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Phase I study of the mTOR inhibitor everolimus in combination with the histone deacetylase inhibitor panobinostat in patients with advanced clear cell renal cell carcinoma

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Abstract

Background—Preclinical studies suggested synergistic anti-tumor activity when pairing mTOR inhibitors with histone deacetylase (HDAC) inhibitors. We completed a phase I, dose-finding trial for the mTOR inhibitor everolimus combined with the HDAC inhibitor panobinostat in advanced clear cell renal cell carcinoma (ccRCC) patients. We additionally investigated expression of microRNA 605 (miR-605) in serum samples obtained from trial participants.

Patients and Methods—Twenty-one patients completed our single institution, non-randomized, open-label, dose-escalation phase 1 trial. miR-605 levels were measured at cycle 1/day 1 (C1D1) and C2D1. Delta Ct method was utilized to evaluate miR-605 expression using U6B as an endogenous control.

Results—There were 3 dosing-limiting toxicities (DLTs): grade 4 thrombocytopenia (n=1), grade 3 thrombocytopenia (n=1), and grade 3 neutropenia (n=1). Everolimus 5 mg PO daily and panobinostat 10 mg PO 3 times weekly (weeks 1 and 2) given in 21-day cycles was the recommended phase II dosing based on their maximum tolerated dose. The 6-month progression-free survival was 31% with a median of 4.1 months (95% confidence internal; 2.0 – 7.1). There

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Declarations of interest: none

Conflict of Interest

Anthony Wood declares that he has no conflict of interest. Saby George declares that he has no conflict of interest. Nabil Adra declares that he has no conflict of interest. Sreenivasulu Chintala declares that he has no conflict of interest. Nur Damayanti declares that she has no conflict of interest. Roberto Pili declares that he has no conflict of interest.

Ethical Approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed Consent

Informed consent was obtained from all individual participants included in the study.

was higher baseline expression of miR-605 in patients with progressive disease (PD) vs those with stable disease (SD) (p=0.0112). PD patients' miR-605 levels decreased after the 1st cycle (p=0.0245), whereas SD patients' miR-605 levels increased (p=0.0179).

Conclusion—A safe and tolerable dosing regimen was established for combination everolimus/panobinostat therapy with myelosuppression as the major DLT. This therapeutic pairing did not appear to improve clinical outcomes in our group of patients with advanced ccRCC. There was differential expression of miR-605 that correlated with treatment response.

Keywords

Kidney; Neoplasm; MicroRNA; miR-605; Targeted Therapy

INTRODUCTION

A bevy of novel immunotherapeutic and molecularly targeted agents have expanded treatment options for renal cell carcinoma (RCC) patients in recent years [1–6]. One such molecularly targeted agent is everolimus, a mammalian target of rapamycin (mTOR) inhibitor [7]. mTOR is a serine/threonine kinase downstream of the phosphatidyl-inositol-3 kinase (PI3K)/Akt pathway that exerts regulatory control over important cellular functions, such as proliferation, angiogenesis, migration, and cellular survival [8,9]. The PI3K/Akt axis often becomes dysregulated in RCC with inappropriate levels of activation and promotion of mTOR's pro-tumorigenic functions; a phenomenon which is combatted with everolimus administration [10]. After its FDA approval in 2009, lackluster results of subsequent trials have demonstrated the limitations of everolimus monotherapy [1,4,11]. The relative ineffectiveness of everolimus monotherapy has been attributed in part to resistance via rebound Akt hyperphosphorylation and unrestrained HIF-2α expression [8,12,13].

Preclinical studies have suggested synergistic anti-tumor activity when pairing mTOR inhibitors with histone deacetylase (HDAC) inhibitors. Nucleosomes are composed of DNA wrapped around a histone octamer consisting of one H3-H4 tetramer and two H2A-H2B dimers. The acetylation status of these histones affects gene expression by altering the accessibility of chromatin to transcription [14]. Increased activity of HDACs, as seen in RCC, contributes to oncogenic transformation by altering transcriptional regulation of genes involved in cellular survival and proliferation [15,16]. Thus, HDACs were identified as a potential therapeutic target for RCC. A phase II clinical trial did not show activity of HDAC inhibitor monotherapy in advanced RCC [17]. However, when HDAC inhibitors were combined with mTOR inhibitors in preclinical studies, the rebound Akt hyperphosphorylation seen with mTOR monotherapy was muted, and HIF-1/2α activity was mitigated through repression of their transactivation potentials and increased degradation of HIF-1α via non-vHL-dependent proteolysis [18,19]. As a result, mTOR inhibitor resistance decreased, anti-angiogenic effects were potentiated, and increased anti-tumor response was noted with mTOR/HDAC inhibitor combination therapy [19].

Based on the synergism seen in these promising pre-clinical studies, we completed a phase I, dose-finding trial for combination therapy of the mTOR inhibitor everolimus with the HDAC inhibitor panobinostat in advanced clear cell renal cell carcinoma (ccRCC) patients.

Panobinostat is a cinnamic hydroxamic acid analog with non-selective inhibition of class I, II, and IV HDACs [20]. It has been previously demonstrated that combination therapy with panobinostat and everolimus is well-tolerated in animal models with myelosuppression as the major side effect [21,22].

As a supplementary investigation, we evaluated the expression of microRNA-605 (miR-605) in serum samples obtained from trial participants. MicroRNA have garnered much attention in the field of oncology in the recent years as potential diagnostic, prognostic, and therapeutic tools. MicroRNA are small, non-coding RNA involved in the regulation of gene expression via post-transcriptional modification of coding RNA [23]. miR-605 plays an intriguing role in the p53/Mdm-2 axis. Mdm-2 suppresses the activity of p53 to facilitate cellular survival under normal conditions. In times of cellular stress, p53 expression increases to mediate cellular repair or promote apoptosis in cells with an overabundance of molecular derangements. As part of this stress response, p53 has been found to increase the expression of miR-605. miR-605, in turn, downregulates the activity of Mdm-2, thus releasing p53 from important negative regulation and promoting its activity [24]. This makes miR-605 an important middleman in the tumor suppressing function of p53. Early investigations have shown single nucleotide polymorphisms (SNPs) and/or decreased expression of miR-605 to be associated with increased cancer risk and tumor aggressiveness [25–27]. With this in mind, we hypothesized that higher expression of circulating miR-605 may be a predictive marker for clinical response to mTOR/HDAC inhibitor combination therapy.

PATIENTS AND METHODS

Study Design and Objectives

This study was a single institution, non-randomized, open-label, dose-escalation phase I clinical trial. The primary objectives were to assess the safety, tolerability, and maximum tolerated dose (MTD) of combination therapy with everolimus and panobinostat. The secondary objective was evaluation of preliminary evidence of efficacy. Novartis Pharmaceuticals Corporation provided both study drugs.

Patient Eligibility

Patients were required to have histologically confirmed metastatic or unresectable renal cell carcinoma with a predominant clear cell phenotype that progressed on or within 6 months of stopping treatment with VEGFR TKIs. All patients were ≥ 18 years of age, had an Eastern Cooperative Oncology Group (ECOG) Performance Status of ≤ 2, and had measurable disease by Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1. Patients were excluded if they were treated with an mTOR or HDAC inhibitor prior. Patients should not have received anticancer therapies (including chemotherapy, radiation therapy, and immunotherapy) within 2 weeks of the start of study drug administration. All patients had adequate bone marrow, liver, kidney, and cardiac function (absolute neutrophil count ≥1,500/mm^3, platelets ≥100,000/mm3, total bilirubin ≤ 1.5 x laboratory upper limit of normal (ULN), AST/ALT ≤2.5 x laboratory ULN, creatinine ≤ 1.5 x laboratory ULN, PT/INR ≤ 1.3 (or ≤ 3 on warfarin therapy), and LVEF ≥ institutional lower limit of normal

(LLN)). Other key exclusion criteria included symptomatic diastolic heart failure, myocardial infarction within 6 months of the start of the study, uncontrolled diabetes mellitus or hyperlipidemia, active bleeding diathesis, impairment of gastrointestinal function that may alter absorption of study drugs, uncontrolled brain or leptomeningeal metastases, active or uncontrolled severe infections, HIV seropositivity, and chronic, systemic treatment with corticosteroids or other immunosuppressive agents. All patients signed informed consent, and the protocol was approved by the Institutional Review Board of Roswell Park Cancer Institute.

Pretreatment Evaluation

Before treatment initiation patients had a complete history and physical exam, evaluation of ECOG performance status, complete blood count, coagulation profile, comprehensive metabolic panel, lipid panel, thyroid function panel, serum pregnancy test, hepatitis B/C screening, urinalysis, EKG, MUGA scan or transthoracic echocardiogram, pulmonary function test, bone scan, and CT scans of the chest, abdomen, and pelvis.

Treatment Protocol

Treatment was administered in 21-day cycles. Panobinostat was administered orally 3 times weekly on Monday, Wednesday, Friday (MWF) during weeks 1 and 2 (days 1, 3, 5, 8, 10, 12), while everolimus was administered orally daily for the duration of the cycle. We used a rule-based, simultaneous dose escalation design with 3 pre-specified dose combinations to assess the MTD (Table 1). Patients were started on dose level 1, which consisted of 10 mg of panobinostat and 5 mg of everolimus per the dosing schedule described prior. If < 2 dose-limiting toxicities (DLTs) occurred in the first 6 patients treated at starting dose level 1 for 1 treatment cycle, the dose would be escalated to dose level 2 with the plan to enroll 6 patients at this dose level. Conversely, if ≥ 2 DLTs occurred in the first 6 patients treated at starting dose level 1 for 1 treatment cycle, the dose would be de-escalated to dose level −1 for the remainder of the trial. Last, if ≥ 2 DLTs occurred in the first 6 patients treated at dose level 2 for 1 treatment cycle, the dose would be de-escalated back to dose level 1 with no further attempts at up-titration. Treatment was continued until disease progression, unacceptable levels of toxicity, withdrawal of consent, or a decision made by the investigator to discontinue therapy.

Evaluation of Response and Toxicity

Patients were assessed for toxicity on day 1 of each 3-week cycle, and tumor response assessment was performed every 9 weeks with appropriate imaging. Radiographic responses were assessed using RECIST version 1.1. Toxicities were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE), version 4.0. A DLT was considered any grade 3 or 4 toxicity occurring within the first treatment cycle.

Endpoints and Statistical Analysis

The primary endpoints were safety, tolerability, and determination of the MTD. The secondary endpoint was evaluation of preliminary evidence of efficacy. As described above, a rule based, simultaneous dose-escalation design with 3 pre-specified dose combinations

was used to determine maximum tolerated dosing. Kaplan-Meier methods were used to estimate progression free survival with a 95% confidence interval. A Fisher's exact test was used to evaluate correlations between treatment response and everolimus dosing.

miR-605 Analysis:

Serum samples analyzed for microRNAs (miRNAs) were collected at cycle 1/day 1 (C1D1) and C2D1. miRNA were isolated from serum samples using the miRNeasy Mini Kit (Qiagen, Germantown, MD, USA) according to the protocols specified by the manufacturer. miRNA purity and concentrations were determined with NanoDrop spectrophotometry. Reverse transcription (RT-PCR) and quantitative polymerase chain reaction (qPCR) were utilized to isolate and amplify miR-605. Both were accomplished according to the protocol provided by the TaqMan Small RNA Assays kit (Applied Biosystems, Foster City, CA, USA). U6B served as the endogenous control. The catalog number for our primer assay was 4427975 with reference numbers of 001568 and 001093 for miR-605 and U6B respectively. The qPCR reaction was performed in triplicate using the Roche Light Cycler 480 (Indianapolis, IN, USA). The delta Ct method was used to calculate the relative expression of miR-605. Statistical analysis was completed utilizing the Wilcoxon signed-rank and Mann-Whitney U tests.

RESULTS

Patient Characteristics

A total of 22 patients were enrolled between October 2010 and August 2015 (Table 2). Median age was 62 years (range, 41 – 75). Participants consisted of 20 males and 2 females with 18 identifying as white, 3 identifying as African American/black, and 1 whose race was unreported. All patients had progressed on VEGFR TKIs without mTOR/HDAC inhibitor exposure prior. Of the 22 patients enrolled, 21 completed at least 1 cycle of treatment and were evaluable for DLTs and efficacy. The 1 patient who did not do so withdrew consent in the process of transitioning to hospice care. Their data was not included in our final analysis.

Safety and Tolerability

Only 1 of the first 6 patients at dose level 1 experienced a DLT (grade 3 neutropenia), therefore the dose was escalated to dose level 2. However, the first 2 patients at dose level 2 experienced dose-limiting thrombocytopenia (grade 3 and grade 4), and the dose was de-escalated back to dose level 1. The next 10 patients enrolled at dose level 1 did not experience a DLT, so the protocol was amended to introduce an intermediate dose level 1A (Table 1) that followed an alternate dose-escalation model. The first 3 patients on dose level 1A did not experience DLTs, but the study closed, and patient accrual was discontinued before reaching our goal of 6 patients. Since our evaluation of dose level 1A was incomplete, we consider dose level 1 to be the MTD, and we recommend it as the phase II dose for future investigations.

The most common side effects were fatigue (12), mucosal inflammation (8), diarrhea (6), dyspnea (6), and thrombocytopenia (5). All grade 3 adverse events possibly attributed to drug therapy included neutropenia (2), dehydration (2), anemia (2), thrombocytopenia (1),

QT prolongation (1), pneumocystis pneumonia (1), arthralgia (1), and deep venous thrombosis (DVT) (1). The grade 4 adverse events possibly attributed to drug therapy were thrombocytopenia (1), pulmonary embolus (1), and anemia (1). Three patients discontinued the study due to toxicity. Please see Table 3 for a full list of grade 3/4 toxicities and adverse events affecting > 10% of patients.

Efficacy

A graphical representation of enrolled patients' courses is depicted in a swimmer plot (Figure 1). The 6-month PFS was 31% with a median PFS of 4.1 months (95% confidence internal [CI]; 2.0 – 7.1) (Figure 2). Stable disease (SD) was attained in 13 patients with the longest duration of treatment lasting 8.9 months prior to progression (PD). All 5 patients treated at either dose level 1A or 2 achieved stable disease, whereas only 8 of 16 patients treated at dose level 1 demonstrated stable disease ($p = 0.11$). A total of 4 patients with stable disease withdrew prior to progression because of toxicity (2 patients at 2.1 and 7.3 months respectively), withdrawal of consent (1 patient at 8.1 months), and treating physician's decision (1 patient at 2.1 months). No partial or complete responses were observed.

miR-605 Analysis

Of our 22 enrolled patients, 13 had serum samples available for analysis. And of these 13 patients, 8 had attained stable disease (SD), whereas 5 patients had progressed (PD) within the first 9 weeks. There was higher baseline expression of miR-605 in patients with PD vs those with SD ($p=0.0112$; Figure 3). PD patients' miR-605 levels decreased after the 1st cycle ($p=0.0245$; Figure 4), whereas SD patients' miR-605 levels increased ($p=0.0179$; Figure 4).

DISCUSSION

We established a safe and tolerable phase II dosing regimen for everolimus and panobinostat combination therapy. While evaluation of preliminary evidence of efficacy was a secondary endpoint, the absence of objective responses, coupled with a modest PFS comparable to everolimus monotherapy, suggests that clinical outcomes were not improved with this therapeutic combination. Our results are consistent with a prior phase I HDAC/mTOR inhibitor clinical trial [28], but the dose levels achieved within our dose-escalation design may have clouded our ability to analyze the therapeutic potential of this combination therapy. A primary limitation of our trial was the fact that the majority of patients were assigned to dose level 1 based on our rule-based design. Within dose level 1, trial participants received everolimus 5 mg daily. It has been previously demonstrated in pharmacodynamic studies that everolimus 10 mg daily is necessary for complete mTOR blockade. And, in line with this, 10 mg daily has been the standard dosing in other major everolimus RCC trials [29]. Looking at our results, there was a trend towards differential response to therapy based on everolimus dosing as all 5 patients receiving 10 mg daily (dose levels 1A and 2) had stable disease (p-value: 0.11). Therefore, we can conclude that combination therapy with everolimus and panobinostat at dose level 1 does not appear to

improve clinical outcomes in this target patient population. But the safety/efficacy of dose level 1A is unknown and could be studied further.

Although clinical outcomes were not favorably altered in this phase I study, there are still potential niches for the expanded use of HDAC and mTOR inhibitors in advanced RCC. In a phase I clinical trial, 2 out of 3 patients with papillary RCC had a PFS of > 1 year on HDAC/mTOR inhibitor combination therapy after having progressed on a mTOR inhibitor previously [28]. Phase I and phase II clinical trials have shown possible benefit when combining HDAC inhibitors with VEGFR TKIs [30,31] and IL-2 [32]. Work within our lab demonstrated enhanced anti-tumor activity of PD-1 inhibition when paired with an HDAC inhibitor in a murine model [33]. And promising phase II results led to the accelerated FDA approval of combination lenvatinib (VEGFR TKI) and everolimus therapy in patients who have progressed on anti-angiogenic therapy [34]. More practical uses for these agents are likely to be unearthed over time.

We hypothesized that higher expression of circulating miR-605 may be a predictive marker for clinical response to mTOR/HDAC inhibitor combination therapy. However, our data suggested the opposite. These results, along with other recent studies that have also found inconsistent associations between miR-605 status and cancer risk [35–38], highlight the complexity of the interplay between serum miR-605 levels, activity of the p53/Mdm2 axis, and clinical phenotype that will need to be accounted for in future miR-605 investigations. Both the concentration of miR-605 and SNP's of the miR-605 gene have been shown to augment cancer risk and tumor aggressiveness. In order to paint a complete picture of miR-605's effects, both the quantity and quality of miR-605 through SNP analysis would need to be evaluated. To build upon this, p53 also has multiple genetic variants seen in cancer cells, including wild-type, loss of function, and gain of function mutants [39]. The p53:miR-605:Mdm2 axis described within the background section is derived from a study involving the wild-type variety, whereas not as much is known about the interplay between miR-605 expression/activity and mutated p53 [24]. Albeit, an accelerated presentation of Li-Fraumeni Syndrome is seen with a SNP-variant of miR-605, hinting that their relationship may be similar [40]. Lastly, it is not known if measurement of miR-605 in the serum is an adequate marker of miR-605 activity as miR-605 applies its actions within the cell. It is conceivable that ccRCC tumor cells may actively pump miR-605 out of the cytosol to protect themselves from its anti-tumorigenic properties, thus leading to increased serum concentrations in patients with more aggressive phenotypes. This active transfer of miR-605 from the intracellular to extracellular space has been previously demonstrated in lung adenocarcinoma cell lines [41]. Furthermore, panobinostat treatment led to increased cytoplasmic distribution of trans-Golgi network COPII vesicles in lung cancer cell lines A549, suggesting enhanced secretory activity in the presence of panobinostat therapy [42]. To overcome these deficiencies in future experiments it would be best to evaluate p53/miR-605 mutational status, compare intracellular and extracellular miR-605 concentrations, and measure the levels of intermediaries in both the pI3K/Akt/mTOR and p53/miR-605/Mdm2 axes to elucidate the functional impact of our data. Regardless of the limitations of this particular study, these results give us a preliminary framework on which we plan to build upon in future investigations.

CONCLUSIONS

In summary, we were able to establish a safe and tolerable dosing regimen for combination everolimus and panobinostat therapy with myelosuppression as the major DLT. This therapeutic pairing did not appear to improve clinical outcomes in our group of patients with advanced ccRCC. There was differential expression of miR-605 that correlated with treatment response. Further investigation of the prognostic and predictive role of miR-605 in this patient population is warranted.

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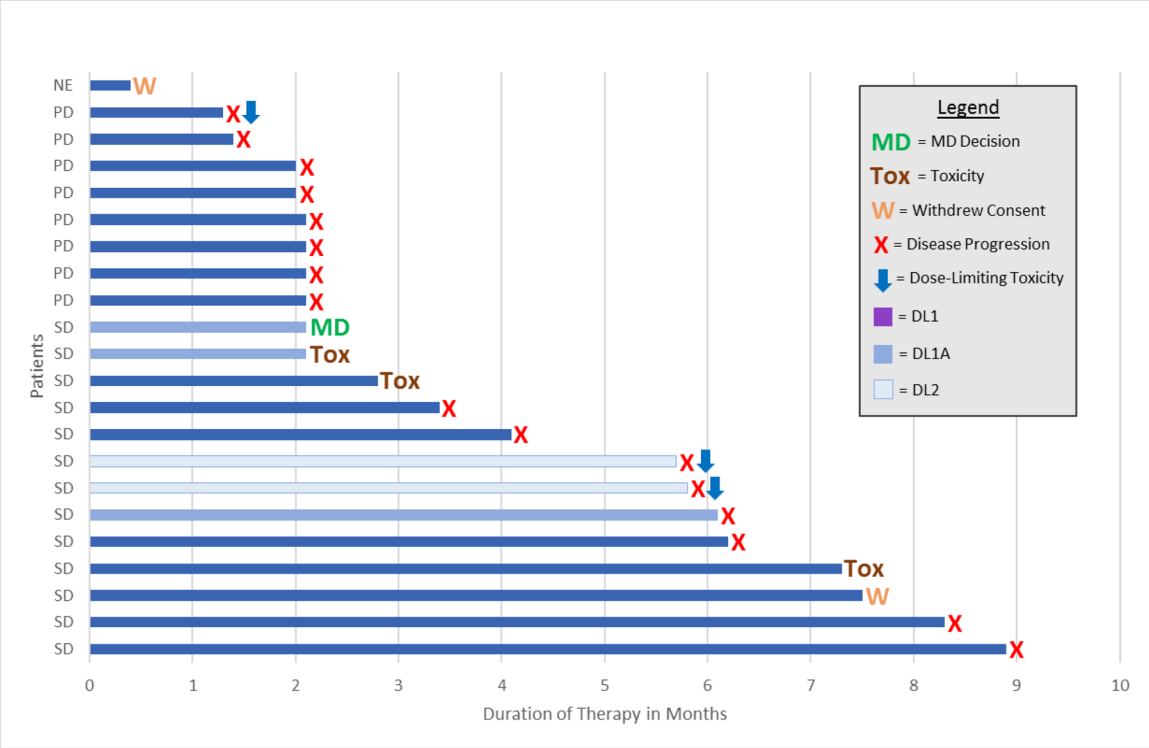

Figure 1. Overview of Patients' Course of Therapy

Swimmer plot depicting clinical course of enrolled patients. Each band represents 1 patient arranged by best response to therapy: PD - progressive disease; SD - stable disease; NE - not evaluable. The bands are color-coded based on the patients' dose levels (DL) and extends for length of therapy with a symbol denoting reason for discontinuation on its right. Patients experiencing dose-limiting toxicities were noted as well.

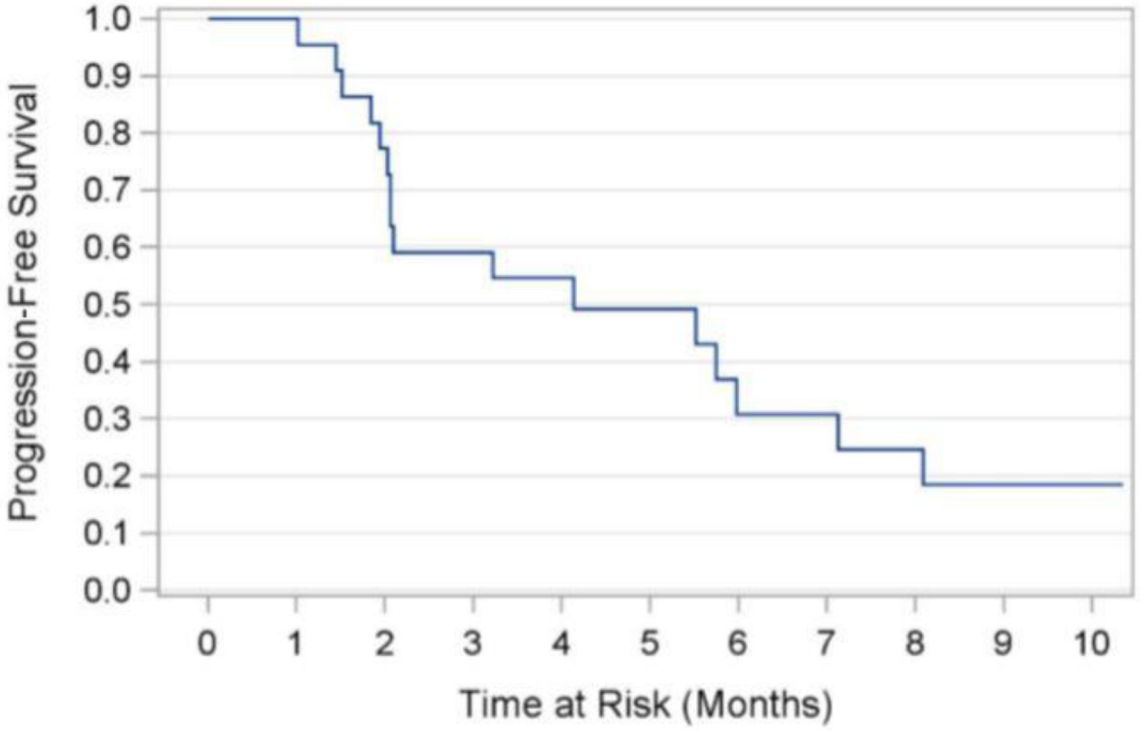

Figure 2. Kaplan-Meier Estimate of Progression-Free Survival

A Kaplan-Meier estimate of progression-free survival (PFS) for patients enrolled in study.

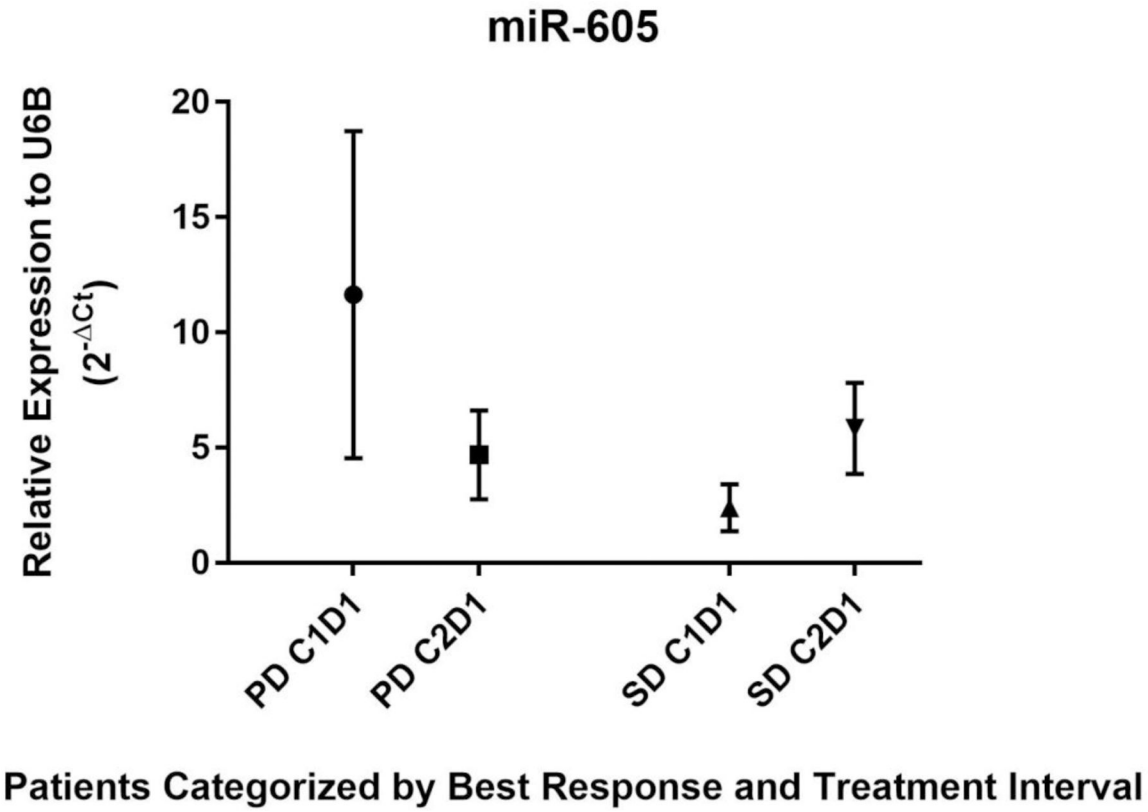

Figure 3. Population miR-605 Expression

Graphical representation of population miR-605 expression relative to U6B at cycle 1/day 1 (C1D1) and C2D2 arranged by best response to therapy. Error bar represents 95% CI of the mean.

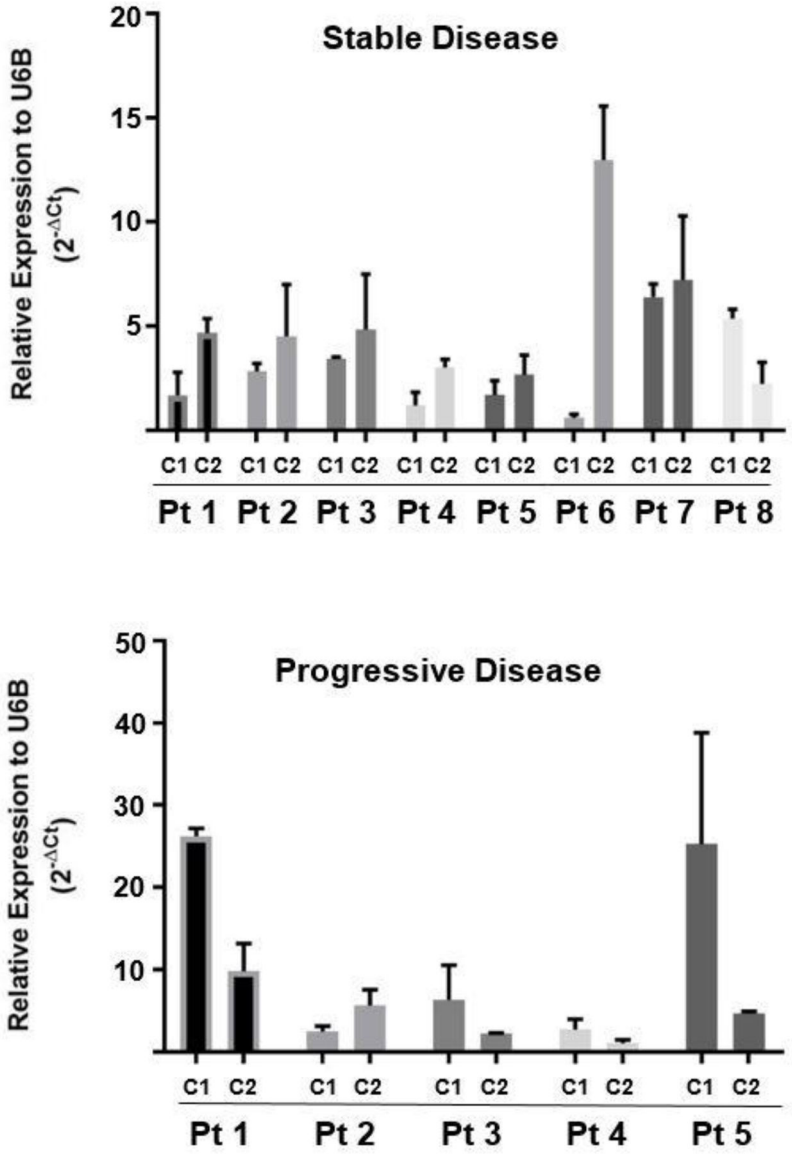

Figure 4. Individual miR-605 Expression per Cycle Grouped by Treatment Response

Graphical representation of individual miR-605 expression relative to U6B at C1D1 and C2D2 arranged by best response to therapy. Each color pair represents an individual patient (Pt - patient #). Thick bar represents the mean, and thin bar with tick mark represents standard deviation.

Table 1.

Dose Levels of Panobinostat + Everolimus - Each Cycle Consists of 21 Days

Dose Level	Panobinostat PO MWF during weeks 1 and 2 (days 1, 3, 5, 8, 10, 12)	Everolimus PO daily for duration of cycle	Number of patients treated	Number of patients experiencing DLT
2	20 mg	10 mg	2	2 (G3 and G4 TCP)
1A	10 mg	10 mg	3	0
1	10 mg	5 mg	16	1 (G3 neutropenia)
−1	5 mg	5 mg EOD	0	0

Abbreviations: DLT - dose-limiting toxicity; G - grade; PO - per os EOD - every other day; TCP - thrombocytopenia; MWF - Monday/Wednesday/Friday

Table 2.

Patient Characteristics

Categories	DL1	DL1A	DL2	All Dose Levels
Number of Patients (%)	17 (77.3)	3 (13.6)	2 (9.1)	22 (100)
Age (yrs): Range Mean/Median	41.0 – 75.6 60.1/75.6	60.6 – 71.7 65.7/64.8	61.8 – 65.2 63.5/63.5	41.0 – 75.6 61.2/62.8
Gender: M/F (%)	16/1 (94.1/5.9)	3/0 (100/0)	1/1 (50/50)	20/2 (90.9/9.1)
*Race: White/AA,Black (%)	15/1 (93.8/5.9)	2/1 (66.7/33.3)	1/1 (50/50)	18/3 (85.7/14.3)

* 1 data point is missing from Race, which accounts for number variation

Abbreviations: DL - dose level; M/F - male/female; AA - African American; Yrs - years

Table 3.

Summary of Adverse Events (AEs)

Adverse Event	≤ Grade 2 (%)	Grade 3 (%)	Grade 4 (%)	Total (%)
Fatigue	12 (57.1)	0	0	12 (57.1)
Mucosal Inflammation	8 (38.1)	0	0	8 (38.1)
Diarrhea	6 (28.6)	0	0	6 (28.6)
Dyspnea	5 (23.8)	1 (4.8)	0	6 (28.6)
Thrombocytopenia	3 (14.3)	1 (4.8)	1 (4.8)	5 (23.8)
Peripheral Edema	4 (19)	1 (4.8)	0	5 (23.8)
Pain in Extremity	3 (14.3)	2 (9.5)	0	5 (23.8)
Nausea	4 (19)	0	0	4 (19)
Chills	4 (19)	0	0	4 (19)
Hemoglobin Decrease	2 (9.5)	1 (4.8)	1 (4.8)	4 (19)
Decreased Appetite	4 (19)	0	0	4 (19)
Hyperglycemia	3 (14.3)	1 (4.8)	0	4 (19)
Arthralgia	3 (14.3)	1 (4.8)	0	4 (19)
Cough	4 (19)	0	0	4 (19)
Neutropenia	1 (4.8)	2 (9.5)	0	3 (14.3)
Atrial Fibrillation	2 (9.5)	1 (4.8)	0	3 (14.3)
AST elevation	3 (14.3)	0	0	3 (14.3)
Alk Phos Elevation	3 (14.3)	0	0	3 (14.3)
Creatinine Elevation	3 (14.3)	0	0	3 (14.3)
Triglyceride Elevation	3 (14.3)	0	0	3 (14.3)
Hyponatremia	3 (14.3)	0	0	3 (14.3)
Abnormal QT Interval	2 (9.5)	1 (4.8)	0	3 (14.3)
Headache	3 (14.3)	0	0	3 (14.3)
Dehydration	0	2 (9.5)	0	2 (9.5)
DVT/PE	0	1 (4.8)	1 (4.8)	2 (9.5)
Vomiting	1 (4.8)	1 (4.8)	0	2 (9.5)
Anemia	0	1 (4.8)	0	1 (4.8)
Pneumocystis PNA	0	1 (4.8)	0	1 (4.8)
Malignant Neoplasm	0	1 (4.8)	0	1 (4.8)
Confusional State	0	1 (4.8)	0	1 (4.8)

This table includes all grade 3/4 AEs and AEs impacting > 10% of patients.

Abbreviations: AST - aspartate aminotransferase; Alk Phos - alkaline phosphatase; DVT - deep vein thrombosis; PE - pulmonary embolus; PNA - pneumonia