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Phase 1 study of romidepsin plus erlotinib in advanced nonsmall cell lung cancer

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Abstract

Purpose—Preclinical studies demonstrated anti-tumor efficacy of the combination of the histone deacetylase (HDAC) inhibitor romidepsin plus erlotinib in non-small cell lung cancer (NSCLC) models that were insensitive to erlotinib monotherapy. We therefore, studied this combination in a phase 1 clinical trial in previously treated advanced NSCLC.

Methods—Romidepsin (8 or 10 mg/m^2) was administered intravenously on days 1, 8, and 15 every 28 days in combination with erlotinib (150 mg orally daily), with romidepsin monotherapy lead-in during Cycle 1. Correlative studies included peripheral blood mononuclear cell HDAC activity and histone acetylation status, and EGFR pathway activation status in skin biopsies.

Results—A total of 17 patients were enrolled. Median number of prior lines of therapy was 3 (range 1–5). No cases had a sensitizing *EGFR* mutation. The most common related adverse events were nausea, vomiting, and fatigue (each 82%), diarrhea (65%), anorexia (53%), and rash (41%). Dose-limiting nausea and vomiting occurred at the romidepsin 10 mg/m² level despite aggressive antiemetic prophylaxis and treatment. Among 10 evaluable patients, the best response was stable disease (n = 7) and progressive disease (n = 3). Median progression-free survival (PFS) was 3.3 months (range 1.4–16.5 months). Prolonged PFS (>6 months) was noted in a *KRAS* mutant

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adenocarcinoma and a squamous cell cancer previously progressed on erlotinib monotherapy. Romidepsin monotherapy inhibited HDAC activity, increased histone acetylation status, and inhibited EGFR phosphorylation.

Conclusions—Romidepsin 8 mg/m² plus erlotinib appears well tolerated, has evidence of disease control, and exhibits effects on relevant molecular targets in an unselected advanced NSCLC population.

Keywords

Non-small cell lung cancer; Epidermal growth factor receptor; Histone deacetylase inhibitor; Epigenetics; Clinical trial; Erlotinib; Romidepsin

1. Introduction

The epidermal growth factor receptor (EGFR) represents a key therapeutic target for the treatment of lung cancer and other malignancies. A number of human malignancies are associated with aberrant or overexpression of EGFR. Over-expression of EGFR in certain human tumors, including non-small cell lung cancer (NSCLC), has been correlated with both chemo-resistance and poor prognosis. In NSCLC, it is now widely recognized that EGFR inhibition has particular efficacy among the subset of patients with tumors harboring sensitizing exon 19 and 21 *EGFR* mutations. 4,5

Beyond this limited population, EGFR inhibition has a less clear role in lung cancer therapy. Compared to best supportive care, the EGFR inhibitor, erlotinib, results in improved progression-free and overall survival⁶ and is U.S. FDA approved for second- and third-line therapy. However, more recent studies have suggested that, in *EGFR* wild-type populations, erlotinib may be inferior to single-agent cytotoxic agents, such as docetaxel.⁷ To improve clinical outcomes, EGFR inhibitors have been combined with numerous other therapies, including vascular endothelial growth factor (VEGF)-targeting agents, ⁸ Src inhibitors, ⁹ insulin-like growth factor (IGF) inhibitors, ¹⁰ and cyclooxygenase-2 (COX-2) inhibitors. ¹¹

There is strong rationale to combine EGFR inhibition with histone deacetylase (HDAC) inhibition. In addition to inducing expression of repressed genes by promoting histone acetylation, HDAC inhibitors exert effects on multiple non-histone targets implicated in erlotinib resistance, including heat shock protein 90 (HSP90), signal transducer and activator of transcription 3 (STAT3), and signaling pathways such as MAP kinase and Akt. ^{12,13} The HDAC inhibitor, romidepsin, (Istodax, Celgene), is FDA approved for the treatment of cutaneous T cell lymphoma. *In vitro*, romidepsin has demonstrated antiproliferative activity against multiple human solid tumor cell lines, ^{14,15} with the most potent effects noted against lung cancer cell lines. ¹⁶ In a phase 2 trial of romidepsin monotherapy in patients with previously treated lung cancer, 9 of 18 patients achieved stable disease. ¹⁷ Romidepsin enhanced histone H4 acetylation, increased p21 expression, and shifted global gene expression profiles in lung cancer cells toward those found in normal bronchial epithelium. ¹⁸ Additionally, preclinical studies suggest that combining erlotinib with romidepsin enhances erlotinib efficacy. Romidepsin blocks signal transduction by Ras and MAPK, intracellular mediators that may contribute to resistance to EGFR TKIs. ^{19,20} Romidepsin also inhibits

EGFR expression in cultured NSCLC cells.¹⁴ The synergistic effects of erlotinib plus romidepsin have been demonstrated in a series of *in vitro* and *in vivo* experiments.²¹

Based on extensive clinical experience in multiple cancers and promising preclinical efficacy, we conducted a phase 1 trial of romidepsin plus erlotinib in previously treated, advanced NSCLC.

2. Patients and Methods

This clinical trial (NCT01302808) was approved by the University of Texas Southwestern Medical Center Institutional Review Board (IRB #012011-004). All subjects provided written informed consent prior to undergoing any study-related procedures. This was an open-label, single-institution, 3+3 dose escalation phase 1 trial. The primary objective of the study was to determine the safety, tolerability, and maximum tolerated dose (MTD) of romidepsin plus erlotinib. Secondary objectives included efficacy and pharmacokinetic analyses. Exploratory objectives included characterizing the pharmacodynamic effects of romidepsin plus erlotinib therapy on (1) histone acetylation and HDAC activity, and (2) activation of EGFR pathway components.

2.1. Patient selection

Eligible patients were age 18 years, had histologically or cytologically confirmed previously treated advanced NSCLC, measurable disease as defined by Response Evaluation Criteria in Solid Tumors (RECIST) 1.0,²² adequate hematologic parameters and liver and kidney function, and performance status ECOG 0–1. There was no limit to the number of prior treatment regimens, and prior treatment with erlotinib was allowed. Previously treated brain metastases were permitted. Due to concerns for potential cardiac toxicity from romidepsin, patients could not have active cardiac disease, QTc prolongation, or other clinically significant ECG abnormalities, and were also required to have serum potassium and magnesium greater than or equal to the lower limit of the institutional normal range (supplementation permitted).²³ Concurrent use of medications known to cause prolongation of the QTc interval and medications that moderately or potently inhibit cytochrome P450 isoenzyme CYP3A4 were prohibited. Prior exposure to romidepsin was not permitted. Pregnant or lactating females were excluded.

2.2. Study treatment

Three romidepsin dose levels were planned in combination with standard erlotinib 150 mg PO daily: romidepsin 8 mg/m², 10 mg/m², and 14 mg/m² (the approved monotherapy dose), administered as a 4-hour intravenous infusion on days 1, 8, and 15 of a28-day cycle. During the conduct of the clinical trial, the emergence of frequent and severe nausea and/or vomiting led to the routine implementation of standard premedication with 5HT3 antagonists and steroids for all patients. Erlotinib was taken at least one hour before or two hours after eating. In Cycle 1, erlotinib was initiated on Day 3 to permit pharmacokinetic and pharmacodynamic analysis of romidepsin monotherapy prior to combination treatment. Treatment was continued until disease progression or unacceptable toxicity.

There was no intra-patient dose escalation. DLT was defined as a grade 3 or greater hematologic or non-hematologic adverse event deemed probably or definitely related to erlotinib and/or romidepsin. Grade 3 nausea/vomiting was considered a DLT only if it occurred in spite of maximum antiemetics (eg, steroids, 5HT3 antagonists, prochlorperazine, lorazepam). Due to potential for CYP3A4 interaction, administration of neurokin in inhibitor antiemetics (aprepitant, fosaprepitant) was not permitted.

Dose reductions of the suspected causative agent were implemented for recurrent grade 3 and any grade 4 non-hematologic toxicities. Romidepsin dose reductions were implemented for recurrent grade 3–4 neutropenia or thrombocytopenia, any episode of neutropenic fever, or thrombocytopenia requiring platelet transfusion. Dose reductions were permanent, with the exception of erlotinib dose reductions for dermatologic toxicity. Erlotinib rash was managed with standard algorithms, including topical and systemic antibacterial agents and steroids.

2.3. Study assessments

Safety assessments consisted of monitoring patient-reported symptoms, vital signs, physical exam findings, blood and urine tests, and ECGs. Toxicities were graded according to the NCI CTCAE, Version 3.0. Patients were assessed for response to therapy using RECIST 1.0 every 2 cycles of therapy.

2.4. Pharmacokinetic studies

On Days 1,2, 8, and 9 of Cycle 1, blood collection and plasma separation were performed at the following times: immediately prior to romidepsin, 2 hours after initiation of infusion, 4 hours, 4.5 hours, 5 hours, 6 hours, and 24–28 hours. Methods for quantitation and pharmacokinetic analysis of romidepsin (see Supplemental Text have been described previously. ²⁴ Erlotinib pharmacokinetic parameters were not analyzed in this trial.

2.5. Correlative studies

We analyzed histone acetylation status and HDAC expression and activity in peripheral blood mononuclear cells (PBMCs) drawn on Cycle 1 Day 1 and Day 8. Such an approach has been utilized in numerous prior studies and appears to correlate with findings in tumor tissue. ^{25–28} We analyzed activation of EGFR pathway components in skin biopsies, a previously employed technique that appears to correlate with tumor EGFR analysis and clinical outcomes. ^{29,30} Detailed methods of these analyses are provided in the Supplemental Text.

2.6. Statistical analysis

Summary statistics for patient characteristics were reported using the mean, median, standard deviation, minimum and maximum for continuous variables and using counts and percentages for discrete variables. Adverse events were summarized in tables and presented by dose level, seriousness, severity, and relatedness. We determined the rate of disease control outcome (partial response or stable disease) and 95% confidence intervals (CI). Progression-free survival (PFS) was determined by the Kaplan-Meier method. We assessed

the association between pharmacodynamic endpoints, pharmacokinetics, toxicity, and clinical outcomes using Pearson correlation, linear regression, and Cox proportional hazards.

3. Results

3.1 Treatment exposure

A total of 17 patients were accrued to this study. The median number of prior treatment regimen was 3 (range 1–5). Additional baseline patient characteristics are presented in Table 1. One patient was enrolled but never received treatment due to the inability to achieve minimum required levels of serum potassium and magnesium despite aggressive electrolyte supplementation. Overall, six patients were treated at the 8 mg/m² dose cohort and 11 patients were treated at the 10 mg/m² dose cohort. In the 8 mg/m² cohort, the median number of treatment cycles was 2 (range 1–16). No DLTs occurred in the 8 mg/m² cohort. In the 10 mg/m² cohort, median number of treatment cycles was 2 (range 1–6). Reasons for treatment discontinuation included disease progression (n = 8), DLT (n = 2), non-DLT toxicities of nausea and fatigue (n = 2), logistical concerns (n = 1), and symptomatic radiation therapy necrosis following prior cranial radiation (n = 1). Two patients died while on study. One of these patients, who had squamous cell lung cancer and a prior history of hemoptysis, developed recurrent hemoptysis considered unrelated to study therapy. The other patient developed acute kidney injury (thought to be acute tubular necrosis) considered related to study therapy. Specifically, approximately five weeks after starting therapy she was admitted with nausea, vomiting, diarrhea, tachycardia, and hypotension. Despite initial clinical improvement with intravenous hydration, serum creatinine continued to rise. On hospital day #3, the patient developed altered mental status, then became unresponsive and pulse less.

After successful treatment of three patients at the 8 mg/m² dose cohort without DLT, three patients were treated at the 10 mg/m² dose cohort, of whom one had DLT of grade 3–4 nausea and/or vomiting related to romidepsin. At that point, study enrollment was suspended and the protocol amended to require standard premedication with a 5HT3 antagonist (most commonly ondansetron 12 mg IV) and steroid (dexamethasone 12 mg IV) prior to each dose of romidepsin. Additionally, patients were given prescriptions for scheduled oral ondansetron and dexamethasone after each romidepsin infusion, plus additional antiemetic agents as needed. An additional four patients were enrolled at the 10 mg/m² dose level employing this standard antiemetic regimen. One patient was not evaluable for DLT and replaced; another experienced DLT. Because clinically significant nausea and vomiting continued to occur despite the aggressive antiemetic regimen in place, the decision was made not to expand the 10 mg/m² dose cohort further and to consider 10 mg/m² to have exceeded the MTD. Romidepsin dose was de-escalated to 8 mg/m² with standard antiemetic prophylaxis, which was well tolerated in three additional patients without DLT. It was deemed the maximum tolerated dose.

3.2. Toxicity

Table 2 lists treatment-related adverse events by category, grade, and relationship to study treatments. In addition to nausea and vomiting, the other most prevalent toxicities were

fatigue, diarrhea, anorexia, and acneiform rash. All cases of rash were considered related to erlotinib and were grade 1–2 in severity. Two cases of sinus tachycardia during romidepsin administration occurred. These episodes resolved upon completion of the romidepsin infusion. One patient developed mild elevation of cardiac enzymes without associated ECG changes.

3.3. Efficacy

Of 10 patients evaluable for radiographic response, the best response was stable disease in 6 patients and progressive disease in 4 patients (disease control rate 60%; 95% CI, 26–88%). The timing and duration of responses are shown in Figure 1. Median PFS was 57 days (range 9–462 days). Of note, some of the greatest apparent benefit occurred in cases not typically associated with erlotinib efficacy. A patient with squamous NSCLC who had most recently experienced disease progression after treatment with erlotinib monotherapy achieved stable disease for 16 months. A patient with *KRAS* mutant lung adenocarcinoma had a minor radiographic response and stable disease for almost 6 months.

3.4. Pharmacokinetics

PK data are summarized in Supplemental Table 1 and Supplemental Figure 1. We found no significant associations between PK parameters (baseline AUC and Cmax) and clinical outcomes (PFS and RECIST response). Likewise, there was no association between PK parameters and toxicity. Finally, there was no association between PK parameters and pharmacodynamic changes.

3.5. Biomarker studies

We evaluated pharmacodynamic effects of treatment on histone acetylation (Figure 2) and HDAC activity in PBMCs (Figure 3) and on EGFR pathway components in skin biopsies (Figure 4). Romidepsin caused a significant, but transient, decrease in HDAC activity (P < 0.001) and concomitant increase in H3 and H4 histone acetylation (P < 0.001) at both 8 mg/m² and 10 mg/m² dose levels. This effect did not appear to be modified by addition of erlotinib. Romidepsin monotherapy resulted in a trend toward decreased expression of phosphorylated EGFR (P = 0.09), but had no discernible effect on expression of EGFR, MAPK, or phospho-MAPK (Supplemental Figure 2).

In exploratory analyses, there were no clear associations between changes in pharmacodynamic endpoints, clinical outcomes, toxicity, and pharmacokinetic parameters. Nor did we find an association between baseline biomarkers and clinical outcomes (data not shown).

4. Discussion

Expanding the efficacy of EGFR inhibitors for lung cancer, which is largely limited to the 10–15% of cases with sensitizing *EGFR* mutations, has been a major focus of lung cancer research. There is strong rationale to combine EGFR inhibiting drugs with epigenetic therapies, such as HDAC inhibitors. HDAC inhibition affects the acetylation status and function of multiple non-histone proteins. Examples described to date include nuclear

transcription factors (including p53, E2F, c-Myc, nuclear factor-kappaB, hypoxia-inducible factor 1a), estrogen and androgen receptors, DNA repair enzymes, the chaperone Hsp90, the intracellular signaling mediator STAT3, angiogenesis and intracellular stress response pathways. Additionally, HDAC inhibitors have activity against EGFR-TKI resistant cell lines, result in depletion of EGFR, and demonstrate synergistic activity with erlotinib. 21,32,33

This phase 1 trial combined standard dose erlotinib with dose escalated romidepsin in patients with advanced NSCLC. Although patients tolerated the combination with romidepsin 8 mg/m² without any antiemetic premedication, severe nausea and vomiting occurred at the 10 mg/m² level despite aggressive multi-agent prophylaxis. Other principal toxicities were fatigue, diarrhea, anorexia, and acneiform rash. The frequency and severity of nausea and vomiting were somewhat unexpected. The approved monotherapy dose of romidepsin for cutaneous T cell lymphoma of 14 mg/m² has been well tolerated with <5% grade 3-4 nausea/vomiting reported with standard antiemetic prophylaxis. In the phase 1 monotherapy trial, dose-limiting toxicities were grade 3 thrombocytopenia and fatigue.²⁴ In combination studies with gemcitabine and with bortezomib, DLTs were primarily hematologic. ^{34,35} Although erlotinib is commonly associated with diarrhea, severe upper gastrointestinal toxicities are unusual. The addition of erlotinib did not modify the romidepsin pharmacokinetic profile, and patients often developed severe nausea/vomiting before the first dose of erlotinib. Addition of romidepsin did not appear to alter the frequency and severity of characteristic erlotinib toxicities, such as rash and diarrhea. Other romidepsin-associated adverse events, such as hematologic and cardiac toxicities, did not appear to occur at rates greater than expected with romidepsin monotherapy.

Although no conclusions can be drawn from this phase 1 clinical trial, the available efficacy data suggest intriguing effects. Among 10 patients evaluable for radiographic response, the disease control rate was 60%, which is comparable to other studies combining erlotinib and HDAC inhibitors.³⁶ To further place these results in context, it is important to consider that in this trial there were no identified cases with sensitizing EGFR mutations, all patients were current or former smokers, and all received prior treatment for their advanced NSCLC diagnosis. In addition, seven patients (41%) were previously treated with erlotinib before enrollment. In a phase 1 study of erlotinib plus the HDAC inhibitor panobinostat, all documented radiographic responses occurred among EGFR-mutant, EGFR inhibitor-naïve patients.³⁶ In this trial, serum romidepsin concentrations achieved at all romidepsin dose levels well exceeded the IC50 of romidepsin against NSCLC cell lines in vitro (2.25 ng/ mL). 16 Consistent with preclinical observations, 21 we observed potential clinical benefit in cases not typically considered responsive to EGFR inhibitors. For instance, a patient with KRAS mutant lung adenocarcinoma experienced a minor radiographic response and disease control for 6 months. This observation may reflect potential effects of HDAC inhibition on protein targets relevant to KRAS function, including cyclin-dependent kinases, nuclear factor-kappa B, and STAT family members. ^{37,38} One patient with squamous cell lung cancer, who had progressed on erlotinib monotherapy immediately prior to enrollment on this trial, achieved disease control for 16 months. To what extent combination with HDAC inhibition contributed to this prolonged clinical stability is not clear. Re-treatment with EGFR inhibitors has demonstrated clinical benefit in patients with prior progression on EGFR inhibitors, although these reports are generally limited to patients with sensitizing

EGFR mutations who receive an alternate intermittent treatment, or have a drug-free interval between EGFR TKI exposures.^{39–41}

We observed evidence of romidepsin on-target effects at all dose levels. Decreased HDAC activity and increased histone H3 and H4 acetylation were noted in PBMCs immediately after romidepsin administration. This effect was not altered by addition of erlotinib. The observation that romidepsin monotherapy may inhibit EGFR activation—evident through a near-significant decrease in phospho-EGFR expression in skin biopsies prior to erlotinib initiation—is intriguing and merits further investigation. Recent evidence suggests that dual blockade with EGFR TKI and the anti-EGFR monoclonal antibody cetuximab may have efficacy against the *EGFR* T790M secondary resistance mutation. A2,43 The clinical effects of such an approach in a broader population remain to be determined. In this trial, possibly due to small patient numbers, we did not identify any baseline or pharmacodynamic biomarkers that predicted benefit from romidepsin plus erlotinib.

5. Conclusion

In conclusion, the maximum tolerated dose of romidepsin in combination with standard erlotinib150 mg orally daily administration is 8 mg/m² on Days 1, 8, and 15 every 28 days with routine multi-drug antiemetic prophylaxis. Although this romidepsin dose is considerably lower than the approved monotherapy dose of 14 mg/m² for cutaneous T cell lymphoma, it achieved target effects of decreased HDAC activity and increased histone acetylation, and may also inhibit EGFR activation. Although baseline and pharmacodynamic biomarkers did not appear to predict clinical outcomes, this small phase 1 trial was not adequately powered for such an analysis. Consistent with preclinical observations, intriguing clinical activity was noted in populations that historically have not derived substantial benefit from EGFR TKI monotherapy, including a patient with squamous NSCLC and a patient with *KRAS* mutant adenocarcinoma. In these populations, confirmation of these initial findings would require further study in randomized clinical trials comparing this regimen not to erlotinib monotherapy (which has little efficacy in these settings), but rather to cytotoxic chemotherapy. Identification of the optimal patient population and development of predictive biomarkers will be key considerations to this future clinical development.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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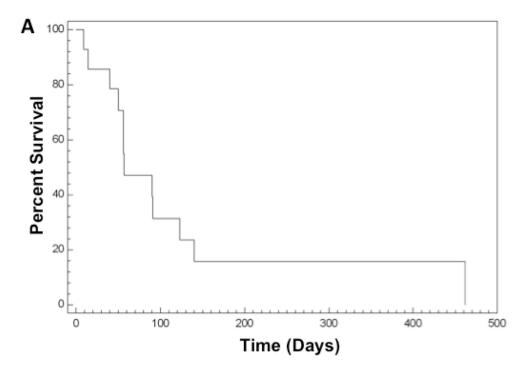
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Highlights

- Romidepsin 8 mg/m² IV on Days 1, 15, and 22 every 28 days plus erlotinib 150 mg PO daily was well tolerated
- At higher doses, dose-limiting nausea and vomiting occurred despite aggressive prophylaxis
- Encouraging findings were seen in EGFR wild type cases, including squamous cell and mutant *KRAS*
- At all doses studied, romidepsin inhibited HDAC activity and increased histone acetylation
- Romidepsin also inhibited EGFR pathway activation in skin biopsies



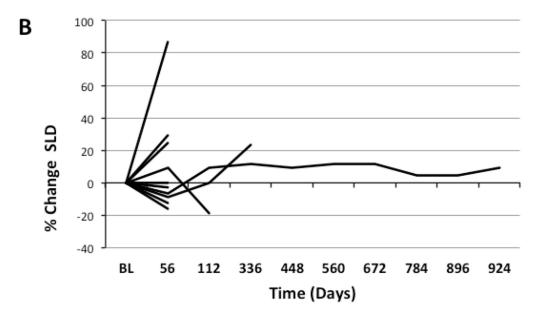


Figure 1. Clinical efficacy of romidepsin plus erlotinib. (A) Progression-free survival estimate (N = 14). (B) Spider plot demonstrating radiographic response over time (N = 10). (SLD: Sum of longest diameter).

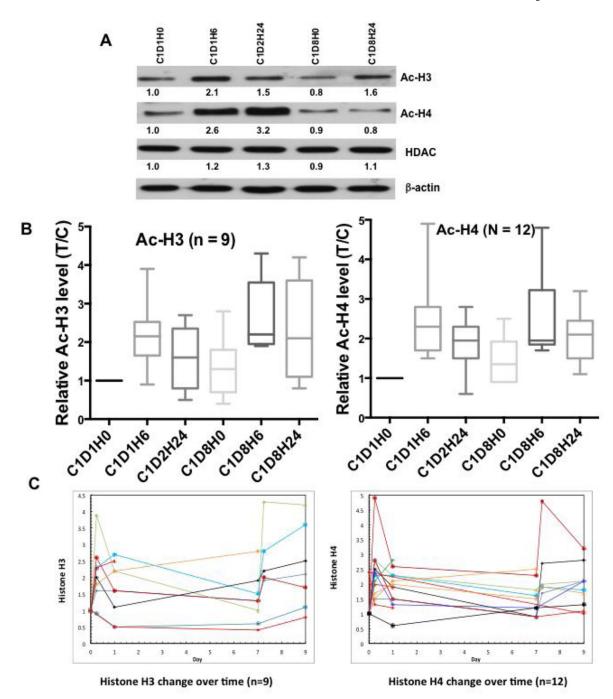


Figure 2. Effects of romidepsin \pm erlotinib on histone H3 and H4 acetylation status. (A) Example Western Blot demonstrating transient increase in histone H3 and H4 acetylation after initiation of romidepsin. (B) Transient increase in histone H3 acetylation after initiation of romidepsin and again after addition of erlotinib. (C) Individual patient data showing histone H3 (N = 9) and H4 (N = 12) acetylation status over time. For normalized H3 acetylation values, mean increase was 2.10 ± 0.71 in the 8 mg/m² cohort (P<0.01) and 2.18 ± 1.09 in the 10 mg/m² cohort (P<0.01). For normalized H4 acetylation values, mean increase was

 3.20 ± 2.40 in the 8 mg/m² cohort (P< 0.01) and 2.26 ± 0.47 in the 10 mg/m² cohort (P< 0.01).

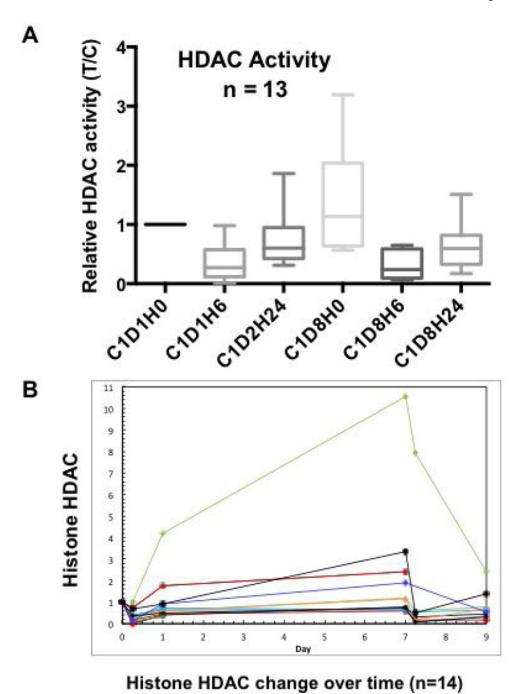


Figure 3. Effects of romidepsin \pm erlotinib on HDAC activity (A) Transient decrease in HDAC activity after initiation of romidepsin and again after addition of erlotinib. (B) Individual patient data showing HDAC activity level over time (n = 14). For normalized HDAC activity values, mean decrease was 0.30 ± 0.16 in the 8 mg/m² cohort (P< 0.01) and 0.40 ± 0.33 in the 10 mg/m² cohort (P< 0.01).

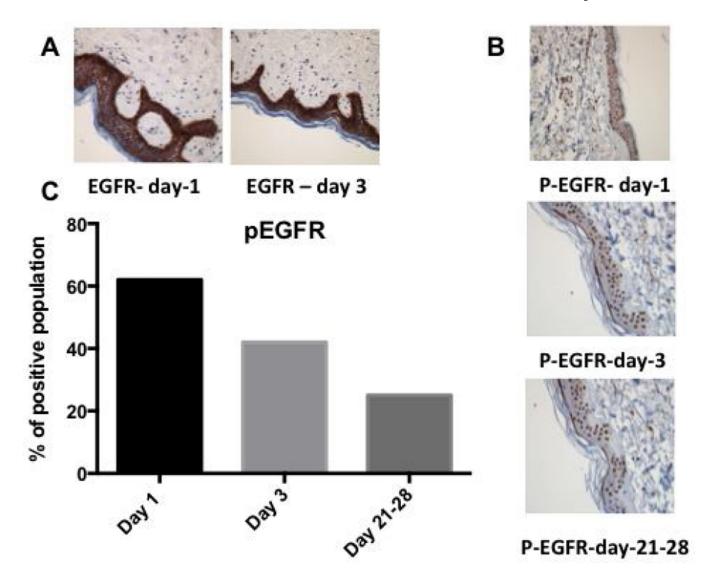


Figure 4. Effects of romidepsin \pm erlotinib on EGFR activation in skin biopsies. (A) Example of EGFR expression not appreciably changing after romidepsin initiation. Magnification 10×20 .

(B) Example of decreasing phospho-EGFR expression after romidepsin initiation (day 3, pre-erlotinib dosing) and after addition of erlotinib (day 21–28). Magnification 10×20 . (C) Median phospho-EGFR expression levels at baseline (day 1 pre-romidepsin dosing), after romidepsin initiation (day 3 pre-erlotinib dosing) (N = 13; P= 0.09), and after addition of erlotinib (day 21–28) (N = 9; P= 0.44).

 $\label{eq:Table 1} \mbox{ Table 1}$ Baseline patient and disease characteristics (N = 17)

Characteristic	Number (%), or median (range)							
Age (y)	60 (48–74)							
Sex								
Female	8 (47)							
Male	9 (53)							
Race								
White	15 (88)							
African-American	2 (12)							
Histology								
Adenocarcinoma	10 (59)							
Squamous cell	6 (35)							
Other	1 (6)							
Molecular profile								
EGFR, KRAS wild type	6 (35)							
KRAS mutation	1 (6)							
Unknown	10 (59)							
Number of lines or prior systemic therapy	3 (1–5)							
Smoking history								
Yes	17 (100)							
No	0 (0)							
Prior erlotinib								
Yes	7 (41)							
No	10 (59)							

Table 2

Treatment-related adverse events in 10% of patients

Grade	Total	14	14	14	11	6	7	5	4	4	3	3	2	2	2	1
	3-4	3	3	2	1	1		2								1 *
	1–2	11	11	12	10	8	7	3	4	4	3	3	2	2	2	
	Possible Relationship to Erlotinib	Y (4/14)	Y (5/14)	Y (9/14)	Y (9/11)	(6/6) A	(L/L) Λ	Y (2/5)	N	Y (4/4)	Y (1/3)	Y (2/3)	Y (2/2)	N	Z	Y (1/1)
	Possible Relationship to Romidepsin	Y (14/14)	Y (14/14)	Y (14/14)	Y (7/11)	(6/6) X	Z	Y (5/5)	Y	N	Y (3/3)	Y (3/3)	N	Y	Y (2/2)	Y (1/1)
	AE Term	Nausea	Vomiting	Fatigue	Diarrhea	Anorexia	Acneiform Rash	↓ Hgb/Anemia	↓ Potassium	Mouth Blister	↓ Glucose	Weight Loss	Dry Skin	Dyspepsia	Sinus tachycardia	Acute kidney injury

Hgb, hemoglobin; N, No; Y, Yes;

* Grade 5 event