A Phase 2 Study of the Histone Deacetylase (HDAC) Inhibitor Mocetinostat in Patients with Urothelial Carcinoma (UC) and Inactivating Alterations of Acetyltransferase Genes

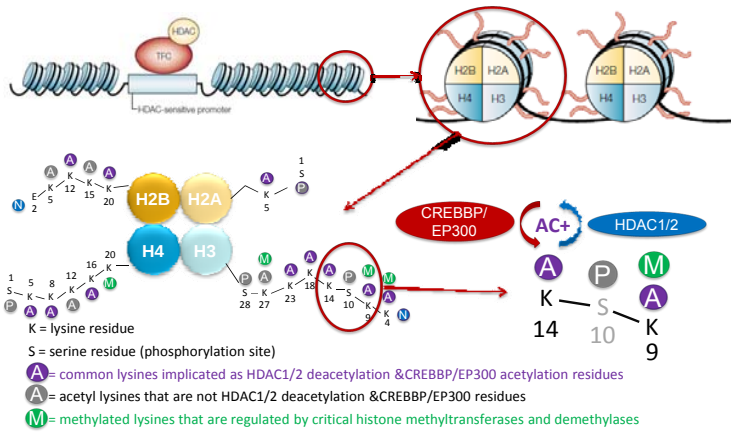
TPS4575

Noah M. Hahn[1], Joel Picus[2], Richard M. Bambury[3], Sumanta Kumar Pal[4], Lowell L. Hart[5], Petros Grivas[6], Matthew I. Milowsky[7], Ajjai Shivaram Alva[8], Guru Sonpavde[9], Amir Mortazavi[10], Joaquim Bellmunt[11], Elizabeth A. Guancial[12], Sumati Gupta[13], Richard Chao[14], Mary A. Collier[14], James Christensen[14], Isan Chen[14], Jonathan E. Rosenberg[3]

[1]The Johns Hopkins School of Medicine, Baltimore, MD, [2]Washington University, St Louis, MO, [3]Memorial Sloan-Kettering Cancer Center, New York, NY, [4]City of Hope, Duarte, CA, [5]Florida Cancer Specialists/SCRI, Fort Myers, FL, [6]Cleveland Clinic, Cleveland, OH, [7]University of North Carolina, Chapel Hill, NC, [8]University of Michigan, Ann Arbor, MI, [9]UAB Comprehensive Cancer Center, Birmingham, AL, [10]The Ohio State University - James Cancer Hospital, Columbus, OH, [11]Dana-Farber Cancer Institute, Boston, MA, [12]University of Rochester, Rochester, NY, [13]University of Utah Huntsman Cancer Institute, Salt Lake City, UT, [14]Mirati Therapeutics, Inc., San Diego, CA

Background

- **Mocetinostat (MGCD0103)** - spectrum selective inhibitor of HDAC 1, 2, 3 and 11
- **CREBBP and EP300** acetyltransferases interact with HDAC 1 and 2 to regulate site specific histone and non-histone lysine acetylation
- *CREBBP* and *EP300* demonstrate loss of function mutations in multiple cancers, including ~28% of bladder cancer and ~25% of DLBCL and ~15% lung SCC
- Mutations in *CREBBP* and *EP300* tend to be mutually exclusive
- Evaluation in multiple cell lines and xenograft tumor models showed those with *CREBBP* or *EP300* mutations highly responsive to mocetinostat treatment
- Clinical responses to HDAC treatment have been reported in patients with bladder cancer
- Significant unmet need exists in the treatment setting of advanced UC following standard chemotherapy.
- **Hypothesis**: Inhibition of specific HDACs by mocetinostat corrects the aberrant hypoacetylation resulting from *CREBBP* and *EP300* loss of function mutations and treatment of patients with these mutations resulting in tumor regression



Study Objectives

Primary Objective: Determine the Objective Response Rate (ORR) with mocetinostat treatment in the selected population having previously treated UC and an inactivating alteration in *CREBBP* and/or *EP300*

Secondary Objectives

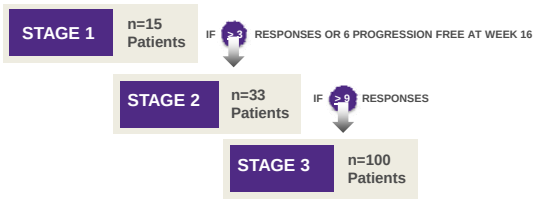
- Evaluate the safety and tolerability of mocetinostat
- Evaluate duration of response, progression-free and overall survival
- Assess pharmacokinetics

Exploratory Objectives

- Correlate other genetic alterations with response and resistance
- Investigate mechanisms of acquired resistance
- Assess circulating tumor DNA (ctDNA) for:
  - Detection and quantification of *CREBBP* and/or *EP300* gene alterations
  - Change in ctDNA burden during therapy, correlation with disease response
  - Change in ctDNA genetic alteration status at disease progression

Methods

Study Design: Single-arm Phase 2 study conducted in 3 stages



Assumption: ORR with standard therapy ≤ 15%, ORR of interest ≥ 35%

Key Entry Criteria:

- Metastatic or unresectable urothelial carcinoma
- Prior treatment that included a platinum agent
- Inactivating mutation or deletion of *CREBBP* and/or *EP300* determined by next generation sequencing of tumor tissue, central laboratory - FoundationOne
- Measurable disease per RECIST 1.1
- ECOG PS 0-2

Treatment Regimen: Mocetinostat oral capsules, once daily, three times per week, 70 mg, if tolerable, escalate to 90 mg in Cycle 2 and beyond

Key Assessments:

- Radiographic assessment at baseline, 8 week intervals for 1-year, then every 12 weeks
- ctDNA at baseline, Week 5, with each disease assessment for 6 months and at progression

Statistical Design:

- If true ORR is 15%, probability of termination at end of Stage 1 is 44% and prior to Stage 3 is 97%
- If true ORR is 35%, probability to declare success at end of Stage 2 is 87%
- Stage 3 population increases the safety data set in the target population and precision of ORR estimate in this setting of unmet medical need

Summary

- **Hypothesis:** Inhibition of specific HDACs by mocetinostat corrects the aberrant hypoacetylation resulting from *CREBBP* and *EP300* loss of function mutations, resulting in tumor regression in patients with UC treated with mocetinostat
- **Primary Objective:** Determine the ORR with mocetinostat treatment in the selected population having previously treated UC and an inactivating alteration in *CREBBP* and/or *EP300*
- **Eligibility Screening:** 138 patients consented to prescreening and/or clinical screening to date
- **Treatment:** First patient treated January 2015; 10 patients treated to date

References

[1]TCGA, *Nature* 2014; 507:315