Mutations within the catalytic domain of the histone methyltransferase EZH2 have been identified in subsets of patients with non-Hodgkin lymphoma (NHL). These genetic alterations are hypothesized to confer a cellular survival dependency on EZH2 enzymatic activity in these cancers. Here, we disclose the discovery of EPZ-6438 (ET438), as a potent, selective and orally bioavailable small molecule inhibitor of EZH2 in preclinical models of NHL. Previously we have disclosed the properties of EPZ005687, a tool compound useful for exploring the in vitro biology of EZH2 inhibition. Multi-parametric optimization of the potency, pharmacokinetics, oral bioavailability and tolerability of this series led to the discovery of EZH2 wild-type and mutant lymphoma cells. Inhibition of EZH2K737 trimethylation (H3K27Me3) leads to selective cell killing of human lymphoma cell lines bearing EZH2 catalytic domain point mutations. Treatment of EZH2-mutant NHL xenograft bearing mice with EPZ-6438 caused a dose-dependent tumor growth inhibition, including complete and sustained tumor regressions with correlative diminution of H3K27Me3 levels in tumors and selected normal tissues. EPZ-6438 recently entered clinical testing as ET438 in a dose escalation phase 1 trial in relapsed or refractory malignancies.

Introduction

EZH2 Inhibition for Genetically Defined Cancers

At least 3 distinct genetically defined cancers
- Non-Hodgkin lymphoma, germinal center (EZH2 point mutations)
- Synovial sarcoma (EZH2-SSX1 fusion)
- MRT (EZH2-deletion)

SWI/SNF COMPLEX
PRC2 COMPLEX

Change of function mutation
- Non-Hodgkin lymphoma
- Synovial sarcoma
- MRT (E2F1-deletion)

EZH2 is the catalytic subunit of the multiprotein PRC2 (polycomb repressive complex 2) complex
PRC2 catalyzes mono-, di- and tri-methylation of H3K27
H3K27 is the only significant substrate for PRC2
H3K27Me3 is a transcriptionally repressive histone mark
Hyper-trimethylation of H3K27 is tumorigenic in a broad spectrum of human cancers, including GC NHL

Results

EPZ-6438 is a Specific and SAM-Competitive Inhibitor of EZH2

EPZ-6438 Selectively Kills EZH2 Mutant Cells Despite Similar Target Inhibition in Both Mutant and WT Cells

Conclusions

EPZ-6438 is a potent and selective small molecule inhibitor of EZH2 and EZH2 SET domain mutants.
EPZ-6438 inhibits cellular H3K27 methylation leading to killing of lymphoma cell lines expressing EZH2 SET domain mutants.
Antitumor activity has been observed in several EZH2 mutant lymphoma xenograft models ranging from tumor growth inhibition to durable regressions (e.g. KARPAS422) at well tolerated doses and schedules.
EPZ-6438 (ET438) has transitioned into clinical development and results from the Phase I study are being presented in a separate oral presentation by V. Ribrag entitled "Phase 1 first-in-human study of the enhancer of zeste-homolog 2 (EZH2) histone methyl transferase inhibitor ET438 as a single agent in patients with advanced solid tumors or B cell lymphoma in Plenary Session S"