Pinometostat, EPZ-5676, Enhances the Anti-Proliferative Activity of MAP Kinase Pathway Inhibitors in Cell Lines Less Sensitive to DOT1L inhibition

Alessandra Raimondi¹, Christine R. Klaus¹, Jeffrey A. Keats¹, Scott R. Daigle¹, Robert A. Copeland¹, Jorge DiMartino², Jesse J. Smith¹, Stephen J. Blakemore¹
¹Epizyme, Inc., Cambridge, MA; ²Celgene, San Francisco, CA

Introduction

Despite recent advances in identifying treatment options for acute leukemias, those bearing rearrangements of MLL (MLL-r) remain a population with significant unmet medical need. Phase 1 clinical trials are underway to investigate the single agent activity of pinometostat (EPZ-5676), a first in class inhibitor of the histone methyltransferase DOT1L, for the treatment of patients with MLL-r acute leukemias. Preliminary results of the adult Phase 1 clinical trial indicate evidence of clinical activity including complete responses in a subset of patients (Blood December 14, 2021 (21) 387). While this activity is encouraging, given that the baseline of effective leukemia therapies are combination regimens, investigations into potential pinometostat combinations are of interest. We have previously shown in vitro synergistic anti-proliferative activity when pinometostat was combined with the current standard of care drugs for acute leukemias, cytarabine and daunorubicin (Klaus, Iwanowicz et al., 2014); the greatest combination benefits of these drugs were observed in cell lines with nanomolar pinometostat IC₅₀ values. Here we report results of an expanded effort, across a leukemia cell line panel to identify novel pinometostat combinations. A high throughput screening platform consisting of a library of approved oncology drugs, emerging therapies and tool compounds (n=250), was utilized to identify synergistic anti-proliferative activity with pinometostat against a panel of cell lines with a range of reported sensitivities to pinometostat alone (IC₅₀ 0.075 to >3 μM). The study paradigm for this effort consisted of pretreating each cell line for 7 days (MLL-r: OCI-AML-4, MLL-2, THP-1, RS4-11, MOLM-13, and non-MLL-r SKM-1) with pinometostat prior to the addition of the enhancer agent for 3 days. Study of dosing schedule of the combination of pinometostat with trametinib revealed that all schedules, no matter the order of compound addition, demonstrated combination benefit. Pretreatment with the DOT1L inhibitor, however, elicited dramatic cell killing at physiologically achievable concentrations.

Methods

Diverse Target Classes Evaluated in cHTS

Results

Pinometostat in vitro antiproliferative activity can be extended to cell lines insensitive to DOT1L inhibition by combination with small molecule inhibitors of several distinct target classes

Analysis of combinatorial effects with inhibitors of the MAPK signaling pathway

Pinometostat with trametinib demonstrated enhanced apoptotic cell death in a time and dose dependent manner

Conclusions

• Combinatorial treatment of pinometostat with trametinib boosts the inhibitory effect on cell lines sensitive and resistant to single agent pinometostat

• Pinometostat pretreatment enhances trametinib-induced apoptotic cell death in MLLr and non-MLLr cell lines

• The degree of combination benefit with MEK inhibition is influenced by dosing schedule

  – Optimal combination was obtained with suppression of DOT1L activity prior to MEK inhibition

  – Taken together these data suggest that a combination of trametinib and pinometostat may potentially have a more robust therapeutic benefit than monotherapy of either agent

Disclosures: Authors: AR,CRK, JAK, SRD, RAC, JJS, SJB: Epizyme Employment, Equity Ownership; JD, Celgene Employment; Equity Ownership

www.epizyme.com