Tazemetostat treatment drives wild-type and mutant EZH2 DLBCL cell lines to a cell fate decision between apoptosis or differentiation.


Epizyme Inc., 400 Technology Square, Cambridge, MA, USA

Abstract

The EZH2 inhibitor tazemetostat (EPZ-6438) is currently being evaluated in Phase II clinical trials for the treatment of non-Hodgkin’s Lymphoma (NHL). EZH2 inhibitors have shown anti-proliferative effects in multiple pre-clinical models of NHL, and phase I studies of tazemetostat have reported objective clinical responses in patients with B-cell lymphomas. In preclinical models, lymphomas bearing gain-of-function mutations in EZH2 were consistently more sensitive to EZH2 inhibition than were lymphomas with wild type (wt) EZH2. For these reasons, our phase I data have demonstrated that objective responses occur in lymphoma patients with both wt and mutant EZH2. This finding is consistent with reports in the literature that demonstrate a role for EZH2 in maintaining the germlinal center phenotype of normal B-cells, as well as regulating the differentiation of both wt and mutant EZH2 B-cell lymphoma cell lines. To understand better the relationship between B-cell maturation and EZH2, we evaluated apoptosis and differentiation in wt and mutant EZH2 DLBCL cell lines. We discovered that cells with mutant EZH2 undergo apoptosis following tazemetostat treatment. In contrast, cell lines with wild-type EZH2 exhibit decreased growth rates and induce PRDM1, a key transcriptional repressor involved in plasma cell differentiation. To further explore these phenomena, we evaluated apoptosis in cell co-treated with tazemetostat and inhibitors or activators of primary B-cell signaling pathways. We discovered that combinations of tazemetostat with inhibitors of B-cell activation, like ibritinib or corticosteroids, demonstrate synergy in both wt and mutant EZH2 cell lines. Moreover, we determined that when combined with brutinib, tazemetostat induces apoptosis in wt cell lines. It was also discovered that addition of recombinant CD40L, a B-cell co-stimulatory molecule can prevent apoptosis and drive lymphoma cells more towards differentiation. These findings demonstrate that EZH2 inhibition drives lymphoma cells towards cell fate decisions and suggests that an important component of tazemetostat’s mechanism of action is to force lymphoma cells to proceed through the normal processes of apoptosis and terminal differentiation.

Background

Does Tazemetostat (EPZ-6438) poise lymphoma cells for terminal differentiation?

1. EZH2 inhibitors are emerging as valuable therapeutic agents for the treatment of non-Hodgkin’s lymphoma.
2. The mechanism by which EZH2 inhibitors inhibit lymphoma cell proliferation is an area of active research.
3. It is known to be a regulator of B-cell maturation and germinial center formation.
4. EZH2 inhibition induces differentiation markers in cell lines derived from multiple lymphoma subtypes.
5. Does EZH2’s role in B-cell maturation contribute to the anti-lymphoma activity of tazemetostat?

Conclusions

- Treatment of B-cell lymphoma cell lines with the EZH2 inhibitor, tazemetostat induces cell fate decisions.
- B-cell maturation events are observed in both WT and mutant EZH2 NHL cell lines in response to tazemetostat.
- EZH2 inhibition creates a dependency on B-cell activation signals.
- Tazemetostat inhibition of EZH2 induces anti-proliferative effects, including B cell differentiation programs, in DLBCL cell lines irrespective of EZH2 mutational status and cell of origin.

www.epizyme.com