COLUMBIA UNIVERSITY MEDICAL CENTER

Administration of Romidepsin plus Pralatrexate for Patients with Relapsed or Refractory T-cell Lymphoma

Treatment Plan:

Patients will be treated with pralatrexate and romidepsin administered intravenously on day 1 and day 15 on a 28-day treatment cycle. All patients receiving pralatrexate will receive folic acid and vitamin B12 supplementation per FDA label. Patients will be dosed based at the MTD established in the Phase I study which is pralatrexate 25 mg/m2 and romidepsin 12 mg/m2.

REGIMEN DESCRIPTION					
Agent	***Premedications/ Precautions***	***Dose***	***Route***	***Schedule***	***Cycle Length***
Romidepsin	Dexamethasone (12 mg IV) Ondansetron (16 mg IVPB)	12 mg/m2	IV over 4 hours (Administered first)	Days 1, 15	*28 days*
Pralatrexate	B12 injection (Q8 weeks) and Folate supplementation (1 mg PO QD)	25 mg/m2	IV over 3-5 m (Administered immediately after the romidepsin infusion)	Days 1, 15	

Drugs Administration:

Drugs should be given by peripheral or central venous access (central access is not necessary).

The prophylactic use of antiemetics is strongly encouraged, but antiemetics that significantly prolong QTc or that significantly inhibit CYP3A4 must be avoided.

- Romidepsin
    - Day 1&15 (Q28): IV over 4 hours (administered first)
    - Dose: 12 mg/m2
    - Dexamethasone (12mg IV)
    - Ondansetron (16mg IV)
- Pralatrexate
    - Days 1&15 (Q28): IV over 3-5 minutes (administered immediately after Romidepsin infusion)

- Dose: 25 mg/m2
- B-12 1000 mg Injection (Q8-10 weeks, may start within 8 weeks prior to first dose of pralatrexate)
- Folic Acid (1mg PO QD starting 7 days prior to administration of pralatrexate)
- Any patient developing mucositis (grade 1 or higher) can be treated with leucovorin 15 mg PO BID on Days 3-13 and 17-27 (holding the day before, day of and day after pralatrexate administration)

Patient Treatment Parameters:

- Patients must have adequate organ and marrow function as defined:
  - Absolute neutrophil count ≥1,000/dL
  - Platelets ≥75,000 total
  - Bilirubin ≤1.5 X institutional limits
  - AST(SGOT)/ALT(SGPT) ≤2.0 X institutional upper limit of normal, or < 3.0 X ULN in presence of demonstrable liver involvement
  - Serum creatinine <2 X institutional upper limits of normal OR creatinine clearance ≥50 mL/min/for patients with creatinine levels above institutional normal.
  - Serum potassium ≥ 3.8 mmol/L
  - Serum magnesium ≥1.8 mg/dL
- Negative urine or serum pregnancy test for females of childbearing potential.
- All females of childbearing potential must use an effective barrier method of contraception (either an IUDC or double barrier method using condoms or a diaphragm plus spermicide) during the treatment period and for at least 1 month thereafter. Male subjects should use a barrier method of contraception during the treatment period and for at least 3 months thereafter. Female subjects should avoid the use of estrogen-containing contraceptives, since Romidepsin may reduce the effectiveness of estrogen-containing contraceptives.

Patients with the following should not be treated:

- Central nervous system metastases, including lymphomatous meningitis
- History of allergic reactions to Pralatrexate or Romidepsin.
- Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, or psychiatric illness/social situations that would limit compliance with study requirements.

- Pregnant or nursing women
- Active concurrent malignancy (except non-melanoma skin cancer or carcinoma in situ of the cervix). If there is a history of prior malignancy, the patient must be disease-free for ≥ 3-years. Patients whose lymphoma has transformed from a less aggressive histology remain eligible.
- Patients known to be Human Immunodeficiency Virus (HIV)-positive
- Patients with active hepatitis A, hepatitis B, or hepatitis C infection
- Concomitant use of CYP3A4 inhibitors
- Any known cardiac abnormalities, such as:
    - Congenital long QT syndrome
    - QTc interval ≥ 500 milliseconds;
    - Patients taking drugs leading to significant QT prolongation (See Appendix 1: Medications That May Cause QTc Prolongation)
    - Myocardial infarction within 6 months of C1D1. [Subjects with a history of myocardial infarction between 6 and 12 months prior to C1D1 who are asymptomatic and have had a negative cardiac risk assessment (treadmill stress test, nuclear medicine stress test, or stress echocardiogram) since the event, may participate];
    - Other significant ECG abnormalities including 2nd degree atrio-ventricular (AV) block type II, 3rd degree AV block, or bradycardia (ventricular rate less than 50 beats/min);
    - Symptomatic coronary artery disease (CAD), *e.g.,* angina Canadian Class II-IV. In any patient in whom there is doubt, the patient should have a stress imaging study and, if abnormal, angiography to define whether or not CAD is present;
    - An ECG recorded at screening showing evidence of cardiac ischemia (ST depression of ≥2 mm, measured from isoelectric line to the ST segment). If in any doubt, the patient should have a stress imaging study and, if abnormal, angiography to define whether or not CAD is present;
    - Congestive heart failure (CHF) that meets New York Heart Association (NYHA) Class II to IV definitions (see Appendix 4) and/or ejection fraction <40% by MUGA scan or <50% by echocardiogram and/or MRI;
    - A known history of sustained ventricular tachycardia (VT), ventricular fibrillation (VF), Torsade de Pointes, or cardiac arrest;
    - Hypertrophic cardiomegaly or restrictive cardiomyopathy from prior treatment or other causes;
    - Uncontrolled hypertension, *i.e.,* blood pressure (BP) of ≥160/95; patients who have a history of hypertension controlled by medication must be on a stable dose (for at least one month) and meet all other inclusion criteria; or

- Any cardiac arrhythmia requiring an anti-arrhythmic medication (excluding stable doses of beta-blockers)

Patient Retreatment Parameters:

- Absolute Neutrophil Count > 1.0
- Platelets > 50
- Creatinine ≤ 2.0 x ULN, or creatinine cl >50 ml/min
- AST and ALT ≤2.0 x ULN (unless known hepatic involvement then < 3.0 x ULN)
- Bilirubin ≤ 2.0 x ULN
- Potassium ≥ 3.8 mmol/L
- Magnesium ≥ 1.8 mg/dL (supplements should be given to patients whose potassium or magnesium is low and must be re-checked prior to romidepsin administration)
- Recovery of any drug-related, non-hematological toxicity to grade 1 or less

Prophylactic Medicines and Supportive Care:

Romidepsin is moderately emetogenic. Standard institutional guidelines for anti-emetics will be used. Supportive treatment may include additional anti-emetics, anti-diarrheal, anti-pyretics, anti-histamines, analgesics, antibiotics, and blood products. Patients who experience indigestion or gastroesophageal reflux symptoms on Romidepsin may be treated with Proton Pump Inhibitors (PPIs) as well as H2 blockers as clinically indicated.

Patients who have pre-existing chronic anemia prior to receiving pralatrexate and romidepsin may continue to receive erythropoietin or darbepoietin. Colony stimulating growth factors) may be used in patients who experience hematological toxicity per American Society of Clinical Oncology (ASCO) guidelines. After initiating treatment, anemia may be managed with growth factors according to the ASCO guidelines: 2006 Update of Recommendations for the Use of White Blood Cell Growth Factors: An Evidence-Based Clinical Practice Guideline http://www.jco.org/cgi/content/full/24/19/3187.

Patients should receive allopurinol or rasburicase and other treatment considered appropriate for tumor lysis prophylaxis in cycle 1 as deemed necessary by the treating physician.

Patients will be permitted to receive appropriate supportive care measures as deemed necessary by the treating physician including but not limited to the items outlined below:

- **Diarrhea:** Diarrhea should be treated promptly with appropriate supportive care, including loperamide. Loperamide should not be taken prophylactically. Patients should be instructed to begin taking loperamide at the first sign of: 1) poorly formed or loose stool, 2) occurrence of more bowel movements than usual in one day or 3) unusually high volume of stool. Loperamide should be taken in the following

manner: 4 mg at first onset of diarrhea, then 2 mg after each unformed stool. The daily dose of loperamide should not exceed 16 mg/day. Loperamide should be deferred if blood or mucus is present in the stool or if diarrhea is accompanied by fever. In this setting, appropriate diagnostic microbiologic specimens should be obtained to exclude an infectious etiology. Patients should also be advised to drink liberal quantities of clear fluids.

- **Nausea/vomiting:** Romidepsin is moderately emetigenic. Ondansteron 16mg IV and Dexamethasone 12 mg IV will be given prior to Romidepsin infusions. Nausea and vomiting should be treated aggressively, with agents such as prochlorperazine, metoclopramide, 5-HT-3 inhibitors, or benzodiazepines. Patients should be strongly encouraged to maintain liberal oral fluid intake during therapy, especially during the initial 14 days of each treatment cycle.

- **Fatigue:** May be cumulative with increasing cycles of therapy. Can be treated as indicated by the treating physician.

- **Anemia:** Treatment with pralatrexate and romidepsin can cause dose-related anemia. Transfusions or erythropoetin may be utilized as clinically indicated for the treatment of anemia, but should be clearly noted as concurrent medications.

- **Thrombocytopenia:** Treatment with Pralatrexate and Romidepsin can cause dose-related thrombocytopenia. Transfusion of platelets may be used if clinically indicated. Dose modification for thrombocytopenia is allowed in a manner consistent with the guidelines for dose modification (Section [6.3]). Prophylactic folic acid and vitamin B12 supplements are necessary to reduce hematologic toxicity.

- **Neutropenia:** Prophylactic use of colony-stimulating factors including G-CSF, pegylated G-CSF or GM-CSF and may be utilized if clinically indicated.

- **Hypokalemia or hypomagnesemia** should be corrected prior to administration of Romidepsin, and consideration should be given to monitoring potassium and magnesium in symptomatic patients (e.g. patients with nausea, vomiting, diarrhea, fluid imbalance or cardiac symptoms.)

- **Oral Mucositis:** Pralatrexate may cause mucositis (includes stomatitis or mucosal inflammation of gastrointestinal and genitourinary tracts); which may require dosage modification. Prophylactic folic acid and vitamin B_{12} supplements are necessary to reduce treatment-related mucositis. Any patient developing mucositis (grade 1 or higher) can be treated with leucovorin 15 mg PO BID on Days 3-13 and 17-27 (holding the day before, day of and day after pralatrexate administration).

- **Hepatotoxicity:** Liver function test abnormalities have been observed with Pralatrexate use. Persistent abnormalities may indicate hepatotoxicity and may require dosage modification.

Cardiac Monitoring
Minor ECG changes are not uncommon following romidepsin administration. Cardiac assessments must be performed for all patients. The treating physician must perform the primary assessment and is responsible for the cardiac safety of the patients (local cardiologist may be consulted, if preferred).

Cardiac Alert Findings
In the event of an alert finding, the individual decision about a delay of administration, dose reduction, or withdrawal from the study will be made by the Investigator (in association with local cardiologist, if preferred). All alerts must be confirmed via a manual read of the patients ECG; the machine reading alone is not adequate. The following findings are considered to be cause for alert and if they occur, should be reported as AEs or SAEs, as appropriate:

- QTc ≥500 msec
- Ventricular arrhythmia: VT (≥3 beats in a row) or VF;
- Sinus tachycardia (pulse >140/min after recumbency);
- Heart rate ≥ 120 bpm with ≥ 20 bpm increase from previous evaluation;
- New occurrence of atrial dysrhythmias (SVT, atrial fibrillation, or atrial flutter); or
- Abnormal ST and/or T-wave changes including ST depression of ≥2 mm (as measured from isoelectric line to the ST segment at a point 60 msec at the end of the QRS complex); T-wave inversion of ≥4 mm (measured from isoelectric line to peak of T-wave) as long as the main QRS vector is positive;
- Ventricular tachycardia, including Torsade de Pointes.

General Concomitant Medication and Supportive Care Guidelines

Because there is a potential for interaction of Pralatrexate and Romidepsin with other concomitantly administered drugs through the cytochrome P450 system, the case report form must capture the concurrent use of all other drugs, over-the-counter medications, or alternative therapies. The Principal Investigator should be alerted if the patient is taking any agent known to affect or with the potential to affect selected CYP450 isoenzymes.

Carefully monitor prothrombin time (PT) and International Normalized Ratio (INR) in patients concurrently administered ISTODAX® and Coumadin derivatives

Patients must be instructed not to take any additional medications (including over-the-counter products) during the trial without prior consultation with the PI. All medications taken within 30 days of screening and medications and supportive therapies that are administered during the study must be recorded in the patient's CRF and in the source documents. Supportive therapy, that is ongoing at baseline, will be permitted during the treatment phase of the study. If other therapy for the disease is required, continuation of the study treatment should be discussed with the lead investigator and sponsor. Concomitant medications for other medical conditions are permitted as clinically indicated subject to specific protocol requirements outlined below.

Permitted medications and treatments

- **The prophylactic use of antiemetics is strongly encouraged**, but antiemetics that significantly prolong QTc (*e.g.*, palonosetron) or that significantly inhibit CYP3A4 (*e.g.*, aprepitant) must be avoided (see Appendix 1, and 2, respectively). Granisetron and ondansetron are the antiemetics most commonly utilized in other romidepsin clinical trials.
- Patient's electrolytes (serum potassium and magnesium) must be measured, and must receive supplement infusions to correct any levels outside of those stipulated per protocol. Patients must then undergo a repeat biochemistry test to demonstrate values are within the accepted range before the patient is re-dosed with romidepsin.

Prohibited concurrent therapy

- Any medications which may cause QTc prolongation or inducing torsades de pointes should not be used.
- Concomitant use of CYP3A4 inhibitors with romidepsin should be avoided (excluding granisetron and ondansetron) to prevent potential increase in romidepsin exposure during concomitant treatment with these drugs. Should a patient already on therapy with romidepsin require treatment with these drugs romidepsin must be interrupted prior to starting these drugs and should not resume until a washout period of at least 5 half-lives has elapsed.
- Strong CYP3A4 inhibitors may increase concentrations of ISTODAX® and should be avoided.
- Potent CYP3A4 inducers may decrease concentrations of ISTODAX® and should be avoided
- Any medications that have the potential to alter serum electrolytes (e.g., diuretics) should be monitored very closely for electrolyte abnormalities as these can contribute to the risk of QT prolongation and ventricular arrhythmias.

Patient Monitoring Parameters:

Patients should be monitored days 1 and 15 of the first cycle and on day 1 of each subsequent cycle.

Dose Modifications:

The criteria for Dose reduction include any recurrent toxicity Grade 3 or greater that has not resolved to a Grade 2 or lower by the next treatment, and at the discretion of the treating physician in the setting of recurrent toxicities

Any patient developing mucositis (grade 1 or higher) can be treated with leucovorin 15 mg PO BID on Days 3-13 and 17-27 (holding the day before, day of and day after pralatrexate administration).

Granulocyte-colony stimulating factor support can be used at the treating physician's discretion.

Dose Level	Pralatrexate	Romidepsin
RP2D	25 mg/m2 Day 1 and 15	12 mg/m2 Day 1 and 15
Dose Level -1	20 mg/m2 Day 1 and 15	12 mg/m2 Day 1 and 15
Dose Level -2	20 mg/m2 Day 1 and 15	10 mg/m2 Day 1 and 15
Dose Level -3	15 mg/m2 Day 1 and 15	10 mg/m2 Day 1 and 15

Efficacy Measurements:

Patients should be evaluated for response following cycle 3 and 6 of treatment and every 3-6 months thereafter at the treating physician's discretion.

Duration of Treatment:

Patients will be treated until one of the following events:

- Disease progression
- Unacceptable adverse event(s), DLTs
- Withdrawal of consent
- General or specific changes in the patient's condition that render the patient unacceptable for further treatment in the judgment of the investigator
- An event that in the judgment of the treating physician warrant's discontinuation of therapy.

Pharmaceutical Information:

A list of the adverse events and potential risks associated with the investigational or commercial agents administered in this study can be found in Section 7.2.

Pralatrexate

Product description:

Pralatrexate Injection is formulated as a sterile solution for injection and will be supplied in single-use glass vials containing an isotonic parenteral solution at a concentration of 20 mg/mL of pralatrexate. The osmolality of Pralatrexate Injection is ~300 mOsmol/kg. The formulation is a clear yellow solution.

Solution preparation:

Pralatrexate Injection is a cytotoxic agent. The institutional, local, and all applicable policies and procedures must be followed for proper handling and disposal of chemotherapy drugs.

Storage requirements:

Pralatrexate Injection must be stored refrigerated at 2-8°C (36-46°F) (see United States Pharmacopeia [USP] Controlled Cold Temperature) and protected from light. Pralatrexate Injection contains no bacteriostatic agent; each vial is for single-use only. Vials of Pralatrexate Injection must be stored under secured conditions with access limited to authorized study personnel only.

Refer to separate Investigational Product (IP) Accountability and Dispensing Instructions for details regarding pralatrexate storage, preparation, and administration.

Stability:

Unopened product has a shelf life of >1 year.

Diluted infusion solution: After dilution as recommended to a concentration of 0.2 or 0.4 mg/ml, the infusion solution has been demonstrated to be physically and chemically stable at 25°C for 96 and 24 hours respectively.

Administration

Before administration, Pralatrexate Injection vials must be inspected for abnormalities such as cracks, sediments, crystals, turbidity, etc. If any abnormalities are noted, Spectrum must be notified and the vial must not be used. Appropriate procedures for cytotoxic agents must be followed for administration of Pralatrexate Injection.

Pralatrexate Injection will be administered as an IV push over a minimum of 30 seconds up to a maximum of 5 minutes into a patent free-flowing IV line containing normal saline (0.9% NaCl) at an initial dose of 30 mg/m2/week administered for 3 of 4 weeks.

Please refer to the FDA approved package insert for further information.

Romidepsin

Romidepsin is a unique bicyclic depsipeptide originally isolated from *Chromobacterium violaceum* strain 968. Romidepsin is an antineoplastic agent that has been identified as a novel HDAC inhibitor. Romidepsin has been shown to induce hyperacetylation of histones and other nonhistone protein species resulting in a variety of phenotypic changes, induction of the upregulation of gene transcription, G1 and G2/M arrest of the cell cycle, morphological reversion of transformed cells, cell growth inhibition, apoptotic cell death, and inhibition of angiogenesis.

The molecular formula of romidepsin is $C_{24}H_{36}N_4O_6S_2$, its molecular weight is 540.71, and its chemical name is: (1S,4S,7Z,10S,16E,21R)-7-ethylidene-4,21-bis(1-methyletheyl)-2-oxa-12,13-dithia-5,8,20,23-tetraazabicyclo[8.7.6]tricos-16-ene-3,6,9,19,22-pentone.

Product description:

ISTODAX® (Romidepsin) is a histone deacetylase (HDAC) inhibitor indicated for the treatment of cutaneous T-cell lymphoma (CTCL) and peripheral T-cell lymphoma (PTCL) in patients who have received at least one prior systemic therapy.

Solution preparation:

Romidepsin is supplied as a kit including a sterile, lyophilized powder in a single-use vial containing 10 mg of romidepsin and 20 mg of the bulking agent, povidone, USP. In addition, each kit includes one sterile Diluent vial containing 2 mL (deliverable volume) of 80% propylene glycol, USP, and 20% dehydrated alcohol, USP.

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NDC 46026-983-01: ISTODAX® KIT containing 1 vial of romidepsin, 10 mg and 1 vial of diluent for romidepsin, 2 mL per carton

Storage requirements:

The dual pack is to be stored at 20 to 25ºC (68 to 77°F), excursions permitted between 15 to 30°C (59 to 86°F) [USP controlled room temperature].Romidepsin (for infusion) is stable for at least 36 months at 25°C/60% relative humidity (RH) as well as for 6 months at 40°C/75% RH and is stable against heat (for 3 months at 50°C) and humidity (for 3 months at 25°C/83% RH). The drug should be reconstituted by appropriately trained personnel using aseptic technique. A volume of 2 mL of reconstitution diluent is added to the lyophilized powder and swirled until contents of the vial are free from visible particles. The reconstituted product stock solution at 5 mg/mL is chemically stable for at least 8 hours at room temperature. However, whenever possible, drug should be prepared within 4 hours of dose administration. A volume of the 5 mg/mL stock solution containing the appropriate dose for the patient will be diluted in 0.9% Sodium Chloride Injection, USP (0.9% saline) for intravenous infusion, as directed by the protocol. This dilution should result in a final drug concentration within the demonstrated stability range of 0.02 to 0.16 mg/mL for reconstituted romidepsin, that is compatible with polyvinyl chloride (PVC), ethylene vinyl acetate (EVA), and polyethylene (PE) intravenous infusion bags; glass bottles may also be used. The romidepsin infusion solution is chemically stable for at least 24 hours at room temperature. However, whenever possible, drug should be prepared within 4 hours of dose administration.

Administration

Romidepsin should be handled in a manner consistent with recommended safe procedures for handling cytotoxic drugs.

The lyophilized, sterile finished product contains romidepsin, 10 mg/vial and 20 mg/single use vial Povidone, USP, and hydrochloric acid to adjust pH. Romidepsin (for infusion) is supplied in a dual-pack configuration with a single use Diluent for Romidepsin vial that contains 2 mL of 80% Propylene Glycol, USP, and 20% Dehydrated Alcohol (ethanol), USP; sterile for use in reconstitution of Romidepsin (for Infusion).

Romidepsin must be reconstituted with the supplied diluent and further diluted with 0.9% Sodium Chloride Injection, USP before intravenous infusion.

- Each 10 mg single-use vial of romidepsin must be reconstituted with 2 mL of the supplied Diluent. With a suitable syringe, aseptically withdraw 2 mL from the supplied Diluent vial, and slowly inject it into the romidepsin for injection vial. Swirl the contents of the vial until there are no visible particles in the resulting solution. The reconstituted solution will contain the romidepsin 5 mg/mL. The reconstituted the romidepsin solution is chemically stable for at least 8 hours at room temperature.
- Extract the appropriate amount of the romidepsin from the vials to deliver the desired dose, using proper aseptic technique. Before intravenous infusion, further dilute the romidepsin in 500 mL 0.9% Sodium Chloride Injection, USP.
- Infuse over 4 hours.

The diluted solution is compatible with polyvinyl chloride (PVC), ethylene vinyl acetate (EVA), polyethylene (PE) infusion bags as well as glass bottles, and is chemically stable for at least 24 hours when stored at room temperature. However, it should be administered as soon after dilution as possible.

Please refer to the FDA approved package insert for further information.