BET Related *In Vivo* Models

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Outline

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- BET related CDX models
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- BET related PDX models
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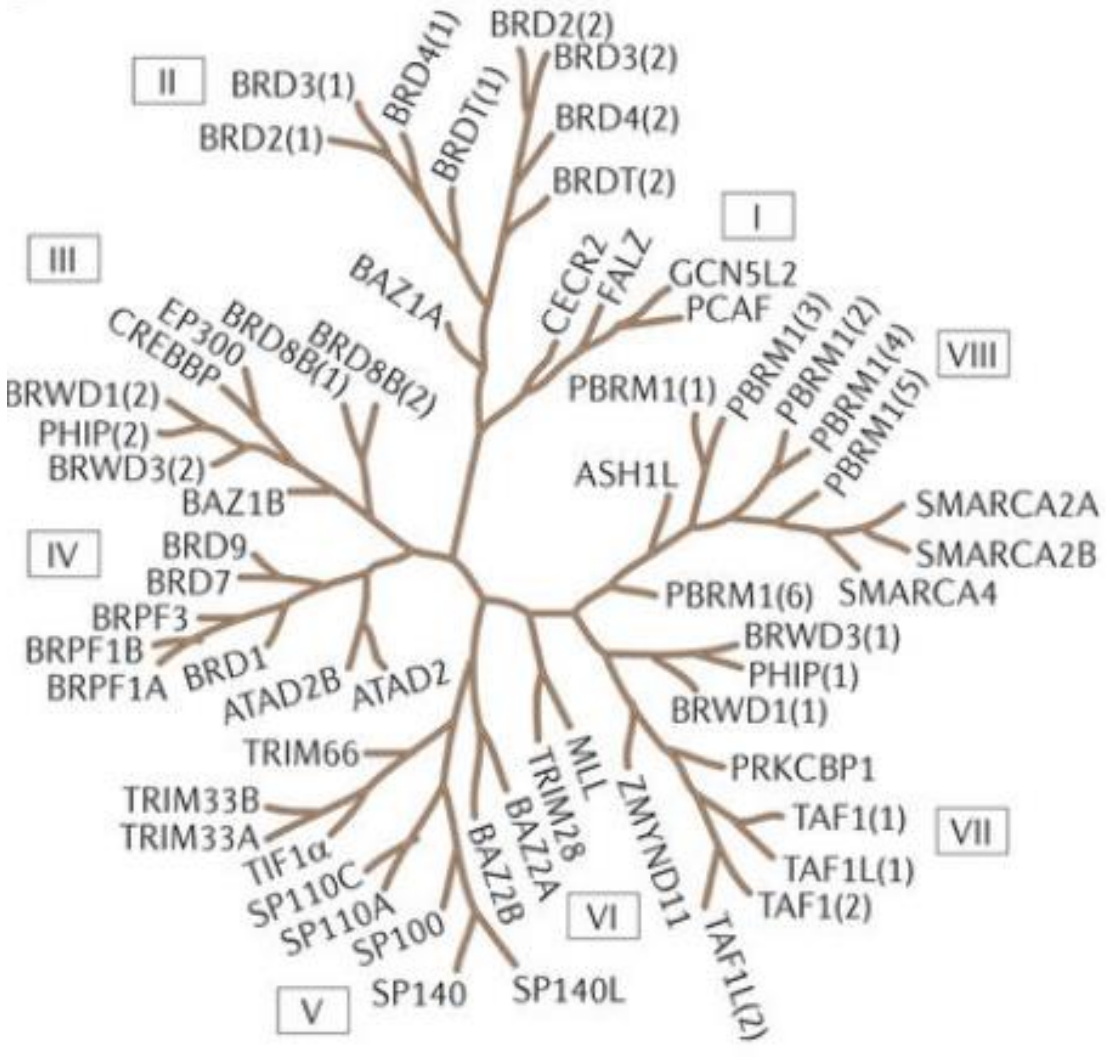
  - BET related PDX SOC or tumor growth curve

BET background as drug target

- Bromodomains (BRDs) function as acetyl-lysine binding domains, modulate enzyme activities, protein assembly and protein protein interactions (PPIs) via lysine acetylation.
- 46 diverse human proteins containing a total of 61 bromodomains.
- BRD proteins mostly contain one or two bromodomains, while some proteins, such as nuclear scaffolding proteins (PB1), contain more than two BRDs.

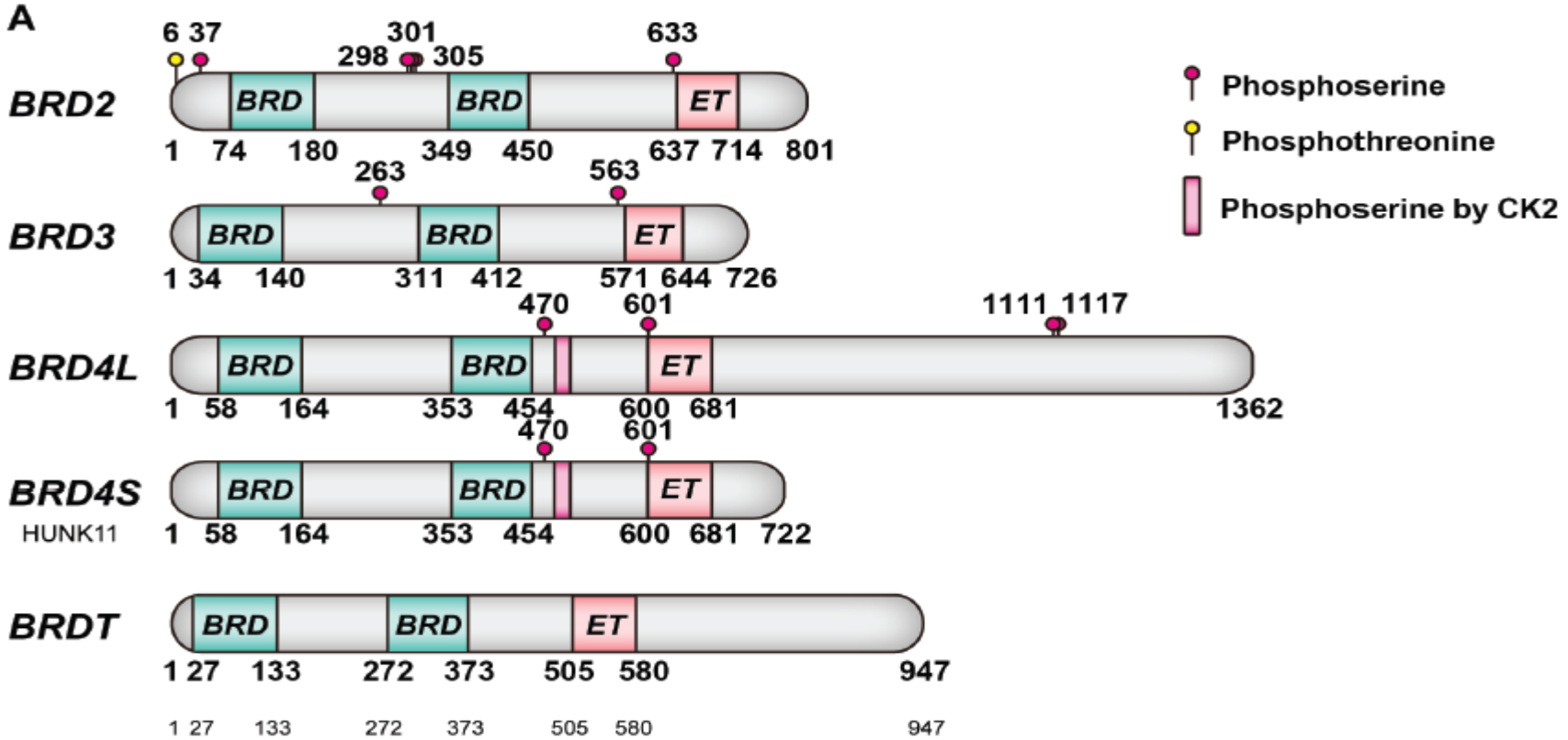
Oncotarget, Vol. 6, No.8, 5501-5503
Nat Rev Drug Discov. 2014 May;13(5):337-356.



Structure-based phylogeny of the human bromodomain family, which consists of 61 modules that are present in 46 proteins.

Biology of BET

- **Bromodomain and extra-terminal (BET)** belongs to human BRD proteins family, and contain two tandems N-terminal BRDs, an extraterminal (ET) domain and a more divergent C-terminal recruitment domain.
- BET family consists of four mammalian members, including **BRD containing 2 (BRD2), BRD3, BRD4 and BRDT**, which both exhibit high levels of sequence.



Crucial post-translational modification sites and main features of BET proteins

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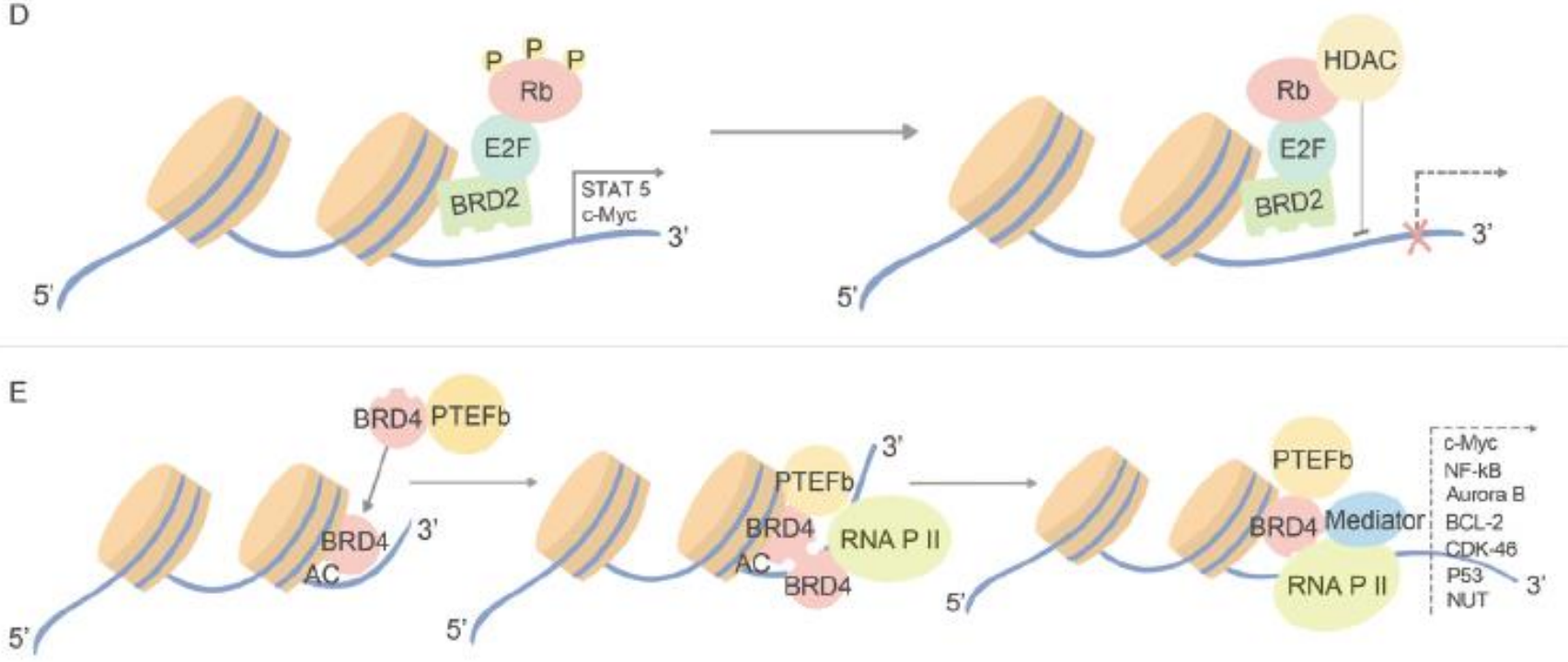
Biological function of BET family

- BET proteins are protein scaffolds, mitotic bookmarks, cell cycle regulators and transcription regulators. They functions as co-activators of transcription factors, such as MYC, ER, AR, NF-kB, and others.
- BRD-containing proteins have a wide range of documented roles in cellular homeostasis, and they have been implicated in human diseases that include neurological and inflammatory diseases, as well as cancer.



(D) The process how HDAC inhibits transcription through binding with BRD2 and E2F-Rb complex.
(E) The process how BRD4 regulate transcription.

Oncotarget, Vol. 6, No.8, 5502-5506 *Nat Rev Mol Cell Biol. 2017 Apr;18(4):246-262.*

BET proteins function in cancer

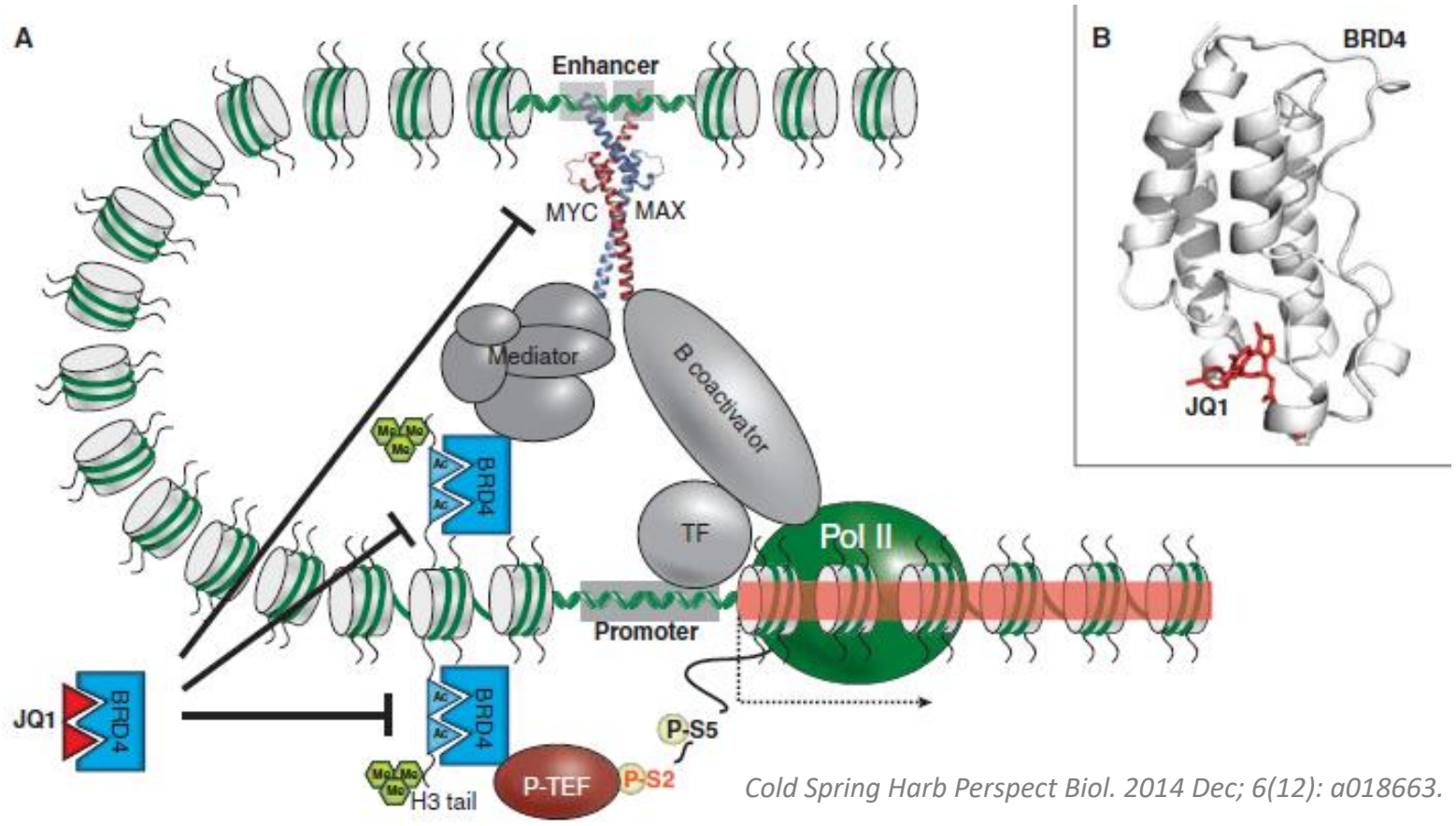
- BRD-containing proteins have been found to be deregulated in cancer and their aberrant expression has been shown to both stimulate and to suppress malignant phenotypes.

Protein	Mutations, Expression and Role(s) in Cancer	Ref.	Fusion Partners
BRD2	• Recurrently mutated in paediatric leukemia • Regulates E2F target genes through H2A.Z.2 in melanoma • Highly expressed in melanoma	(1, 9, 10)	-
BRD3	• Fusion with NUT in NMC	(11)	NUT
BRD4	• Regulates Myc transcription • Contributes to either MYCN or c-MYC over-expression in High-grade serous ovarian carcinoma • Required for the replication of tumour viruses • Increased expression in HCC, melanoma, glioblastoma and malignant peripheral nerve sheath tumors (MPNST) • BRD4-Twist interaction leads to tumorigenicity in basal-like breast cancer. • Significantly up-regulated in hepato-cellular carcinoma tissues; primary and metastatic melanoma tissues • Involved in the androgen receptor-mediated gene transcription in castration-resistant prostate cancer • Targeting BRD4 and PI3K together, but not alone, inhibits growth of many tumour cells • Simultaneous inhibition of CDK9 and MYC/BRD4 efficiently induces growth arrest and apoptosis of cancer cells • Together with hematopoietic transcription factors and p300/CBP acts to promote transcriptional activation, supporting leukemia maintenance	(10, 12-22)	NUT
BRDT	• Highly expressed in non-small-cell lung cancer (NSCLC) • Recurrently mutated in paediatric leukemia	(1, 25)	-
BAZ1A	• Mutated in carcino-sarcomas	(15, 26, 27)	-

Nat Rev Mol Cell Biol. 2017 Apr;18(4):246-262.

BET proteins function in cancer

- The aberrant transcriptional activation of MYC target genes (indicated as red shaded regions of chromatin requires the bromodomain “reading” function of BRD4, which recognizes acetylation marks (“Ac”-labeled cyan triangles) on histone H3 tails at promoter-proximal target sequences.
- The Acetyl-bound BRD4 interacts with both the MYC-MAX complex bound to enhancer sequences and the PTEFb phosphorylase.
- The competitive binding of the JQ1 (red triangle) to BRD4 reduces transcription of the MYC gene and its target genes by abrogating recruitment of enhancer complexes and PTEFb.

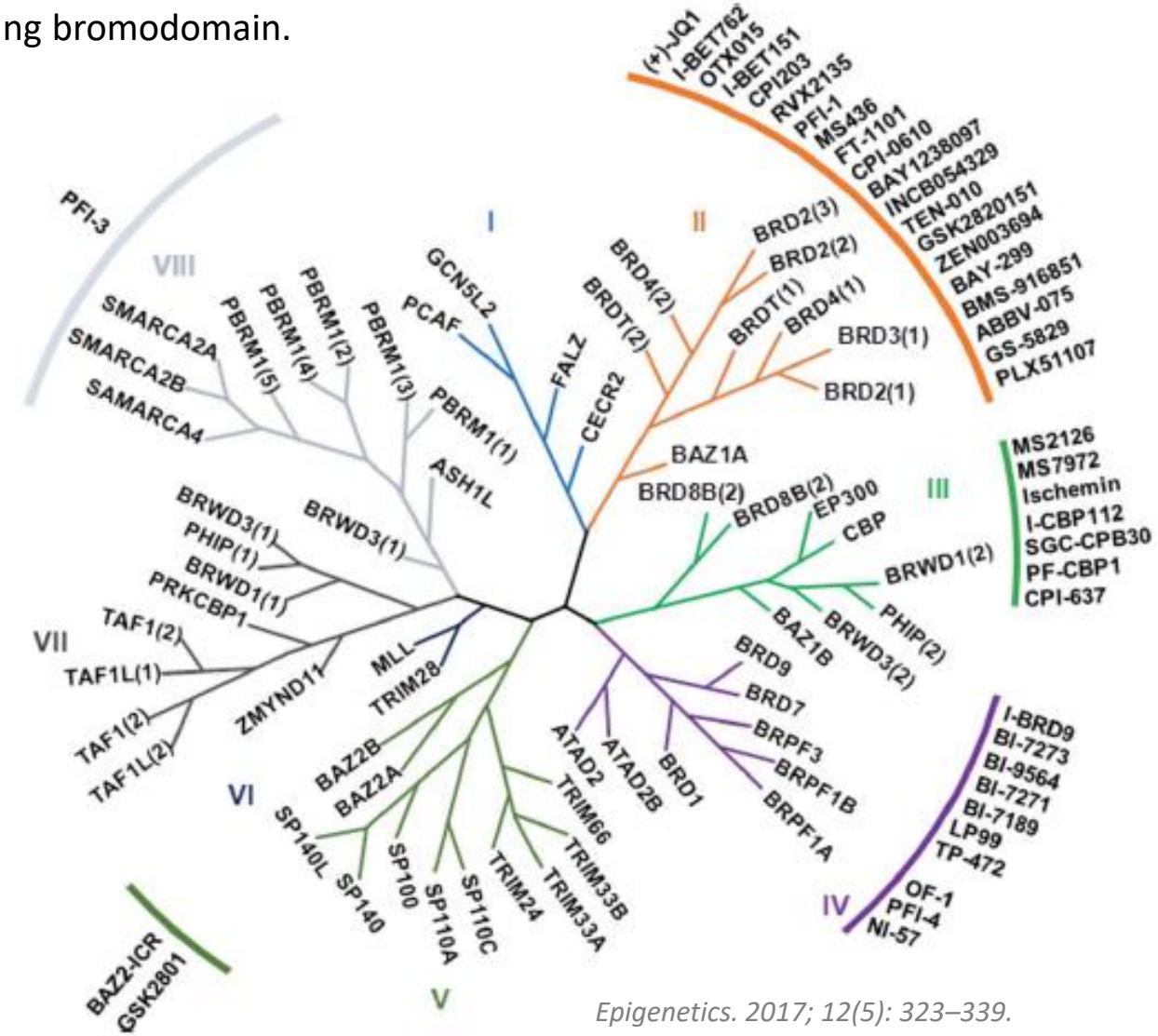


Cold Spring Harb Perspect Biol. 2014 Dec; 6(12): a018663.

Model for JQ1 small-molecule inhibition of the BRD4 bromodomain in cancer

BET inhibitors

- Structure-based phylogeny of the human bromodomains and their inhibitors. The inhibitors are indicated next to the corresponding bromodomain.



Epigenetics. 2017; 12(5): 323–339.

BET inhibitors in cancer

Drug	Cancer type	Target	Mechanism/pathway
JQ1	Tam-R breast cancer	BRD3/4	Suppresses the classic estrogen receptor-α signaling pathway and growth of Tam-R breast cancer cells in culture
	NUT midline carcinoma (NMC)	BRD3/4	Suppress different BRD4-NUT translocation
	AML cells	BRD4	Reduce binding of BRD4 and RNA polymerase Ⅱ to the DNA of c-MYC and BCL2
	OCI-AML3 cell line	BRD4	Trigger caspase3/7-mediated apoptosis and DNA damage response
	Erythroleukemia cell line UT7	BRD4	Inhibit Epo-induced UT7 proliferation and restoring terminal erythroid differentiation
	B-cell non-Hodgkin lymphoma	BRD4	Induce cell death through MYC-CYCLON pathway
	Neuroblastoma	BRD4	Induce cell death through targeting MYCN
	Primary glioblastoma xenograft lines	BRD4	Induce marked G1 cell-cycle arrest and apoptosis through Bcl-xL and p21(CIP1/WAF1)
	Osteosarcoma cells	BRD4	Trigger transcriptional silencing of MYC and RUNX2, resulting from the depletion of BRD4
		BRD2	Decrease STAT5-dependent transcription of both heterologous reporter genes and endogenous STAT5 target genes

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BET inhibitors in cancer

Drug	Cancer type	Target	Mechanism/pathway
I-BET151	Myeloma cell	BRD2/3/4	Induce apoptosis and exerts strong anti-proliferative effect associating with contrasting effects on oncogenic MYC and HEXM1 , and inhibit transcriptional activator PTEFb.
	AML	BRD4	Suppress cell growth in a HOX gene independent manner, but relieving upon NPM1c mutation and cytoplasmic dislocation.
	Erythroleukemic (HEL) cells	BRD4	Suppress myeloproliferative neoplasma by constitutively active JAK2 kinase.
I-BET762（GSK525762A）	Myeloma	BRD2/3/4	Inhibit myeloma cell proliferation, resulting in survival advantage in a systemic myeloma xenograft model
	Neuroblastoma tumor models	BRD2/3/4	Suppress cell growth in a apoptosis signaling, and N-Myc-driven pathway, including the direct suppression of BCL2 and MYCN.
CPI203	Mantle cell lymphoma (MCL)	BRD2/3/4	Decreased tumor burden, involving simultaneous MYC and IRF4 downregulation and apoptosis induction.
RVX2135	Myc-induced murine lymphoma	BRD2/3/4	Exhibit broad transcriptional effects in Myc-transgenic lymphoma cells affecting many transcription factor networks.
Dinaciclib	Leukemia	BRDT, CDKs	Interact with the acetyl-lysine recognition site of the bromodomain testis-specific protein BRDT
PFI-1	Leukemia	BRD2/4	Induce G1 cell-cycle arrest, downregulation of MYC expression, downregulation of Aurora B kinase.

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BET inhibitors in cancer

Drug	Inventor	Cancer type	Target	Mechanism/pathway
MK-8628 (OTX015)	MK	Diffuse large B-cell lymphoma (DLBCL)	BRD4	Inhibit the growth of hematologic malignances through directly regulating MYC expression and activity, exert anti-proliferative activity.
RVX-208	Resverlogix Corporation		BRD3 (BD2)	Raise apoA-Ⅰ and increase preβ-HDL particles. Displace BET proteins from chromatin modestly affecting BET-dependent gene transcription.

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BET inhibitors in clinical trial

Drug	Inventor	Condition	Target	Status
RVX-208	Resverlogix	Atherosclerosis, Dyslipidemia CAD Diabetes	BRD3 (BD2)	II
I-BET762	GSK	NMC & other solid tumors Hematological Malignancies	BRD2/3/4	I
MK-8628 (OTX015)	Oncoethix (Merck)	AML, DLCBL, NMC, CRPC & other solid tumors Glioblastoma Multiforme	BRD2/3/4	Clinical Trials Completed
CPI-0610	Constellation pharmaceuticals	Lymphoma, Multiple myloma	BRD2, BRD3, BRD4, BRDT	II
TEN-010	Tensha Therapeutics	NMC & other solid tumors, AML, MDS	BRD2, BRD3, BRD4, BRDT	I
BAY 1238097	Bayer	Advanced malignancies	BRD4	Terminated
ABBV-075	Abbvie	Breast cancer, multiple myeloma, NSCLC, AML	BRD2, BRD4, BRDT	Clinical Trials Completed
INCB 054329	Incyte	Advanced malignancies	BRD2, BRD3, BRD4	Terminated

BET inhibitors in clinical trial (continued)

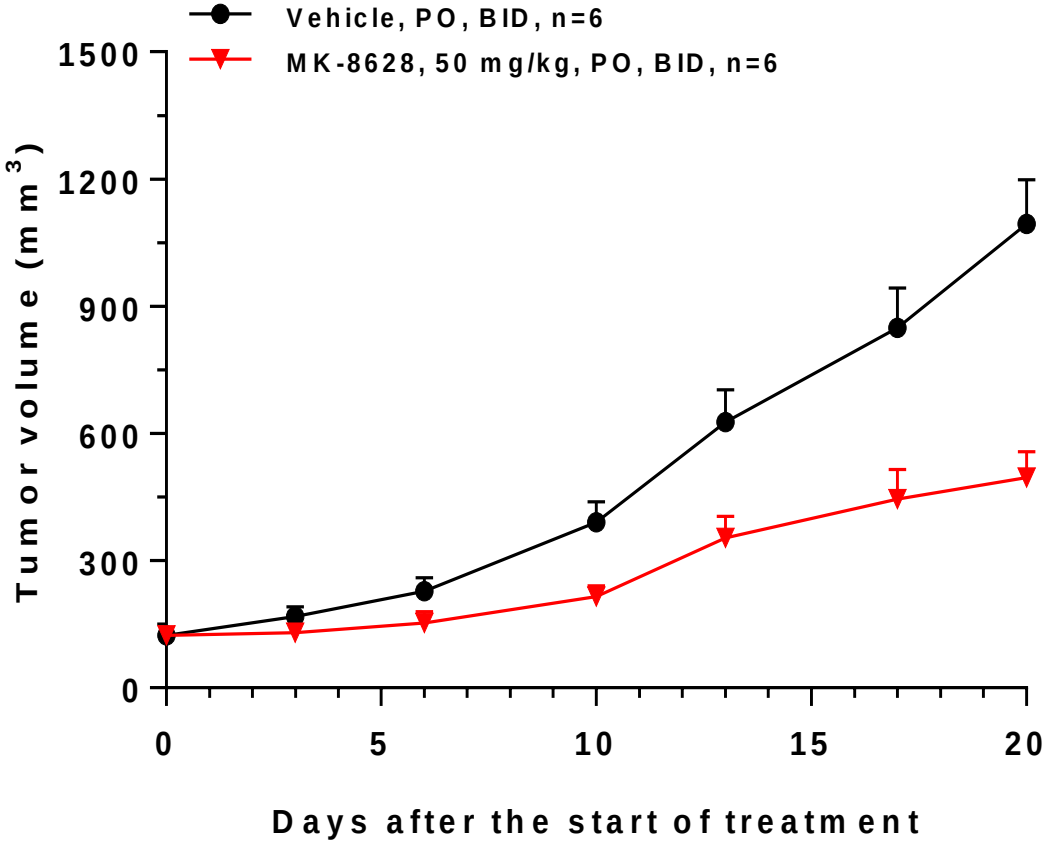
Drug	Inventor	Condition	Target	Status
BMS-986158	Bristol-Myers Squibb	NMC & other solid tumors, AML, MDS	(undisclosed BRD small-molecule inhibitor)	I, II
FT-1101	Forma Therapeutics	AML, MDS	BRD2, BRD3, BRD4, BRDT	Clinical Trials Completed
GS-5829	Gilead Sciences	Diffuse large B-cell lymphoma non-Hodgkin's lymphoma Solid tumors	(undisclosed BRD small-molecule inhibitor)	Clinical Trials Completed
GSK525762	GSK	Solid tumors	(undisclosed BRD small-molecule inhibitor)	I
PLX51107	Daiichi Sankyo	Cancer	BRD4	Terminated
AZD5153	AstraZeneca	Malignant Solid Tumors Lymphoma Ovarian Cancer	BRD4	I

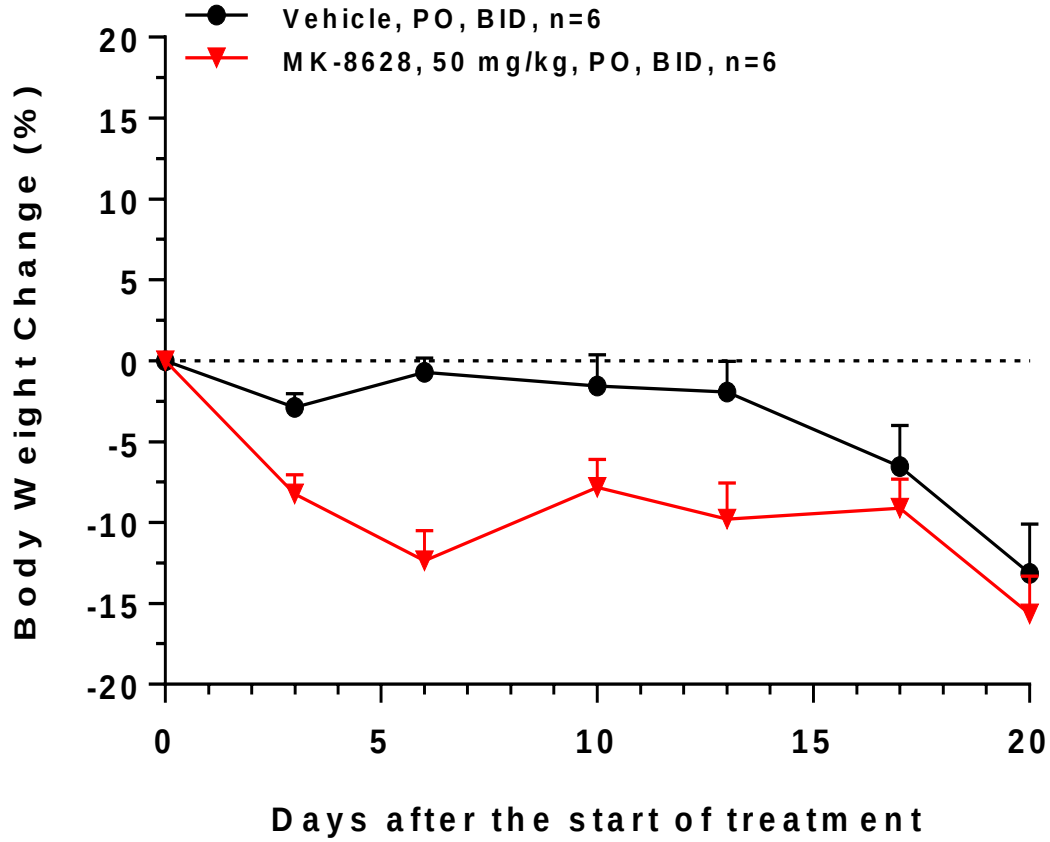
Oncotarget, Vol. 6, No.8, 5502-5506
Nature Biotechnology 2016, 34, 361–362
https://clinicaltrials.gov/

BET related CDX models: WuXi profiled

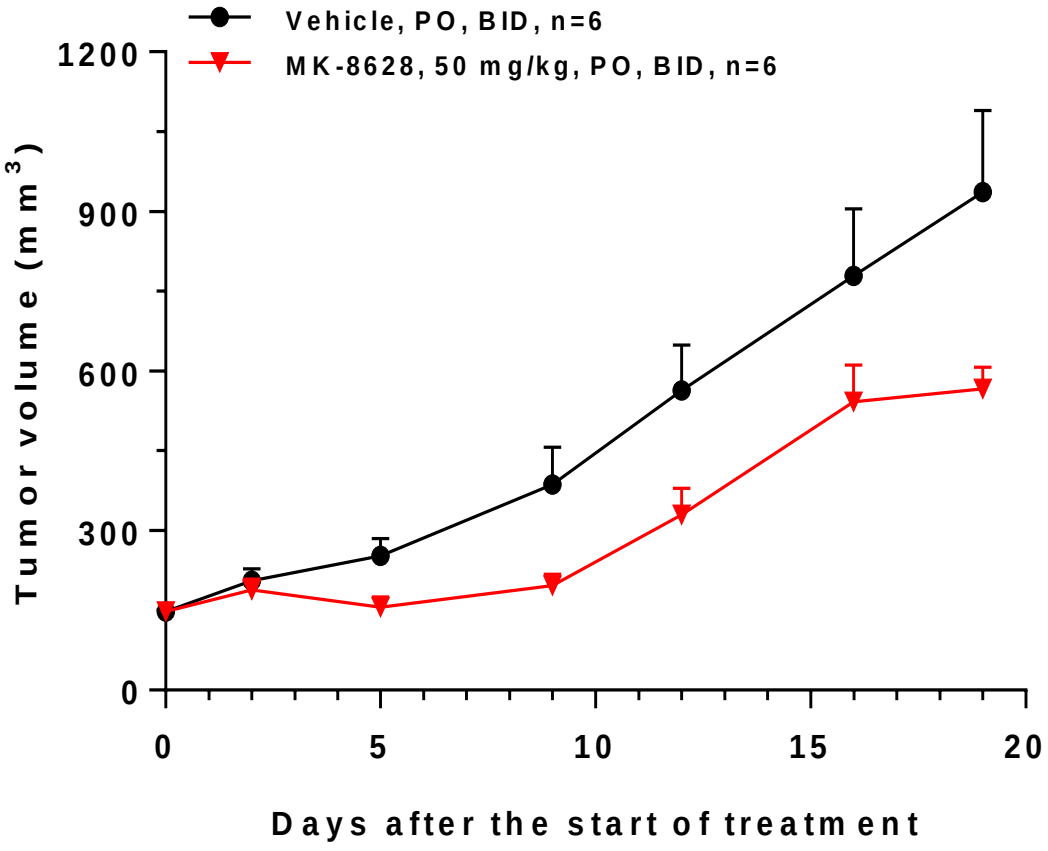
Cancer type	Model ID	Tumor growth curve	Drugs tested	Dosage	TGI
Prostate	PC-3	Yes	MK-8628(OTX015)	50 mg/kg	71%
Breast	MDA-MB-231-luc	Yes	MK-8628(OTX015)	50 mg/kg	91%
			BMS-986158	3 mg/kg	63%
Lung	NCI-H526	Yes	BMS-986158	3 mg/kg	87%
Ovary	ES-2	Yes	BMS-986158	3 mg/kg	62%
Leukemia	Kasumi-1	Yes	CPI0610	15 mg/kg	
	MV4-11	Yes	CPI0610	15 mg/kg	
			AZD5153	5 mg/kg	

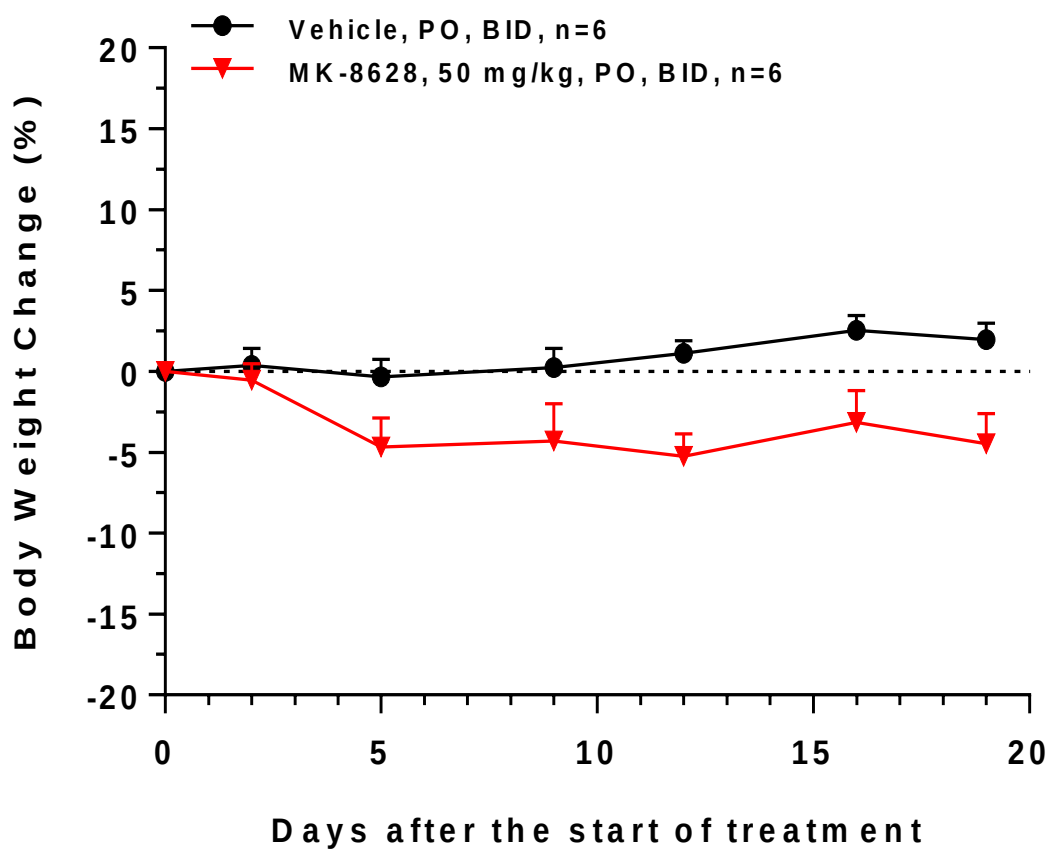
BET inhibitors in PC-3 xenograft model



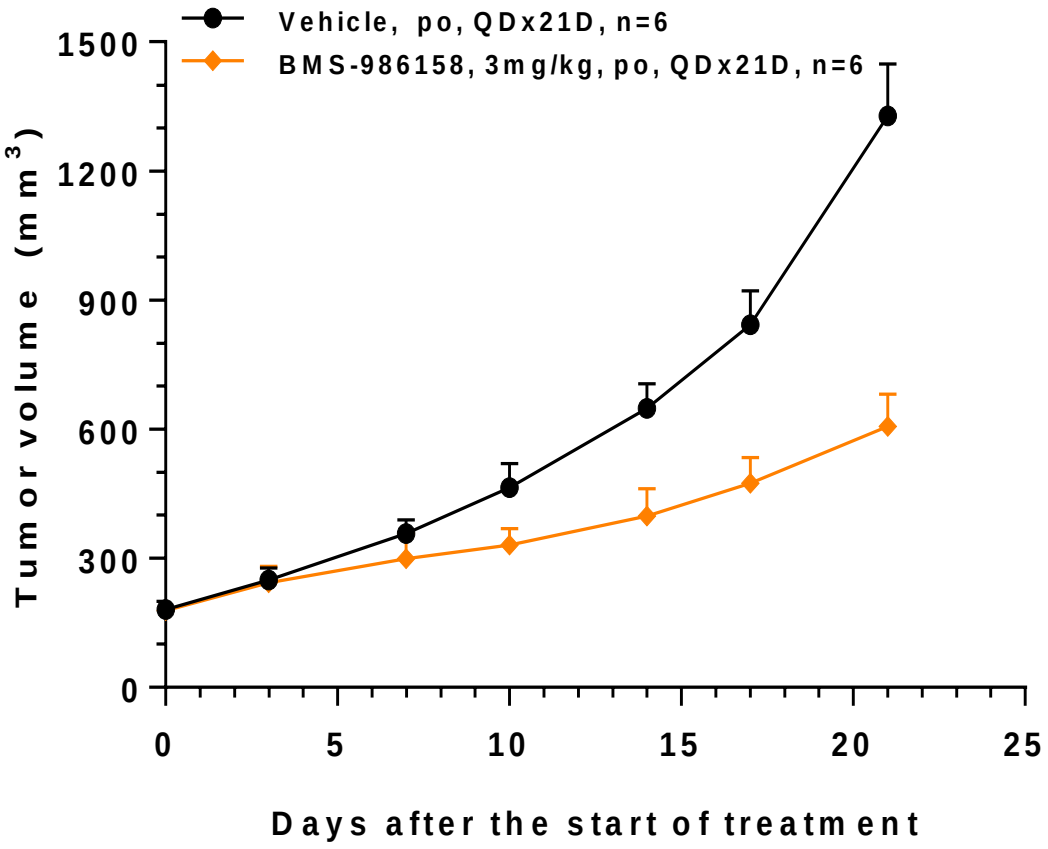


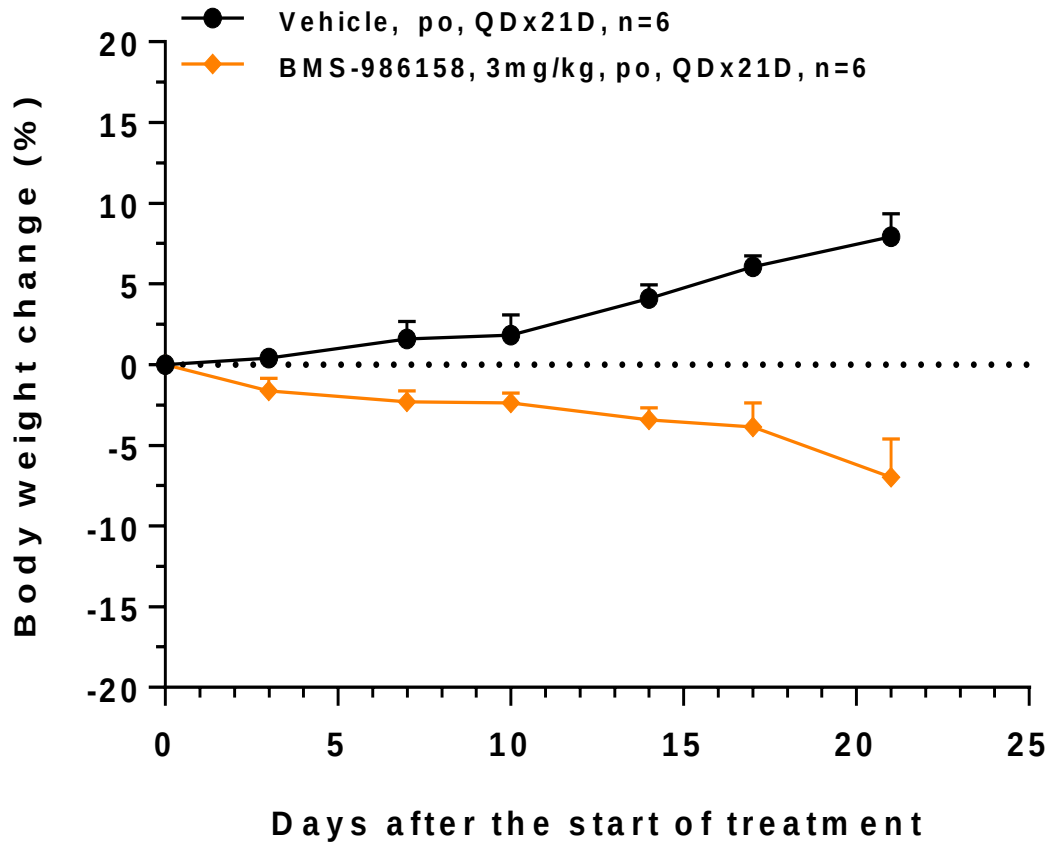
BET inhibitors in MDA-MB-231_luc xenograft model



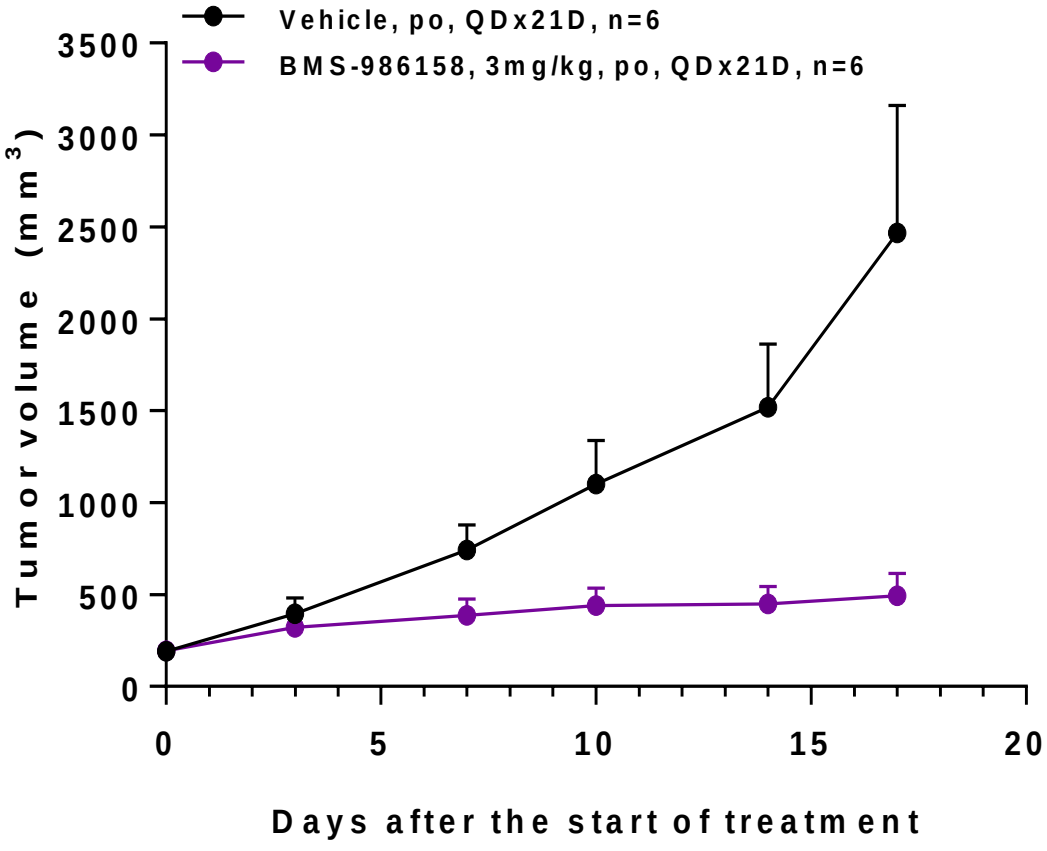


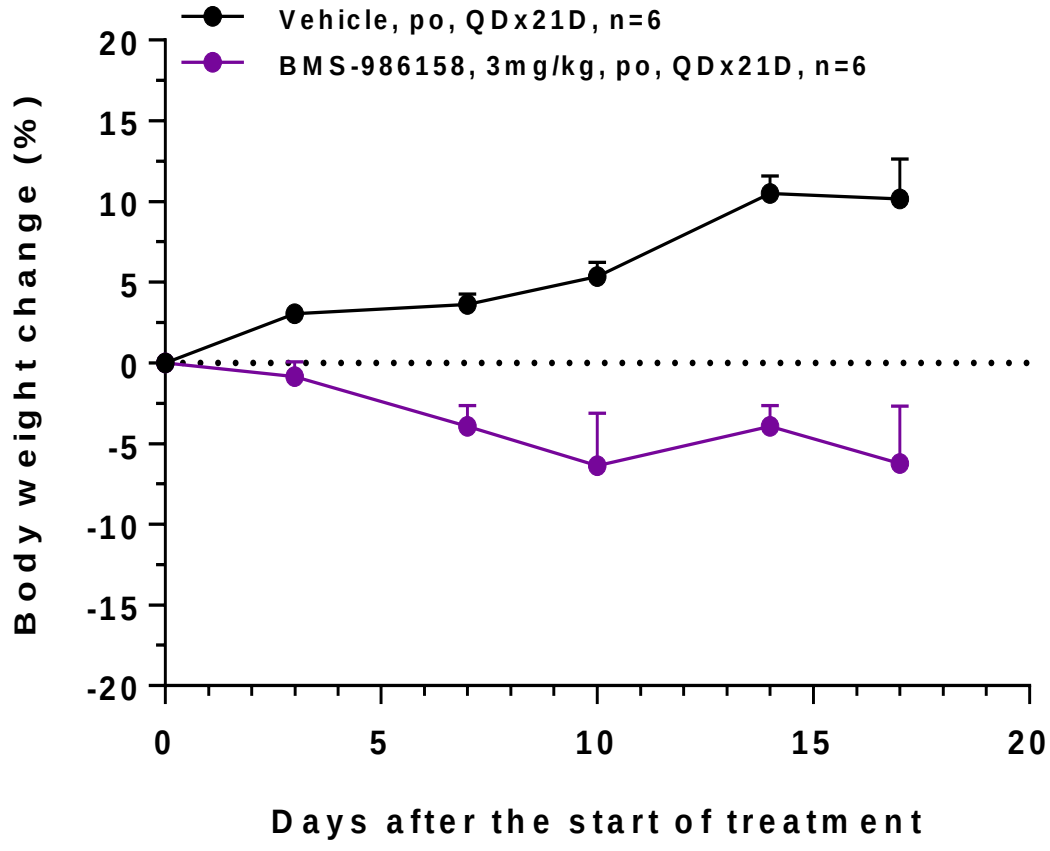
BET inhibitors in MDA-MB-231_luc xenograft model



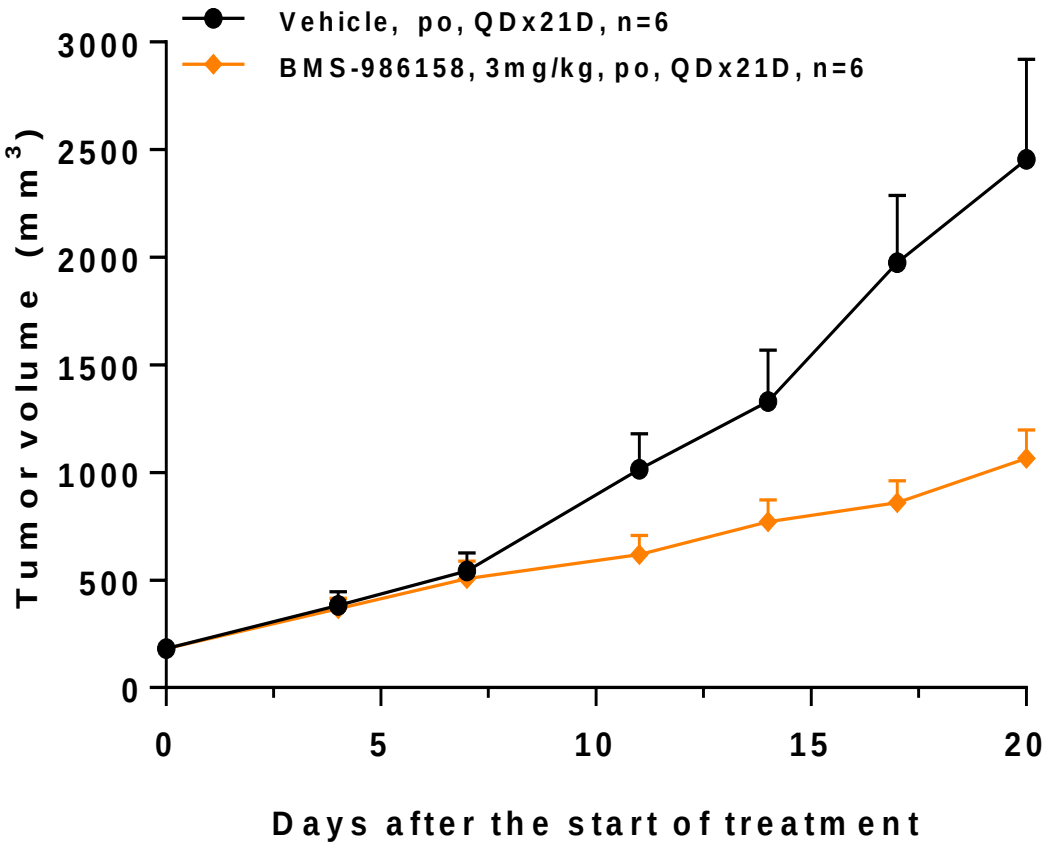


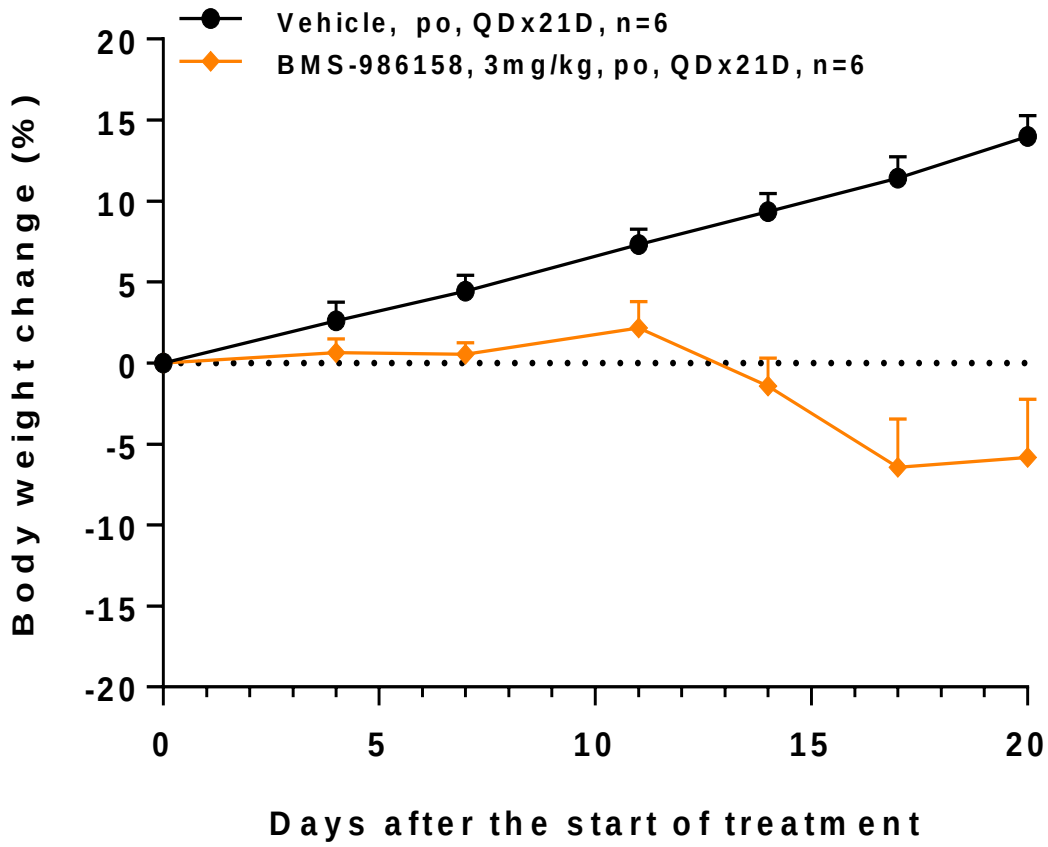
BET inhibitors in NCI-H526 xenograft model



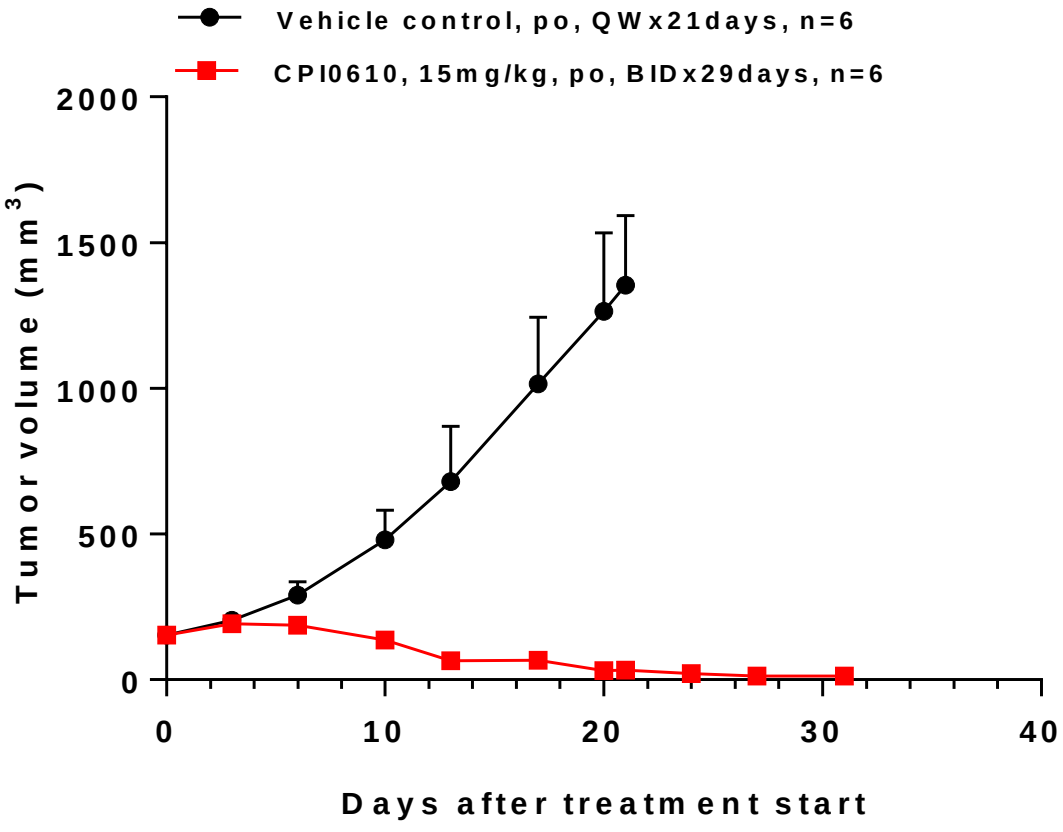


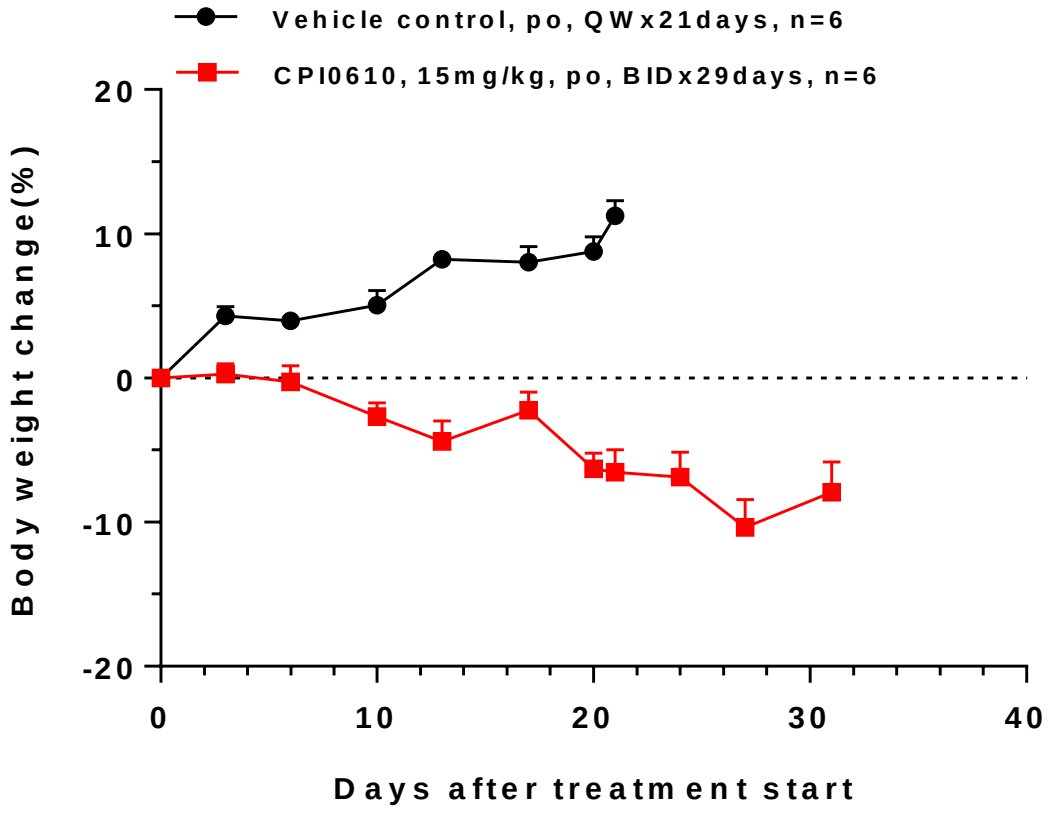
BET inhibitors in ES-2 xenograft model



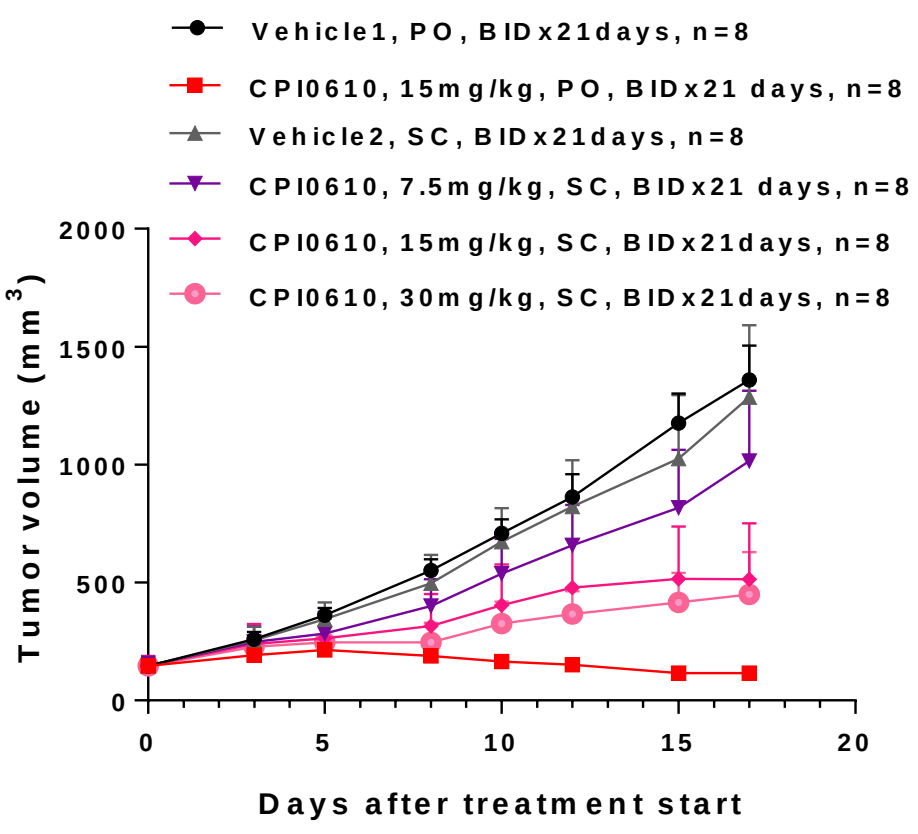


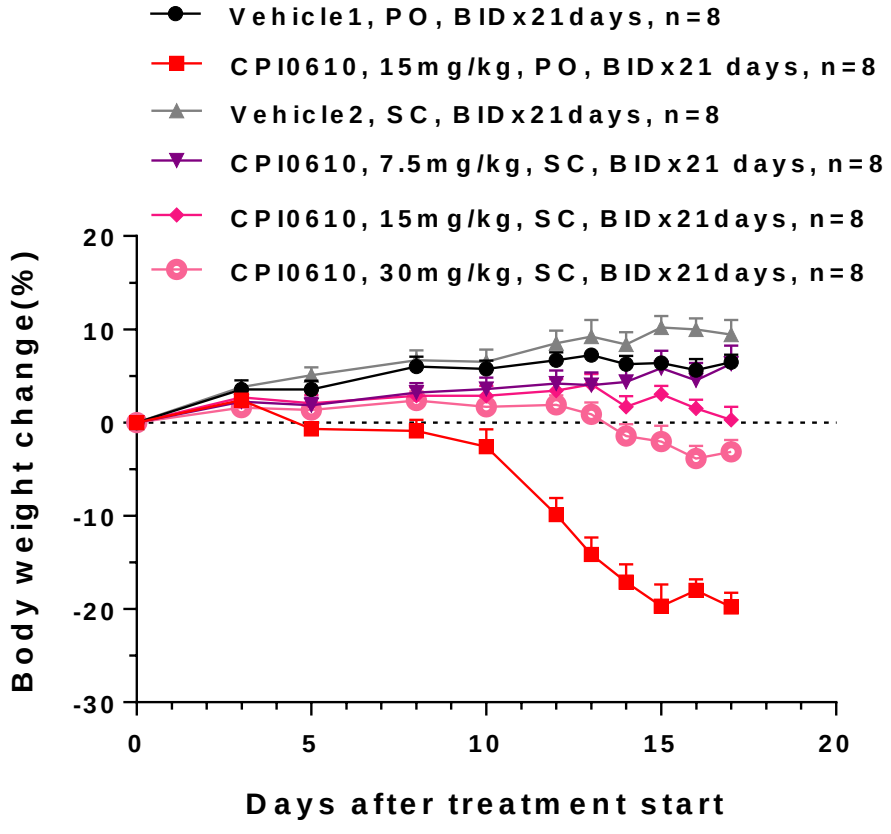
BET inhibitors in Kasumi-1 xenograft model



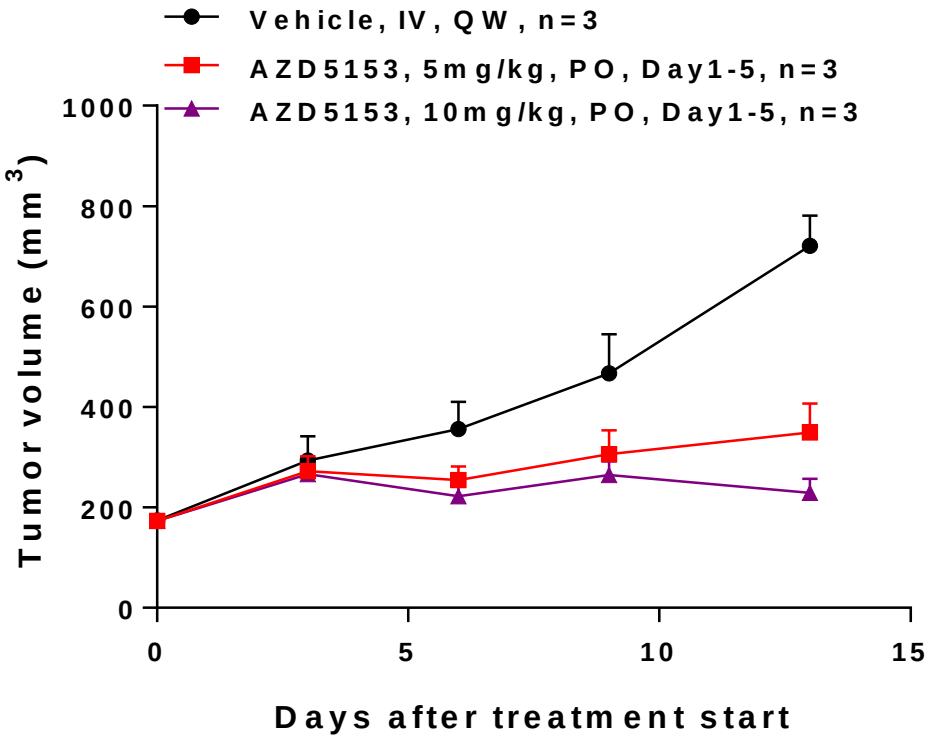


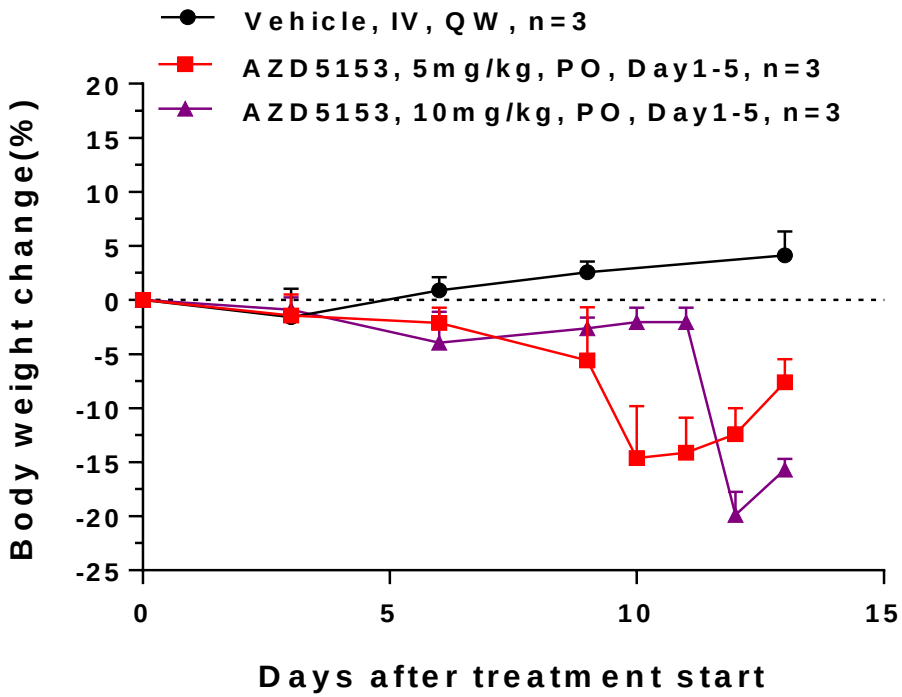
BET inhibitors in MV4-11 xenograft model





BET inhibitors in MV4-11 xenograft model

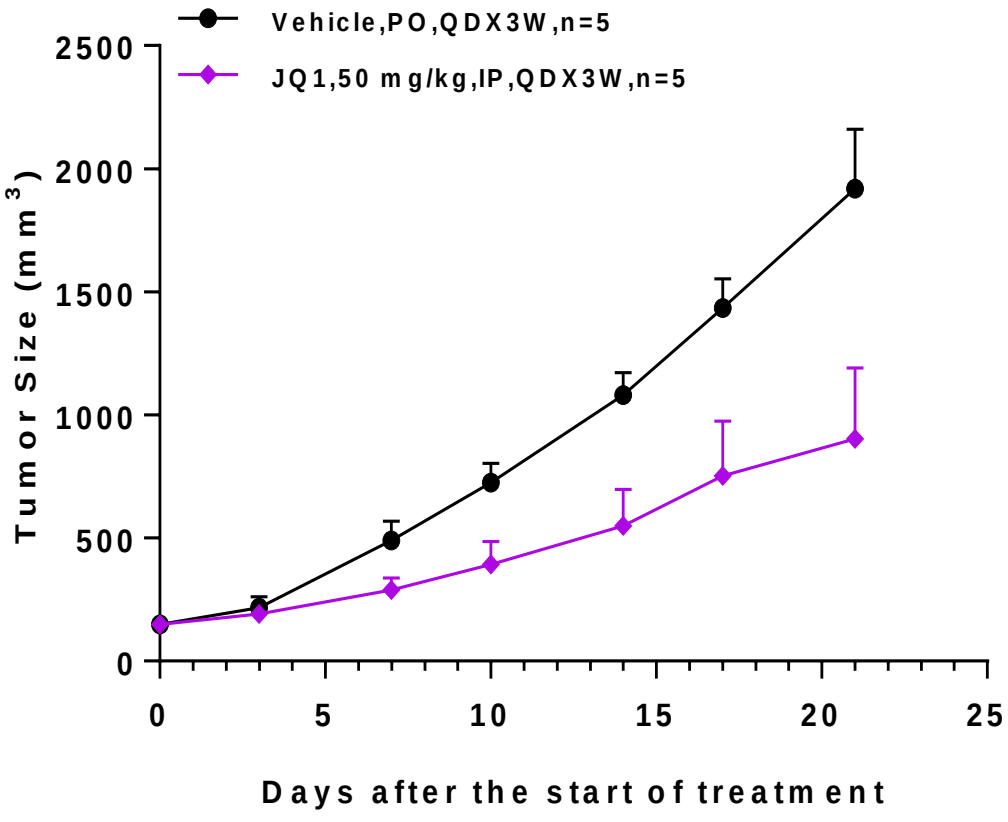


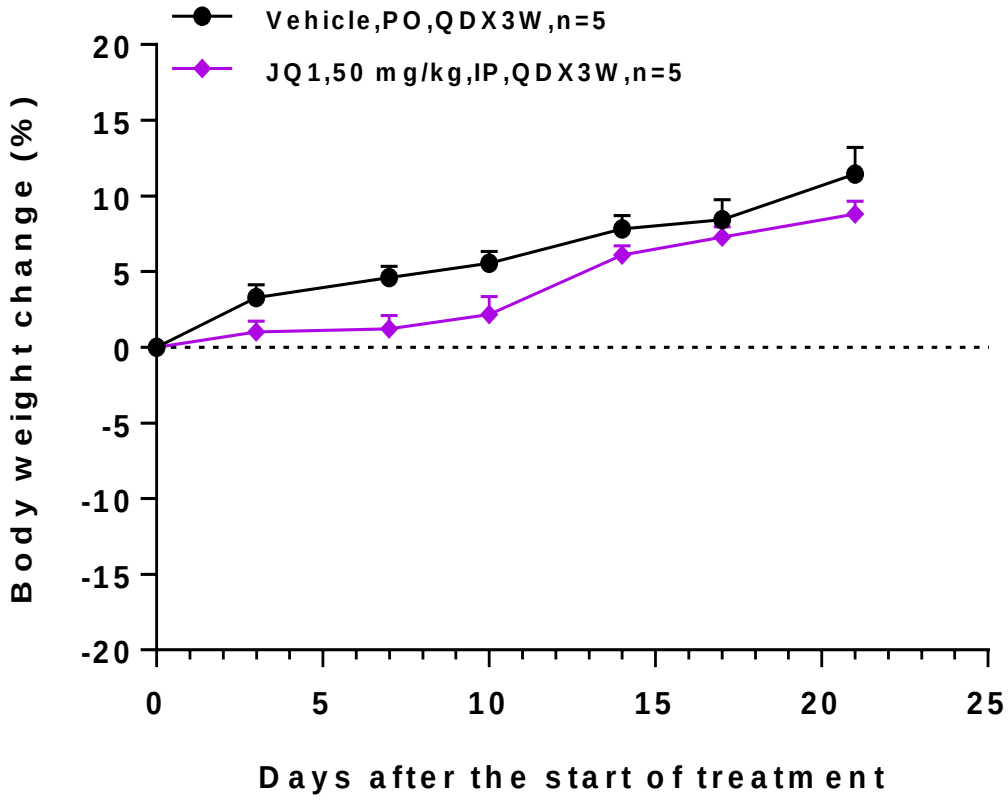


BET-related PDX models: WuXi profiled

Cancer type	Model ID	Tumor growth curve	Drugs tested	Dosage	TGI
Breast	BR-05-0020	Yes	JQ1	50 mg/kg	57%

BET inhibitors in BR-05-0020 xenograft model





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