*Annals of Oncology* 25: 1807–1812, 2014
doi:10.1093/annonc/mdu231
Published online 19 June 2014

# Final results of a multicenter phase II study of the purine nucleoside phosphorylase (PNP) inhibitor forodesine in patients with advanced cutaneous *t*-cell lymphomas (CTCL) (Mycosis fungoides and Sézary syndrome)

R. Dummer[1*,†], M. Duvic[2,†], J. Scarisbrick[3], E. A. Olsen[4], S. Rozati[1], N. Eggmann[1], S. M. Goldinger[1], K. Hutchinson[5], L. Geskin[6], T. M. Illidge[7], E. Giuliano[8], J. Elder[9] & Y. H. Kim[10]

*[1]Department of Dermatology, University Hospital Zurich, Zurich, Switzerland; [2]Department of Dermatology, MD Anderson Cancer Center, Houston, USA; [3]Department Dermatology, Hospital Birmingham, Birmingham, UK; [4]Department of Dermatology, Duke University Medical Center, Durham, USA; [5]Clinical Research, AMS Ltd, London, UK; [6]Department of Dermatology, University of Pittsburgh, Pittsburgh, USA; [7]School of Cancer and Imaging Sciences, University of Manchester, Manchester, UK; [8]Clinical Development, BioCryst Pharmaceuticals, Inc., Durham; [9]Statistics, PharPoint Research, Inc., Chapel Hill; [10]Clinical Research, Stanford Cancer Center, Stanford, USA*

*Received 3 April 2014; revised 2 June 2014; accepted 10 June 2014*

**Background:** Forodesine is a potent inhibitor of purine nucleoside phosphorylase (PNP) that leads to intracellular accumulation of deoxyguanosine triphosphate (dGTP) in T and B cells, resulting in apoptosis. Forodesine has demonstrated impressive antitumor activity in early phase clinical trials in cutaneous T-cell lymphoma (CTCL).

**Patients and methods:** In this phase II study, patients with CTCL who had already failed three or more systemic therapies were recruited. We investigated the response rate, safety and tolerability of oral forodesine treatment in subjects with cutaneous manifestations of CTCL, stages IB, IIA, IIB, III and IVA. The safety population encompassing all stages was used for analysis of accountability, demographics and safety. The efficacy population differed from the safety population by exclusion of stage IB and IIA patients.

**Results:** All 144 patients had performance status 0–2. The median duration of CTCL from diagnosis was 53 months (5–516 months). The median number of pretreatments was 4 (range: 3–15). No complete remissions were observed. In the efficacy group of patients, 11% achieved partial remission and 50% had stable disease. The median time to response was 56 days and the median duration of response was 191 days. A total of 96% of all treated patients reported one or more adverse events (AEs) and 33% reported a serious AE. The majority of AEs were classified as mild or moderate in severity. The most commonly reported AEs (>10%) were peripheral edema, fatigue, insomnia, pruritus, diarrhea, headache and nausea. Overall eight patients died during the study: five due to sepsis and infections, one due to a second malignancy (esophageal cancer), one due to disease progression and one due to liver failure.

**Conclusion:** Oral forodesine at a dose of 200 mg daily is feasible and shows partial efficacy in this highly selected CTCL population and some durable responses.

**Key words:** forodesine, purine nucleoside phosphorylase inhibitor, cutaneous T-cell lymphomas, mycosis fungoides, Sézary syndrome

## introduction

Cutaneous T-cell lymphomas (CTCLs) are a heterogeneous group of diseases characterized by the accumulation of clonal T cells in the skin [1]. Although rare in incidence, they deserve a specific therapeutic treatment algorithm [2] and are currently intensively investigated in order to improve their therapeutic repertoire [3].

Purine nucleoside phosphorylase (PNP) is an essential enzyme for the phosphorolysis of purine nucleosides. Congenital defects in this enzyme result in severe immunodeficiency syndromes through selective depletion of T cells but without any significant change in the B-cell population [4, 5]. It was hypothesized that malignant T-cell clones are extremely sensitive to the inhibition of PNP due to their increased nucleoside metabolism [6]. Taking into account that PNP deficiency leads to a profound T-cell-mediated immunosuppression, scientists

*Correspondence to: Prof. Reinhard Dummer, Department of Dermatology, University Hospital Zurich, Gloriastrasse 31, 8091 Zurich, Switzerland. Tel: +41-44-255-2507; Fax: +41-44-255-8988; E-mail: reinhard.dummer@usz.ch

†MD shared first authorship.

searched for an equivalent to use in patients with T-cell proliferating malignancies.

Forodesine (also known as BCX1777 and Immucillin H) is a potent inhibitor of PNP and has been shown to induce apoptosis of T-cell lymphocytes by accumulation of deoxyguanosine triphosphate (dGTP) [7]. Early preclinical and clinical trials with forodesine appeared to be promising for the treatment of relapsed/refractory hematologic malignancies [8] and demonstrated clinical activity in subjects with refractory CTCL, with an acceptable toxicity profile.

## patients and methods

### study design

This study (NCT00501735) was an open label, single-arm, multicenter, phase II study of oral forodesine 200 mg daily in relapsed or refractory CTCL. The primary objective was to determine its efficacy by assessing the objective response rate in patients with advanced Mycosis fungoides (MF) or Sézary syndrome (SS). Secondary objectives included the assessment of safety and tolerability. This study was carried out in compliance with Good Clinical Practice and in accordance with the Declaration of Helsinki.

### patients

Eligible patients were ≥18 years old, had histologically proven CTCL stage IB to IVA (including MF and SS) that was persistent, progressive or recurrent with at least three prior systemic therapies, including bexarotene, unless bexarotene therapy was not tolerated or medically contraindicated. Compliance with study medication was assessed using drug-accountability forms, records of medication disposition to patients (including data, time and lot numbers) and records of any medication accidentally destroyed. Patients were asked to return all unused study medication and empty medication containers at each visit to assess patient's compliance.

### response criteria

The efficacy population differed from the safety population by exclusion of stage IB and IIA patients. The safety population encompassing all stages was used for analysis of accountability, demographics and safety.

The modified Severity Weighted Assessment Tool (mSWAT) was used to assess clinical involvement unless progressive lymph node disease was clinically observed.

Confirmation of objective response was carried out by a second assessment after at least 28 days. A computed tomography (CT) scan (neck, chest, abdomen and pelvis) was carried out to confirm the absence of any new lymph node disease involvement or the absence of progression of any pre-existing lymph node disease.

Study treatment was continued until the patient was judged to have progressive disease (PD), uncontrolled intercurrent illness, unacceptable toxicity or if the patient withdrew for any reason. PD was defined as a >25% increase in the mSWAT score from the nadir value that is sustained for at least 28 days or ≥50% increase in the sum of the products of the greatest diameters of enlarged lymph nodes (by CT) compared with baseline CT or the presence of a new lymph node. Complete response (CR) was defined as no evidence of cutaneous disease (i.e. mSWAT = 0) and sustained for at

**Table 1.** Patient characteristics

| Characteristics | mITT (IIB + III + IVA) | Safety (mITT + IB + IIA) |
|---|---|---|
| Total number | 101 | 144 |
| Age | | |
| Median years (min, max) | 62 (30, 84) | 62 (30, 84) |
| Male : female | 63 : 38 | 86 : 58 |
| Duration of CTCL | | |
| Median months (min, max) | 52.5 (5, 516) | 53.0 (5, 516) |
| ECOG 0, 1, 2 (*n*) | 59, 35, 7 | 91, 45, 8 |
| Stage of CTCL at baseline, *n* (%) | | |
| IB | 0 | 30 (21%) |
| IIA | 0 | 13 (9%) |
| IIB | 38 (38%) | 38 (26%) |
| III | 35 (35%) | 35 (24%) |
| IVA | 28 (28%) | 28 (19%) |
| Sézary syndrome at baseline, *n* (%) | | |
| Yes | 19 (19%) | 19 (13%) |
| No | 79 (78%) | 122 (85%) |
| Unknown | 3 (3%) | 3 (2%) |
| Prior systemic therapies, *n* (%) | | |
| ≥3 | 101 (100%) | 144 (100%) |
| Prior oral bexarotene therapy, *n* (%) | | |
| Yes | 92(91%) | 134 (93%) |
| No | 9 (9%) | 10 (7%) |
| Prior treatment with Vorinostat, *n* (%) | | |
| Yes | 30 (30%) | 47 (33%) |
| No | 69 (68%) | 95 (66%) |
| Missing | 2 (2%) | 2 (1%) |

CTCL, cutaneous T-cell lymphoma; ECOG, Eastern Cooperative Oncology Group; mITT, modified intent-to-treat population; *n*, number of patients.

**Table 2.** Summary of therapy response

| Parameters | mITT | Safety population |
|---|---|---|
| Total number | 101 | 144 |
| Cutaneous response, *n* (%) | | |
| CR | 0 | 2 (1%) |
| PR | 11 (11%) | 22 (15%) |
| SD | 51 (50%) | 69 (48%) |
| PD | 35 (35%) | 47 (33%) |
| Not evaluable | 4 (4%) | 4 (3%) |
| Achieved objective cutaneous response (CR or PR) | | |
| *n* (%) | 11 (11%) | 24 (17%) |
| 95% CI | 6–19% | 11% to 24% |
| Time to response | | |
| Median day (95% CI) | 56 (31–85) | 75.5 (51–85) |
| Reported loss of response | | |
| *n* (%) | 5/11 (45%) | 8/24 (33%) |
| Time to progressive disease (PD) | | |
| Median day (95% CI) | 191 (112–420) | 261 (145–420) |

mITT, modified intent-to-treat population; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; CI, confidence interval.

least 28 days and a partial response (PR) was defined as an increase in mSWAT that is >50% increase from the nadir score that was sustained for at least 28 days.

Before and during treatment laboratory tests included complete blood cell count. Electrocardiogram was carried out monthly up to visit 7.

The severity of each adverse event (AE) was determined according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE Version 3.0). AEs were also categorized by causality to the study medication.

### statistical analysis

Descriptive statistical methods were used to summarize the data from this study, with hypothesis testing carried out for the primary and other selected efficacy end points. This study was deemed successful if the lower bound of the 95% confidence interval about the objective response rate is >15%.

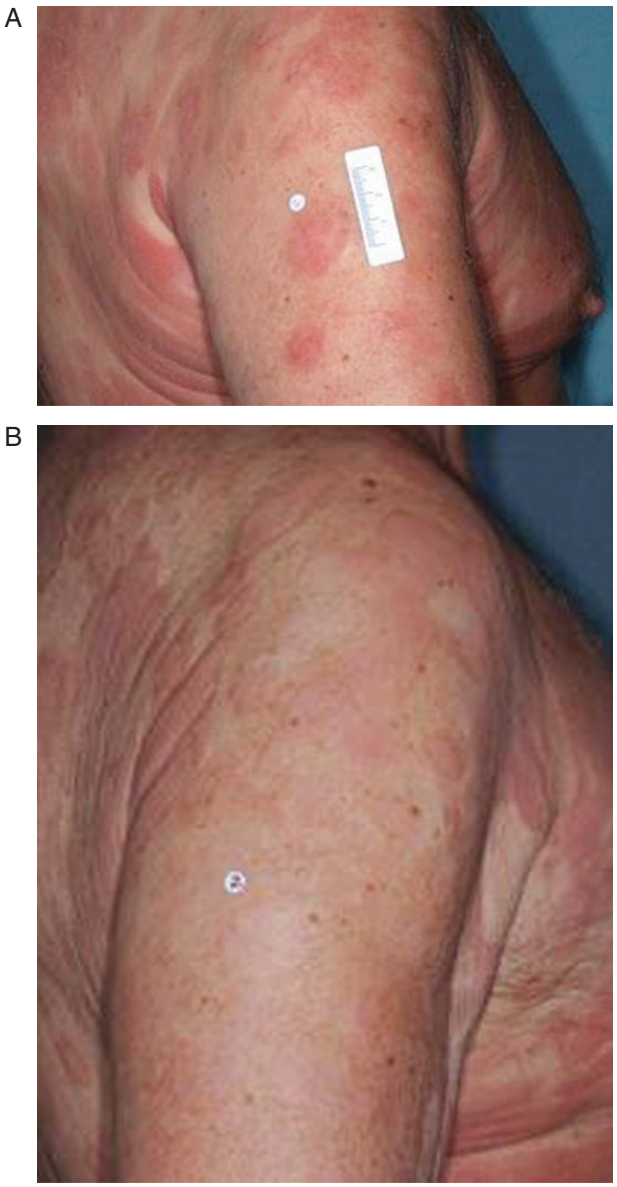


**Figure 1.** (A) Mycosis fungoides patient before treatment. (B) Mycosis fungoides patient after 10 weeks of treatment.

## results

### patients' baseline characteristics

A total of 144 patients (86 males and 58 females) were enrolled and had three or more prior lines of systemic therapies for MF/SS (Table 1). The median age was 62 years (30–84

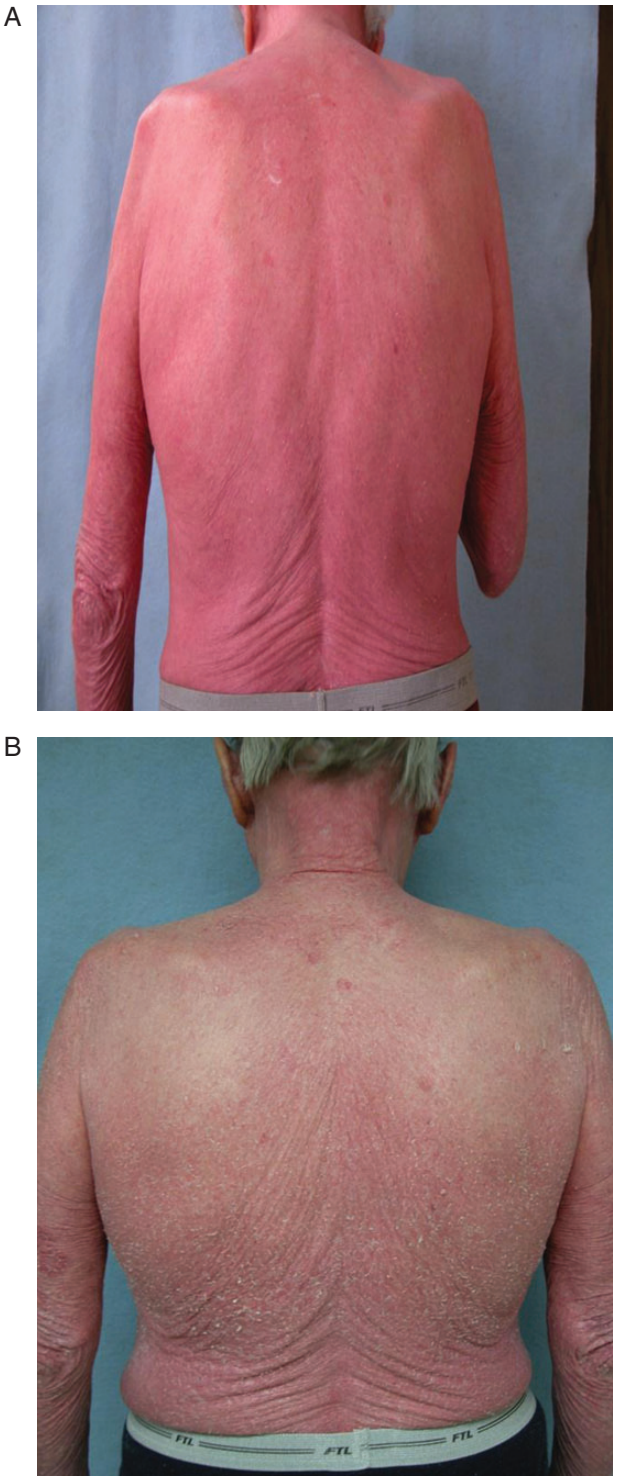


**Figure 2.** (A) Sézary syndrome patient before treatment. (B) Sézary syndrome patient after three courses of therapy.

years). Of the patients in the safety population, 91 (63%) had an ECOG performance status of 0, 45 (31%) had 1 and 8 (6%) had 2. The median duration of CTCL was 53 months (5–516 months).

## treatment duration and response

Fifty-three (37%) patients completed the study to visit 7 (168 days) and 51 (35%) continued on the study beyond visit 7. Ten patients continued in the study for over a year; of these, five

**Table 3.** Adverse events by system organ class and preferred term (>3%) in the safety population

| System organ class | Frequency, *n* (%) | | | | | |
|---|---|---|---|---|---|---|
| Preferred term | Total | Mild | Moderate | Severe | Life threatening | Death |
| Blood and lymphatic system | 28 (19%) | | | | | |
| Anemia | 11 (8%) | 3 (2%) | 4 (3%) | 4 (3%) | | |
| Lymphopenia | 10 (7%) | | 3 (2%) | 6 (4%) | 1 (1%) | |
| Cardiac disorders | 20 (14%) | | | | | |
| Atrial Fibrillation | 6 (4%) | | 4 (3%) | 2 (1%) | | |
| Gastrointestinal disorder | 54 (38%) | | | | | |
| Constipation | 15 (10%) | 14 (10%) | 1 (1%) | | | |
| Diarrhea | 18 (13%) | 15 (10%) | 3 (2%) | | | |
| Nausea | 17 (12%) | 13 (9%) | 4 (3%) | | | |
| Vomiting | 6 (4%) | 5 (3%) | 1 (1%) | | | |
| General disorders and administration site conditions | 81 (56%) | | | | | |
| Asthenia | 8 (6%) | 2 (1%) | 5 (3%) | 1 (1%) | | |
| Chills | 13 (9%) | 9 (6%) | 4 (3%) | | | |
| Fatigue | 24 (17%) | 12 (8%) | 10 (7%) | 2 (1%) | | |
| Edema | 7 (5%) | 4 (3%) | 2 (1%) | 1 (1%) | | |
| Peripheral edema | 32 (22%) | 22 (15%) | 8 (6%) | 2 (1%) | | |
| Pain | 8 (6%) | 4 (3%) | 3 (2%) | 1 (1%) | | |
| Pyrexia | 11 (8%) | 6 (4%) | 5 (3%) | | | |
| Infections and infestations | 71 (49%) | | | | | |
| Herpes zoster | 11 (8%) | 1 (1%) | 6 (4%) | 4 (3%) | | |
| Nasopharyngitis | 11 (8%) | 10 (7%) | 1 (1%) | | | |
| Skin infection | 8 (6%) | | 5 (3%) | 3 (2%) | | |
| Urinary tract infection | 8 (6%) | 4 (3%) | 4 (3%) | | | |
| Investigations | 37 (26%) | | | | | |
| CD4 lymphocytes decreased | 8 (6%) | | 3 (2%) | 5 (3%) | | |
| Metabolism and nutrition disorders | 21 (15%) | | | | | |
| Decreased appetite | 6 (4%) | 3 (2%) | 3 (2%) | | | |
| Musculoskeletal and connective tissue disorders | 35 (24%) | | | | | |
| Arthralgia | 6 (4%) | 4 (3%) | 2 (1%) | | | |
| Back pain | 6 (4%) | 3 (2%) | 2 (1%) | 1 (1%) | | |
| Pain in extremity | 9 (6%) | 4 (3%) | 5 (3%) | | | |
| Neoplasms benign, malignant and unspecified (including cysts and polyps) | 22 (15%) | | | | | |
| Nervous system disorders | 46 (32%) | | | | | |
| Dizziness | 6 (4%) | 6 (4%) | | | | |
| Headache | 18 (13%) | 15 (10%) | 2 (1%) | 1 (1%) | | |
| Tremor | 7 (5%) | 6 (4%) | 1 (1%) | | | |
| Psychiatric disorders | 42 (29%) | | | | | |
| Anxiety | 6 (4%) | 3 (2%) | 3 (2%) | | | |
| Depression | 9 (6%) | 4 (3%) | 3 (2%) | 2 (1%) | | |
| Insomnia | 22 (15%) | 16 (11%) | 6 (4%) | | | |
| Respiratory, thoracic and mediastinal disorders | 34 (24%) | | | | | |
| Cough | 12 (8%) | 11 (8%) | 1 (1%) | | | |
| Dyspnea | 11 (8%) | 8 (6%) | 3 (2%) | | | |
| Skin and subcutaneous tissue disorders | 56 (39%) | | | | | |
| Pruritus | 20 (14%) | 5 (3%) | 12 (8%) | 3 (2%) | | |
| Rash | 7 (5%) | 3 (2%) | 2 (1%) | 2 (1%) | | |

Data are not provided in this table for visits beyond 24 weeks following initiation of treatment of the last subject.

patients were in the study for over 2 years and a further two patients were in the study for over 3 years. The longest duration of treatment was 1415 days.

The response to therapy is shown in Table 2. There were no CRs. Eleven percent of the efficacy group achieved a PR (Figures 1 and 2). The median time to response was 56 days. Of the 11 patients that achieved a PR, five (45%) patients reported a loss of response (median time: 56 days). 50% had stable disease and 35% had PD: the median time to PD was 191 days. In four patients, there were not enough data available to determine response.

### safety and adverse events

AEs which occurred in >3% patients are summarized in Table 3. Almost all patients (96%) experienced an AE, the majority of which were moderate (35%) or severe (34%). The most common AEs (occurrence in >10% of patients) by preferred term were as expected for this indication and class of compound. Of these AEs, none were classified as life threatening or led to death. Approximately 2% of the AEs reported were classified as being related to the study medication; lymphopenia and reduced CD4+ counts have been observed and are considered drug related. The clinical significance of these findings remains unclear.

A third of patients reported a serious adverse event (SAE) and approximately half of these were considered to be related to the study medication. A total of 108 SAEs were reported: 63 SAEs were classified as severe, 9 SAEs as life threatening and 8 SAEs resulted in death, the remaining SAEs were mild or moderate in nature. The most commonly reported SAEs included herpes zoster (8%) and skin infection (6%).

Overall, there were eight reported deaths: five due to sepsis (including septic shock, infection and cellulitis), one due to a second malignancy (esophageal carcinoma), one due to disease progression (MF) and one due to liver failure. Six cases were considered by the investigator not to be related to treatment with forodesine, one case of sepsis had a doubtful causality and one case of liver failure was deemed possibly related to the study medication.

Other common infections included: nasopharyngitis (8%), urinary tract infections (6%) and skin infections (6%). The majority of these infections were considered to be unrelated to the study medication or had a doubtful causality. Lymphopenia was observed in 10 patients (7%), and a decline in $CD4^+$ lymphocyte count in 8 patients (7%). There was no evidence of nephrotoxicity or bone marrow toxicity. MF and SS have been reported/suggested to cause immunosuppression; therefore, the etiology of some infectious event can be to the disease itself [9].

## discussion

In a previous study, oral forodesine (40–320 mg/m$^2$, daily) was administered to determine the maximum tolerated dose (MTD) and/or the optimal biologic dose, and PNP inhibition as evidenced by elevation of plasma deoxyguanosine levels. Patients with previously treated, refractory CTCL with stage IB disease or higher were eligible. From 36 of 56 subjects were treated with the optimal biologic oral dose of 80 mg/m$^2$, which corresponded approximately to 200 mg daily. The MTD was not reached. The median time to response was 42 days (25%–75%, range: 29–58 days). The overall response rate (ORR) was 39%, the median duration of response was 127 days (25%–75%) and the median time on treatment was 131 days (range: 1–479) [10].

These promising results were not confirmed by this study and here we did not observe any CRs, and only 11% of patients experienced a PR. The median time to response was much longer and the duration of response shorter. A reason for the poor outcome could be under dosing. In a Japanese phase I study in T/NK malignancies, a single oral dose of 300 mg was considered safe and tolerable with similar pharmacokinetic findings as in the phase I/II CTCL study mentioned above [11]. The MTD was not reached at a dose of 300 mg/day and a dose-finding study with up to 300 mg BID dosing is currently ongoing.

Forodesine is one of the most potent PNP inhibitors to enter clinical development [12]. In contrast to other purine nucleoside analogues (PNA) such as cladribine which inhibits adenosine deaminase, forodesine does not act via incorporation into DNA and inhibition of DNA synthesis but displays a highly selective PNP inhibitory action [13, 14], through competitive binding to the enzyme active site. Therefore, it was hypothesized that it could be superior to the other members of its family not only because of its more convenient oral administration, but also due to a potentially higher ORR and an optimally milder toxicity profile.

In this study, the response rate of forodesine was lower than in other studies with similar patient populations, such as the histone deacetylase inhibitors vorinostat [15], romidepsin [16] and panobinostat [17]. These agents are able to produce a response rate of between 20% and 35% with some durable responses.

Monochemotherapy with pegylated liposomal doxorubicin has resulted in a response rate of ~40% in a uniform patient population of patients with tumor-stage MF with and without lymph node involvement [18]. The progression-free survival in this study was ~6 months. Chemotherapy with pegylated liposomal doxorubicin was better tolerated than forodesine.

Almost all patients experienced at least one AE. The frequency of infections, some of them with fatal outcome, was significant in the patients treated with forodesine. This was not unexpected given that these CTCL patients are already immunosuppressed [19, 20]. However, the patients need careful monitoring for infectious episodes [9].

Despite some durable responses (median of 261 days until progression in the safety population), forodesine monotherapy showed limited efficacy in this, heavily treated CTCL population, who had already failed other therapies. The safety data support the use of forodesine with other CTCL therapies. Further investigations with optimized dosing and in combination are therefore warranted [21].

## acknowledgements

The authors thank all investigators from all study sites for taking part in this study. Mundipharma Research Limited provided a courtesy review for scientific accuracy.

## funding

This study was sponsored by BioCryst Pharmaceuticals, Inc.

## disclosure

RD participated as an investigator in this study and has consultant or advisory board relationship with, Merck Sharp & Dhome, and Spirig. MD participated as an investigator in this study. JS participated as an investigator in this study and received an honorarium as a speaker from Mundipharma International. EO participated as principal investigator in this study and received an honorarium from BioCryst Pharmaceuticals, Inc., as a speaker. SG received travel grants from MSD and BMS, and received research funding from the University of Zurich. TI participated as an investigator in this study. EG was an employee of BioCryst Pharmaceuticals, Inc. JE is a Consultant for BioCryst Pharmaceuticals, Inc. All remaining authors have declared no conflicts of interest.

## references


1. Willemze R, Jaffe ES, Burg G et al. WHO-EORTC classification for cutaneous lymphomas. Blood 2005; 105(10): 3768–3785.
2. Belloni B, Johansen N, Glass LF, Dummer R. Recent advances in the management of cutaneous lymphomas. Semin Oncol 2012; 39(2): 150–162.
3. Dummer R, Goldinger SM, Cozzio A et al. Cutaneous lymphomas: molecular pathways leading to new drugs. J Invest Dermatol 2012; 132(3 Pt 1): 517–525.
4. Bantia S, Ananth SL, Parker CD et al. Mechanism of inhibition of T-acute lymphoblastic leukemia cells by PNP inhibitor—BCX-1777. Int Immunopharmacol 2003; 3(6): 879–887.
5. Markert ML. Purine nucleoside phosphorylase deficiency. Immunodefic Rev 1991; 3(1): 45–81.
6. Gandhi V, Kilpatrick JM, Plunkett W et al. A proof-of-principle pharmacokinetic, pharmacodynamic, and clinical study with purine nucleoside phosphorylase inhibitor immucillin-H (BCX-1777, forodesine). Blood 2005; 106(13): 4253–4260.
7. Kicska GA, Long L, Horig H et al. Immucillin H, a powerful transition-state analog inhibitor of purine nucleoside phosphorylase, selectively inhibits human T lymphocytes. Proc Natl Acad Sci USA 2001; 98(8): 4593–4598.
8. Al-Kali A, Gandhi V, Ayoubi M et al. Forodesine: review of preclinical and clinical data. Future Oncol 2010; 6(8): 1211–1217.
9. Axelrod PI, Lorber B, Vonderheid EC. Infections complicating mycosis fungoides and Sézary syndrome. JAMA 1992; 267(10): 1354–1358.
10. Duvic M, Forero-Torres A, Foss F et al. Response to oral forodesine in refractory cutaneous T-Cell lymphoma: interim results of a phase I/II study. Blood (ASH Annual Meeting Abstracts) 2007; 110: 122.
11. Ogura M, Tsukasaki K, Nagai H et al. Phase I study of BCX1777 (forodesine) in patients with relapsed or refractory peripheral T/natural killer-cell malignancies. Cancer Sci 2012; 103(7): 1290–1295.
12. Robak T, Korycka A, Lech-Maranda E, Robak P. Current status of older and new purine nucleoside analogues in the treatment of lymphoproliferative diseases. Molecules 2009; 14(3): 1183–1226.
13. Alonso R, Lopez-Guerra M, Upshaw R et al. Forodesine has high antitumor activity in chronic lymphocytic leukemia and activates p53-independent mitochondrial apoptosis by induction of p73 and BIM. Blood 2009; 114(8): 1563–1575.
14. Lech-Maranda E, Robak E, Robak T. Novel systemic drugs for cutaneous T-cell lymphoma. Recent Pat Anticancer Drug Discov 2011; 6(1): 70–93.
15. Duvic M, Olsen EA, Breneman D et al. Evaluation of the long-term tolerability and clinical benefit of vorinostat in patients with advanced cutaneous T-cell lymphoma. Clin Lymphoma Myeloma 2009; 9(6): 412–416.
16. Whittaker SJ, Demierre MF, Kim EJ et al. Final results from a multicenter, international, pivotal study of romidepsin in refractory cutaneous T-cell lymphoma. J Clin Oncol 2010; 28(29): 4485–4491.
17. Duvic M, Dummer R, Becker J et al. Panobinostat activity in both bexarotene-exposed and -naïve patients with refractory cutaneous T-cell lymphoma: results of a phase II trial. Eur J Cancer 2013; 49(2): 386–394.
18. Dummer R, Quaglino P, Becker JC et al. A prospective international multicentre phase II trial of intravenous pegylated liposomal doxorubicin (PLD) mono-chemotherapy in patients with advanced Mycosis fungoides stage IIB, IVA and IVB (Final Results from EORTC 21012). J Clin Oncol 2012; 30(33): 4091–4097.
19. Dalton JA, Yag-Howard C, Messina JL, Glass LF. Cutaneous T-cell lymphoma. Int J Dermatol 1997; 36(11): 801–809.
20. Kim YH, Hoppe RT. Mycosis fungoides and the Sézary syndrome. Semin Oncol 1999; 26(3): 276–289.
21. Guenova E, Hoetzenecker W, Rozati S et al. Novel therapies for cutaneous T-cell lymphoma: what does the future hold? Expert Opin Investig Drugs 2014; 23(4): 457–467.