Anti-pruritic properties of Remetinostat (SHAPE),a topical histone deacetylase inhibitor (HDACi); Data from a randomised Phase 2 study in patients with stage IA-IIA Mycosis Fungoides

M.Duvic[1], J.Guitart[2], A.Huen[1], P.Porcu[3], N.LeBoeuf[4], J.Skolnik[5], K.Owen[6], J.Öhd[6], Y.Kim[7] *

[1]MD Anderson Cancer Center, TX, [2]Northwestern University, IL, [3]Ohio State University Medical Center, OH, [4]Dana-Farber Cancer Institute/Brigham & Women's Hospital, MA, [5]TetraLogic, PA, [6]Medivir AB, Sweden, [7]Stanford Cancer Center, CA.

*Corresponding author Dr M.Duvic, mduvic@mdanderson.org

Introduction

- Cutaneous T-Cell Lymphomas are rare, life altering forms of Non-Hodgkin's Lymphoma presenting in the skin; the most common form, Mycosis Fungoides type Cutaneous Lymphoma (MF-CTCL) affects approximately 20,000 people in the US. Early stage MF-CCTCL is confined to the skin, chronic and slowly progressing
- For many patients with MF-CTCL, pruritus is a major concern, significantly affecting quality of life[1,2]
- Histone deacetylase (HDAC) enzymes catalyze removal of acetyl groups from lysine side chains in histones and other proteins
- MF-CTCL is sensitive to HDACi, which causes cell cycle arrest and cell death
- Systemic histone deacetylase inhibitors (HDACi) can be efficacious, but toxicity is problematic for MF-CTCL patients
- Remetinostat is a unique topical HDACi, stable in skin with rapid breakdown by esterases in human blood (t½ ~4 mins)
- A confirmed CAILS ORR of 40% was observed in the 1% BID treatment arm in a Ph2 open-label study of 6-12 months' duration
- Phase 2 data indicate a potential benefit of remetinostat, in addition to promising CAILS ORR, of a dose-dependent clinically meaningful reduction (CMRP) in pruritus for MF-CTCL without the typical systemic adverse effects of oral or intravenous HDACi

Hypothesis

Remetinostat will have an anti-pruritic effect, in addition to a significant anti-tumour effect, when applied topically to MF-CTCL lesions, without the systemic adverse effects of oral or intravenous HDAC inhibitors

Methods

A phase 2 open label, multi-centre, randomized, 3 arm study to evaluate the efficacy and safety of remetinostat gel applied topically to specific skin lesions in patients with stage IA-IIA MF-CTCL (Clin trials.gov:NCT02213861) was completed.

60 patients were randomised to one of 3 treatment arms in a 1:1:1 ratio
- Remetinostat gel 1% QD
- Remetinostat gel 0.5% BID
- Remetinostat gel 1% BID

Standard inclusion/exclusion criteria were applied. Concomitant medications which may affect the assessment of pruritus, such as corticosteroids and antihistamines, were prohibited.

The primary endpoint was to assess the effect of remetinostat on CAILS ORR after 6 and 12 months' dosing. Secondary endpoints included assessment of mSWAT, ORR, time to & duration of responses, safety & tolerability, QoL by Skindex-29 and reduction in pruritus severity using the visual analogue scale (VAS). Patients used a VAS to measure pruritus monthly throughout the study. Clinically significant pruritus (CSP) at baseline was defined as a VAS score ≥ 30 mm and a clinically meaningful reduction in pruritus (CMRP) was defined as a ≥ 30mm decrease. A confirmed pruritus response was defined as a clinically meaningful reduction in pruritus (CMRP), observed on 2 consecutive visits, at least 4 weeks apart.

Results

Baseline Demoraphics by Treatment Arm N=60, n= 20/arm

Category	1% QD	0.5% BID	1% BID
Male n(%)	12(60)	13(35)	10(50)
Median Age (years)	59.5	55.5	53
Disease Stage IA n(%)	7(35)	9(45)	9(45)
Disease Stage IB n(%)	13(65)	10(50)	11(55)
Disease Stage IIA n(%)	0	1(5)	0
CTCL therapy experienced n(%)	19(95)	20(100)	19(95)
Prior chlormethamine n(%)	9(45)	9(45)	7(35)

Table 1 Baseline demographics by treatment arm

References
1. Demierre MF, Gan S, Jones J, et al . Significant impact of cutaneous T-cell lymphoma on patients ' quality of life: results of a 2005 National Cutaneous Lymphoma Foundation Survey. Cancer 2006;107:2504-2511.
2. Meyer N, Paul C, Misery L. Pruritus in cutaneous T-cell lymphomas: frequent, often severe and difficult to treat . Acta Derm Venereol 2010 ; 90 : 12 – 17 .

Results

Change in Pruritus Severity from Baseline, by VAS, in Patients with Clinically significant pruritus at baseline	1% QD n (%)	0.5% BID n (%)	1% BID n (%)
Patients with clinically significant pruritus at baseline (VAS ≥ 30 mm at baseline)	8/20 (40%)	6/20 (30%)	10/20 (50%)
Confirmed response (CMRP) in patients with clinically significant pruritus at baseline	**3/8 (37.5%)**	**3/6 (50%)**	**8/10 (80%)**

Table 2 Change in pruritus severity from baseline

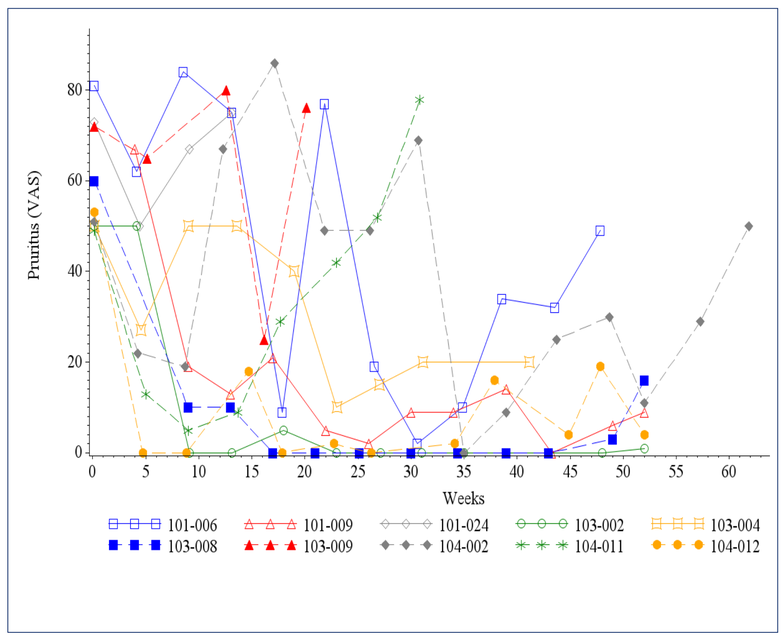


Figure 1. Individual plots of pruritus status measured using VAS from basline, day 0 until end of treatment, for patients with clinically significant pruritus at baseline (≥30mm) in the 1% BID treatment arm, n=10

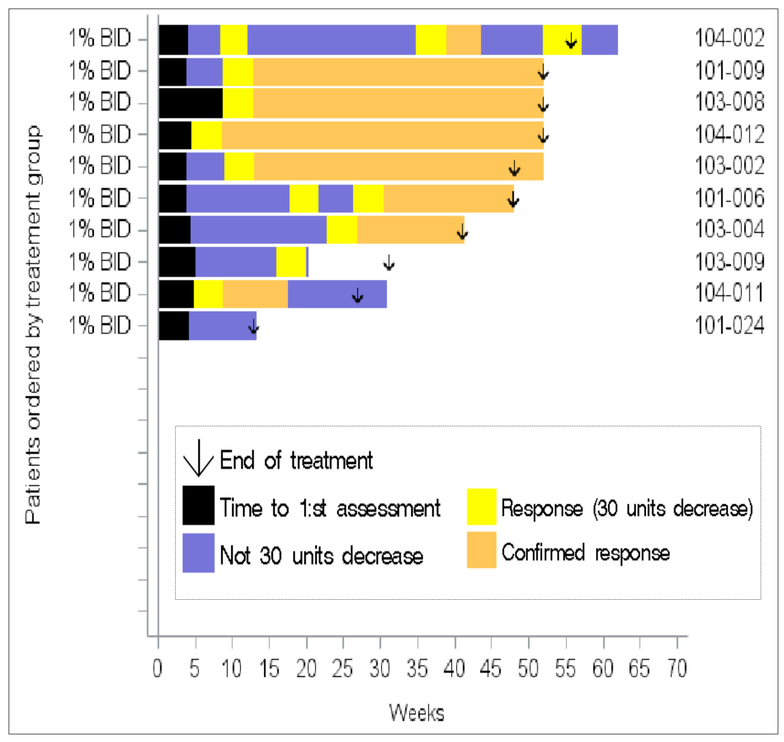
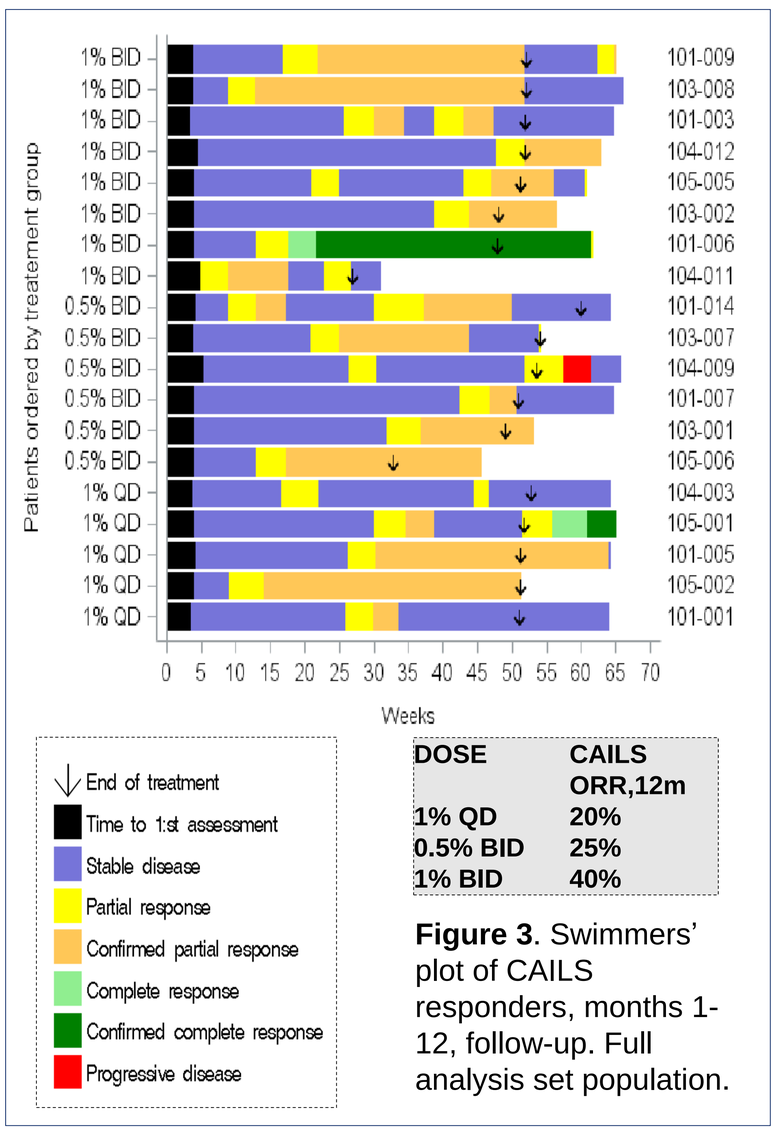


Figure 2. Swimmers plot showing pruritus (VAS) status and responses over time (month1 -12, follow up visit) in patients with clinically significant pruritus at baseline (n=10) in the 1% BID treatment arm

Results



DOSE	CAILS ORR,12m
1% QD	20%
0.5% BID	25%
1% BID	40%

Figure 3. Swimmers' plot of CAILS responders, months 1-12, follow-up. Full analysis set population.

Safety results

Treatment related Adverse Events (TRAEs) seen in ≥ 1patient	No of Patients (n=20/arm)		
	1% QD	0.5% BID	1% BID
Any AE	11	10	11
Pruritus	5	3	1
Any Other Skin (excludes pruritus): irritation, dermatitis, erythema, dry skin, rash, exfoliation, skin lesion, inflammation, pain, paraesthesia, erythema, application site reaction	9	10	11
Infections	3	1	0
Skin papilloma	0	0	1

Table 3 Safety and Tolerability. Treatment related adverse events seen in ≥1 patient, per treatment arm

- TRAEs were predominantly mild (CTC grades 1&2) and balanced across the 3 treatment arms
- There were 4 treatment related CTC grade 3 AEs (skin irritation in the 0.5% BID (1 event) and 1% BID (2 events) arms and 1 event of application site reaction in the 1% QD arm
- There was a trend of an inverse correlation between dose and AEs of pruritus
- No treatment related SAEs or systemic AEs were reported, consistent with minimal systemic exposure to remetinostat
- Mean duration of treatment for all treatment arms was 274 days (median 350 days), with a mean of 278 days, median of 336 days for the 1% BID arm

Summary

- Ph2 data indicate a dose-dependent response for pruritus for remetinostat in MF-CTCL patients with clinically significant pruritus at baseline
- Mean time to effect on pruritus (any response) was <80 days
- There was a high degree of maintained pruritus response with a median duration of response for all treatment arms of 5 months, plus a trend to longer duration of response in the highest dose arm
- A dose dependent response was observed for CAILS ORR reaching 40% in the 1% BID arm
- Remetinostat demonstrated a favourable safety and tolerability profile with no treatment related SAEs or systemic AEs
- Predominantly mild skin events remain the AEs of interest

Conclusions

- ❑ **These data demonstrate a potential benefit of topical remetinostat treatment in terms of a clinically meaningful reduction in pruritus, which is an major unmet need in patients with MF-CTCL. Importantly, without the typical systemic effects of oral or intravenous HDACi.**
- ❑ **A phase 3 study is planned with pruritus severity reduction (CMRP) a key secondary endpoint**