[1]Medicine/Hematology-Oncology, Weill Cornell Medical College, New York, United States; [2]Department of Medicine, Washington University in St. Louis, St Louis, United States; [3]Department of Medicine, Memorial Sloan Kettering Cancer Center, New York, United States; [4]Department of Medicine, Moffitt Cancer Center, Tampa, United States; [5]Department of Pathology, Weill Cornell Medical College, New York, United States

Introduction: Peripheral T-cell lymphomas (PTCL) are an uncommon and heterogeneous group of non-Hodgkin lymphomas with divergent cells of origin and mechanisms of lymphomagenesis. Cyclophosphamide, doxorubicin, vincristine and prednisone (CHOP) chemotherapy, the most commonly prescribed initial treatment for systemic PTCL, provides suboptimal complete remission rates and response duration in the majority of non-ALCL patients. Emerging genetic studies have shown recurrent mutations affecting TET2, DNMT3A, IDH2 and RHOA in PTCL subtypes, particularly in nodal peripheral T-cell lymphoma with T-follicular helper phenotype (PTCL-TFH) such as angioimmunoblastic T-cell lymphoma. The association of aberrant DNA methylation with PTCL lymphomagenesis provides rationale for clinical application of hypomethylating agents. Azacitidine is an epigenetic modifier of DNA methylation by inhibition of DNA methyltransferase at low doses. In human PTCL patients, treatment with 5-azacitidine produced sustained responses (ORR 75%, CR/Cru 50%) in R/R AITL in a retrospective cohort study (Lemonnier et al. Blood 2018;132:2305). The feasibility of combining CHOP chemotherapy with azacitidine has been evaluated in 2 phase 1 studies in B-cell lymphoma, one with injectable 5-azaticidine (Clozel et al. Cancer Discov 2013;3:1002), the other with oral azacitidine (CC-486) (Martin et al. Blood 2017;130:192). We initiated a multi-center phase 2 study in 5/2018 to evaluate the efficacy and safety of chemo-sensitization with oral azacitidine (CC-486) in combination with CHOP for initial treatment of PTCL (ClinicalTrials.gov - NCT03542266).

Methods: This exploratory phase 2 study prioritizes enrollment of nodal TCL with TFH phenotype (PTCL-TFH). Additional eligible subtypes include PTCL/NOS and ATLL. Subjects receive standard dose CHOP on day 1 of each cycle for a total of 6 cycles. Priming with oral azacitidine (CC-486) at 300 mg daily is administered for 7 days prior to CHOP cycle 1 initiation, and for 14 days (days 8-21) before CHOP cycles 2-6. Supportive care includes mandatory G-CSF and recommended prophylaxis against PCP and VZV. The primary endpoint is CR per 2014 IWG criteria. Secondary endpoints include ORR, safety and survival. The study has a sample size of 20, and follows two-stage minimax design for primary efficacy analysis. Correlative biomarker studies are prospectively planned to assess changes in genome-wide methylation, gene expression and immune profile in response to DNMT inhibitor. The study is actively enrolling patients at Weill Cornell Medicine, with additional 3 US sites due to open in the 2nd quarter of 2019.

Keywords: angioimmunoblastic T-cell lymphoma (AITL); epigenetics; peripheral T-cell lymphomas (PTCL).

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OT16
DOSE FINDING STUDY TO ASSESS SAFETY, PK AND EFFICACY OF FIMEPINOSTAT (CUDC-907) WITH VENETOCLAX OR RITUXIMAB PLUS BENDAMUSTINE IN PATIENTS WITH RELAPSED/REFRACTORY LYMPHOMA

A. Younes[1] | C.L. Batlevi[1] | J.B. Cohen[2] | K. Kelly[3] | D.J. Landsburg[4] | K. Patel[5] | T. Phillips[6] | S. Smith[7] | J. Westin[8] | A.W. Ma[9] | D. Grayson[9] | S. Barta[4]

[1]Department of Medicine, Memorial Sloan Kettering Cancer Center, New York, United States; [2]Hematology & Medical Oncology, Emory University Winship Cancer Institute, Atlanta, United States; [3]Department of Medicine, University of Southern California, Norris Cancer Center Hospital, Los Angeles, United States; [4]Department of Medicine, University of Pennsylvania, Perelman Center, Philadelphia, United States; [5]Oncology, Swedish Cancer Institute, Seattle, United States; [6]Rogel Cancer Center, University of Michigan, Ann Arbor, United States; [7]Hematology/Oncology, University of Chicago, Chicago, United States; [8]Department of Lymphoma/Myeloma, The University of Texas MD Anderson Cancer Center, Houston, United States; [9]Research & Development, Curis, Inc., Lexington, United States

Background: The 2016 WHO reclassification of lymphoid tumors distinguishes double-hit (DHL) and triple-hit (THL) lymphomas as clinically important subtypes, now classified as high-grade B-cell lymphoma (HGBL) with *MYC* and *BCL2* and/or *BCL6* rearrangements. Double-expressor lymphoma with MYC and BCL2 protein overexpression without rearrangement (included within DLBCL-NOS) also has prognostic importance. This reclassification highlights the dismal outcomes for patients with tumors harboring MYC and/or BCL2 alterations. Currently, there are no approved therapies that target MYC. Fimepinostat (F) is an investigational small-molecule dual inhibitor of PI3Ks and HDACs. F inhibited both PI3K and HDAC in non-clinical studies and substantially reduced MYC protein levels. PI3K and HDAC were also inhibited by F in patients. F demonstrated synergistic antitumor effects with venetoclax (V) in DHL and DEL models *in vitro* and

TABLE

Arm	Cohort: Dose/Schedule
F + V	1: F 30 mg daily, 5/2 + V 400 mg QD 2: F 60 mg daily, 5/2 + V 400 mg QD 3: F 60 mg daily, 5/2 + V 800 mg QD
F + B + R	1: F 30 mg daily, 5/2 + B 90 mg/m^2 Day 1,2 + R 375 mg/m^2 Day 1 2: F 60 mg daily, 5/2 + B 90 mg/m^2 Day 1,2 + R 375 mg/m^2 Day 1 3: F 60 mg daily, 5/2 + B 120 mg/m^2 Day 1,2 + R 375 mg/m^2 Day 1

in vivo. In clinical studies, F as monotherapy or in combination with rituximab (R) was well tolerated with a favorable safety profile in patients with R/R lymphoma, and resulted in robust and durable objective response rates (ORR) in patients with R/R MYC-altered DLBCL.

Methods: CUDC-907-101 is a Phase 1/2, multi-center, dose-finding study that was recently amended to study F in combination with V, or F with R plus bendamustine (B) in pts with R/R lymphoma, including DLBCL or HGBL with MYC and BCL2 alterations. The primary objectives are to determine the MTD, safety and tolerability of each combination, and to assess preliminary efficacy, as measured by ORR and DOR. Pts must be R/R to ≥1 prior regimen, have measurable disease (Lugano criteria), and have archived or fresh tumor tissue. Approximately 12 pts (dose escalation; 3+3 design) and 30 pts (dose expansion) will be enrolled into each combination arm. Clinical trial: **NCT01742988**.

Keywords: "double-hit" lymphomas; high-grade B-cell lymphoma with or without rearrangement of MYC and BCL2 and/or BCL6; MYC.

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OT17
SOLAR: A PHASE 2, GLOBAL, RANDOMIZED, ACTIVE COMPARATOR STUDY TO INVESTIGATE THE EFFICACY AND SAFETY OF COBOMARSEN IN SUBJECTS WITH MYCOSIS FUNGOIDES (MF)

A.M. James[1] | **J. Ruckman**[1] | **L.A. Pestano**[2] | **R.D. Hopkins**[1] | **R.C. Rodgers**[1] | **W.S. Marshall**[3] | **P. Rubin**[3] | **D. Escolar**[1]

[1]*Clinical & Regulatory, miRagen Therapeutics, Boulder, United States;* [2]*Translational Science, miRagen Therapeutics, Boulder, United States;* [3]*Management, miRagen Therapeutics, Boulder, United States*

Introduction: Mycosis fungoides (MF, the most prevalent subtype of peripheral T-cell lymphomas, is characterized by proliferation of atypical T lymphocytes in the skin, forming patches, plaques, or nodular tumors. The goal of treatment is to minimize morbidity and limit disease progression; however, most therapies have significant side effects which limit their chronic use.

Cobomarsen is an inhibitor of microRNA-155, which is elevated and plays an important role in the proliferation and survival of malignant cancer cells in MF. In vitro, cobomarsen reduces proliferation and increases apoptosis in lymphoma cells. A Phase I clinical trial of cobomarsen in MF showed improvement in skin disease in 92% of subjects, with a durable response lasting at least 4 months in 77% of those achieving a PR (ORR4 based on mSWAT). The mean duration of response was 276 days and no significant side effects were attributed to cobomarsen.

Methods: MRG106-11-201 or SOLAR is a randomized, controlled, open-label study to assess the efficacy and safety of cobomarsen in patients with MF. The active comparator is vorinostat, an HDAC inhibitor approved in the US for the treatment of MF. The trial is currently recruiting subjects with a target of 126 subjects (63 per arm). Eligible subjects must have MF Stage IB-IIIB with a minimum mSWAT score of 10, B0-1, N0-1, no visceral involvement, and no large cell transformation. Prior treatment with an HDAC inhibitor is prohibited. Stratification will be performed based on age and LDH level at diagnosis. The primary endpoint is the proportion of subjects achieving ORR4 using composite global response criteria; secondary endpoints include progression free survival, patient reported outcomes, time to progression, time to next treatment, and overall survival. Subjects will receive weekly cobomarsen 282 mg IV infusions or daily 400 mg oral vorinostat. Assessments include changes in skin lesion severity, disease-associated symptoms and quality of life, as well as the length of time that the subject's disease remains stable or improved. Safety and tolerability will include assessment of the frequency and severity of side effects, as well as laboratory and ECG changes. Treatment will continue until the subject becomes intolerant, develops clinically significant side effects, progresses, or the trial is terminated.

Subjects assigned to receive vorinostat who experience confirmed disease progression during their participation in this study may have the option to enroll in a single arm study of cobomarsen (MRG106-11-203 or PRISM), if they meet the entry criteria for that study.

ClinicalTrials.gov Identifier: NCT03713320

Keywords: cutaneous T-cell lymphoma (CTCL); microRNA; mycosis fungoides (MF).

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