Gene Expression **2026** vol. 25(2) | e00067
DOI: 10.14218/GE.2025.00067

Mini Review

Inhibition of Bromodomain and Extra-Terminal Domain Proteins in Solid Tumors: Advances, Challenges, and Future Directions

Madhunika Agrawal[1] and Satyam Kumar Agrawal[2*]

[1]*Centre for Pharmaceutical Nanotechnology, Department of Pharmaceutics, National Institute of Pharmaceutical Education and Research, S.A.S. Nagar, Punjab, India;* [2]*Centre for in Vitro Studies and Translational Research, Chitkara College of Pharmacy, Chitkara University, Rajpura, Punjab, India*

Received: August 26, 2025 | **Revised:** March 11, 2026 | **Accepted:** March 24, 2026 | **Published online:** April 14, 2026

Abstract

The bromodomain and extra-terminal domain (BET) protein family, particularly BRD4, is critical for the control of oncogenic transcriptional programs in solid tumors. Although initial-generation BET inhibitors, such as JQ1, molibresib, and birabresib, have demonstrated preclinical efficacy in repressing MYC-dependent pathways, their clinical translation has been hampered by low monotherapy activity, pharmacokinetic heterogeneity, and dose-limiting toxicities. This review aims to update the mechanistic foundations, clinical trial results, and development of therapeutic approaches to BET inhibition in solid tumors, outlining its evolving role in the next generation of cancer treatment strategies. Various clinical trials in different phases have demonstrated heterogeneous responses among solid tumor types, with greater effects in NUT carcinoma and castration-resistant prostate cancer. Resistance mechanisms, including BRD4 isoform switching and compensatory signaling activation, emphasize the need for advanced and innovative BET-targeting modalities. BD2-selective BET inhibitors and proteolysis-targeting chimeras are likely to overcome these limitations by increasing target specificity and reducing systemic side effects. In addition, combination strategies, such as PARP inhibitors, AR antagonists, and immune checkpoint blockade, have synergistic potential to augment anticancer activity. In conclusion, this review provides a comprehensive overview of the advances, challenges, and future directions of BET bromodomain inhibition in solid tumors.

Introduction

The bromodomain and extra-terminal domain (BET) protein family (a key modulator of gene expression) regulates transcriptional programs that support both healthy cellular activities and cancerous ones. The BET family comprises four members, BRDT, BRD2, BRD3, and BRD4, which share a conserved domain design that includes an extra-terminal domain and two tandem N-terminal bromodomains (BD1 and BD2) (Fig. 1a). Bromodomains bind to acetylated histone tails and serve as acetyl-lysine recognition motifs that attract BET proteins to active chromatin locations.[1] BET bromodomains also recognize acetylated non-histone proteins, including transcription factors and co-activators, enabling BET proteins to integrate diverse chromatin and signaling inputs beyond classical histone–acetylation marks.[2]

BET proteins can act as scaffolding platforms, forming transcriptional complexes and facilitating RNA polymerase II elongation.[3] BRD4 has been exhaustively investigated and is often regarded as the "master regulator" within the BET family because of its unique capacity to remain associated with chromatin throughout the cell cycle, including mitosis. BRD4 binds to hyperacetylated chromatin regions, including promoters and super-enhancers, and to large clusters of enhancers that drive the robust expression of lineage-specific or oncogenic genes such as MYC, BCL2, and CCND1.[4] BRD4 enables RNA polymerase II phosphorylation and promotes the transcriptional elongation of key oncogenes by interacting with positive transcription elongation factor b (P-TEFb) and other co-activators (Fig. 1b).[5] This process is crucial in cancers with super-enhancer reprogramming, in which BRD4 amplifies oncogene expression far beyond physiological levels. Mechanistically, BRD4 functions as a scaffold that recruits and stabilizes the P-TEFb complex (CDK9–Cyclin T1), enabling phosphorylation of the RNA polymerase II C-terminal domain and release of paused

Keywords: BRD4 inhibition; Proteolysis-targeting chimera; PROTAC; Bromodomain and extra-terminal domain protein targeting; BET targeting; Oncogenic transcription; Solid tumors; Clinical trials.

***Correspondence to:** Satyam Kumar Agrawal, Centre for in Vitro Studies and Translational Research, Chitkara College of Pharmacy, Chitkara University, Rajpura, Punjab 140401, India. ORCID: https://orcid.org/0000-0001-8127-6380. Tel: +91-89-20139002, E-mail: satyamka@gmail.com; satyam.ka@chitkara.edu.in

How to cite this article: Agrawal M, Agrawal SK. Inhibition of Bromodomain and Extra-Terminal Domain Proteins in Solid Tumors: Advances, Challenges, and Future Directions. *Gene Expr* 2026;25(2):e00067. doi: 10.14218/GE.2025.00067.

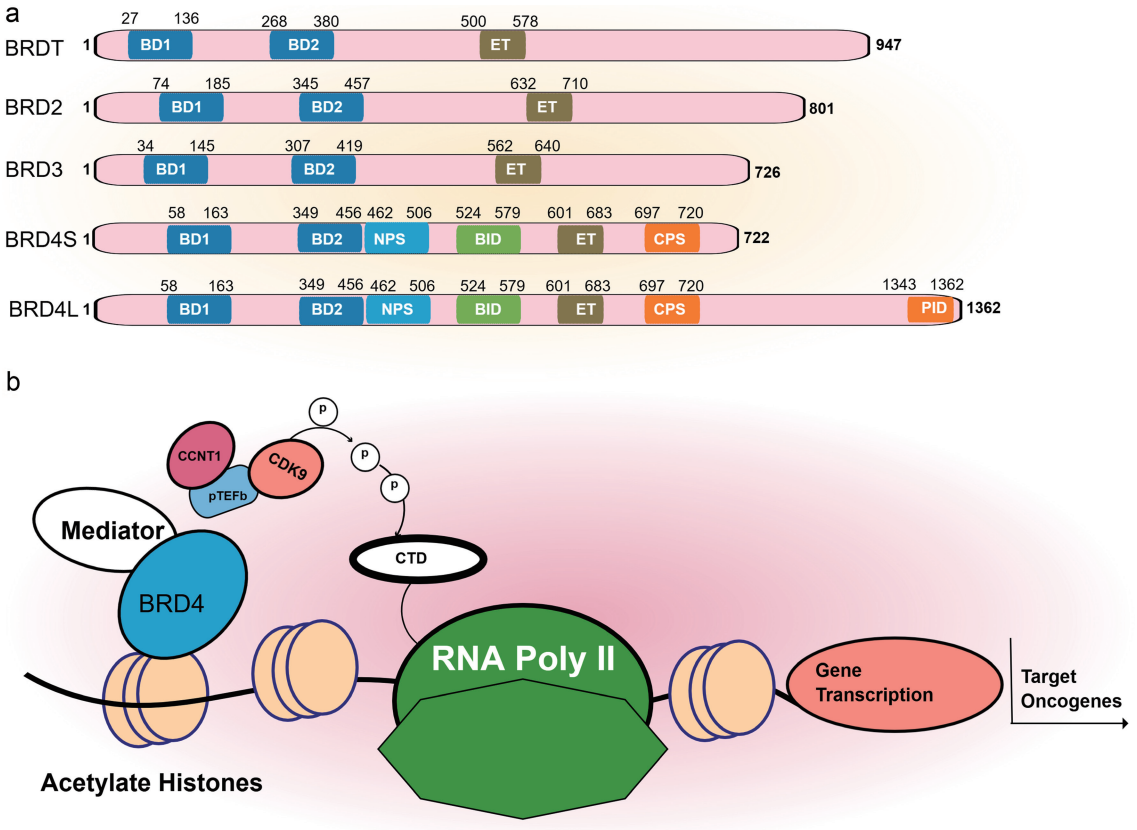

Fig. 1. BET protein family and BRD4 mechanism of action. (a) BET protein family members. BRDT, BRD2, BRD3, and BRD4 are the four mammalian members of this family. (b) BRD4 associates with acetylated histones and recruits P-TEFb to promote phosphorylation of RNA polymerase II, thereby enabling transcriptional elongation of oncogenic targets. BD1, bromodomain 1; BID, basic residue-enriched interaction domain; BRD2, bromodomain-containing protein 2; BRDT, bromodomain testis-specific protein; CCNT1, cyclin T1; CDK9, cyclin-dependent kinase 9; CPS, C-terminal phosphorylation sites; CTD, C-terminal domain; ET, extra-terminal domain; NPS, N-terminal phosphorylation sites; P-TEFb, positive transcription elongation factor b; PID, P-TEFb-interacting domain; RNA Pol II, RNA polymerase II.

polymerase into productive elongation.[5] In some reports, BRD4 has been suggested to display intrinsic kinase activity toward RNA polymerase II, CDK9, TAF7, and MYC, and a significant part of the PDID with phosphorylated NPS and BID (amino acids 351–359) has been coined as being responsible for its intrinsic kinase activity.[6] However, later structural and enzymology analyses question whether this activity is truly intrinsic to BRD4, suggesting rather that the phosphorylation effects arise through recruitment of P-TEFb and associated co-activators.[5,7,8]

BRD4 is expressed predominantly as two isoforms: the long isoform (BRD4-L), which contains an extended C-terminal domain that engages P-TEFb and supports transcriptional elongation, and the short isoform (BRD4-S), which lacks this domain and has been implicated in promoting chromatin compaction and therapy resistance. Similar isoform diversity is evident in BRD2 and BRD3, which contain alternative splicing variants that differentially influence enhancer selection and lineage-specific transcription.[9,10]

In triple-negative breast cancer (TNBC) and prostate cancer, dysregulation of BRD4 binding to the super-enhancer region directly upregulates MYC, thus triggering unchecked proliferation, metastasis, and therapeutic resistance. Thus, BRD4 acts as a critical node in tumor cell survival, proliferation, and therapeutic resistance owing to its key role in sustaining aberrant gene expression.[11] Although the basic mechanism of BET-mediated transcriptional activation is similar across malignancies, differences exist between hematologic cancers and solid tumors. Acute myeloid leukemia (AML) and certain other hematologic malignancies usually depend on well-defined transcriptional genes sustained by BET proteins such as BRD4. Thus, blocking BRD4 alone is often sufficient to downregulate these genes.[12,13] However, in tumors, complex transcriptional networks and signaling cross-talk exist that compensate for BET blockade, resulting in more modest responses to monotherapy. Moreover, the tumor microenvironment in solid cancers can indirectly modulate BET protein function, thereby impacting treatment outcomes.[14,15]

Several preclinical studies have demonstrated that disruption of BRD4 binding to chromatin leads to the downregulation of MYC and other oncogenic drivers, inducing tumor cell cycle arrest and apoptosis.[16,17] Small-molecule BET bromodomain inhibitors have been developed as a result of this molecular insight. The first of these, JQ1, showed that binding to BRD4 prevents it from binding to acetylated histones, and its pharmacological inhibition may limit tumor growth.[18] Although BET inhibitor (BETi) therapy has shown promising efficacy in preclinical studies, early clinical trials in solid tumors have revealed significant challenges. Dose-limiting toxicities (DLTs) and modest single-agent activities, largely due to intrinsic and acquired resistance mechanisms, are predominant.[19] One mechanism involves BRD4 isoform overexpression, specifi-

cally BRD4-L, which further increases resistance to chemotherapy.[10] Additionally, feedback activation of compensatory pathways, including PI3K/AKT or WNT signaling, can restore oncogene expression or promote survival despite BET blockade.[20,21] These resistance mechanisms highlight the need for next-generation inhibitors, degraders, and rational combination therapies to achieve consistent responses in solid tumors.

Recent research has focused on creating novel proteolysis-targeting chimeras (PROTACs) that cause BET protein degradation in addition to inhibition, as well as next-generation BETi with enhanced selectivity.[22] Furthermore, combination strategies, such as pairing BETi with PARP inhibitors (PARPi), androgen receptor (AR) antagonists, or immune checkpoint blockades, have renewed hope for overcoming resistance and improving therapeutic outcomes.[23–25] Therefore, the present review aims to summarize the molecular basis of BET protein function in solid tumors, along with the development of BET-targeted treatments and new approaches to fully utilize BET inhibition in clinical oncology.

First-generation BETi: Achievements and limitations

The development of first-generation BETi has marked a turning point in the pursuit of epigenetic cancer therapies. JQ1, discovered as a prototype small-molecule BET bromodomain inhibitor, demonstrated that pharmacologically displacing BRD4 from acetylated chromatin could effectively suppress oncogene expression, notably MYC.[26] Although JQ1 itself remains a research compound, its promising results in preclinical models have provided a foundation for clinical candidates. Trotabresib (CC90010/BMS986378), molibresib (GSK525762/I-BET762), and birabresib (OTX-015/MK8628) have emerged as early-generation BETi with improved drug-like properties, advancing into phase I and II clinical trials for both hematologic and solid tumors.[27–29] Preclinical studies on these compounds have demonstrated promising antitumor activity in solid tumors. JQ1 and molibresib were shown to disrupt super-enhancer function, downregulate MYC, induce cell cycle arrest, and promote apoptosis in tumor models highly dependent on BRD4-driven transcriptional programs.[30,31] In early clinical trials, molibresib showed modest responses in NUT midline carcinoma (NMC), where BRD4 fusions directly drive tumorigenesis, while birabresib demonstrated disease stabilization in subsets of solid tumors, such as TNBC and prostate cancer.[28,29] Despite promising preclinical results, first-generation BETi have faced significant challenges in clinical studies. One major challenge is suboptimal pharmacokinetics due to the short half-lives of many compounds, which require frequent dosing and reduce patient compliance. Furthermore, DLTs, including thrombocytopenia, gastrointestinal effects, and fatigue, restrict the maximum tolerated dose, thereby affecting the effective dose range.[32] Additionally, acquired resistance has emerged as a formidable barrier, driven by mechanisms such as BRD4 isoform switching, activation of bypass signaling pathways (e.g., PI3K/AKT), and adaptive rewiring of transcriptional networks. Thus, there is a need for next-generation BETi with improved selectivity and alternative modes of action to enhance efficacy and overcome resistance in solid tumors.

Advances in BETi design

Over the past few years, the field has expanded beyond classic pan-BETi to include selective bromodomain targeting, PROTACs, and novel dual-action molecules. Next-generation strategies focus on enhancing on-target efficacy, reducing systemic toxicity, and overcoming resistance mechanisms that restrict efficient responses in solid tumors. BD2-selective BETi represents a promising approach to improve selectivity and minimize side effects. Conventional BETi typically target both bromodomains (BD1 and BD2) in BRD2, BRD3, and BRD4. Emerging evidence suggests that BD1 and BD2 have distinct biological roles in different contexts. BD2 binds to acetylated histones to induce gene expression, whereas BD1 contributes to the attachment of proteins to chromatin to maintain basal gene expression. Hence, selective targeting of BD2 or BD1 may have a differential impact on disease activity.[33] GSK620 is one significant BD2-selective inhibitor and displays effective reduction in the expression of proinflammatory and profibrotic genes in liver biopsies taken from treated animals.[34] ABBV-744 is a prominent BD2-selective inhibitor in the clinical development phase, showing promising early results in prostate cancer xenografts and acute myeloid leukemia.[35] Preclinical data demonstrate that ABBV-744 preferentially displaces BRD4 from inflammatory and oncogenic transcriptional programs while sparing the BD1-related pathways that underlie thrombocytopenia, one of the main DLTs of pan-BETi.[36] In a preclinical study, it has been shown to suppress the growth of gastric cancer cells in a xenograft mouse model. However, its phase I clinical trial (NCT03360006) in relapsed/refractory (R/R) AML patients was terminated for non-drug-related reasons. INCB054329, a pan-BETi, as monotherapy, and INCB057643, a BD2-selective compound, as monotherapy or in combination with standard of care, were studied in two separate phase I/II trials (NCT02431260 & NCT02711137, respectively) for advanced solid tumors, where treatment-related thrombocytopenia leading to limited target inhibition was observed.[37] However, the studies were terminated owing to pharmacokinetic variability and safety issues. Growing interest in BD2 selectivity has further kindled drug discovery efforts to develop isoform-specific BET modulators that can balance efficiency and safety. Recent mechanistic studies also demonstrate that BD1 plays a dominant role in regulating stimulus-responsive transcription, including rapid activation of inflammatory and oncogenic genes, whereas BD2 contributes variably depending on chromatin context and cell type.[38,39] GSK778 and GSK789 are potent selective BD1 inhibitors and have demonstrated promising efficacy in both *in vitro* and animal oncological models and have a significant role in the downregulation of IL-1β-stimulated inducible nitric oxide synthase expression.[39–41] Beyond selective inhibition, an exciting frontier in BET targeting involves PROTACs, bifunctional molecules designed to hijack the cell's ubiquitin-proteasome system for targeted protein degradation (Fig. 2a). Instead of merely blocking bromodomain activity, as in the case of inhibition (Fig. 2b), PROTACs induce the complete removal of BET proteins from the cell, potentially offering a more profound and sustained suppression of oncogenic transcription. Among the leading BET-targeting PROTACs, ARV-771 and ARV-825 have demonstrated potent BRD4 degradation in preclinical models of solid tumors such as prostate cancer and TNBC.[42,43] These degraders link a BET ligand to an E3 ligase-recruiting moiety, such as a von Hippel–Lindau protein ligand or Cereblon ligand, forming a ternary complex that tags BRD4 for proteasomal destruction.[44] By achieving near-complete depletion of BRD4, PROTACs can circumvent resistance mechanisms linked to BRD4 isoform switching and residual bromodomain activity.

MZ1, a prototypical BET PROTAC developed as an academic tool compound, further validated this concept by showing that targeted degradation yields stronger and longer-lasting transcriptional suppression than conventional inhibitors.[45] Preclinical studies have indicated that BET degraders may display distinct phar-

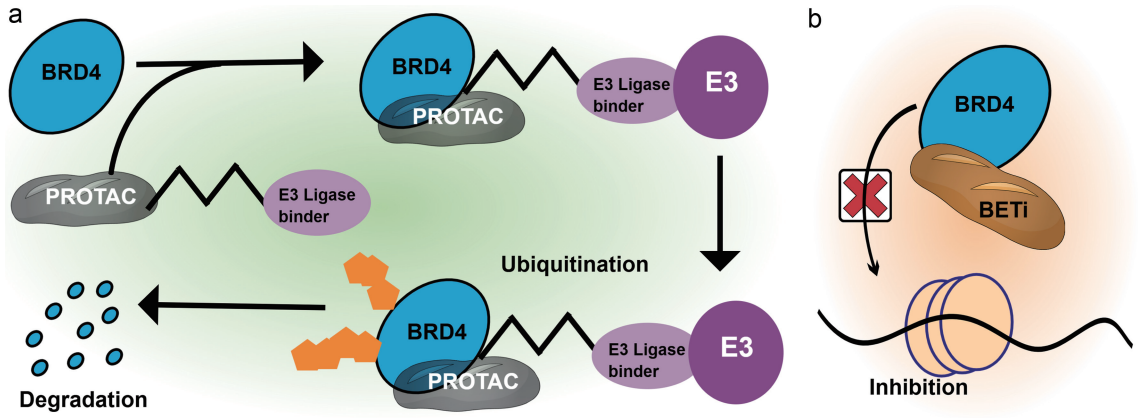

Fig. 2. BET inhibition and BRD4 degradation. (a) Schematic representation of PROTAC-mediated BRD4 degradation. The PROTAC molecule simultaneously engages BRD4 and an E3 ubiquitin ligase, resulting in BRD4 ubiquitination and subsequent proteasomal degradation. (b) BET inhibitors (BETi) competitively prevent BRD4 from binding to acetylated chromatin, leading to functional inhibition without protein degradation. BRD4, bromodomain-containing protein 4.

macodynamic and toxicity profiles. As they do not depend on the continuous high-level presence of bromodomains, degraders may also allow exploration of intermittent dosing schedules that reduce hematologic toxicity.[46] However, making this approach tangible for patients will require careful optimization of linker design, E3 ligase selection, and degradation efficiency to avoid off-target effects. In addition to BD2 selectivity and targeted degradation, other emerging BET modalities have sought to fine-tune the pharmacological profile of BET inhibition. Dual BETi, which simultaneously target additional oncogenic pathways, are under development to enhance synergistic antitumor effects. For example, dual BET/kinase inhibitors and BET/HDAC inhibitors are being explored to exploit synthetic lethality and prevent compensatory pathway activation.[47,48] Likewise, bivalent ligands (molecules designed to simultaneously engage both bromodomains within a BET protein) can increase binding affinity and residence time, potentially improving potency at lower doses.[49] AZD5153 is a bivalent BET/BRD4 bromodomain inhibitor that binds to both BD1 and BD2 and has shown preclinical activity against various solid tumors. It is in the clinical development phase.[50] In a first-in-human phase I study, AZD5153, alone or with olaparib, was given to patients with R/R solid tumors. Toxicities observed included fatigue, hematologic adverse events (AEs), and gastrointestinal AEs. Successful peripheral target interaction was observed.[51] MT-1 is another bivalent ligand, significantly potent against prostate cancer cells and mouse xenografts.[52] Additionally, BET bromodomain-mediated acetylated internucleosome multivalent scaffolding may maintain cellular chromatin interactions in active genetic regions.[53] Another notable area of innovation is the development of BETi that modulate phase separation, a recently acknowledged mechanism through which BRD4 organizes transcriptional condensates at super-enhancers.[54] Disrupting BRD4-driven phase separation may dismantle transcriptional hubs that sustain high-level oncogene expression, providing an additional angle to combat tumors that remain dependent on BRD4 even after conventional bromodomain blockade.[55]

Combination therapeutic strategies

Although there is complete remission in both NMC and non-NMC cancer with BETi monotherapy, these remissions are often short-lived, and DLTs can be observed in patients. Further, primary as well as acquired resistance may emerge. Therefore, the combination of BETi with other traditional and targeted therapies can provide meaningful clinical benefit. Emerging data from preclinical studies reveal that BETi have better activity when used in combination therapy.[19] The rationale for combination approaches also stems from the unique position of BET proteins such as BRD4 as central nodes within complex transcriptional and signaling networks. When BET activity is arrested, tumor cells can activate other mechanisms, such as the PI3K/AKT, WNT, or DNA damage response pathways, which restore oncogene expression or support survival. Combining BETi with agents that target these compensatory pathways can deepen antitumor effects and potentially delay resistance. One of the most promising avenues is the combination of BET and PARPi.[56] BET inhibition causes the downregulation of DNA repair genes and dysregulation of homologous recombination repair, thereby sensitizing tumor cells to DNA damage. In TNBC and ovarian cancer models, combining BETi, such as birabresib or JQ1, with PARPi, such as olaparib, results in enhanced DNA damage accumulation and tumor size reduction.[57] Several early-phase trials are now investigating this combination in patients, aiming to expand the benefit of PARP inhibition beyond traditional indications.[58] ZEN-3694 (ZEN-003694/EN-003694), along with talazoparib, has displayed anticancer properties in pretreated metastatic TNBC without BRCA1/2 mutations.[59] Further, BETi (JQ1 or I-BET762) were evaluated in combination with PARPi (olaparib or veliparib) in CCA cell lines, with enhanced activity.[56]

Another notable tactic has been BETi in combination with AR antagonists, particularly against castration-resistant prostate cancer.[60,61] Emerging evidence also supports improved activity with the combination of BETi and immune checkpoint blockade.[62] To evaluate the efficacy of BETi (e.g., JQ1) and the checkpoint inhibitor ipilimumab, a mathematical model was prepared, and the two drugs are positively correlated in reducing tumor volume.[63] Further, an enhanced effect of the combined administration of TW9, an adduct of the BETi (+)-JQ1 and the class I HDAC inhibitor CI-994, was observed in inhibiting the proliferation of PDAC cells compared with treatment alone.[64] BETi MS436 and HDAC inhibitor CI-944 scaffolds were merged with a class I HDAC-selective benzamide moiety, which resulted in promising biological activities in PDAC and NMC cells.[65] Likewise, dinaciclib, a kinase inhibitor, and AZD5153, a BETi, together decreased tumor size and increased tumor lymphocyte infiltration *in vivo* and can be effective against MYCN-amplified and TERT-overexpressing neuro-

blastoma tumors.[66] In a study, the combination of RO6870810 and atezolizumab was given to patients. Although target engagement was confirmed by established BETi pharmacodynamic markers in both blood and tumor samples, the study was withdrawn prematurely due to prominent immune-related adverse effects.[25]

BETi in clinical trials for solid tumors

Therapeutic exploration of BET bromodomain inhibitors has steadily advanced from preclinical models to clinical testing in the past decade. Several BETi, alone or in combination, have entered phase I and II trials targeting a range of solid tumors, with different levels of success and unique challenges that have been shaping ongoing drug development (Table 1). In the phase I study with TEN-010 in patients with NUT carcinoma and other solid tumors (NCT01987362), safety, favorable pharmacokinetics, target interaction, and preliminary single-agent activity were established, validating proof of principle for BET inhibition in MYC-driven cancers. A study was conducted on the NUT carcinoma cohort (phase I, NCT01587703) with molibresib. Several patients with NUT carcinoma achieved partial responses or durable stable disease, confirming BET dependency in fusion-positive tumors. Thrombocytopenia was the dominant DLT, so an intermittent dosing pattern was applied that prevented sustained BET inhibition. Similarly, in a solid tumor expansion (phase I, NCT02259114) study, birabresib produced partial responses in a subset of NUT carcinoma patients and occasional disease stabilization in selected solid tumors, including prostate cancer. Future studies of birabresib must consider intermittent scheduling to possibly mitigate the toxicities of chronic dosing. A combination study with ZEN-3694 and enzalutamide in metastatic castration-resistant prostate cancer (phase Ib/II, NCT02711956) showed improved radiographic progression-free survival in patients resistant to AR-targeted therapy. In the same trial, early-phase TNBC combination studies (ZEN-003694 with PARPi or chemotherapy) demonstrated manageable safety and signs of disease stabilization in heavily pretreated patients. These trials highlighted combination potential but also underscored the low activity of single-agent BET inhibition in TNBC.

Future perspective and limitations

The potential of BET inhibition in solid tumors lies in overcoming the current limitations through improved drug design and strategic combinations. The creation of BD2-selective inhibitors and BET degraders will be essential to maximize therapeutic benefit while minimizing systemic toxicity. Efforts must be focused on biomarker-stratified patient selection and finding genetic or epigenetic markers, such as MYC amplification or BRD4 dependency, to inform therapy. The combination of BETi shows promising synergy and can potentially overcome resistance. Hence, the rational design of combination therapies, guided by mechanistic insights, is fundamentally important. In addition, intermittent administration and improved formulations will be able to improve tolerability. Their upfront use is still experimental, except in rare cancers like NUT carcinoma, where the tumor strongly depends on BET proteins. Hence, ongoing attention to rare but responsive tumor types, such as NUT carcinoma, could further define its clinical use and facilitate regulatory advancement.

Conclusions

The translational paradigm of BET bromodomain inhibitors in solid

Table 1. Clinical trials for BET inhibitors in solid tumors

Drug name	Solid tumor indications	Trial phase	NCT number/status/duration	Key notes
I. BET monotherapy & domain selective agents				
Molibresib (BETi)	NUT carcinoma, TNBC, PC, LC, CRC	Phase I/II, open-label, dose escalation, interventional	NCT01587703/C/2012-19	Observations: Partial responses in NUT carcinoma, CRPC; thrombocytopenia, nausea, decreased appetite, dose reduction & interruptions
Birabresib (BETi)	NUT, TNBC, PDAC, CRPC	Phase Ib	NCT02259114/C/2014-17	Observations: RP2D - 80 mg (OD with continuous dosing) intermittent scheduling to possibly mitigate the toxicities of chronic dosing
Birabresib (BETi)	Recurrent glioblastoma	Phase IIa	NCT02296476/T/2014-15 (lack of clinical activity)	Primary endpoint: PFS
Birabresib (BETi)	NMC, TNBC, NSCLC, CRPC	Phase Ib, dose exploration	NCT02698176/T/2016-17 (limited efficacy)	Primary endpoint: DLT
Trotabresib (BETi)	Advanced solid tumors	Phase I, 2-Part, open-label	NCT05678283/W/2023-24 (business objectives changed)	Primary endpoint: Cmax, Tmax, AUC[0-T], total radioactivity, cumulative elimination of radioactivity

(continued)

Table 1. *(continued)*

Drug name	Solid tumor indications	Trial phase	NCT number/status/duration	Key notes
Trotabresib (BETi)	Advanced solid tumors	Phase Ia, open-label, dose escalation & expansion	NCT03220347/T/2017-24 (business objectives changed)	Primary endpoint: AE, MTD, DLT
ZEN-3694 (BETi)	mCRPC	Phase I	NCT02705469/C/2016-17	Primary endpoint: Safety and tolerability
ZEN-3694 (BETi)	Advanced SCLC with mutated NSD3 gene	Phase II, open-label, single arm	NCT05607108/R/2022-26	Primary endpoint: Efficacy of ZEN003694
INCB054329 (BETi)	Solid tumors	Phase I/II, open-label, dose-escalation	NCT02431260/T/2015-18 (PK variability)	Variable PK, thrombocytopenia
Trotabresib (BETi)	Pediatric solid tumors	Phase I	NCT03936465/C/2019-24	Primary endpoint: DLT, AEs
		II. BET inhibitors + DNA-damage response (PARP) combinations		
ZEN-3694 (BETi) + talazoparib (PARPi)	Recurrent ovarian, Fallopian tube or Primary peritoneal Carcinoma	Phase I, open-label	NCT05071937/R/2023-33	Primary endpoint: Safety and efficacy of the combination
ZEN-3694 (BETi) + talazoparib (PARPi)	TNBC	Phase IIb, open-label, non-randomized	NCT03901469/T/2019-24 (based on results from an interim futility analysis)	Primary endpoint: Safety, tolerability, ORR
ZEN-3694 (BETi) + niraparib (PARPi)	Metastatic or Recurrent Solid Tumors	Phase I, open-label	NCT06161493/W/2024-29 (investigator discretion)	Primary endpoint: TRAEs, SAE, MTD/RP2D
ZEN-3694 (BETi) + talazoparib (PARPi)	Advanced/Unresectable/ Metastatic Malignant Solid Neoplasm	Phase II	NCT05327010/R/2022-26	Primary endpoint: ORR
NUV-868 (BETi) + olaparib (PARPi)/ enzalutamide (ARi)	BC, BT	Phase I/II, open-label, dose escalation & expansion	NCT05252390/T/2022-24 (sponsor achieved its objectives)	Primary endpoint: DLT, PK, ORR, CRR, rPFS
		III. BET inhibitors + AR-targeted therapies		
ZEN-3694 (BETi) + enzalutamide (ARi)	mCRPC	Phase Ib/IIa	NCT02711956/C/2016-19	Observations: Acceptable tolerability & potential efficacy
ZEN-3694 (BETi) + testosterone followed by ZEN-3694 (BETi) + enzalutamide (ARi)	PC	Phase II	NCT06922318/ NY/R/2025-31	Primary endpoint: Combined suppression of MYC
ZEN-3694 (BETi) + enzalutamide (ARi)	mCRPC	Phase IIb, open-label, randomized	NCT04986423/R/2021-26	Primary endpoints: Time from date of randomization to the date of first disease radiographic progression/death
Molibresib (BETi) + enzalutamide (ARi) + abiraterone + prednisone	CRPC	Phase Ib, open-label, dose escalation & expansion	NCT03150056/T/2017-21 (meeting protocol defined futility)	Primary endpoint: AE, SAE, CR, DCR

(continued)

Table 1. *(continued)*

Drug name	Solid tumor indications	Trial phase	NCT number/status/duration	Key notes
ZEN-3694 (BETi) + enzalutamide (ARi) + pembrolizumab (PD-1i)	mCRPC	Phase II	NCT04471974/R/2021-28	Primary endpoint: CRR, ORR, PFS
IV. BET inhibitors + immune checkpoint & programmed death ligand inhibitors				
BMS-986158 (BETi) + nivolumab (ICi)	Advanced solid tumors	Phase I/IIA	NCT02419417/C/2015-21	Primary endpoint: number of participants experiencing AEs, abnormal hepatic test values
ZEN-3694 (BETi) + nivolumab (PD-1i) +/− ipilimumab (ICi)	R/R platinum resistant OC, R/ malignant solid neoplasm	Phase I/IB	NCT04840589/R/2022-26	Primary endpoint: safety/tolerability, RP2D
(BETi) ZEN-3694 + (PD-1i) (pembrolizumab), to standard chemotherapy (Nab-paclitaxel) treatment	Advanced TNBC	Phase Ib	NCT05422794/R/2023-27	Primary endpoint: MTD, RP2D
(BETi) INCB057643 + (PD-1i) pembrolizumab + (DO1i) epacadostat	Solid tumors, advanced solid tumors & previously treated stage IIIB/IV NSCLC & stage IV microsatellite-stable colorectal cancer	Phase I/II, open-label	NCT02959437/T/2017-20 (by sponsor)	Primary endpoint: AE, ORR
V. BET inhibitors + targeted pathway agents (MEK/EGFR/CDK/HDAC etc.)				
(BETi) ZEN-3694 + (HDACi) entinostat	Advanced + refractory solid tumors & lymphomas	Phase I/II	NCT05053971/R/2022-26	Primary endpoint: MTD, ORR
(BETi) molibresib besylate (GSK525762C) + (HDACi) entinostat	Advanced malignant solid neoplasm	Phase I	NCT03925428/W/2020 (protocol moved to disapproved)	Primary endpoint: MTD, ORR, PFS, safety profile of combination
(BETi) ZEN-3694 + (MEKi) binimetinib	Advanced/metastatic or unresectable solid tumors with RAS alterations & TNBC	Phase I	NCT05111561/R/2022-27	Primary endpoint: MTD, RP2D
(BETi) molibresib + (MEKi) trametinib	Solid tumor	Phase I/II, open-label, dose escalation	NCT03266159/W/2017-20 (before active to fully evaluate impact of changing practice) in target population	Primary endpoint: AE, SAE, DLT, ORR, CR, PR
(BETi) ZEN-3694 + (Ki) abemaciclib	Metastatic/unresectable NUT carcinoma, BC & other solid tumors	Phase I	NCT05372640/R/2023-26	Primary endpoint: MTD, RP2D, TTR, DOR, CRR

(continued)

Table 1. *(continued)*

Drug name	Solid tumor indications	Trial phase	NCT number/status/duration	Key notes
(BETi) ZEN-3694 + (ATRi) M1774	Recurrent ovarian	Phase Ib	NCT05950464/R/2023-26	Primary endpoint: MTD, DLTs
(BETi) molibresib + (ERi) fulvestrant	(HR+)/(HER2-) advanced or metastatic BC	Phase I/II	NCT02964507/T/2019-21 (meeting protocol defined futility)	Primary endpoint: AE, SAE, DLT, ORR, CR
(BETi) EP31670 + CBP/p300 i	Targeted solid tumor	Phase I	NCT05488548/R/2022-25	Primary endpoint: MTD, DLT, RP2D
(BETi) ZEN-3694 + (EGFRi) cetuximab + encorafenib	CRC	Phase I	NCT06102902/R/2024-27	Primary endpoint: RP2D, MTD
VI. BET inhibitors + chemotherapy/cytotoxic agents/multi-agent SOC				
(BETi) ZEN-3694 + etoposide & cisplatin	NUT carcinoma	Phase I/II	NCT05019716/R/2022-26	Primary endpoint: RP2D, MTD, ORR
(BETi) molibresib + etoposide & cisplatin	NUT carcinoma	Phase I/II, open-label, dose escalation	NCT04116359/W/2020 (Protocol moved to disapproved)	Primary endpoint: MTD, RP2D
(BETi) INCB057643 + standard of care drugs gemcitabine, paclitaxel, rucaparib, abiraterone, Ruxolitinib, azacitidine	Solid tumors	Phase I/II, open-label, dose-escalation/expansion	NCT02711137/T/2016-19 (safety issues)	Observations: exposure-dependent thrombocytopenia with both drugs limiting the target inhibition
(BETi) ZEN-3694 + capecitabine	Metastatic/unresectable solid tumors	Phase I	NCT05803382/R/2023-26	Primary endpoint: MTD, RP2D
(BETi) trotabresib (trotabresib) + vinorelbine + radiation therapy	HER2+ BC with CNS leptomeningeal metastasis	Phase I/Ib	NCT06137651/W/2023-24 (by sponsor)	Primary endpoint: DLT, AE

Data for the table were collated from database searches of the NCI clinical trials database (clinicaltrials.gov), where C: completed, R: recruiting, W: withdrawn, T: terminated, NYR: not yet recruiting. AE, adverse event; ARi, androgen receptor inhibitor; ATRi, ataxia telangiectasia and Rad3-related inhibitor; AUC, area under the plasma drug concentration–time curve; BC, breast cancer; BT, brain tumor; Cmax, maximum drug concentration; CNS, central nervous system; CR, complete response; CRC, colorectal cancer; CRPC, castration-resistant prostate cancer; CRR, composite response rate; DCR, disease control rate; DLT, dose-limiting toxicity; DO1i, indoleamine 2,3-dioxygenase 1 inhibitor; DOR, duration of response; DRR, durable response rate; EGFRi, epidermal growth factor receptor inhibitor; HR+, hormone receptor positive; ICi, immune checkpoint inhibitor; mCRPC, metastatic castration-resistant prostate cancer; MTD, maximum tolerated dose; TNBC, triple-negative breast cancer; NMC, NUT midline carcinoma; NSCLC, non-small cell lung cancer; ORR, objective response rate; PARPi, poly (ADP-ribose) polymerase inhibitor; PC, prostate cancer; PD-1i, programmed cell death protein 1 inhibitor; PDAC, pancreatic ductal adenocarcinoma; PFS, progression-free survival; PK, pharmacokinetics; rPFS, radiographic progression-free survival; SAEs, serious adverse events; SCLC, small cell lung cancer; SOC, standard of care; Tmax, time to maximum observed drug concentration; TRAEs, treatment-related adverse events; TTR, time to response; ULN, upper limit of normal.

DOI: 10.14218/GE.2025.00067 | Volume 25 Issue 2, April 2026

tumors is a promising yet challenging path. Despite the clear mechanistic rationale and strong preclinical efficacy, first-generation BETi have demonstrated limited clinical success in monotherapy settings, probably because of modest activity, resistance development, and DLTs, particularly thrombocytopenia. Although combination approaches have shown encouraging safety profiles and early signs of synergism, several trials have also been withdrawn or terminated due to a lack of efficacy, toxicity, or sponsor-related decisions, pointing to problems in translating preclinical potential to clinical benefit. This signals that the field is still in a developmental and optimization phase rather than near regulatory approval. Therefore, it is equally crucial to design combination therapies based on mechanistic understanding rather than relying solely on empirical escalation.

Acknowledgments

None.

Funding

None.

Conflict of interest

The authors declare that there are no conflicts of interest.

Author contributions

Conceptualization (MA, SKA), writing–original draft preparation (MA), writing–reviewing and editing (MA, SKA). Both authors have approved the final version of the manuscript for publication.

References

[1] Morgado-Pascual JL, Rayego-Mateos S, Tejedor L, Suarez-Alvarez B, Ruiz-Ortega M. Bromodomain and Extraterminal Proteins as Novel Epigenetic Targets for Renal Diseases. Front Pharmacol 2019; 10:1315. doi:10.3389/fphar.2019.01315, PMID:31780938.

[2] Hajmirza A, Emadali A, Gauthier A, Casasnovas O, Gressin R, Callanan MB. BET Family Protein BRD4: An Emerging Actor in NFκB Signaling in Inflammation and Cancer. Biomedicines 2018;6(1):16. doi:10.3390/biomedicines6010016, PMID:29415456.

[3] Cheung KL, Kim C, Zhou MM. The Functions of BET Proteins in Gene Transcription of Biology and Diseases. Front Mol Biosci 2021;8:728777. doi:10.3389/fmolb.2021.728777, PMID:34540900.

[4] Qian H, Zhu M, Tan X, Zhang Y, Liu X, Yang L. Super-enhancers and the super-enhancer reader BRD4: tumorigenic factors and therapeutic targets. Cell Death Discov 2023;9:470. doi:10.1038/s41420-023-01775-6.

[5] Donati B, Lorenzini E, Ciarrocchi A. BRD4 and Cancer: going beyond transcriptional regulation. Mol Cancer 2018;17(1):164. doi:10.1186/s12943-018-0915-9, PMID:30466442.

[6] Weissman JD, Singh AK, Devaiah BN, Schuck P, LaRue RC, Singer DS. The intrinsic kinase activity of BRD4 spans its BD2-B-BID domains. J Biol Chem 2021;297(5):101326. doi:10.1016/j.jbc.2021.101326, PMID:34688663.

[7] Itzen F, Greifenberg AK, Bösken CA, Geyer M. Brd4 activates P-TEFb for RNA polymerase II CTD phosphorylation. Nucleic Acids Res 2014;42(12):7577–7590. doi:10.1093/nar/gku449, PMID:24860166.

[8] Rahman S, Sowa ME, Ottinger M, Smith JA, Shi Y, Harper JW, Howley PM. The Brd4 extraterminal domain confers transcription activation independent of pTEFb by recruiting multiple proteins, including NSD3. Mol Cell Biol 2011;31(13):2641–2652. doi:10.1128/MCB.01341-10, PMID:21555454.

[9] Werner MT, Wang H, Hamagami N, Hsu SC, Yano JA, Stonestrom AJ, *et al*. Comparative structure-function analysis of bromodomain and extraterminal motif (BET) proteins in a gene-complementation system. J Biol Chem 2020;295(7):1898–1914. doi:10.1074/jbc.RA119.010679, PMID:31792058.

[10] Drumond-Bock AL, Wang L, Wang L, Cybula M, Rostworowska M, Kinter M, *et al*. Increased expression of BRD4 isoforms long (BRD4-L) and short (BRD4-S) promotes chemotherapy resistance in high-grade serous ovarian carcinoma. Genes Cancer 2023;14:56–76. doi:10.18632/genesandcancer.233, PMID:37705995.

[11] Yongprayoon V, Wattanakul N, Khomate W, Apithanangsiri N, Kasitipradit T, Nantajit D, *et al*. Targeting BRD4: Potential therapeutic strategy for head and neck squamous cell carcinoma (Review). Oncol Rep 2024;51(6):74. doi:10.3892/or.2024.8733, PMID:38606512.

[12] Ma T, Chen Y, Yi ZG, Li YH, Bai J, Li LJ, *et al*. BET in hematologic tumors: Immunity, pathogenesis, clinical trials and drug combinations. Genes Dis 2023;10(6):2306–2319. doi:10.1016/j.gendis.2022.03.004, PMID:37554207.

[13] Bauer K, Hauswirth A, Gleixner KV, Greiner G, Thaler J, Bettelheim P, *et al*. BRD4 degraders may effectively counteract therapeutic resistance of leukemic stem cells in AML and ALL. Am J Hematol 2024;99(9):1721–1731. doi:10.1002/ajh.27385, PMID:38822666.

[14] Deng C, Ma J, Liu Y, Tong X, Wang L, Dong J, *et al*. Targeting intracellular cancer proteins with tumor-microenvironment-responsive bispecific nanobody-PROTACs for enhanced therapeutic efficacy. MedComm 2025;6(2):e70068. doi:10.1002/mco2.70068, PMID:39830023.

[15] Nair R, Somasundaram V, Kuriakose A, Krishn SR, Raben D, Salazar R, *et al*. Deciphering T-cell exhaustion in the tumor microenvironment: paving the way for innovative solid tumor therapies. Front Immunol 2025;16:1548234. doi:10.3389/fimmu.2025.1548234, PMID:40236693.

[16] Pang Y, Bai G, Zhao J, Wei X, Li R, Li J, *et al*. The BRD4 inhibitor JQ1 suppresses tumor growth by reducing c-Myc expression in endometrial cancer. J Transl Med 2022;20(1):336. doi:10.1186/s12967-022-03545-x, PMID:35902869.

[17] Ma L, Zhang X, Xu S, Dai J, Huang Z, Ruan Z, *et al*. NHWD-870 suppresses tumor proliferation via the BRD4/STRADA/CCND1 axis in small cell lung cancer. Lung Cancer 2025;210:108841. doi:10.1016/j.lungcan.2025.108841, PMID:41242286.

[18] Zhang Y, Duan S, Jang A, Mao L, Liu X, Huang G. JQ1, a selective inhibitor of BRD4, suppresses retinoblastoma cell growth by inducing cell cycle arrest and apoptosis. Exp Eye Res 2021;202:108304. doi:10.1016/j.exer.2020.108304, PMID:33080301.

[19] Sarnik J, Popławski T, Tokarz P. BET Proteins as Attractive Targets for Cancer Therapeutics. Int J Mol Sci 2021;22(20):11102. doi:10.3390/ijms222011102, PMID:34681760.

[20] Wang R, Qu Z, Lv Y, Yao L, Qian Y, Zhang X, *et al*. Important Roles of PI3K/AKT Signaling Pathway and Relevant Inhibitors in Prostate Cancer Progression. Cancer Med 2024;13(21):e70354. doi:10.1002/cam4.70354, PMID:39485722.

[21] Yuan Y, Wu D, Hou Y, Zhang Y, Tan C, Nie X, *et al*. Wnt signaling: Modulating tumor-associated macrophages and related immunotherapeutic insights. Biochem Pharmacol 2024;223:116154. doi:10.1016/j.bcp.2024.116154, PMID:38513742.

[22] Raina K, Lu J, Qian Y, Altieri M, Gordon D, Rossi AM, *et al*. PROTAC-induced BET protein degradation as a therapy for castration-resistant prostate cancer. Proc Natl Acad Sci U S A 2016;113(26):7124–7129. doi:10.1073/pnas.1521738113, PMID:27274052.

[23] Karakashev S, Zhu H, Yokoyama Y, Zhao B, Fatkhutdinov N, Kossenkov AV, *et al*. BET Bromodomain Inhibition Synergizes with PARP Inhibitor in Epithelial Ovarian Cancer. Cell Rep 2017;21(12):3398–3405. doi:10.1016/j.celrep.2017.11.095, PMID:29262321.

[24] Asangani IA, Wilder-Romans K, Dommeti VL, Krishnamurthy PM, Apel IJ, Escara-Wilke J, *et al*. BET Bromodomain Inhibitors Enhance Efficacy and Disrupt Resistance to AR Antagonists in the Treatment of Prostate Cancer. Mol Cancer Res 2016;14(4):324–331. doi:10.1158/1541-7786.MCR-15-0472, PMID:26792867.

[25] Marbach D, Brouer-Visser J, Brennan L, Wilson S, Davydov II, Staedler N, *et al*. Immune modulation in solid tumors: a phase 1b study of RO6870810 (BET inhibitor) and atezolizumab (PD-L1 inhibitor). BMC Cancer 2025;25(1):500. doi:10.1186/s12885-025-13851-4, PMID:401

02759.
[26] To KKW, Xing E, Larue RC, Li PK. BET Bromodomain Inhibitors: Novel Design Strategies and Therapeutic Applications. Molecules 2023;28(7):3043. doi:10.3390/molecules28073043, PMID:37049806.
[27] Moreno V, Vieito M, Sepulveda JM, Galvao V, Hernández-Guerrero T, Doger B, *et al*. BET inhibitor trotabresib in heavily pretreated patients with solid tumors and diffuse large B-cell lymphomas. Nat Commun 2023;14(1):1359. doi:10.1038/s41467-023-36976-1, PMID:36914652.
[28] Piha-Paul SA, Hann CL, French CA, Cousin S, Braña I, Cassier PA, *et al*. Phase 1 Study of Molibresib (GSK525762), a Bromodomain and Extra-Terminal Domain Protein Inhibitor, in NUT Carcinoma and Other Solid Tumors. JNCI Cancer Spectr 2019;4(2):pkz093. doi:10.1093/jncics/pkz093, PMID:32328561.
[29] Lewin J, Soria JC, Stathis A, Delord JP, Peters S, Awada A, *et al*. Phase Ib Trial With Birabresib, a Small-Molecule Inhibitor of Bromodomain and Extraterminal Proteins, in Patients With Selected Advanced Solid Tumors. J Clin Oncol 2018;36(30):3007–3014. doi:10.1200/JCO.2018.78.2292, PMID:29733771.
[30] Wen N, Guo B, Zheng H, Xu L, Liang H, Wang Q, *et al*. Bromodomain inhibitor jq1 induces cell cycle arrest and apoptosis of glioma stem cells through the VEGF/PI3K/AKT signaling pathway. Int J Oncol 2019;55(4):879–895. doi:10.3892/ijo.2019.4863, PMID:31485609.
[31] Llombart V, Mansour MR. Therapeutic targeting of "undruggable" MYC. EBioMedicine 2022;75:103756. doi:10.1016/j.ebiom.2021.103756, PMID:34942444.
[32] Piha-Paul SA, Sachdev JC, Barve M, LoRusso P, Szmulewitz R, Patel SP, *et al*. First-in-Human Study of Mivebresib (ABBV-075), an Oral Pan-Inhibitor of Bromodomain and Extra Terminal Proteins, in Patients with Relapsed/Refractory Solid Tumors. Clin Cancer Res 2019;25(21):6309–6319. doi:10.1158/1078-0432.Ccr-19-0578, PMID:31420359.
[33] Shi M, Zheng X, Zhou Y, Yin Y, Lu Z, Zou Z, *et al*. Selectivity Mechanism of Pyrrolopyridone Analogues Targeting Bromodomain 2 of Bromodomain-Containing Protein 4 from Molecular Dynamics Simulations. ACS Omega 2023;8(37):33658–33674. doi:10.1021/acsomega.3c03935, PMID:37744850.
[34] Gilan O, Rioja I, Knezevic K, Bell MJ, Yeung MM, Harker NR, *et al*. Selective targeting of BD1 and BD2 of the BET proteins in cancer and immunoinflammation. Science 2020;368(6489):387–394. doi:10.1126/science.aaz8455, PMID:32193360.
[35] Faivre EJ, Wilcox D, Ha-Bui M, Hessler P, Sehgal V, Lu X, *et al*. First-in-class, highly BDII-selective BET family inhibitor ABBV-744 displays potent anti-tumor activity in androgen receptor positive prostate cancer models and an improved tolerability profile. Cancer Res 2018;78(13_Suppl):4960. doi:10.1158/1538-7445.AM2018-4960.
[36] Zhang L, Cai T, Lin X, Huang X, Bui MH, Plotnik JP, *et al*. Selective Inhibition of the Second Bromodomain of BET Family Proteins Results in Robust Antitumor Activity in Preclinical Models of Acute Myeloid Leukemia. Mol Cancer Ther 2021;20(10):1809–1819. doi:10.1158/1535-7163.MCT-21-0029, PMID:34253595.
[37] Falchook G, Rosen S, LoRusso P, Watts J, Gupta S, Coombs CC, *et al*. Development of 2 Bromodomain and Extraterminal Inhibitors With Distinct Pharmacokinetic and Pharmacodynamic Profiles for the Treatment of Advanced Malignancies. Clin Cancer Res 2020;26(6):1247–1257. doi:10.1158/1078-0432.CCR-18-4071, PMID:31527168.
[38] Muhar M, Ebert A, Neumann T, Umkehrer C, Jude J, Wieshofer C, *et al*. SLAM-seq defines direct gene-regulatory functions of the BRD4-MYC axis. Science 2018;360(6390):800–805. doi:10.1126/science.aao2793, PMID:29622725.
[39] Nord JA, Wynia-Smith SL, Gehant AL, Jones Lipinski RA, Naatz A, Rioja I, *et al*. N-terminal BET bromodomain inhibitors disrupt a BRD4-p65 interaction and reduce inducible nitric oxide synthase transcription in pancreatic β-cells. Front Endocrinol (Lausanne) 2022;13:923925. doi:10.3389/fendo.2022.923925, PMID:36176467.
[40] Wellaway CR, Bamborough P, Bernard SG, Chung CW, Craggs PD, Cutler L, *et al*. Structure-Based Design of a Bromodomain and Extraterminal Domain (BET) Inhibitor Selective for the N-Terminal Bromodomains That Retains an Anti-inflammatory and Antiproliferative Phenotype. J Med Chem 2020;63(17):9020–9044. doi:10.1021/acs.jmedchem.0c00566, PMID:32787145.
[41] Watson RJ, Bamborough P, Barnett H, Chung CW, Davis R, Gordon L, *et al*. GSK789: A Selective Inhibitor of the First Bromodomains (BD1) of the Bromo and Extra Terminal Domain (BET) Proteins. J Med Chem 2020;63(17):9045–9069. doi:10.1021/acs.jmedchem.0c00614, PMID:32691589.
[42] Yang L, Jing Y, Xia X, Yin X. ARV-825 Showed Antitumor Activity against BRD4-NUT Fusion Protein by Targeting the BRD4. J Oncol 2023;2023:9904143. doi:10.1155/2023/9904143, PMID:38130463.
[43] Bai L, Zhou B, Yang CY, Ji J, McEachern D, Przybranowski S, *et al*. Targeted Degradation of BET Proteins in Triple-Negative Breast Cancer. Cancer Res 2017;77(9):2476–2487. doi:10.1158/0008-5472.CAN-16-2622, PMID:28209615.
[44] Gao J, Jiang X, Lei S, Cheng W, Lai Y, Li M, *et al*. A region-confined PROTAC nanoplatform for spatiotemporally tunable protein degradation and enhanced cancer therapy. Nat Commun 2024;15(1):6608. doi:10.1038/s41467-024-50735-w, PMID:39098906.
[45] Zengerle M, Chan KH, Ciulli A. Selective Small Molecule Induced Degradation of the BET Bromodomain Protein BRD4. ACS Chem Biol 2015;10(8):1770–1777. doi:10.1021/acschembio.5b00216, PMID:26035625.
[46] Wang ZQ, Zhang ZC, Wu YY, Pi YN, Lou SH, Liu TB, *et al*. Bromodomain and extraterminal (BET) proteins: biological functions, diseases, and targeted therapy. Signal Transduct Target Ther 2023;8(1):420. doi:10.1038/s41392-023-01647-6, PMID:37926722.
[47] Burmeister A, Stephan A, Alves Avelar LA, Müller MR, Seiwert A, Höfmann S, *et al*. Establishment and Evaluation of Dual HDAC/BET Inhibitors as Therapeutic Options for Germ Cell Tumors and Other Urological Malignancies. Mol Cancer Ther 2022;21(11):1674–1688. doi:10.1158/1535-7163.MCT-22-0207, PMID:35999659.
[48] Lyu K, Ren Y, Mou J, Yang Y, Pan Y, Zhang H, *et al*. Structure-Based Rational Design and Evaluation of BET-Aurora Kinase Dual-Inhibitors for Treatment of Cancers. J Med Chem 2025;68(2):1344–1364. doi:10.1021/acs.jmedchem.4c01933, PMID:39844725.
[49] Guan X, Cheryala N, Karim RM, Chan A, Berndt N, Qi J, *et al*. Bivalent BET Bromodomain Inhibitors Confer Increased Potency and Selectivity for BRDT via Protein Conformational Plasticity. J Med Chem 2022;65(15):10441–10458. doi:10.1021/acs.jmedchem.2c00453, PMID:35867655.
[50] Zhang X, Yang Y, Zou H, Yang Y, Zheng X, Corey E, *et al*. Effective therapeutic targeting of tumor lineage plasticity in neuroendocrine prostate cancer by BRD4 inhibitors. Acta Pharm Sin B 2025;15(3):1415–1429. doi:10.1016/j.apsb.2025.01.007, PMID:40370549.
[51] Hamilton EP, Wang JS, Oza AM, Patel MR, Ulahannan SV, Bauer T, *et al*. First-in-human Study of AZD5153, A Small-molecule Inhibitor of Bromodomain Protein 4, in Patients with Relapsed/Refractory Malignant Solid Tumors and Lymphoma. Mol Cancer Ther 2023;22(10):1154–1165. doi:10.1158/1535-7163.MCT-23-0065, PMID:37486983.
[52] Shukla S, Riveros C, Al-Toubat M, Chardon-Robles J, Osumi T, Serrano S, *et al*. The Bivalent Bromodomain Inhibitor MT-1 Inhibits Prostate Cancer Growth. Cancers (Basel) 2023;15(15):3851. doi:10.3390/cancers15153851, PMID:37568667.
[53] Olp MD, Bursch KL, Wynia-Smith SL, Nuñez R, Goetz CJ, Jackson V, *et al*. Multivalent nucleosome scaffolding by bromodomain and extraterminal domain tandem bromodomains. J Biol Chem 2025;301(3):108289. doi:10.1016/j.jbc.2025.108289, PMID:39938804.
[54] Wang C, Lu H, Liu X, Gao X, Tian W, Chen H, *et al*. A natural product targets BRD4 to inhibit phase separation and gene transcription. iScience 2022;25(1):103719. doi:10.1016/j.isci.2021.103719, PMID:35072011.
[55] Zhang Y, Lou J, Liu Y, Jin P, Tan Y, Song H, *et al*. Phase separation of PML/RARα and BRD4 coassembled microspeckles governs transcriptional dysregulation in acute promyelocytic leukemia. Proc Natl Acad Sci USA 2024;121(34):e2406519121. doi:10.1073/pnas.2406519121, PMID:39136995.
[56] Fehling SC, Miller AL, Garcia PL, Vance RB, Yoon KJ. The combination of BET and PARP inhibitors is synergistic in models of cholangiocarcinoma. Cancer Lett 2020;468:48–58. doi:10.1016/j.canlet.2019.10.011, PMID:31605774.
[57] Zou Y, Zhang H, Chen P, Tang J, Yang S, Nicot C, *et al*. Clinical approaches to overcome PARP inhibitor resistance. Mol Cancer 2025;24(1):156. doi:10.1186/s12943-025-02355-1, PMID:40442774.
[58] Xia M, Guo Z, Hu Z. The Role of PARP Inhibitors in the Treatment

of Prostate Cancer: Recent Advances in Clinical Trials. Biomolecules 2021;11(5):722. doi:10.3390/biom11050722, PMID:34066020.
[59] Aftimos PG, Oliveira M, Punie K, Boni V, Hamilton EP, Gucalp A, *et al*. A phase 1b/2 study of the BET inhibitor ZEN-3694 in combination with talazoparib for treatment of patients with TNBC without gBRCA1/2 mutations. J Clin Oncol 2022;40(16_suppl):1023. doi:10.1200/JCO.2022.40.16_suppl.1023.
[60] Park IH, Yang HN, Jeon SY, Hwang JA, Kim MK, Kong SY, *et al*. Antitumor activity of BET inhibitors in androgen-receptor-expressing triple-negative breast cancer. Sci Rep 2019;9(1):13305. doi:10.1038/s41598-019-49366-9, PMID:31527644.
[61] Aggarwal R, Starodub AN, Koh BD, Xing G, Armstrong AJ, Carducci MA. Phase Ib Study of the BET Inhibitor GS-5829 as Monotherapy and Combined with Enzalutamide in Patients with Metastatic Castration-Resistant Prostate Cancer. Clin Cancer Res 2022;28(18):3979–3989. doi:10.1158/1078-0432.CCR-22-0175, PMID:35816286.
[62] Tseng HY, Alavi S, Gallagher S, McGuire HM, Hersey P, Al Emran A, *et al*. BET inhibition sensitizes innate checkpoint inhibitor resistant melanoma to anti-CTLA-4 treatment. Pigment Cell Melanoma Res 2024;37(6):744–751. doi:10.1111/pcmr.13174, PMID:38725219.
[63] Lai X, Stiff A, Duggan M, Wesolowski R, Carson WE 3rd, Friedman A. Modeling combination therapy for breast cancer with BET and immune checkpoint inhibitors. Proc Natl Acad Sci U S A 2018;115(21):5534–5539. doi:10.1073/pnas.1721559115, PMID:29735668.
[64] Zhang X, Zegar T, Weiser T, Hamdan FH, Berger BT, Lucas R, *et al*. Characterization of a dual BET/HDAC inhibitor for treatment of pancreatic ductal adenocarcinoma. Int J Cancer 2020;147(10):2847–2861. doi:10.1002/ijc.33137, PMID:32599645.
[65] Bauer N, Balourdas DI, Schneider JR, Zhang X, Berger LM, Berger BT, *et al*. Development of Potent Dual BET/HDAC Inhibitors via Pharmacophore Merging and Structure-Guided Optimization. ACS Chem Biol 2024;19(2):266–279. doi:10.1021/acschembio.3c00427, PMID:38291964.
[66] Wood L, Huang M, Zeki J, Gong M, Taylor J, Shimada H, *et al*. Combining inhibitors of Brd4 and cyclin-dependent kinase can decrease tumor growth in neuroblastoma with MYCN amplification. J Pediatr Surg 2021;56(7):1199–1202. doi:10.1016/j.jpedsurg.2021.03.037, PMID:33838899.