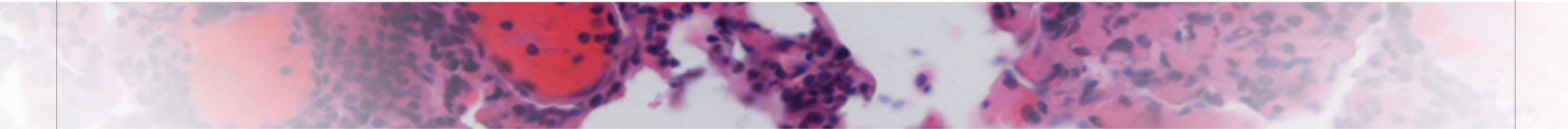




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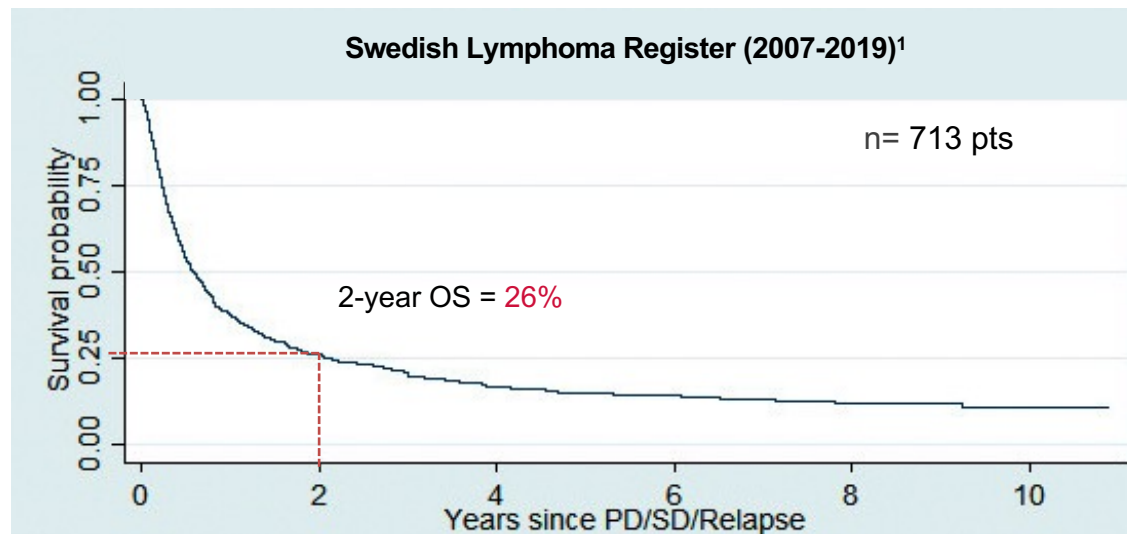


Btm-3566, a Novel Activator of the Mitochondrial Stress Response Promotes Robust Therapeutic Responses in Diffuse Large B-Cell Lymphoma

Adrian Schwarzer, M.D., Ph.D.

Dept. of Hematology, Oncology, Hemostaseology and Stem Cell Transplantation
Hannover Medical School

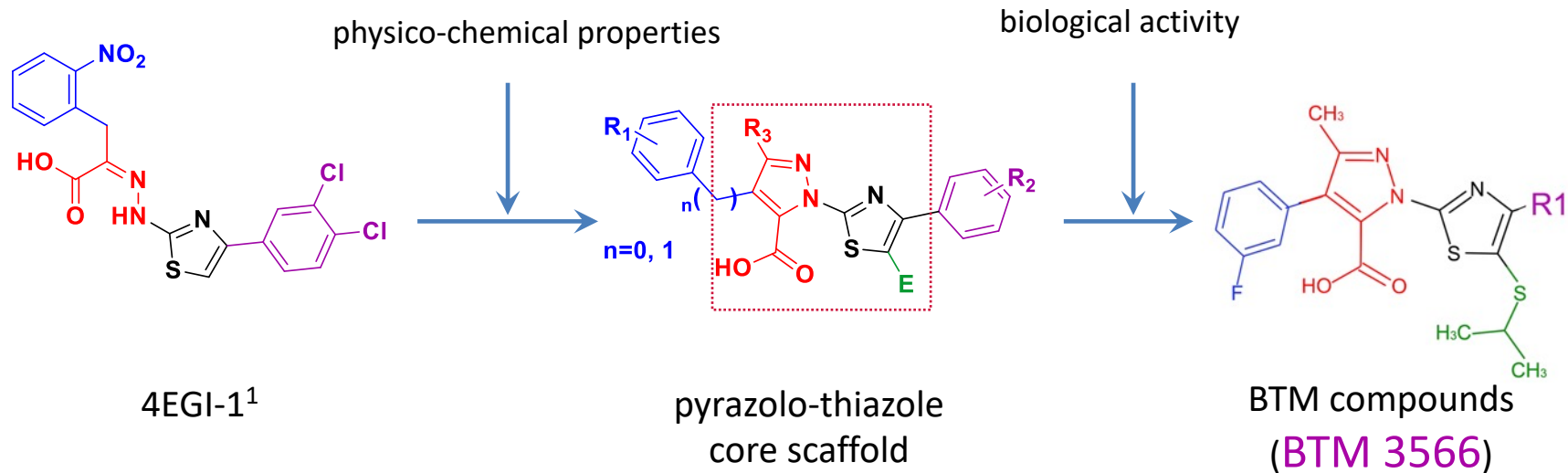
r/r-DLBCL is a therapeutic challenge



¹Ekstrom et al. Blood, Volume 134, Supplement 1, 2019.



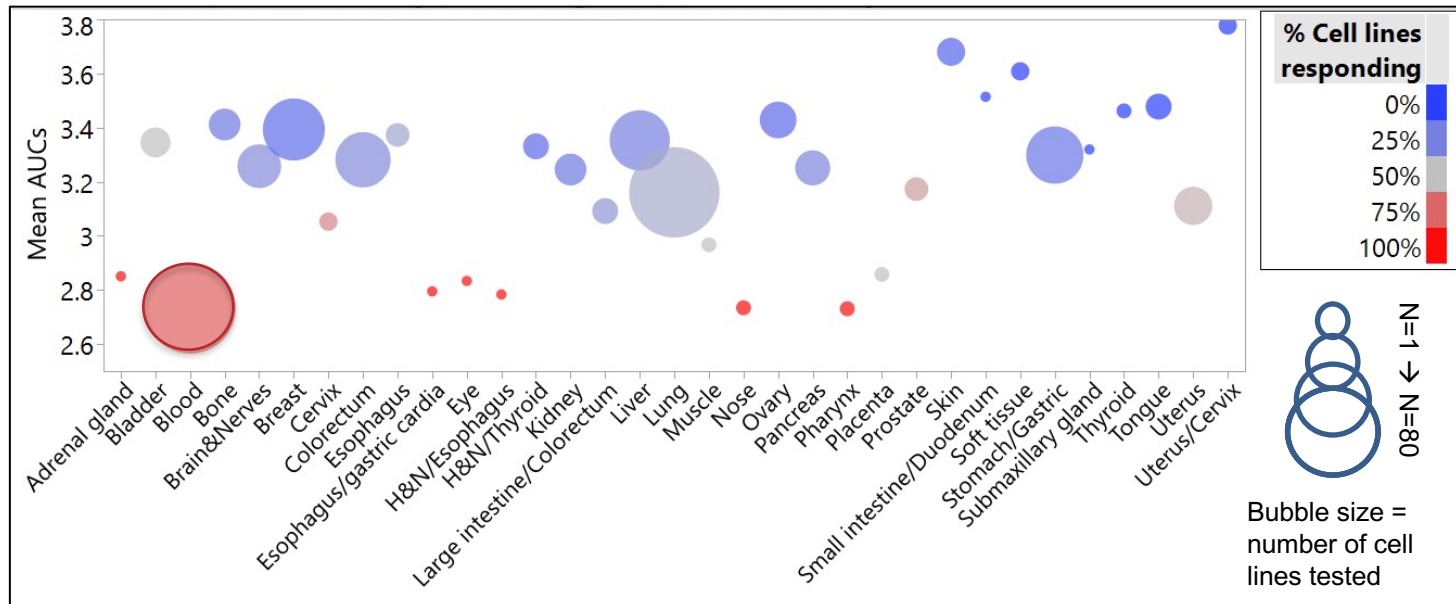
Pyrazolo-thiazol derivatives as anti-cancer agents



1. Moerke, N. J. *et al.* Small-molecule inhibition of the interaction between the translation initiation factors eIF4E and eIF4G. *Cell* **128**, 257–267 (2007).

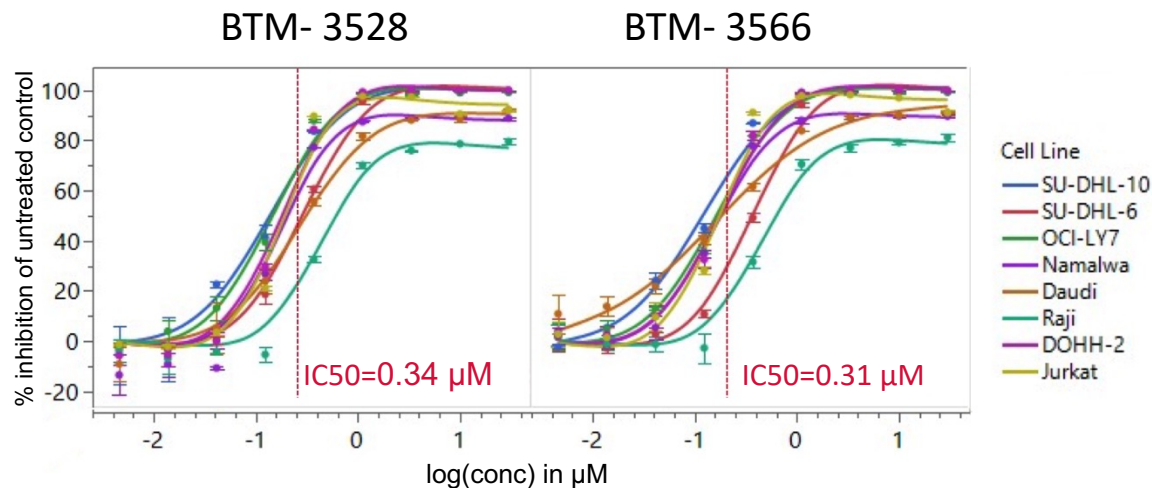


BTM-3566 is mainly effective in hematologic tumors



- Response and potency tested in **n=406** tumor cell lines

BTM-compounds are potently active in DLBCL

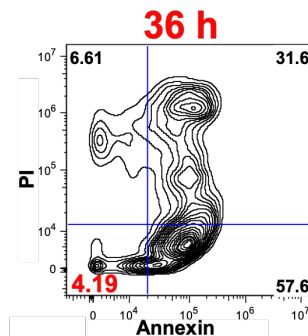
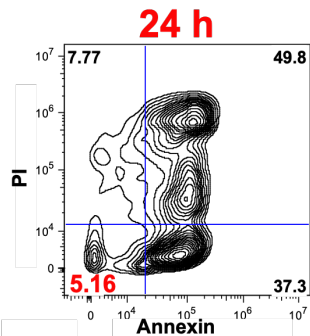
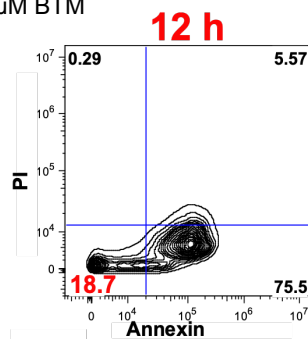
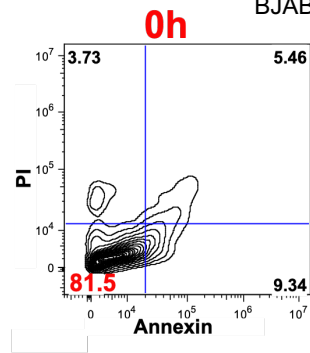


Subtype	Cell Line	IC ₅₀ (μM)
Double Hit (GCB)	SU-DHL 10	0.14
Double Hit (GCB)	SU-DHL 6	0.29
Double Hit (GCB)	SU-DHL 4	0.51
Triple Hit (GCB)	DOHH-2	0.18
GCB/Burkitt	BJAB	0.31
Burkitt	Raji	0.55
Burkitt	Daudi	0.2
Burkitt	Nawalma	0.18
ABC	SU-DHL 2	0.11
ABC	U2932	0.46
ABC	OCI-Ly3	0.68
"Type 3"	OCI-Ly7	0.15

BTM-compounds induce rapid and complete apoptosis in DLBCL

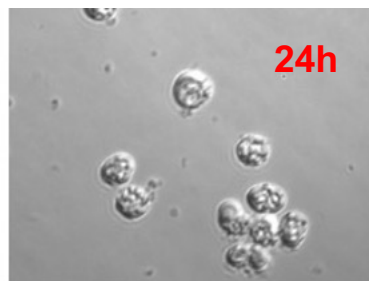
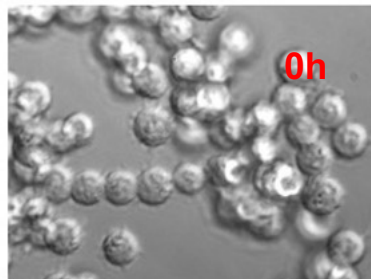
Annexin-PI

BJAB + 2 μ M BTM



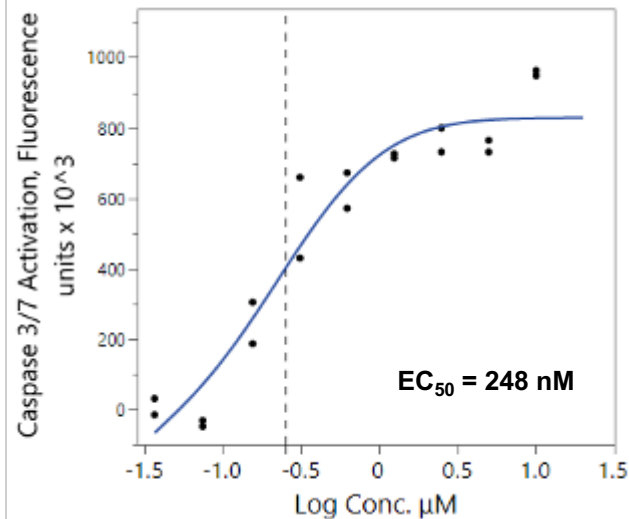
Microscopy

BJAB + 2 μ M BTM

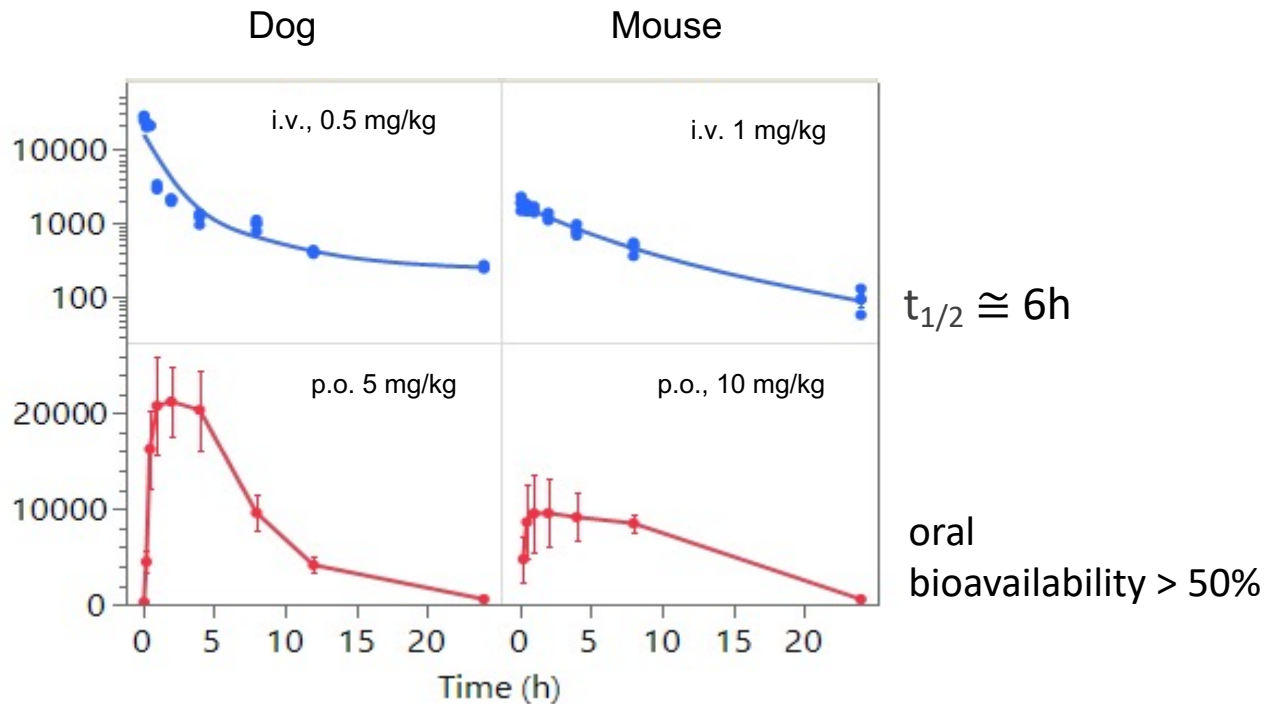
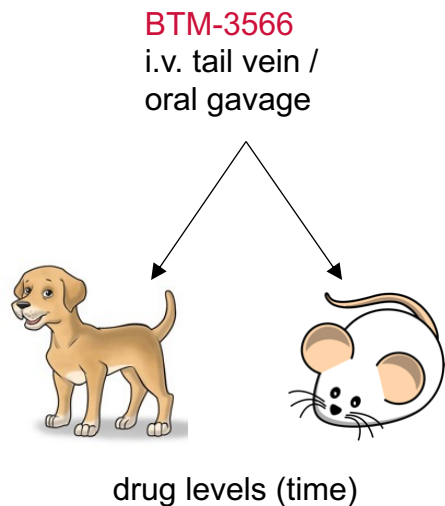


Induction of Caspase Activity

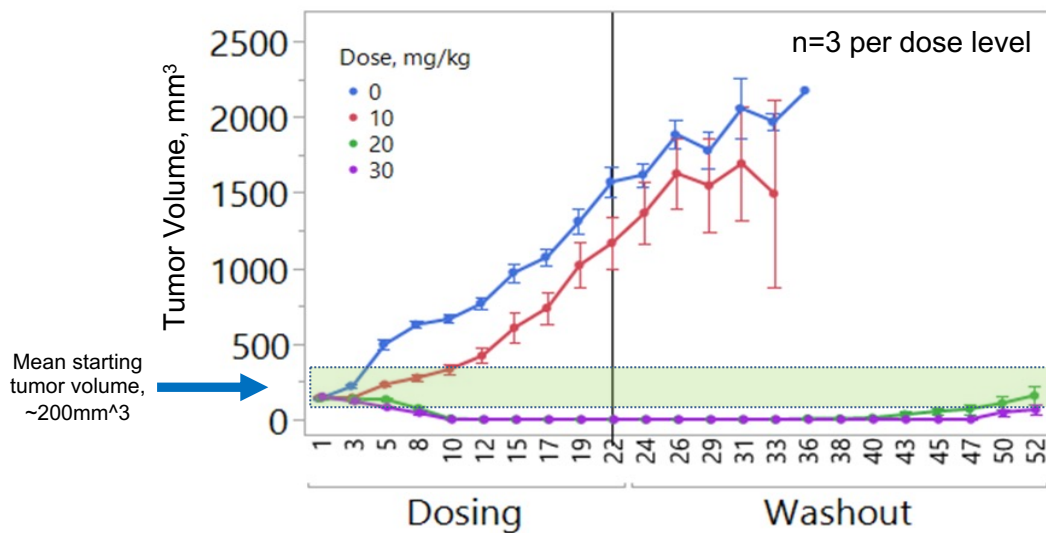
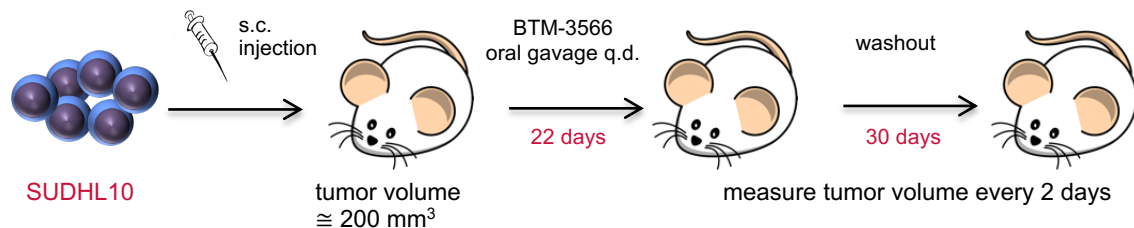
BJAB + BTM-3566



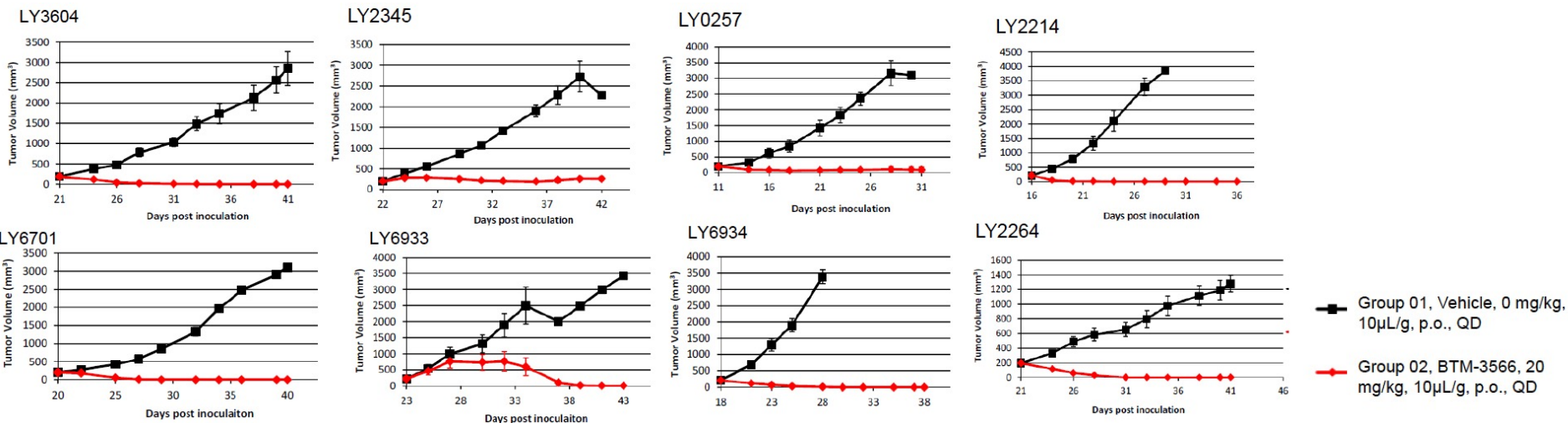
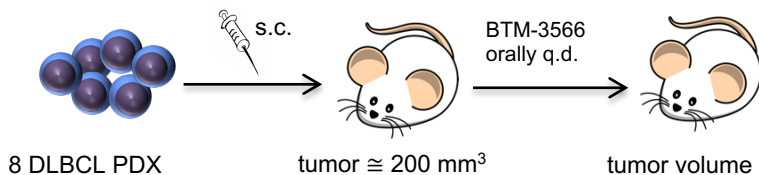
BTM-3566 has good oral bioavailability



BTM-3566 activity in SU-DHL10 DLBCL xenograft model



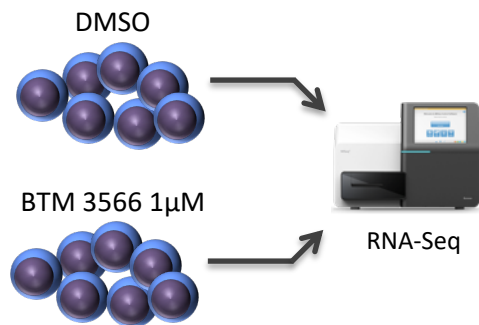
BTM-3566 induces complete remissions in DLBCL PDX-Models



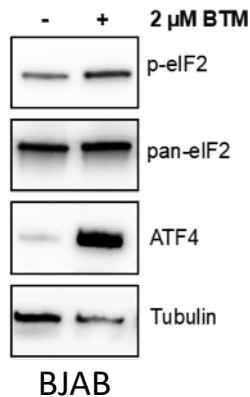
$\Sigma = 19 \text{ CR} / 2 \text{ PR} / 3 \text{ SD}$



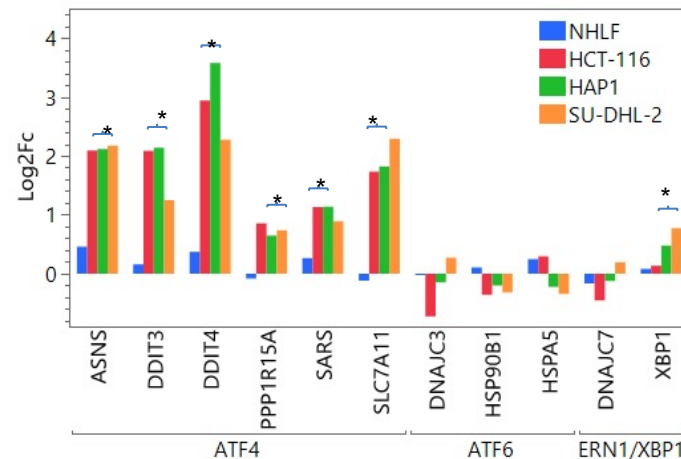
BTM-compounds activate the integrated stress response (ISR)



ISR → p-eIF2α → ATF4

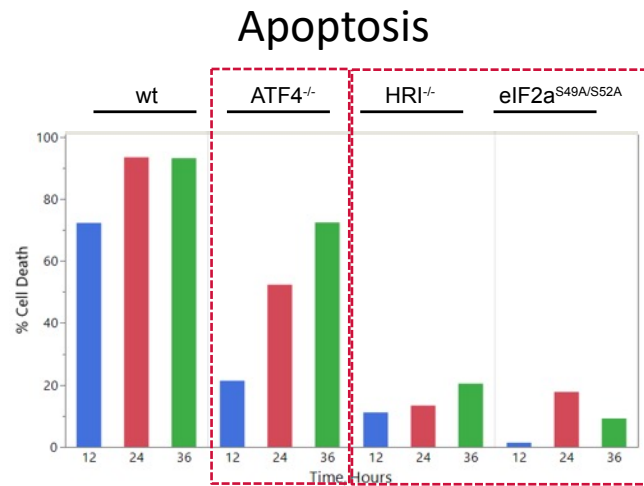
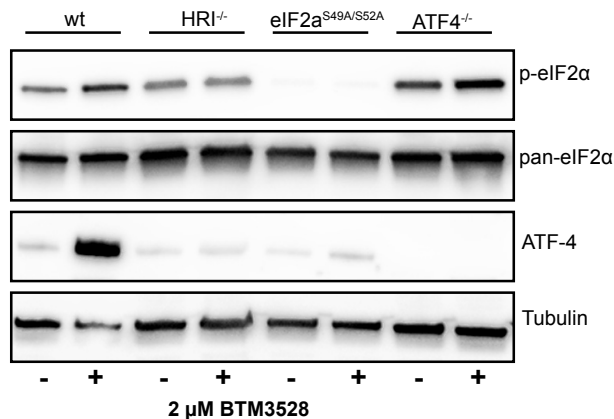
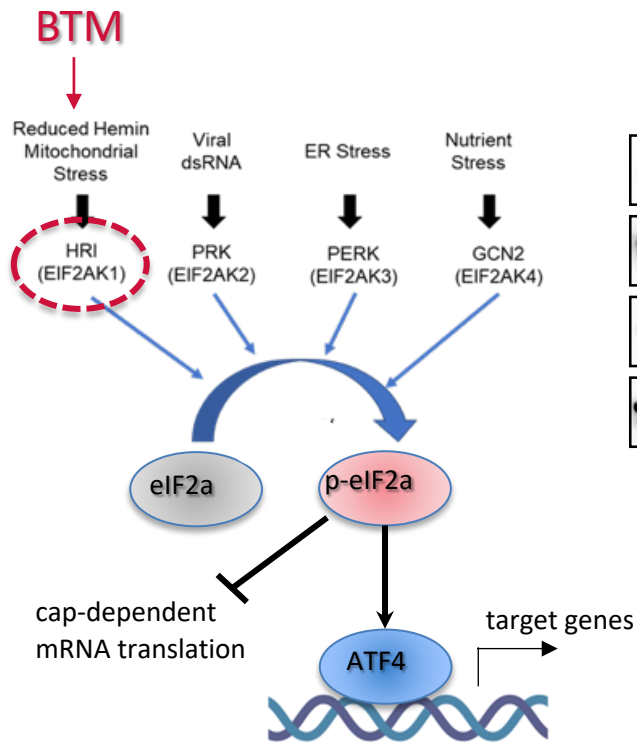


qPCR for ATF-4 target genes

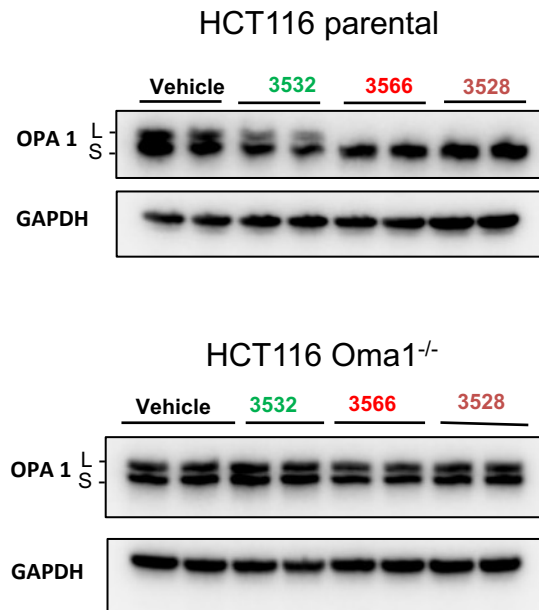
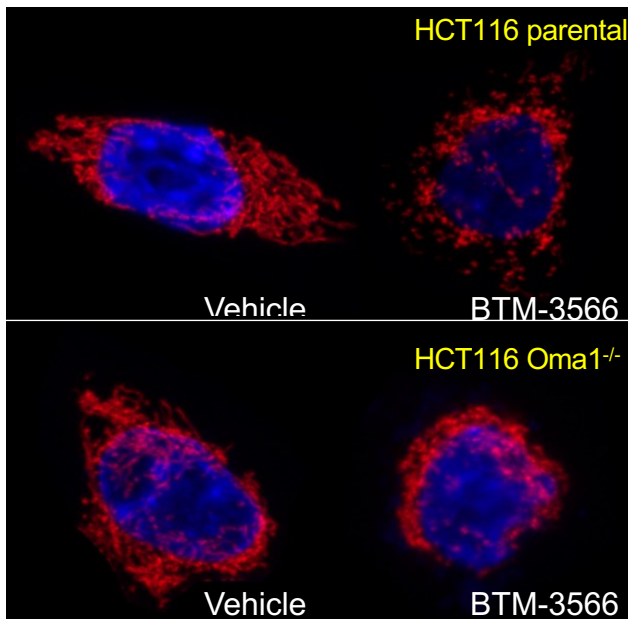
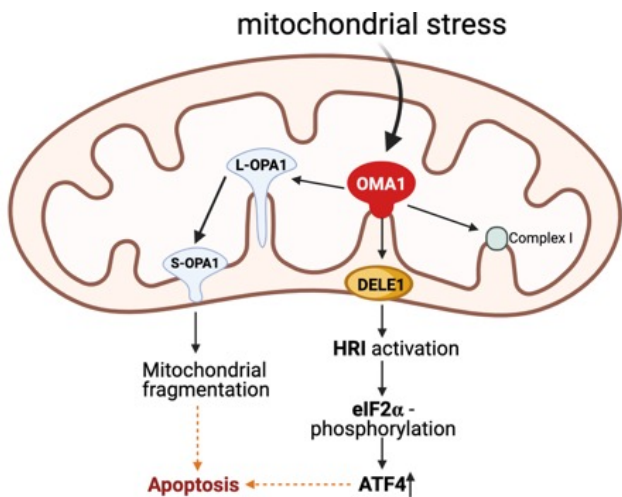


Reactome Pathway	Fold Enrichment	FDR
Response of EIF2AK1 (HRI) to heme deficiency	33.2	4.00E-07
Cytosolic tRNA aminoacylation	18.5	4.00E-05
Amino acid transport across the plasma membrane	17.3	3.00E-06
ATF4 activates genes in response to endoplasmic reticulum stress	16.4	6.00E-05

HRI relays the BTM-induced stress signal to induce apoptosis

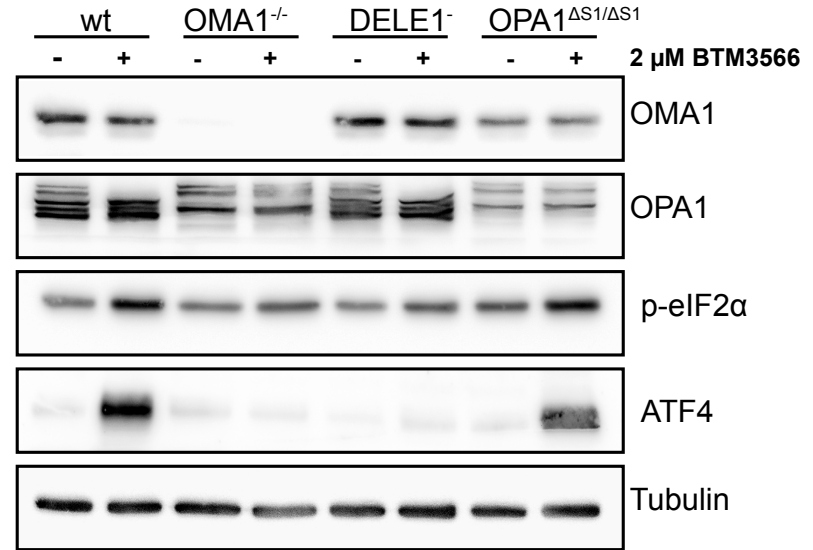
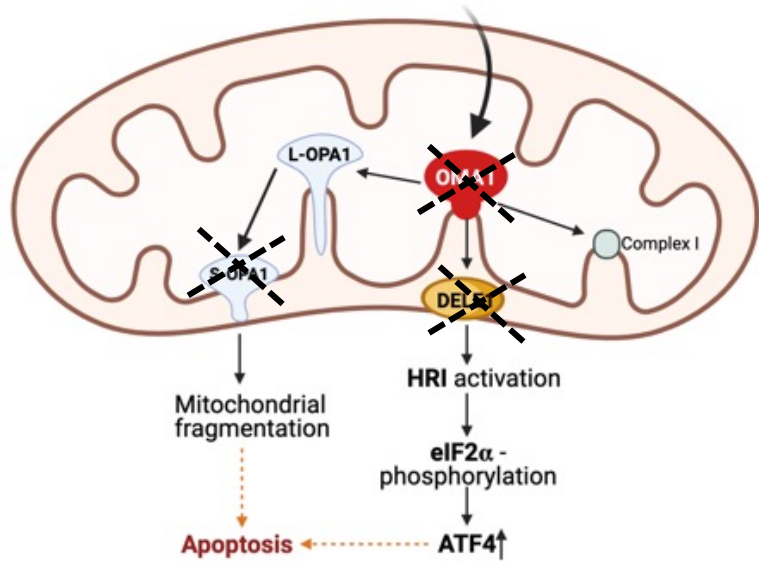


BTM-compounds activate OMA1 and induce fragmentation of the mitochondrial network

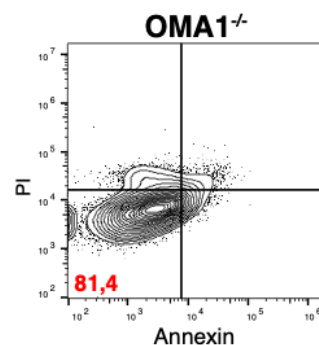
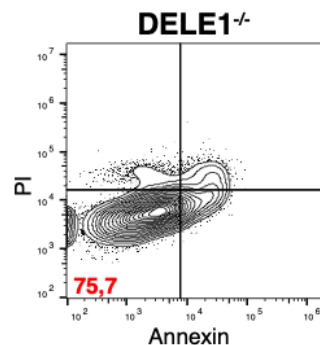
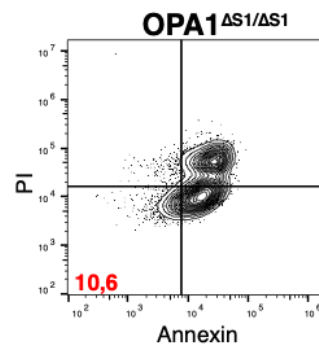
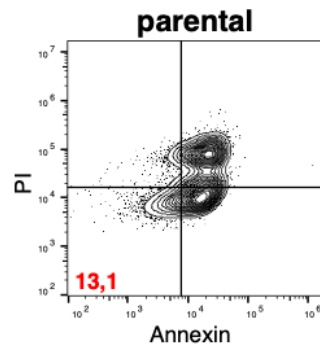
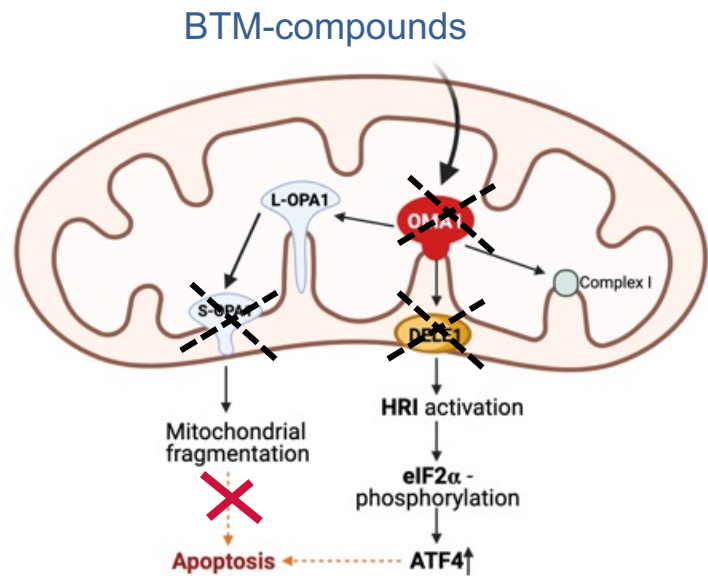


The OMA1-DELE1-HRI pathway relays BTM-induced mitochondrial stress to the cytosol

BTM-compounds

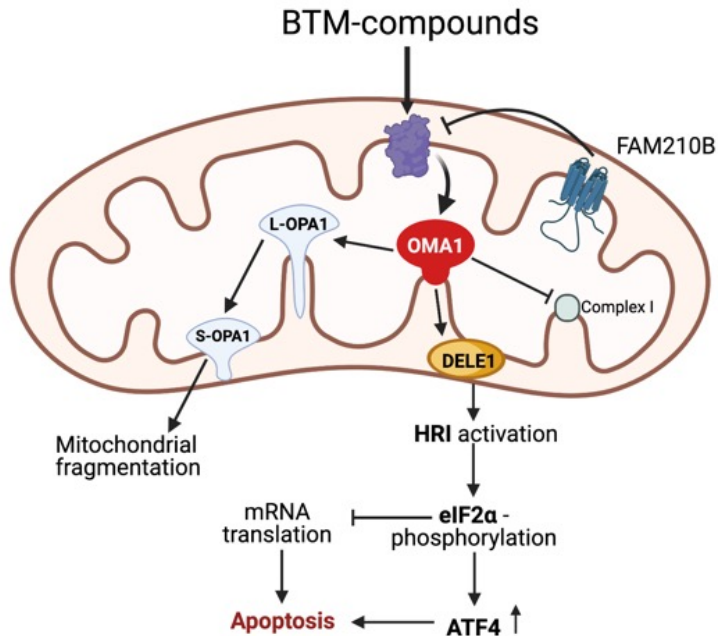


The OMA1-DELE1-HRI pathway relays BTM-induced mitochondrial stress to the cytosol



BJAB
2 μ M BTM-3566 /
48h

Summary



- BTM-3566: novel small molecule with **potent single agent** activity in DLBCL
- orally available, well tolerated in mice
- BTMs selectively disrupt mitochondrial function in DLBCL leading to **apoptosis** via **OMA1-DELE1-HRI**
- preclinical studies for an IND-application are under way

Acknowledgements

BANTAM Pharmaceutical

- **Matthew Kostura[#]**
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*contributed equally
[#]supervised jointly

