Title

Safety and Efficacy of Vorinostat Plus Sirolimus or Everolimus in Patients with Relapsed Refractory Hodgkin Lymphoma

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Targeting HDAC and mTOR in patients with refractory Hodgkin lymphoma

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STATEMENT OF TRANSLATIONAL RELEVANCE

In our early-phase study, we demonstrated that combination of the HDAC inhibitor vorinostat with mTOR inhibitors sirolimus or everolimus has encouraging activity in patients with heavily pretreated Hodgkin lymphoma, which warrants further investigation.

ABSTRACT

Purpose: Preclinical and early clinical data suggested that combining HDAC and mTOR inhibitors can synergistically inhibit Hodgkin lymphoma (HL).

Experimental design: During the dose escalation study (ClinicalTrials.gov number: NCT01087554) with the HDAC inhibitor vorinostat and the mTOR inhibitor sirolimus (V+S), a patient with HL refractory to 9 prior therapies demonstrated a partial response (PR) lasting for 18.5 months, which promoted additional enrollment of patients with HL as well as exploration of an alternative combination of vorinostat and mTOR inhibitor everolimus (V+E).

Results: A total of 40 patients with refractory HL received V+S (n=22) or V+E (n=18). Patients received a median of 5 prior therapies, including brentuximab (n=39), autologous stem cell transplantation (n=26), and allogeneic stem cell transplantation (n=12). The most frequent grade $\geq$ 3 treatment-related adverse event was thrombocytopenia in 55% and 67% of patients treated with V+S and V+E, respectively. Complete response (CR) was reported in 6 (27%) patients treated with V+S and 2 (11%) patients treated with V+E, PR in 6 patients (27%) treated with V+S and 4 (22%) patients treated with V+E (objective response rate of 55% and 33%, respectively). In summary, combined HDAC and mTOR inhibition had encouraging activity in heavily pretreated patients with relapsed/refractory HL and warrants further investigation.

Conclusions: Combined HDAC and mTOR inhibition has salutary activity in patients with relapsed refractory HL and warrants further investigation.

Key words: Hodgkin lymphoma, mTOR, HDAC, vorinostat, sirolimus, everolimus

INTRODUCTION

Approximately 10% of patients with early-stage Hodgkin lymphoma (HL) and 20-30% of patients with advanced HL develop refractory disease after initial therapy, and patients with early relapse have poor outcomes (1). Therapeutic options for patients with relapsed or refractory HL include salvage chemotherapy followed by high-dose chemotherapy and autologous stem cell transplantation (ASCT) in patients whose disease responds to chemotherapy (2,3). For patients whose disease is refractory to primary therapy even with aggressive approaches such as ASCT, the 5-year survival rate is around 32% (4). Patients whose disease relapses after ASCT may be candidates for allogeneic stem cell transplantation (alloSCT), which yields a 3-year relapse-free survival of around 31% (5). However, alloSCT is associated with a treatment-related mortality rate of approximately 20% (6). The approval of the targeted CD30 antibody-drug conjugate brentuximab, which leads to durable complete response (CR) in about third of the patients, further expanded therapeutic options (7-11). Later, pembrolizumab and nivolumab, antibodies targeting the immune checkpoint programmed cell death protein 1 (PD-1), were approved for patients with refractory HL, and cellular immunotherapy is under clinical investigation(12-15). However, there continues to be an unmet need for new therapies for relapsed HL refractory to standard treatment.

The phosphoinositide 3-kinase /protein kinase B (AKT)/mammalian target of rapamycin (mTOR) signaling results in cell proliferation and resistance to apoptosis

as we and others previously described (16-19). In addition, post-translational modifications of chromatin histones are key regulators of gene expression (20). These modifications include acetylation and deacetylation of lysine residues in the tails of the core histones controlled by the balanced action of histone deacetylases (HDACs) and histone acetyltransferases, and aberrant HDAC expression is associated with diverse lymphomas (21,22). Preclinical data suggest that mTOR and HDAC inhibitors can have synergistic activity against HL (23). Furthermore, in an early-phase clinical trial, the combination of the mTOR inhibitor everolimus and the HDAC inhibitor panobinostat had promising activity in HL patients; however, 43% of the patients had to withdraw from the study owing to toxicity (24). Allosteric mTOR complex 1 inhibitors such as sirolimus or everolimus have immunosuppressive and antitumor activity (25). They inhibit ribosomal protein S6 kinase beta-1 and eukaryotic translation initiation factor 4E-binding protein 1 phosphorylation, which decreases the translation of mRNAs that are critical for cell cycle progression, such as cyclin D1, and thus leads to cell cycle arrest and apoptosis. A paradoxical increase in p-AKT through disruption of a ribosomal protein S6 kinase beta-1-dependent negative feedback loop has been suggested as a mechanism of resistance to mTOR complex 1 inhibition. The HDAC inhibitor vorinostat targets both class I and II HDACs and has antitumor activity through diverse mechanisms, including induction of oxidative injury, upregulation of death receptors, disruption of the cell cycle checkpoint, induction of heat shock protein 90 acetylation (leading to increased degradation of p-AKT), and upregulation of proapoptotic proteins (26).

In a phase I trial with vorinostat and sirolimus in patients with advanced cancers, we observed a partial response (PR) lasting for 18.5 months in a patient with relapsed HL that was refractory to 9 prior therapies. Therefore, we amended

the study protocol to include an expansion cohort for patients with relapsed refractory HL at the recommended phase 2 dose (RP2D) of vorinostat and sirolimus. We also added an arm to determine maximum tolerated dose (MTD) and/or RP2D of an alternative combination of vorinostat and mTOR inhibitor everolimus, which is a chemical derivative of sirolimus with enhanced bioavailability and shorter half-life and which also demonstrated promising activity in HL in preclinical and early clinical studies (27-32). Here we report the safety and efficacy in patients with relapsed refractory HL.

MATERIALS AND METHODS

Study Design and Patients

This study was a non-randomized, open-label, dose-escalation phase I clinical trial of vorinostat and sirolimus in patients with histologically confirmed metastatic or locally advanced cancers (NCT01087554) that included an expansion cohort for patients with relapsed/refractory HL. Patients received RP2D of vorinostat 300 mg orally daily and sirolimus 4mg orally daily as determined by a previously published dose escalation part of this study (19). The trial was also amended to include a cohort of patients with advanced cancers, including patients with relapsed refractory HL, who received an alternative combination of vorinostat 300 mg orally daily with escalating dose of everolimus 5-10 mg orally daily utilizing 3+3 design (Table 1, Supplementary File 1). Addition of vorinostat and evorolimus cohort was supported by preclinical and early clinical data (24,27-32). Everolimus compared to siroliumus has enhanced bioavailability, shorter half-live and has been used as an approved cancer drug. The protocol was approved by the MD Anderson's Institutional Review Board (MD Anderson IRB) and performed in accordance with its guidelines and in accordance with the Declaration of Helsinki.

Eligible patients had no available standard therapies associated with survival prolongation, the Eastern Cooperative Oncology Group performance status (ECOG PS) of 0-3 and adequate organ and bone marrow function as detailed in the protocol (Supplementary File 1). Patients with previous cytotoxic chemotherapy must have been off treatment for at least three weeks. Patients must have had measurable or evaluable disease, and signed a written informed consent document to enroll on the trial. A full list of eligibility and treatment criteria is included in the trial protocol

(Supplementary File 1). Patients continued on therapy until disease progression, unacceptable toxicity, consent withdrawal or withdrawal for other reasons such as physician decision or non-compliance.

Safety and Efficacy Evaluations

Adverse events (AEs) were evaluated according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 4 at each study visit as specified in the protocol (Supplementary File 1). Therapy response (CR, PR, and stable disease [SD]) was defined and assessed according to the Revised Response Criteria for Malignant Lymphoma (Cheson criteria) and was performed at baseline and every two cycles (8 weeks) (33). Progression-free survival (PFS) was calculated from day 1 of therapy until disease progression or death, whichever occurred first. Overall survival (OS) was calculated from day 1 of therapy until death.

Statistical Analysis

Median PFS and OS durations were calculated using the Kaplan-Meier method. The log-rank test and Cox proportional hazards regression models were used to assess associations between patient characteristics and PFS. All tests were 2-sided, and P values <0.05 were considered statistically significant. All statistical analyses were performed with the GraphPad (GraphPad Software, Inc., La Jolla, CA) or SPSS 23 (SPSS, Chicago, IL) software programs.

Siroliumus and Vorinostat Off-Label

While the main protocol was being amended we treated additional 9 patients with relapsed/refractory HL in urgent need for therapy with vorinostat and sirolimus at RP2D off-protocol. The data were analyzed under the MD Anderson IRB-approved clinical protocol DR11-0039, which allows to assess treatment outcomes of patients treated off-protcol (Supplementary File 2). Efficacy data for these patients are briefly reported in this mansucript separately from the main study analysis.

RESULTS

Patient Characteristics

Of 40 patients enrolled between July 2010 and June 2015, 22 (55%) received vorinostat and sirolimus and 18 (45%) received vorinostat and everolimus (Figure 1). Most patients were white (55%), had nodular sclerosis HL (84%), and stage IV disease (69%). Patients received a median of 5 prior therapies (range, 1 to 11). Prior therapies included brentuximab in 39 patients (98%), ASCT in 26 (65%), alloSCT in 12 (30%), treatment with AKT or mTOR inhibitors in 8 (20%), and treatment with HDAC inhibitors in 7 (18%). None of the patients received prior treatment with PD-1 inhibitors, which had not yet been approved at the time of enrollement. The characteristics of the 40 patients, who enrolled in the study and received at least one dose, are detailed in Table 2.

Safety

All 40 patients were evaluated for adverse events (AEs). A detailed safety analysis for the entire dose escalation phase of vorinostat and sirolimus in patients with diverse advanced cancers was published previously and vorinostat 300 mg orally daily and sirolimus 4 mg orally daily every 28 days was declared as RP2D (19).

In the vorinostat and everolimus arm, grade 3 transaminitis at dose level 3 (vorinostat 300 mg orally daily and everolimus 10 mg orally daily) was the only dose-limiting toxicity (defined as treatment-related grade 4 hematological or grade 3 or 4 non-hematological AE within the first 28 days, Table 2). The MTD has not been reached and vorinostat 300 mg and everolimus 10 mg (both orally daily) was declared as RP2D.

Among the 22 patients with HL who received vorinostat and sirolimus, the most frequent treatment-related AEs were thrombocytopenia (82%), neutropenia (55%), anemia (45%), transaminitis (45%), and mucositis (41%), and the most frequent grade 3 or 4 treatment-related AEs were thrombocytopenia (55%), neutropenia (27%), and anemia (23%, Table 3).

Among the 18 patients who received vorinostat and everolimus, the most frequent treatment-related AEs were thrombocytopenia (94%), anemia (50%), mucositis (33%), and neutropenia (28%), and the most frequent grade 3 or 4 toxicities were thrombocytopenia (67%), neutropenia (22%), and anemia (17%, Table 3).

Dose interruptions and/or reductions, mostly because of thrombocytopenia, were required for 15 of the 22 patients (68%) receiving vorinostat and sirolimus, and 12 of the 18 patients (67%) receiving vorinostat and everolimus. Detailes are listed in Supplementary Table 1 and Supplementary Figure 1 for vorinostat with sirolimus and in Supplementary Table 2 and Supplementary Figure 2 for vorinostat and everolimus.

Efficacy

Of the 40 patients, 4 had clinical disease progression (vorinostat and sirolimus, n=1; vorinostat and everolimus, n=3) and 1 withdrew consent (vorinostat and everolimus) before the first restaging scan.

In the vorinostat and sirolimus arm, 6 (27%) patients attained a complete response (CR) and 6 (27%) patients attained PR with a combined objective response rate (ORR) of 55% (Table 4). In addition, 8 (36%) patients had stable disease (SD), which in 7 (32%) of them was associated with >20% tumor shrinkage (Figure 2A,

Supplementary Figure 3). Of the patients with a CR or PR, 3 (1 with a CR and 2 with a PR) received prior treatment with the AKT inhibitor MK-2206, and 1 with a CR received prior treatment with the HDAC inhibitor panobinostat. We also analyzed associations between ORR and clinical factors such as ECOG PS (0 vs. $\geq$ 1), serum LDH (normal vs. high), serum albumin (normal vs. low), number of metastatic sites involved ($\leq$ 2 vs. > 2), stage (IV vs. < IV) and found a trend towards higher ORR in patients with ECOG 0 compared to $\geq$ 1 (6/7, 86% vs. 6/15, 40%; P = 0.07).

In the vorinostat and everolimus arm, 2 (11%) patients attained CR and 4 (22%) patients attained PR with a combined ORR rate of 33% (Table 4) and responses were observed across all 3 dose levels. In addition, 8 (44%) patients had SD, which in 6 (33%) of them was associated with >20% tumor shrinkage (Figure 2B). We also analyzed associations between ORR and clinical factors such as ECOG PS, LDH, albumin, number of metastatic sites involved, stage and found that higher ORR in patients with $\leq$ 2 metastatic sites compared to > 2 (4/5, 80% vs. 2/13, 15%; P = 0.022) and in patients stage < IV compared to IV (5/7, 71% vs. 1/11, 9%; P = 0.013). There was no difference in ORR between vorinostat and sirolimus compared to vorinostat and everolimus (12/22, 55% vs. 6/18, 33%; P = 0.22).

While our protocol was being amended we treated additional 9 patients with heavily pretread HL (all had prior brentuximab, 3 had prior AKT/mTOR inhibitors and 1 prior HDAC inhibitor), who had no alternative treatment options and were urgent need for therapy, with vorinostat and sirolimus at RP2D off-label. Of these 9 patients, 4 (44%) atained CR and 3 (33%) PR (ORR rate of 78%). These patients are not included in the study analysis.

Progression-Free and Overall Survival

The median follow-up for 22 patients treated with vorinostat and sirolimus was 43.3 months. At the time of analysis, 13 patients discontinued therapy because of disease progression, 1 patient withdrew consent due to grade 3 neuropathy, 3 patients withdrew consent and continued on therapy outside of the study due to logistical reasons (inability to travel), 1 patient was removed from study for noncompliance and 2 patients (1 with a CR, and 1 with a PR) were removed from study because of referral for alloSCT. In addition, 2 patients with CR continue on therapy for 43.3 and 46.3 months, respectively. The median PFS duration was 5.8 months (95% confidence interval [CI] 3.7 - 7.9, Figure 3A) and patients with CR or PR had a longer median PFS than patients without (18 months, 95% CI 3.1- 32.9 vs. 3.2 months, 95% CI 1.0 – 5.4; P = 0.019; Figure 3B). We also analyzed associations between PFS and clinical factors such as ECOG PS (0 vs. $\geq$ 1), serum LDH (normal vs. high), serum albumin (normal vs. low), number of metastatic sites involved ($\leq$ 2 vs. > 2), stage (IV vs. < IV) and found a trend towards a longer median PFS in patients with ECOG 0 compared to $\geq$ 1 (not reached vs. 4.6 months, 95% CI 1.5-7.7; P = 0.06, Supplementary Figure 4). At the time of analysis, 9 (41%) patients had died and a median OS had not been reached.

The median follow-up for 18 patients treated with vorinostat and everolimus was 21 months. At the time of analysis, 14 patients discontinued therapy because of disease progression, 1 patient withdrew consent due to grade 3 thrombocytopenia, 1 patient was removed from study for noncompliance, 1 patient with a CR was removed from study because of referral for donor lymphocyte infusion and 1 patient was removed from the study due to physician decision. The median PFS duration was 4.8 months (95% CI, 3.0 - 6.6, Figure 3A) and there was no difference in median PFS between patients with CR or PR and patients without

(5.7 months, 95% CI 4.0 – 7.4 vs. 4.8 months, 95% CI 2.7 – 6.9; P = 0.9; Figure 3C). We also analyzed associations between PFS and clinical factors such as ECOG PS, LDH, albumin, number of metastatic sites involved, stage and found a longer median PFS in patients with normal LDH compared to high (5.8 months, 4.4 – 7.2 vs. 1.6 months, 95% CI 1.3-1.9; P < 0.001; Supplementary Figure 5) and in patients with normal albumin compared to low (5.8 months, 4.4 – 7.2 vs. 1.6 months, 95% CI 1.3-1.9; P < 0.001; Supplementary Figure 6). There was no difference in a median PFS between vorinostat and sirolimus compared to vorinostat and everolimus (5.8 months vs. 4.8 months; P = 0.13; Figure 3A). At the time of analysis, 5 patients (28%) had died and a median OS had not been reached.

DISCUSSION

Our study demonstrated that the combined inhibition of HDAC and mTOR can be effective in patients with relapsed/refractory HL. Responses appeared to be more frequent in patients who received vorinostat and sirolimus; however, small numbers and absence of randomization precludes definitive conclusions. Of note, responses were seen even in patients who received prior treatment with AKT or HDAC inhibitors.

Both combinations had similar, manageable safety profiles, which were comparable to safety results of our phase I dose escalation part of this study of vorinostat and sirolimus, which enrolled patiengts with advanced cancers (19). The most frequent AEs were hematological AEs such as thrombocytopenia (grade 4 in 11% to 36% of patients), and 67% to 68% patients required dose interruptions and/or reductions.

Historically, vorinostat demonstrated modest single agent activity in a phase 2 SWOG S0517 study of 25 relapsed/refractory HL patients (median of 3 prior therapies) with only 1 (4%) PR and median PFS of 4.8 months (34). Similarly, single agent administration of another HDAC inhibitor entinostat in a phase 2 study in 49 patients with relapsed/refractory HL demonstarted an ORR of 12% with median PFS of 5.5 months (35). Other HDAC inhibitors such as mocetinostat and panobinostat reported higher ORR of 21% to 35% and 27%, respectively (36,37).

Single agent mTOR inhibitors such as everolimus demonstrated ORRs of 46% to 47% in phase 2 settings with relatively low CR rates of 5% to 9% despite patients were less pretreated with brentuximab vedotin (up to 26%) compared to our study (98%) (31,32). In addition, our results compare favorably to the phase I study of panobinostat and everolimus, in which patients with HL demonstrated an ORR of 43%, CR rate of 15%, and median PFS duration of 4 months (24). Compared with patients in our study, those in the panobinostat and everolimus study had a lower median number of prior therapies (3 vs. 5) and a lower rate of prior ASCT (40% vs. 65%); however, 80% of the patients receiving panobinostat plus everolimus required dose interruptions, and 59% of the patients treated with the recommended dose for expansion had grade 4 thrombocytopenia. Compared to vorinostat and sirolimus, both panobinostat with everolimus and vorinostat with everolimus

attained fewer CRs; however, small patient numbers and absence of randomization precludes any conclusion about whether everolimus is indeed inferior to sirolimus as a partner for combinations withb HDAC inhibitors in the treatment of HL.

Patients were enrolled to our study before the PD-1 immune checkpoint inhibitors nivolumab and pembrolizumab received approval for the treatment of relapsed/refractory HL. That approval was based on early clinical studies showing ORR rate of 87% and 74%, CR rates of 17% and 22%, and PFS rates 86% at 24 weeks and 63.4% at 9 months for nivolumab and pembrolizumab, respectively (13,14). Compared with patients in those early studies, patients in our study had higher rates of prior treatment with brentuximab (98% vs. 78% and 83%), ASCT (65% vs. 61% and 65%), and alloSCT (30% vs. 0%). In a large phase 2 study with 243 relapsed/refractory HL patients after ASCT failure (74% received prior brentuximab) nivolumab demonstrated an ORR of 69% with a CR rate of 16% and a median PFS of 14.7 months (15). PD-1 inhibitors compared combinations of HDAC and mTOR inhibitors have mostly non-overlapping AEs, and their combined use could plausbly increase efficacy against HL, given that both HDAC and mTOR inhibitors have been suggested to increase anticancer immune response (23,26,38,39).

Our study had several limitations. First, it enrolled a relatively small number of patients all in an early-phase setting. Second, none of the patients received prior PD-1 inhibitors, and it is unclear if the same salutary activity can be achieved in a post-PD-1 inhibitor setting. Third, while patients treated with vorinostat and sirolimus received RP2D, patients treated on the dose escalation study with vorinostat and everolimus were treated with everolimus doses from 5mg to 10 mg daily, which could have impacted efficacy. Fourth, the most promising combination

of vorinostat and sirolimus comprised older drugs that are now off-patent, potentially complicating the drug development trajectory beyond early-phase trials.

In summary, combined HDAC and mTOR inhibition has encouraging activity in patients with relapsed and/or refractory HL and warrants further investigation.

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TABLES

Table 1. Treatment dose levels and dose-limiting toxicities (DLTs)

Vorinostat and Everolimus (Dose Escalation)				
Dose Level	**Vorinostat (mg orally daily)**	**Everolimus (mg orally daily)**	**No. Patients (DLT evaluable)**	**DLT Event**
1	300	5	6(4)	None
2	300	7.5	6(1)	None
3	300	10	6(2)	Grade 3 Transaminitis

Table 2. Patient characteristics (n=40)

Characteristics	All Patients (n=40)	Vorinostat and Sirolimus (n=22)	Vorinostat and Everolimus (n=18)
Median age, years (range)	33 (18-83)	33.5 (18-53)	31 (21-83)
Gender, N (%)			
Female	20 (50)	13 (59)	7 (39)
Male	20 (50)	9 (41)	11 (61)
Ethnicity, N (%)			
White	22 (55)	11 (50)	11 (61)
African-American	5 (12.5)	2 (9)	3 (17)
Hispanic	11 (27.5)	8 (36)	3 (17)
Asian	2 (5)	1 (5)	1 (5)
ECOG performance status, N (%)			
0	12 (30)	7 (32)	5 (28)
1	20 (50)	11 (50)	9 (50)
2	8 (20)	4 (18)	4 (22)
Hodgkin lymphoma type, N (%)			
Classical Hodgkin lymphoma, nodule sclerosis	32 (80)	18 (82)	14 (78)
Classical Hodgkin lymphoma, not specified	7 (17.5)	4 (18)	3 (17)
Classical Hodgkin lymphoma, lymphocyte depletion	1 (2.5)	0	1 (5)
Stage, N (%)			
Stage II	8 (20)	4 (18)	4 (22)
Stage III	6 (15)	3 (14)	3 (17)
Stage IV	26 (65)	15 (68)	11 (61)
Median lines of prior therapies, N (range)	5 (1-11)	6 (4-9)	5 (1-11)
Prior autologous stem cell transplant, N (%)	26 (65)	17 (77)	9 (50)
Prior allogeneic stem cell transplant, N (%)	12 (30)	6 (27)	6 (33)
Prior brentuximab vedotin, N (%)	39 (97.5)	21 (95)	18 (100)
Prior AKT/mTOR inhibitor, N (%)	8 (20)	6 (27)	2 (11)
Prior HDAC inhibitor, N (%)	7 (17.5)	3 (14)	4 (22)
Prior PD1 inhibitor, N (%)	0 (0%)	0 (0%)	0 (0%)

Adverse event	Vorinostat and Sirolimus (22 patients)				Vorinostat and Everolimus (18 patients)				All cohorts combined (40 patients)			
	Grade1/ 2 (%)	Grade 3 (%)	Grade 4 (%)	All grades (%)	Grade1/ 2 (%)	Grade 3 (%)	Grade 4 (%)	All grades (%)	Grade 1/2 (%)	Grade 3 (%)	Grade 4 (%)	All grades (%)
Any*	18 (82)	14 (64)	10 (45)	21 (95)	17 (94)	13 (72)	2 (11)	18 (100)	35 (88)	27 (68)	12 (30)	39 (98)
Thrombocytopenia	6 (27)	4 (18)	8 (36)	18 (82)	5 (28)	10 (55)	2 (11)	17 (94)	11 (28)	14 (35)	10 (25)	35 (88)
Neutropenia	6 (27)	4 (18)	2 (9)	12 (55)	1 (6)	4 (22)	0	5 (28)	7 (18)	8 (20)	2 (5)	17 (43)
Febrile neutropenia	0	1 (5)	0	1 (5)	0	0	0	0	0	1 (3)	0	1 (3)
Anemia	5 (23)	5 (23)	0	10 (45)	6 (33)	3 (17)	0	9 (50)	11 (28)	8 (20)	0	19 (48)
Mucositis	9 (41)	0	0	9 (41)	5 (28)	1 (6)	0	6 (33)	14 (35)	1 (3)	0	15 (38)
Rash	11 (36)	0	0	11 (36)	1 (6)	0	0	1 (6)	12 (30)	0	0	12 (30)
Transaminitis	9 (41)	1 (5)	0	10 (45)	3 (17)	1 (6)	0	4 (22)	12 (30)	2 (5)	0	14 (35)
Elevated bilirubin	1 (5)	0	0	1 (5)	0	0	0	0	1 (3)	0	0	1 (3)
Elevated creatinine	5 (23)	0	0	5 (23)	3 (17)	0	0	3 (17)	8 (20)	0	0	8 (20)
Elevated cholesterol	2 (9)	0	0	2 (9)	2 (11)	0	0	2 (11)	4 (10)	0	0	4 (10)
Elevated triglycerides	4 (18)	1 (5)	0	5 (23)	5 (28)	2 (11)	0	7 (39)	9 (23)	3 (8)	0	12 (30)
Dry skin	1 (5)	0	0	1 (5)	0	0	0	0	1 (3)	0	0	1 (3)
Neuropathy	3 (14)	1 (5)	0	4 (18)	0	0	0	0	3 (8)	1 (3)	0	4 (10)
Anorexia	2 (9)	0	0	2 (9)	3 (17)	0	0	3 (17)	5 (13)	0	0	5 (13)
Pneumonitis	0	0	0	0	0	0	0	0	0	0	0	0
Nausea	0	0	0	0	2 (11)	0	0	2 (11)	2 (5)	0	0	2 (5)
Fatigue	0	0	0	0	5 (28)	0	0	5 (28)	5 (13)	0	0	5 (13)
Diarrhea	0	0	0	0	1 (6)	0	0	1 (6)	1 (3)	0	0	1 (3)

*Number of patients with ≥ 1 adverse event

Table 3. Treatment-related adverse events in 40 treated patients

Table 4. Objective responses

Treatment Cohort	No. of Patients	Complete Response, N (%)	Partial Response, N (%)	Objective Response, N (%)
Vorinostat and Sirolimus	22	6 (27)	6 (27)	12 (55)
Vorinostat and Everolimus	18	2 (11)	4 (22)	6 (33)
All patients combined	40	8 (20)	10 (25)	18 (45)

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FIGURE LEGENDS

Figure 1. Consort diagram depicting enrollment into both arms.

Figure 2. Changes in sum of target tumor lesions per Cheson Criteria. Tumor changes in patients treated with sirolimus and vorinostat (**A.**), or everolimus and vorinostat (**B.**). Blue bars indicate patients who stopped therapy because of disease progression at the time of analysis, and orange bars indicate patients who continued therapy or stopped therapy without progression. Numbers adjacent to each bar indicate the time on therapy in months. Red plus signs indicate patients who were still receiving therapy at the time of the analysis.

Figure 3. Progression-free survival (PFS). A. There was no difference in a median PFS between vorinostat and sirolimus (VS, 5.8 months, 3.7 - 7.9) compared to vorinostat and everolimus (VE, 4.8 months, 95% CI, 3.0 - 6.6; P = 0.13). **B.** Patients with complete (CR) or partial response (PR) to vorinostat and sirolimus had a longer median PFS than patients without CR or PR (18 months, 95% CI 3.1- 32.9 vs. 3.2 months, 95% CI 1.0 – 5.4; P = 0.019). **C.** There was no difference in a median PFS between in patients with CR or PR to vorinostat and everolimus (5.7 months, 95% CI 4.0 – 7.4) compared to patients without CR or PR (4.8 months, 95% CI 2.7 – 6.9; P = 0.9).