BET Proteins as Targets for Anticancer Treatment

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ABSTRACT Bromodomain and extraterminal domain (BET) proteins are epigenetic readers that regulate gene expression and are involved in cancer pathogenesis. Over the last years, several BET inhibitors have been developed and clinically tested. Results from the first clinical trials show limited single-agent activity in a small subset of patients with hematologic malignancies and in NUT carcinoma. Adverse events have been observed and may limit treatment compliance. Here, we review the preclinical rationale for targeting BET proteins in cancer and the preliminary results from clinical trials, and outline future directions for the use of BET inhibitors as antitumor agents.

Significance: BET inhibitors represent a new class of anticancer agents. Results from the first clinical trials confirm the antitumor potential of BET inhibitors, but their efficacy as single agents seems to be limited. Based on preclinical data, combination therapies with other anticancer agents and the development of a new generation of compounds may open new possibilities for targeting BET proteins as effective anticancer strategies. *Cancer Discov; 8(1); 24–36. ©2017 AACR.*

BET PROTEINS AS EPIGENETIC READERS

Human cells contain tens of thousands of active promoter regions and enhancer regions that are highly cell-type dependent, and a few hundred superenhancers, which are clusters of enhancers characterized by a very high binding of Mediator complexes and master transcription factors (1–3). For example, in a multiple myeloma cell line, Loven and colleagues have identified approximately 10,000 annotated active transcription start sites, 8,000 enhancers, and 308 superenhancers (1). Superenhancer-associated transcripts comprise the key cell identity genes and are expressed at higher levels than genes associated with normal enhancers (2–4).

Bromodomain and extraterminal domain (BET) proteins are epigenetic readers characterized by the presence of two tandem bromodomains (BD1 and BD2), an extraterminal domain (ET), and a C-terminal domain (CTD; ref. 5). They comprise the ubiquitously expressed BRD2, BRD3, and BRD4 and the testis-restricted BRDT, and mainly recognize acetylated lysine of histone 4 (5, 6). BET proteins also recognize acetylated nonhistone proteins, including different transcription factors (5–8). Examples are the binding of BRD4 to the acetylated transcription

factor TWIST, involved in mesoderm formation (9); to acetylated RelA, regulating the transcriptional activity of NF-kappaB (10); or to acetylated ERG in acute myeloid leukemia (AML) cells (8). BET proteins can also bind other proteins, including transcription factors, in a bromodomain-independent manner, such as the binding of BRD4 to FLI1, MYB, SPI1 (PU.1), CEBPA, CEBPB (8), or p53 (11). Finally, BET can also have kinase activity (9), a function not yet fully understood.

The fundamental role of BET proteins is demonstrated by the fact that homozygous deletion of BRD2 or BRD4 is embryonic lethal (12–15). BET proteins, acting as scaffolds to recruit other proteins, are localized at promoters and especially at enhancers of active genes, participating with the Mediator complex, as master transcription elongation factors (refs. 4, 5, 7, 16, 17; Fig. 1). BET proteins match the chromatin acetylation status with transcriptional elongation via displacing HEXIM1/7SK snRNP from the transcription elongation factor b Cyclin T1/CDK9 complex (P-TEFb), allowing the latter to activate RNA polymerase II via phosphorylation at serine 2 (refs. 4, 7, 16, 18; Fig. 1). In addition, especially at enhancers, BET proteins also recruit the demethylase JMJD6, which induces degradation of 7SK snRNP and P-TEFb activation (7, 9, 19). However, the exact role of BET proteins in the transcription machinery has yet to be elucidated. Data obtained studying BRD4 in AML cells show that the recruitment of BET proteins at promoters and enhancers is mediated by transcription factors mainly due to the binding of BRD4 to p300/CBP acetyltransferase–mediated acetylated lysine residues (8). Moreover, a recent publication provided evidence that BRD4 is fundamental for the creation of the productive transcription elongation factor complex but not for the direct recruitment of P-TEFb (4).

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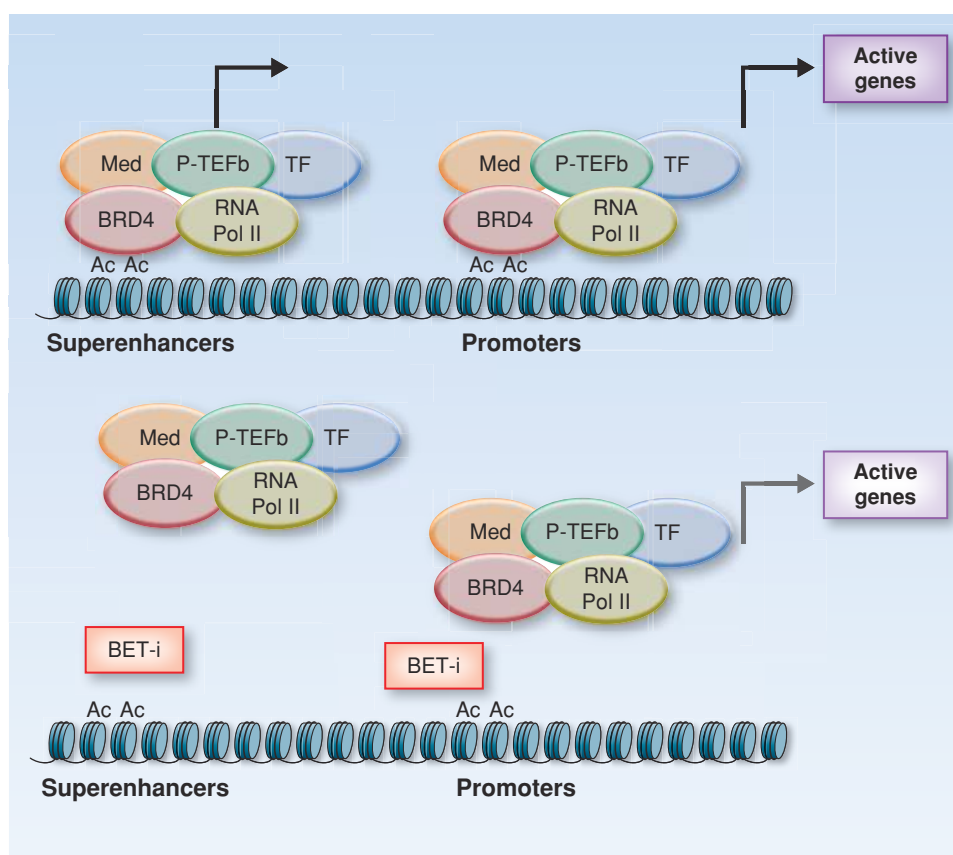
Figure 1. Schematic representation of the mechanism of action of BET inhibitors. BET proteins recognize acetylated lysine of histone 4 and act as scaffolds to recruit many other proteins to promoters and at enhancers of active genes, especially at the superenhancers of key genes, driving the transcription process. Exposure of tumor cells to BET inhibitors reduces the levels of BRD4 at enhancers and at promoters at a genome-wide level, but the reduction is more marked at superenhancers, and the genes associated with superenhancers undergo stronger and faster downregulation than genes regulated by standard enhancers. Examples of such genes are *MYC, NMYC, IL7R, FOSL1, AR, ER, BCL2, BCL6, PAX5, CDK4*, and *CDK6*. BET-i, BET inhibitor; Med, mediator; TF, transcription factor.

PRECLINICAL RATIONALE FOR TARGETING BET PROTEINS IN HUMAN CANCER

Several lines of evidence coming from preclinical studies indicate a role of BET proteins in human cancer and have provided the rationale for targeting BET proteins as a strategy for the development of new anticancer drugs. Genetic screening programs performed in different tumor types have recurrently identified the genes encoding BET proteins as genes on which neoplastic cells depend for their survival (20–23). Overexpression of *BRD2/BRD4* genes also occurs in human cancers (23, 24). Finally, the most direct and clear evidence of the involvement of BET proteins in the pathogenesis of human cancer derives from NUT carcinoma, a rare and aggressive form of undifferentiated squamous cell carcinoma that mainly affects midline structures. Initially thought of as a disease of children and adolescents, NUT carcinoma can actually occur at any age. NUT carcinoma is genetically defined by chromosomal rearrangements involving the *NUT* gene on chromosome 15q14 fused to the BET gene *BRD4* on chromosome 19p13.1, or less commonly to other genes, including *BRD3* and *NSD3BRD* (25, 26). The translocation creates an in-frame *BRD4–NUT* oncogene driven by the *BRD4* promoter that is considered

a major pathogenetic driver of cellular transformation (26). Silencing of the *BRD4–NUT* fusion gene results in differentiation and growth arrest of NUT carcinoma cells (26). More importantly, the displacement of the BRD4 oncoprotein from chromatin using the BET inhibitor JQ1 has antiproliferative activity with squamous differentiation in BRD4-dependent cell lines and patient-derived xenograft models (27).

Exposure of tumor cells to BET inhibitors results in a genome-wide reduction of the levels of BRD4 at enhancers and at promoters with important changes at the gene expression level, largely represented by a downregulation of transcripts (refs. 1, 4, 17, 27–30; Fig. 1). Downregulation of key oncogenes that are associated with superenhancers, such as *MYC*, represents a possible mechanism of the antitumor activity of BET inhibitors (1). Biomarkers of exposure to BET inhibitors have been proposed, such as transcriptional modulation of *MYC* and *HEXIM1* (31, 32) and *CCR1* and *IL1RN* (33).

Signatures of exposure to BET inhibitors are relatively similar among different tumor types (31, 34, 35), but specific changes predominate in different cellular contexts in which BET inhibitors directly affect key tissue- or cancer-specific genes, mainly transcription factors (1, 4, 8, 28, 29, 31, 36–42).

Examples of key genes are *MYC* (4, 20, 22, 24, 35–38, 43–47), *AR* and *TMPRSS2–ETS* fusion genes (48, 49), *FOSL1* (50, 51), *E2F2* (38), *ITK* (31), *IL7R* (35, 38, 44, 50), *TERT* (24, 46), *BCL2* (22, 24, 43, 46), *CDK6* (17, 22, 38, 43), *IRF4* (24, 37, 45), and *IKZF1* (24, 45). There are data indicating that the reduction in BRD4 binding is more marked at superenhancers and that their corresponding genes undergo stronger and faster downregulation than genes regulated by standard enhancers (1, 17, 37, 52).

BET INHIBITORS

After the initial description done by Yoshitomi Pharmaceuticals (then Mitsubishi Tanabe Pharma) of thienotriazolodiazepines with antitumor activity and the ability to inhibit the binding between acetylated histone and bromodomain-containing proteins (patent PCT/JP2008/073864), in 2010 there were two seminal papers demonstrating that BET inhibitors can induce terminal differentiation and apoptosis in preclinical NUT carcinoma models (27) and can have important anti-inflammatory activity (53). Many other publications followed describing novel BET inhibitors and, more importantly, demonstrating that pharmacologic BET inhibition has clear preclinical antitumor activity in a variety of solid tumors and hematologic cancers (54, 55). BRD2 and BRD4 have 80% homology, and their different specificities are believed to mainly depend on their ET and CTD domains (5). Because all of the currently available BET inhibitors target the bromodomains, they are to be considered pan-BET inhibitors, although they can differ in their capacity to bind both BD1 and BD2 or preferentially one of the two bromodomains (56–58).

Several compounds have entered clinical development in phase I or II studies for patients with solid tumors and hematologic malignancies (Table 1). Although results of most of these

Table 1. BET inhibitors in clinical trials, from ClinicalTrials.gov (https://clinicaltrials.gov/), last accessed on September 10, 2017

Drug (administration)	ClinicalTrials.gov # (start date)	Phase	Tumor type	Status	Results
GSK525762 (oral)	NCT01587703 (March 2012)	I	Solid tumors, NUT carcinoma	Ongoing/recruiting patients	Abstract (67)
	NCT01943851 (May 2014)	I	Hematologic malignancies	Ongoing/recruiting patients	Not reported
	NCT02706535 (May 2016)	I	Advanced malignancies, effects of itraconazole and rifampicin on the pharmacokinetics of GSK525762	Completed	Not reported
	NCT03150056 (May 2017)	I	Prostate cancer, in combination with androgen deprivation	Ongoing/recruiting patients	Not reported
	NCT02964507 (February 2017)	II	Estrogen receptor–positive breast cancer, in combination with fulvestrant	Ongoing/recruiting patients	Not reported
OTX015/MK-8628 (oral)	NCT01713582 (December 2012)	I	Hematologic malignancies	Completed	Reported (60, 61)
	NCT02259114 (October 2014)	I	Solid tumors	Completed	Abstract (65)
	NCT02296476 (October 2014)	I	Glioblastoma	Terminated	Abstract (69)
	NCT02698176 (May 2016)	I	Solid tumors	Terminated	Not reported
CPI-0610 (oral)	NCT01949883 (September 2013)	I	Non-Hodgkin lymphomas	Ongoing/recruiting patients	Abstract (62)
	NCT02157636 (July 2014)	I	Multiple myeloma	Ongoing/recruiting patients	Not reported
	NCT02158858 (June 2014)	I	Myelodysplastic syndrome, leukemia	Ongoing/recruiting patients	Not reported
RO6870810/TEN-010 (subcutaneous injection)	NCT01987362 (October 2013)	I	Solid tumors	Ongoing/not recruiting patients	Abstract (66)
	NCT02308761 (November 2014)	I	Myelodysplastic syndrome, leukemia	Ongoing/recruiting patients	Not reported
	NCT03068351 (June 2017)	I	Multiple myeloma, single agent and in combination with daratumumab	Ongoing/recruiting patients	Not reported
	NCT03255096 (August 2017)	I	Lymphomas, in combination with venetoclax and rituximab	Ongoing/recruiting patients	Not reported

(continued)

Table 1. BET inhibitors in clinical trials, from ClinicalTrials.gov (https://clinicaltrials.gov/), last accessed on September 10, 2017 (*Continued*)

Drug (administration)	ClinicalTrials.gov # (start date)	Phase	Tumor type	Status	Results
BAY1238097 (oral)	NCT02369029 (February 2015)	I	Solid tumors, non-Hodgkin lymphomas	Terminated	Abstract (70)
GS-5829 (oral)	NCT02392611 (March 2015)	I	Solid tumors and lymphomas; expansion cohort in breast cancer in combination with exemestane or fulvestrant	Ongoing/not recruiting patients	Not reported
	NCT02607228 (December 2015)	I/II	Prostate cancer, single agent and in combination with enzalutamide	Ongoing/recruiting patients	Not reported
	NCT02983604 (January 2017)	I/II	Breast cancer, in combination with exemestane or fulvestarant	Ongoing/recruiting patients	Not reported
ABBV-075 (oral)	NCT02391480 (April 2015)	I	Solid tumors and hematologic malignancies; expansion cohorts in combination with venetoclax	Ongoing/recruiting patients	Not reported
FT-1101 (oral)	NCT02543879 (September 2015)	I	Hematologic malignancies	Ongoing/recruiting patients	Not reported
INCB054329 (oral)	NCT02431260 (May 2015)	I/II	Solid tumors, non-Hodgkin lymphomas, acute leukemia, chronic myeloid leukemia, multiple myeloma	Ongoing/not recruiting patients	Not reported
BMS-986158 (oral)	NCT02419417 (June 2015)	I/II	Solid tumors	Ongoing/recruiting patients	Not reported
BI 894999 (oral)	NCT02516553 (July 2015)	I	Solid tumors, non-Hodgkin lymphomas	Ongoing/not recruiting patients	Not reported
N-methyl pyrrolidone (oral)	NCT02468687 (August 2015)	I	Multiple myeloma	Ongoing/recruiting patients	Not reported
PLX51107 (oral)	NCT02683395 (March 2016)	I	Solid tumors, hematologic malignancies	Ongoing/recruiting patients	Not reported
GSK2820151 (oral)	NCT02630251 (April 2016)	I	Solid tumors	Ongoing/recruiting patients	Not reported
ZEN-3694 (oral)	NCT02705469 (April 2016)	I	Prostate cancer	Ongoing/recruiting patients	Not reported
	NCT02711956 (December 2016)	I	Prostate cancer, in combination with enzalutamide	Ongoing/not recruiting patients	Not reported
INCB057643 (oral)	CT02711137 (May 2016)	I/II	Solid tumors, hematologic malignancies	Ongoing/recruiting patients	Not reported
ODM-207 (oral)	NCT03035591 (December 2016)	I/II	Solid tumors	Ongoing/recruiting patients	Not reported

studies are only preliminary, some first signals of clinical activity have emerged and together with the adverse events observed may direct their further clinical development (Fig. 2). In the following sections, we have summarized information on the preliminary clinical activity of BET inhibitors and their toxicity profiles.

Leukemia and Lymphoma

The first published clinical results of a BET inhibitor derive from the thienotriazolodiazepine OTX015 (MK-8682). In preclinical experiments, OTX015 resulted in cell growth inhibition, cell-cycle arrest, and apoptosis in acute leukemia cell lines in which it also decreased the expression of BRD2,

BRD4, and MYC and increased the expression of the MYC-negative regulator HEXIM1 (59).

OTX015 was also evaluated in a large panel of cell lines derived from mature B-cell lymphoid malignancies, showing antiproliferative activity among all the different histologic subtypes. The activity of OTX015 in lymphoma cell lines is mainly cytostatic, with the exception of a subgroup of cell lines derived from non–germinal center B cell–like diffuse large B-cell lymphoma (DLBCL) bearing wild-type *TP53* and mutations in *MYD88*, *CD79B*, or *CARD11* in which it induces apoptosis (36). Both *in vitro* and *in vivo*, OTX015 inhibits NFκB/TLR/JAK/STAT signaling pathways and MYC- and E2F1-regulated genes (36).
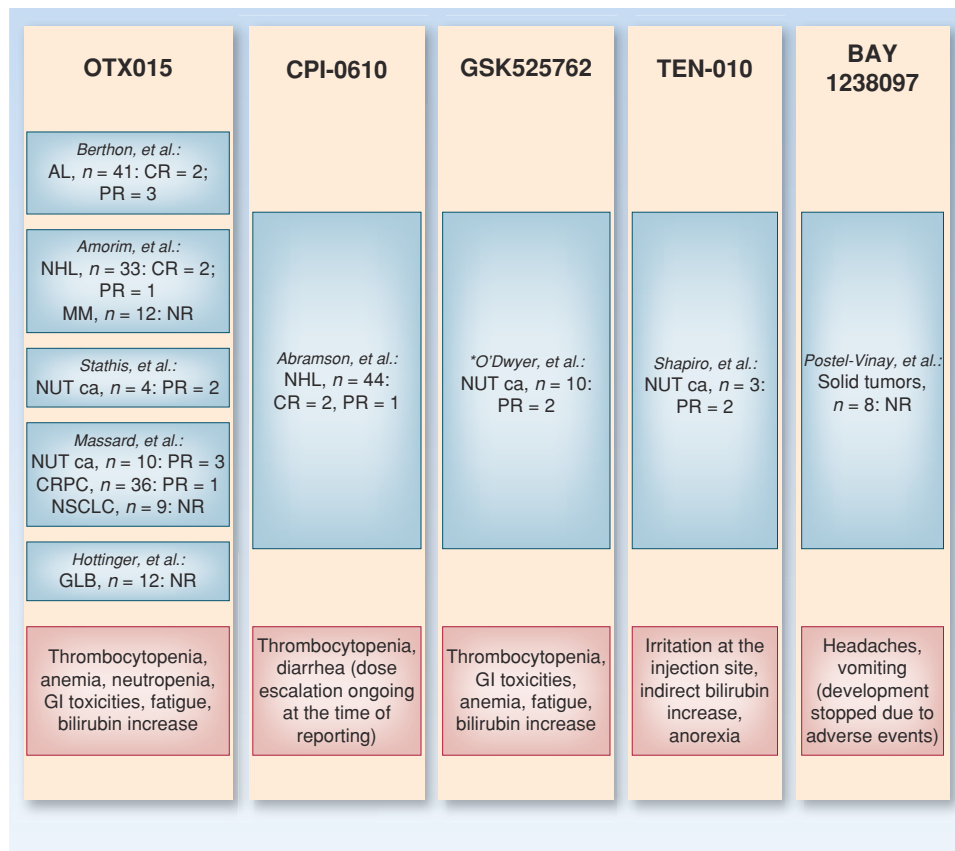
OTX015	CPI-0610	GSK525762	TEN-010	BAY 1238097
Berthon, et al.: AL, *n* = 41: CR = 2; PR = 3				
Amorim, et al.: NHL, *n* = 33: CR = 2; PR = 1 MM, *n* = 12: NR				
Stathis, et al.: NUT ca, *n* = 4: PR = 2	*Abramson, et al.:* NHL, *n* = 44: CR = 2, PR = 1	*O'Dwyer, et al.:* NUT ca, *n* = 10: PR = 2	*Shapiro, et al.:* NUT ca, *n* = 3: PR = 2	*Postel-Vinay, et al.:* Solid tumors, *n* = 8: NR
Massard, et al.: NUT ca, *n* = 10: PR = 3 CRPC, *n* = 36: PR = 1 NSCLC, *n* = 9: NR				
Hottinger, et al.: GLB, *n* = 12: NR				
Thrombocytopenia, anemia, neutropenia, GI toxicities, fatigue, bilirubin increase	Thrombocytopenia, diarrhea (dose escalation ongoing at the time of reporting)	Thrombocytopenia, GI toxicities, anemia, fatigue, bilirubin increase	Irritation at the injection site, indirect bilirubin increase, anorexia	Headaches, vomiting (development stopped due to adverse events)

Figure 2. Schematic representation of available clinical data including preliminary antitumor activity and main toxicities observed with BET inhibitors. AL, acute leukemia; NHL, non-Hodgkin lymphoma; MM, multiple myeloma; NUT ca, NUT carcinoma; GLB, glioblastoma; GI, gastrointestinal; n, number of patients included; CR, complete remission; PR, partial remission; NR, no response. *This study included 70 patients at the time of reporting, and preliminary activity was reported in 10 patients with NUT carcinoma (67). Cited references: Berthon, et al. (60); Amorim, et al. (61); Stathis, et al. (64); Massard, et al. (65); Hottinger, et al. (69); Abramson, et al. (62); O'Dwyer, et al. (67); Shapiro, et al. (66); Postel-Vinay, et al. (70).

Based on its preclinical activity, OTX015 was investigated in a phase I dose-finding study in two parallel cohorts of patients with advanced hematologic malignancies: one cohort of patients with acute leukemia and one cohort of patients with nonleukemic hematologic malignancies (including lymphoma and multiple myeloma). Doses from 10 to 160 mg daily in either continuous or different intermittent schedules were evaluated, establishing the recommended phase II dose at 80 mg once daily for 14 days every 21 days in both cohorts.

In the acute leukemia cohort, among 41 patients (36 with AML, 3 with acute lymphoblastic leukemia, 1 with acute undifferentiated leukemia, and 1 with refractory anemia with excess of blasts) previously failing a median of 2 systemic treatments, preliminary activity was observed in 5 patients: 2 (1 with acute leukemia treated at 40 mg once a day and 1 with refractory anemia with excess of blasts treated at 160 mg once a day) achieved complete remission lasting 5 and 3 months, respectively, and 1 with acute leukemia treated at 80 mg achieved a complete remission with incomplete recovery of platelets. In addition, 2 patients (1 with AML secondary to polycythemia vera treated at 10 mg and 1 with myelodysplastic syndrome treated at 80 mg) had partial blast clearance. No correlation was found between somatic mutations in 42 genes (including *NPM1, IDH2, FLT3, EV11*, and *MLL*) and response to OTX015 comparing 5 responders versus 28 nonresponders (60).

In the nonleukemic cohort, among 45 patients (33 with lymphoma and 12 with multiple myeloma) previously treated with a median of three systemic lines, 2 patients with DLBCL, both initially treated at 120 mg once a day, achieved complete remissions lasting 4.5 and 13.7 months, respectively, and another patient with DLBCL treated at 80 mg once a day achieved a partial remission lasting 6 months. Additionally, 6 patients (2 with DLBCL, 2 with follicular lymphoma, 1 with extranodal marginal zone lymphoma, and 1 with lymphoplasmacytic lymphoma) had tumor reductions not meeting the criteria for objective response. In a retrospective subgroup analysis, out of the 10 patients with non–germinal center B cell–like DLBCL, 4 (40%) had evidence of clinical activity versus 2 of 12 (17%) patients with germinal center B cell–like DLBCL. With regard to MYC protein expression, among 5 patients with MYC-positive DLBCL, only 1 responded to treatment. No activity was detected in any of the 12 patients with multiple myeloma (61).

Antitumor activity has also been reported with CPI-0610, a benzoisoxazoloazepine compound currently in evaluation in a phase I study in patients with relapsed or refractory

lymphomas. Preliminary results in 44 patients who received CPI-0610 orally once daily on days 1 to 14 in 21-day cycles at doses ranging from 6 to 230 mg have been reported (62). Two patients with DLBCL achieved a complete response (1 maintained after 7 cycles and 1 followed by allogeneic transplantation after 6 cycles), and 1 patient with follicular lymphoma achieved a partial response (lasting at least 6 cycles). Five patients experienced smaller decreases in tumor volume not meeting the criteria for objective response. Expression of the BET target gene *CCR1* was suppressed at the 170-mg once-daily and 230-mg dose levels.

The above-reported clinical results, albeit coming from a small number of patients, provide evidence that BET inhibitors used in tolerable doses can result in clinical activity in patients with acute leukemia and lymphoma, in particular in DLBCL. Results from the OTX015 phase I trial might suggest an association between the non–germinal center B cell–like phenotype and treatment response, in line with preclinical data reporting strong capacity of BET inhibitors to downregulate the NF-κB, TLR, and JAK/STAT3 signaling pathways (28, 36), crucial in this subtype of DLBCL (63). However, this finding will need confirmation in additional studies. On the other hand, no association was found between MYC expression and sensitivity to OTX015. Future studies should aim to identify molecularly defined subsets of patients with DLBCL that are most likely to benefit from BET inhibitors.

NUT Carcinoma

NUT carcinoma represents a disease prototype for the clinical testing of BET inhibitors due to the strong preclinical rationale, as reported above, and to the need for novel therapeutic approaches. Indeed, NUT carcinoma is one of the most lethal solid tumors, characterized by a very aggressive course, lack of benefit from chemotherapy or radiotherapy, and an overall survival of 6 to 9 months (26).

Our institution was one of the centers participating in the dose-escalation phase I study of OTX015 in patients with hematologic malignancies. Four patients were referred to our center with advanced, previously treated NUT carcinoma with confirmed BRD4–NUT fusions and received OTX015 on a compassionate basis (64). The schedule consisted of 80 mg once daily, administered orally in 3-week cycles, based on the dose that was already tested and declared safe in the phase I hematologic study (61). Among the 4 treated patients, 2 responded and 1 had a meaningful disease stabilization with a minor metabolic response (64). Responses were rapid with symptomatic relief (including a clinical response after 1 week of treatment in 1 of the patients presenting at treatment start with a bulky tumor involving the left maxillary and mandibular region) and were confirmed by PET-CT after two cycles of treatment. The duration of response was 13 cycles in 1 patient and 3 cycles in the second patient (64).

Following the phase I study in hematologic malignancies, OTX015 was subsequently evaluated in a phase I study in patients with selected solid tumors, including patients with NUT carcinoma. In a preliminary report of this study, among 10 patients with NUT carcinoma, 3 patients achieved a partial response (65).

At least two other BET inhibitors that are currently in clinical development have been evaluated in small numbers of

patients with NUT carcinoma. Similar to OTX015, evidence of clinical activity was observed. TEN-010, a BET inhibitor structurally related to JQ1, is under clinical evaluation in solid tumors, including NUT carcinoma, and hematologic malignancies. Preliminary data were reported for the 3 patients with NUT carcinoma treated with subcutaneous daily dosing of TEN-010 for 3 weeks in 4-week cycles. One patient received TEN-010 at 0.1 mg/kg and 2 received 0.45 mg/kg. Although the patient treated at the low dose had a rapid tumor progression, both patients treated at the higher dose had clinical responses, 1 with a 30% and 1 with a 50% tumor regression after 1 and 2 cycles of treatment, respectively. A symptomatic improvement was rapidly obtained in both patients. At the time of reporting of these results, 1 of the responding patients had experienced disease progression after 2 cycles of treatment and treatment of the second patient was ongoing in cycle 3 (66).

GSK525762 is another pan-BET inhibitor that is being evaluated in patients with hematologic malignancies and solid tumors (67). Preliminary results after the inclusion of 70 patients (including 17 patients with NUT carcinoma) showed good tolerability at the dose of 80 mg once daily, which was the dose selected for expansion cohorts. The most common adverse events of any grade included thrombocytopenia, gastrointestinal adverse events (nausea, vomiting, decreased appetite, diarrhea, and dysgeusia), anemia, and fatigue. At the time of reporting of these results, among 10 response-evaluable patients with NUT carcinoma, 2 patients achieved partial response and 4 had stable disease.

Results from this small number of patients provide clinical evidence of the activity of BET inhibition in NUT carcinoma and represent an important example of therapy with small molecules resulting in antitumor activity by targeting the causative oncoprotein.

Based on the available data, it is not possible to estimate what the clinical impact of BET inhibitors used as monotherapy could be in NUT carcinoma. Not all patients responded; in fact, only 30% of patients with NUT carcinoma responded in the phase I trial of OTX015 in solid tumors, and 20% in the phase I trial of GSK525762. On the other hand, among those patients who achieved a response and for which follow-up data were available, all patients relapsed during treatment. Genetic data from tumor biopsies before treatment start and at time of disease progression are available from only one of the first 4 patients treated with OTX015, but they did not detect any genetic alterations at the time of progression that could possibly explain the development of resistance to treatment (64). Future studies should aim to molecularly characterize patients with NUT carcinoma who are treated with BET inhibitors. In addition, although FISH confirmation of the chromosomal translocation is not necessary for diagnostic purposes (68), it should be implemented in clinical trials to assess whether the partner gene (*BRD4* vs. other genes) fused to *NUT* may predict response to BET inhibition. Finally, combination therapies may be necessary to overcome the resistance that can develop to BET inhibition.

Other Solid Tumors

The currently available clinical data in other solid tumors are very scant. Preliminary results of the phase I study of OTX015

in patients with NUT carcinoma, castration-resistant prostate cancer (CRPC), or *KRAS*-mutated or *ALK*-positive non–small cell lung cancer (NSCLC) showed evidence of clinical activity in NUT carcinoma as reported above and in CRPC. Among 46 patients treated (26 CRPC, 10 NUT carcinoma, 9 *KRAS*-mutated, and 1 *ALK*-positive NSCLC), 4 patients had a partial response (including the 3 patients with NUT carcinoma and 1 patient with CRPC). In addition, prolonged stable disease was observed in 5 patients with CRPC (4–8 months) and 2 patients with *KRAS*-mutated NSCLC (65).

On the other hand, no clinical activity was seen in a small phase IIa study in 12 patients with glioblastoma, and the trial was closed due to lack of clinical activity (69).

Adverse Events

Similar to the data reporting on their clinical activity, the adverse events profile of BET inhibitors must be better defined, because the results of most of the compounds currently in phase I trials are preliminary. The main toxicities seen with OTX015 in the phase I study in patients with hematologic malignancies were represented by reversible thrombocytopenia (which indeed required a schedule of administration of 2 weeks on/1 week off to permit platelet recovery), anemia, neutropenia, gastrointestinal symptoms (including nausea, diarrhea, and dysgeusia), fatigue, and bilirubin elevation. Overall, OTX015 was well tolerated, and the toxicities were reversible with treatment interruptions. The favorable safety profile of OTX015 was confirmed in the phase I trial in patients with solid tumors (65). Thrombocytopenia, fatigue, gastrointestinal symptoms, and hyperbilirubinemia are among side effects also reported in patients treated with other BET inhibitors (62, 66, 67), although the results of these trials are currently preliminary and reported only in abstract form. Additional results from the ongoing studies will add information on the safety of these compounds, and the impact that these adverse events could have in treatment compliance. On the other hand, the development of another BET inhibitor, BAY 1238097, was prematurely interrupted due to severe adverse events (mainly headaches) that occurred at doses below the predicted therapeutic dose (70).

Further side effects might be predicted based on preclinical data. Human BET proteins, mainly BRD4, interact with viral proteins and are involved in viral life cycles (18, 71–81). There is preclinical evidence that BET inhibitors activate DNA replication of human immunodeficiency virus (HIV; refs. 76, 77, 79), human papillomavirus (HPV) 16 (80), human herpes simplex virus 1 and 2 (HSV-1 and HSV-2; ref. 78), and hepatitis B virus (HBV; ref. 73). Although this can be therapeutically exploited to eliminate latent viral infections (76, 77, 82), it advises for a close monitoring of patients with cancer receiving BET inhibitors for reactivation of viral infections.

The complete lack of either BRD2 or BRD4 is lethal (12–15) and, in general, low BET protein level is associated with reduced cell growth (12, 13). Mice with reduced BRD4 levels present different reversible phenotypes with a decrease in the number of hematopoietic cells, skin hyperplasia with abnormal hair follicles, and disruption of the intestinal crypts with loss of the secretory cells and increased intestinal toxicity after exposure to radiation or doxorubicin (83). Mice with reduced levels of BRD2 show important neuronal defects

and obesity with hyperinsulinemia in the presence of a lowered blood glucose (13–15). Impaired long-term memory (84), reduced explorative motor activity, and heightened anxiety-like behavior in the open field (85) have been observed in mice exposed to the BET inhibitors JQ1 (84) and I-BET858 (85), further suggesting that neurologic symptoms might be expected. Finally, a tumor-suppressor role for BET proteins has also been reported in which their inhibition would result in a reduced immune surveillance (86) and reduced capacity of healthy cells to counteract the neoplastic transformation process (87). These observations suggest monitoring for second tumors in patients exposed to BET inhibitors.

Resistance

Mechanisms of resistance to BET inhibitors so far derive from preclinical models. Resistance does not appear to derive from somatic mutations or copy-number changes affecting BET bromodomain genes (42, 88). Increased WNT signaling with β-catenin–mediated MYC expression in AML (88, 89), activation of the Hedgehog pathway with GLI2-mediated MYC expression in pancreatic cancer (90), hyperphosphorylation of BRD4 that leads to a bromodomain-independent binding to MED1 in triple-negative breast cancer (42), kinome reprogramming in ovarian cancer (91), activation of the MAPK pathway in colorectal cancer (45), AMPK–ULK1-mediated autophagy (92) or MCL1 upregulation in AML (29), and RAS pathway activation with BCL2 upregulation in lymphoma (93) all represent possible mechanisms of resistance to BET inhibitors. The presence of concomitant *KRAS* and *LKB1* mutations in NSCLC (38, 46) and *PIK3CA* mutations in breast cancer (23) has been also associated with resistance to BET inhibitors. Mutations of the *SPOP* gene, coding for a ubiquitin ligase adaptor protein, are associated with high sensitivity to BET inhibition in endometrial cancer cell lines but to resistance in prostate cancer cell lines due to an increased or decreased, respectively, degradation of the BET proteins in cases bearing *SPOP* mutations (94).

Gene expression signatures associated with sensitivity to BET inhibitors have been identified in different tumor models, but they still need to be further validated in the clinical context (36, 39, 41).

FUTURE DIRECTIONS

The above-reported preliminary information on BET inhibitors in clinical trials provides evidence of their antitumor potential in a subset of patients with hematologic malignancies and in NUT carcinoma. Although results of ongoing trials are awaited and may add information on activity in other solid tumors, two areas of preclinical research are being actively pursued and may guide future development of BET inhibitors. Below we report the preclinical rationale for combination treatments and outline the current research aiming at developing a new generation of BET inhibitors.

Combinations

BET inhibitors have shown preclinical synergism with different classes of compounds and in almost all the different tumor types that have been investigated (Table 2). Synergism largely appears to be due to the ability of BET inhibitors to block protective feedback mechanisms that would lead to

Table 2. Combination partners that have shown synergism with BET inhibitors in preclinical tumor models

Classes	Second compound	Experimental disease model
Small molecules		
	ALK inhibitors	Lymphoma (31)
	BTK inhibitors	Lymphoma (28, 31, 35, 36, 100, 101, 114)
	CDK inhibitors	Lymphoma (100, 101), osteosarcoma (51)
	BCL2/MCL1 inhibitors	ALL (115), AML (29, 116), LC (117), lymphoma (99–101)
	EGFR/ERBB2 inhibitors	BC (97)
	FLT3 inhibitors	AML (118)
	Hedgehog inhibitors	Lymphoma (31)
	JAK inhibitors	AML (119)
	MEK/ERK inhibitors	Lymphoma (120), OC (91)
	mTOR inhibitors	BC (40), glioblastoma (121), lymphoma (28, 35, 36, 114), osteosarcoma (122)
	PARP inhibitors	BC (96), OC (96)
	PI3K inhibitors, pan or selective	BC (95), CC (95), lymphoma (28, 36, 102), glioblastoma (95), OC (90, 95)
	Proteasome inhibitors	MM (116, 123)
Antibodies		
	Anti-CD20 monoclonal antibodies	Lymphoma (36, 114, 124)
Immune modulators		
	Immunomodulatory drugs (IMiD)	Lymphoma (36, 125, 126), MM (45)
	Anti–PD-1 monoclonal antibodies	Lymphoma (30)
	Anti–4-1BB monoclonal antibodies	Lymphoma (30)
	Chimeric antigen receptor (CAR) T cells	ALL (105)
Epigenetic drugs		
	EZH2 inhibitors	Lymphoma (35, 127)
	HDAC inhibitors	AML (128), BC (129), LC (130), lymphoma (31, 36, 101, 114, 131), melanoma (132), neuroblastoma (133), PC (134)
	Azacytidine	AML (116)
	Decitabine	Lymphoma (36)
Chemotherapy		
	Temozolomide	Glioblastoma (121)
Hormone therapy		
	Antiandrogen	PrC (49)
	Estrogen receptor degrader	BC (135)

Abbreviations: ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; BC, breast cancer; CC, colorectal cancer; LC, lung cancer; MM, multiple myeloma; OC, ovarian cancer; PC, pancreatic cancer, PrC; prostate cancer.

the upregulation of additional kinases by a BRD-mediated mechanism (35, 95).

Several preclinical studies have explored BET inhibitors in combination with molecularly targeted agents in solid tumors and hematologic malignancies (Table 2). A benefit has been observed when combining BET inhibitors with PI3K inhibitors in breast, ovarian, and colorectal cancers (95), ERK inhibitors in ovarian cancer (91), PARP inhibitors in ovarian and breast cancers (96), and the ERBB2 inhibitor lapatinib in breast cancer (97). In lymphomas, synergistic activity has been observed in combinations with small molecules that have established single-agent clinical activity such as BTK, PI3K, or BCL2 inhibitors (28, 35, 36, 98–102). At least two clinical trials are currently testing BET inhibitors in combination with BCL2 inhibitors in patients with relapsed lymphoma (NCT02391480 and NCT03255096).

Interestingly, some kinase inhibitors, such as the PLK1 inhibitor BI-2536 or the JAK2/FLT3 inhibitor TG-101348, also inhibit BET proteins (103, 104). Considering the observed synergisms of combinations containing BET inhibitors and kinase inhibitors, the possibility of targeting both classes of proteins is under active investigation (103).

Table 3. BET degraders (PROTACs) with their components and mechanism of action

Compound	BET inhibitor component	Small-molecule component	E3 ubiquitin ligase complex	Reference
ARV-771	JQ1	VHL ligand	Von Hippel–Lindau-containing complex	(111)
ARV-825	OTX015	Thalidomide	Cereblon E3 ubiquitin ligase complex	(107)
AT1	JQ1	VHL ligand	Von Hippel–Lindau-containing complex	(136)
BETd-246	RX-37	Thalidomide	Cereblon E3 ubiquitin ligase complex	(113)
BETd-260/ZBC260	HJB97/Beti-211	Lenalidomide	Cereblon E3 ubiquitin ligase complex	(113, 137)
dBET1	JQ1	Thalidomide	Cereblon E3 ubiquitin ligase complex	(138)
dBET6	JQ1	Thalidomide	Cereblon E3 ubiquitin ligase complex	(4)
MZ1	JQ1	VHL ligand	Von Hippel–Lindau-containing complex	(139)

Due to the diffuse use of immune checkpoint modulators in solid tumors and in some hematologic cancers, it is important to highlight that BET inhibitors have shown synergism with this class of compounds in preclinical models (30, 105). BET inhibitors decrease BRD4 binding to the *CD274* locus with downregulation of PD-L1 expression on tumor cells and improvements of the response to anti–PD-1 or anti–4-1BB (30). BET inhibitors also increase the response to chimeric antigen receptor–transduced T cells via supporting the maintenance of CD8$^+$ T cells with a phenotype of central memory T cells or stem cell–like memory T cells (105). Finally, BET inhibitors downregulate ITK expression in T-cell lymphomas (31), and this, if confirmed in normal T cells, could favor the generation of Th$_1$ cells, IFNγ production, and increased antitumor immunity as observed with the BTK inhibitor ibrutinib that also inhibits ITK (106).

Finally, BET inhibitors have been tested in CRPC and tamoxifen-resistant breast cancer in combination with enzalutamide and fulvestrant, respectively, showing synergistic activity. At least five clinical trials (NCT02392611, NCT02964507, NCT02607228, NCT02983604, and NCT02711956) are currently evaluating combination therapies of BET inhibitors with hormone therapy in patients with prostate or breast cancer (Table 1).

Next Generation of Compounds

Different experimental models show that tumor cells resistant to BET inhibitors are still dependent on BET proteins (42, 88) and, in general, exposure to BET inhibitors results in downregulation of BET proteins that is reversible and often followed by an upregulation of the BET proteins themselves (36, 107). Thus, there are ongoing efforts to obtain stronger and more sustained suppression of the BET protein activity, which would lead to increased antitumor activity. Compounds such as "biBET (6)" (108), MT1 (109), and AZD5153

(31), which engage both bromodomains simultaneously in a bivalent mode, have shown promising *in vitro* results. Another extremely active field is the creation of BET degraders, chimeric compounds that merge a BET inhibitor that allows the binding to BET proteins, linked to an additional small molecule that mediates the binding to an E3 ubiquitin ligase complex, thus degrading the BET proteins via the proteasome. These compounds are based on the idea of the proteolysis targeting chimeras (PROTAC), first described in 2001 (110). Currently available BET degraders, which are still at the preclinical level, differ both in the use of the BET inhibitor component and in the exploited E3 ligase complex (Table 3).

BET degraders appear to have a different mechanism of action from BET inhibitors, due to the loss of both bromodomain-dependent and bromodomain-independent functions of the BET proteins and to a collapse of the core transcriptional machinery, with wider changes at the gene expression level (4, 100). Accordingly, degradation of BET proteins induced by BET degraders results in a higher cytotoxic effect than that achieved with BET inhibitors (4, 107, 111–113). ARV-825, a heterobifunctional PROTAC that exploits the E3 ubiquitin ligase cereblon and leads to rapid BRD4 degradation, induces increased apoptosis in Burkitt lymphoma cell lines in comparison to either JQ1 or OTX015, and a more effective suppression of MYC levels and downstream genes (107). ARV-771, a von Hippel–Landau (VHL) E3 ligase–based BET PROTAC, has superior *in vitro* and *in vivo* activity in CRPC in comparison to BET inhibitors and results in attenuation of androgen receptor transcript levels (111). BETd-246 and its further optimized analogue BETd-260, both using cereblon as E3 ubiquitin ligase, show potent *in vitro* and *in vivo* antitumor activity, superior to the parental BET inhibitor BETi-211, in triple-negative breast cancer models (113).

CONCLUSIONS

Seven years following the first description of the preclinical activity of JQ1 in models of NUT carcinoma, a tumor type driven by an oncogenic form of BRD4, several BET inhibitors have entered clinical evaluation, while many others are currently in preclinical development. Clinical activity has been observed in NUT carcinoma and in hematologic malignancies. Regarding their safety, with the exception of one compound whose development was stopped due to the emergence of adverse events, preliminary information from other BET inhibitors shows a favorable safety profile. Hematologic (mainly thrombocytopenia) and nonhematologic adverse events are reversible with treatment interruption but, alongside potential side effects foreseen based on experimental models, will need to be taken into consideration in the planning of future trials, especially if in combination with other agents. Additional data from ongoing clinical trials will be able to determine the impact of these adverse events in treatment compliance. Although final results of most of the ongoing studies are still awaited, current evidence supports further clinical development of BET inhibitors in hematologic malignancies and in solid tumors. Combination strategies alongside the development of new generations of compounds, not limited to targeting the bromodomains, will open new possibilities for future clinical development of BET inhibitors as anticancer agents.

Disclosure of Potential Conflicts of Interest

Acknowledgments

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