F, an ongoing phase II clinical trial is currently evaluating elisidepsin over 30 min q3wk in patients with squamous non-small cell lung cancer. Furthermore, the finding of one complete response and cases of long-lasting stable disease in phase I trials has prompted a phase Ib/II trial in patients with advanced/metastatic esophageal, gastric or gastroesophageal junction cancer.

SYNTHESIS*

Elisidepsin is prepared by two related synthetic methods.

Coupling of polypeptide derivative (I) with the cyclic depsipeptide (II) in the presence of PyAOP and DIEA in DMF yields the side chain-protected elisidepsin (III) (1), which is then deprotected by means of TFA in CH_2Cl_2 (1-3). The protected precursor (III) is alternatively obtained by cyclization of the branched depsipeptide (IV) by means of DIC, HOBt and DIEA in CH_2Cl_2 (2, 3). Scheme 1.

The linear hexapeptide building block (I) is prepared by solid-phase peptide synthesis as follows. Attachment of Fmoc-Orn(Boc)-OH (V) to 2-chlorotrityl chloride (CTC) resin using DIEA in CH_2Cl_2 gives the resin-bound protected ornithine (VI), whose Fmoc group is selectively removed with piperidine in DMF, yielding Orn(Boc) resin (VI). Sequential couplings with the protected amino acids Fmoc-D-Pro-OH (VIII), Fmoc-D-Val-OH (X), Fmoc-L-Val-OH (XI), Fmoc-L-Thr(*t*-Bu)-OH (XIII) and Fmoc-D-Val-OH (X) by means of DIC and HOBt, each followed by the corresponding Fmoc deprotection steps with piperidine in DMF, provides the intermediate peptide resins (IX), (XII) and (XIV). Then, coupling of peptide resin (XIV) with 4(*S*)-methylhexanoic acid (XV) in the presence of DIC and HOBt, followed by cleavage from the solid support by treatment with TFA in CH_2Cl_2, affords the target intermediate (I) (1). Scheme 2.

Preparation of the cyclic depsipeptide derivative (II) starts with the attachment of Fmoc-D-Val-OH (X) onto 2-chlorotrityl chloride resin by means of DIEA in CH_2Cl_2 to give resin-bound Fmoc-D-valine (XVI), which is then deprotected with piperidine in DMF, yielding D-valine resin (XVII). Stepwise couplings of resin-bound D-valine (XVII) with Fmoc-D-*allo*-Ile-OH (XVIII) and Fmoc-D-*allo*-Thr-OH (XIX) by means of DIC and HOBt in DMF, each followed by Fmoc deprotection with piperidine, and then coupling again with Fmoc-D-*allo*-Ile-OH (XVIII), leads to tetrapeptide resin (XX). The side chain hydroxyl of threonine (XX) is then esterified with Alloc-D-valine (XXI) in the presence of DIC, DIEA and DMAP to furnish depsipeptide resin (XXII) (1, 3, 4). After selective removal of the *N*-Alloc group of (XXII) utilizing $Pd(PPh_3)_4$ and $PhSiH_3$, amide coupling with Alloc-Phe-*Z*-Dhb-OH (XXIII) (prepared by solution-phase coupling of Alloc-L-Phe-OH [XXIV] with threonine *tert*-butyl ester [XXV] by means of EDC and DIEA in CH_2Cl_2, followed by dehydration in the presence of EDC and CuCl and *tert*-butyl ester cleavage with TFA/CH_2Cl_2/H_2O) in the presence of DIC and HOAt in DMF yields the fully protected linear intermediate (XXVI). Protecting group exchange in (XXVI) by removal of the Fmoc group with piperidine and then treatment with Boc_2O and DIEA in DMF, followed by *N*-Alloc deprotection with $Pd(PPh_3)_4$ and $PhSiH_3$, and peptide cleavage from the resin with TFA in CH_2Cl_2, gives rise to (XXVII). Subsequent cyclization of the partially protected peptide (XXVII) in the presence of HOBt and DIEA, and *N*-Boc deprotection by means of TFA in H_2O, affords the desired intermediate (II) (1). Scheme 3.

For the preparation of intermediate (IV), depsipeptide resin (XXII) is Fmoc-deprotected with piperidine in DMF, followed by coupling with Fmoc-L-Orn(Boc)-OH (V) by means of either HATU/DIEA (2, 4) or DIC/HOBt (3) to produce (XXVIII). Sequential incorporation of Fmoc-D-Pro-OH (VIII), Fmoc-D-Val-OH (X), Fmoc-L-Val-OH (XI), Fmoc-L-Thr(*t*-Bu)-OH (XIII), Fmoc-D-Val-OH (X) and 4(*S*)-methylhexanoic acid (XV) to the peptide resin (XXVIII) utilizing solid-phase peptide synthesis techniques, as above (Fmoc removal with piperidine in DMF, and couplings by means of HATU/DIEA or DIC/HOBt), leads to intermediate (XXIX) (2-4). Then, Alloc group deprotection using $Pd(PPh_3)_4$ and $PhSiH_3$, followed by amide coupling with Alloc-Phe-*Z*-Dhb-OH (XXIII) in the presence of DIC and HOAt in DMF, furnishes peptide resin (XXX) (2, 3). The open-chain depsipeptide precursor (IV) is then obtained by *N*-Alloc-deprotection in (XXX) with $Pd(PPh_3)_4$ and $PhSiH_3$, followed by cleavage from the solid support using TFA in CH_2Cl_2 (2, 3). Scheme 4.

BACKGROUND

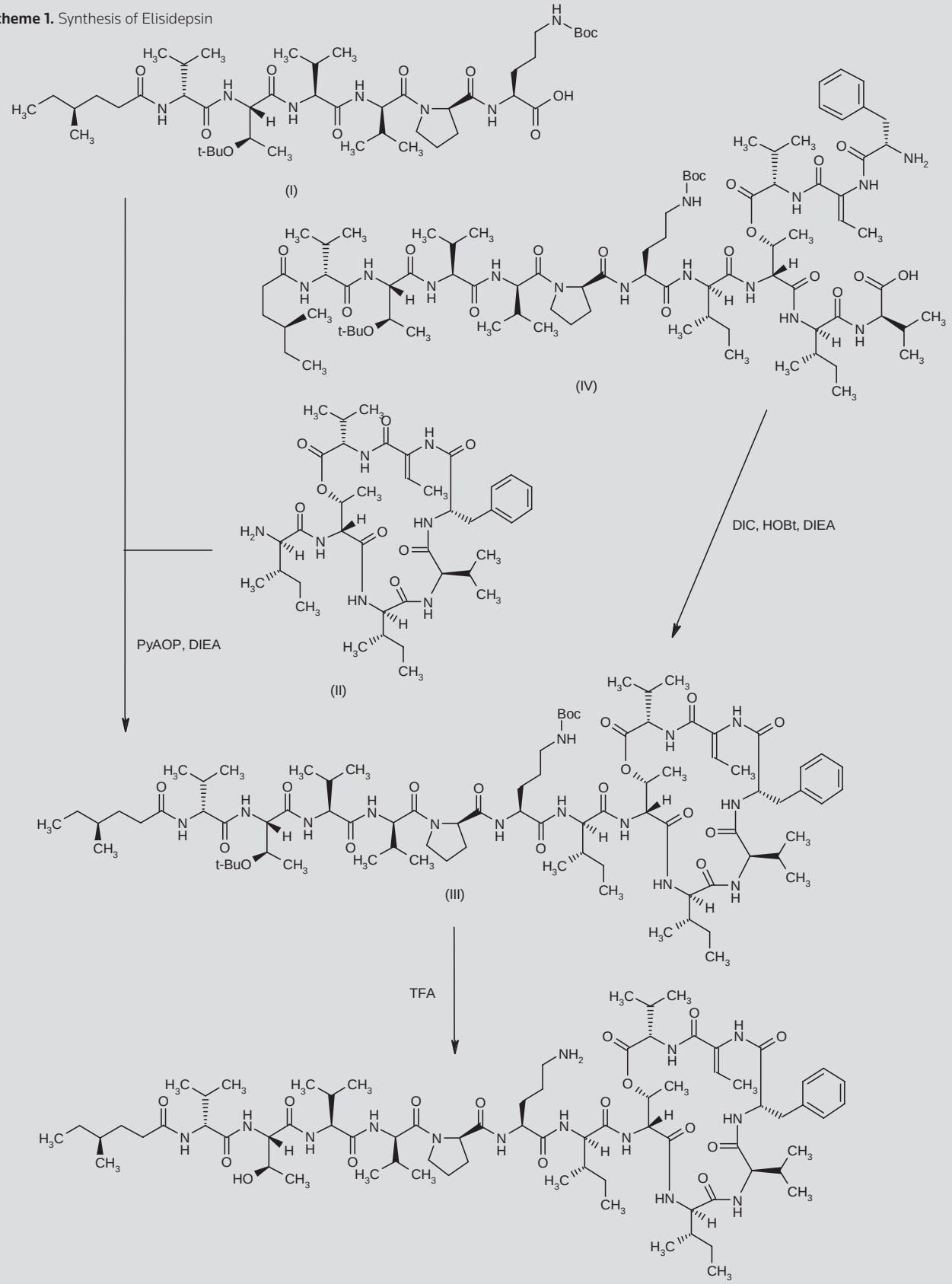
Elisidepsin (Irvalec®, PM02734) is a synthetic cyclic depsipeptide related to kahalalide F, an antitumor compound and moderately soluble marine product that belongs to a family of dehydroaminobutyric acid-containing peptides isolated from the herbivorous marine mollusk *Elysia rufescens* (5-8). Elisidepsin was selected for clinical development as an antineoplastic agent based on its in vitro activity against human solid tumor cell lines and its in vivo activity in hollow fibers (HF) and human tumor xenografts, as well as its acceptable preclinical toxicology profile.

PRECLINICAL PHARMACOLOGY

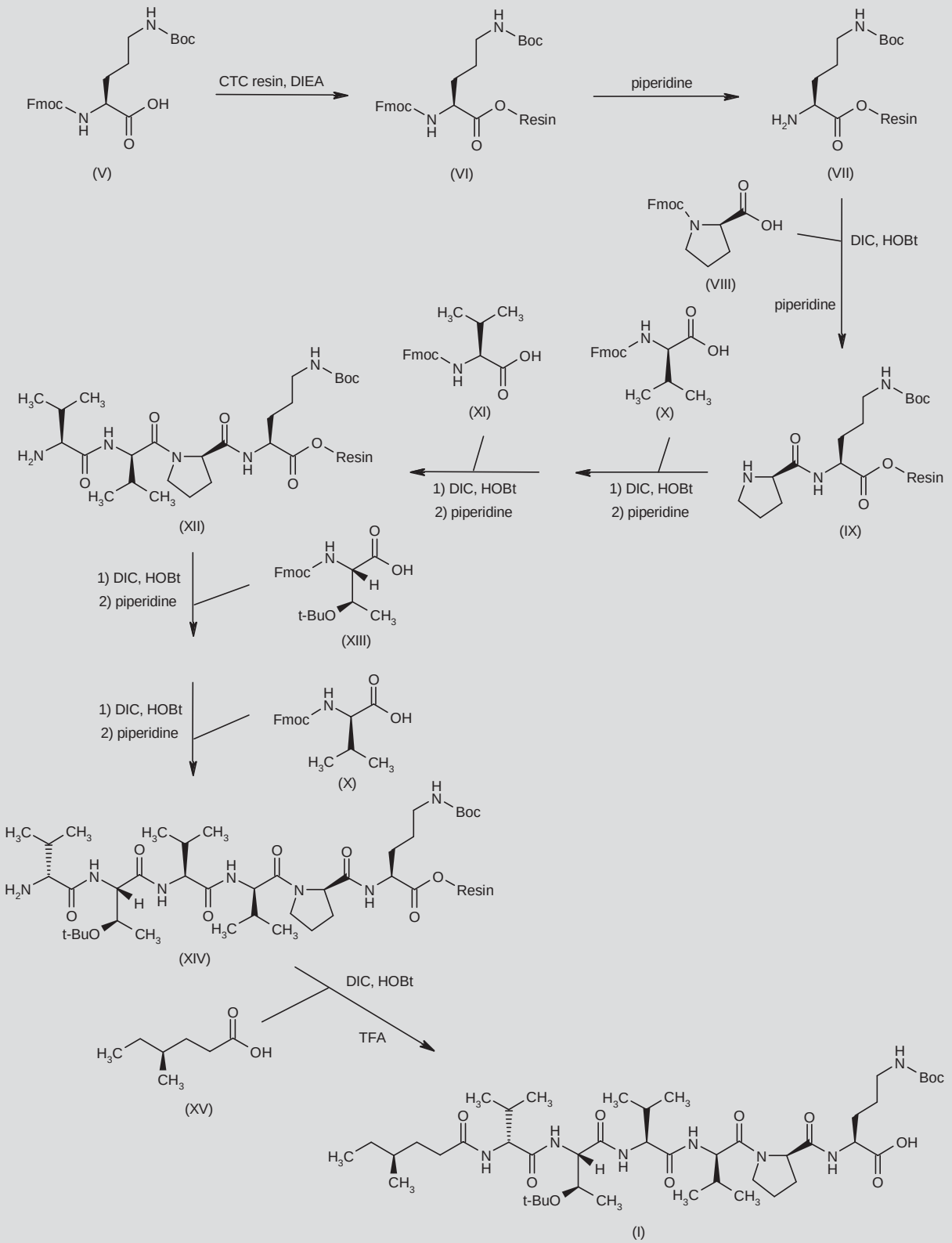
Preliminary mechanism of action investigations showed that elisidepsin neither induces cell cycle arrest nor inhibits certain recognized antitumor targets, but, however, does induce deep alterations in the morphology of tumor cells. A recent study suggested that the drug induces necrosis rather than apoptotic cell death. The treatment of tumor cells with effective concentrations of elisidepsin resulted in rapid morphological changes and membrane permeabilization, characterized by immediate internalization of propidium iodide and release of lactate dehydrogenase, as well as preloaded calcein-AM from treated cells (9). These effects were associated with the appearance of membrane blebs and severe cell swelling that finally led to cell lysis, reflecting severe membrane damage caused by the drug. Interestingly, cell membrane damage was observed only after reaching a threshold concentration. These results confirm those previously obtained in the yeast *Saccharomyces cerevisiae* (10), where cells treated with elisidepsin had rapid necrosis-like death, with accumulation of internal small vesicles.

A systematic screen of a set of 4,848 viable *S. cerevisiae* haploid deletion mutants was conducted to identify genes involved in sensitivity or resistance to elisidepsin. Several of the 76 identified genes were related to lipid metabolism or vesicle trafficking from the Golgi apparatus. A mutant strain lacking the sphingolipid fatty acyl hydroxylase SCS7 was found to be the most resistant to elisidepsin, whereas overexpression of *SCS7* rendered the cells hypersensitive. Small interfering RNA experiments were conducted in human can-

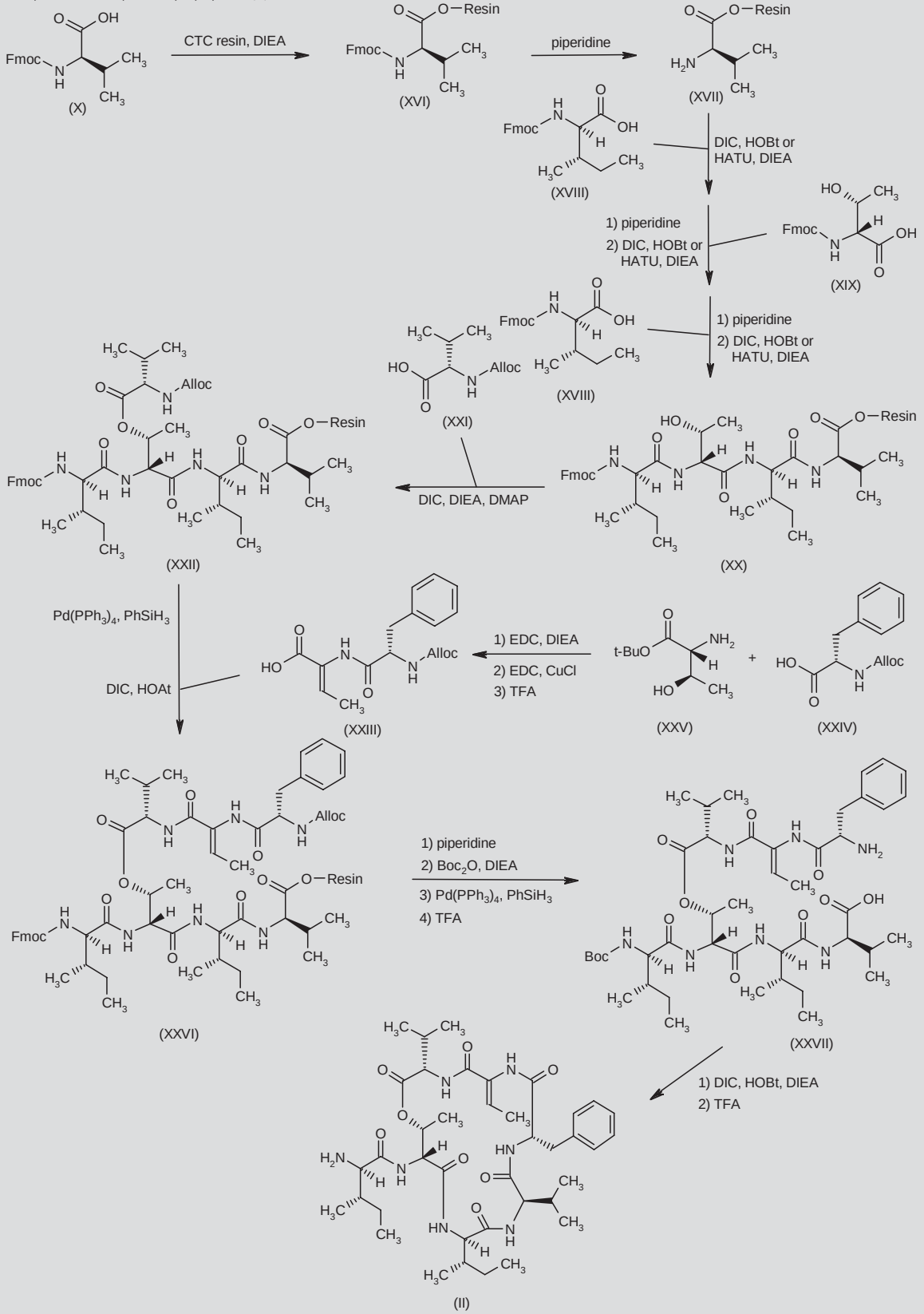
Scheme 1. Synthesis of Elisidepsin



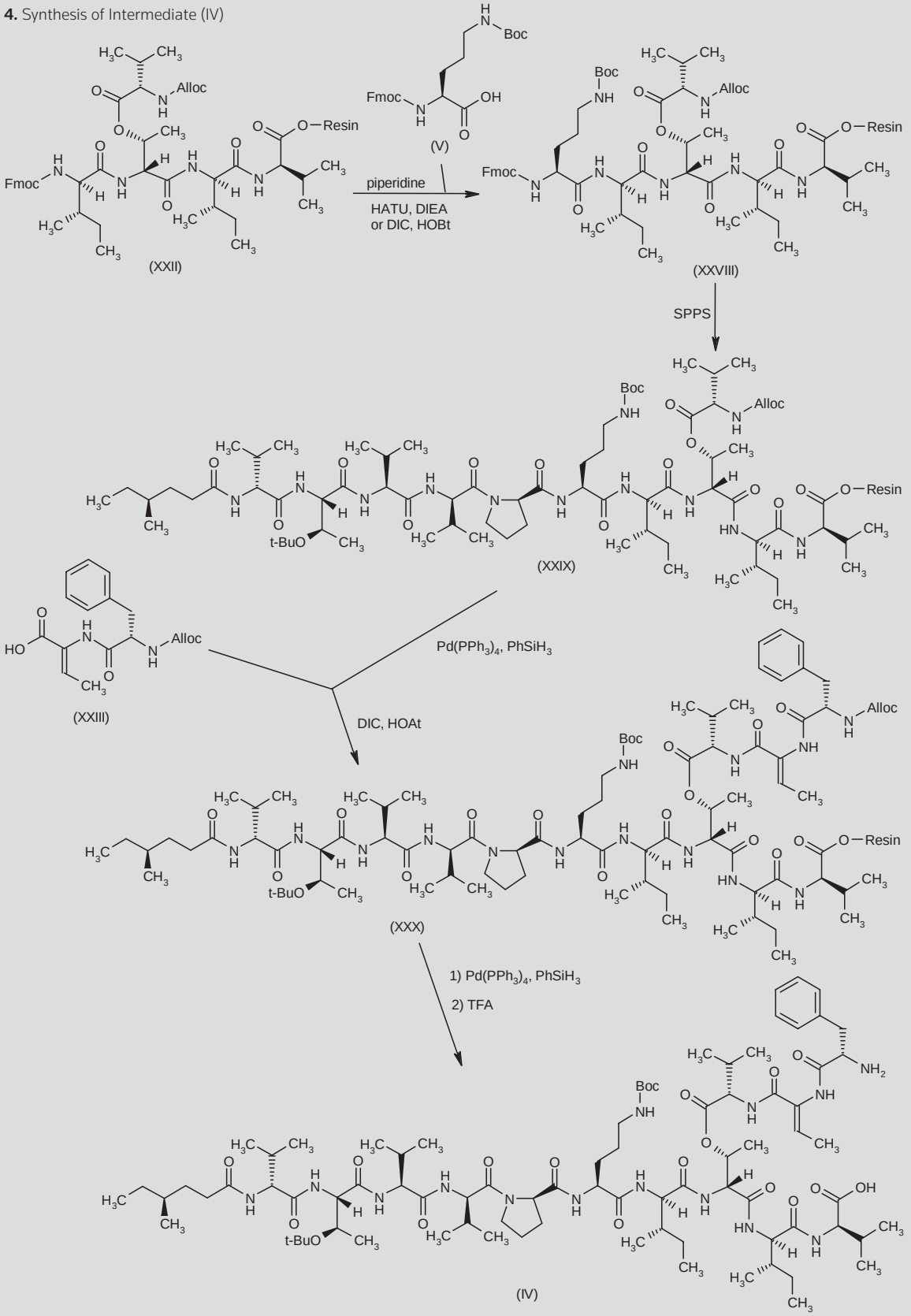
Scheme 2. Synthesis of Hexapeptide (I)



Scheme 3. Synthesis of Cyclic Depsipeptide (II)



Scheme 4. Synthesis of Intermediate (IV)



cer cell lines to silence or overexpress the *SCS7* human homologue *FA2H* (10). As in yeast, *FA2H* silencing made the cells resistant to the drug, whereas *FA2H* overexpression led to increased sensitivity. Furthermore, exogenous addition of the 2-hydroxylated fatty acid 2-hydroxypalmitic acid to different human cell lines increased their sensitivity to this cytotoxic compound. Altogether, these results suggested that elisidepsin exerts its potent necrotic cytotoxic activity by inducing rapid and severe membrane damage that appears to involve 2-hydroxy fatty acids located at the cell membrane.

With respect to molecular pharmacodynamics, in vitro studies suggested that receptor tyrosine-protein kinase erbB-3 could be associated with the greater cytotoxic activity of elisidepsin. In a panel of non-small cell lung cancer (NSCLC) cell lines, the sensitivity to elisidepsin was shown to correlate with protein expression levels of erbB receptors (11). However, the expression of erbB genes did not predict efficacy in a second panel of cell lines, although the activity of elisidepsin appeared to be related with erbB-3 expression (12). Altogether these results indicated that erbB-3 alterations after drug exposure are not involved in the mechanism of action of the compound and should be secondary and could be ascribed to cell membrane modifications induced by elisidepsin treatment.

Preliminary in vitro studies (13) identified elisidepsin as a new antiproliferative drug demonstrating activity against a broad spectrum of solid tumor types (including breast, colon, lung, neuroblastoma, prostate, sarcoma and thyroid cancer) with IC_{50} values ranging from 0.01 to 1 μM. Based on these in vitro data, in vivo experiments with HF and human tumor xenografts were peformed. In the HF system, elisidepsin demonstrated statistically significant antitumor activity against human hepatocellular carcinoma, hepatoma and pancreatic tumor cell lines. In murine xenograft models using human cell types such as breast, lung, prostate and melanoma, elisidepsin showed statistically significant activity (11, 14).

The antiproliferative effects of several combinations of elisidepsin with cytotoxics and targeted therapeutics classically used in the treatment of cancer were evaluated to support the clinical use of this compound. The effects of sequential and simultaneous exposure to elisidepsin combined with oxaliplatin, cisplatin, gemcitabine, 5-fluorouracil (5-FU), rapamycin, lapatinib and sunitinib were studied in a panel of colon, breast, ovarian, lung, prostate, head and neck, and pancreatic cancer cell lines using the MTT assay (15). Elisidepsin strongly potentiated the antiproliferative activity of platinum compounds (oxaliplatin and cisplatin), gemcitabine and targeted therapies such as rapamycin and lapatinib. The combination with sunitinib showed at least an additive effect. Another study demonstrated that tumor cell lines marginally sensitive to gefitinib and erlotinib retained sensitivity to elisidepsin, thereby suggesting a lack of or partial cross-resistance between these drugs (12).

PHARMACOKINETICS AND METABOLISM

Preclinical pharmacokinetic studies of elisidepsin after single i.v. bolus administration were conducted in CD-1 mice, Sprague-Dawley rats and beagle dogs (13, 16). For all species, the elimination kinetics of i.v. elisidepsin were multiexponential and characterized by long terminal half-lives of 35-40 h in mice and rats, and 90-100 h in dogs, thereby suggesting slow plasma clearance. No apparent gender differences were found in maximum plasma concentrations (C_{max}), area under the curve (AUC) or volume of distribution (V_d) for all species. Dose-normalized AUCs were similar in rodents (mice and rats), but higher in dogs. In all animal species V_d was higher than plasma volume, thus suggesting extensive extravascular distribution. A high degree (> 98%) of in vitro plasma protein binding was found in all species tested, including humans. Several in vitro studies were carried out to assess the biotransformation pathways of elisidepsin in animals and humans. Two different approaches were explored: microsomal-mediated metabolism and nonmicrosomal, i.e., esterase-mediated, metabolism. No degradation was observed after incubation in either plasma or microsomes.

Preliminary pharmacokinetic data from phase I clinical trials with elisidepsin (17, 18) have shown a long half-life (> 100 h in some patients), high V_d (500-1000 L), dose proportionality maintained along the studied dose range (0.090-5.467 mg/m^2), and no relevant correlation between plasma clearance and body surface area (BSA). Therefore, BSA-based dosing is no longer justified and all clinical protocols have been amended to switch to flat dose based on an average BSA of 1.8 m^2.

SAFETY

The safety evaluation of elisidepsin was carried out both in vitro (hERG assay) and in vivo using rats (Irwin test and respiratory function) and dogs (cardiovascular function). With respect to the cardiovascular system, in vitro data (15-min exposure of HEK-293 cells stably transfected with hERG cDNA) showed a similar percentage of the hERG tail current in cells exposed to 1 μM of elisidepsin compared to vehicle-treated cells. The effect of elisidepsin on cardiovascular parameters (arterial blood pressure, heart rate and lead II electrocardiogram) was evaluated in conscious, telemetered dogs from 30 min before to 6 h after dosing. No clinical signs or electrocardiogram findings were observed in any of the animals following i.v. bolus administration of placebo or elisidepsin at doses of 0.075 and 0.100 mg/kg (1.5 and 2.0 mg/m^2, respectively).

The effect on respiratory function of elisidepsin administered as a single i.v. bolus injection was assessed in rats by recording changes in respiratory rate and/or tidal volume at 15 and 60 min after administration. Intravenous elisidepsin administered to male rats (0.075 and 0.150 mg/kg; 0.45 and 0.90 mg/m^2, respectively) did not significantly affect either respiratory rate or tidal volume.

The effect of elisidepsin administration on gross behavioral and physiological state was assessed by recording changes based on the Irwin test in rats at 0-5, 20 and 120 min after administration of a single i.v. bolus injection. No changes were observed in male rats receiving doses of 0.075 and 0.150 mg/kg (0.45 and 0.90 mg/m^2, respectively).

Therefore, elisidepsin has an acceptable cardiovascular safety profile both in vitro (hERG assay) and in vivo (study in dogs) and no relevant observations were made during evaluation of respiratory function and neurotoxicity after administration to rats.

Elisidepsin was tested in rats and dogs treated i.v. both as a bolus and as a 24-h infusion in both single- and multiple-cycle studies. The maximum tolerated doses (MTDs) in rats and dogs are shown in Table I. Toxicity findings associated with elisidepsin were similar

Table I. *Maximum tolerated dose (MTD) of elisidepsin in different animal species.*

Species	Gender	MTD mg/kg (mg/m^2)	
		Single i.v. bolus	24-h i.v. infusion
Sprague-Dawley rat	Male	0.251 (1.5)	0.8 (4.8)
	Female	0.249 (1.49)	0.8 (4.8)
Beagle dog	Male	0.11 (2.2)	0.6 (12)
	Female	0.11 (2.2)	1.2 (24)

between genders both in terms of frequency and severity. The most common clinical signs associated with elisidepsin administration were vomiting, soft feces, dehydration and slight decreases in food consumption and body weight. The onset of these symptoms was 1-3 days after administration, and animals returned to normal thereafter. No evidence for a higher frequency of these symptoms occurred during multiple-cycle studies. Across species, liver and kidney were the target organs for toxicity, as noted by clinical chemistry changes evidenced by significant dose-dependent increases in alanine aminotransferase (ALT), γ-glutamyltransferase (GGT), blood urea nitrogen (BUN) and creatinine. These changes were recorded 3-4 days after administration, with an apparent tendency towards recovery on day 7. Histopathological evaluation performed during the study period, either prior to a second dose or at the end of the recovery period, demonstrated no liver alterations and only minor renal changes. No signs of accumulation in the increases in enzyme levels were seen in multiple-cycle studies, despite the use of a weekly schedule. No elisidepsin-related hematotoxicity was noted either by peripheral blood examination or by bone marrow staining (for any dose or administration schedule used). Although injection-site changes were noted predominantly in dogs receiving bolus doses (24-h infusion studies were carried out with catheterized animals), no such inflammatory changes were observed in rats. However, in a formal study in male New Zealand White rabbits, elisidepsin showed potential for causing irritation after both i.v. and perivenous administration. The mutagenic activity of elisidepsin was assessed as negative by the bacterial reverse mutation assay (dose levels tested up to 5000 mg/plate).

CLINICAL STUDIES

Two phase I trials are currently evaluating elisidepsin as a single-agent i.v. infusion in patients with advanced solid tumors (17, 18). In the first of these trials, patients were treated with a 30-min or a 3-h i.v. infusion using an q3wk schedule. Dose-limiting toxicities (DLTs) consisted of grade 3-4 asymptomatic and reversible transaminase elevations, which were associated with early plasma concentrations (17). Once the analysis of data from this first study had found no relevant correlation between plasma clearance and BSA, all ongoing clinical trials were amended to switch to a flat dose. This trial is currently evaluating a 3-h infusion schedule with BSA-independent dosing. In the second single-agent phase I trial, patients with advanced solid tumors were treated with elisidepsin as a 24-h i.v. infusion q3wk (18). DLTs consisted of grade 3 transaminase increases. Based on the safety data available, the most common elisidepsin-related adverse events were transaminase increases (mainly ALT), asthenia, nausea and pruritus. Most were grade ≤ 2. Transaminase increases were asymptomatic and transient, as they appeared approximately 48 h after dosing and lasted for < 12 days. None of these patients had treatment-related increases in other liver enzymes or liver function tests (e.g., bilirubin, alkaline phosphatase) or in coagulation tests, or acute or fatal liver failure. Hence, the available preliminary safety data for elisidepsin indicate an acceptable safety profile.

A summary of the clinical trials currently ongoing or planned with elisidepsin is shown in Table II.

As mentioned above, elisidepsin is related to kahalalide F (KF). KF showed preliminary evidence of antitumor activity in lung cancer in phase I clinical trials: of 18 patients with lung cancer, 1 (5.6%) had a minor response (tumor shrinkage of 25-50%) and 4 (22.2%) had stable disease lasting > 3 months (8, 19). Of note, of the two patients with squamous NSCLC enrolled in these phase I trials, one showed stable disease and a progression-free survival (PFS) of 3.8 months.

Based on these results, a phase II trial was conducted to assess the antitumor activity of weekly KF at the recommended dose (650 μg/m^2 by 1-h infusion) in patients with stage IIIb NSCLC and pleural effusion or stage IV NSCLC after one line of chemotherapy (20). Nine of 31 enrolled patients (29.0%) had either a partial response (n = 1) or stable disease lasting > 3 months (n = 8). The progression-free survival rate at 3 months (PFS3) found in this trial was 26.9% for patients with advanced lung cancer (mostly consisting of squamous NSCLC) pretreated with at least one prior line of platinum-based chemotherapy. This PFS3 together with the fact that almost 40% of patients with advanced lung cancer were still alive at 1 year after beginning treatment with KF in this trial, and the finding of a partial response in one very heavily pretreated (four lines of chemotherapy) squamous NSCLC patient, suggested that KF may be active in patients with pretreated NSCLC, particularly in those with squamous histology.

On the basis of previous KF experience in NSCLC and the similarities between elisidepsin and KF, a phase II trial is currently ongoing evaluating elisidepsin in patients with squamous NSCLC progressing after at least one line of platinum-based chemotherapy (8). Furthermore, two phase I trials are currently evaluating elisidepsin in combination with drugs frequently used in NSCLC, such as erlotinib, carboplatin or gemcitabine.

Preliminary evidence of activity in esophageal/gastric cancer has been reported for elisidepsin in phase I trials. One long-lasting complete response was found in a patient with a large-cell undifferentiated carcinoma of the esophagus and multiple lymph node metastases treated with elisidepsin for 24 h q3wk, with a time to progression of 31.1+ months and an overall survival of 31.3+ months at last follow-up (18). Furthermore, stable disease lasting longer than 3 months was found in one patient with esophageal cancer (17) and one patient with gastric cancer (18). On the basis of these results, a phase Ib/II trial is currently planned to be conducted in patients with unresectable, locally advanced/metastatic esophageal cancer, gastric cancer or gastroesophageal junction cancer after at least one prior line of systemic therapy. Other tumors in which stable disease lasting longer than 3 months was found in phase I trials are

Table II. *Clinical trials (ongoing or planned) with elisidepsin.*

Phase I single-agent
Elisidepsin q3wk i.v. over 30 min or 3 h (17) Planned sample size: 35 patients to find the recommended dose and at least 12 patients treated at this recommended dose
Elisidepsin q3wk i.v. over 24 h (18) Planned sample size: 35 patients to find the recommended dose and at least 12 patients treated at this recommended dose
Phase I combination
Elisidepsin for 3 h weekly in combination with daily erlotinib Planned sample size: 35 patients to find the recommended dose and at least 12 patients treated at this recommended dose
Elisidepsin in combination with carboplatin (arm A: carboplatin day 1 and elisidepsin day 1 and 8 q3wk) or gemcitabine (arm B: both drugs day 1 and 15 q4wk) Planned sample size: 35 patients to find the recommended dose in each arm (total of 70 patients) and at least 12 patients treated at the recommended dose in each arm (total of at least 24 patients)
Phase II
Eisidepsin i.v. over 30 min q3wk in patients with squamous non-small cell lung cancer Planned sample size: 20 evaluable patients.
Elisidepsin i.v. over 24 h fortnightly q4wk or over 3 h weekly q4wk in patients with advanced or metastatic esophageal or gastric cancer or gastroesophageal junction cancer Planned sample size: 40 evaluable patients in each arm (total of 80 patients)

colorectal adenocarcinoma, pancreatic cancer, pleural mesothelioma, prostate adenocarcinoma and soft tissue sarcoma.

SOURCE

PharmaMar S.A. (ES).

DISCLOSURES

The authors are employees of PharmaMar and have stock ownership in Zeltia.

REFERENCES

1. Tubby, D.G., Francesch Solloso, A., Lopez Macia, A. et al. (PharmaMar SA). *Convergent synthesis for kahalalide compounds*. EP 1749023, JP 2008506633, US 2007207948, WO 2005103072.
2. Faircloth, G.T., Elices, M., Sasak, H., Aviles Marin, P.M., Cuevas Marchante, M.D.C. (PharmaMar SA). *4-Methylhexanoic kahalalide F compound*. CA 2501089, EP 1572726, JP 2006517195, US 2006234920, US 2008119397, WO 2004035613.
3. Albericio Palomera, F., Giralt Lledo, E., Lopez Rodriguez, P. et al. (PharmaMar SA). *New antitumoral compounds*. EP 1664093, EP 1918296, JP 2007526904, US 2007117743, WO 2005023846.
4. Albericio, F., Giralt, E., Jimenez, J.C., Royo, M., Manzanares, I., Rodrigues, I., Lopez, A. (PharmaMar SA). *Kahalalide compounds*. WO 2001058934.
5. Faircloth, G., Cuevas, C. *Kahalalide F and ES285: Potent anticancer agents from marine molluscs*. Prog Mol Subcell Biol 2006, 43: 363-79.
6. Hamann, M.T., Otto, C.S., Scheuer, P.J., Dunbar, D.C. *Kahalalides: Bioactive peptides from a marine mollusk Elysia rufescens and its algal diet Bryopsis sp. (1)*. J Org Chem 1996, 61(19): 6594-600.
7. Sparidans, R.W., Stokvis, E., Jimeno, J.M., Lopez-Lazaro, L., Schellens, J.H., Beijnen, J.H. *Chemical and enzymatic stability of a cyclic depsipeptide, the novel, marine-derived, anti-cancer agent kahalalide F*. Anticancer Drugs 2001, 12(7): 575-82.
8. Provencio, M., Sanchez, A., Gasent, J., Gomez, P., Rosell, R. *Cancer treatments: Can we find treasures at the bottom of the sea?* Clin Lung Cancer 2009, 10(4): 295-300.
9. Molina-Guijarro, J.M., Moneo, V., Martínez-Leal, J.F., Cuevas, C., García-Fernández, L.F., Galmarini, C.M. *PM02734, a new marine-derived antitumoral compound, has rapid effects on membrane integrity and permeability in tumor cells.* Proc Am Assoc Cancer Res (AACR) 2009, 50: Abst 888.
10. Herrero, A.B., Astudillo, A.M., Balboa, M.A., Cuevas, C., Balsinde, J., Moreno, S. *Levels of SCS7/FA2H-mediated fatty acid 2-hydroxylation determine the sensitivity of cells to antitumor PM02734*. Cancer Res 2008, 68(23): 9779-87.
11. Ling, Y.H., Aracil, M., Jimeno, J., Perez-Soler, R., Zou, Y. *Molecular pharmacodynamics of PM02734 (elisidepsin) as single agent and in combination with erlotinib; synergistic activity in human non-small cell lung cancer cell lines and xenograft models*. Eur J Cancer 2009, 45(10): 1855-64.
12. Serova, M., Bieche, I., Astorgues-Xerri, L. et al. *Characterization of genetic factors associated with sensitivity to Irvalec, a novel marine-derived compound*. Proc Am Assoc Cancer Res (AACR) 2009, 50: Abst 857.
13. Sasak, H., Yin, J., Elices, M., LePage, D., Cuevas Marchante, C., Avilés, P., Faircloth, G. *PM02734 cytotoxicity in vitro and pharmacokinetics*. Proc Am Assoc Cancer Res (AACR) 2006, 47: Abst 1911.
14. Elices, M., Lepage, D. J., Grant, W. et al. *Activity of PM02734 against human breast and prostate tumors*. Proc Am Assoc Cancer Res (AACR) 2006, 47: Abst 1107.
15. Serova, M., Astorgues-Xerri, L., Koumaravel, J., Aracil, M., Faivre, S., Raymond, E. *Irvalec, a novel marine cyclic peptide, enhances the antiproliferative effects of other anticancer drugs in human cancer cell lines*. Proc Am Assoc Cancer Res (AACR) 2009, Abst 4569.
16. Yin, J., Aviles, P., Lee, W. et al. *Development of a liquid chromatography/tandem mass spectrometry assay for the quantification of PM02734, a novel antineoplastic agent, in dog plasma*. Rapid Commun Mass Spectrom 2006, 20(18): 2735-40.

17. Bruce, J.Y., Geary, D., de las Heras, B. et al. *Phase I study of PM02734: Association of dose-limiting hepatotoxicity with plasma concentrations*. J Clin Oncol [44th Annu Meet Am Soc Clin Oncol (ASCO) (May 30-June 3, Chicago) 2008] 2008, 26: Abst 2513.

18. Evans, T.R., Oaknin, A., Jones, R.J. et al. *Phase I dose-escalating study of PM02734 in a 24-hour infusion schedule every 21 days in advanced solid tumors*. J Clin Oncol [45th Annu Meet Am Soc Clin Oncol (ASCO) (May 29-June 2, Orlando) 2009] 2009, 27(15, Suppl.): Abst 2511.

19. Pardo, B., Paz-Ares, L., Tabernero, J. et al. *Phase I clinical and pharmacokinetic study of kahalalide F administered weekly as a 1-hour infusion to patients with advanced solid tumors*. Clin Cancer Res 2008, 14(4): 1116-23.

20. Provencio, M., Izquierdo, A., Viñolas, N., Paz-Ares, L., Feliu, J., Constenla, M.I. *Phase II clinical trial of kahalalide F (KF) as a second line therapy in patients with advanced non-small cell lung cancer (NSCLC)*. Ann Oncol [31st Eur Soc Med Oncol Congr (ESMO) (Sept 29-Oct 3, Istanbul) 2006] 2006, 17: Abst 755P.