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A phase 2 study of mocetinostat, a histone deacetylase inhibitor, in relapsed or refractory lymphoma

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Summary

Deregulation of histone deacetylase (HDAC) is important in the pathogenesis of follicular lymphoma (FL) and diffuse large B-cell lymphoma (DLBCL). Mocetinostat, an isotype-selective HDAC inhibitor, induces accumulation of acetylated histones, cell cycle arrest and apoptosis in several cancers. This phase 2 study evaluated mocetinostat in patients with relapsed/refractory (R/R) DLBCL and FL. Seventy-two patients received mocetinostat (starting doses: 70–110 mg TIW, 4-week cycles). The best overall response rate (95% CI) was 18.9% (7.2, 32.2) for the DLBCL cohort ($n = 41$), and 11.5% (1.7, 20.7) for the FL cohort ($n = 31$). Responses were durable (≥90 days in 7 of 10 responses). Overall, 54.1% and 73.1% of patients derived clinical benefit (response or stable disease) from mocetinostat in the DLBCL and FL cohorts, respectively. Progression-free survival ranged from 1.8 to 22.8 months and 11.8 to 26.3 months in responders with DLBCL and FL, respectively. The most frequent treatment-related adverse events were fatigue (75.0%), nausea (69.4%) and diarrhoea (61.1%). Although mocetinostat had limited single-agent activity in R/R DLBCL and FL, patients with clinical benefit had long-term disease control. The safety profile was acceptable. This drug class warrants further investigation, including identifying patients more likely to respond to this agent, or in combination with other agents.

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Authorship

All authors participated in the acquisition, analysis and/or interpretation of the data reported in this manuscript and had access to the primary clinical study data (CA, AS, CB, AC, MC, SF, RvdJ and AY collected clinical data; CB, RC and DP made substantial contributions to the analysis and interpretation of the study results). CB and RC contributed substantially to the drafting of the manuscript, and all authors were involved in the critical review of the content and approved the submitted draft.

Keywords

diffuse large B-cell lymphoma; follicular lymphoma; histone deacetylase; mocetinostat; phase 2 study

Non-Hodgkin lymphoma (NHL) accounts for an estimated 200 000 deaths annually worldwide (Ferlay *et al*, 2015). Follicular lymphoma (FL) and diffuse large B-cell lymphoma (DLBCL) are the most common types of NHL, comprising approximately 60% of NHL diagnoses in the US (Anderson *et al*, 1998). DLBCL is an aggressive disease, and patients with relapsed/refractory (R/R) DLBCL harbour a particularly poor prognosis; only a small subset of these patients are cured despite intensive therapy with high-dose chemotherapy and autologous stem cell transplant (SCT) (Martelli *et al*, 2013). FL has a more indolent disease course, characterized by multiple relapses and eventual resistance to standard therapies, ultimately resulting in fatality (Johnson *et al*, 1995; Swenson *et al*, 2005; Montoto *et al*, 2007). Furthermore, histological transformation of FL to an aggressive malignancy, typically DLBCL, is observed in approximately one-third of patients (Montoto *et al*, 2007; Pasqualucci *et al*, 2014). Consequently, given the poor prognosis associated with R/R DLBCL and R/R FL and the current limited therapeutic options available, novel therapies are needed.

Common to DLBCL and FL are genetic alterations in chromatin-modifying genes regulating histone acetylation (Morin *et al*, 2011; Pasqualucci *et al*, 2011). Post-translational modification of histone proteins via acetylation and de-acetylation plays a key role in regulating gene transcription. Acetylation of chromatin by histone acetyltransferases (HATs) is generally associated with elevated transcription, while deacetylation, mediated by histone de-acetyltransferases (HDACs), is associated with repressed transcription (Mottamal *et al*, 2015). The HDAC family comprises 18 members that differ in subcellular location, tissue-specific expression and function. These are subgrouped as ‘classical’ Zn^{2+}-dependent metalloproteases (Classes I, IIa, IIb and IV) and Class III HDACs (or sirtuins), which harbour NAD-dependent catalytic sites and have some overlapping function to the classical HDACs (Mottamal *et al*, 2015). Deregulation of HDAC activity has been linked to silencing of tumour suppressor genes and uncontrolled tumour growth in lymphomas and a variety of other cancers (Chauchereau *et al*, 2004; Gupta *et al*, 2012; Haery et *al*, 2015). HDACs are also implicated in the pathogenesis of DLBCL by altering acetylation and expression of non-histone proteins, including the transcriptional repressor, BCL6 (required for germinal centre formation), and the tumour suppressor, TP53 (p53). Hypo-acetylation of BCL6 leads to constitutive activation of the oncoprotein and hypo-acetylated TP53 results in reduced tumour suppressor activity (Bereshchenko et *al*, 2002; Andersen et *al*, 2012). Lastly, mutations in histone acetyltransferases (*CREBBP, EP300*), histone methyltransferases (*KMT2C, KMT2D, EZH2*) and regulators of higher order chromatin structure (*HIST1H1C/D/E, ARID1A, SMARCA4*) are reported in lymphomas of germinal centre origin, including DLBCL and FL (Lunning & Green, 2015).

Addressing altered gene expression by rebalancing acetylation and deacetylation is a viable strategy for targeting lymphomas, with three HDAC inhibitors (vorinostat, belinostat and

romidepsin) currently approved in T-cell lymphomas (Mann *et al*, 2007; Coiffier *et al*, 2012; O'Connor *et al*, 2015). Furthermore, inhibition of proliferation and induction of apoptosis has been observed in DLBCL cell lines treated with HDAC inhibitors, and early clinical data support the use of HDAC inhibitors in patients with DLBCL (Sakajiri *et al*, 2005; O'Connor *et al*, 2006).

Mocetinostat is an investigational HDAC inhibitor that specifically inhibits Class I and IV HDACs (isoforms 1, 2, 3 and 11) (Fournel *et al*, 2008; Zhou *et al*, 2008). It exhibits potent anti-proliferative activity, inducing cell cycle arrest and apoptosis across a broad spectrum of human cancer cell lines and inhibited tumour growth in xenograft models (Fournel *et al*, 2008; Zhou *et al*, 2008). Furthermore, mocetinostat has demonstrated clinical activity and an acceptable safety profile in some early stage clinical trials in patients with haematological malignancies (Garcia-Manero *et al*, 2008; Blum *et al*, 2009; Younes *et al*, 2011). Here, we report a phase 2 study, which evaluated the efficacy and safety of single-agent mocetinostat in patients with R/R DLBCL and FL.

Methods

Patients and study design

This phase 2, open-label, non-randomized, multicentre study evaluated mocetinostat in two independent cohorts of patients with R/R lymphoma – DLBCL and FL – between September 2006 and March 2011.

Individuals aged ≥18 years with pathological confirmation of R/R DLBCL (Stage II–IV) or R/R FL were recruited into this study. Patients with DLBCL had experienced disease progression following initial therapy and SCT or were considered ineligible for or declined stem cell transplantation, and there was no limit to the number of prior therapies. Patients with FL had R/R disease following ≥3 prior therapies. All patients had significant disease-related manifestations defined as one or more of the following symptoms: local symptoms or compromised normal organ function due to bulky disease; B symptoms; symptomatic extranodal disease; or cytopenias due to marrow infiltration, autoimmune haemolytic anaemia or thrombocytopenia, or hypersplenism. All patients also had ≥1 site of measurable disease (≥2 cm). Other inclusion criteria included adequate haematological, hepatic and renal function and Eastern Cooperative Oncology Group performance status ≤1. Key exclusion criteria included concurrent illness that would compromise study compliance or interpretation of results. Individuals who had received an investigational drug ≤28 days prior to study initiation were also excluded along with those with central nervous system lymphoma, known human immunodeficiency virus infection, active hepatitis B or C, hypersensitivity to HDAC inhibitors and significant cardiac disease. The protocol was amended during the study to exclude patients with current or past history of pericardial disease.

Mocetinostat was administered orally 3 times a week in 4-week treatment cycles (i.e., 12 doses per 28-day cycle) until documented disease progression, unacceptable toxicity or discontinuation for any other reason. Each dose of mocetinostat was taken with a low pH beverage. The initial starting dose of mocetinostat was 110 mg; in subsequent protocol

amendments the starting dose was reduced to 85 mg and then to 70 mg because of non-life-threatening toxicities observed in other mocetinostat studies, and as a conservative approach to the limit the potential risk of pericardial events (Younes *et al*, 2011).

If the treatment was well tolerated, dose-escalation to 135 mg or 110 mg was permitted for patients receiving 110 mg or 85 mg mocetinostat, respectively. Dose reductions were required for drug-related Grade 3 non-haematological toxicity and drug-related Grade 4 haematological toxicity (lasting for ≥7 days) that could not be managed with routine supportive care. Mocetinostat was held until the toxicity recovered to Grade ≤1 or baseline, and treatment resumed at the next lower dose level. If the toxicity recurred at the same severity, a second dose reduction was implemented following recovery. Mocetinostat was discontinued for a third occurrence of the toxicity, any Grade 4 non-haematological toxicity, any Grade 4 haematological toxicity that did not resolve within 2 weeks, and any pericardial toxicity regardless of relationship to drug.

Ongoing supportive and palliative care was permitted throughout the study, including growth factor support and anti-emetic prophylaxis. Other anticancer treatments, corticosteroids directed for cancer therapy and investigational therapies were not allowed.

An optimal 2-stage Simon design was utilized (Simon, 1989). The null hypothesis was that the true probability of response was ≤5% and the alternate hypothesis was for a true probability of response ≥20% (using a 5% Type I error rate and 90% power). Each cohort enrolled 21 patients; if ≥2 responses were observed in a cohort, an additional 20 patients were enrolled (total of 41 patients per cohort), and if ≥5 responses were observed, treatment was to be considered sufficiently active to warrant further study.

The protocol was approved by the Institutional Review Boards at each institution, and the study was conducted in accordance with the Declaration of Helsinki and the International Conference on Harmonization Guidelines for Good Clinical Practice. All patients provided written, informed consent. The study was registered at www.clinicaltrials.gov (NCT00359086).

Outcomes and assessments

Baseline disease assessment and medical history were assessed at screening along with physical examination; haematological, biochemical and coagulation profiles; thyroid function test; pregnancy test (if appropriate); urinalysis; electrocardiogram (ECG); and echocardiogram (added in an amendment to the study protocol). Tumours were assessed via imaging (computed tomography, magnetic resonance imaging) and bone marrow biopsies (if indicated) prior to initiating treatment, at the end of Cycle 2, and every 2 cycles thereafter. Patients who discontinued mocetinostat treatment without disease progression were assessed every 3–4 months thereafter. Responses were determined by the investigators and categorized based on International Workshop Criteria (Cheson *et al*, 1999).

Safety assessments were performed throughout the study and included an evaluation of adverse events (AEs), graded using the National Cancer Institute Common Terminology Criteria of Adverse Events, Version 3.0 (http://ctep.cancer.gov/protocolDevelopment/

electronic_applications/docs/ctcaev3.pdf), laboratory assessments, ECGs, echocardiograms, vital signs and physical examinations.

The primary objective was to estimate the best overall response rate (ORR) in each cohort, defined as complete response (CR), CR unconfirmed (CRu) or partial response (PR). Secondary endpoints included duration of response, progression-free survival (PFS), safety, overall survival (OS), duration of stable disease (SD) and time to response (TTR). Duration of response was measured from the time of the first scan demonstrating CR or PR, while duration of SD, PFS, OS and TTR were measured from the date of first dose of mocetinostat.

Statistical analysis

The efficacy population comprised patients who received ≥8 doses of mocetinostat during a treatment cycle and had a post-baseline disease assessment, as well as patients who received ≥1 dose of mocetinostat and discontinued due to disease progression or cancer-related death. Safety was evaluated in all patients who received ≥1 dose of mocetinostat.

Time-to-event endpoints were estimated using the Kaplan–Meier method using SAS® Version 9.3. PFS was defined as the time from the first dose of mocetinostat until disease progression, or death (whichever occurred first) and OS was defined as the time from the first dose until death from any cause. Patients who discontinued the study for any reason other than disease progression or death were censored using the last date of contact. Duration of response (and duration of SD) was defined as the time a response (or SD) was first documented until the date of relapse, progression, or death. Other data, including safety, were summarized using descriptive statistics.

Results

Patient characteristics

Of the 73 patients enrolled in this study, 72 were treated with mocetinostat (one patient discontinued prior to treatment). Both the DLBCL and FL cohorts met the criteria for expansion. The DLBCL cohort completed enrolment with 41 patients treated while the FL cohort was closed prematurely by the Sponsor due to administrative reasons after 31 patients were treated. Patients initiated 1–23 and 1–17 cycles of treatment in the DLBCL and FL cohorts, respectively, and, overall, 68 patients were recorded as discontinuing mocetinostat, the most common reasons being disease progression/relapse [DBLCL: $n = 27$ (67.5%); FL: $n = 11$ (39.3%)] and treatment-related AEs [DLBCL: $n = 12$ (30.0%); FL: $n = 7$ (25.0%); Table I].

Baseline disease and demographic characteristics in the DLBCL and FL cohorts were suggestive of adverse prognoses (Table II). The median age was 60 years (range, 31–80 years) and 64 years (range, 36–76 years) for patients with DLBCL and FL, respectively. Most patients in the DLBCL cohort (80.5%) had Stage III or IV disease. All patients had received prior cancer systemic therapy with a median of 3 prior regimens for DLBCL and 4 prior regimens for FL, including high dose chemotherapy with stem cell rescue (induction therapy, mobilization and preparative regimens were considered a single line of treatment)

and anti-CD20 radioimmunotherapy. Rituximab was a prior component of therapy in majority of patients: DLBCL 97.6%, FL 93.5%. A minority of patients had received a prior SCT: DLBCL 34.1%; FL 22.6%. Twelve patients (29.3%) in the DLBCL cohort were originally diagnosed with FL and developed transformation.

Mocetinostat dosing

A total of 32 patients received an initial starting dose of mocetinostat 110 mg (21 with DLBCL and 11 with FL), 37 patients received 85 mg (20 with DLBCL and 17 with FL), and 3 received 70 mg (all with FL). Patients received a median of 3 cycles of mocetinostat (range, 1 to 23). Most patients (83.3%) required at least 1 dose reduction, most commonly due to AEs (55.6%) including fatigue (23.6%), nausea (13.9%), vomiting (9.7%), and diarrhoea (8.3%).

Efficacy: DLBCL cohort

Of the 37 patients evaluable for efficacy with DLBCL, ORR (95% CI) was 18.9% (7.2, 32.2) with $n = 1$ CR and $n = 6$ PRs observed (Table III). Duration of response ranged from 1.8+ months (55+ days) to 7.4 months (225 days; median 90 days [with post hoc adjudication of duration of response for one patient]). Four of 7 responses experienced were durable (≥90 days). TTR in the 7 responses ranged from 1.6 to 19.9 months (50–605 days), with all but one response occurring between 1.6 and 2.1 months (50 and 64 days). Of the 13 patients with SD (35.1%), median duration (95% CI) of SD was 3.5 (1.6, 8.4) months [107 (50, 257) days]. Overall, 54.1% of patients with DLBCL derived clinical benefit from therapy (response or SD). Maximum percentage reductions from baseline in target lesions for patients with available data are shown in Fig 1.

Median (95% CI) PFS was 2.1 (1.6, 3.6) months [63 (49, 110) days; Fig 2] and 14 patients with DLBCL (37.8%) remained progression free for ≥90 days. Among the 7 subjects with an objective response, PFS ranged from 1.8 to 22.8 months (54–694 days) and was ongoing at last evaluation in 5 individuals. Median OS (95% CI) was 12.3 (5.8, 17.8) months [373 (117, 541) days].

Efficacy: FL cohort

Of the 26 patients with FL who were evaluable for efficacy, ORR (95% CI) was 11.5% (1.7, 20.7; Table III) with $n = 1$ CR and $n = 2$ PRs observed. Duration of response ranged from 4.4 to 22.7 months (134–689 days). TTR in the 3 responders ranged from 3.7 to 7.9 months (111–240 days). In the 16 patients (61.5%) with SD as best response, median duration of SD (95% CI) was 4.0 [3.5, not estimable (NE)] months [122 (107, NE) days]. Overall clinical benefit (response or SD) was observed in 73.1% of evaluable patients. Maximum percentage reductions from baseline in target lesions for patients with available data are shown Fig 1.

Median PFS for evaluable patients with FL was 3.7 (95% CI: 2.1, NE) months [113 (65, NE) days; Fig 2] and 13 patients (50.0%) remained progression free for ≥90 days. Among the 3 responses, PFS ranged from 11.8 to 26.3 months (358–799 days) and was ongoing at last evaluation in all 3 individuals. The median OS has not been reached as approximately three-quarters (76.9%) of all FL patients were alive at last evaluation.

Safety

Almost all patients (98.6%) experienced at least 1 AE. The most common treatment-related AEs were fatigue (75.0%), nausea (69.4%), diarrhoea (61.1%), vomiting (37.5%) and anorexia (29.2%) (Table IV). Treatment-related haematological adverse events included anaemia (23.6%), neutropenia (19.4%) and thrombocytopenia (19.4%). The overall incidence of drug-related AEs was similar between the DLBCL and FL cohorts and no clear dose relationship was evident for any AEs. Treatment-related AEs of Grade ≥3 occurred in 41 patients (56.9%); the most common were fatigue (23.6%), neutropenia (15.3%) and thrombocytopenia (12.5%).

Thirty-six patients (50.0%) experienced treatment-related AEs that resulted in dose modifications (reduction or interruption), and these events occurred more frequently with mocetinostat 110 mg (n = 20, 62.5%) compared with 85 mg dose (n = 13, 35.1%). The most common treatment-related AEs resulting in dose modifications were fatigue (22.2%), nausea (13.9%), vomiting (9.7%) and diarrhoea (8.3%). Treatment-related AEs resulting in discontinuation occurred at a similar frequency in the mocetinostat 110 mg (n = 7, 21.9%) and 85 mg (n = 9, 24.3%) dose groups, the most common events being fatigue (6.9%) and pericardial effusion (5.6%).

Serious AEs (SAEs), regardless of relationship to mocetinostat, were reported for 26 patients (36.1%), including hypotension (8.3%), pyrexia (4.2%), pleural effusion (4.2%) and pericardial effusion (4.2%). There was no apparent relationship between incidence of SAEs and mocetinostat dosage. No deaths occurred on treatment.

Six patients (8.3%) experienced a total of 9 pericardial AEs and discontinued treatment; four patients experienced a total of 5 events which were considered related to mocetinostat: pericardial effusion (n = 3), pericarditis (n = 1) and cardiac tamponade (n = 1). There was no clear relationship between the occurrences of pericardial events and starting dose of mocetinostat or type of lymphoma.

Discussion

Lack of standard therapies for R/R DLBCL and the long natural history of FL necessitating numerous sequential therapies are key drivers for research into novel therapies to manage these diseases. This multicentre phase 2 study demonstrated that mocetinostat, a selective class I and IV HDAC inhibitor, has promising activity in these settings. The ORRs were 18.9% and 11.5% for patients with R/R DLBCL and FL, respectively, and responses were generally durable, lasting in excess of 90 days in 7 of 10 responders. While the response rates observed did not meet the stated 20% threshold, it is noteworthy that these responses were observed in heavily pre-treated patients (median of 3 to 4 lines of prior therapy). Progression-free survival ranged from 1.8 to 22.8 months and 11.8 to 26.3 months in patients with responses from the DLBCL and FL cohorts, respectively.

Mocetinostat-related AEs were primarily associated with fatigue, gastrointestinal disorders, weight loss and myelosuppression. This is consistent with the safety profiles observed with mocetinostat in other settings, and the safety profiles of other HDAC inhibitors (Garcia-

Manero *et al*, 2008; Blum *et al*, 2009; Younes et *al*, 2011; Foss et *al*, 2014; Ogura et *al*, 2014; Sawas et *al*, 2015). Additionally, four patients reported 5 pericardial events that were considered related to mocetinostat (pericardial effusion $n = 3$; pericarditis $n = 1$, cardiac tamponade $n = 1$). Pericardial events have been observed in prior clinical trials of mocetinostat in other indications, and while no correlation with mocetinostat exposure has been confirmed, history of pericardial disease, lung lesions, chest pain and pleural effusion may be risk factors (Boumber *et al*, 2011). To mitigate the potential risks of pericardial events with mocetinostat, all ongoing studies include specific exclusion criteria and study assessments related to pericardial events (Boumber *et al*, 2011). The aetiology of mocetinostat-related AEs is not yet understood; no dose relationships were observed and there were no drug-related deaths.

This study was designed to provide proof-of-concept for a role of mocetinostat in R/R DLBCL and FL. As such, it was associated with a number of limitations, including the small number of patients (recruitment of the FL cohort comprised 31 of 41 planned patients due to administrative reasons), the open-label design and absence of a placebo or comparator arm. It was also not powered to compare the effectiveness of the 70 mg, 85 mg and 110 mg doses. However, the preliminary findings from this investigation can be used to inform the design of subsequent studies.

While response rates to mocetinostat did not meet the stated 20% threshold in this study (18.9% and 11.5% in the DLBCL and FL cohorts, respectively), based on the long, durable responses observed in some patients (5.5–22.7 months in 4 of 10 responders), identification of predictive markers of activity might improve observed outcomes. Common genetic alterations in both DLBCL and FL include inactivating mutations of the HATs, *CREBBP* and *EP300* (Lunning & Green, 2015). The presence of *CREBBP/EP300* mutations in DLBCL cell lines has been shown confer preferential sensitivity to HDAC inhibitors (Andersen *et al*, 2012). However, in a recent phase 2 study of panobinostat in R/R DLBCL, responses were reported in 11 of 40 patients (28%), including only 2 of 13 patients with either *CREBBP* or *EP300* mutations (Assouline *et al*, 2016). Further studies are required to understand the impact of *CREBBP/EP300* mutation status on response to HDAC inhibitors in NHL patients. Indeed, an ongoing phase 2 study is currently investigating the efficacy of mocetinostat in selected patients with R/R DLBCL or FL harbouring *CREBBP/EP300* alterations (NCT02282358).

In conclusion, this study demonstrates that mocetinostat at doses 70–110 mg administered orally 3 times a week has limited single-agent activity in patients with R/R DLBCL and FL with responses not meeting the study threshold of 20%. The toxicity profile was acceptable and manageable. Given the limited treatment options available for refractory lymphomas, these findings warrant further investigation, including studies of mocetinostat in combination with other agents and studies with molecular selection to identify those most likely to respond to mocetinostat.

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Disclosures

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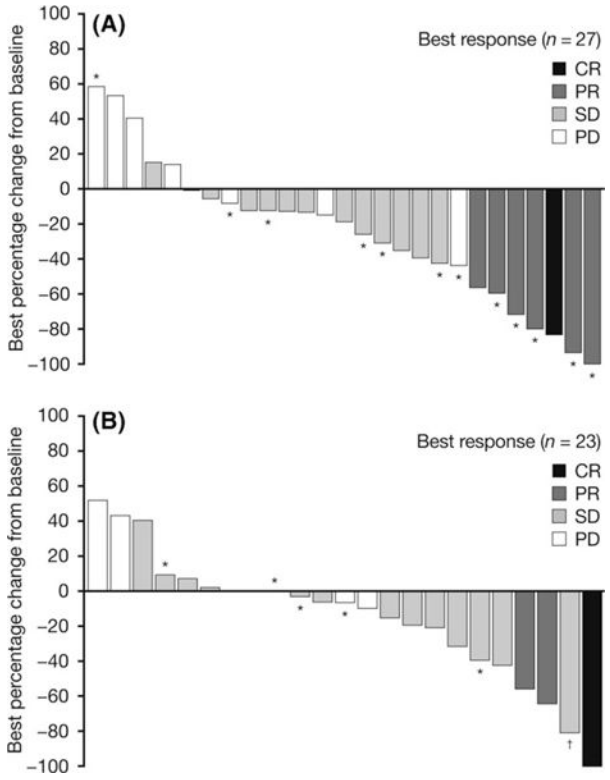

Fig 1.

Maximum per cent reduction in target lesions. This waterfall plot shows the magnitude of change in target lesions relative to baseline in patients with (A) diffuse large B-cell lymphoma (DLBCL) and (B) and follicular lymphoma (FL) from the efficacy population with available target lesion measurements (patients with missing best percentage change data are not shown). Mean overall tumour reduction was 25.3% in the DLBCL cohort and 14.8% in the FL cohort. CR, complete response; PD, disease progression; PR, partial response; SD, stable disease. *Patients who received prior stem cell transplant. †Patient had SD as best response corresponding to a 31% reduction in target lesion during Cycle 2, and disease progression in non-target lesions at later time points that coincided with greater reductions in target lesion measurements, and overall was recorded as PD.

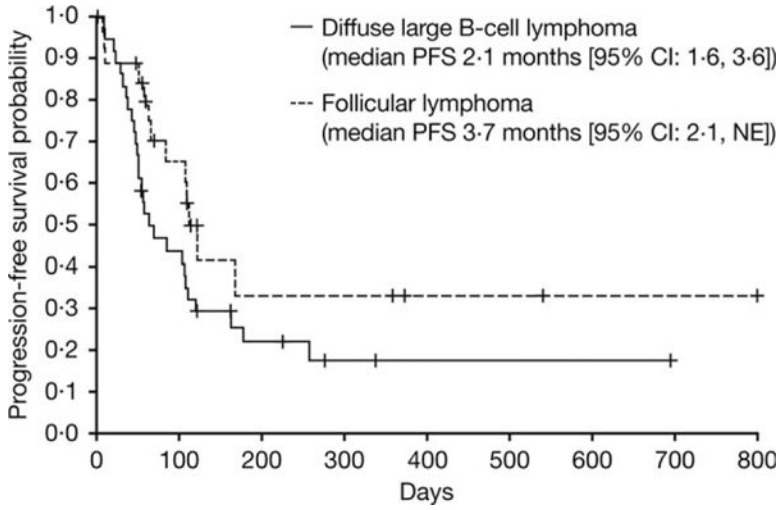

Fig 2.

Progression-free survival. Kaplan-Meier progression-free survival curves for patients with diffuse large B-cell lymphoma (solid line) and follicular lymphoma (hashed line) in the efficacy evaluable population. +, censored; 95% CI, 95% confidence interval; NE, not estimable; PFS, progression-free survival).

Table I

Patient disposition (enrolled subjects).

n **(%)**	**DLBCL**	**FL**
Enrolled	42 (100)	31 (100)
Discontinued prior to receiving study treatment *	1 (2.4)	0
Discontinued study treatment	40 (95.2)	28 (90.3)
Disease progression or relapse †	27 (67.5)	11 (39.3)
Treatment-related AE †	12 (30.0)	7 (25.0)
Patient decision †	1 (2.5)	4 (14.3)
Investigator decision †	0	1 (3.6)
Non-compliance †	0	1 (3.6)
Missing †	0	1 (3.6)
Other †	0	3 (10.7)

AE, adverse event; DLBCL, diffuse large B-cell lymphoma; FL, follicular lymphoma.

*Defined as first dose of mocetinostat.

†Denominator is the number of patients discontinuing study treatment.

Table II

Patient demographics and baseline disease characteristics (safety population).

	DLBCL (*N* = 41)	**FL (*N* = 31)**
Age, years; median (range)	60.0 (31–80)	64.0 (36–76)
Sex, *n* (%)		
Male	27 (65.9)	14 (45.2)
Female	14 (34.1)	17 (54.8)
Disease stage, *n* (%)		
II	7 (17.1)	2 (6.5)
III–IV	34 (82.9)	29 (93.5)
Prior cancer therapy, *n* (%)		
Median lines of prior systemic therapy, *n* (range)	3 (1.11)	4 (1.8)
Prior SCT	14 (34.1)	7 (22.6)
Prior anti-CD20 radioimmunotherapy	2 (4.9)	11 (35.5)
Prior radiation therapy	20 (48.8)	10 (32.3)
Prior surgery	3 (7.3)	1 (3.2)
Prior rituximab	40 (97.6%)	29 (93.5%)

DLBCL, diffuse large B-cell lymphoma; FL, follicular lymphoma; SCT, stem cell transplant.

Table III

Summary of best treatment responses.

	Initial starting dose of mocetinostat			
	110 mg ***N*** **= 19**	**85 mg** ***N*** **= 18**	**70 mg** ***N*** **= 0**	**Total** ***N*** **= 37**
Diffuse large B-cell lymphoma				
Overall response rate, % (95% CI)*	26.3	11.1	N/A	18.9 (7.2, 32.2)
Complete response, *n* (%)	1 (5.3)	0	N/A	1 (2.7)
Complete response unconfirmed, *n* (%)	0	0	N/A	0
Partial response, *n* (%)	4 (21.1)	2 (11.1)	N/A	6 (16.2)
Stable disease, *n* (%)	8 (42.1)	5 (27.8)	N/A	13 (35.1)
Progressive disease, *n* (%)	5 (26.3)	11 (61.1)	N/A	16 (43.2)
Not evaluated, *n* (%)	1 (5.3)	0	N/A	1 (2.7)
Follicular lymphoma	*N* = 8	*N* = 15	*N* = 3	*N* = 26
Overall response rate, % (95% CI)*	12.5	13.3	0	11.5 (1.7, 20.7)
Complete response, *n* (%)	0	1 (6.7)	0	1 (3.8)
Complete response unconfirmed, *n* (%)	0	0	0	0
Partial response, *n* (%)	1 (12.5)	1 (6.7)	0	2 (7.7)
Stable disease, *n* (%)	5 (62.5)	9 (60.0)	2 (66.7)	16 (61.5)
Progressive disease, *n* (%)	2 (25.0)	4 (26.7)	1 (33.3)	7 (26.9)

Response assessed by Investigators.

ORR, overall response rate (complete response + unconfirmed complete response + partial response).

*95% confidence interval applicable for overall cohort only due to small *N* values in individual dose subgroups.

Table IV

Most common treatment-related adverse events (≥10% of all patients; safety population, $N = 72$)[*].

Preferred term *n* (%)	All grade events	Grade 3 or 4 events[†]
Any treatment-related AE	67 (93.1)	41 (56.9)
Fatigue	54 (75.0)	17 (23.6)
Nausea	50 (69.4)	3 (4.2)
Diarrhoea	44 (61.1)	2 (2.8)
Vomiting	27 (37.5)	1 (1.4)
Anorexia	21 (29.2)	3 (4.2)
Weight decreased	19 (26.4)	2 (2.8)
Anaemia	17 (23.6)	6 (8.3)
Neutropenia	14 (19.4)	11 (15.3)
Thrombocytopenia	14 (19.4)	9 (12.5)
Decreased appetite	12 (16.7)	NR
Dyspepsia	12 (16.7)	NR
Abdominal pain	9 (12.5)	NR

If a patient experienced more than one drug-related adverse event within a System Organ Class (SOC), the patient was counted once under that SOC.

AE, adverse event; NR, not reported.

[*]AE considered ‘unknown’, ‘possibly’, ‘probably’ or ‘definitely’ related to mocetinostat.

[†]There were no Grade 5 AEs during study treatment.