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EMERGING DRUG PROFILE:

Enhancer of Zeste Homolog 2 (EZH2) Inhibitors

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Abstract

Dysregulation of the histone methyltransferase EZH2 plays a critical role in the development of a variety of malignancies including B-cell lymphomas. As a result, a series of small molecule inhibitors of EZH2 have been developed and studied in the pre-clinical setting. Three EZH2 inhibitors: tazemetostat (EPZ-6438), GSK2816126 and CPI-1205 have moved into phase I/phase II clinical trials in patients with non-Hodgkin lymphoma and genetically defined solid tumors. Early data from the tazemetostat trials indicate an acceptable safety profile and early signs of activity in diffuse large B-cell lymphoma and follicular lymphoma, including patients with EZH2 wild-type and mutant tumors. In this review, we present the rationale, key pre-clinical and early clinical findings of small molecule EZH2 inhibitors for use in lymphoma as well as future challenges and potential opportunities for combination therapies.

Introduction:

The post-translational modification of histones plays a key role in the regulation of gene expression and cellular differentiation [1, 2]. Aberrant histone modification has been observed in a variety of cancers and thus represents a potential therapeutic target [3–8]. Enhancer of zeste homolog 2 (EZH2) is a histone methyltransferase that functions as the catalytic subunit of the polycomb repressive complex 2 (PRC2). PRC2 methylates lysine 27 on histone 3 (H3K27), resulting in the transcriptional silencing of target genes (Figure 1A) [9–15]. Alterations in EZH2 or the SWI/SNF complex, which antagonizes polycomb function, have been described in multiple cancer subtypes including breast cancer, ovarian cancer, prostate cancer, non-Hodgkin lymphoma (NHL), and T-cell ALL [7, 16–19]. Recurrent gain-of-function alterations in EZH2 occur in up to 30% of germinal center B-cell like diffuse large B-cell lymphoma (GCB-DLBCL) and 27% of follicular lymphoma (FL) [20–22]. In addition, DLBCL cells with wild type (WT) EZH2 are sensitive to genetic and pharmacologic EZH2 inhibition [23–25]. Small molecule inhibitors of EZH2 have recently been developed and are currently being evaluated in clinical trials. Clinical responses have

been observed in patients with lymphoma as well as solid tumors with genomic perturbations in PRC2 function including alterations in the SWI/SNF family members SMARCA-4 and SMARCB1 and loss of SMARCB1/INI1. For the purpose of this review, we will focus on the role of EZH2 targeting in NHL. We will summarize the rationale for EZH2 inhibition and review the development and early clinical findings of small molecule EZH2 inhibitors.

Role of EZH2 in normal and malignant B-cells:

In a normal humoral immune response, mature, resting B cells are stimulated to differentiate into antibody-secreting plasma cells. A subset of B cells, however, suspend the plasma cell program and instead transiently become germinal center (GC) B-cells with a phenotype characterized by rapid proliferation and somatic hyper mutation associated with immunoglobulin affinity maturation [26]. This is achieved by transient repression of the plasma cell transcription program and repression of cellular checkpoint genes [27]. Once GC B-cells complete affinity maturation, they resume their normal path of plasma cell differentiation [28]. The majority of B-cell lymphomas including GCB-DLCBL and FL arise from this inherently tumorigenic GC B-cell phenotype (Figure 1B) [27, 29].

EZH2 is essential to maintain the GC phenotype. During lymphopoiesis, EZH2 is required for developing pre-B cells to acquire a full spectrum of immunoglobulin VDJ recombinants [30]. EZH2 expression reaches its peak when mature B-cells are stimulated to form GCs [9, 31]. Conditional deletion of EZH2 in established GC B-cells results in their failure to form functional GCs [32, 33]. EZH2 enables GC formation and suspension of plasma cell differentiation at least in part by suppressing cell cycle checkpoint genes, like CDKN1A [34], and genes required for B cells to undergo further plasma cell differentiation, such as IRF4 and PRDM1 [32].

EZH2 is highly expressed in GCB-DLBCL and is required to maintain lymphoma cell proliferation and survival [9, 31, 32]. A subset of FL and GCB-DLBCL harbor recurrent gain-of-function mutations affecting tyrosine 641 (Y641) in the catalytic domain of EZH2. These alterations enhance the efficiency of H3K27 trimethylation (H3K27me3), and result in more pronounced repression of EZH2 target genes [35, 36]. Mice engineered to express mutant *Ezh2*^{Y641} in GC B cells develop hyperplasia of GC and accumulate high levels of H3K27me3 [32]. Accordingly, patients with EZH2 overexpression or Y641 somatic mutation exhibit a characteristic gene expression signature showing hyper-repression of genes involved in terminal differentiation and proliferation checkpoints [32].

In summary, EZH2 enables GC B-cell formation by promoting cell proliferation and inhibiting differentiation. Dysregulation or somatic mutation of EZH2 “locks in” this program contributing to the malignant GC B-cell phenotype. Given the frequent dysregulation of EZH2 in GC-derived lymphomas and the oncogenic functions of both wild type and mutant EZH2, inhibition of EZH2 may be of therapeutic benefit in patients with B-cell NHL.

EZH2 inhibitors in clinical trials:

Several small molecules that suppress the enzymatic activity of EZH2 have been recently developed. While most compounds are still in preclinical development, three agents (tazemetostat, GSK2816126 and CPI-1205) have moved into in phase I/II clinical trials (Table 1). Below we discuss the preclinical activity and available clinical data for each of these three compounds. An overview of the active clinical trials of these agents in lymphoma is presented in Table 2.

EPZ-6438 (E7438/Tazemetostat)

Tazemetostat is an orally bioavailable small molecule inhibitor of EZH2 (Table 3) [24]. Tazemetostat was optimized from EPZ 005687, a molecule identified in 2012 by a high throughput screen of a chemical diversity library against PRC2 [37]. EPZ 005687 demonstrates high affinity and selectivity for EZH2, however has suboptimal pharmacokinetic properties that limit its clinical utility. Tazemetostat has increased potency and improved pharmacokinetics including oral bioavailability [17]. Tazemetostat inhibits EZH2 through competitive inhibition with the cofactor *S*-adenosyl-L-methionine (SAM), which is required for EZH2 function. Tazemetostat inhibits both wild type and mutant forms of EZH2 with a 50% inhibitory concentration (IC₅₀) ranging from 2–38nM. Tazemetostat is also highly selective for EZH2 with 35-fold increased potency relative to EZH1 and >4,500-fold increased potency relative to 14 other histone methyltransferases [17].

Preclinical Studies: The preclinical activity of tazemetostat has been evaluated in NHL, multiple myeloma (MM) and select solid tumors with dependency on PRC2 function. In DLBCL, tazemetostat reduces H3K27me₃ and inhibits cellular growth *in-vitro* and *in-vivo* [24]. Treatment of DLBCL cell lines with tazemetostat results in a dose-dependent reduction in H3K27me₃ with a methylation IC₅₀ ranging from 2–90 nM. Inhibition of H3K27me₃ occurs at similar potency in both EZH2 wild type (WT) and EZH2 mutant DLBCL. Maximal inhibition of H3K27me₃ occurs after 3–4 days of incubation with tazemetostat. Inhibition of DLBCL proliferation is also observed after treatment with tazemetostat with the maximal effect seen after 6–11 days of treatment. The proliferation IC₅₀ ranges from <0.001 to 7.6 μM with increased sensitivity observed in EZH2 mutant cell lines compared to EZH2 WT [38]. An increase in the percentage of cells in G₁ phase is observed at early time points (after 2 days of drug exposure) with subsequent apoptosis-mediated cell death after 11–14 days of drug exposure. De-repression of PRC2 target genes is also noted upon treatment in both EZH2 WT and mutant DLBCL. In xenograft mice bearing EZH2 mutant DLBCL cell tumors, treatment with tazemetostat results in global suppression of H3K27me₃ as well as inhibition of tumor growth (in WSU-DLCL2 xenografts) or complete tumor regression (in KARPAS-422 and Pfeiffer xenografts) [24].

In multiple myeloma, single agent treatment with tazemetostat inhibits *in-vitro* proliferation including cells with common recurrent translocations such as t(11;14); t(14;16), t(20,22); and t(14;14). EPZ011989, a selective small molecule inhibitor of EZH2 with properties similar to tazemetostat has been evaluated in MM xenograft models. Suppression of

H3K27me3 and tumor growth inhibition were observed in four MM cell line xenograft models with maximal effect at day 14–20 [39].

In addition, tazemetostat has been studied in solid tumors with notable preclinical activity in pediatric malignant rhabdoid tumors, which harbor inactivating biallelic mutations in the SWI/SNF subunit SMARCB1 [17] as well as SMARCB1-deficient synovial sarcoma [40].

Clinical Trials: The encouraging preclinical studies of tazemetostat led to the clinical development of this compound which is now being studied in a series of phase I and phase II trials in NHL and genetically defined solid tumors (Table 2). Preliminary results from a large phase I/II trial of tazemetostat () have recently been reported [41–43]. This clinical trial opened to enrollment in June 2013 and, at the time of this publication, is ongoing. The trial is a multi-center open label study of tazemetostat administered as a single agent, which is being conducted in two parts: 1) a phase I dose escalation with expansion cohorts at two dose levels as well as cohorts to evaluate potential drug-drug interactions and the impact of food on bioavailability; 2) a phase II evaluation of the safety and efficacy of tazemetostat administered at the recommended phase II dose (RP2D). The phase I portion included patients with advanced solid tumors and B-cell lymphomas and completed accrual in January 2016. The phase II portion, which is currently ongoing, is restricted to patients with DLBCL and FL.

The phase I portion enrolled 58 patients including 21 with NHL (14 with DLBCL, 6 with FL, and 1 with marginal zone lymphoma) [42]. Tazemetostat was administered orally twice daily (BID) at a starting dose of 100mg BID. Dosing was escalated in a 3+3 design to a maximum dose of 1600mg PO BID. The most frequent treatment-related adverse events were fatigue, nausea, and thrombocytopenia. Grade 3 or higher treatment-related adverse events were rare and included thrombocytopenia (n=1), hypertension (n=1), neutropenia (n=1), and hepatocellular injury (n=1). Pharmacokinetic analysis demonstrated rapid absorption and clearance (t_{max} = 1–2 hrs., mean terminal $t_{1/2}$ = 3–5hrs.) [44]. Pharmacodynamic analysis was performed by evaluating H3K27me3 in skin by immunohistochemistry from punch biopsies. Target inhibition was demonstrated at week 4 at all doses. H3K27me3 inhibition was equivalent at the 800mg and 1600mg BID doses. The RP2D was determined to be 800mg PO BID based on safety, efficacy, and PK/PD data. Among the 21 patients with NHL, responses were seen in 8 patients including 5 patients with partial responses (PRs) (4 DLBCL, 1 marginal zone lymphoma) and 3 patients with complete responses (CRs) (1 DLBCL, 2 FL). Among the patients with NHL treated at or above the RP2D, responses were seen in 7/12 (58%) with 6 PRs and 1 CR. Responses were seen in both EZH2 WT and EZH2 mutant tumors [42].

The phase II portion of this study is enrolling patients with DLBCL and FL to one of 6 cohorts based on cell-of-origin and EZH2 mutation status. The study was initiated with 5 monotherapy cohorts: (3 cohorts of DLBCL: non-GCB-DLBCL, EZH2 WT GCB-DLBCL and EZH2 mutant GCB-DLBCL) and 2 cohorts of FL (EZH2 WT and mutant). A 6th cohort of tazemetostat in combination with prednisolone for patients with DLBCL was added in 2017 based on preclinical data to support this combination [38]. Interim data from the phase II study was recently presented with safety data on 210 patients and efficacy data on 203

patients [41]. The most common treatment-related adverse events of any grade were nausea (14%), thrombocytopenia (13%), anemia (10%) and neutropenia (9%). The most common grade 3 or higher treatment-related adverse events were thrombocytopenia (6%), anemia (4%) and neutropenia (6%). Treatment-related adverse events leading to dose reductions or drug discontinuation/study withdrawal were 3% and 2% respectively. Among the 203 patients who were evaluable for efficacy, responses were seen in 49/203 (24%) including 14 CRs and 35 PRs. Responses were seen in both tumor types and in EZH2 mutant and WT tumors. The subset of patients with EZH2 mutant FL had a 92% (12/13) overall response rate (ORR) including 11 PRs and 1 CRs. In contrast, patients with EZH2 WT FL had an ORR of 26% (14/54) with 3 CRs and 11 PRs. The ORR for patients with EZH2 mutant and WT DLBCL was 29% (5/17) and 15% (18/119) respectively (EZH2 mutant DLBCL with no CRs and 5 PRs and EZH2 WT DLBCL with 10 CRs and 8 PRs) [41]. The response was delayed in both histologic subtypes with the median time to first response ranging from 8 to 15 weeks and a number of patients converting from PR to CR at later times. [41]. This trial is ongoing at the time of this publication and is expected to complete in January 2020.

Other ongoing studies evaluating tazemetostat in patients with NHL include a phase Ib/II trial of tazemetostat in combination with R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone) in patients with previously untreated DLBCL, a phase I trial of tazemetostat in combination with the PD-1 inhibitor atezolizumab in patients with relapsed/refractory DLBCL or FL, and a phase II trial in pediatric patients with lymphoma or genetically defined solid tumors. Tazemetostat is also being evaluated in solid tumors including: a phase II trial in adults with INI1-negative tumors or relapsed/refractory synovial sarcoma (); a phase II trial in adults with mesothelioma characterized by BAP1 loss of function (); and a phase I trial in pediatric patients with INI1-negative tumors or synovial sarcoma ().

The United States Food and Drug Administration has granted tazemetostat a Fast Track designation for EZH2 mutant DLBCL and for FL regardless of EZH2 mutation status as well as an Orphan Drug designation for malignant rhabdoid tumors.

GSK2816126 (GSK126):

GSK126 is a small molecular inhibitor of EZH2, which was generated through chemical optimization of a compound identified from a high throughput biochemical screen of compounds targeting EZH2 [25, 45]. Similar to EPZ-6438, GSK126 inhibits both WT and mutant EZH2 through competitive inhibition with *S*-adenosylmethionine (SAM). The predicted docking site of GSK126 is the SAM binding pocket of EZH2. GSK126 inhibits WT and mutant EZH2 with similar potency ($K_i^{app} = 0.5\text{--}3\text{ nM}$) and is highly selective when compared to EZH1 (150-fold increased potency) or 20 other methyltransferases (>1000-fold increased potency) [25].

Preclinical Studies:

In DLBCL cell lines, GSK126 induces a dose dependent decrease in H3K27me3 with IC₅₀ ranging from 7–252 nM. The maximal effect on H3K27me3 is after 2 days. GSK126 also inhibits *in-vitro* cellular proliferation in a range of NHL subtypes. The most sensitive cells

are EZH2 mutant DLCL (Pfeiffer and WSU-DLCL2) however sensitivity is also observed in EZH2 WT DLBCL and Burkitt lymphoma [25]. The mechanism of action might be context-specific as cytostatic (G1 cycle arrest) and cytotoxic (caspase-induced apoptosis) effects are observed in KARPAS-422 and Pfeiffer DLBCL cell lines respectively. Expression profiling of DLBCL cells exposed to GSK126 reveals de-repression of PRC2 target genes. GSK126 has also been evaluated in xenograft mice bearing EZH2 mutant tumors (KARPAS-422 and Pfeiffer) where treatment results in tumor growth inhibition at low doses and tumor regression at higher doses [25].

Clinical Evaluation of GSK126:

GSK126 was recently evaluated in a multicenter phase I clinical trial (). This study, which opened to accrual in April 2014, was designed to evaluate the safety and recommended phase II dose of GSK126. The study was conducted in two parts: Part 1) a dose escalation of GSK126 in patients with refractory non-Hodgkin lymphoma, multiple myeloma, and solid tumors; Part 2) expansion cohorts at the RP2D in patients with EZH2 mutant and WT DLBCL, transformed FL, and multiple myeloma [46]. GSK126 was administered intravenously twice weekly for 3 weeks on and 1 week off per treatment cycle.

The first part of the study enrolled 30 patients including 10 patients with DLBCL, 2 patients with transformed FL, 2 with other NHL (FL and MZL) and 16 patients with solid tumors. GSK126 was administered at a starting dose of 50mg and was escalated in a 3+3 design to a maximum dose of 3000mg. The most frequent drug-related adverse events were fatigue (53%), nausea (30%), anemia (20%) and vomiting (20%). At 3000mg pharmacokinetic analysis demonstrated C_{max} of 22 ± 34.1mg/ml; and t_{1/2} 33.3±11.5 hours. Of 22 evaluable patients, one patient with GCB-DLBCL showed a PR and 7 patients had stable disease [47]. The study was recently terminated as the drug showed insufficient evidence of clinical activity and thus did not justify further clinical investigation [48]

CPI-1205:

Constellation pharmaceuticals has reported a series of indole-based EZH2 inhibitors which are structurally unique from the pyridine based compounds GSK126 and tazemetostat [49–51]. CPI-1205 is an orally bioavailable, indole-based, small molecule inhibitor of EZH2. It is a N-trifluoroethylpiperidine analogue of the chemical probe CPI-169 [50]. CPI-169 demonstrated antitumor activity and PD target engagement *in-vivo*, however it had limited oral bioavailability. CPI-1205 binds to the EZH2 catalytic pocket and partially overlaps with the SAM binding site. It has shown modest selectivity for EZH2 over EZH1 (EZH1 IC₅₀ 52 ± 1nm) and selectivity when tested against 30 other histone or DNA methyltransferases [23].

Preclinical Studies:

CPI-1205 alters PRC2 target gene expression and causes dose and time dependent cell killing in both EZH2 WT and mutant B-cell NHL (biochemical IC₅₀ = 0.0022μM and 0.0031μM respectively). It inhibits PRC2 enzymatic activity at picomolar concentrations and

global H3K27me3 levels at low nanomolar concentrations ($IC_{50} = 0.032\mu M$) in a reversible manner [23].

In a xenograft model of EZH2 mutant DLBCL (KARPAS-422), treatment with CPI-1205 results in significant inhibition of tumor growth relative to vehicle control by day 25. PD studies show *in-vivo* reduction of H2K27me3. Further analysis in rats and dogs showed a high clearance in both species, good oral bioavailability and an acceptable safety profile [23].

Clinical Evaluation of CPI-1205:

CPI-1205 is currently being evaluated in a phase I clinical trial in patients with relapsed or refractory B-cell lymphoma (). This study opened in March 2015 and is expected to accrue approximately 41 patients through October 2018. The primary objective is to describe the dose-limiting toxicities of CPI-1205. PK, PD, and response assessment will also be studied. No interim results are available at the time of the publication.

EZH2 Inhibitors in preclinical development:

With an increasing understanding of the role that EZH2 plays in oncogenesis and encouraging data from clinical trials, additional EZH2 inhibitors continue to be synthesized and evaluated in the preclinical setting (reviewed in detail [52]). Many of the most of the potent EZH2 inhibitors have a pyridone moiety, however several groups have patented alternative EZH2 inhibitors and are testing the effect of replacement or addition of different substituents to the 2-pyridone moiety on the efficacy and potency of the drug [52–60]. Another strategy to optimize efficacy has been to develop agents that target both EZH2 and EZH1 simultaneously. The function of EZH1 and its relationship to EZH2 is incompletely understood however dual targeting may improve the anti-tumor effect in certain malignancies. For example, the dual EZH1/EZH2 inhibitor UNC 1999 has been demonstrated to inhibit growth of MLL-rearranged leukemia *in-vitro* and *in-vivo*, while the EZH2-specific GSK126 had little effect in the same models [61]. In addition the recently described dual EZH1/EZH2 inhibitors OR-S1 and OR-S2 demonstrated greater antitumor activity than selective EZH2 inhibitors, both *in-vitro* and *in-vivo* against DLBCL cells harboring gain of function mutations in EZH2 [62]. OR-S1 and OR-S2 also demonstrated enhanced antitumor activity when compared to GSK126 in AML cells *in-vitro*. Both drugs were also found to impair leukemia progression and prolong survival in AML mouse models and patient derived xenografts[63]. In total, more than 50 small molecular inhibitors of EZH2 are currently in various stages of pre-clinical development. As these agents become optimized for clinical use, we will likely see additional trials of new compounds used either as a single agent or in combination.

Potential Combination Therapy:

Since single agent treatment with EZH2 inhibition is unlikely to be curative in aggressive lymphomas, rational combinations will need to be utilized. A number of combination trials with tazemetostat are currently ongoing in patients with DLBCL including tazemetostat in

combination with: prednisone (), R-CHOP chemo-immunotherapy (), and the anti-PDL1 antibody atezolizumab ().

Synergy between tazemetostat and components of R-CHOP has been demonstrated in preclinical studies in DLBCL. *In-vitro* studies in EZH2 mutant DLBCL demonstrated additive or synergistic effect of tazemetostat with cyclophosphamide, doxorubicin and vincristine. Among the components of CHOP, the strongest synergistic effects were seen with prednisolone. The combination of tazemetostat and prednisolone rendered refractory GCB-DLBCL cell lines sensitive to tazemetostat irrespective of EZH2 mutational status. *In-vivo* synergy in several EZH2-mutant DLBCL xenograft models was also observed in using the combination of tazemetostat with prednisolone; tazemetostat with CHOP, and tazemetostat with cyclophosphamide, vincristine, and prednisone (COP) [38].

EZH2 inhibition in combination with targeted agents may also improve efficacy and minimize the emergence of resistance. The apoptosis regulator BCL2 is frequently translocated in lymphomas with EZH2 gain-of-function mutations [22], and mutant EZH2 and BCL2 have shown to cooperate in accelerating lymphomagenesis in mice [32]. Consequently, the combination of anti-EZH2 (GSK126) with BCL2 directed therapies such as obatoclax and ABT737 (BH3 mimetics) has been evaluated in pre-clinical models with the combination demonstrating enhanced anti-lymphoma effect in GCB-DLBCL cell lines and xenograft models [32]. BCL6, a transcriptional repressor that is required for GC B-cell formation, has also been shown to cooperate with EZH2 dysregulation, resulting in accelerated lymphomagenesis. Combinatorial EZH2 and BCL6 targeted therapy yields enhanced growth suppression of GCB-DLBCL cell lines, xenograft models and primary GCB-DLBCL lymphomas [64]. Other agents that have been found to be synergistic with EZH2 inhibition in DLBCL preclinical models include: modulators of the B-cell receptor pathway, such as ibrutinib (BTK inhibitor), tamatinib (SYK inhibitor), idelalisib (PI3K inhibitor), everolimus (mTOR inhibitor) and trametinib (MEK inhibitor) [65]; and the HDAC inhibitor romidepsin [66, 67]. Combinations have also been evaluated in models of multiple myeloma where EZH2 inhibition is synergistic immunomodulatory drugs such as pomalidomide and lenalidomide [39, 68], glucocorticoid receptor agonists [39], proteasome inhibitors and HDAC inhibitors [39, 69].

Mechanisms of Resistance:

Understanding potential mechanisms of resistance to EZH2 inhibitors will be critical to future drug design and potential combination strategies. Secondary mutations in the EZH2 D1 domain (Y111 and I109) and SET domain (Y661) have been found to confer resistance to EZH2 inhibitors in EZH2 wild type and mutant DLBCL [70, 71]. The Y111 and I109 mutants require histone methyltransferase catalytic activity and the PRC2 components SUZ12 and EED to drive drug resistance [70]. Inhibitors of EED, therefore, may potentially bypass this mechanism of resistance. Agents that disrupt the EED-EZH2 protein-protein interaction are currently in preclinical and clinical development. [72–77]. Notably, a phase I/II trial evaluating the EED inhibitor MAK683 in DLBCL, nasopharyngeal carcinoma, and other advanced solid tumors is currently ongoing (). Similarly, given the requirement of

chromodomain protein CBX8 for EZH2 biological effects [64], the development of CBX8 inhibitors might also circumvent resistance to drugs targeting PRC2.

Conclusions and future directions:

The pathogenic role for EZH2 in a wide variety of cancers has triggered intense interest in EZH2 targeted therapy. There are several phase I/phase II clinical trials of small molecule EZH2 inhibitors enrolling patients across a wide disease spectrum including NHL, mesothelioma, INI1-negative tumors, synovial sarcoma, and pediatric lymphomas and solid tumors. Tazemetostat is furthest along in clinical development and has been granted a Fast Track designation from the US FDA for FL regardless of the EZH2 mutational status and for EZH2-mutant DLBCL. This was based on encouraging responses observed in patients, most notably those with EZH2 mutated FL where the ORR is 92%. The phase I clinical trial of the EZH2 inhibitor GSK126 was less encouraging and was recently terminated as the maximal dose and schedule showed insufficient evidence of clinical activity. The results of the phase I trial with CPI-1205 are still awaited. A number of groups are working on the further development of more potent, bioavailable compounds that can be used as tools to further explore the role of EZH2 in pathobiology as well as potential second generation EZH2 inhibitors for clinical use. These efforts will both expand the repertoire of EZH2 inhibitors for use in lymphomas as well as aid in understanding EZH2 function in lymphoma and other malignancies driven by alterations in PRC2 function.

The unique biology and biochemistry of EZH2 will present potential challenges to rational clinical implementation of EZH2 inhibitors which will need to be addressed in future studies. First, there are currently no validated predictive biomarkers to select patients for EZH2 therapy. EZH2 mutation status alone is insufficient to select patients as responses have been observed in patients with EZH2 WT tumors. Current trials of tazemetostat are investigating a 62-gene panel as a potential biomarker however additional testing is needed [78]. Second, the goal of epigenetic therapy is not to kill cells but to erase aberrant epigenetic programming, which occurs well below the maximal tolerated dose for EZH2 inhibitors, as seen in preclinical studies where EZH2 inhibitors were not cytotoxic at doses that maximally suppress H3K27me3 [24, 25]. Thus, to maintain on-target activity and avoid toxicity EZH2 inhibitors must be titrated to pharmacodynamic endpoints (i.e. changes in epigenetic modification) rather than maximal tolerated dose. This strategy was utilized with tazemetostat where the RP2D was not the maximally tolerated dose but one dose level below based on maximal inhibition of H3K27me3. Lastly, understanding how best to combine EZH2 inhibitors with conventional chemotherapy or other targeted agents will be essential to their effective use. Combination trials are currently underway; however, the optimal timing of drug administration is not yet known and a variety of potential targeted combinations have yet to be explored.

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Figure 1. Mechanism of EZH2 in normal and malignant B-cells:

(A) EZH2 forms the catalytic subunit of the Polycomb Repressive Complex 2 (PRC2). The other core subunits in this complex include: embryonic ectoderm development (EED), suppressor of zeste 12 (SUZ12), and retinoblastoma (Rb) associated protein 46. EZH2 is responsible for methylating lysine 27 of histone 3 to generate H3K27me₃, a histone mark associated with a more condensed chromatin and transcriptional gene repression. (B) When naïve B-cells are activated, they differentiate into antibody-secreting plasma cells or, alternatively, suspend the plasma cell program to enter the germinal center (GC) reaction. The transition to GC B-cells is characterized by increased expression of EZH2, which results in repression of genes that control plasma cell differentiation. Once GC B-cells complete affinity maturation, EZH2 levels decrease, enabling the expression of genes that control cell proliferation and mediate terminal differentiation, ultimately resulting in plasma cell formation. The occurrence of EZH2 somatic mutations aberrantly sustains repression of these proliferation checkpoint and differentiation genes, resulting in GC hyperplasia. Additional oncogenic hits, such as BCL2 or BCL6 translocations, enable transformation of GC B-cells to GCB-DLBCL or FL.

Figure 2. Schematic representation of mechanism of action of EZH2 inhibitors:

(A) The SET domain is the catalytic domain of the EZH2 methyltransferase. It catalyzes transfer of a methyl group from a universal methyl donor SAM (S-Adenosyl-L-methionine) methylating lysine 27 on Histone H3 (H3K27) associated with a more condensed chromatin and transcriptional gene repression. (B) The EZH2 inhibitors in clinical trials inhibit EZH2 through competitive inhibition with SAM causing de-repression of plasma cell transcription program and of checkpoint genes and eventually cell death.

Table 1:

Chemical structure and activity of EZH2 inhibitors in clinical trials

Compound	Structure	In vitro IC ₅₀ (nM)	Methylation IC ₅₀ (nM)	Route of administration	Ref.
EPZ6438 (Tazemetostat)		2–38	2–90	Oral	[24]
GSK126		10–29	7–252	Intravenous	[25]
CPI-1205		2.2–3.1	32	Oral	[23]

Table 2:

Current Clinical Trials of EZH2 inhibitors in lymphoma

Agent	Study Name	NCT ID	Phase	Eligible Lymphoma Subtypes	Expected accrual	Status
Tazemetostat (EPZ-6438)	Open-Label, Multicenter, phase 1/2 Study of Tazemetostat as a Single Agent in Subjects with Advanced Solid Tumors or with B-cell Lymphomas and Tazemetostat in Combination with Prednisolone in Subjects with DLBCL		I/II	Phase I: B-cell NHL and solid tumors; Phase II: DLBCL, FL	420	Phase I closed, phase II ongoing
	Pediatric MATCH: Tazemetostat in Treating Patients With Relapsed or Refractory Advanced Solid Tumors, Non-Hodgkin Lymphoma, or Histiocytic Disorders With EZH2, SMARCB1, or SMARCA4 Gene Mutations	Phase II sub protocol:	II	NHL and solid tumors	49	Recruiting
	Study of Tazemetostat in Newly Diagnosed Diffuse Large B Cell Lymphoma Patients Treated by Chemotherapy (Epi-RCHOP)		Ib-II	DLBCL	133	Recruiting
	A Safety and Pharmacology Study of Atezolizumab Administered With Obinutuzumab or Tazemetostat in Participants With Relapsed/Refractory Follicular Lymphoma and Diffuse Large B-cell Lymphoma		I	DLBCL, FL	92	Recruiting
	Tazemetostat in Treating Patients with Metastatic or Unresectable Solid Tumors or B-Cell Lymphomas with Liver Dysfunction		I	B-cell NHL and solid tumors	48	Anticipated start date: 3/16/2018
CPL-1205	A Study Evaluating CPL-1205 in Patients With B-Cell Lymphomas		I	B-cell NHL	41	Recruiting
GSK2816126	A Study to Investigate the Safety, Pharmacokinetics, Pharmacodynamics and Clinical Activity of GSK2816126 in Subjects With Relapsed/Refractory Diffuse Large B Cell Lymphoma, Transformed Follicular Lymphoma, Other Non-Hodgkin's Lymphomas, Solid Tumors and Multiple Myeloma		I	NHL, MM Expansion cohort: DLBCL	41	Closed to enrollment

Abbreviations: Diffuse Large B -cell Lymphoma (DLBCL); Follicular Lymphoma (FL); Non-Hodgkin's lymphomas (NHL); Multiple myeloma (MM)

Table 3:

Tazemetostat Quick Profile

Drug Name	Tazemetostat
Company	Epizyme, Inc.
Other Names	E7438/ EPZ-6438
MOA (Mechanism of action)	EZH2 inhibitor, Competitive inhibition with the cofactor <i>S</i> -adenosyl-L-methionine (SAM)
MOR (Mechanism of resistance)	Not well characterized. <i>In-vitro</i> data suggests that secondary mutations in the EZH2 D1 domain (Y111 and I109) and SET domain (Y661) may confer resistance
MTD	1600mg PO BID
Schedule	800 mg PO BID
Plasma half-life	T max = 1–2 hrs., mean terminal t _{1/2} = 3–5hrs
Other unique features	<ul style="list-style-type: none"> - Fast Track designation for EZH2 mutant DLBCL and for FL regardless of EZH2 mutation status - Orphan Drug designation for malignant rhabdoid tumors