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EVOLVING THERAPIES (RM BUKOWSKI, SECTION EDITOR)

BET and EZH2 Inhibitors: Novel Approaches for Targeting Cancer

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Abstract
Purpose of Review Increasing evidence suggests that epigenome plays a central role in cancer development making it a promising target for anticancer treatments. Here, we review two new classes of epigenome-targeting agents: the bromodomain and extraterminal domain proteins (BET) inhibitors and the enhancer of zeste homolog (EZH2) inhibitors.
Recent Findings Clinical research evaluating BET and EZH2 inhibitors is still at an early stage; however, both classes of drugs have demonstrated activity among different hematologic malignancies and solid tumors.
Summary Several studies on BETi and EZH2i are ongoing to better define their potential role in cancer treatment, which patients are most likely to benefit and if the association with other drugs can improve their efficacy.

Keywords Bromodomain and extraterminal motif proteins inhibitor (BETi) · Enhancer of zeste homolog 2 inhibitor (EZH2i) · Epigenetic agents · Hematological malignancies · Solid tumors

Introduction

Over the last years, significant progress has been made in the comprehension of tumor biology, and many genetic alterations linked to cell survival, proliferation, differentiation, and apoptosis have been discovered. This has permitted the development of several drugs able to target specific genomic aberrations and some of them have now become the standard of care in the treatment of different tumors.

Gene expression does not depend only on DNA integrity but it is also regulated by different mechanisms including epigenetic processes such as DNA methylation, histone modification, and non-coding RNA-associated gene silencing [1].

Epigenetic abnormalities are common in cancer and they include global hypomethylation which can determine the activation of different oncogenes, promoter hypermethylation resulting in silencing of tumor suppressor genes and loss of imprinting on normally silenced genes [2–4].

Approved Treatments Targeting Epigenome

The elucidation of the roles played by epigenome in gene regulation and its involvement in cancer has permitted the development of several drugs targeting epigenetic components with some of them already approved for the treatment of selected hematologic malignancies.

DNA methyltransferase (DNMT) inhibitors such as decitabine and azacitidine, which induce an anticancer effect through GpC island hypomethylation, are currently used in the treatment of myelodysplastic syndromes (MDS) [5–8], chronic myelomonocitic leukemia (CMML), and acute myeloid leukemia (AML) [9–11]. Another class of drugs approved for cancer treatment is represented by histone deacetylase (HDAC) inhibitors. These agents inhibit histone deacetylation causing increased expression in genes involved in cell cycle arrest, antiangiogenesis, induction of cell differentiation and apoptosis. Four different HDAC inhibitors have been approved by the US Food and Drug Administration (FDA): vorinostat, belinostat, and romidepsin for the treatment of some T cell lymphomas [12–16] and panobinostat for multiple myeloma [17].

Besides HDAC and DNMT inhibitors, other types of drugs have been recently developed and tested in clinical trials. In

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Fig. 1, we represent the main mechanism of action of the principal classes of drugs targeting the epigenome. Among the recently developed compounds, bromodomain and extraterminal motif (BET) protein inhibitors and enhancer of zeste homolog 2 (EZH2) inhibitors have shown activity among different tumor types and have now advanced to combination phase I/II trials. Here, we review the role of BET proteins and EZH2 in cancer and the results of clinical trials testing these new classes of compounds in solid tumors and hematologic malignancies.

The Role of BET Proteins in Cancer Development

BET proteins are a family of chromatin readers characterized by the presence of two N-terminal bromodomains (BD1 and BD2) and one extraterminal domain (ET) including four different members: Brd2, Brd3, Brd4, and bromodomain testis-specific protein (BRDT) [18].

By binding acetylated histone tails and other acetylated proteins such as transcription factors, BET proteins act as regulators of RNA transcription and cell cycle progression [19].

Molecular mechanisms at the bases of these processes are not fully understood; however, in the last years, several studies have partially clarified some of the roles exerted by BET proteins and their possible involvement in human cancer.

Brd4 is involved both in transcription starting and elongation. Phosphorylating C-terminal domain of RNA polymerase II, Brd4 allows transcription initiation [19, 20] and, through the recruitment of the positive transcription elongation factor (PTEFb), consents transcription elongation [21].

Brd4 is also responsible for cell cycle progression and its knockdown is known to be associated with cellular arrest in G1 phase [22]; furthermore, it plays a key role during mitosis in the control of chromosomal segregation by regulating the expression of Aurora kinase B (AURKB) [23].

Brd2 is part of the mediator complex, a group of proteins whose binding to RNA polymerase II is essential for transcription initiation [24].

Both Brd2 and Brd3 can activate through E2F-Rb pathway proteins, the promoters of different genes involved in cell cycle control such as cyclin D11 and cyclin E [25–27]. In addition, these two BET proteins are known to have a chaperone function in remodeling histones to allow RNA polymerase II movements along DNA [27].

The first evidence of the involvement of BET proteins in cancer emerged from preclinical studies on hematological malignancies such as multiple myeloma (MM) and AML. Brd4 and mediator complex co-occupy super-enhancers associated with genes involved in oncogenesis such as MYC. It was observed that the displacement of Brd4 caused by BET inhibitors could result in transcription elongation defects affecting MYC and other genes associated with the enhancers [28–30].

It was subsequently shown that BET proteins regulate the expression of several other genes involved in the development of tumors including androgen receptor (AR) in prostate cancer [31], extracellular signal-regulated kinase 1 (ERK1), small conductance potassium channel type 2 (SK2), p21 and p27 in melanoma [32] and FoxM1 transcription factor in ovarian cancer [33].

Furthermore, in ovarian cancer xenograft models, BET inhibition resulted in decreased PD-L1 expression in immune and cancer cells suggesting a possible synergism between BET and immune checkpoint inhibitors [34].

Finally, a particular example of the oncogenic role of BET proteins is represented by the nuclear protein in testis (NUT) midline carcinoma (NMC), a rare and aggressive squamous cell carcinoma characterized by chromosomal translocations

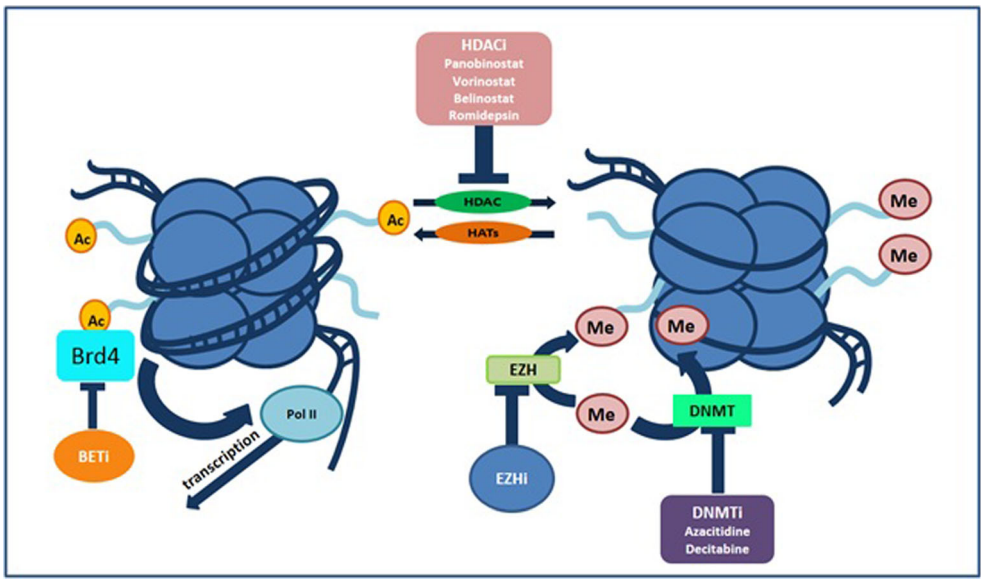

Fig. 1 Targeting epigenome: mechanism of action of HDACi, DNMTi, EZHi, and BETi. Ac = acetyl groups; BETi = bromodomain and extraterminal motif proteins inhibitors; Brd4 = bromodomain containing protein 4; DNMT = DNA methyltransferase; DNMTi = DNA methyltransferase inhibitors; EZH = enhance of zeste homolog; EZHi = enhance of zeste homolog inhibitors; HATs = histone acetyltransferase; HDAC = histone deacetylase; HDACi = histone deacetylase inhibitors; Me = methyl groups; Pol II = RNA polymerase II$

commonly involving the NUT and Brd4 orBrd3 genes. These translocations result in a chimeric fusion protein (BRD-NUT) which indeed represents the major pathogenic event that drives the malignant transformation [35].

BET Inhibitors: Clinical Evidence in Cancer Treatment

Several BET inhibitors have been tested in patients with solid and hematological tumors (results are summarized in Table 1). Among patients with solid cancers, radiological responses have been mainly observed in NUT midline carcinoma (NMC). Birabresib, also known as MK-8628 or OTX015, is a potent BET inhibitor tested in several clinical trials. The first data on Birabresib clinical activity were published in 2016. Among 4 patients with NMC and confirmed BRD4-NUT fusion 2 rapid responses were observed and a third patient achieved a disease stabilization with a minor metabolic response [36•]. Recently, results of a phase I trial have been reported by Lewin and colleagues. A total of 46 patients have been enrolled: 26 with castration-resistant prostate cancer (CRPC), 10 with non-small cell lung cancer (NSCLC) and 10 with NMC. Patients were divided in two cohorts: cohort A at a starting dose of 80 mg daily continuously and cohort B at 100 mg daily for 7 days in 3-week cycles.

No dose-limiting toxicities (DLTs) were observed in cohort B while in cohort A 4 patients experienced thrombocytopenia ≥ G3 (3 patients at 80 mg/day and 1 patient at 100 mg/day). One patient treated at 80 mg/day had an AST increase and hyperbilirubinemia, and another patient treated at 100 mg/day had anorexia requiring > 7 days of treatment delay. Three patients with NMC treated in cohort A at 80 mg/day achieved a partial response (PR) [37•].

Molibresib or GSK525762 is another BET inhibitor which has been tested in 70 patients with advanced malignancies including 17 NMC patients, treated at doses ranging from 2 to 100 mg once a day and 20 and 30 mg twice a day. The most commonly reported adverse events were thrombocytopenia, anemia, nausea, vomiting, and fatigue. Among 10 patients with NMC evaluable for response, 2 had PR and 4 stable disease (SD) [38].

The third BET inhibitor, which has shown clinical activity in NMC, is RO6870810/TEN-010 that has been recently investigated in patients with advanced solid tumors including 3 with NMC. Of these 3 patients, 1 was treated at 0.1 mg/kg and 2 at 0.45 mg/kg. The patient treated at the lower dose had disease progression while both patients treated at 0.45 mg/kg dose had a PR. Data regarding other tumor types are not yet available [39].

Aftimos and colleagues reported the results of a first-in-men trial of the BET inhibitor BI 894999 in patients with other types of solid malignancies. Twenty-eight patients were treated at 0.25–5 mg/day continuously or at 1.5–2 mg on an intermittent schedule. Among 27 evaluable patients, 3 obtained PR and 1 SD. DLTs included grade 4 thrombocytopenia, grade 3 hypophosphatemia, and grade 3 troponin increase [40].

Another agent named INCB054329 has been tested in a phase I trial in solid tumors and lymphomas: 54 patients were enrolled and received the drug at doses ranging from 15 to 30 mg once a day or 15–25 mg twice a day. Dose-limiting thrombocytopenia was observed at 30 mg daily. Only one PR was obtained in a NSCLC patient [41].

PLX51107 and ABBV-075 are two BET inhibitors tested in phase I trials in patients with solid cancers obtaining SD as best responses. Thrombocytopenia, fatigue, and gastrointestinal events were the most frequent observed toxicities. Regarding hematological malignancies, limited activity has been reported in AML and diffused large B cell lymphoma (DLBCL).

Birabresib was evaluated in a phase I trial in patients with AML or acute lymphatic leukemia (ALL). Three patients treated at three different dose levels (40, 80, and 160 mg/day) achieved CR and 2 had a partial blast clearance [42, 43•]. Main toxicities included fatigue and diarrhea.

Molibresib was tested in 46 AML patients obtaining 2 CR (at 100 and 120 mg/day) and 3 PR (2 at 60 mg/day and 1 at 80 mg/day). DLTs observed were grade 3 diarrhea and grade 3 decreased ejection fraction [44].

Preliminary results of a trial evaluating ABBV-075 with or without venetoclax in AML patients have been presented at 2018 American Society of Clinical Oncology (ASCO) annual meeting. Efficacy data were available only for 11 patients treated with ABBV-075 in monotherapy: 4 had a bone marrow blast count decrease of ≥ 50% from baseline and 1 patient achieved a CR [45].

Among lymphoma patients, 2 CR and 1 PR were observed in 45 patients (with lymphoma or MM) treated with Birabresib. The 3 responders had DLBCL. Dose-liming thrombocytopenia, gastrointestinal events, fatigue, and hyponatremia were observed at different dose levels [46].

Other evidences of activity in lymphomas have been obtained with CPI-0610, tested in 64 patients and resulting in 2 CR in DLBCL patients and 3 PR (1 in FL and 2 in DLBCL). DLTs observed were thrombocytopenia and grade 3 diarrhea [47].

BET Inhibitors: Future Perspectives

Several preclinical evidences suggest a possible synergism of BET inhibition with different classes of drugs including mTor and Pi3K inhibitors, hormone therapy, rituximab, ibrutinib, HDAC inhibitors, CDK inhibitors, bcl2 inhibitors, and chemotherapy [48].

Table 1 Available clinical data with BET and EZH inhibitors

Agent	Class of action	Author	No of patients	Population	DLTs and AEs of interest	Responses
PLX51107	BET inhibitor	Patnaik A. et al.	36	Advanced solid tumors	DLTs: thrombocytopenia, nausea, kidney injury	9 SD
ABBV-075 ± Venetoclax	BET inhibitor	Borthakur et al.	19	Relapsed/refractory AML	No DLTs Other AEs: anemia, febrile neutropenia, thrombocytopenia, fatigue, nausea, diarrhea	1 CR 4 partial blast clearance
ABBV-075	BET inhibitor	Piha-Paul SA et al.	72	Relapsed/refractory solid tumors	Thrombocytopenia, fatigue, AST elevation, gastrointestinal bleed, hypertension	25 SD mPFS 1.8 m
BI 894999	BET inhibitor	Aftimos PG et al.	28	Relapsed/refractory solid tumors	Thrombocytopenia G4 ($N = 3$), hypophosphatemia G3 ($N = 1$), increased troponin G3 ($N = 1$) multiple G2 events preventing adequate dose intensity in cycle 1 ($N = 1$)	3 PR 1 SD
MK-8628 (OTX015)	BET inhibitor	Hottinger AF et al.	12	Recurrent glioblastoma	Thrombocytopenia G3 > 7 days ($N = 2$) G3 hyperbilirubinemia	1 SD
MK-8628 (OTX015)	BET inhibitor	Berthon C et al.	41	Acute leukemia	DLTs:G 3 diarrhea G3 fatigue	3 CR 2 partial blast clearance
MK-8628 (OTX015)	BET inhibitor	Amorim S et al.	45	Relapsed/refractory lymphoma or MM	DLTs:Thrombocytopenia, fatigue, hyponatriemia, diarrhea, vomiting, mucositis, dysgeusia	2 CR (DLBCL) 1 PR (DLBCL)
MK-8628 (OTX015)	BET inhibitor	Lewin J et al.	46	CRPC (26), NMC (10), NSCLC (10)	Thrombocytopenia ≥ G3 ($N = 4$) increased ALT/hyperbilirubinemia ($N = 1$) anorexia/nausea with treatment delay > 7 days ($N = 1$)	3 PR (NMC)
CPI-0610	BET inhibitor	Blum KA et al.	64	Relapsed/refractory lymphoma	Thrombocytopenia ($N = 1$)	2 CR (DLBCL) 3 PR (1 FL, 2 DLBCL) 5 SD
RO6870810/TEN-010	BET inhibitor	Shapiro GI et al.	3	NMC	Not available	2 PR
GSK525762	BET inhibitor	O'Dwyer PJ et al.	70 (17 NMC)	Advanced malignancies	Thrombocytopenia (44%), nausea (40%), vomiting (29%), anemia (26%), fatigue (26%), decreased appetite (24%), diarrhea (23%) and dysgeusia (20%) 5 DLT	2 PR (NMC) 4 SD (NMC) Data for non-NMC patients are not available
GSK525762	BET inhibitor	Dawson M et al.	46	Relapsed/refractory AML	Diarrhea G3 ($N = 1$) Ejection fraction decrease G3 ($N = 1$)	2 CR 3 PR
INCB054329	BET inhibitor	Falchook G et al.	54 (50 solid tumors and 4 lymphomas)	Advanced malignancies	Thrombocytopenia ≥ G3 ($N = 1$)	1 PR (NSCLC) 3 SD ≥ 6 m 14 SD < 6 m
DS-3201b	EZH1/EZH2 inhibitor	Maruyama D et al	15	Non-Hodgkin lymphomas	DLTs: 3 grade 4 thrombocytopenia and 1 grade 3 anemia	1 CR 7PR 5 SD
Tazemetostat	EZH2 inhibitor	Schoffski P et al	33	Synovial sarcoma	Grades 1 and 2 dyspnea, fatigue and cough	11 SD
Tazemetostat	EZH2 inhibitor	Italiano et al.	64	INI1-negative solid tumors or lymphomas	DLT: G4 thrombocytopenia ($N = 1$) Grades 1 and 2 asthenia, anemia, nausea and vomiting	7 OR or SD
CPI-1205	EZH2 inhibitor	Harb W et al	32	Lymphomas	No DLTs Grade 3 nausea, leucopenia, anemia, hypertension and skin toxicity	1 CR 5 SD
GSK126	EZH2 inhibitor	Timothy A et al	30	Solid tumors, MM, and NHL	No DLTs nausea, vomiting	1 PR 7 SD

Trials aimed at evaluating different associations in specific tumor types are ongoing (see Table 2); for example, both ZEN003694 and molibresib are under investigation in patients with castration-resistant prostate cancer in association with enzalutamide or abiraterone. The association of molibresib with fulvestrant is being tested in an ongoing phase I/II trial in women with ER positive breast cancer. Regarding the association of BET proteins inhibitors and immunotherapy there are two phase I trials currently evaluating respectively the activity of RO6870810/TEN-010 and atezolizumab in patients with ovarian or triple negative breast cancer and of BMS-986158 alone or with nivolumab in patients with advanced solid tumors with specific genomic profiles. RO6870810/TEN-010 is also under investigation in combination with daratumumab in MM patients. Another phase I trial is evaluating ABBV-075 as single agent or in combination with venetoclax in advanced tumors.

There are many studies still ongoing aimed at better defining the role of these agents as a monotherapy in different settings. In addition, different innovative strategies to target BET proteins are in development such as the proteolytic targeting chimera (PROTAC) induced degradation of Brd4 which have shown interesting activity in preclinical models [49]. Results of these studies may open new possibilities for the use of BET inhibitors in cancer treatment.

EZH2 Roles in Oncogenesis

Enhancer of zeste homolog 2 (EZH2) is an histone-lysine N-methyltransferase enzyme. It is a catalytic subunit of the polycomb repressive complex 2 (PRC2) responsible for transferring methyl groups from S-adenosyl-*L*-methionine (SAM) to Lys-27 on histone H3 (H3K27) through the Su(var)3–9 enhancer of zeste thrithorax (SET) domain [50, 51]. The PRC2 includes other core members such as suppressor of zeste 12 (SUZ12), embryonic ectoderm development (EED), and histone-binding proteins RbAp46/48 [52].

EZH2 is involved in cell cycle-regulatory retinoblastoma-E2F pathway, in silencing of E-cadherin and DNA damage repair pathways and can be involved in promoting oncogenesis [53].

In the hematopoietic system, EZH2 regulates cell proliferation, T cell differentiation while in B cells induces a correct V(D)J recombination of immunoglobulin heavy chains. In fact, EZH2 is expressed in high division rate cells, such as B cells entering in germinal center (GC) where the process of somatic hypermutation and isotypic switching occurr [54].

EZH2 can be replaced by its analogous EZH1 that has lower methyltransferase activity and is expressed ubiquitously, usually in less actively dividing cells [55]. Alterations in EZH2 have been described in multiple cancer types including breast, ovarian, prostate cancer, non-Hodgkin lymphoma (NHL), and T cell ALL. At a molecular level, different types of EZH2 alterations have been found including point mutations resulting in gain or loss of function in EZH2.

EZH2 gain of function mutations are frequent in FL and GC-DLBCL, while loss of function in myelodysplastic syndrome (MDS), myelodysplastic syndrome/myeloproliferative disorders (MDS/MPN), myelofibrosis, AML, and T-acute lymphoblastic leukemia (T-ALL) [56–59].

Finally, overexpression of EZH2 has been described in prostate, breast, bladder, gastric, lung, hepatocellular and renal cell carcinomas, melanoma, and NHLs. In solid tumors, alterations of MEK-ERK-Elk-1 pathway or retinoblastoma (Rb)-E2F pathway have been found to induce an EZH2 overexpression [60–64].

In NHL, a MYC overexpression induces an EZH2 overexpression binding directly EZH2 promoter or inducing a miRNA dysregulation [65, 66].

In these tumors, EZH2 overexpression is associated with aggressiveness, metastasis, and poor outcome [67].

EZH2 Inhibitors: Clinical Activity

During the last years, several EZH2 inhibitors have been developed and clinically tested.

The first compound is DZNep (3-deazaneplanocin A), a *S*-adenosylhomocysteine hydrolase inhibitor, which induces an increase of 5-adensylhomocystein levels leading to inhibition of the global methyltransferase activity, including histone methylation mediated by EZH2, without selectivity [68].

However, a suboptimal safety and pharmacokinetic profile of DZNe encouraged the development of more potent and selective small molecules such as the SAM-competitive catalytic EZH2 inhibitors which have been tested in vitro like EPZ0005687, EI1, and GSK126 [69–71].

While most compounds are still in preclinical development, DS-3201b, tazemetostat (EPZ-6438), CPI-1205, SHR2554, have recently moved into phase I/II clinical trials (clinical results are reassumed in Table 1).

Tazemetostat is a competitive inhibitor of the SAM pocket of the EZH2 SET domain.

Knutson and colleagues have demonstrated the activity of tazemetostat in preclinical models of Malignant Rhabdoid tumors (MRT) [72]. These rare and aggressive pediatric tumors are characterized by loss of the INI1 protein, a component of the Switch Sucrose Non-fermentable (SWI/SNF) multimeric chromatin-modifying complex.

SWI/SNF complex and the PRC2 complex have an antagonistic role in the regulation of tumor suppressor genes. Loss of INI1 in SWI/SNF complex, induce an aberrant recruitment

Table 2 Ongoing clinical trials with BET and EZH inhibitors in lymphomas, multiple myeloma, and solid tumors

Drug	Class of action	Study population	Phase	State	Id number
FT-11-01 in association with azacitine	BET inhibitor DNMT inhibitor	Advanced hematologic malignancies including NHL	I	Recruiting	NCT02543879
RO6870810/TEN-010	BET inhibitor	Advanced solid tumors	I	Completed	NCT01987362
RO6870810/TEN-010 ± daratumumab	BET inhibitor Anti-CD38	Advanced MM	I	Recruiting	NCT03068351
RO6870810/TEN-010 + atezolizumab	BET inhibitor anti-PD-L1	Advanced ovarian cancer or triple negative breast cancer	I	Recruiting	NCT03292172
ABBV-075 ± venetoclax	BET inhibitor anti-BCL2	Advanced malignancies	I	Recruiting	NCT02391480
GSK525762	BET inhibitor	Advanced hematologic malignancies including NHL and MM	I	Recruiting	NCT01943851
GSK525762	BET inhibitor	NUT midline carcinomas and other cancers	I	Active not recruiting	NCT01587703
GSK525762 + enzalutamide or abiraterone and prednisone	BET inhibitor antiandrogen	Castration-resistant prostate cancer	I	Recruiting	NCT03150056
Fulvestrant ± GSK525762	ER downregulator BET inhibitor	ER+ Breast cancer	I/II	Recruiting	NCT02964507
BMS-986158 ± nivolumab	BET inhibitor Anti-PD-1	Advanced cancers with specific genetic profile	I/II	Recruiting	NCT02419417
CPI-0610	BET inhibitor	Malignant peripheral nerve sheath tumors	II	Recruiting	NCT02986919
CPI-0610	BET inhibitor	HL or NHL in progression after previous treatments	I	Not yet recruiting	NCT01949883
CPI-0610	BET inhibitor	Previously treated MM	I	Completed	NCT02157636
ZEN003694	BET inhibitor	Metastatic castration-resistant prostate cancer	I	Completed	NCT02705469
ZEN003694 + enzalutamide	BET inhibitor antiandrogen	Metastatic castration-resistant prostate cancer	I/II	Recruiting	NCT02711956
OTX105/MK-8628	BET inhibitor	Advanced solid tumors	I	Completed	NCT02259114
OTX015/MK-8628	BET inhibitor	Advanced hematologic malignancies including DLBCL	I	Active not recruiting	NCT02698189
OTX015/MK-8628	BET inhibitor	Advanced solid tumors	I	Terminated	NCT02698176
PLX51107	BET inhibitor	Advanced malignancies	I	Recruiting	NCT02683395
INCB054329	BET inhibitor	Advanced malignancies	I/II	Completed	NCT02431260
SHR2554	EZH inhibitor	Relapsed/refractory mature lymphoid neoplasms	I	Recruiting	NCT03603951
Tazemetostat	EZH inhibitor	INI1-negative tumors or relapsed/refractory synovial sarcoma	II	Recruiting	NCT02601950
Tazemetostat ± prednisolone	EZH inhibitor	Advanced solid tumors and B cell lymphomas	I/II	Recruiting	NCT01897571
Tazemetostat	EZH inhibitor	B cell lymphomas and advanced solid tumors	I	Recruiting	NCT03010982
Tazemetostat	EZH inhibitor	Advanced solid tumors and B cell lymphomas	II	Recruiting	NCT02875548
DS-3201b	EZH inhibitor	Lymphomas	I	Recruiting	NCT02732275
Tazemetostat	EZH inhibitor	Malignant mesothelioma with BAP 1 loss of function	II	Active not recruiting	NCT02860286
Tazemetostat	EZH inhibitor	Pediatric patients with relapsed/refractory INI1-negative tumors or synovial sarcoma	I	Active not recruiting	NCT02601937
Atezolizumab with obinotuzumab or tazemetostat	Anti-PD-L1 Anti-CD20 EZH inhibitor	Relapsed/refractory FL/DLBCL	I	Active not recruiting	NCT02220842
CPI-1205	EZH inhibitor	B cell lymphomas in progression after previous treatments	I	Active not recruiting	NCT02395601
CPI-1205 ± enzalutamide or abiraterone and prednisone	EZH inhibitor antiandrogen	Metastatic castration-resistant prostate cancer	I/II	Recruiting	NCT03480646
CPI-1205 ± ipilimumab	EZH inhibitor Anti-CTLA4	Advanced solid tumors	I/II	Recruiting	NCT03525795
Tazemetostat	EZH inhibitor	Relapsed/refractory NHLs	I	Recruiting	NCT03456726
PF 06821497	EZH inhibitor	Advanced solid tumors	I	Recruiting	NCT03460977

of EZH2, increasing H3K27 methylation and consequent repression of these tumor suppressors genes [73].

According to these observations, tazemetostat has been evaluated in a first-in-human, phase 1 study in relapsed or refractory patients with INI1-negative tumors or B cell NHLs, showing clinical activity with a favorable safety profile. In this trial, 64 pretreated patients (21 with B cell NHL and 43 with solid tumors) received tazemetostat. The phase 1 part of the study is complete while the phase 2 is ongoing (NCT01897571). In the phase 1 trial, tazemetostat was administered orally starting from 100 mg to 1600 mg twice a day in 28-day cycles. The most common adverse events observed, mainly of grade 1 or 2, included asthenia, anemia, muscle spasms nausea, and vomiting. One patient developed a DLT consisting in grade 4 thrombocytopenia at the highest dose of 1600 mg. The overall response rate (ORR) was 38% (8/21) and 5% (2/43) in lymphomas and solid tumors respectively. Seven patients who had an objective response or a stable disease lasting at least 11 months were transferred from this study to the EZH-501 study and continued tazemetostat for a median of 28 months after initial dosing [74•].

Further clinical investigation of tazemetostat monotherapy is ongoing in a phase 2 trial in adult patients with relapsed or refractory B-NHLs. Interim results after the inclusion of 210 patients were presented in June 2017 in Lugano, at the International Conference of Malignant Lymphoma. Among patients with follicular lymphoma, objective response rate (ORR) was 92% in patients EZH2-mutated and 26% in EZH2 wild type. In DLBCLs, ORR was 29% in patients with mutated EZH2 and 15% in wild type. A low incidence of adverse events was observed, mainly thrombocytopenia and neutropenia, each observed in 6% of patients [75•].

Tazemetostat was recently evaluated in a phase II study in 33 patients with previously treated synovial sarcoma (SS). In this tumor, there is a low expression of INI1 in SWI/SNF complex and the mechanism of INI1 reduction is distinct from malignant rhabdoid tumors, epithelioid sarcoma, or other INI1 negative tumors. Best response observed was SD in 11 patients (33%) and 5 patients (15%) had SD lasting ≥ 16 weeks. Tazemetostat has shown a favorable safety profile (grades 1and 2 cough, dyspnea, and fatigue were the only toxicities reported) and it was considered for combination therapy [76].

DS-3201b is a potent inhibitor with high specificity for EZH1 and EZH2 under investigation in a phase I study in patients with relapsed or refractory NHLs, including adult T cell leukemia-lymphoma (ATL) associated with human T-lymphotropic virus type I. Fifteen patients with different lymphoma subtypes have been enrolled. This dose escalation study started at a dose of 150 mg and escalated through 200 mg and 300 mg dose levels. Four DLTs (three grade 4 platelet count decreased and one grade 3 anemia requiring transfusion) occurred in three patients at 200 mg QD and 300 mg QD. The most frequent adverse events were hematological toxicities; only one grade 3 non-hematologic adverse event was described consisting in pneumonia, while other non-hematological events were represented by dysgeusia, diarrhea, nasopharyngitis, and alopecia. Preliminary data showed an ORR of 53% among evaluable patients (1 CR, 7 PR, and 5 SD) and 80% among 5 patients with T cell lymphoma (1 CR and 3 PR) [77].

CPI-1205 is an oral small molecule inhibitor of EZH2 which binds to the EZH2 catalytic region and partially overlaps with the SAM-binding site. A phase I study is ongoing (NCT 02395601) in patients with relapsed or refractory B cell lymphoma. Among 32 patients enrolled (17 DLBCL, 4 FL, 2 marginal zone lymphoma and 9 other lymphomas, 1 patient had a CR at cycle 6 and 5 patients a SD (3 remained on SD ≥ 6 months). Seven patients developed grade 3 events, nausea ($n = 1$), lymphocyte count decreased ($n = 3$), anemia (n = 1), hypertension ($n = 1$), and toxic epidermal necrolysis ($n = 1$); other toxicities were grade 2 or lower such as nausea, diarrhea, anemia, and fatigue. No DLTs were reported. [78]

Finally, GSK2816126 (GSK 126), a highly selective SAM pocket EZH2 inhibitor, induces a decrease of H3K27me3 levels in preclinical studies [70]. GSK126, was evaluated in a multicenter phase I clinical trial. 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 50 mg and was escalated to a maximum dose of 3000 mg. The most frequent drug-related adverse events were fatigue (53%), nausea (30%), anemia (20%), and vomiting (20%). Of 22 evaluable patients, 1 patient with GCB-DLBCL showed a PR and 7 patients had SD. Unfortunately, the study was closed due to the low efficacy in this patient population [79].

EZH2 Inhibitors: Future Directions

Further clinical investigation is ongoing with tazemetostat in a phase 2 study in INI1-negative or SMARCA2/A4-negative tumors (NCT02601950), and BAP1-negative mesothelioma (NCT02860286), as well as in a phase 1 study in children with INI1-negative tumors. Clinical trials evaluating the combination of tazemetostat with R-CHOP chemotherapy, prednisone, and the PDL1 antagonist atezolizumab are ongoing in adults with DLBCL.

Two studies are evaluating the role of CPI-1205 in non-hematological malignancies (Table 2), a phase 1b/2 trial in combination with either enzalutamide or abiraterone/prednisone in patients with metastatic castration-resistant prostate cancer and a phase 1/2 study with ipilimumab in patients with advanced solid tumors.

Finally, the selective EZH2 inhibitor SHR2554, has recently entered clinical evaluation in a phase I trial in relapsed or

refractory mature lymphoid neoplasms. This study opened in August 2018 and is expected to enroll approximately 42 patients through September 2020.

Conclusions

Over the last years, following the approvals of DNMTi and HDACi, new classes of epigenetic targets have been identified and new compounds have been developed with some of them already in clinical development. BET and EZH2 inhibitors represent two new classes of epigenome-targeting compounds that have entered clinical development and may open new possibilities for cancer treatment. Despite available data are based mainly on phase I/II trials, BET inhibitors have shown clinical activity in NUT midline carcinoma and limited activity in lymphomas and AML. Adverse events observed have been generally mild to moderate; however, they could limit treatment compliance, may request dose reduction or interruptions and they will need to be taken in consideration when planning combinations with other drugs. On the other hand, EZH2 inhibitors have shown significant clinical activity in patients with relapsed or refractory lymphomas and future studies may define their possible role in the treatment of different lymphoma subtypes defining also the patient population that may most benefit. Finally, several combination trials are currently ongoing aiming at investigating the possible synergisms between these compounds and other anticancer drugs as observed in preclinical studies.

Compliance With Ethics Guidelines

Conflict of Interest Sofia Genta declares that she has no conflict of interest.

Maria Cristina Pirosa declares that she has no conflict of interest.

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