Horizon Scanning in Oncology

Romidepsin (Istodax®) for the treatment of patients with relapsed or refractory peripheral T-cell lymphoma (PTCL) after prior systemic therapy

Ludwig Boltzmann Institut
Health Technology Assessment

DSD: Horizon Scanning in Oncology Nr. 025
ISSN online 2076-5940

Horizon Scanning in Oncology

Romidepsin (Istodax®) for the treatment of patients with relapsed or refractory peripheral T-cell lymphoma (PTCL) after prior systemic therapy

Ludwig Boltzmann Institut
Health Technology Assessment

Vienna, April 2012

Institute for Health Technology Assessment
Ludwig Boltzmann Gesellschaft

Author(s):	Katharina Hintringer, BA
Internal review:	Dr. Anna Nachtnebel, MSc
External review:	Prim. Univ. Doz. Dr. Michael A. Fridrik Innere Medizin 3, Zentrum für Hämatologie und medizinische Onkologie AKH Linz

DISCLAIMER

CONTACT INFORMATION

Publisher:
Ludwig Boltzmann Gesellschaft GmbH
Nußdorferstr. 64, 6 Stock, A-1090 Vienna
http://www.lbg.ac.at/de/lbg/impressum

Responsible for Contents:

Ludwig Boltzmann Institute of Health Technology Assessment (LBI-HTA)
Garnisongasse 7/20, A-1090 Vienna
http://hta.lbg.ac.at/

Decision support documents of the LBI-HTA do not appear on a regular basis and serve to publicize the research results of the Ludwig Boltzmann Institute of Health Technology Assessments.

Decision support documents of the LBI-HTA are only available to the public via the Internet at "http://eprints.hta.lbg.ac.at":

DSD: Horizon Scanning in Oncology Nr. 025
ISSN online 2076-5940

http://eprints.hta.lbg.ac.at/view/types/dsd.html

1 Drug description

Generic/Brand name/ATC code:

Romidepsin, (formerly referred to as depsipeptide, FK228) / Istodax ® / ATC code not yet assigned

romidepsin (Istodax®)

Developer/Company:

Celgene Corporation, USA

developer: Celgene Corporation

Description:

Romidepsin is a histone deacetylase inhibitor (HDI) with high inhibitory activity for class I histone deacetylases (HDACs). Currently, HDIs (e.g. vorinostat, romidepsin) are a promising class of chemotherapeutic agents in T-cell lymphomas but their exact mechanism by which their anti-tumour activity is mediated is not yet fully understood [1-4]. Descriptions of the mechanisms of action of romidepsin suggest that it leads to various antineoplastic effects including cell-cycle arrest and apoptosis by inhibiting the HDAC enzyme, induction of autophagy, reactive oxygen species generation, Hsp90 inhibition and disruption of the aggresome pathway [1, 3, 5].

romidepsin is a histone deacetylase inhibitor

its exact mechanism of action is not yet fully understood

Romidepsin is approved at a dose of 14mg/m^2 as a 4-hour intravenous infusion on days 1, 8 and 15 of a 28-day cycle for the treatment of patients suffering from cutaneous T-cell lymphoma (CTCL) or peripheral T-cell lymphoma (PTCL) [6-8]. Temporary delays, temporary or permanent dosage reduction to 10mg/m^2 or discontinuation of romidepsin may be necessary, depending on each individual patient's response and tolerability [1]. One trial in PTCL [9] and one in CTCL [10] limited the number of treatment cycles to a maximum of 6 with the option of extension for patients with stable disease or response [9, 10]. The US Food and Drug Administration (US FDA) recommends to repeat the treatment cycle every 28 days provided the patient continues to benefit from and tolerates the drug [11]. Currently no contraindications are listed for romidepsin. The most common and most severe adverse events observed with romidepsin are leucopoenia, lymphopenia, granulocytopenia, thrombocytopenia, fatigue and anaemia [1] and therefore, close monitoring of hematologic parameters is recommended in order to adjust the dosage of romidepsin if necessary [11].

recommended dose: 14mg/m^2 iv on days 1, 8 and 15 of a 28-day cycle

treatment continuation as long as the patient benefits from and tolerates the drug

2 Indication

Romidepsin (Istodax®) is indicated for the treatment of patients with relapsed or refractory peripheral T-cell lymphoma (nodal, extranodal or leukemic/disseminated) after prior systemic therapy.

relapsed or refractory PTCL

3 Current regulatory status

EMA: not yet approved orphan drug designation for CTCL and PTCL since 2005

In 2005, the European Medicines Agency (EMA) granted orphan drug designation for romidepsin (formerly depsipeptide) for the treatment of CTCL [12] and PTCL (nodal, extranodal and leukemic/disseminated) [13]. Romidepsin is not yet approved for any of these two indications in Europe, but is currently under authorisation review for the treatment of PTCL. In addition, a product-specific waiver was granted by the paediatric committee for this indication [14]. The Paediatric Committee of the EMA can waive the requirement to submit a paediatric investigation plan with the marketing authorisation application if the medicinal product a) is likely to be ineffective or unsafe in part or all of the paediatric population, b) is intended for indications that occur only in adult populations or c) does not represent a significant therapeutic benefit over existing treatment for paediatric patients [15].

FDA: 2009 – approval for CTCL 2011 – approval for PTCL

In 2004, the US Food and Drug Administration (FDA) issued an orphan drug designation for romidepsin for the treatment of non-Hodgkin's T-cell lymphomas, which includes CTCL and PTCL [16]. In November 2009, the FDA approved romidepsin for the treatment of CTCL in patients who have received at least one prior systemic therapy and extended the approved indication in June 2011 for the treatment of PTCL also to patients who have received at least one prior therapy [11]. The approval for both indications was issued in the fast track programme, which allows companies to submit modules of a new drug application (NDA) on an ongoing basis for a "rolling review" by the FDA as soon as the modules are submitted [17].

4 Burden of disease

NHL are a heterogeneous group of lymphoproliferative disorders

T-cell lymphomas belong to Non-Hodgkin's lymphomas (NHL), a heterogeneous group of lymphoproliferative disorders, and originate in T-cells (10-15%) [7]. Two of the most common subsets of T-cell lymphomas are cutaneous T-cell lymphomas (CTCL) and peripheral T-cell lymphomas (PTCL). About 5% to 10% of all NHLs are PTCLs [18-20]. PTCL arises from post-thymic T-cells at various stages of differentiation, and may be leukemic, nodal (i.e. lymphoma arises in lymph nodes or other lymphatic tissues such as the spleen) or extranodal (i.e., substantial part of NHL arises in other organs e.g., skin and gastrointestinal tract) in nature. The latter three form the basis of the World Health Organisation (WHO) classification of PTCL [21, 22].

5-10% of all NHLs are PTCL

most common PTCL subtypes: PTCL NOS, AILT, NKTCL, ATLL and ALCL

The most common types of PTCL include

- PTCL-not otherwise specified or unspecified (PTCL NOS, 25.9%),
- angioimmunoblastic T-cell lymphoma (AILT, 18.5%)
- natural killer/T-cell lymphomas (NKTCL, 10.4%)
- adult T-cell leukaemia/lymphoma (ATLL, 9.6%)
- anaplastic large-cell lymphoma (ALCL), which can be further distinguished into anaplastic lymphoma kinase (ALK) positive (ALCL ALK-positive; 6.6%) and ALCL ALK-negative (5.5%) [1, 23].

With regard to the different sub-types of PTCL there is geographical variation in the frequency of occurrence. In Europe, PTCL-NOS, ALCL and AITL account for about 75% of all PTCL cases [13]. Under PTCL-NOS a heterogeneous category of nodal and extranodal lymphomas are summarised that cannot be grouped into other more specifically defined T-cell lymphomas [24]. Because of the rarity and diversity of PTCLs, biology of the disease and definition of the optimal treatment is not well understood and developed [14]. PTCL is clinically highly variable, but in general very aggressive and does therefore not respond well to conventional chemotherapy; with exception of ALK-positive ALCL [1].

due to the diversity of PTCL the biology of the disease and the optimal treatment are not fully established

The median age at time of diagnosis over all subtypes is around 60 years with a range from 17 to 90 years [13, 25], with men being more often affected than women (2:1) [11]. The SEER (Surveillance, Epidemiology, and End Results) data in the US reports an incidence of 1.77/100,000 per year for T-cell and NK-cell lymphoma. Most PTCL patients present extranodal disease at time of diagnosis, which often contributes to a delay in diagnosis. Subsequently patients tend to present with more advanced stages of disease, a poorer performance status and an increased incidence of B-symptoms such as fever, weight loss and night sweats [13, 21]. Approximately 14%, 17%, 26% and 43% of cases are at stage I, II, III or IV, respectively, and bone marrow is involved in about 20% of patients at time of diagnosis [11].

median time at diagnosis: ~60 years

annual incidence: 1.77 per 100,000

PTCL is diagnosed by using various tests (e.g. examination of the peripheral blood or tissue biopsy for histological features supplemented by detailed immunochemistry, flow cytometry, cytogenetics and molecular genetics) by an expert haematology review in order to classify the presenting subtype correctly. Further, staging of the disease and subsequently assigning a prognostic score is essential for determining the therapeutic treatment management process [13]. Currently, the causes of T-cell lymphoma are not exactly known and most people diagnosed, have no known risk factors. One assumption is that certain infections may play an important role in causing/developing selected types of NHL [25].

diagnostic tests

staging of patients and assignment of a prognostic score is essential to define treatment strategy

Overall, PTCL is associated with a poor prognosis with a median 5-year overall survival (OS) rate of ~35%; except for the ALK-positive ALCL, which is associated with a better prognosis and a 5-year OS rate of around 70% [7, 14].

median 5-year OS for PTCL: ~35%

ALK-positive ALCL has a better prognosis

Based on the Ann Arbor staging classification for Hodgkin lymphoma (HL) and NHL four disease stages (stage I, II, III and IV) can be discriminated. Staging of the disease depends on the area(s) involved (i.e. stage I is attributed to NHL with a single lymph node group involved and stage IV disease is defined as the involvement of multiple extranodal sites or lymph nodes and extranodal sites) [23]. Additionally, different sub-classifications are added to describe the characteristics of the disease in more detail. For example the letters A and B are added for the absence (A) or presence (B) of B symptoms (i.e., fever >38°C, night sweat, weight loss >10% over 6 months) [4, 9], the letter X is added when the tumour bulk is >10 cm and E indicates extranodal disease [23]. The Ann Arbor classification was originally developed for HL. As HL and NHL spread differently, the Ann Arbor classification is less accurate for NHL patients and thus, new predictive models were developed [26].

Ann Arbor staging

sub-classification according to presence or absence of B symptoms, size of the bulk and extranodal disease

two prognostic models:

- IPI

- prognostic model developed by Gallamini et al.

Two prognostic models are widely used in T-cell lymphomas. The International Prognostic Index (IPI) was originally developed for diffuse large B-cell lymphomas, successfully separating patients with PTCL-NOS and ALCL into distinct prognostic categories. However, it has limited applicability in other subtypes of peripheral T-cell lymphoma. In 2004, Gallamini et al. developed another prognostic model for PTCL-NOS, which takes advanced age (>60 years), poor performance status (≥2), increased lactate dehydrogenase (LDH) (≥upper limit of normal (ULN)) and marrow infiltration into account [24].

regular monitoring of response to therapy is essential

After initial therapy patients are monitored regularly in order to confirm response, remission or relapsed/refractory disease. Unfortunately, most patients will not achieve remission or will relapse. Progressive disease generally presents with B symptoms and should be confirmed by biopsy of the involved lymph node or mass and evaluation for a potential change in histology (e.g. patient with PTCL can develop B-cell lymphoma at the time of relapse). Patients refractory or resistant to initial therapy are defined as those who fail to obtain an at least partial response determined as at least 50% decrease in lesion size with no new lesions [9].

~60-120 newly diagnosed PTCL patients in Austria per year

In 2009, 1,225 (8 per 100,000 habitants) patients were newly diagnosed with NHL in Austria. Men were more often affected than women (men: 577 vs women: 548; 9.5 vs. 6.7 per 100,000 habitants, respectively) [27]. Applying the above mentioned estimates approximately 60 to 120 patients are newly diagnosed with T-cell lymphoma per year in Austria.

5 Current treatment

histological subtype, extent and sites of disease and PS are important aspects in the choice of therapy

Prior to treatment initiation the precise histological subtype, the extent and sites of disease and the performance status of a patient have to be determined [28]. No consensus on the preferred first-line therapy in PTCL exists, but patients are encouraged whenever possible to enrol onto clinical trials.

For patients who are not eligible, who do not have the possibility or who do not want to enrol in a clinical trial the selection of therapy should be based on expected toxicities, patient co-morbidities and convenience. The most common chemotherapy regimens are CHOP or EPOCH:

- CHOP includes cyclophosphamide, doxorubicin, vincristine and prednisone (CHOEP - with etoposide)
- EPOCH includes etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin.

Though the role of consolidation therapy with autologous hematopoietic stem cell transplantation (HSCT) or radiation therapy is discussed controversially, it might be a feasible option in certain PTCL subgroups where patients have poor outcomes after conventional therapy [9].

patients responding to second-line therapy are eligible for HSCT

Those patients who relapse after or are resistant to initial therapy generally receive a second-line combination therapy aiming to achieve a complete remission (CR). Responders are then eligible for autologous or allogeneic HSCT. The advantage of HSCT is the potential for long-term disease-free survival in comparison to chemotherapy alone [9, 23].

Novel agents for the treatment of PTCL are currently recommended only after relapses following initial chemotherapy due to higher response rates observed with traditional chemotherapy and the chance of the patients to achieve long-term survival when eligible for HSCT after response to chemotherapy [9].

no standard therapy for PTCL exists

patients are encouraged to participate in clinical trials

For patients eligible for HSCT the following therapy regimens, originally developed for aggressive lymphoma are available:

chemotherapy regimens for patients eligible for HSCT

- ICE (ifosfamide, carboplatin and etoposide)
- DHAP (dexamethasone, high dose cytarabine and cisplatin)
- ESHAP (etoposide, methyl-prednisolone, cytarabine and cisplatin)
- Single agent gemcitabine
- Gemcitabine, cisplatin and dexamethasone
- Gemcitabine and oxaliplatin [9].

Patients with PTCL were included in these trials for aggressive lymphomas. Due to the small sample size of PTCL patients the impact of each chemotherapy regimen on PTCL could not be assessed. Up to now, there are no randomized studies comparing chemotherapy exclusively in PTCL [9, 19].

up to now no RCTs have compared chemotherapy options exclusively in PTCL patients

For patients unresponsive to therapy, best supportive care with the primary aim of symptomatic relief and palliation is indicated [19, 23].

6 Evidence

A literature search was conducted on February 10th, 2012 in four databases (Cochrane Library, EMBASE, Ovid, and CRD Database) yielding 148 references overall. In addition a hand search was performed including the websites of the EMA and the US FDA.

literature search in 4 databases

+ hand search

Within the efficacy and safety chapter of this report only studies which enrolled patients with relapsed or refractory PTCL after at least one prior systemic therapy were considered. This resulted in the inclusion of 2 single-arm phase II studies.

2 single-arm phase II studies were included

6.1 Efficacy and safety – pivotal studies

Table 1 Summary of efficacy of study NCT00426764

Study title Results from a pivotal, open-label, phase II study of romidepsin in relapsed or refractory peripheral t-cell lymphoma after a prior systemic therapy [20]			
Study identifier	NCT00426764 (formerly registered as NCT00924378); EudraCT Number: 2006-006228-21; GPI-06-0002		
Design	Prospective, single-arm, phase II trial in 48 sites in Europe, Australia and United States		
	Duration	Enrolment: NA Median follow-up: NA Cut-off date for final analysis: October 31, 2010	
Hypothesis	Single-arm study		
Funding	Celgene		
Treatment groups	Intervention	Romidepsin 14 mg/m² as a 4-hour intravenous infusion on days 1, 8 and 15 of each 28-day cycle for up to six cycles patients with stable disease (SD), partial response (PR), or complete response (CR)/ unconfirmed CR (CRu) could elect to extend therapy until progressive disease (PD) or another withdrawal criterion was met	
	Control	-	
Endpoints and definitions	Complete response or unconfirmed complete response (primary outcome)	CR or CRu	Disease response was assessed every two cycles by individual site investigators and an independent review committee (IRC) by using the IWC guidelines [29] for response assessment for non-Hodgkin's lymphoma. CR requires: 1. complete disappearance of all detectable clinical and radiographic evidence of disease and disappearance of all disease-related symptoms if present before therapy, and normalization of those biochemical abnormalities (e.g., LDH) definitely assignable to NHL, 2. all lymph nodes and nodal masses must have regressed to normal size, 3. the spleen, if considered to be enlarged before therapy on the basis of a CT scan, must have regressed in size und must not be palpable on physical examination, 4. if bone marrow was involved by lymphoma before treatment, the infiltrate must be cleared on repeat bone marrow aspirate and biopsy of the same site. CRu includes those patients who fulfil criteria 1 and 3 above, but with one or more of the following features: 1. a residual lymph node mass greater than 1.5 cm in greatest transverse diameter that has regressed by more than 75% in the sum of the products of the greatest diameters (SPD). Individual nodes that were previously confluent must have regressed by more than 75% in their SPD compared with the size of the original mass, 2. indeterminate bone marrow (increased number or size of aggregates without cytologic or architectural atypia) [29].

	Partial response	PR	PR is defined as: 1. ≥50% decrease in SPD of the six largest dominant nodes or nodal masses, 2. no increase in the size of the other nodes, liver, or spleen, 3. splenic and hepatic nodules must regress by at least 50% in the SPD, 4. with the exception of splenic and hepatic nodules, involvement of other organs is considered assessable and not measurable disease, 5. bone marrow assessment is irrelevant for determination of a PR because it is assessable and not measurable disease, 6. no new sites of the disease [29].
	Objective response rate	ORR	CR/Cru + PR
	Duration of response	DOR	Time from the first date of a response to the date of PD or date of last study assessment
	Time to objective disease progression	-	Time from the first infusion to the date of PD or last disease assessment
	Change in ECOG PS	-	Not specified
	Progression-free survival	PFS	Time from the first infusion to the date of PD, last study assessment, or death
	Stable disease	SD	No definition provided.
	Progressive disease	PD	Time from the first infusion to the date of PD or last disease assessment.
Results and analysis			
Analysis description	Time-to-event data were summarized by using Kaplan-Meier methods		
Analysis population	Characteristics		Median age: 61 years (range 20 to 83) Sex: 32% females; 68% males White race/ethnicity: 89% ECOG PS 0/1/2: 35%/51%/13% IPI <2/≥2: 24%/76% Median time since diagnosis: 1.3 years (range 0.2 to 17.0) Most common PTCL subtypes (≥5%) PTCL NOS: 53% Angioimmunoblastic T-cell lymphoma: 21% ALK-1-negative ALCL: 16% Enteropathy-type T-cell lymphoma: 5% Type of prior systemic therapy (chemotherapy/ monoclonal antibody therapy/ other type of immunotherapy): 99%/15%/11% Number of prior systemic therapies Mean (range): 2 (1 to 8) 1/2/3/4/>4: 29%/34%/15%/12%/11% Received prior autologous stem-cell transplantation: 16% Refractory to most recent therapy: 38%

	Inclusion	- histological types according to WHO classification: PTCL NOS, AITL, extranodal NK/TCL nasal type, enteropathy-type TCL, subutaneous panniculitis-like TCL, cutaneous gamma/delta TCL, transformed mycois fungoides, hepatosplenic TCL, ALK-1-negative ALCL; ALK-1-positive ALCL patients were only enrolled if relapsed following ASCT; - ≥18 years of age; - relapsed or refractory disease to at least one systemic therapy; - adequate bone marrow and organ function (haemoglobin ≥9.0 g/dL, absolute neutrophil count >1.0 x 10^9/L, platelet count ≥100 x 10^9/L or ≥75 x 10^9/L if bone marrow involvement was documented); - total bilirubin, AST and ALT ≤2 x upper limit of normal (ULN) or ≤ 3 x ULN if liver involvement was present; - and serum creatinine ≤2 x ULN; - measureable disease according to IWC and/or measureable cutaneous disease; - ECOG PS 0 to 2
	Exclusion	- patients who had nontransformed mycosis fungoides or Sézary syndrome, known CNL lymphoma, clinically significant active infection, previous extensive radiotherapy, prior exposure to romidepsin, or any known significant cardiac abnormalities; - use of any investigational agent, chemotherapy or immunotherapy within 4 weeks of study entry (within 6 weeks for nitrosoureas) was not allowed

Descriptive statistics and estimated variability	Treatment group	*Overall IRC Assessment*	*Investigator's assessment*
	Number of subjects	n=130	
	ORR, n (%) CR/CRu CR CRu PR SD PD or not evaluable	33 (25) 19 (15) 13 (10) 6 (5) 14 (11) 33 (25) 64 (49)	38 (29) 21 (16) 19 (15) 2 (2) 17 (13) 22 (17) 70 (54)
	Median time to response (n=33), months (range) All responders CR/CRu + PR) CR/CRu	 1.8 (1.4 to 5.3) 3.7 (1.6 to 13.7)	 1.8 (1.0 to 4.3) 2.4 (1.6 to 9.6)
	Median DOR (n=33), months (range) All responders CR/CRu + PR CR/CRu	 16.6 (<0.1 to 34.0) 16.6 (<0.1 to 34.0)	 11.6 (0.5 to 34.0) NA (1.2 to 34.0)
	Improvement in ECOG PS (n=82), % CR/CRu PR SD PD or N/E	 83 60 52 18	NA
	Median PFS, months Overall CR/CRu PR SD PD or N/E	 4 18 7 6 <2	NA

Abbreviations: IRC – independent review committee; ECOG PS – Eastern Cooperative Oncology Group performance status; NA – not available; N/E – not evaluable

130 patients included for efficacy assessment

Overall, 131 patients were enrolled in the study. One patient with a diagnosis of diffuse large B-cell lymphoma was excluded from the efficacy assessment but included in the safety assessment. The median age of the 130 included PTCL patients was 61 years (range 20-83). 13% of patients had an ECOG PS 2 at enrolment. The median time since first diagnosis of PTCL was 1.3 years (range 0.2 to 17.0). The majority of included patients presented with the subtype PTCL NOS (53%). All included patients received prior chemotherapy, monoclonal antibody therapy or another type of immunotherapy The median number of prior therapies was 2 (range 1-8). 16% received prior HSCT and 38% of patients were refractory to prior therapy.

most common PTCL subtypes: PTCL NOS, angioimmunoblastic T-cell lymphoma, ALCL

ORR: 25%

median duration of ORR: 16.6 months

ORR as assessed by the independent review committee (IRC) was 25% including 10% CR, 5% CRu and 11% PR. The median duration of response for all responders was the same as for patients with CR/CRu (16.6 months (range <0.1 to 34.0). At the time of data cut-off 17 (90%) of 19 patients with CR/CRu remained in remission. The median follow-up in these patients was 13.4 months. According to subgroup-analyses, baseline disease characteristics, prior therapeutic regimens and the number of prior therapies did not have an impact on the ability of patients to respond to romidepsin.

improvements in ECOG PS in 34 patients

The assessment of the ECOG PS showed improvements in 34 (41%) of 82 patients for whom baseline and post-baseline PS data were available over the course of therapy.

most frequent AEs: nausea, infections, fatigue, thrombocytopenia, vomiting and diarrhoea

Table 3 provides an overview of the most commonly observed adverse events (AEs). These were nausea, infections (all types), fatigue, thrombocytopenia, vomiting and diarrhoea. Generally, most AEs were considered to be mild to moderate in severity. The most common grade ≥3 AEs were thrombocytopenia, neutropenia and infection of any type. The most common severe AEs were infections of all types (19%), pyrexia (7%) and vomiting (5%). 47% of patients required at least one dose interruption of romidepsin and 10% required a dose reduction to 10mg/m^2 for the management of AEs. The most common reasons for dose interruptions were thrombocytopenia (18%), infections (12%) and neutropenia (11%). As a result of AEs, treatment discontinuation was reported in 19% of the patients and 10% were considered to be drug-related. 8 (6%) patients died within 30 days of the last study drug dose due to progressive disease (n=3), infection or an event that occurred during infection (n=5). One death was reported to be study drug related.

8 patients died within 30 days after administration of last study drug

Table 2 Summary of efficacy of study NCT00007345

Study title Depsipeptide to treat patients with cutaneous T-cell lymphoma and peripheral T-cell lymphoma. Results in patients with CTCL were previously reported [30] and this analysis is limited to the patients with PTCL [7].			
Study identifier	NCT00007345 (formerly: NCT00020436)		
Design	multi-institutional, single-arm phase II study		
	Duration	Enrolment: NA Median follow-up: NA Cut-off date for final analysis: February 22, 2010	
Hypothesis	single-arm study		
Funding	National Institutes of Health, National Cancer Institute, Center for Cancer Research and by a Cooperative Research and Development Agreement with Gloucester Pharmaceuticals (and Celgene Corporation).		
Treatment groups	Intervention	14mg/m² romidepsin as a 4-hour intravenous infusion on days 1, 8 and 15 of a 28-day cycle	
	Control	-	
Endpoints and definitions	Response assessment (primary endpoint)		Responses in patients with nodal disease were assessed using the IWG guidelines [29]. Responses in patients with skin or visceral lesions were assessed using Response Evaluation Criteria in Solid Tumors (RECIST) [31].
	complete response	CR	CR requires: 1. complete disappearance of all detectable clinical and radiographic evidence of disease and disappearance of all disease-related symptoms if present before therapy, and normalization of those biochemical abnormalities (e.g., LDH) definitely assignable to NHL, 2. all lymph nodes and nodal masses must have regressed to normal size, 3. the spleen, if considered to be enlarged before therapy on the basis of a CT scan, must have regressed in size und must not be palpable on physical examination, 4. if bone marrow was involved by lymphoma before treatment, the infiltrate must be cleared on repeat bone marrow aspirate and biopsy of the same site [29].
	partial response	PR	PR is defined as: 1. ≥50% decrease in SPD of the six largest dominant nodes or nodal masses, 2. no increase in the size of the other nodes, liver, or spleen, 3. splenic and hepatic nodules must regress by at least 50% in the SPD, 4. with the exception of splenic and hepatic nodules, involvement of other organs is considered assessable and not measurable disease,

			5. bone marrow assessment is irrelevant for determination of a PR because it is assessable and not measurable disease, 6. no new sites of the disease [29].
	stable disease	SD	less than PR but not progressive disease
	progressive disease	PD	≥50% increase from nadir in the SPD of any previously identified abnormal node for PRs or non-responders and the appearance of any new lesion during or at the end of therapy
Results and analysis			
Analysis description	duration of response was assessed by Kaplan-Meier method		
Analysis population	Characteristics		Male vs female, n (%): 25 (53) vs 22 (47) Median age, years (range): 59 (27-84) ECOG PS 0/1/2, n (%): 20 (43) / 23 (49) / 4 (9) Stage II/III/IV disease, n (%): 2 (4) / 11 (24) / 34 (72) Median number of prior therapies, n (range): 3 (1-11) Type of prior therapy, n (%) (cytotoxic chemotherapy / interferon / bexarotene / experimental and other / stem-cell transplant / radiation therapy): 47 (100) / 3 (6) / 3 (6) / 3 (6) /18 (38) / 19 (40) Median number of prior cytotoxic therapies, n (range): 2 (1-6) Primary diagnosis, n (%): PTCL NOS: 27 (57) angioimmunoblastic: 7 (15) ALCL, ALK-pos / ALCL, ALK-neg / primary cutaneous anaplastic large T-cell / cutaneous γδ T-cell: each 2 (4) hepatosplenic PTCL / enteropathy associated T-cell lymphoma / PTCL, unspecified of the skin / CD30 lymphoproliferative disorder / diffuse large B-cell lymphoma: each 1 (2)
	Inclusion		initially, patients with relapsed or refractory PTCL NOS or primary cutaneous anaplastic large cell lymphoma who had not received more than 2 systemic cytotoxic chemotherapy regimens. Trial was amended and other mature T-cell lymphoma subtypes and patients who had previously received more than 2 cytotoxic therapies measurable disease, age ≥18 years, ECOG PS 0 to 2, life expectancy of >12 weeks. required laboratory values: absolute neutrophil count (ANC) ≥1 x 10^9 cells/L, platelets ≥100 x 10^9/L, bilirubin ≤1.5 x the institutional ULN, AST ≤3x ULN, and creatinine ≤1.5 x ULN.
	Exclusion		CNS involvement, HIV infection or prior therapy with an HDAC inhibitor, pregnant women; chemotherapy within four weeks prior study entry unstable angina, myocardial infarction within the previous 12 months, left ventricular ejection fraction below normal (<45% if performed by MUGA or <50% if performed by echocardiogram or cardiac MRI), or corrected QT interval of >480 ms

Descriptive statistics and estimated variability	Treatment group	
	Number of subjects	n = 45
	ORR, n (%) CR PR	17 (38) (95% CI 24% to 53%) 8 (18) 9 (20)
	SD, n (%)	5 (11)
	PD, n (%)	18 (40)
	median duration of ORR, months (range) median duration of CR median duration of PR median duration of SD	8.9 (2 to 74) 29.7 (3 to 74) 5.2 (2 to 23+) 6 (3 to 12)

45 patients considered for efficacy assessment

median age: 59 years

In this pivotal single-arm phase II trial 47 PTCL patients were enrolled. 45 were considered for efficacy assessment and all included patients were included in the safety assessment. The median age of the study population was 59 years with 23 patients being aged >60 years. The majority of included patients had an ECOG PS of 0 or 1. The most common subtypes of PTCL were PTCL NOS (57%) and angioimmunoblastic T-cell lymphoma (15%). All patients had received prior cytotoxic chemotherapy with a medium number of 2 (1-6). Overall, 118 prior cytotoxic regimes were administered to the 47 patients with the majority being either CHOP (n=32), ICE (n=11) or other combination regimens (not specified, n=59).

417 of 1062 doses were reduced

overall ORR: 38%

median duration of ORR: 8.9 months

Overall, 373 treatment cycles were administered. The median number of administered therapies per patient was 3 (range 1 to 57) corresponding to a total number of 1,062 administered doses. Of these, 417 doses were reduced and among doses reduced, 137 doses were reduced due to toxicity. ORR, the primary outcome, was 38% (95% CI, 24% to 53%) consisting of 18% CR and 20% PR. Median duration of overall response was 8.9 (range 2 to 74) months. Median duration of CR and PR was 29.7 (range 3 to 74) and 5.2 (2 to 23+), respectively. 11% and 40% of patients showed stable disease and progressive disease, respectively, while on study.

most frequent and most severe AEs

The most common AEs of the study NCT00007345 are presented in Table 3. The incidence of AEs reported in this study are derived from the highlights of prescribing information provided by the US FDA [8] because in the full text publication of the NCT00007345 study [7], only AEs after the first cycle are presented which were, overall, less frequent and less severe than those reported in the FDA document.

2 patients died while on study and 5 within 30 days after last study drug dose

Overall the observed AEs were comparable in terms of frequency and severity to those in the NCT00426864 trial. Two patients died while on study due to progressive disease and as a result of a past cardiac history, whereas 5 died within 30 days of removal from study due to progressive disease and haemophagocytosis syndrome. Even though the patient with cardiac history experienced CR on romidepsin, the protocol enrolment criteria were amended to exclude patients with significant cardiovascular disease as well as other patients at risk for sudden death.

Table 3 Adverse Reactions Occurring in ≥10% of Patients with PTCL in Study NCT00426764 [20] and corresponding Incidence in Study NCT00007345 [7], derived from the Highlights of Prescribing Information, FDA [8]

Outcome, n (%)		Study *NCT00426764*, (n=131)		Study *NCT00007345*, (n=47)	
		All Grades	Grade 3 or 4	All Grades	Grade 3 or 4
Any adverse reactions, n (%)		127 (97)	86 (66)	47 (100)	40 (85)
Gastrointestinal disorders					
	Nausea	77 (59)	3 (2)	35 (75)	3 (6)
	Vomiting	51 (39)	6 (5)	19 (40)	4 (9)
	Diarrhoea	47 (36)	3 (2)	17 (36)	1 (2)
	Constipation	39 (30)	1 (1)	19 (40)	1 (2)
	Abdominal pain	18 (14)	3 (2)	6 (13)	1 (2)
	Stomatitis	13 (10)	0	3 (6)	0
General disorders and administration site conditions					
	Asthenia/Fatigue	72 (55)	11 (8)	36 (77)	9 (19)
	Pyrexia	46 (35)	7 (5)	22 (47)	8 (17)
	Chills	14 (11)	1 (1)	8 (17)	0
	Oedema, peripheral	13 (10)	1 (1)	3 (6)	0
Blood and lymphatic system disorders					
	Thrombocytopenia	53 (41)	32 (24)	34 (72)	17 (36)
	Neutropenia	39 (30)	26 (20)	31 (66)	22 (47)
	Anaemia	32 (24)	14 (11)	29 (62)	13 (28)
	Leucopoenia	16 (12)	8 (6)	26 (55)	21 (45)
Metabolism and nutrition disorders					
	Anorexia	37 (28)	2 (2)	21 (45)	1 (2)
	Hypokalaemia	14 (11)	3 (2)	8 (17)	1 (2)
Nervous system disorders					
	Dysgeusia	27 (21)	0	13 (28)	0
	Headache	19 (15)	0	16 (34)	1 (2)
Respiratory, thoracic and mediastinal disorders					
	Cough	23 (18)	0	10 (21)	0
	Dyspnoea	17 (13)	3 (2)	10 (21)	2 (4)
Investigations					
	Weight decreased	13 (10)	0	7 (15)	0
Cardiac disorders					
	Tachycardia	13 (10)	0	0	0

Other outcomes					
	Infections SOC*	72 (55)	25 (19)		
	Death (all cause) within 30 days of last romidepsin dose	6%		17%	
	Discontinuation due to AE	19%		28%	

Adverse Events according to the National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI-CTCAE, Version 3.0);

Abbreviation: *SOC – system organ class (according to Medical Dictionary for Regulatory Activities);*

**None of the individual preferred term events in the infections SOC were reported with an incidence of 10% or greater*

6.2 Efficacy and safety - further studies

No further trials of romidepsin for the treatment of PTCL were included.

no further studies included

7 Estimated costs

To date, romidepsin is not approved in Europe, therefore, no price estimates are available yet in Austria.

no price estimate yet available

8 Ongoing research

One on-going phase III study using romidepsin as a comparator in the treatment of patients with relapsed or refractory peripheral T-cell lymphoma (PTCL) is registered at ClinicalTrials.gov.

1 ongoing phase III trial with romidepsin as a comparator identified

NCT01482962: evaluates the effectiveness of alisernib compared to single-agent treatment, as selected by the investigator from the offered options of pralatrexate, romidepsin (in countries where it is permitted to be used), or gemcitabine in patients with relapsed or refractory peripheral T-cell lymphoma. This study was initiated in January 2012 and the estimated study completion date is April 2017.

No further phase III trial was identified for this indication on the EU Clinical Trials Register (www.clinicaltrialsregister.eu), but one phase IV, rollover study for T-cell lymphoma patients previously already recruited in a romidepsin trial is ongoing.

No further phase III trials investigating romidepsin in other indications are registered at ClinicalTrials.gov and at the EU Clinical Trials Register. Several phase I and II trials are registered and on-going and investigate the effi-

cacy and safety of romidepsin in other indications (e.g. different types of T-cell and B-cell lymphoma, chronic lymphocytic leukaemia or solid tumours such as lung, pancreatic or thyroid cancer, glioma and melanoma).

9 Commentary

not yet approved in Europe

2011: approval in the US for PTCL

Romidepsin for the treatment of relapsed or refractory PTCL patients after prior systemic chemotherapy is currently under review for marketing authorisation in Europe. In 2004 and 2005, the US FDA and the EMA, respectively, granted orphan drug designation for romidepsin for the treatment of PTCL and CTCL [12]. In the US, romidepsin was approved based on the fast track program for the treatment of CTCL and PTCL in 2009 and 2011, respectively [8]. Approval options like fast track status, accelerated approval and priority review were implemented by the FDA in order to provide more extensive and timely guidance to sponsors about the nature of the evidence that is needed to support approval and to speed reviews for drugs that are intended for the treatment of serious or life-threatening conditions for which unmet needs for treatment exist [17].

178 patients enrolled in two single-arm phase II studies

most common PTCL subtypes: PTCL NOS, angioimmunoblastic T-cell lymphoma, ALCL

primary efficacy endpoint: ORR

ORR: 25% to 38%

median duration of ORR: 8.9 to 16.6 months

29% of patients with refractory PTCL achieved ORR

Two pivotal studies including 178 patients overall led to the approval of romidepsin in the US [7, 20]. These studies were two multicenter, single-arm phase II studies. The median age of the included patients was around 60 years (range 20 to 84) and more than 50% of included patients were male. In both trials the most commonly represented subgroups were PTCL NOS (~55%), angioimmunoblastic T-cell lymphoma (15% to 21%) and ALCL ALK-negative (4% to 16%). All patients had received prior systemic therapy for the treatment of PTCL. In the NCT00426764 trial 38% patients were refractory to their most recent therapy; the second trial did not provide such information. The primary efficacy endpoint in both studies was overall ORR consisting of CR/CRu and PR. ORR ranged from 25% to 38%. Median duration of ORR was 16.6 months (range <1.0 to 34) and 8.9 months (range 2 to 74). The median duration of CR/CRu in the NCT00426764 trial is equal to the median duration of ORR and the median duration of PR in this trial is not reported. On the other hand the median duration of CR and PR is 29.7 months (range 3-74) and 5.2 (2 to 23+), respectively, in the NCT00007345 trial. Thus, it seems that duration of response is mainly driven by those patients achieving a CR/CRu.

Within the NCT00426764 trial subgroup analyses were conducted according to baseline disease characteristics and prior therapeutic regimens, which appeared not to have an impact on the ability of patients to respond to romidepsin. Of patients refractory to their most recent prior therapy, 14 of 49 patients (29%) responded to romidepsin therapy. 9 of these 14 patients achieved a CR/CRu [20].

limitations inherent to single-arm design

Due to the single-arm design of the studies neither time-to-event endpoints such as progression-free survival and overall survival nor observed adverse events can be reliably estimated [32]. A further limiting factor was the small sample size of both studies. Thus, efficacy evaluation in these two single-arm trials was limited to response rates and duration of response, as these outcomes represent a direct treatment effect of the drug [33].

According to the authors of the two studies romidepsin was well tolerated and the reported AEs were generally considered to be manageable and are similar to those observed in other clinical trials and reported for other HDAC inhibitors [7]. The most commonly reported AEs were nausea, infections (all types), fatigue, thrombocytopenia, vomiting and diarrhoea.

overall romidepsin was considered to be well tolerated

In the study NCT00007345 a protocol amendment was conducted to exclude PTCL patients with significant cardiovascular disease and other patients at risk for sudden death due to a death observed in one patient with past cardiac history and CR to romidepsin [7]. Overall, 2 patients in the NCT00007345 trial died while on study and 13 patients of the 178 patients died within 30 days the after last dose of the study drug; 7 due to progressive disease, and the remaining 5 died of infections or an event that occurred during infection.

patients at risk for sudden death were excluded from the study

As described in chapter 5, currently no standard of care for the treatment of relapsed or refractory PTCL patients exists and enrolment onto a clinical trial is strongly recommended. Piekarz et al. 2011 [7] pointed out that due to several characteristics of T-cell lymphomas (rarity, aggressiveness and heterogeneity) it was not possible to fully establish standard therapies for this disease despite the fact that a number of different chemotherapeutics and biologic agents have shown activity in T-cell lymphomas. Within that context, romidepsin might be an important therapeutic option for patients not responding to existing therapeutic regimens for the treatment of PTCL. On the other hand, with 40% of patients responding to romidepsin therapy and not yet knowing the exact mechanism of anti-tumour activity of romidepsin in T-cell lymphoma, one focus of future research has to be the clarification of the mechanism of action and the identification of patients that might benefit of romidepsin treatment in order to spare patients not likely to respond to romidepsin unnecessary side effects.

currently no standard of care exists for relapsed or refractory PTCL = unmet medical need

romidepsin might be an important treatment option in this indication

mechanism of action not yet clear

Since median duration of response to romidepsin is 29.7 months in patients with CR compared to 5.2 months for patients with PR, romidepsin should preferably be given to patients achieving a CR. Another question that remains unanswered refers to the efficacy and safety of romidepsin given in combination with other anti-cancer drugs or whether it is most effective when given as a single-agent.

Up to now, no RCT exists that compares different treatment options in relapsed or refractory PTCL patients. As more and more chemotherapeutic and biologic agents are currently investigated and become available in this indication, RCTs to compare their efficacy and safety in order to enable the establishment of treatment recommendations based on direct head-to-head comparison data are necessary. Currently, there is one phase III RCT ongoing that evaluates the efficacy of the new agent alisernib to single-agent therapy chosen by the investigator. One of the possible comparators is romidepsin in countries where it is permitted for use.

need for comparison of new and existing therapy options to establish treatment recommendations

References

1. Yang, L.P.H., *Romidepsin: In the treatment of T-cell lymphoma.* Drugs, 2011. **71**(11): p. 1469-1480.
2. Khan, O. and N.B. La Thangue, *HDAC inhibitors in cancer biology: emerging mechanisms and clinical applications.* 2012. **90**(gh8, 8706300): p. 85-94.
3. Robey, R.W., et al., *Histone deacetylase inhibitors: emerging mechanisms of resistance.* 2011. **8**(101197791): p. 2021-31.
4. US Food and Drug Administration. *Romidepsin. Summary Review - Application Number 22-393.* 2009 29.2.2012]; Available from: http://www.accessdata.fda.gov/drugsatfda_docs/nda/2009/022393s000_SumR.pdf.
5. Rodriguez-Gonzalez, A., et al., *Role of the aggresome pathway in cancer: targeting histone deacetylase 6-dependent protein degradation.* Cancer Res, 2008. **68**(8): p. 2557-60.
6. Bishton, M.J., et al., *Overview of histone deacetylase inhibitors in haematological malignancies.* Pharmaceuticals, 2010. **3**(8): p. 2674-2688.
7. Piekarz, R.L., et al., *Phase 2 trial of romidepsin in patients with peripheral T-cell lymphoma.* Blood, 2011. **117**(22): p. 5827-5834.
8. US Food and Drug Administration. *Highlights of Prescribing Information - ISTODAX® (romidepsin) for injection.* 2011 22.02.2012]; Available from: http://www.accessdata.fda.gov/drugsatfda_docs/label/2011/022393s006lbl.pdf.
9. Jacobsen, E. and A. Freedman. *Treatment of relapsed or refractory peripheral T-cell lymphoma.* 2011 01.03.2012]; Available from: http://www.uptodate.com/contents/treatment-of-relapsed-or-refractory-peripheral-t-cell-lymphoma?view=print.
10. Whittaker, S.J., et al., *Final results from a multicenter, international, pivotal study of romidepsin in refractory cutaneous T-cell lymphoma.* Journal of Clinical Oncology, 2010. **28**(29): p. 4485-4491.
11. Freedman, A. and J. Aster. *Clinical manifestations, pathologic features, and diganosis of peripheral T-cell lymphoma, not otherwise specified.* 2011 01.03.2012]; Available from: http://www.uptodate.com/contents/clinical-manifestations-pathologic-features-and-diagnosis-of-peripheral-t-cell-lymphoma-not-otherwise-specified?source=search_result&search=peripheral+t-cell+lymphoma&selectedTitle=1%7E26.
12. European Medicines Agency. *Public Summary of Opinion on Orphan Designation, EMA/COMP/122781/2005 Rev.4.* 2005 22.02.2012]; Available from: http://www.emea.europa.eu/docs/en_GB/document_library/Orphan_designation/2009/10/WC500006141.pdf.
13. Dearden, C.E., et al., *Guidelines for the management of mature T-cell and NK-cell neoplasms (excluding cutaneous T-cell lymphoma).* Br J Haematol, 2011. **153**(4): p. 451-85.
14. Savage, K.J., *Aggressive peripheral T-cell lymphomas (specified and unspecified types).* Hematology Am Soc Hematol Educ Program, 2005: p. 267-77.

15. European Medicines Agency. *Class waivers*. 05.05.2012]; Available from: http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000036.jsp&mid=WC0b01ac05801177cd.
16. Business Wire. *Gloucester Pharmaceuticals Receives Fast Track Designation for Romidepsin in Peripheral T-Cell Lymphoma*. 2007 07.05.2012]; Available from: http://www.thefreelibrary.com/Gloucester+Pharmaceuticals+Receives+Fast+Track+Designation+for...-a0163419237.
17. IOM (Institute of Medicine). *Rare Diseases and Orphan Products: Acclerated Research and Development*. 2010 07.05.2012]; Available from: http://www.nap.edu/catalog.php?record_id=12953#orgs.
18. Lansigan, F. and F.M. Foss, *Current and emerging treatment strategies for cutaneous T-cell lymphoma.* 2010. **70**(ec2, 7600076): p. 273-86.
19. National Institute for Health and Clinical Excellence. *Single Technology Appraisal - Pralatrexate for the treatment of relapsed or refractory peripheral T-cell lymphoma*. 2011 02.03.2012]; Available from: http://www.nice.org.uk/nicemedia/live/13261/54301/54301.pdf.
20. Coiffier, B., et al., *Results From a Pivotal, Open-Label, Phase II Study of Romidepsin in Relapsed or Refractory Peripheral T-Cell Lymphoma After Prior Systemic Therapy.* J Clin Oncol, 2012. **30**(6): p. 631-6.
21. Pro, B., S. Horwith, and J. Atmar, *T-cell lymphoma: Where are we?* Clinical Advances in Hmeatology & Oncology, 2010. **8**(6): p. Supplement11.
22. Krol, A.D., et al., *Primary extranodal non-Hodgkin's lymphoma (NHL): the impact of alternative definitions tested in the Comprehensive Cancer Centre West population-based NHL registry.* Ann Oncol, 2003. **14**(1): p. 131-9.
23. National Comprehensive Cancer Network. *NCCN Guidelines Version 1.2012 - Peripheral T-Cell Lymphoma* 2012 20.2.2012]; Available from: http://www.nccn.org/professionals/physician_gls/pdf/nhl.pdf.
24. Kwong, Y.L., et al., *Management of T-cell and natural-killer-cell neoplasms in Asia: consensus statement from the Asian Oncology Summit 2009.* Lancet Oncol, 2009. **10**(11): p. 1093-101.
25. O'Connor, O. *Getting the Facts - Peripheral T-Cell Lymphoma*. 2009 02.03.2012]; Available from: http://www.lymphoma.org/atf/cf/%7B0363cdd6-51b5-427b-be48-e6af871acec9%7D/PTCL09.PDF.
26. The International Non-Hodgkin's Lymphoma Prognostic Factors Project, *A predictive model for aggressive non-Hodgkin's lymphoma.* NEnglJMed, 1993. **329**(14): p. 987-994.
27. Statistik Austria. *Non-Hodgkin (C82-C85,C96) - Krebsinzidenz (Neuerkrankungen pro Jahr), Österreich ab 1983*. 2011 29.4.2012]; Available from: http://www.statistik.at/web_de/statistiken/gesundheit/krebserkrankungen/non-hodgkin/index.html.
28. Jacobsen, E. and A. Freedman. *Initial treatment of peripheral T-cell lymphoma*. 2012 01.03.2012]; Available from: www.uptodate.com.
29. Cheson, B.D., et al., *Report of an international workshop to standardize response criteria for non-Hodgkin's lymphomas. NCI Sponsored International Working Group.* J Clin Oncol, 1999. **17**(4): p. 1244.
30. Piekarz, R.L., et al., *Phase II multi-institutional trial of the histone deacetylase inhibitor romidepsin as monotherapy for patients with cutaneous T-cell lymphoma.* Journal of Clinical Oncology, 2009. **27**(32): p. 5410-5417.

31. Therasse, P., et al., *New guidelines to evaluate the response to treatment in solid tumors. European Organization for Research and Treatment of Cancer, National Cancer Institute of the United States, National Cancer Institute of Canada.* J Natl Cancer Inst, 2000. **92**(3): p. 205-16.
32. US Food and Drug Administration. *Systemic Anaplstic Large Cell Lymphoma - Medical Review(s). (Application number: 125399Orig1s000).* 2011 03.04.2012]; Available from: http://www.accessdata.fda.gov/drugsatfda_docs/nda/2011/125399Orig1s000MedR.pdf.
33. US Food and Drug Administration. *Hodgkin Lymphoma - Medical Review(s) (Application number: 125388Orig1s000).* 2011 20.03.2012]; Available from: http://www.accessdata.fda.gov/drugsatfda_docs/nda/2011/125388Orig1s000MedR.pdf.