BTK Related *In Vivo* Models

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Outline

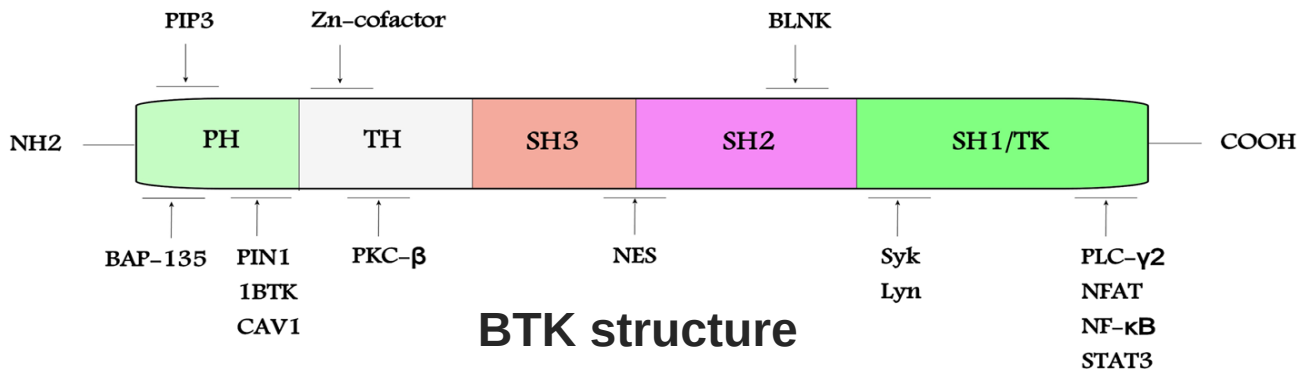
- BTK background as a drug target
  - BTK biology
  - BTK inhibitors
- BTK related CDX models
  - BTK related CDX summary
  - BTK related CDX SOC or tumor growth curve
- BTK related PDX models
  - BTK related PDX summary
  - BTK related PDX SOC and model characterization

BTK biology

- BTK (Bruton tyrosine kinase) is a non-receptor tyrosine kinase belonging to the Tec family of kinases which is involved in BCR signaling and is critical for B-cell development, differentiation, and signaling. Moreover, BTK expression is assumed to be a prerequisite for B-cell proliferation and survival.

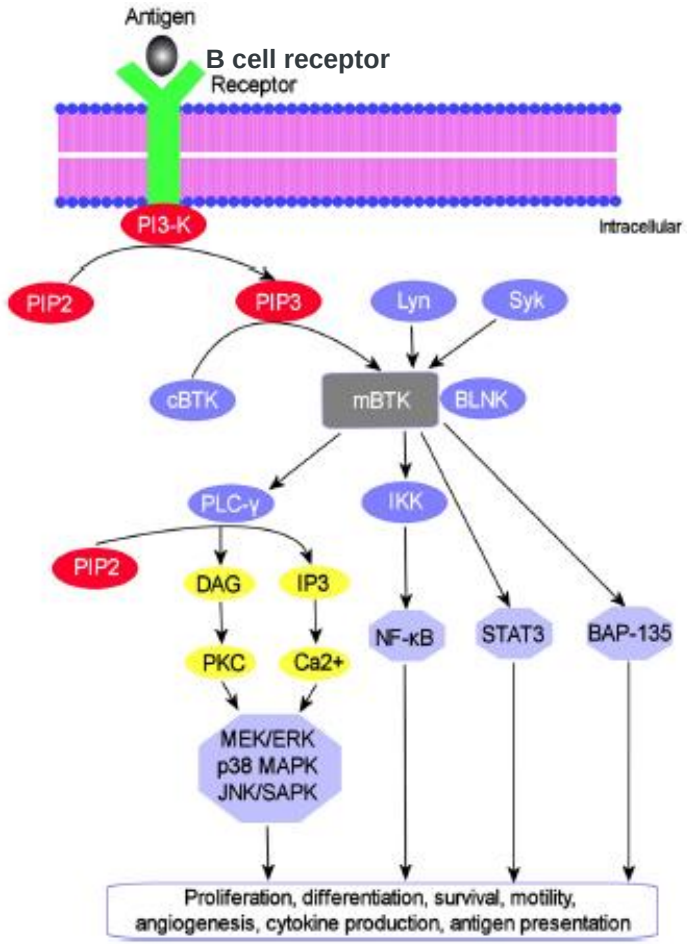
- With the exception of T lymphocytes and plasma cells, all other hematopoietic lineages have been shown to express BTK.

- Upon activation of BTK, PI3K is then activated and produced. Subsequently, BTK is mobilized to the plasma membrane. Phosphorylation of the BTK is done by LYN and FYN. The phosphorylated BTK activates PLCγ2, leading to downstream activation of protein kinases, and finally activation of transcription factor NF-κB. The stimulation of NF-κB pathway leads to inhibition of apoptosis.



BTK structure

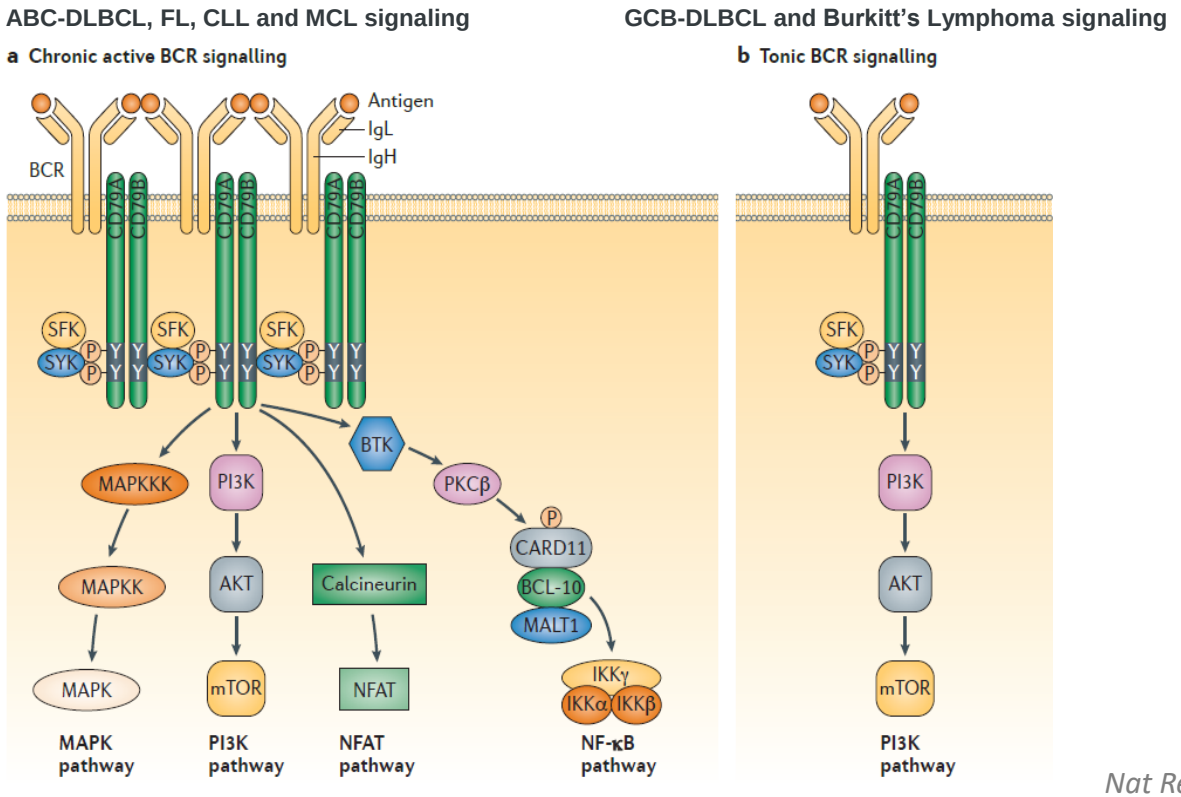
Journal of Hematology & Oncology 2013, 6:59



Journal of Hematology & Oncology 2013, 6:59

BTK and BCR signaling in disease

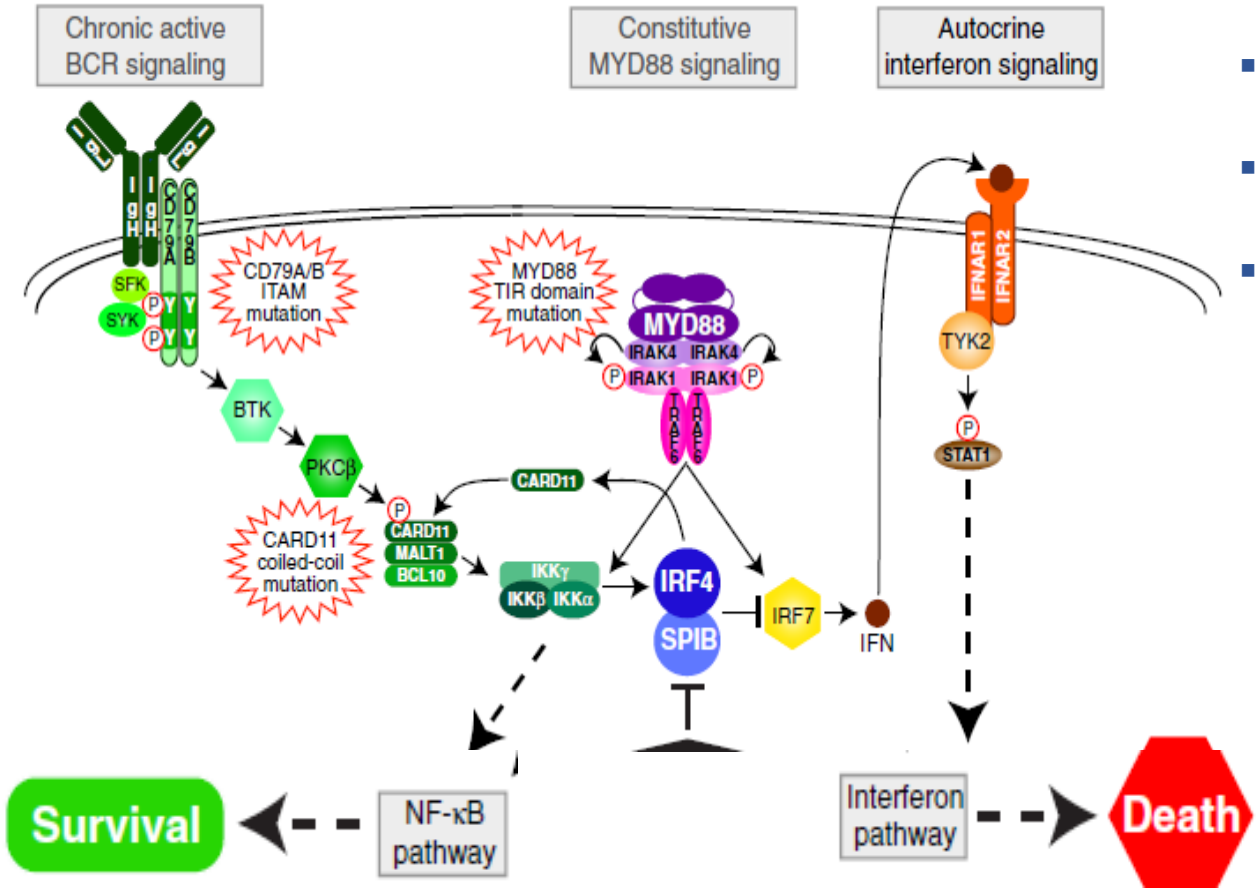
- Most lymphomas originate from B lymphocytes, aberrant activation of the BTK-dependent pathways has been implicated in B cell malignancies, such as chronic lymphocytic leukemia (CLL), ALL (the most common form of cancer in children and adolescents) and activated B cell-like diffuse large B-cell lymphoma (ABC-DLBCL).
- It was discovered that BTK is expressed not only in malignant lymphohematopoietic cells but in solid tumor cells as well, such as prostate cancer.
- A point mutation E41K (gain-of-function) was found in BTK at domain, which increased membrane targeting and tyrosine phosphorylation.



Nat Rev Drug Discov 2013;12:229–43

BTK and BCR signaling in disease

- Activated B cell-like diffuse large B-cell lymphoma (ABC-DLBCL) shows sensitive to BTK inhibitor (Ibrutinib), in which ~10% harboring CARD11 mutation, ~20% harboring CD79A and CD79B subunits mutation and ~29% harboring MYD88 mutation. MYD88 mutation is also observed in chronic lymphocytic leukemia (CLL). The most prevalent mutation of MYD88 is the L265P missense substitution.



- CARD11: a key regulator of NF-kB signaling;
- CD79A and CD79B subunits: augment receptor signaling of BCR;
- MYD 88: promote NF-KB signaling.

Cancer Cell, 2012, 21: 723–737

BTK-targeted drugs

Drug	Inventor	Indications	Status
Ibrutinib	Janssen	R/R CLL/SLL, MCL, FL, DLBCL, MM	Launched
Acalabrutinib	AstraZeneca	MCL, CLL, WM	Launched
Zanubrutinib	BeiGene	CLL, DLBCL, FL, MCL	Launched
SNS-062 (Vecabrutinib)	Biogen, Sunesis	Blood cancer	Phase Ⅱ
ONO/GS-4059	ONO, Gilead	CLL	Phase Ⅱ
M-7583	Merck	B-cell malignancies	Phase Ⅱ
ARQ-531	ArQule	Blood cancer	Phase Ⅱ
GDC-0853	Genentech	B-cell malignancies	Phase Ⅱ
SHR1459	Hengrui, Shendi, TG Therapeutics	B-cell malignancies	Phase Ⅰ

BTK-targeted drugs in solid tumors

Drug	Inventor	Indications	Treatment Combination	Status
Ibrutinib	Janssen	Pancreatic Cancer	nab-paclitaxel and gemcitabine	II/III
Ibrutinib	Janssen	Renal/Urethelial/Gastric/Colorectal Cancer	chemotherapy/small molecule	Ib/II
Ibrutinib	Janssen	HER2/MYC + Oesophageal Cancer	--	I
Ibrutinib	Janssen	EGFR + Non-small Cell Lung Cancer	--	I/II
Ibrutinib	Janssen	NSCLC/Breast Cancer/Pancreatic Cancer	Durvalumab (anti-PD-L1)	I/II
Ibrutinib	Janssen	Pancreatic Neuro-endocrine tumors (pNET)/metastatic Carcinoid	--	II
Ibrutinib	Janssen	Stage IV Cutaneous Melanoma	--	II
Ibrutinib	Janssen	Metastatic Renal Cancer	Nivolumab (anti-PD-L1)	Ib/II
Ibrutinib	Janssen	Localized Prostate Cancer	--	I/II

BTK-targeted drugs in solid tumors

Drug	Inventor	Indications	Treatment Combination	Status
Acalabrutinib	AstraZeneca	Advanced/Metastatic Pancreatic Cancer	Pembrolizumab (anti-PD-L1)	II
Acalabrutinib	AstraZeneca	Recurrent Ovarian Cancer	Pembrolizumab (anti-PD-L1)	II
Acalabrutinib	AstraZeneca	Glioblastoma		Ib/II
Acalabrutinib	AstraZeneca	NSCLC	Pembrolizumab (anti-PD-L1)	II
Acalabrutinib	AstraZeneca	Head and Neck Squamous Cell Carcinoma (HNSCC)	Pembrolizumab (anti-PD-L1)	II
Acalabrutinib	AstraZeneca	Platinum-resistant Urethelial (Bladder) Cancer	Pembrolizumab (anti-PD-L1)	II

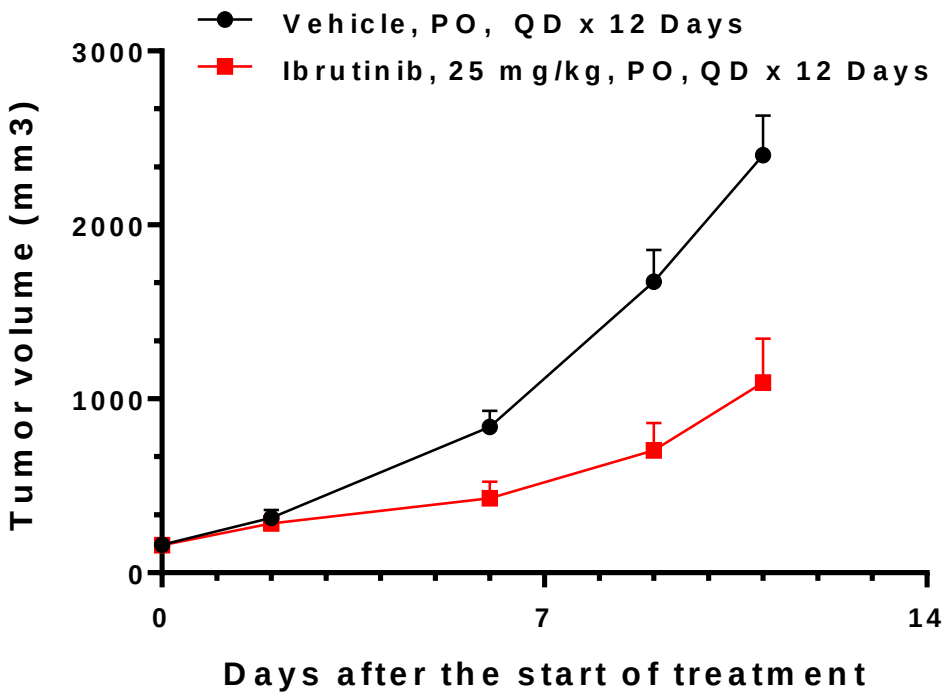
BTK related CDX models

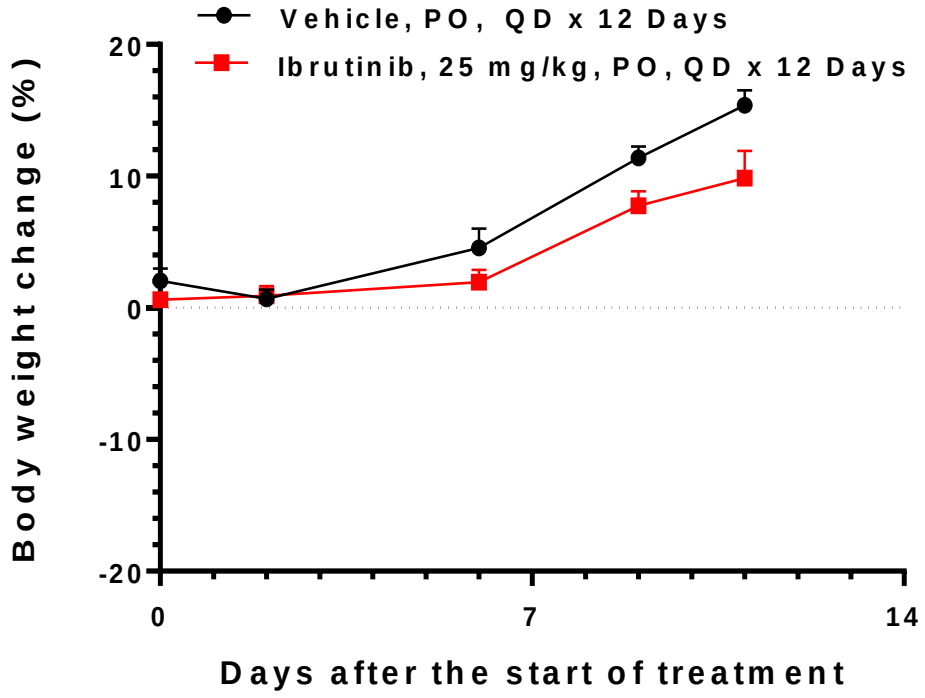
Cancer type	Model ID	Tumor growth curve	Drugs tested	Dosage	TGI
Mantle cell lymphoma	REC-1	yes	Ibrutinib	25 mg/kg, PO, QD 25 mg/kg, PO, QD 25 mg/kg, PO, QD 25 mg/kg, PO, QD	57% 56% 56% 56%
B cell lymphoma	DOHH-2	yes	Ibrutinib	25 mg/kg, PO, BID 25 mg/kg, PO, QD	-5.7% 33%
Mantle cell lymphoma	Mino	yes	Ibrutinib	25 mg/kg, PO, QD	8.5%
B cell lymphoma	RL	yes	--	--	--
GCB-DLBCL	SU-DHL-6	Yes	Ibrutinib	25 mg/kg, PO, QD	26.2%
GCB-DLBCL	SU-DHL-10	yes	Ibrutinib	25 mg/kg, PO, QD 90 mg/kg, PO, QD	45.9% 38%
ABC-DLBCL	SU-DHL-2	yes	--	--	--
ABC-DLBCL	TMD-8	Not available	--	--	--
ABC-DLBCL	OCI-LY10	Not available	--	--	--

Note:

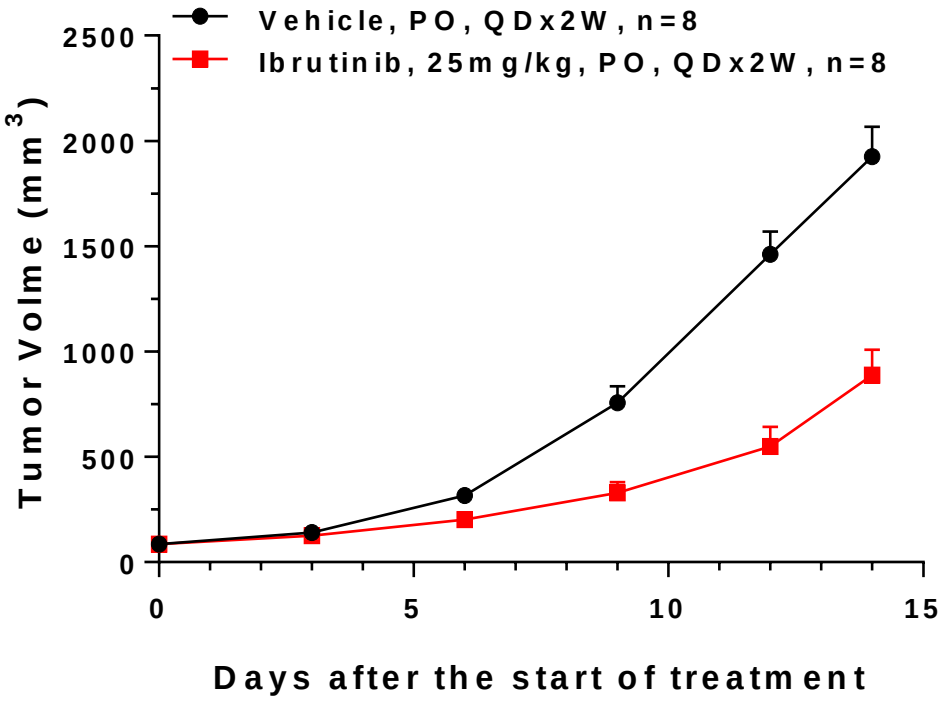
1) GCB-DLBCL: Germinal center B cell-like subtype of diffuse large B cell lymphoma
2) ABC-DLBCL: Activated B cell-like subtype of diffuse large B cell lymphoma

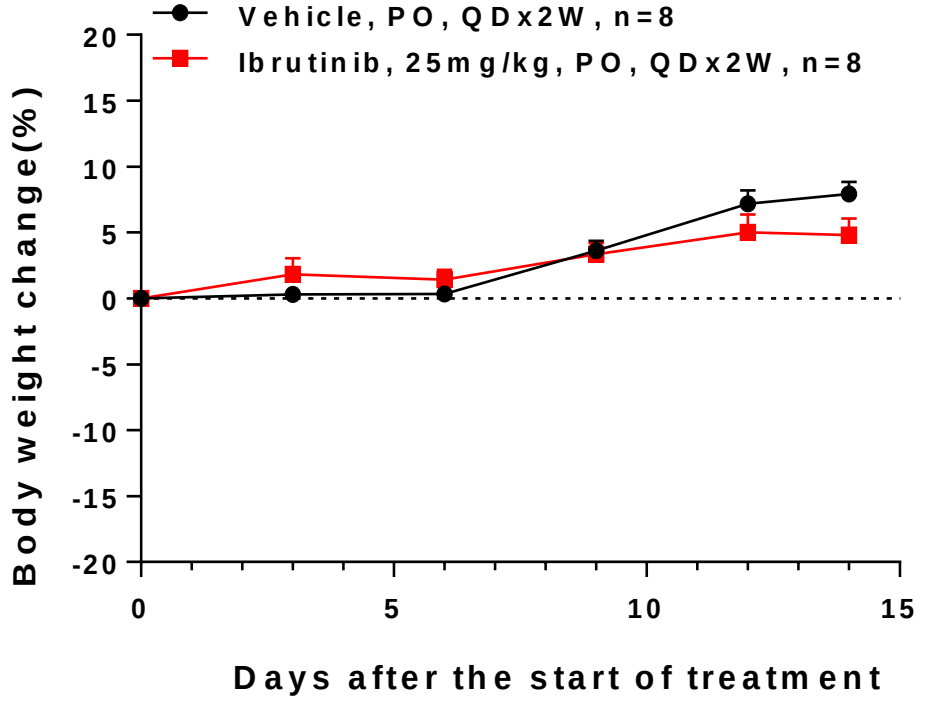
BTK inhibitor in REC-1 xenograft model



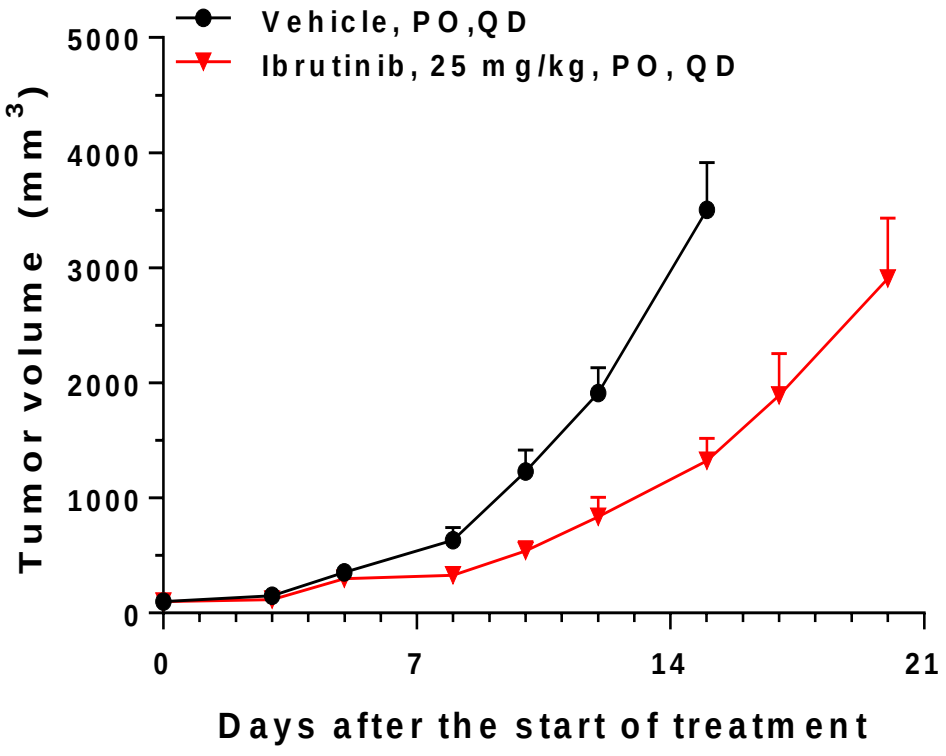


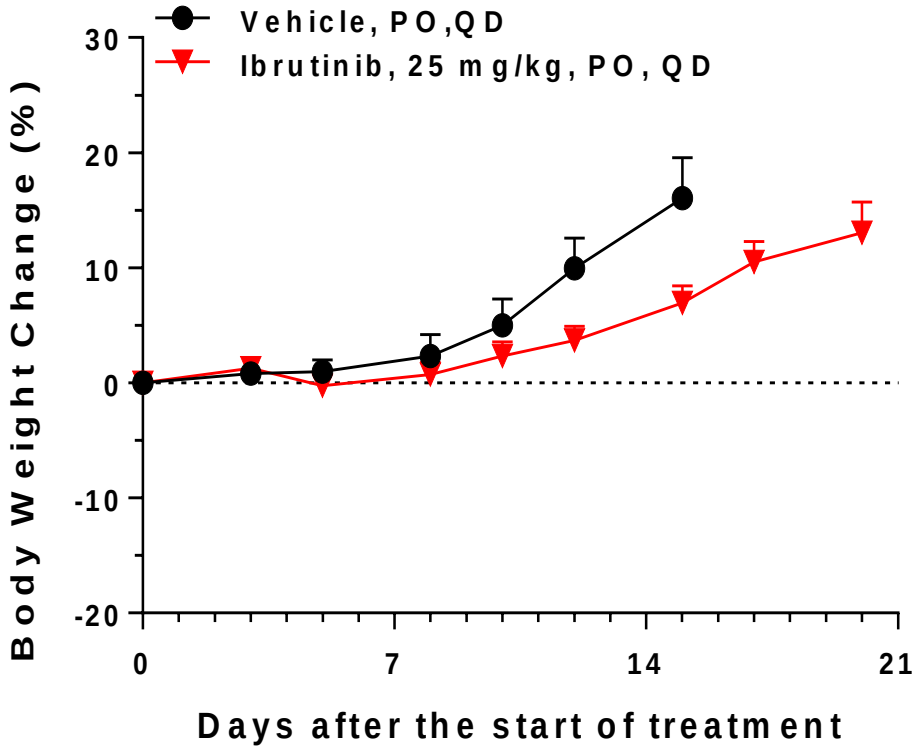
BTK inhibitor in REC-1 xenograft model



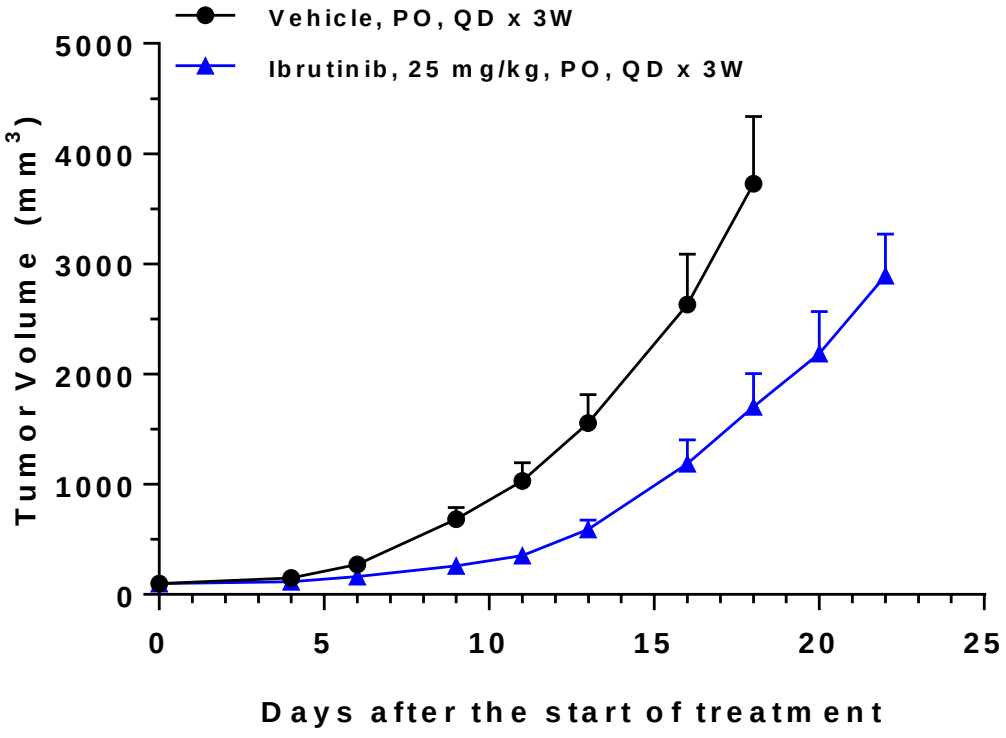


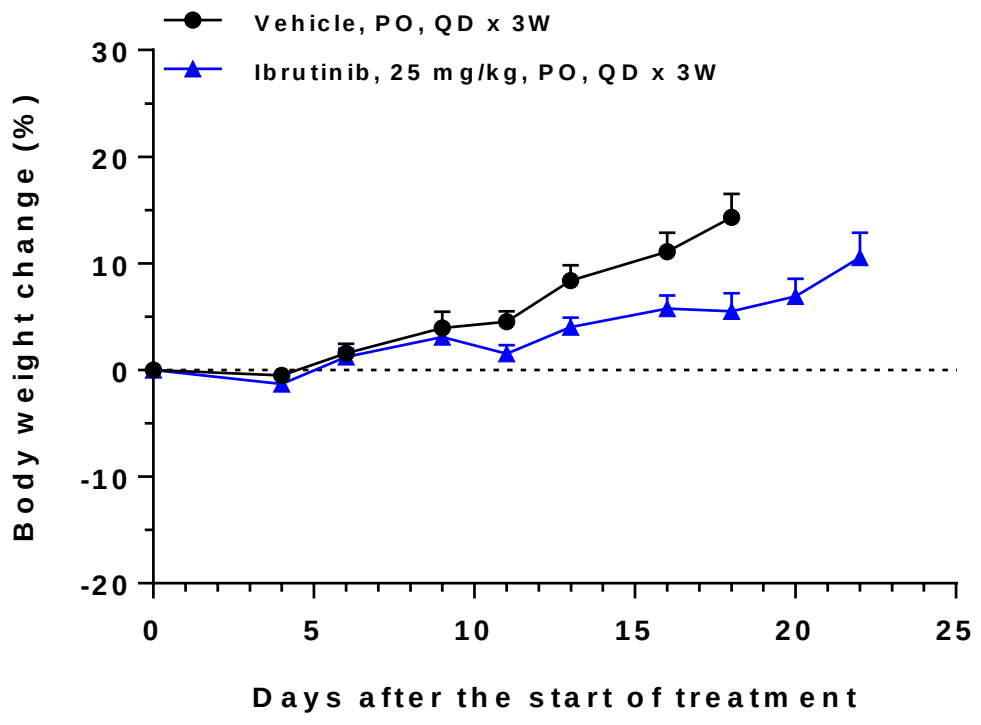
BTK inhibitor in REC-1 xenograft model



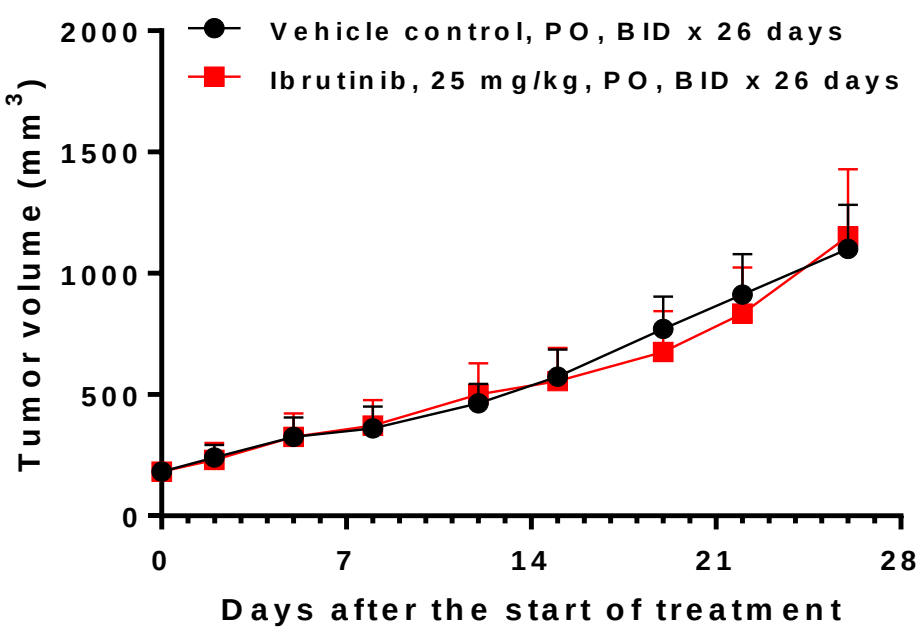


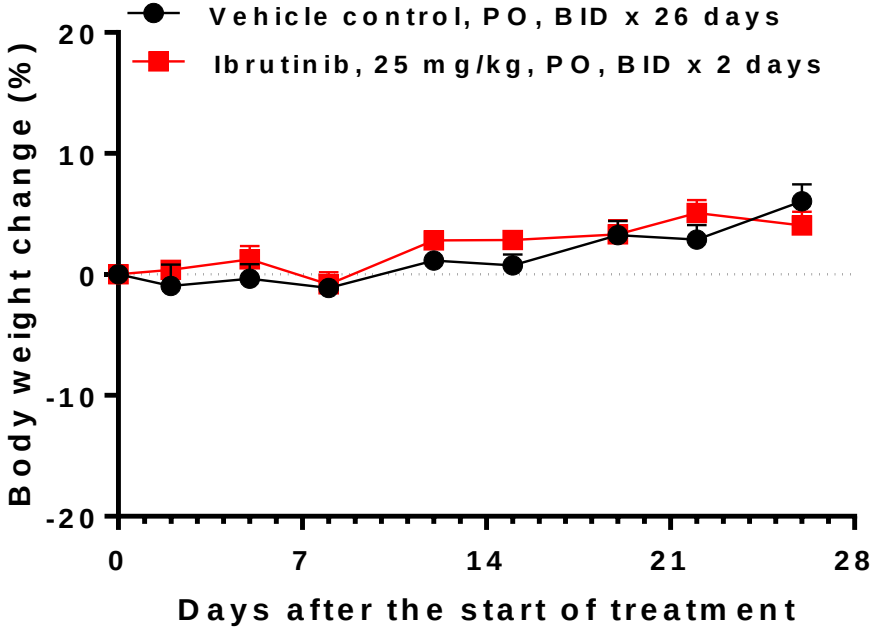
BTK inhibitor in REC-1 xenograft model



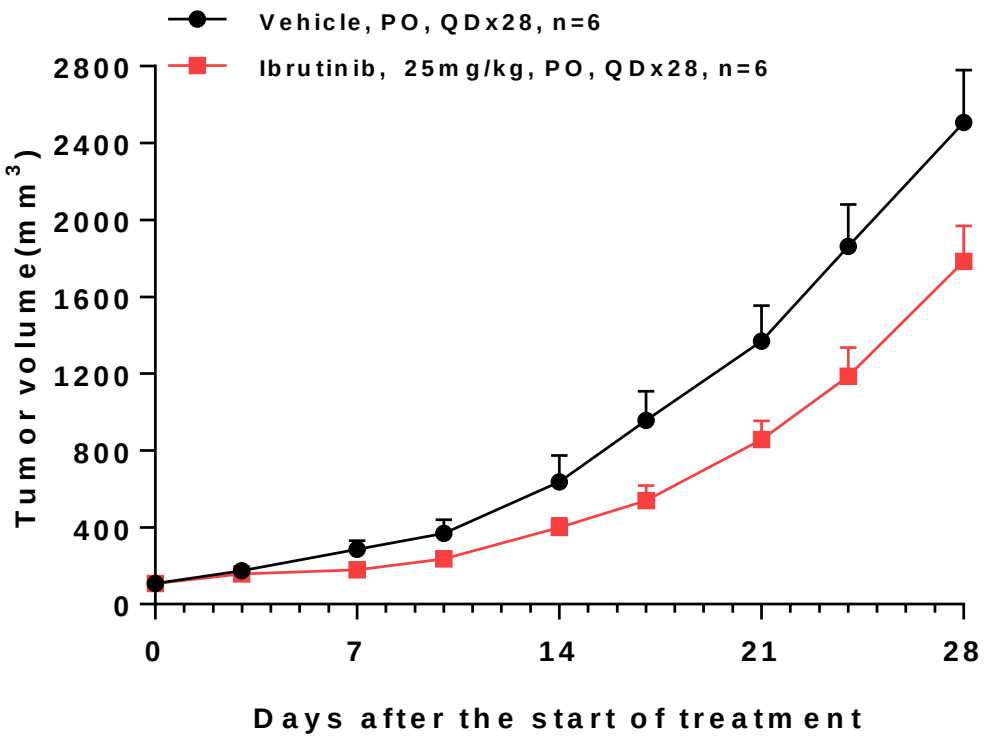


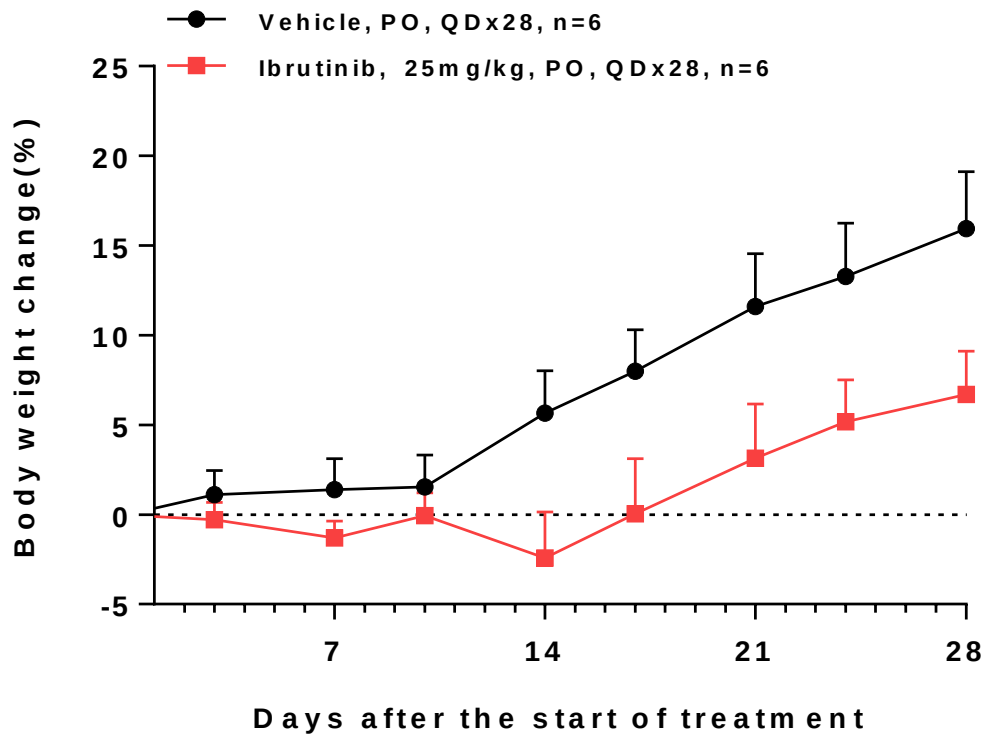
BTK inhibitor in DoHH-2 xenograft model



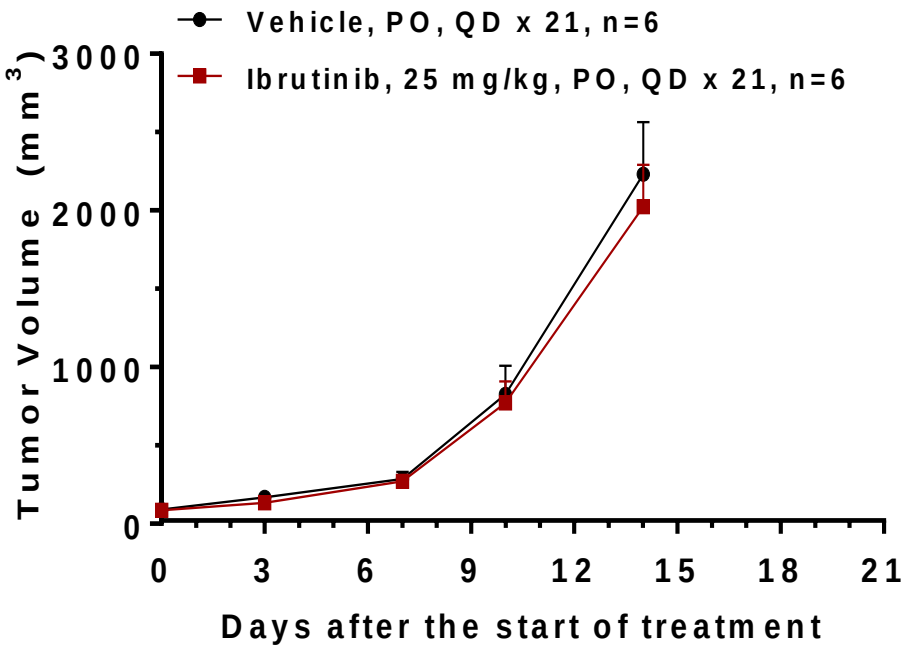


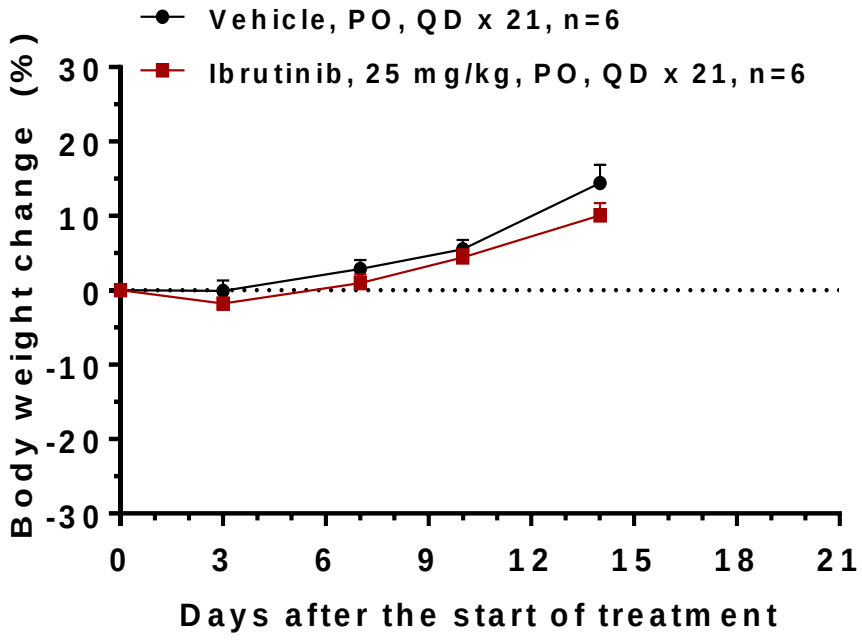
BTK inhibitor in DoHH-2 xenograft model



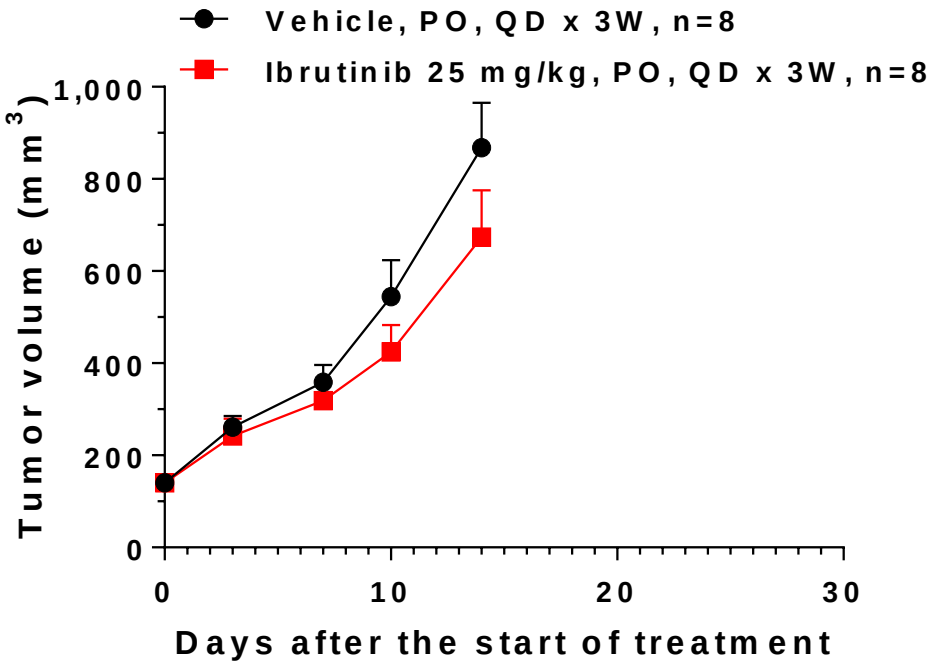


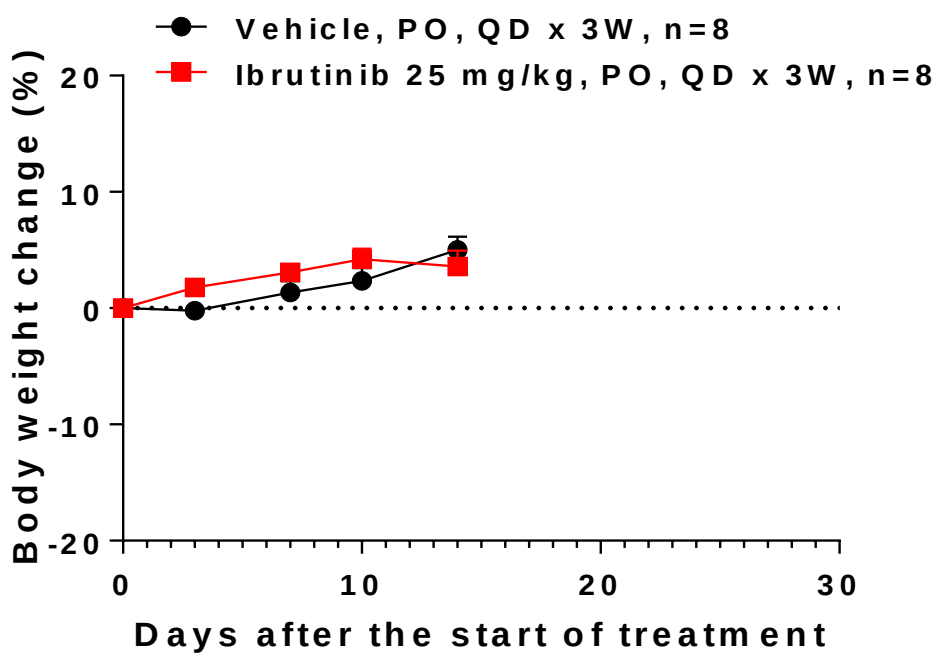
BTK inhibitor in Mino xenograft model



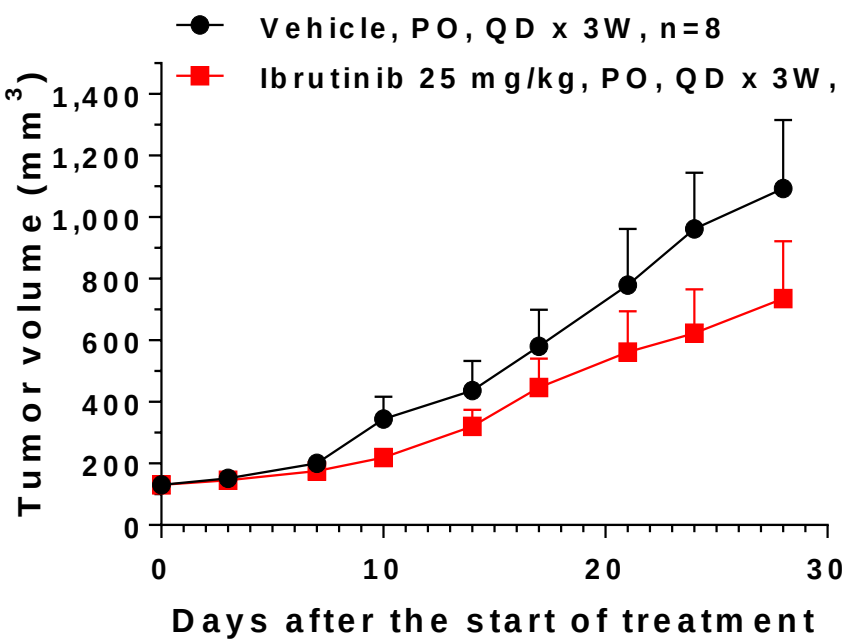


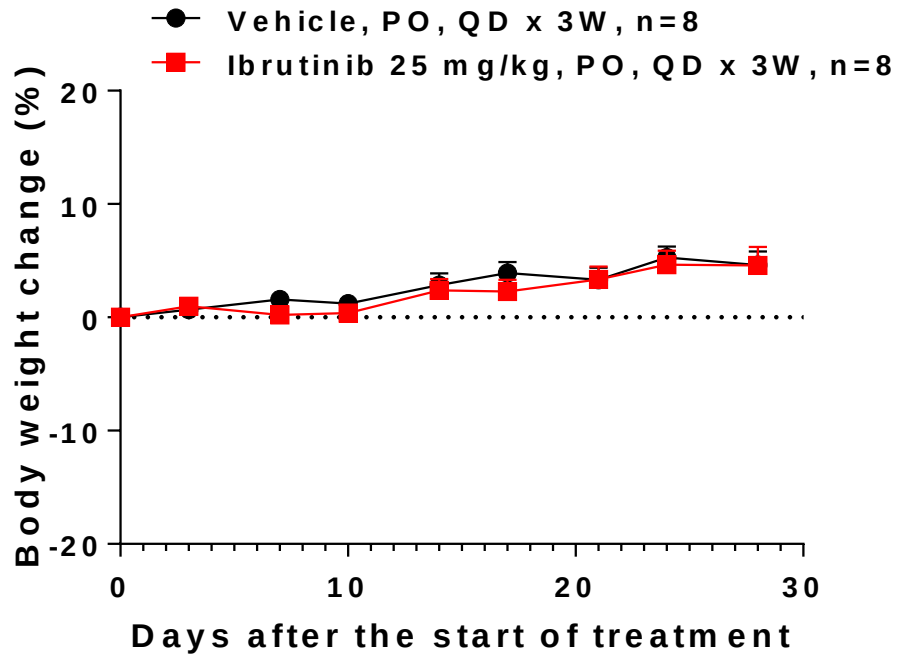
BTK inhibitor in SU-DHL-6 xenograft model



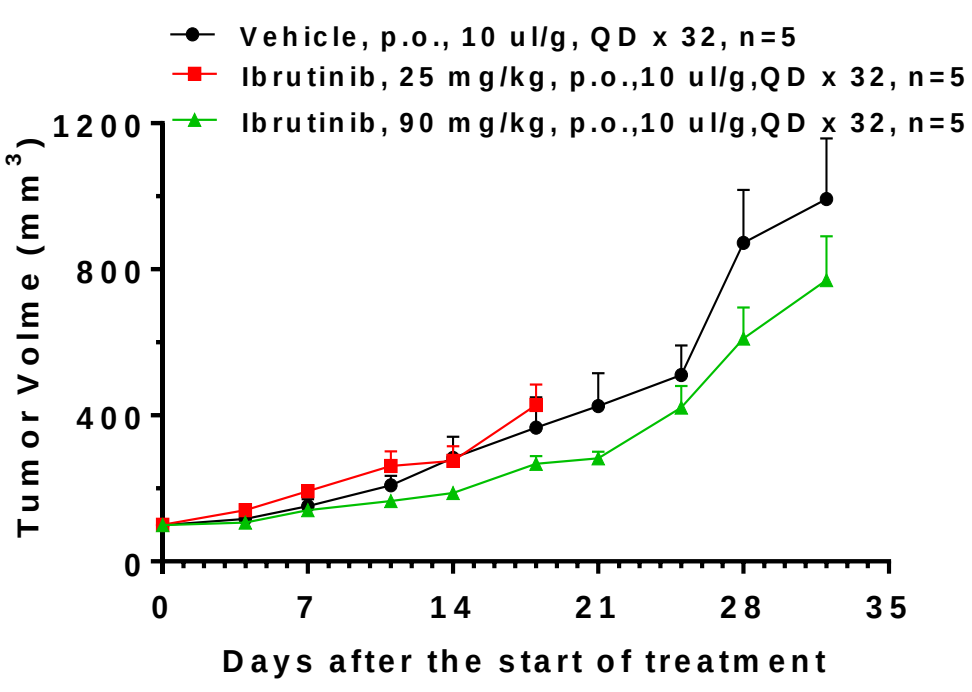


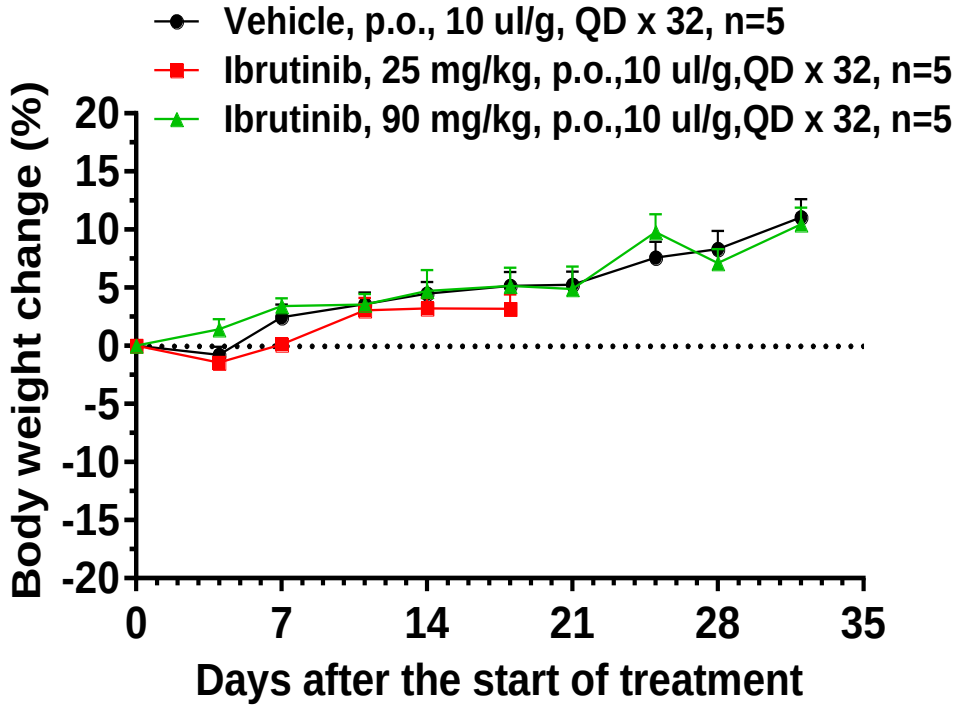
BTK inhibitor in SU-DHL-10 xenograft model





BTK inhibitor in SU-DHL-10 xenograft model





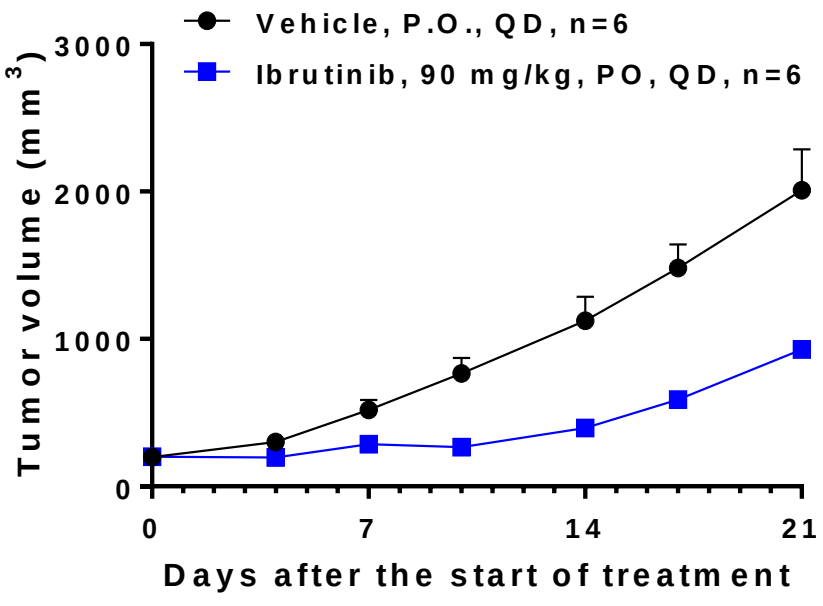
BTK relevant PDX models

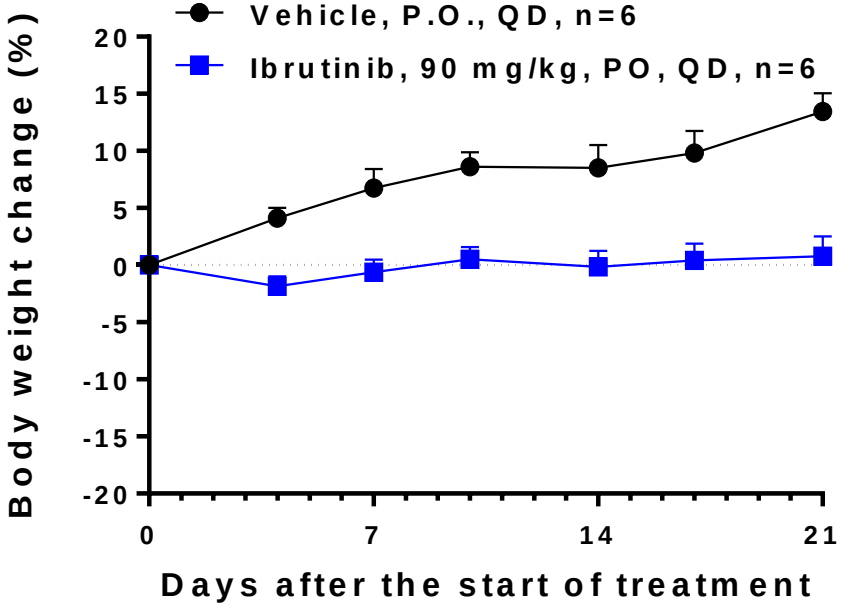
Cancer type	Model ID	Tumor growth curve	Drugs tested	Dosage	TGI
ABC-DLBCL	LY-24-0004	Yes	Ibrutinib	90 mg/kg, PO, QD	60%
ABC-DLBCL	LY-24-0014	Yes	Ibrutinib	90 mg/kg, PO, QD	-56%
GCB-DLBCL	LY-24-0019	Yes	Ibrutinib	50 mg/kg, PO, QD 90 mg/kg, PO, QD	41% 47%

Note:

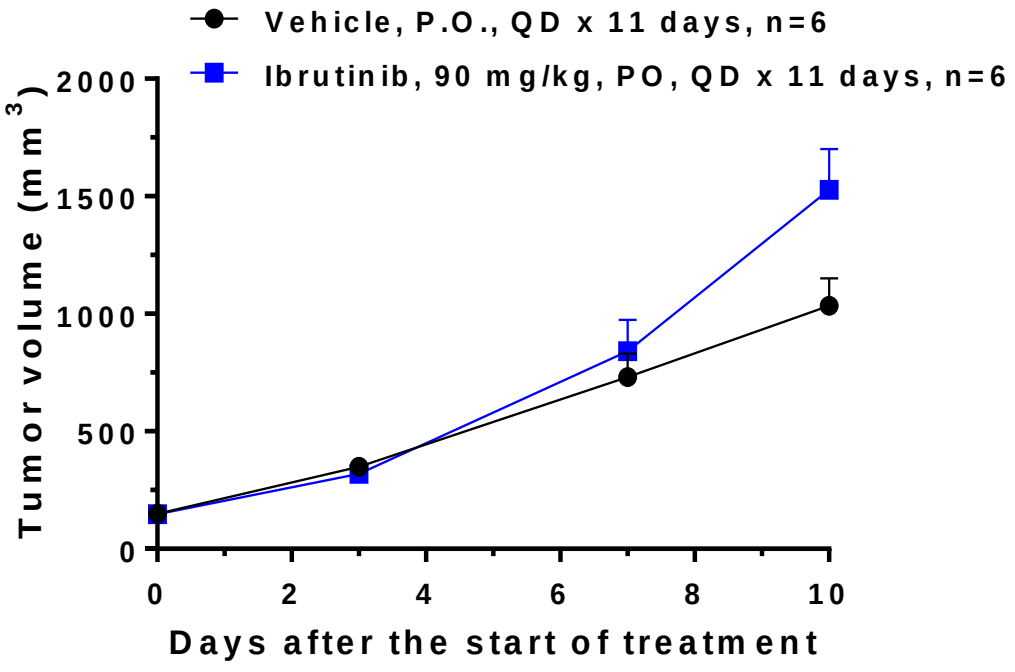
1) GCB-DLBCL: Germinal center B cell-like subtype of diffuse large B cell lymphoma
2) ABC-DLBCL: Activated B cell-like subtype of diffuse large B cell lymphoma

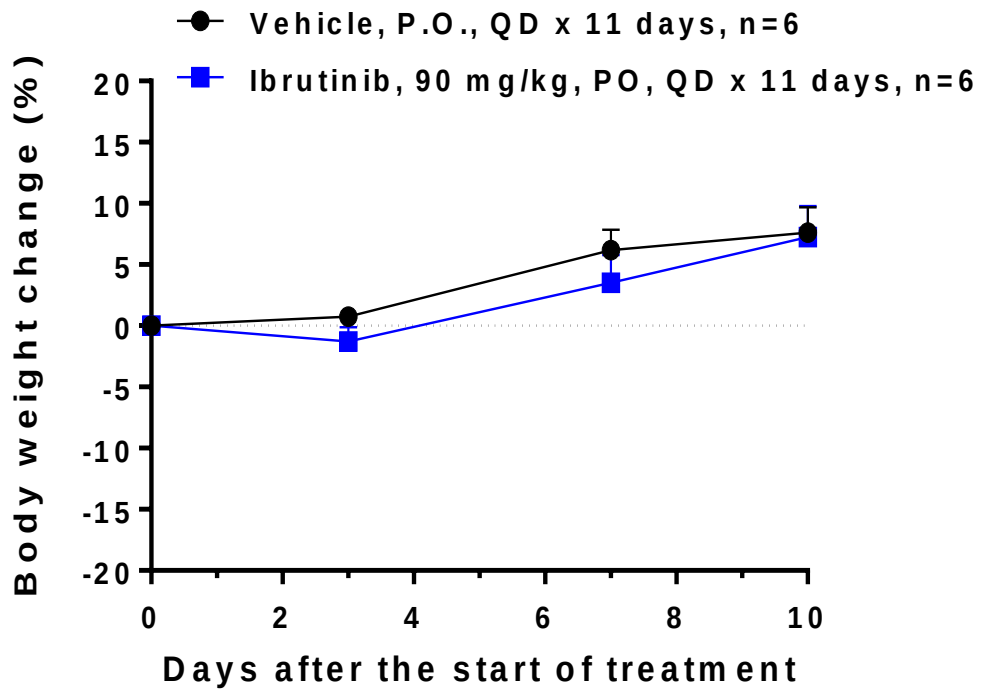
BTK inhibitor in LY-24-0004



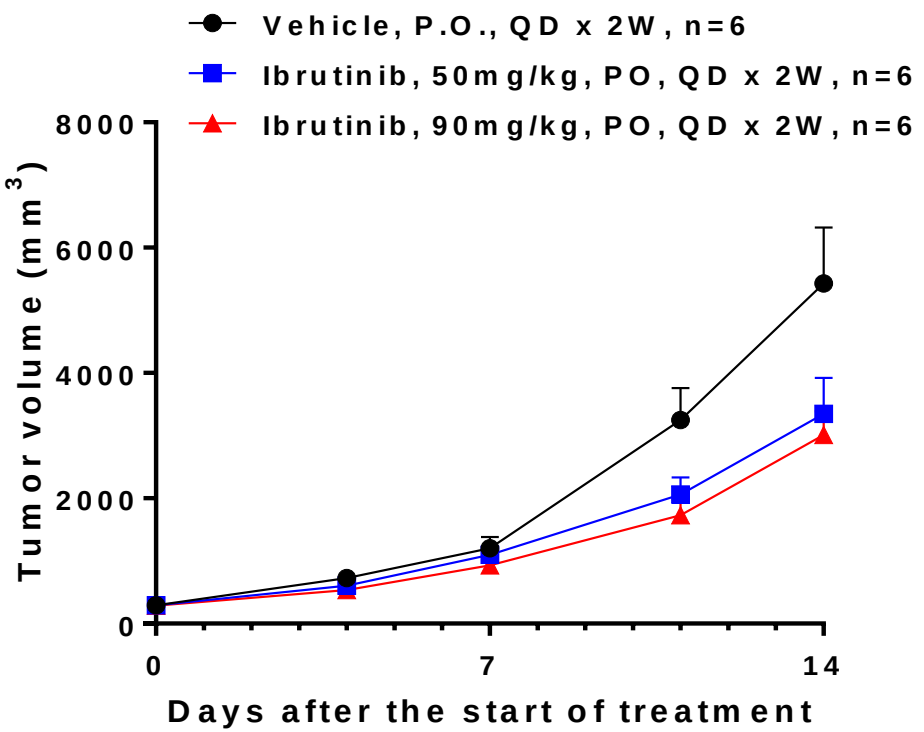


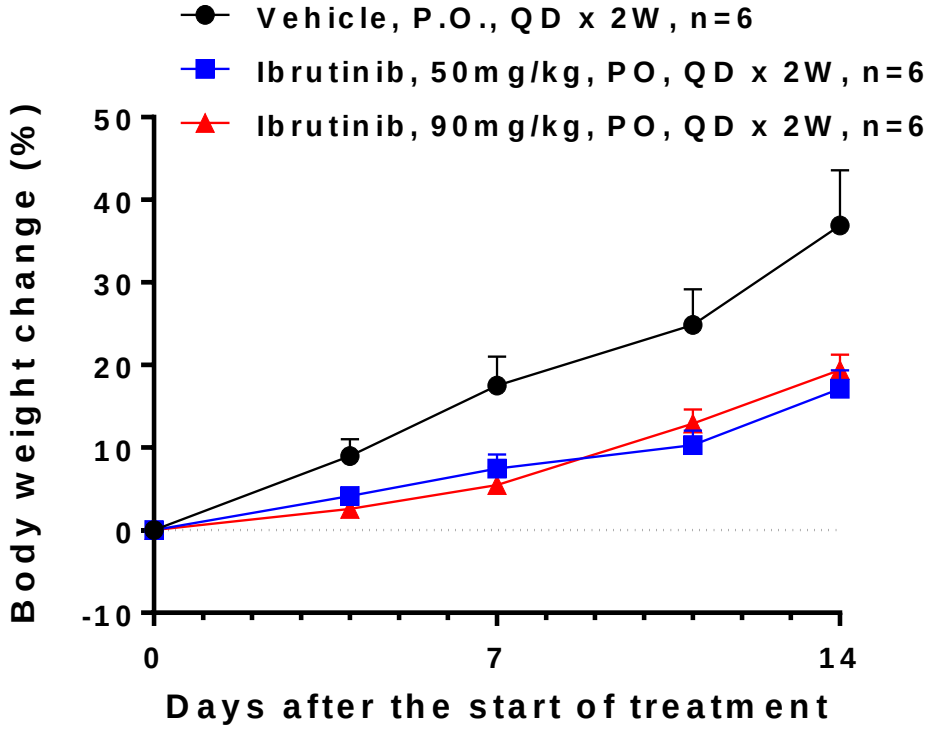
BTK inhibitor in LY-24-0014





BTK inhibitor in LY-24-0019





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