Drugs of the Future 2010, 35(7): 547-552

CCC: 0377-8282/2010
DOI: 10.1358/dof.2010.35.7.1493928

MONOGRAPH

PALIFOSFAMIDE TROMETHAMINE

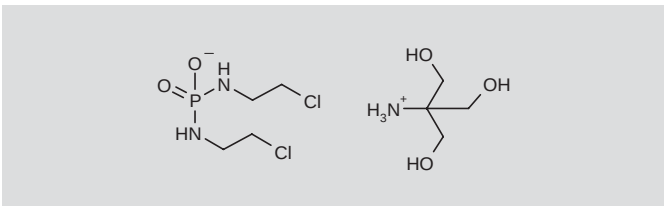
DNA-Alkylating Agent
Oncolytic

Prop INNM; USAN

IPM-tris
Isophosphoramide tromethamine salt
Palifosfamide-tris
ZIO-201
Zymafos™

N,*N*'-Bis(2-chloroethyl)phosphorodiamidic acid tris(hydroxymethyl)methylamine salt

InChI: 1S/C4H11Cl2N2O2P.C4H11NO3/c5-1-3-7-11(9,10)8-4-2-6;5-4(1-6,2-7)3-8/h1-4H2,(H3,7,8,9,10);6-8H,1-3,5H2



$C_8H_{22}Cl_2N_3O_5P$
Mol wt: 342.1570
CAS: 31645-39-3 (free acid)
EN: 687337

SUMMARY

Palifosfamide is a novel, bifunctional DNA cross-linker that is the stabilized active metabolite of ifosfamide. Isophosphoramide mustard, the active metabolite of ifosfamide, is not suitable for administration because of chemical instability. Isophosphoramide mustard is active in various cancer models but its chemical instability precluded pharmaceutical development. ZIOPHARM Oncology, under license from Dekk-Tec, has developed palifosfamide tromethamine, a formulation of isophosphoramide mustard with tris(hydroxymethyl)aminomethane salt. Unlike ifosfamide, this agent is not metabolized to acrolein or chloroacetaldehyde, metabolites associated with bladder and CNS toxicities, respectively. In addition, because palifosfamide does not require activation by aldehyde dehydrogenase, it may overcome the tumor resistance seen with ifosfamide. Preclinical studies have shown that palifosfamide has activity in leukemia and various solid tumors, especially sarcomas. Palifosfamide has demonstrated activity in human sarcoma xenograft models and is also active in ifosfamide-resistant xenografts. These studies also indicate that palifosfamide has a better safety profile than ifosfamide. Phase I and II studies as a single agent and in combination with doxorubicin have been completed in soft tissue sarcomas with promising early results.

Kanwaldeep K. Rasila and Claire F. Verschraegen. University of New Mexico Cancer Center, Division of Hematology - Oncology, 1202 Camino de Salud, Albuquerque, NM 87131, USA. E-mail: KKaurRasila@salud.unm.edu.
*Synthesis prepared by R. Pandian, R. Castañer. Thomson Reuters, Provença 388, 08025 Barcelona, Spain.

SYNTHESIS*

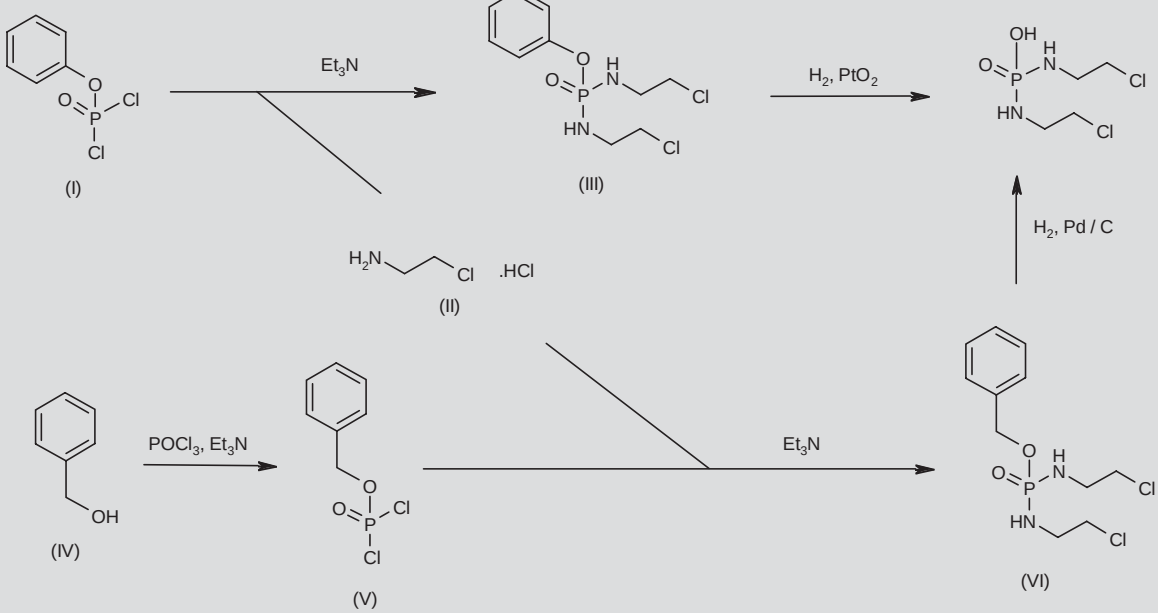
The condensation of phenyl dichlorophosphonate (I) with 2-chloroethylamine hydrochloride (II) in the presence of Et_3N in cold CH_2Cl_2 provides phenyl *N,N'*-bis(2-chloroethyl)phosphorodiamidate (III), which is finally converted to the corresponding phosphorodiamidic acid by catalytic hydrogenation over PtO_2 in EtOH (1). In an alternative method, acylation of benzyl alcohol (IV) with $POCl_3$ in the presence of Et_3N in cold acetonitrile gives benzyl dichlorophosphonate (V), which is further condensed with 2-chloroethylamine hydrochloride (II) in the presence of Et_3N to yield benzyl *N,N'*-bis(2-chloroethyl)phosphorodiamidate (VI). Finally, benzyl ester (VI) is then submitted to hydrogenolysis over Pd/C in acetonitrile (2, 3). Scheme 1.

BACKGROUND

Ifosfamide and cyclophosphamide are widely used anticancer agents. Both are prodrugs that must be metabolized in the liver to release the active drug. Although quite effective in treating certain cancers, their use is limited by toxicities associated with metabolites that do not contribute to clinical efficacy. The other major limitation is tumor resistance, which is due to multiple mechanisms, including increased DNA repair, increased cellular thiol levels, glutathione *S*-transferase and aldehyde dehydrogenase activities, and altered cell death response to DNA damage (4).

The active metabolite of ifosfamide is isophosphoramide mustard (palifosfamide). Ifosfamide is converted to 4-hydroxyifosfamide in the liver, which undergoes further metabolism by the aldehyde dehydrogenase class of enzymes to either the active metabolite isophosphoramide mustard or the inactive metabolite carboxyphosphamide. The metabolic pathway of ifosfamide is shown in Figure 1. Isophosphoramide mustard is a bifunctional alkylator that cross-

Scheme 1. Synthesis of Palifosfamide



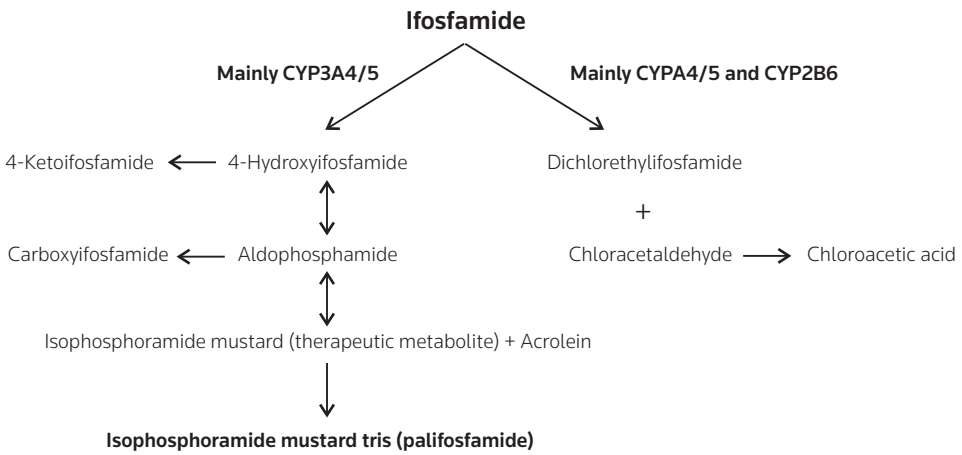


Figure 1. Metabolism of ifosfamide.

links DNA through GC base sequences, resulting in irreparable DNA damage and cell death. Isophosphoramide mustard alkylates DNA as a phosphorodiamidate and may cross-link DNA differently from phosphoramide mustard, the major DNA cross-linking moiety of cyclophosphamide. The proprietary salt formulations of isophosphoramide mustard (palifosfamide tromethamine and palifosfamide lysine) have demonstrated antitumor activity in various cancer models in vitro and in vivo, including ifosfamide- and cyclophosphamide-refractory cancers. The chemical instability of isophosphoramide mustard initially precluded its pharmaceutical development, but stabilization led to palifosfamide, a proprietary formulation licensed to ZIOPHARM, which is developing this compound clinically (5).

Isophosphoramide mustard is the active breakdown product of ifosfamide and is therefore not associated with the adverse effects of other metabolites generated from the metabolism of ifosfamide. Protective measures, such as the use of 2-mercaptoethane sulfonate sodium (Mesna) and intensive intravenous hydration, are not required. Thus, palifosfamide, formulated as a tromethamine salt

stabilized with mannitol, conceptually lacks toxicities that are associated with ifosfamide treatment, is much easier to administer and can be given on an outpatient basis. In addition, because palifosfamide does not require activation by aldehyde dehydrogenase, it may overcome the tumor resistance caused by overexpression of aldehyde dehydrogenase (6). Therefore, administration of palifosfamide may avoid many of the toxicities of ifosfamide without compromising the activity of the drug.

Originally, ZIOPHARM developed this drug as a stabilized lysine formulation. In early phase I studies of palifosfamide lysine, a reversible Fanconi syndrome was observed (7). A reduction of the dose of palifosfamide lysine administered in all subsequent active clinical trials translated into a decrease in the number of reported cases of Fanconi syndrome. However, clinical laboratory results collected as part of the ongoing monitoring program suggested that the incidence of acute renal failure (while low) increased in patients treated over the longer term with palifosfamide lysine. Lysine, which has some nephrotoxicity as a single agent, when combined with palifosfamide exacerbated the potential for renal toxicity. The other limitations associated with palifosfamide lysine included the need for –70 °C conditions when storing long-term, short post-reconstitution stability and a 2:1 ratio of salt-to-active pharmaceutical ingredient (API).

Subsequently, ZIOPHARM developed a new formulation of palifosfamide as the tromethamine salt to overcome several limitations associated with the original palifosfamide lysine formulation. Palifosfamide tromethamine has the capability of being stored at –20 °C for at least 6 months, has a 1:1 salt-to-API ratio and has twice the reconstitution stability compared to palifosfamide lysine. Therefore, palifosfamide tromethamine was developed as an alternative to the original lysine salt formulation in order to improve the storage and reconstitution stability, enhance the solubility characteristics, and increase the concentration of isophosphoramide mustard active drug substance per vial. The tromethamine formulation does not have the renal toxicity thought to be caused by the lysine itself. Whereas the majority of the preclinical work was conducted with the palifosfamide lysine formulation, the basis for testing the palifosfamide tromethamine formulation in clinical settings was that both formulations contained the same active pharmaceutical ingredient, API, and produced similar impurity profiles. Hence, since palifosfamide tromethamine is more soluble and more stable in solution than palifosfamide lysine, the development of palifosfamide tromethamine has gone forward as an oral and an injectable salt of palifosfamide. The drug product currently in clinical trials is supplied as a lyophilized powder for reconstitution with saline prior to administration. The oral form of palifosfamide has been developed preclinically and is in the Investigational New Drug (IND) application stage.

PRECLINICAL PHARMACOLOGY

Palifosfamide and its proprietary salt formulations (palifosfamide tromethamine and palifosfamide lysine) have demonstrated antitumor activity in diverse cancer models in vitro and in vivo, including ifosfamide- and cyclophosphamide-refractory cancers.

Palifosfamide lysine was investigated in vitro for effects on the viability and proliferation of human rhabdomyosarcoma (RD and RH30), Ewing's sarcoma (SK-PN-DW and SK-ES-1), osteosarcoma (Saos-2, OS222, OS29 and OS230) and synovial sarcoma (HSSYII and SYOI) cell lines. After a 24-h pretreatment period, sarcoma cell lines were incubated with increasing concentrations of palifosfamide lysine, either as a single daily application or for 3 consecutive days with fresh drug added daily. The treated cells were incubated for an additional 72 h and cell viability was determined by the MTT assay. Palifosfamide lysine was cytotoxic against all the cell lines tested, with the IC_{50} ranging from 0.5 to 1.5 μg/mL, except for OS222, which had an IC_{50} of 7 μg/mL. In vitro in most lines evaluated, the IC_{50} values for a single daily application and for consecutive days were comparable (8).

Phosphoramide mustard and the lysine and tromethamine forms of palifosfamide have been compared in multiple preclinical models. Palifosfamide has been shown to be 10- to 30-fold more active than ifosfamide in most in vitro and in vivo models of leukemia/lymphoma and has antitumor activity in ifosfamide-resistant lymphoma xenograft models (9).

The effect on tumor growth and event-free survival was assessed at the maximum tolerated dose (MTD) in three sarcoma xenografts (Ewing sarcoma, rhabdomyosarcoma and cyclophosphamide-resistant OS31 and -sensitive OS33 osteosarcomas). Tumor growth inhibition was seen in both OS31 and OS33 xenografts and the rhabdomyosarcoma xenograft, resulting in a significant difference in survival between the control and the treated groups. Palifosfamide lysine was also active against the cyclophosphamide-resistant OS31 tumor, which overexpresses aldehyde dehydrogenase, suggesting that it might have the potential to overcome this resistance mechanism against oxazaphosphorines and may be an active agent in patients with resistant or relapsed sarcomas (10).

In the MX-1 human breast cancer model in mice, i.v. palifosfamide lysine was superior to isophosphoramide mustard, with an MTD of 93 versus 40 mg/kg and life extension of 10.2 and 2.1 days, respectively, for treated and untreated control xenografts. No kidney, bladder or CNS toxicity was seen (11).

The antitumor effects of palifosfamide tromethamine, palifosfamide lysine and isophosphoramide mustard were again compared in the MX-1 breast carcinoma xenograft model. Two studies were performed in which the i.p. route of administration was investigated. Doses of the compounds were selected to allow for comparison of antitumor effects at isophosphoramide mustard-equivalent doses for each salt. MX-1 tumor fragments were implanted s.c. in the mammary fat pads of athymic nude mice. In the first study, the i.p. administration of palifosfamide lysine was toxic at 36 mg/kg/day, but palifosfamide tromethamine and isophosphoramide mustard at 36 and 24 mg/kg/day, respectively, did not appear to cause toxicity. In the second study, the i.p. administration of palifosfamide tromethamine at dose levels of 24, 36 and 54 mg/kg/day and palifosfamide lysine and isophosphoramide mustard at dose levels of 24 and 36 mg/kg/day did not appear to cause toxicity. The toxic dose for palifosfamide tromethamine was 81 mg/kg/day, the highest dose level (12).

The oral formulation of palifosfamide tromethamine has also undergone extensive preclinical testing. The antitumor activity of oral palifosfamide tromethamine was tested in a murine leukemia model at 280 mg/kg administered once daily for 1, 5 or 10 days. P388 murine

leukemia cells were inoculated i.p. in CD2F1 mice. The day of tumor implantation was designated as day 0, with treatment beginning on day 1. Survival was increased with prolonged periods of treatment, indicating that the oral formulation of palifosfamide tromethamine could have a clinical advantage in terms of activity and convenience of administration. In the MX-1 xenograft model, oral treatment of tumors weighing 75-198 mg was equally active at MTDs as systemically administered palifosfamide tromethamine. Thus, oral palifosfamide tromethamine has antitumor activity in a rodent leukemia model and in a human breast cancer xenograft model. The extent of antitumor activity is similar for oral or parenteral administration at respective MTDs. Both stabilized forms of isophosphoramide mustard are equally active in the human MX-1 xenograft model (13).

Thus, palifosfamide tromethamine elicits significant antitumor activity when administered orally, i.v. or i.p., with equivalent activity. These results supported the clinical development of oral palifosfamide tromethamine.

The antitumor activity of palifosfamide tromethamine in combination with doxorubicin was also investigated in the MX-1 breast carcinoma xenograft model. Fragments of in vivo-passaged MX-1 tumors were implanted s.c. in the mammary fat pads of athymic nude mice. Palifosfamide tromethamine doses of 54, 24 or 12 mg/kg/day were administered i.p. for 5 days, and doxorubicin doses of 8, 5.3 or 3.5 mg/kg/day were administered i.v. on days 1, 4 and 8. In combination the agents were administered by the same routes and schedules and at the same respective dose levels. Drug administration started on day 10 after tumor implantation. Antitumor effects and toxicity were assessed. A synergistic interaction was observed between doses of 12 or 24 mg/kg palifosfamide tromethamine in combination with the MTD of doxorubicin (8 mg/kg). In two separate studies, the combination inhibited tumor growth of orthotopically implanted MX-1 xenografts to a significantly greater extent than treatment with either agent alone. The greater antitumor activity of the palifosfamide tromethamine and doxorubicin combination resulted in a statistically significantly increased survival ($P < 0.001$). The combination was well tolerated, without weight loss. The combination of palifosfamide tromethamine with docetaxel was also studied in the same xenograft model and showed increased antitumor effect over each single agent alone (14).

PHARMACOKINETICS AND METABOLISM

The pharmacokinetics of isophosphoramide mustard were studied in the plasma of Sprague-Dawley rats following an i.v. dose of 40 mg/kg. The elimination of isophosphoramide mustard exhibited a monoexponential decline, with an average half-life of 12.7 min, and could therefore be described by one-compartment kinetics. The mean total clearance value was 11.0 ± 4.4 mL/min (range: 6.0-18.3) and the mean volume of distribution was 220 ± 156 mL. Protein binding in fresh rat plasma was estimated by ultrafiltration and found to be 55.1 ± 0.1%. The partition of isophosphoramide mustard between plasma and red blood cells was also evaluated and it was shown to partition into red cells less readily, with a ratio of 4.9:1 in favor of plasma (15).

The pharmacokinetic profile of orally and intravenously administered palifosfamide tromethamine was determined in female Sprague-Dawley rats. Animals were administered palifosfamide tromethamine once daily via gavage or bolus i.v. injection. Palifosfamide tromethamine was administered at doses of 20, 30 and 40 mg/kg. Blood samples for pharmacokinetic evaluation were obtained predose and at 0.5, 1, 2, 4, 6, 8, 12 and 24 h postdose from the retro-orbital sinus. Three animals per group were sampled at each time point. Time to peak plasma concentrations (t_{max}) appeared to be approximately 0.5 h. Estimates of terminal $t_{1/2}$ ranged from 0.25 to 0.64 h. For each dose, AUC values were used to estimate absolute bioequivalence of orally administered palifosfamide tromethamine as the ratio: AUC post-p.o. dose/AUC post-i.v. dose. Bioavailability of the 20, 30 and 40 mg/kg p.o. doses of palifosfamide tromethamine was 48, 65 and 73%, respectively. Overall mean bioavailability was 62% in females. Similar pharmacokinetic results were observed in male rats; however, mean bioavailability in males was estimated to be 41% (5).

SAFETY

In vivo, the MTD of palifosfamide lysine was determined in SCID mice based on a 3-day i.v. administration schedule. The i.v. MTD of palifosfamide lysine in mice was 100 mg/kg per day for 3 consecutive days.

To determine the lethal dose, palifosfamide tromethamine was given i.v. daily for 3 days. The LD_{10} and LD_{50} values for palifosfamide tromethamine in adult mice of both sexes were 133 and 220 mg/kg, respectively, compared to 119 and 149 mg/kg, respectively, for isophosphoramide mustard. Bone marrow failure was the dose-limiting toxicity (DLT) for both drugs.

A single-arm, nonrandomized, open-label phase I study in advanced cancers (Study IPM1001) using the original lysine salt formulation has been completed. The treatment consisted of multiple 3-week cycles of either daily administration of palifosfamide for 3 days repeated every 21 days, or a single administration of palifosfamide given every 21 days. Patients were treated up to 6 cycles, or until DLT or disease progression. Dose levels of palifosfamide were initially increased in successive cohorts of single patients for the first 8 cohorts (dose levels of 30, 42, 59, 83, 116, 162, 227 and 318 mg/m^2) and then 3 patients per dose level for the remaining cohorts. At each dose level, the first 3 patients were treated and evaluated for toxicity over a 3-week post-dosing observation period. The most frequently reported adverse events included nausea, fatigue and anorexia. There was little bone marrow toxicity and no significant hepatic or cardiac toxicities (16).

A single-arm, nonrandomized, open-label, two-stage phase I/II study in advanced sarcomas (Study IPM2001) with the lysine formulation has been completed and data retrieval is ongoing. The study design consisted of multiple 3-week cycles of daily doses on 3 consecutive days repeated every 21 days. Patients were treated for up to 6 cycles or until DLT or disease progression. The phase I starting dose was 590 mg/m^2. Four patients were enrolled at this dose level. This starting dose was found to be too high, resulting in renal toxicity. Per protocol, the dose was reduced to 413 mg/m^2, which proved to be the MTD. The phase II portion of the study was conducted

using the dose of 413 mg/m^2. This study also incorporated a single i.v. dose of palifosfamide tromethamine (the new formulation, replacing lysine) for bioequivalence evaluation. Preliminary safety results from the phase I portion and preliminary efficacy data for the phase II portion have been reported. The most frequently reported adverse events from phase I include nausea (44%), hypokalemia (44%), fatigue (32%), anemia (34%), hypophosphatemia (32%), increased blood alkaline phosphatase (32%), increased blood creatinine (24%), microhematuria (24%), vomiting (22%) and hypocalcemia or increased blood lactate dehydrogenase (20% each). There were no significant hepatic or cardiac toxicities reported. In the cohort with the new tromethamine salt formulation stabilized with mannitol there was no significant renal toxicity reported (17, 18).

CLINICAL STUDIES

The marked preclinical synergistic efficacy of palifosfamide in combination with doxorubicin provided the rationale for a phase I study that enrolled subjects with advanced refractory tumors if no standard therapy existed and if doxorubicin treatment was medically acceptable. Palifosfamide was administered on days 1-3 of a 21-day cycle at a starting dose of 100 mg/m^2. Doxorubicin was administered on day 1 at a starting dose of 60 mg/m^2. Doses were escalated up to an MTD of palifosfamide of 150 mg/m^2 and doxorubicin 75 mg/m^2. Pharmacokinetics for palifosfamide were determined and compared to those obtained in murine studies. Thirteen patients (8 with soft tissue sarcoma and 5 with small cell lung cancer, neuroendocrine or osteosarcoma) were treated, with 8 patients still on treatment at the time of data reporting. All had an ECOG performance status of 0 or 1, the median age was 58 years and 3 had received prior ifosfamide. With 73 cycles administered, the combination has been well tolerated, with no DLTs reported. No mesna or hydration was given. Study-related grade 3/4 adverse events included neutropenia and thrombocytopenia. Pharmacokinetic evaluation indicated that palifosfamide exposure and C_{max} at clinically well-tolerated doses were comparable with those in murine models, resulting in marked synergy with doxorubicin. Of 12 assessable patients, 3 had a partial response, including 2 patients with soft tissue sarcoma. The median progression-free survival was 20 weeks. The conclusions were that palifosfamide in combination with doxorubicin is easy to administer and is well tolerated, without encephalopathy, hemorrhagic cystitis or renal toxicity (19, 20).

A randomized phase II trial of palifosfamide and doxorubicin versus doxorubicin in subjects with unresectable or metastatic soft tissue sarcoma was conducted. The PICASSO study (**P**hase II multicenter, parallel-group, randomized study of pal**I**fosfamide tris plus doxorubicin versus doxorubi**C**in in subjects with unresect**A**ble or metastatic **S**oft tissue **S**arc**O**ma) had as the primary objective the assessment of progression-free survival. The secondary objectives were to assess the safety, tolerability and the overall response rate. The arms of the trial were well balanced by two predetermined stratifications for age (> or < 65 years) for histopathological subtypes (leiomyosarcoma, synovial sarcoma or "other") and for front- or second-line treatment. An initial interim analysis of this trial was presented at the 15th Annual Connective Tissue Oncology Society (CTOS) Meeting in November 2009. As of the cut-off date (October 5), there were 67 patients randomized, 65 under treatment and 61 eligible for analysis. There were 20 documented progressions (14 for single-agent doxorubicin and 6 for the combination). The hazard ratio was 0.63 favoring palifosfamide and doxorubicin, with a two-sided Wilcoxon-Gehan *P* value of 0.026. Statistically, palifosfamide prolonged the progression-free survival by at least 50%, with a median progression-free survival for doxorubicin of 4.4 months, while the progression-free survival for palifosfamide and doxorubicin had not yet been reached. The interim safety data analysis indicated that the addition of palifosfamide does not increase toxicity over single-agent doxorubicin. The most frequently reported side effects in both arms of the study included neutropenia and fatigue, followed by hypokalemia, nausea, anemia, leukopenia and alopecia (21).

These results were recently updated at the American Society of Clinical Oncology (ASCO) meeting in June 2010. The median progression-free survival for the palifosfamide plus doxorubicin arm was 7.8 months versus 4.4 months with doxorubicin alone, with a hazard ratio of 0.427 and a *P* value of 0.019. The study has a median follow-up time of 9 months. The response rate was 23% for palifosfamide plus doxorubicin versus 9% for doxorubicin alone, with clinically similar toxicity (22).

CONCLUSIONS

Palifosfamide tromethamine has demonstrated clinical activity without the degree of bone marrow suppression, bladder and neurotoxicity seen with ifosfamide treatment. These findings also suggest that palifosfamide tromethamine may be a promising candidate for combination chemotherapy to enhance activity without overlapping toxicities. A confirmatory phase III trial in patients with soft tissue sarcoma is currently being planned and the manufacturer intends to expand the use of palifosfamide for pediatric cancers, lymphomas and breast cancer.

SOURCE

ZIOPHARM Oncology, Inc. (US).

DISCLOSURES

The University of New Mexico signed a contract with ZIOPHARM to conduct the randomized phase II study in sarcoma, and the money allocated supported staff and in small part some patient care.

REFERENCES

1. Morgan, L. (Dekk-Tec, Inc.). *Salts of isophosphoramide mustard and analogs thereof as anti-tumor agents*. EP 1805192, JP 2008517929, US 2006089333, US 2008267945, WO 2006047575.
2. Amedio, J.C., Wallner, B.P., Komarnitsky, P.B. (ZIOPHARM Oncology, Inc.). *Salts of isophosphoramide mustard and analogs thereof.* EP 2155682, JP 2010523571, US 2008255056, WO 2008124097.
3. Waligora, F.W., Amedio, J.C. (ZIOPHARM Oncology, Inc.). *Synthesis and formulations of salts of isophosphoramide mustard and analogs thereof.* WO 2010014841.
4. Zhang, J., Tian, Q., Chan, S.Y., Li, S.C., Zhou, S., Duan, W., Zhu, Y.Z. *Metabolism and transport of oxazaphosphorines and the clinical implications.* Drug Metab Rev 2005, 37(4): 611-703.

5. Komarnitsky, P., Amedio, J., Wallner, B. *Oral availability and drug combination activity of palifosfamide tris (ZIO-201) in preclinical studies.* Proc Am Assoc Cancer Res (AACR) 2008, 49: Abst 5685.
6. Magni, M., Shammah, S., Schiro, R., Mellado, W., Dalla-Favera, R., Gianni, A.M. *Induction of cyclophosphamide-resistance by aldehyde-dehydrogenase gene transfer*. Blood 1996, 87(3): 1097-103.
7. Maki, R., Morgan, R., Lewis, J. *Palifosfamide - A novel molecule for the treatment of soft tissue sarcoma (STS): A primer.* Electronic Sarcoma Update Newsletter 2009, 6(3).
8. Kolb, E.A., Gidwani, P., Gale, R.P., Gorlick, R. *A preclinical evaluation of ZIO-201 (isophosphoramide mustard (IPM)-lysine) in sarcoma.* 12th Annu Meet Connective Tissue Oncol Soc (Nov 2-4, Venice) 2006, Abst 610.
9. Gale, R.P., Morgan, L.R., Struck, R.F., Rosen, L., Lo Russo, P. *ZIO-201 (isophosphoramide mustard-lysine): A new alkylator for lymphoma active in ifosfamide (IFOS)-resistant cancers.* 31st World Congr Int Soc Hematol (ISH) (March 20-24, Punta del Este) 2007, Abst 95.
10. Hingorani, P., Zhang, W., Piperdi, S., Pressman, L., Lin, J., Gorlick, R., Kolb, E.A. *Preclinical activity of palifosfamide lysine (ZIO-201) in pediatric sarcomas including oxazaphosphorine-resistant osteosarcoma.* Cancer Chemother Pharmacol 2009, 64(4): 733-40.
11. Morgan, L., Struck, R., Rodgers, A., Jursic, B., Waud, W., Papagiannis, C., Gale, R.P. *Isophosphoramide mustard-lysine (IPM-L; ZIO-201): A new alkylator for bone marrow transplants.* Biol Blood Marrow Transplant 2006, 12(2): 44.
12. Waud, W.R. *Response of SC implanted MX-1 human mammary tumors to IP and PO administration of IPM-tris, IPM, and IPM-lysine (Study ZP-14).* ZIOPHARM Oncology, Inc. 2007.
13. Komarnitsky, P.B., Amedio, J.C. Jr., Schwartz, B., Wallner, B.P. *ZIO-201 (isophosphoramide mustard; IPM): An orally active anti-cancer agent.* ZIOPHARM Oncology Inc.
14. Waud, W.R., Miller, G. *Antitumor efficacy of ifosfamide and palifosfamide-tris in combination with doxorubicin in MX-1 xenograft model in mice (Study ZP-29).* Southern Research Institute 2008.
15. Zheng, J.J., Chan, K.K., Muggia, F. *Preclinical pharmacokinetics and stability of isophosphoramide mustard.* Cancer Chemother Pharmacol 1994, 33(5): 391-8.
16. Benjamin, R.S., Lo Russo, P., Rosen, L., Kolb, E.A., Gorlick, R.G., Gale, R.P. *Phase-1 trials of ZIO-201 (isophosporamide mustard-lysine) (IPM): The active moiety of ifosfamide: Potential role in sarcoma.* 12th Annu Meet Connective Tissue Oncol Soc (Nov 2-4, Venice) 2006, Abst.
17. Chugh, R., Chawla, S., Benjamin, R., Heaton, J., Stevens, J., Schwartz, B. *Phase I/II study of ZIO-201 in advanced sarcoma*. Ann Oncol [Eur Soc Med Oncol (ESMO) Sci Edu Conf (July 5-8, Lugano) 2007] 2007, 18(Suppl. 9): Abst 95P.
18. Chugh, R., Schuetze, S., Benjamin, R., Keohan, M., Maki, R., Stevens, J. *ZIO-201: A bi-functional DNA alkylator in advanced sarcomas.* 13th Annu Meet Connective Tissue Oncol Soc (Nov 1-3, Seattle) 2007, Abst.
19. Chawla, S., Camacho, L., Chua, V., Abbadessa, G., LoBue, L., Lewis, J. *A study of palifosfamide in combination with doxorubicin: Safety and preliminary efficacy.* 14th Annu Meet Connective Tissue Oncol Soc (Nov 13-15, London) 2008, Abst.
20. Camacho, L.H., Chawla, S.P., Chua,V., Abbadessa, G., Komarnitsky, P.B., Lewis, J. *A phase I study of palifosfamide in combination with doxorubicin: Safety and preliminary efficacy.* J Clin Oncol [45th Annu Meet Am Soc Clin Oncol (ASCO) (May 29-June 2, Orlando) 2009] 2009, 27(15, Suppl.): Abst 10577.
21. Verschraegen, C.F., Chawla, S., Mita, M. et al. *A phase II randomized controlled trial of palifosfamide plus doxorubicin vs. doxorubicin in patients with soft tissue sarcoma (PICASSO).* 15th Annu Meet Connective Tissue Oncol Soc (Nov 5-7, Miami Beach) 2009, Abst.
22. Verschraegen, C.F., Chawla, S.P., Mita, M.M. et al. *A phase II, randomized, controlled trial of palifosfamide plus doxorubicin versus doxorubicin in patients with soft tissue sarcoma (PICASSO).* J Clin Oncol [46th Annu Meet Am Soc Clin Oncol (ASCO) (June 4-8, Chicago) 2010] 2010, 28(7, Suppl.): Abst 10004.