Acta Derm Venereol 2015; 95: 72–77

CLINICAL REPORT

# Vorinostat for Refractory or Relapsing Epidermotropic T-cell Lymphoma: A Retrospective Cohort Study of 15 Patients

Anne KOGGE, Christelle VOLTEAU, Mélanie SAINT-JEAN, Lucie PEUVREL, Annabelle BROCARD, Anne-Chantal KNOL, Jean-Jaques RENAUT, Brigitte DRÉNO and Gaëlle QUÉREUX
*Department of Dermato-Oncology, Nantes University Hospital, INSERM 892, Nantes, France*

**Since the approval of vorinostat for the treatment of refractory cutaneous epidermotropic T-cell lymphoma (CTCL) in 2006, very little data about this treatment have been published. The aim of this retrospective study was to assess the efficacy and safety of vorinostat in patients with CTCL treated between 2007 and 2013 in our department. Fifteen patients (median age 64 years) were included: 9 with Sézary syndrome and 6 with mycosis fungoides. They were all in progression and the median number of systemic treatments previously administered was 3 (range 1–7). With vorinostat treatment, the best response was partial remission in 5 patients (33%) and stabilization in 4 patients (27%). Six patients experienced disease progression. The mean time to response and response duration were 70 (range 31–140) and 300 days (range 157–663) , respectively. The most frequent adverse events were asthenia, weight loss, nausea and anaemia. Vorinostat could be a therapeutic alternative for CTCL after treatment failure.** ***Key words: CTCL; cutaneous T-cell lymphoma; vorinostat; Zolinza; efficacy; tolerance; safety.***

Accepted Apr 24, 2014; Epub ahead of print May 7, 2014

Acta Derm Venereol 2015; 95: 72–77.

Gaëlle Quereux, Department of Dermato-Oncology, Nantes University Hospital, INSERM 892; 1 place Alexis Ricordeau, FR-44093 Nantes Cedex, France. E-mail: gaelle.quereux@gmail.com

Cutaneous T-cell lymphomas (CTCL) are a heterogeneous group of lymphoproliferative disorders characterized by an initial cutaneous location. They are classified according to the WHO/EORTC classification (1). Mycosis fungoides (MF) is the most common form, accounting for more than half of CTCL, while Sézary syndrome (SS) is a rare leukaemic or erythrodermic form of CTCL (1).

Although early stages of MF (IA, IB, IIA) usually have an indolent course and an excellent prognosis with a 5-year survival of 73–93% (2), more advanced stages of MF (IIB or above) and SS have a poorer prognosis, with a 5-year survival of 27–44% and 24%, respectively (3).

Disease stage is therefore one of the main criteria when deciding on treatment for CTCL. Early forms (IA–IIA) are usually treated with topical agents, such as dermocorticoids, topical chemotherapy or phototherapy (psoralen plus ultraviolet A (PUVA)-therapy and ultraviolet B (UVB)-TL01). Conversely, more advanced forms (IIB–IV) usually require systemic treatments, such as interferon-α, retinoids or mono- or polychemotherapies (4, 5). Some patients are refractory to these conventional treatments or relapse rapidly after their discontinuation. Thus, new drugs are developed to treat these refractory CTCL.

Vorinostat (Zolinza®; Merck & Co., Whitehouse Station, NJ, USA) is one of these new therapies. Vorinostat is the first histone deacetylase inhibitor (HDACi) approved by the Food and Drug Administration for the treatment of CTCL (6).

*In vitro*, vorinostat has been shown to induce an accumulation of acetylated histones and cause cell cycle arrest and apoptosis in tumour cell lines derived from various tumour types including CTCL (7, 8).

The clinical efficacy of vorinostat alone or in combination with other treatments has been assessed in several tumours such as non-small cell lung cancer (9, 10), myeloid leukaemia (11) and breast cancer (12), and is currently under investigation in numerous cancers.

In CTCL patients, the clinical efficacy of vorinostat has been shown in 2 phase II studies (13, 14) conducted in 74 and 33 patients, respectively, with a response rate of 29.7% and 23.4%, respectively. Vorinostat is indicated for the treatment of refractory or relapsing CTCL after failure of at least 2 first-line systemic treatments (6). Since these 2 pivotal studies published in 2007, there has been little published data on vorinostat for the treatment of CTCL.

We therefore decided to conduct a retrospective study to assess the efficacy and safety of vorinostat in standard practice, outside the context of a clinical study, in a cohort of patients with CTCL treated with vorinostat between December 2007 and March 2013.

## MATERIALS AND METHODS

### *Patients*

This retrospective study included all patients with CTCL who were treated with vorinostat in the Dermato-Oncology Department, Nantes University Hospital between December 2007 and March 2013.

The diagnosis of CTCL was based on clinical, histological, immunohistochemical and molecular biology features (T-cell receptor gene rearrangement in the blood and skin).

All patients were classified according to the TNMB classification of the International Society for Cutaneous Lymphomas (ISCL)/EORTC (2).

For each patient, the following data were collected before treatment initiation: age, gender, duration of lymphoma, topical and systemic treatments previously received, medical history, extension assessment including thoraco-abdomino-pelvic computed tomography, biopsies of suspicious adenopathies, laboratory tests, such as kidney, liver and thyroid function, lipid profile, and Sézary cell count.

### *Assessment*

The objective of this study was to assess the efficacy and safety of vorinostat in patients with CTCL persisting or progressing after failure of at least 2 first-line systemic treatments.

The therapeutic response was assessed globally in all compartments (skin, nodes, blood). A complete response was defined as the complete clinical, biological and histological disappearance of the CTCL. A partial response was defined as a reduction in at least 50% of the lesions. A progression was defined as a worsening of 30% of the lesions, blood or visceral lymph node spreading of the CTCL, or a major CTCL-related degradation of the general condition. Patients not meeting these definitions were considered stabilized.

Patients were assessed monthly through clinical and biological parameters, and some patients underwent skin biopsies (for histology and molecular biology).

The time to response was defined as the time between the first vorinostat administration and the first response to treatment observed. The time to the best response under treatment was defined as the time between the first vorinostat administration and the best response observed under vorinostat. The response duration was determined from the first response observed until disease progression.

Vorinostat-related adverse events were graded according to the Common Terminology Criteria for Adverse events (CTCAE) classification Version 4.0 (15).

### *Treatment*

The treatment was prescribed after obtaining a Temporary Use Authorization (TUA). Vorinostat was administered orally, once a day, at a dose of 300–400 mg/day, on an outpatient basis. The starting dose was determined individually: in the absence of comorbidities treatment was initiated at a dose of 400 mg/day, and in patients at high risk of thromboembolism or with liver or renal failure, the starting dose was 300 mg/day. In case of poor tolerance, the dose was reduced to 300 mg/day or 300 mg/day 5 days a week. The treatment was continued until disease progression or occurrence of an unacceptable adverse event.

## RESULTS

### *Patients*

Fifteen patients were included (9 men, 6 women, median age 64 years (range 36–76 years)). There were 2 early stages (2 stages IB), 13 more advanced stages (2 stages IIB, 2 stages IIIA, 9 stages IVa). Nine patients had SS (60%), 6 patients had MF (40%) of whom 2 had pilotropic MF and 1 had CD30-transformed MF (Table I).

Eighty-seven percent of patients had received at least one topical treatment before vorinostat initiation.

Table I. *Baseline patient characteristics* (n = *15*)

| Patient | Age[a]/Sex | CTCL type | CTCL duration (months)[a] | Staging[a] | Topical treatments[b] | Systemic treatments[b] | Associated treatments | Dose (mg/day) | Response | TTR (days) | DOR (days) | Treatment duration (days) | Follow-up duration (days) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 66/F | Sézary syndrome | 7 | IVA1 | 3 | 4 | UVB-TL01 | 300 | PR | 87 | 187 | 783 | 783 |
| 2 | 64/F | Pilotropic MF | 7 | IIIA | 7 | 1 | – | 400 | DP | – | – | 9 | 9 |
| 3 | 49/M | MF | 5 | IIB | 4 | 3 | PUVA | 400 | S | – | – | 256 | 531 |
| 4 | 66/F | MF | 20 | IB | 2 | 3 | UVB-TL01 | 300 | PR | 32 | 663 | 664 | 695 |
| 5 | 44/M | Sézary syndrome | 4 | IVA1 | 0 | 1 | – | 300 | PR | 60 | 157 | 205 | 302 |
| 6 | 67/M | Sézary syndrome | 2 | IVA1 | 1 | 2 | – | 400 | S | – | – | 55 | 112 |
| 7 | 58/F | Sézary syndrome | 2 | IVA1 | 0 | 3 | – | 300 | S | – | – | 88 | 122 |
| 8 | 36/F | MF | 3 | II B | 3 | 2 | – | 400 | DP | – | – | 63 | 307 |
| 9 | 72/F | Sézary syndrome | 7 | IVA1 | 1 | 3 | – | 300 | PR | 31 | 238 | 535 | 1,410 |
| 10 | 76/M | CD30- transformed MF | 11 | IIIA | 4 | 5 | BCNU | 400 | PR | 140 | 259 | 486 | 523 |
| 11 | 60/F | Sézary syndrome | 5 | IVA1 | 2 | 2 | – | 400 | S | – | – | 396 | 1,594 |
| 12 | 61/F | Sézary syndrome | 15 | IVA1 | 6 | 3 | UVB-TL01 | 300 | DP | – | – | 74 | 129 |
| 13 | 47/M | Pilotropic MF | 9 | IB | 5 | 7 | Interferon-α | 400 | S | – | – | 263 | 731 |
| 14 | 67/M | Sézary syndrome | 19 | IVA1 | 2 | 1 | – | 300 | S | – | – | 93 | 213 |
| 15 | 76/F | Sézary syndrome | 2 | IVA1 | 2 | 1 | – | 300 | DP | – | – | 2 | 2 |
| Mean | 60.6 | | 7.42 | | 2.8 | 2.8 | | 346.7 | | 70 | 300.8 | 264.8 | 497.5 |
| Median | 64 | | 6.70 | | 2 | 3 | | 300 | | 60 | 238 | 205 | 307 |

[a]At the time of vorinostat initiation.
[b]Before initiating vorinostat therapy.
MF: mycosis fungoides; PR: partial response; DP: disease progression; S: stabilization; TTR: time to response; DOR: duration of response; CTCL: cutaneous T-cell lymphomas; BCNU: bis-chloroethylnitrosourea.

The median number of topical treatments previously administered was 3 (range 0–7). The topical treatments previously received were: carmustine in 6 patients, mechlorethamine in 6 patients, dermocorticoids in 2 patients, PUVA therapy in 7 patients, UVB-TL01 in 10 patients, and radiotherapy in 5 patients.

Most patients (87%) had previously received at least two systemic treatments. Only 2 patients (13%) were treated with vorinostat who had previously received only one systemic treatment, because of a contra-indication to the other systemic treatments available at that time. The median number of systemic treatments previously administered was 3 (range 1–7).

The systemic treatments previously administered were: interferon-α in 12 patients, pegylated liposomal doxorubicin in 4 patients, bexarotene in 14 patients, alitretinoin in 1 patient, acitretin in 1 patient, methotrexate in 2 patients, and romidepsin in 4 patients.

The mean CTCL duration was 7.4 years (range 1.6–20.3; median 6.7 years) at the time of vorinostat initiation.

### *Treatment*

Vorinostat was administered at a dose of 300 mg/day in 8 patients and 400 mg/day in 7 patients. The mean treatment duration was 264 (range 2–783) days (median 205 days). At the end of the study, 1 patient was still being treated with vorinostat.

### *Response to treatment*

With a mean follow-up duration of 497 (range 2–1594) days (median 307 days), the best response observed was a partial response in 5 patients (33%); no complete response was observed. Respectively, 6 (40%) and 4 (27%) patients experienced disease stabilization and progression under treatment (Table I).

The responses obtained according to the type of lymphoma, disease stage and vorinostat dose are shown in Table II.

Table II. *Best response to vorinostat in all patients and according to the type and stage of lymphoma and dose of vorinostat*

| | CR | PR % (*n*) | SD % (*n*) | PD % (*n*) |
|---|---|---|---|---|
| All patients (*n* = 15) | 0 | 33 (5) | 40 (6) | 27 (4) |
| Type of lymphoma | | | | |
| MF (*n* = 6) | 0 | 13 (2) | 13 (2) | 13 (2) |
| SS (*n* = 9) | 0 | 20 (3) | 27 (4) | 13 (2) |
| Lymphoma stage | | | | |
| Early stage (IA–IIA) (*n* = 2) | 0 | 50 (1) | 50 (1) | 0 (0) |
| Advanced stage (IIIB) (*n* = 13) | 0 | 27 (4) | 33 (5) | 27 (4) |
| Dose of vorinostat | | | | |
| 300 mg/day (*n* = 8) | 0 | 27 (4) | 13 (2) | 13 (2) |
| 400 mg/day (*n* = 7) | 0 | 7 (1) | 27 (4) | 13 (2) |

CR: complete response; PR: partial response; SD: stable disease; PD: progressive disease; MF: mycosis fungoides.

In univariate survival analysis, no factor influencing the response was found, including age (HR = 1.0 [0.97; 1.17] $p = 0.1992$), gender (HR = 1.60 [0.27; 9.63], $p = 0.6069$), number of topical (HR = 0.71 [0.40; 1.26], $p = 0.2391$) or systemic treatments (HR = 1.4 [0.63; 1,71], $p = 0.8923$) previously received, duration of CTCL (HR = 1.00 [0.99; 1.02], $p = 0.5440$), stage of CTCL (HR = 0.6 [0.07; 5.43], $p = 0.6488$), or dose of vorinostat administered (HR = 0.18 [0.002; 1.68], $p = 0.1337$). The mean time to response was 70 days (range 31–140) (median 60 days). The mean response duration was 300 days (range 157–663, median 238 days).

The reasons for treatment discontinuation were its ineffectiveness in 11 patients (53%) and the occurrence of adverse events in 3 patients (26%). Only 1 patient was still being treated at the end of the study.

Vorinostat was prescribed as monotherapy in 9 patients, in combination with UVB-TL01 phototherapy in 3 patients, PUVA-therapy in 1 patient, interferon-α in 1 patient and bis-chloroethylnitrosourea in 1 patient.

Among the 5 responders at the end of the study, 1 was still being treated with vorinostat as maintenance therapy. Vorinostat was discontinued in the 4 remaining responders due to prolonged hyperthermia in 1 patient and disease progression after initial response in the 3 remaining patients.

In the 9 patients with Sézary syndrome, the rate of Sézary cells under treatment with vorinostat had decreased in 2 patients (including 1 responder and 1 non-responder) and was stable or increased in the remaining patients.

### *Adverse events*

The most frequent grade I–II adverse events were weight loss (47%), asthenia (40%), anaemia (40%), anorexia (33%), increase in serum creatinine (27%), thrombopaenia (20%), and vomiting (20%) (Table III).

Five grade III adverse events were observed: sepsis in 2 patients, asthenia in 1 patient, anorexia in 1 patient and chronic renal failure in one patient. Concerning this patient, he had a pre-existing chronic renal failure grade 2, which worsened into chronic renal failure grade 3 under treatment.

Four grade IV adverse events were observed: 3 deaths unrelated to vorinostat, but due to disease progression, and 1 anaemia at 5.6 g/dl. Complete aetiological assessment of the case of anaemia highlighted a hypoplastic normocytic anaemia with normal vitamin B12, folate and iron status, normal haptoglobin, normal thyroid function and absence of inflammatory syndrome.

## DISCUSSION

This study revealed a response rate of 33% (5/15) in patients with refractory or resistant CTCL treated

Table III. *Vorinostat-related adverse events*

| Adverse events | Total *n* (%) | Grade according to CTCAE v4.0 I–II *n* (%) | III *n* (%) | IV *n* (%) |
|---|---|---|---|---|
| Asthenia | 7 (47) | 6 (40) | 1 (7) | |
| Anorexia | 5 (33) | 5 (33) | | |
| Weight loss | 7 (47) | 7 (47) | | |
| Digestive disorders | | | | |
| Diarrhoea | 2 (13) | 2 (13) | | |
| Constipation | 1 (7) | 1 (7) | | |
| Nausea/vomiting | 3 (20) | 3 (20) | | |
| Abdominal pain | 1 (7) | 1 (7) | | |
| Xerostomia | 1 (7) | 1 (7) | | |
| Dysgeusia | 2 (13) | 2 (13) | | |
| Infectious complications | | | | |
| Herpes simplex virus | 2 (13) | 2 (13) | | |
| Urinary | 1 (7) | 1 (7) | | |
| ENT | 1 (7) | 1 (7) | | |
| Folliculitis | 1 (7) | 1 (7) | | |
| Septicaemia | 3 (20) | 1 (7) | 2 (13) | |
| Unexplained fever | 1 (7) | 1 (7) | | |
| Haematology | | | | |
| Lymphopaenia | 2 (13) | 1 (7) | 1 (7) | |
| Anaemia | 7 (47) | 6 (40) | | 1 (7) |
| Macrocytosis | 3 (20) | 3 (20) | | |
| Thrombopaenia | 3 (20} | 3 (20) | | |
| Other | | | | |
| Hypokalaemia | 1 (7) | 1 (7) | | |
| Hepatic cytolysis | 4 (27) | 4 (27) | | |
| y-Glutamyltranspeptidase | 2 (13) | 2 (13) | | |
| Renal failure | 5 (33) | 4 (27) | 1 (7) | |
| Depression | 1 (7) | 1 (7) | | |
| Maculopapular rash | 1 (7) | 1 (7) | | |
| Alopecia | 2 (13) | 2 (13) | | |
| Cramps | 1 (7) | 1 (7) | | |
| Death | 3 (20) | | | 3 (20) |

CTCAE: Common Terminology Criteria for Adverse Events.

with vorinostat after failure of 2 first-line systemic treatments. This rate was slightly higher than those reported in the 2 pivotal studies published previously.

This study was the first retrospective study to assess the use of vorinostat in patients with epidermotropic CTCL conducted in standard practice since its marked authorization was obtained in 2007.

Since the 2 pivotal studies published in 2007, there has been little published data on vorinostat for treatment of CTCL; only 3 studies have been published. The first study was a *post hoc* analysis performed in 2009 in the 74 patients of the multicentric phase IIB study (14). Among the 6 patients responding to vorinostat and treated for at least 2 years, 5 maintained a clinical benefit (16). Regarding long-term adverse events, the following grade III/IV adverse events were observed: anorexia ($n=1$), increase in phosphokinase creatinine ($n=1$), pulmonary embolism ($n=1$), rash ($n=1$) and thrombocytopaenia ($n=1$) (16).

The second study was a phase I study (17), published in 2012, on vorinostat at a dose of 400 mg/day in 6 Japanese patients. This study did not show any difference in terms of tolerance to, and pharmacodynamics of, vorinostat between the Japanese and non-Japanese populations studied previously (13, 14). Assessing efficacy was not the primary objective of this study, but no objective response was observed in any of the 6 patients. However, there was an unconfirmed partial response and at least 12-week stabilization in 6 patients, suggesting the efficacy of vorinostat in the Japanese population (17).

The third study was an *in vitro* study coupled with a phase I clinical trial of vorinostat in combination with bexarotene in 23 patients with CTCL. A synergistic effect of the 2 agents was highlighted *in vitro*. A partial clinical response was observed in 4 patients and a reduction in pruritus in 7 patients (18).

The results of our study were obtained with off-protocol use of vorinostat in unselected patients with significant comorbidities and some elderly patients (median age 64 years; age range 36–76 years).

This 33% response rate is particularly interesting, given that this population with CTCL was already resistant to 2 first-line systemic treatments and most of them had an advanced form of the disease (13 patients were at least IIB stage).

In this study, tolerance to vorinostat was good. The most frequent adverse events observed were asthenia, weight loss, anaemia, increase in serum creatinine and anorexia in accordance with the previous studies on vorinostat. The frequency of renal failure was higher in our cohort ($n=5$, 33%) than in the clinical trials of Duvic et al. (13) and Olsen et al. (14) (16% and 14.9%, respectively).

The very low number of severe infectious complications in our study should be noted. Indeed, 2 grade III (13%) and no grade IV infections were observed. In the study by Duvic et al. (13), no infectious complication was observed. In the study by Olsen et al. (14), which included 77 patients, only one case (1.4%) of grade III/IV infectious complication (a streptococcal bacteraemia) was observed.

Regarding infections, vorinostat has a considerable advantage compared with conventional chemotherapy, which is usually used at this stage of the disease. This is due to the absence of use of peripheral or central parenteral route and to the absence of major immunosuppression.

The absence of thromboembolic complications should be noted in this study, while they have been reported in 5% of patients in both pivotal studies as grade III/IV adverse events.

The time to response (TTR) was 10 weeks, in accordance with those previously observed (from 8 (14) to 12 (13) weeks). This TTR is important knowledge in clinical practice; it may appear relatively long, but it must be taken into account before considering treatment failure. The response duration in our study was 9.8 months. This is a sustained response compared with the other studies, which measured a response duration of 3.45–6 months.

No factor influencing the response was found: the response was not influenced by age, gender, stage of lymphoma, number or type of previous treatment or dose of vorinostat.

The absence of influence of the number and type of previous treatments on the response seems to confirm the absence of cross-reactivity with currently available treatments, especially with bexarotene (received by all responder patients), as shown previously.

This study provides information on the efficacy of vorinostat in patients previously treated with another HDACi, the romidepsin. Among the 4 patients previously treated with romidepsin, 2 partial responses with vorinostat were noted. Among the 2 responders to romidepsin, 1 also responded to vorinostat, and the other remained stable. Among the 2 non-responders to romidepsin, 1 progressed and the other presented a PR>50% with vorinostat therapy.

The main limitations of this study were its retrospective nature with the resulting biases, which led to a global assessment of the response, which was not based on a tool such as mSWAT. Moreover, the sample size was limited, but it should be noted that CTCL is a rare condition and that patients treated with vorinostat necessarily had to be refractory to conventional treatments.

Although the response to vorinostat is promising, treatment escape is common. The mechanisms leading to histone deacetylase inhibitors (HDACi) resistance in CTCL are poorly known, they are probably multifactorial and have resulted in numerous studies (19).

Recent advances in the knowledge of these resistance factors support the use of HDACi in combination with other therapies. The loss of the pro-apoptotic protein Bim and the abnormal activation of the mitogen-activated protein kinase pathway could be a fundamental resistance mechanism to HDACi compared with parental cells (19). Chakraborty et al. (20) have therefore studied *in vitro* the combination of romidepsin, which is another HDACi, with an anti-mitogen-activated kinase (MEK) for the treatment of CTCL. *In vitro*, the anti-MEK combined with romidepsin leads specifically to apoptosis and could then be correlated with the restoration of Bim. HDACi combined with anti-MEK could therefore increase apoptosis in resistant mutated cells compared with HDACi alone, encouraging the use of this bi-therapy in future clinical studies.

Since pre-clinical studies have shown that the combination of RAR/RXR agonists and HDACi increases the action of RAR/RXR on gene activation and transcription, Dummer et al. (18) have recently studied the *in vitro* and *in vivo* efficacy of the combination of bexarotene and vorinostat for advanced resistant or refractory CTCL. They have shown that, when used in combination, vorinostat and bexarotene decrease CTCL cell line survival more significantly than each treatment alone. However, the clinical impact was low.

Overall, the results of the current study confirm those of previous clinical trials on refractory or relapsing CTCL after failure of 2 first-line systemic treatments in a population that have received numerous pre-treatments in real-life conditions.

Vorinostat and, more broadly, the class of HDACi, represent promising therapies for the future for CTCL patients. The mechanisms of action of vorinostat and its resistance factors are unknown, but recent studies suggest clinical benefits of vorinostat when used in association with other treatments, such as bexarotene or anti-MEK, in combination or sequential regimen.

Many molecules belonging to the HDACi family have therefore been developed recently: belinostat, panabinostat, abexinostat, SB939, resminostat, givinostat, quisinostat, pentobinostat, and CUDC-101 and are currently under investigation as anticancer agents.

*The authors declare no conflicts of interest.*

## REFERENCES

1. Willemze R, Jaffe ES, Burg G, Cerroni L, Berti E, Swerdlow SH, et al. WHO-EORTC classification for cutaneous lymphomas. Blood 2005; 105: 3768–3785.
2. Olsen E, Vonderheid E, Pimpinelli N, Willemze R, Kim Y, Knobler R, et al. Revisions to the staging and classification of mycosis fungoides and Sezary syndrome: a proposal of the International Society for Cutaneous Lymphomas (ISCL) and the cutaneous lymphoma task force of the European Organization of Research and Treatment of Cancer (EORTC). Blood 2007; 110: 1713–1722.
3. Kim YH, Liu HL, Mraz-Gernhard S, Varghese A, Hoppe RT. Long-term outcome of 525 patients with mycosis fungoides and Sézary syndrome: clinical prognostic factors and risk for disease progression. Arch Dermatol 2003; 139: 857–866.
4. Beylot-Barry M, Dereure O, Vergier B, Barete S, Laroche L, Machet L, et al. Prise en charge des lymphomes T cutanés: recommandations du Groupe français d'étude des lymphomes cutanés. Ann Dermatol Venereol 2010; 137: 611–621.
5. Trautinger F, Knobler R, Willemze R, Peris K, Stadler R, Laroche L, et al. EORTC consensus recommendations for the treatment of mycosis fungoides/Sézary syndrome. Eur J Cancer 2006; 42: 1014–1030.
6. Mann BS, Johnson JR, Cohen MH, Justice R, Pazdur R. FDA approval summary: vorinostat for treatment of advanced primary cutaneous T-cell lymphoma. Oncologist 2007; 12: 1247–1252.
7. Zhang C, Richon V, Ni X, Talpur R, Duvic M. Selective induction of apoptosis by histone deacetylase inhibitor SAHA in cutaneous T-cell lymphoma cells: relevance to mechanism of therapeutic action. J Invest Dermatol 2005; 125: 1045–1052.
8. Marks P, Rifkind RA, Richon VM, Breslow R, Miller T, Kelly WK, Histone deacetylases and cancer: causes and therapies. Nat Rev Cancer 2001; 1: 194–202.
9. Ramalingam SS, Maitland ML, Frankel P, Argiris AE, Koczywas M, Gitlitz B, et al. Carboplatin and Paclitaxel in combination with either vorinostat or placebo for first-line therapy of advanced non-small-cell lung cancer. J Clin Oncol 2010; 28: 56–62.
10. Traynor AM, Dubey S, Eickhoff JC, Kolesar JM, Schell K,

Huie MS, et al. Vorinostat (NSC# 701852) in patients with relapsed non-small cell lung cancer: a Wisconsin Oncology Network phase II study. J Thorac Oncol 2009; 4: 522–526.
11. Garcia-Manero G, Tambaro FP, Bekele NB, Yang H, Ravandi F, Jabbour E, et al. Phase II trial of vorinostat with idarubicin and cytarabine for patients with newly diagnosed acute myelogenous leukemia or myelodysplastic syndrome. J Clin Oncol 2012; 30: 2204–2210.
12. Munster PN, Thurn KT, Thomas S, Raha P, Lacevic M, Miller A, et al. A phase II study of the histone deacetylase inhibitor vorinostat combined with tamoxifen for the treatment of patients with hormone therapy-resistant breast cancer. Br J Cancer 2011; 104: 1828–1835.
13. Duvic M, Talpur R, Ni X, Zhang C, Hazarika P, Kelly C, et al. Phase 2 trial of oral vorinostat (suberoylanilide hydroxamic acid, SAHA) for refractory cutaneous T-cell lymphoma (CTCL). Blood 2007; 109: 31–39.
14. Olsen EA, Kim YH, Kuzel TM, Pacheco TR, Foss FM, Parker S, et al. Phase IIb multicenter trial of vorinostat in patients with persistent, progressive, or treatment refractory cutaneous T-cell lymphoma. J Clin Oncol 2007; 25: 3109–3115.
15. National Institutes of Health, National Cancer Institute. Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0 [Internet]. 2009. Available from: http: // evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf.
16. Duvic M, Olsen EA, Breneman D, Pacheco TR, Parker S, Vonderheid EC, 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: 412–416.
17. Wada H, Tsuboi R, Kato Y, Sugaya M, Tobinai K, Hamada T, et al. Phase I and pharmacokinetic study of the oral histone deacetylase inhibitor vorinostat in Japanese patients with relapsed or refractory cutaneous T-cell lymphoma. J Dermatol 2012; 39: 823–828.
18. Dummer R, Beyer M, Hymes K, Epping MT, Bernards R, Steinhoff M, et al. Vorinostat combined with bexarotene for treatment of cutaneous T-cell lymphoma: in vitro and phase I clinical evidence supporting augmentation of retinoic acid receptor/retinoid X receptor activation by histone deacetylase inhibition. Leuk Lymphoma 2012; 53: 1501–1508.
19. Robey RW, Chakraborty AR, Basseville A, Luchenko V, Bahr J, Zhan Z, et al. Histone deacetylase inhibitors: emerging mechanisms of resistance. Mol Pharm 2011; 8: 2021–2031.
20. Chakraborty AR, Robey RW, Luchenko VL, Zhan Z, Piekarz RL, Gillet J-P, et al. MAPK pathway activation leads to Bim loss and histone deacetylase inhibitor resistance: rationale to combine romidepsin with an MEK inhibitor. Blood 2013; 121: 4115–4125.