Università della Svizzera Italiana (USI)
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The BET Bromodomain inhibitor OTX015 affects pathogenetic pathways in preclinical B-cell Tumor models and synergizes with targeted drugs

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Overview on OTX015 in lymphoid tumors

- Introduction
- BET Bromodomain inhbitors as single agent in mature B-cell lymphomas: activity and mechanisms of action of OTX015
- Combination studies
- Possible biomarkers
- Conclusions

Haematological cancers are among the commonest cancers

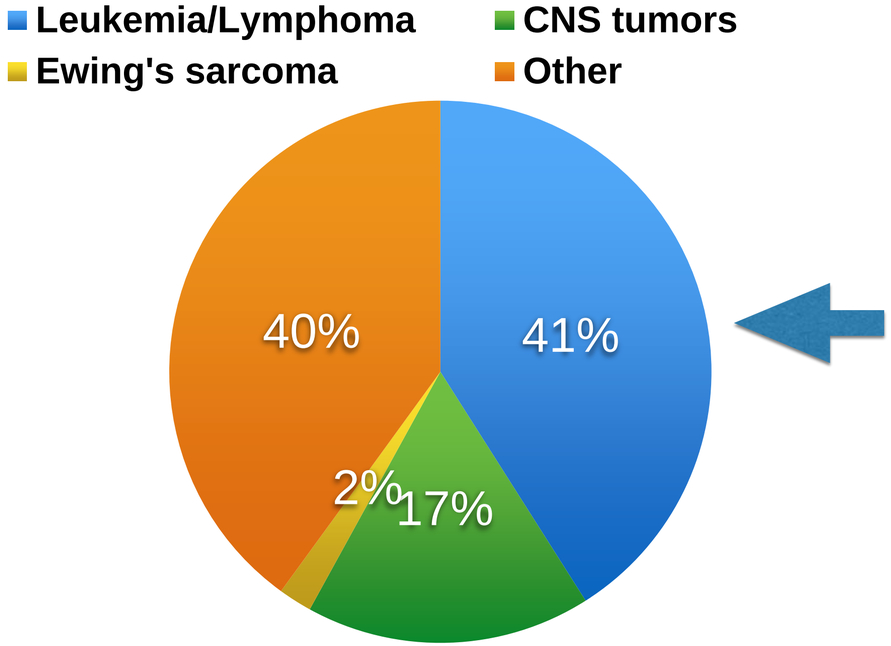
Estimated New Cases

	Males			Females	
Prostate	220,800	26%		Breast	231,840	29%
Lung & bronchus	115,610	14%		Lung & bronchus	105,590	13%
Colon & rectum	69,090	8%		Colon & rectum	63,610	8%
Urinary bladder	56,320	7%		Uterine corpus	54,870	7%
Melanoma of the skin	42,670	5%		Thyroid	47,230	6%
Non-Hodgkin lymphoma	39,850	5%		Non-Hodgkin lymphoma	32,000	4%
Kidney & renal pelvis	38,270	5%		Melanoma of the skin	31,200	4%
Oral cavity & pharynx	32,670	4%		Pancreas	24,120	3%
Leukemia	30,900	4%		Leukemia	23,370	3%
Liver & intrahepatic bile duct	25,510	3%		Kidney & renal pelvis	23,290	3%
All Sites	**848,200**	**100%**		**All Sites**	**810,170**	**100%**

Estimated Deaths

	Males			Females	
Lung & bronchus	86,380	28%		Lung & bronchus	71,660	26%
Prostate	27,540	9%		Breast	40,290	15%
Colon & rectum	26,100	8%		Colon & rectum	23,600	9%
Pancreas	20,710	7%		Pancreas	19,850	7%
Liver & intrahepatic bile duct	17,030	5%		Ovary	14,180	5%
Leukemia	14,210	5%		Leukemia	10,240	4%
Esophagus	12,600	4%		Uterine corpus	10,170	4%
Urinary bladder	11,510	4%		Non-Hodgkin lymphoma	8,310	3%
Non-Hodgkin lymphoma	11,480	4%		Liver & intrahepatic bile duct	7,520	3%
Kidney & renal pelvis	9,070	3%		Brain & other nervous system	6,380	2%
All Sites	**312,150**	**100%**		**All Sites**	**277,280**	**100%**

adults

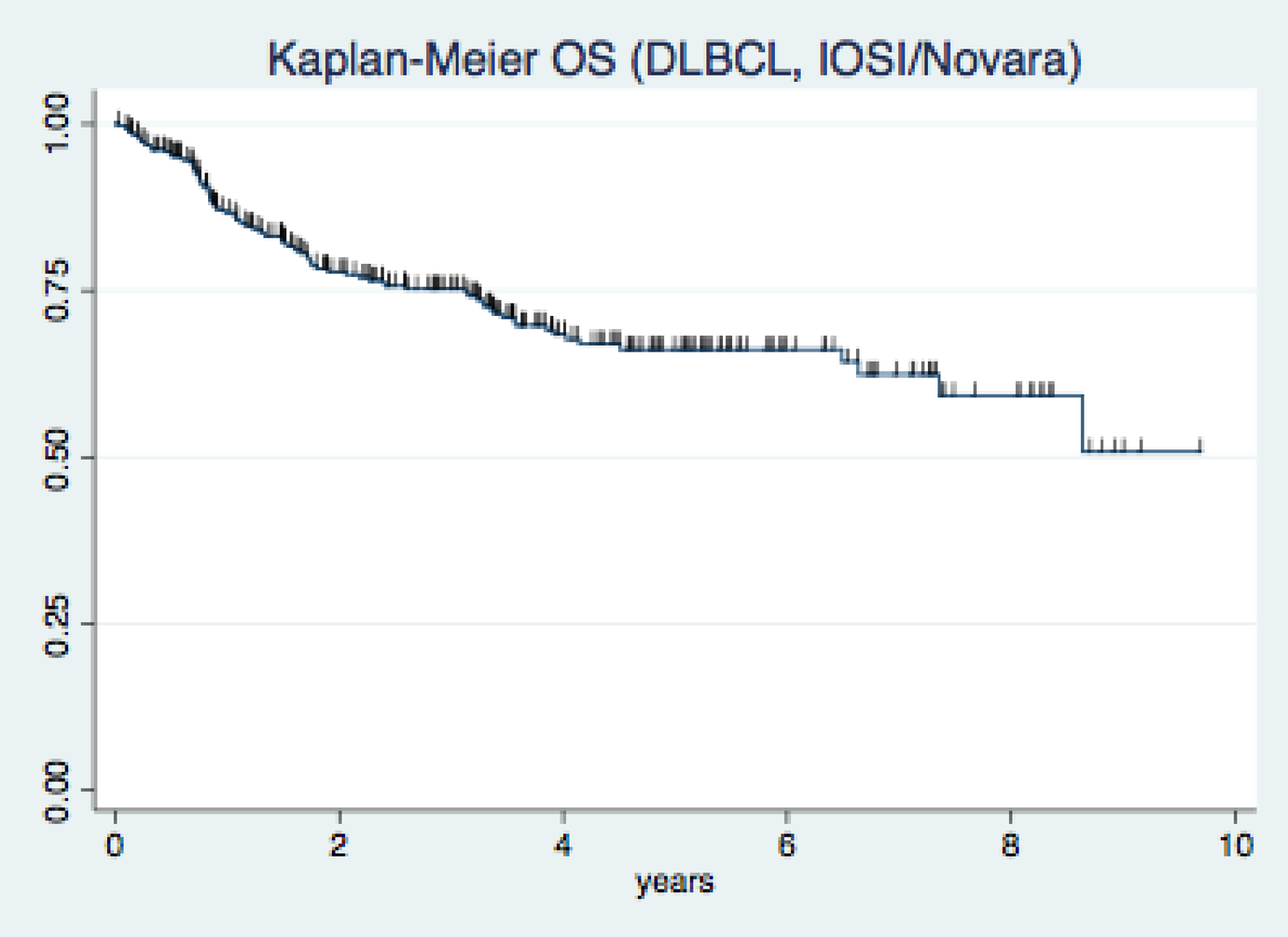


< 20 years of age

Siegel et al, CA: Cancer 2015

Stewart & Wild eds. World Cancer Report 2014

Still too many patients die due to lymphoma



Need of novel therapies

IOSI, unpublished

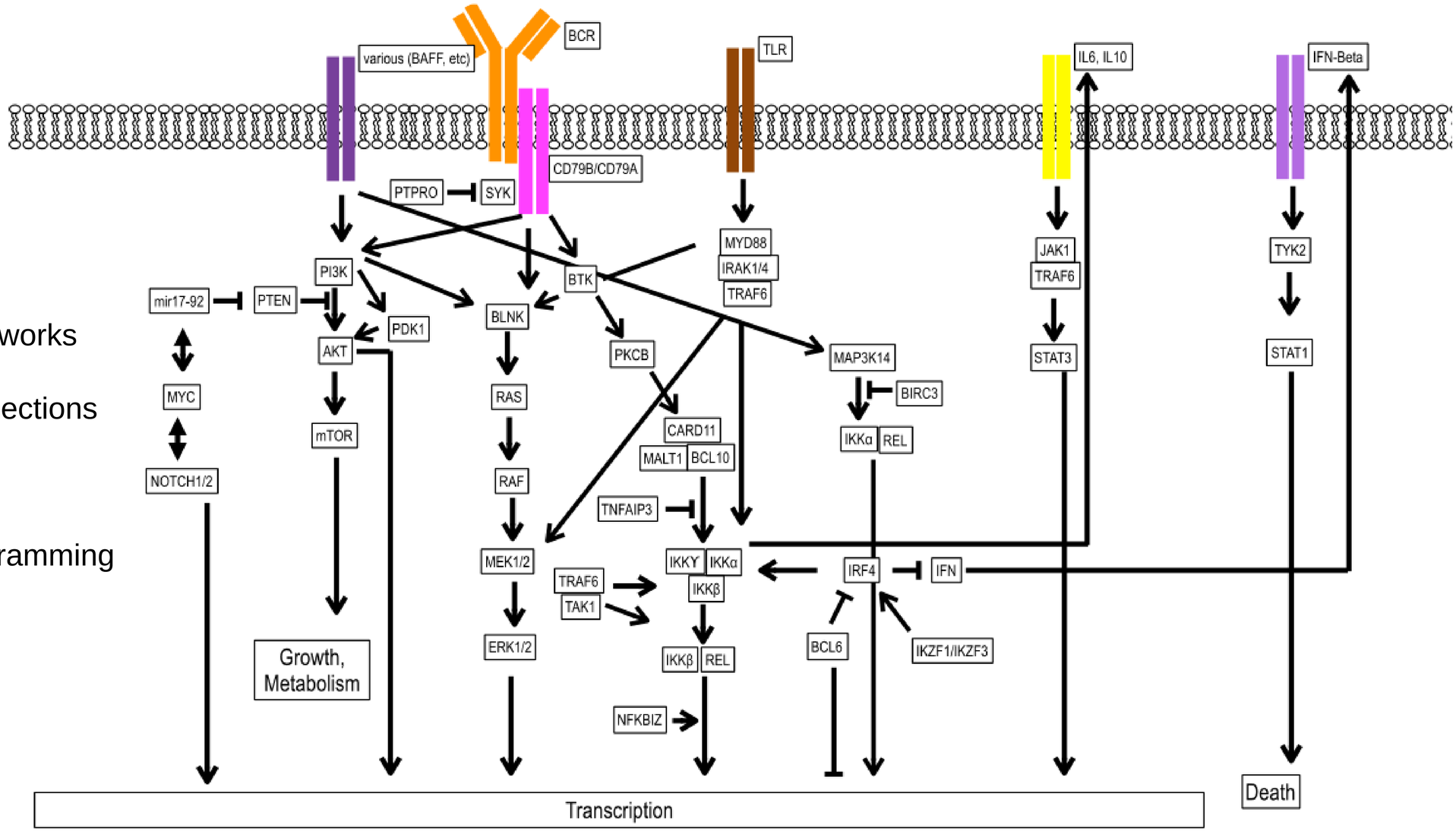
Many altered pathways = Many therapeutic targets

Very complex networks

Multiple interconnections

High redundancy

Flexibility/Reprogramming



modified from Testoni et al, Ann Oncology 2015

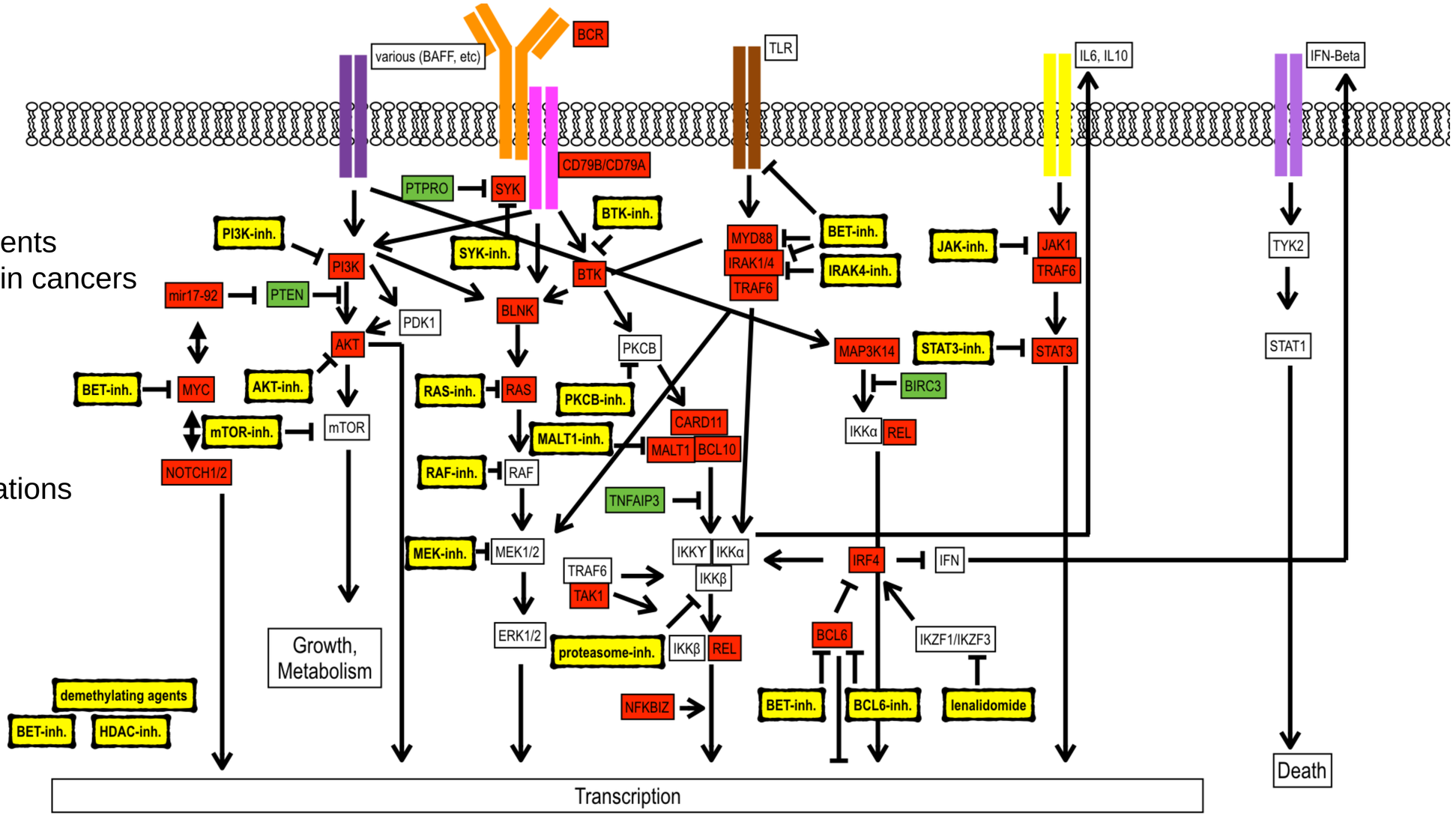
Many altered pathways = Many therapeutic targets

Multiple components are deregulated in cancers

Multiple targets

Many drugs

Need of combinations



modified from Testoni et al, Ann Oncology 2015

Epigenome as a therapeutic target

Epigenome alterations, such as abnormal DNA methylation and chromatin structure, are common in cancers

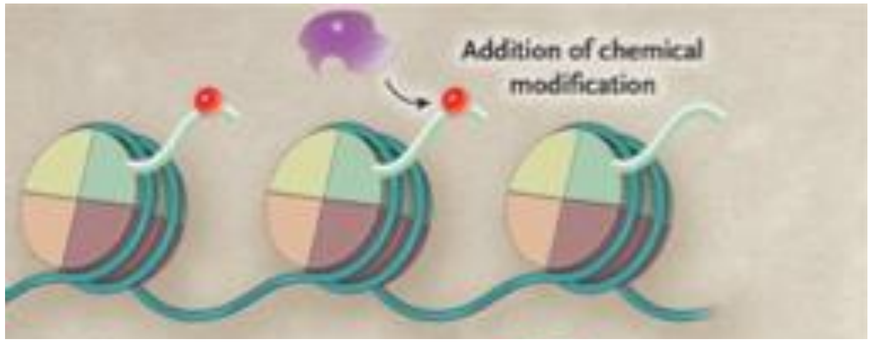
Chromatin modifications are fundamental for the regulation of:

- transcription
- DNA repair
- DNA replication

Importantly, chromatin modifications can be reversible

Different classes of proteins are involved in transcription regulation

Writers



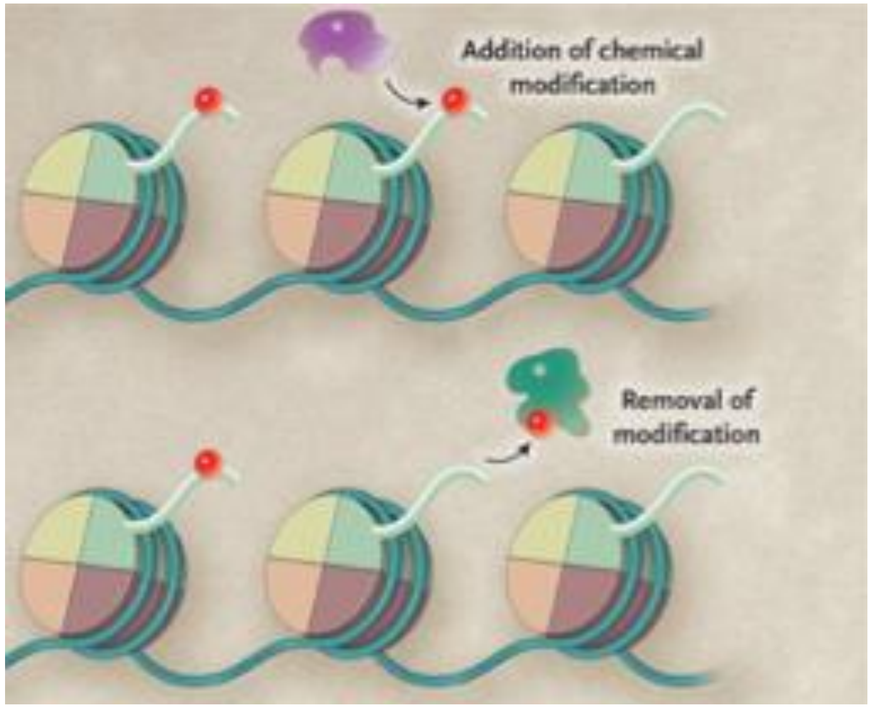
EZH2

Dawson et al, NEJM 2012

Different classes of proteins are involved in transcription regulation

Writers

EZH2



Erasers

HDAC

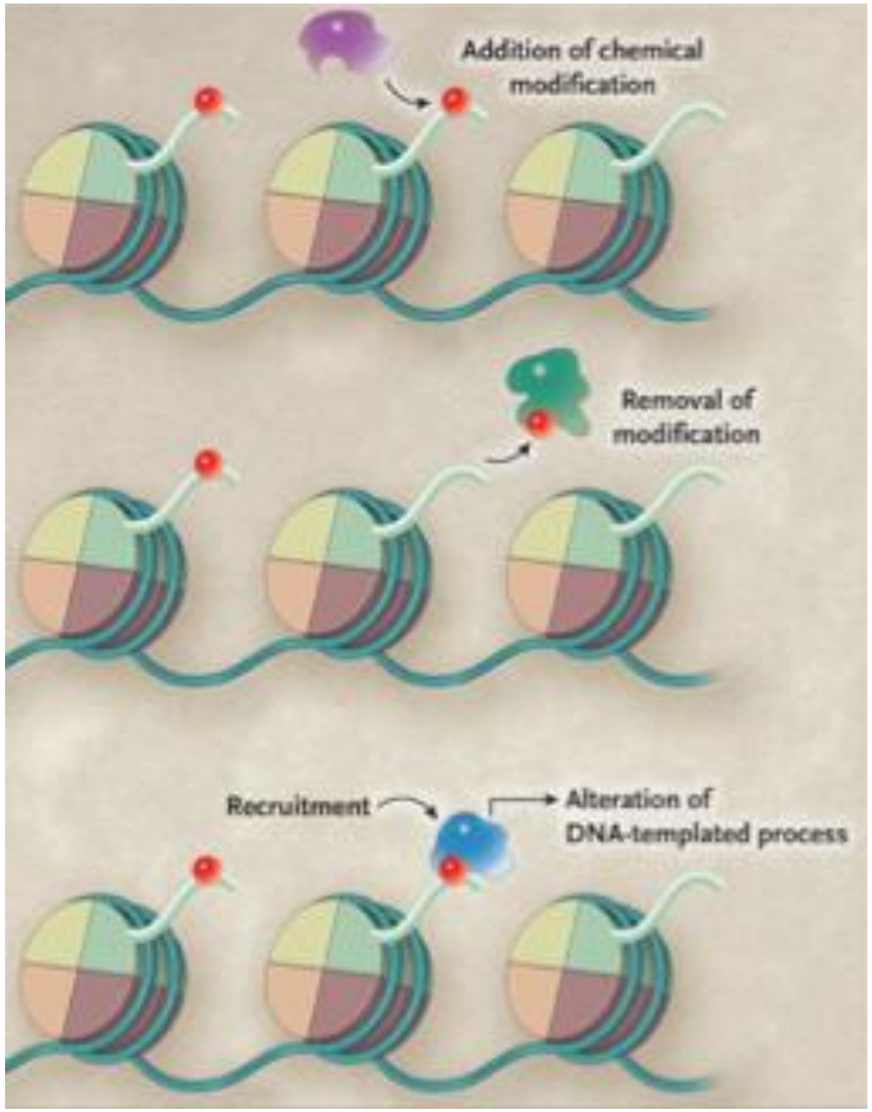
Dawson et al, NEJM 2012

Different classes of proteins are involved in transcription regulation

Writers

Erasers

Readers



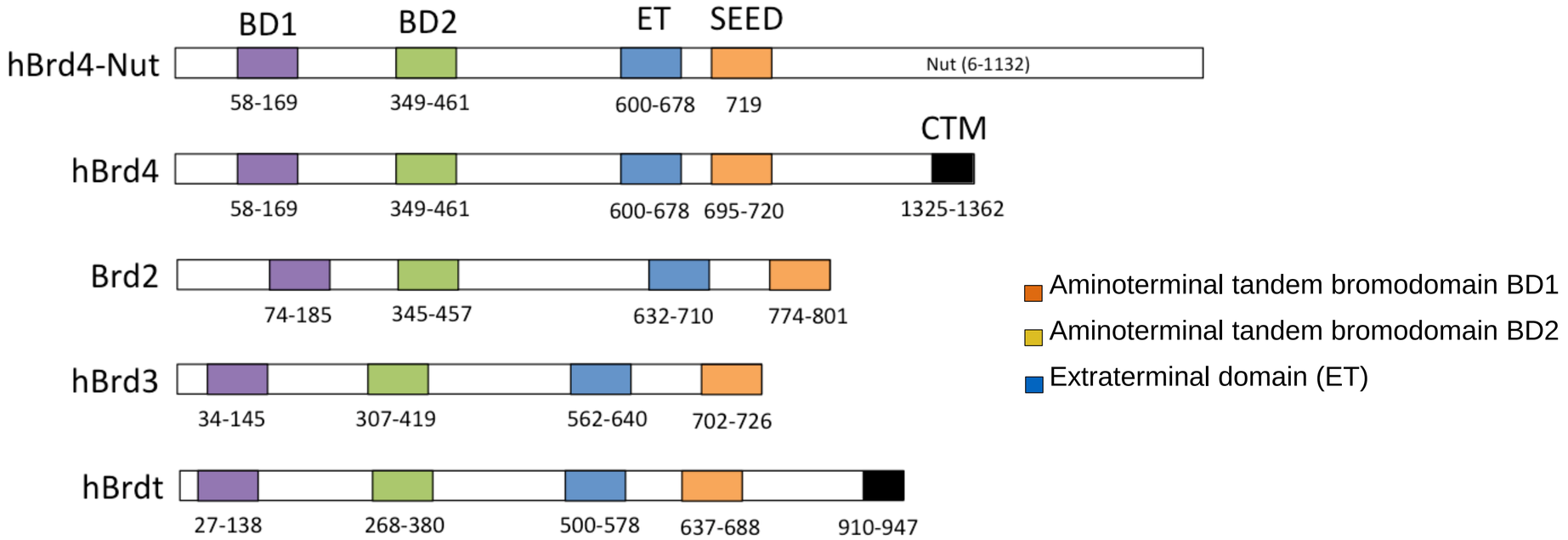
EZH2

HDAC

BET Bromodomain proteins

Dawson et al, NEJM 2012

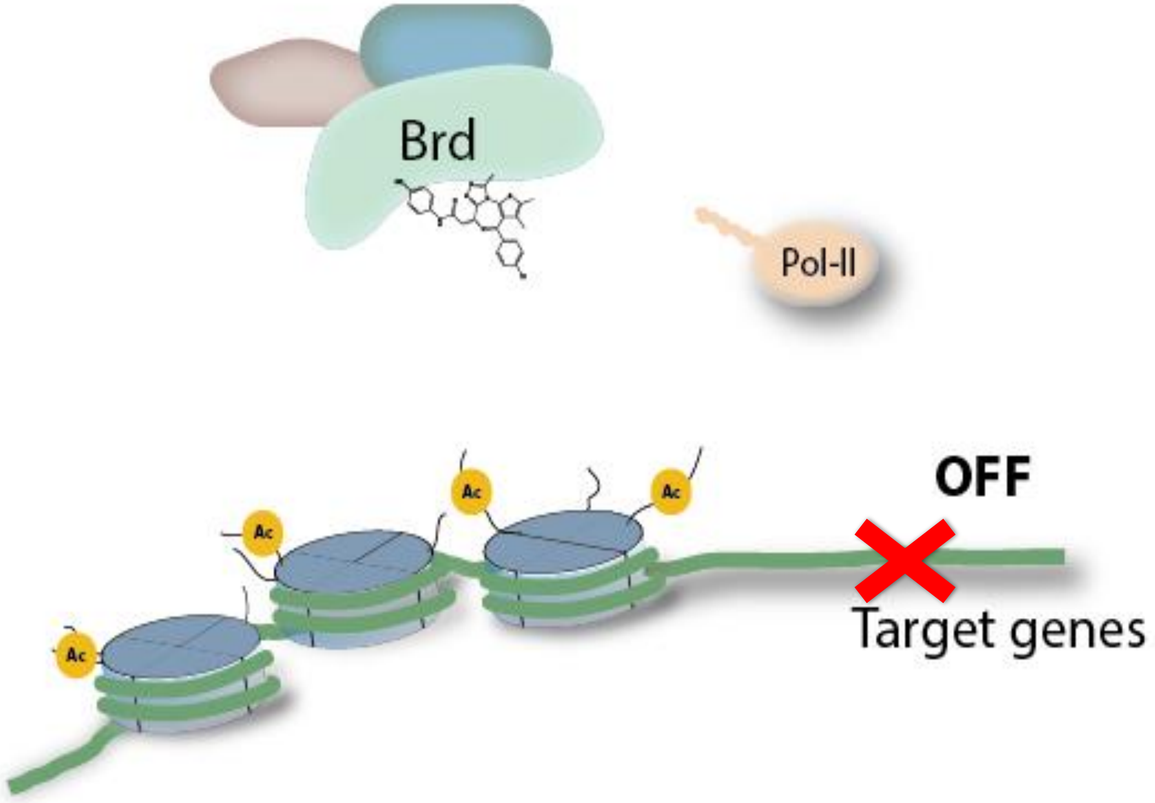
Bromodomain and extra-terminal (BET) protein family



- Nuclear proteins
- Widely expressed
- Recruit transcription factors (P-TEFb) to acetylated chromatin

Mod. From Chiang, Biol Rep 2009

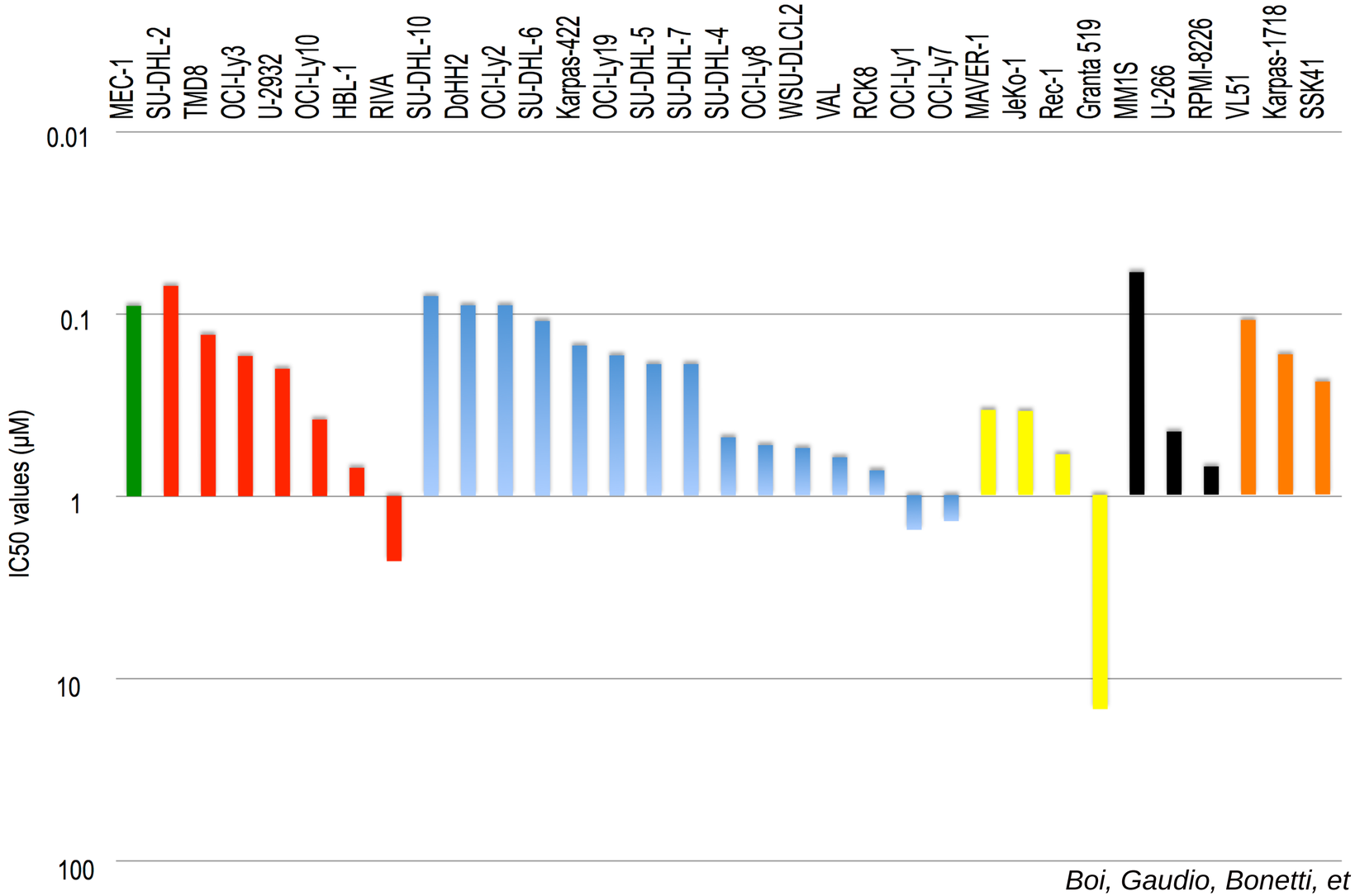
OTX015 Inhibits Binding of BET Bromodomain (BRD) Proteins to Acetylated Histones



Wide anti-proliferative activity in lymphomas

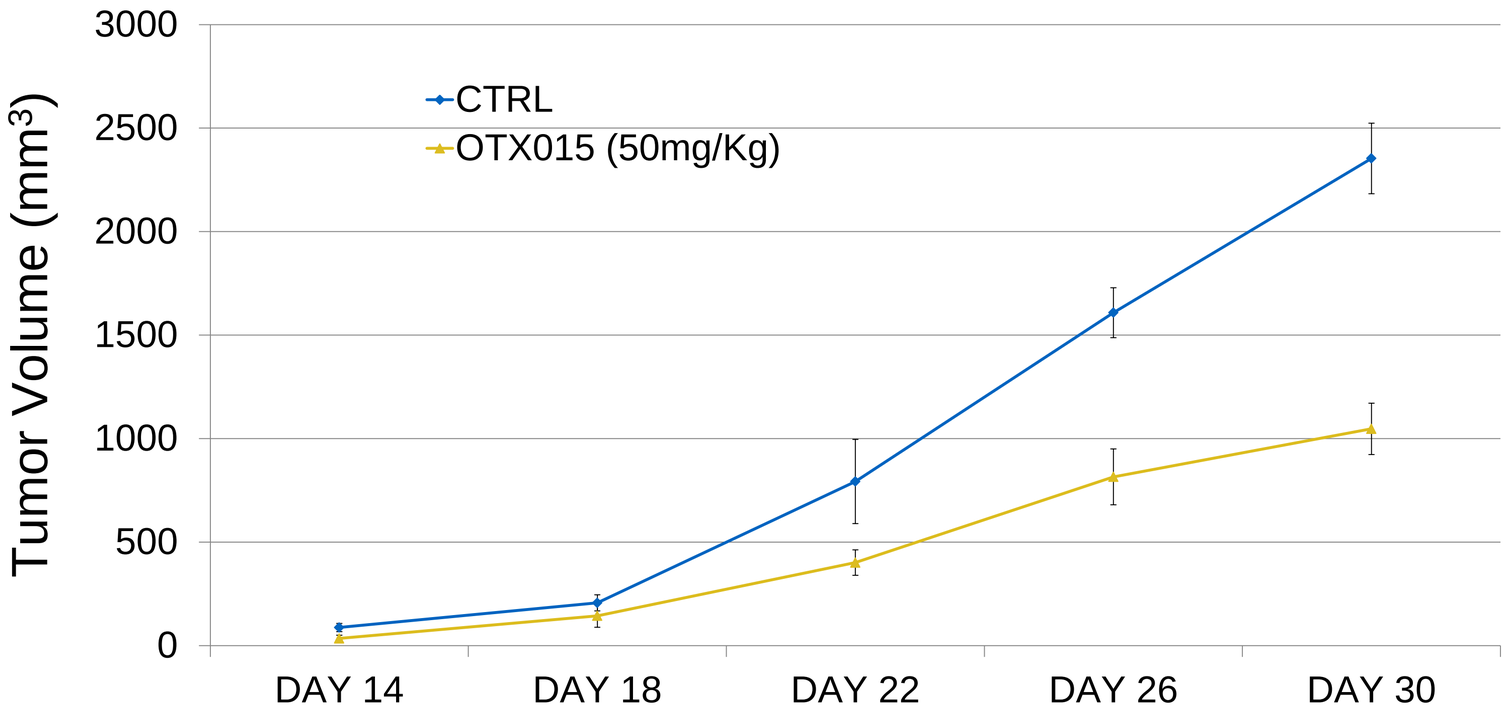
G1 arrest and decreased S-phase

Induction of a senescence-like phenotype



Boi, Gaudio, Bonetti, et al. Clinical Cancer Res 2015

In vivo anti-tumor activity in lymphoma

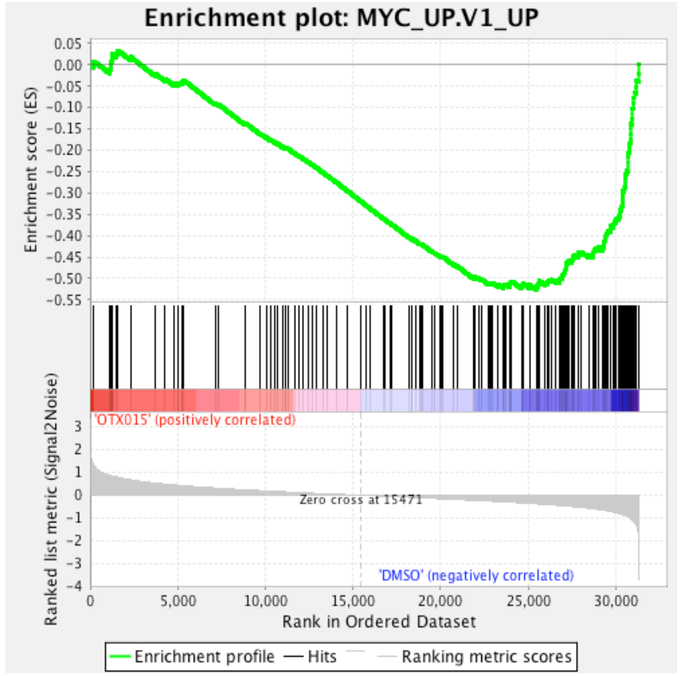


REC1 MCL
XENOGRAFT

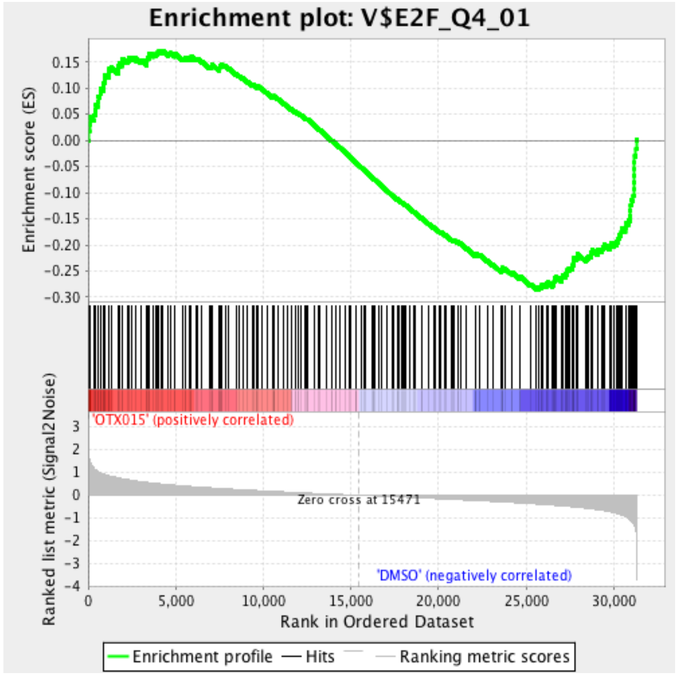
Gaudio, et al. EORTC-NCI-AACR 2015

BET Bromodomain inhibitor OTX015

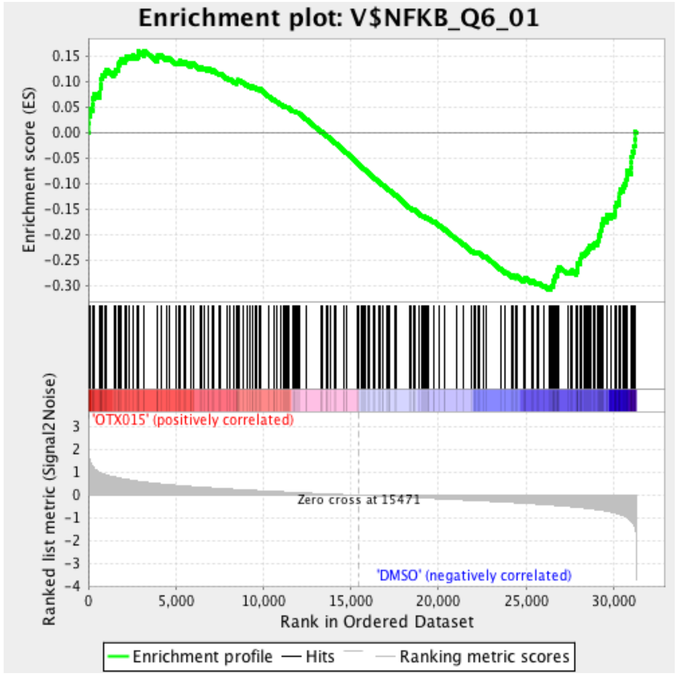
Inhibition of the activity of important transcription factors



MYC



E2F1



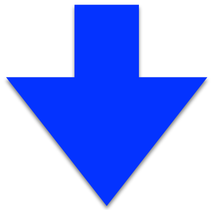
NFKB

DLBCL cell lines

Boi, Gaudio, Bonetti, et al. Clinical Cancer Res 2015

OTX015 affects important biologic processes

transcripts coding for histones, overlapping with those up-regulated by HDAC-inhibitors

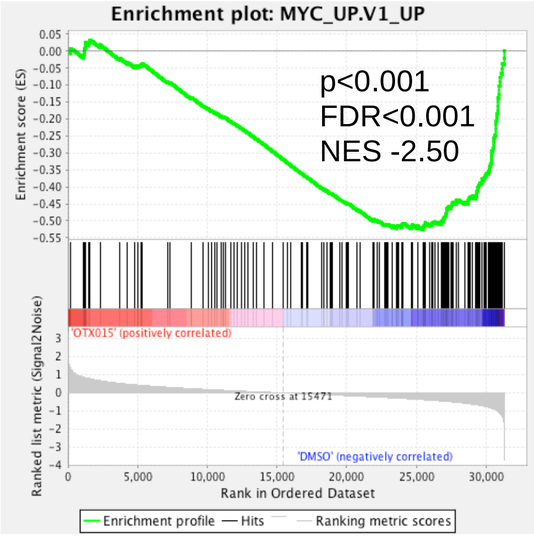


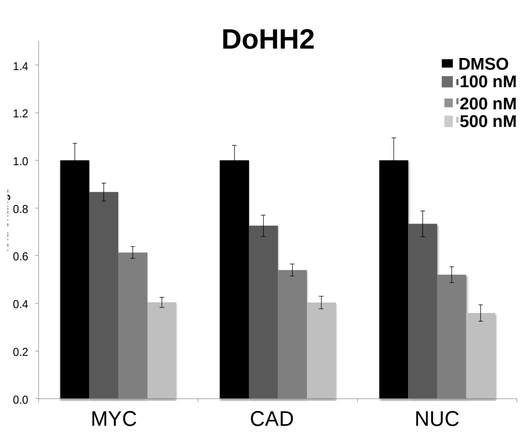
MYC and E2F1 targets, genes involved in NFKB/TLR/JAK/STAT pathways

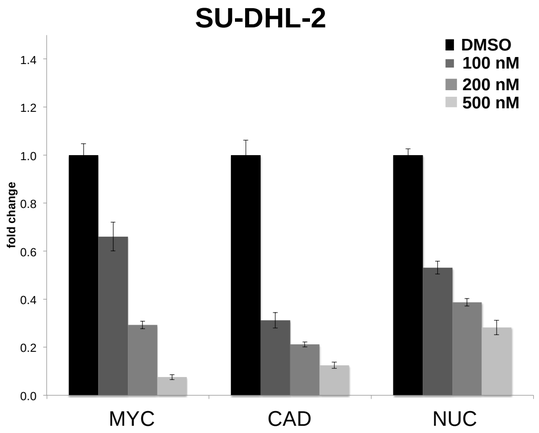
Boi, Gaudio, Bonetti, et al. Clinical Cancer Res 2015

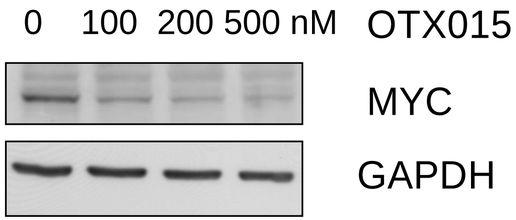
OTX015 in lymphomas

Down-regulation of MYC and MYC targets

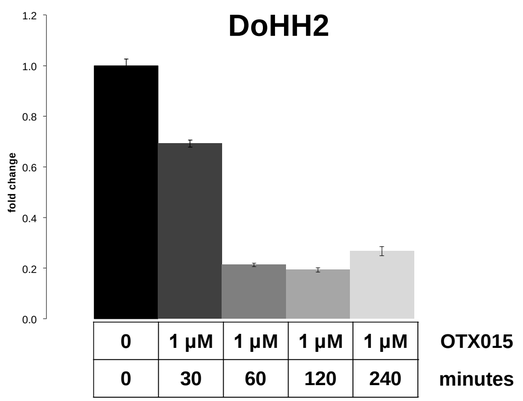


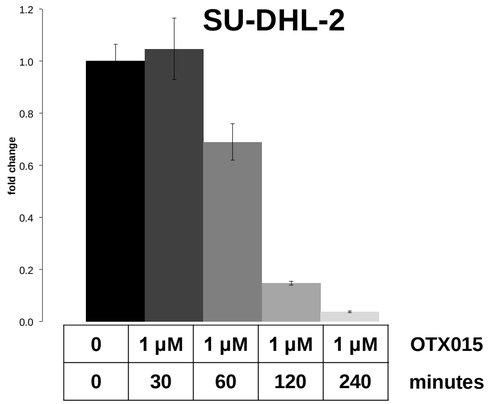






SU-DHL-2

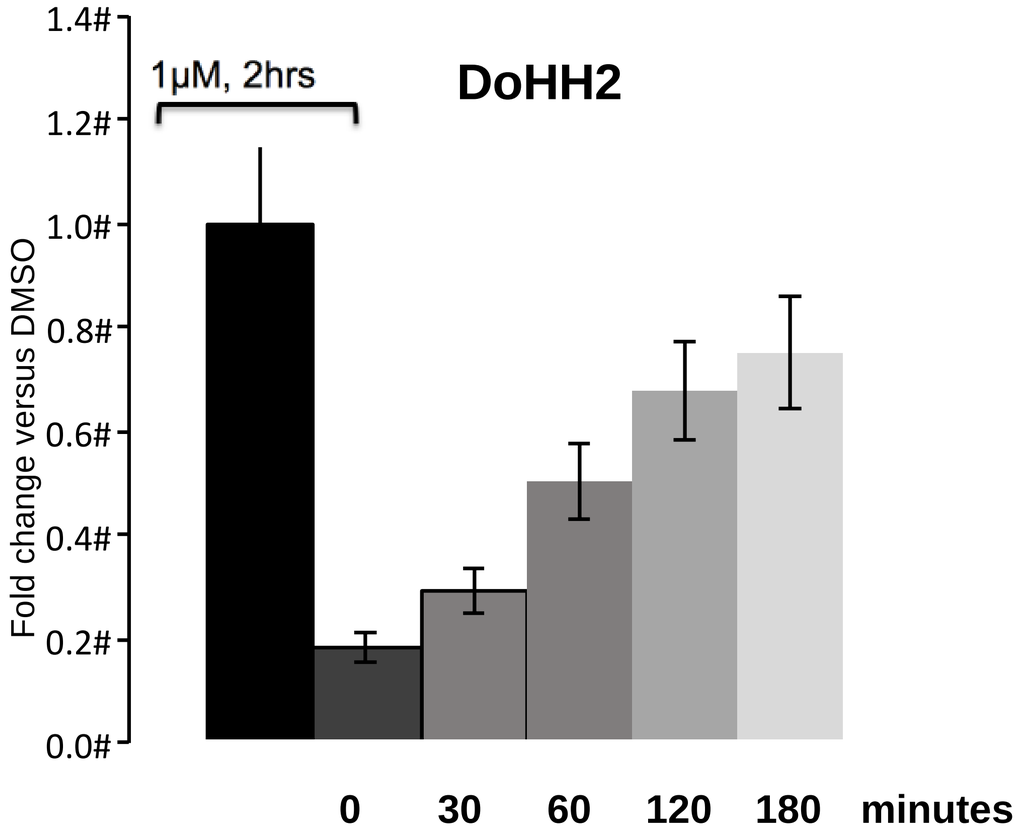


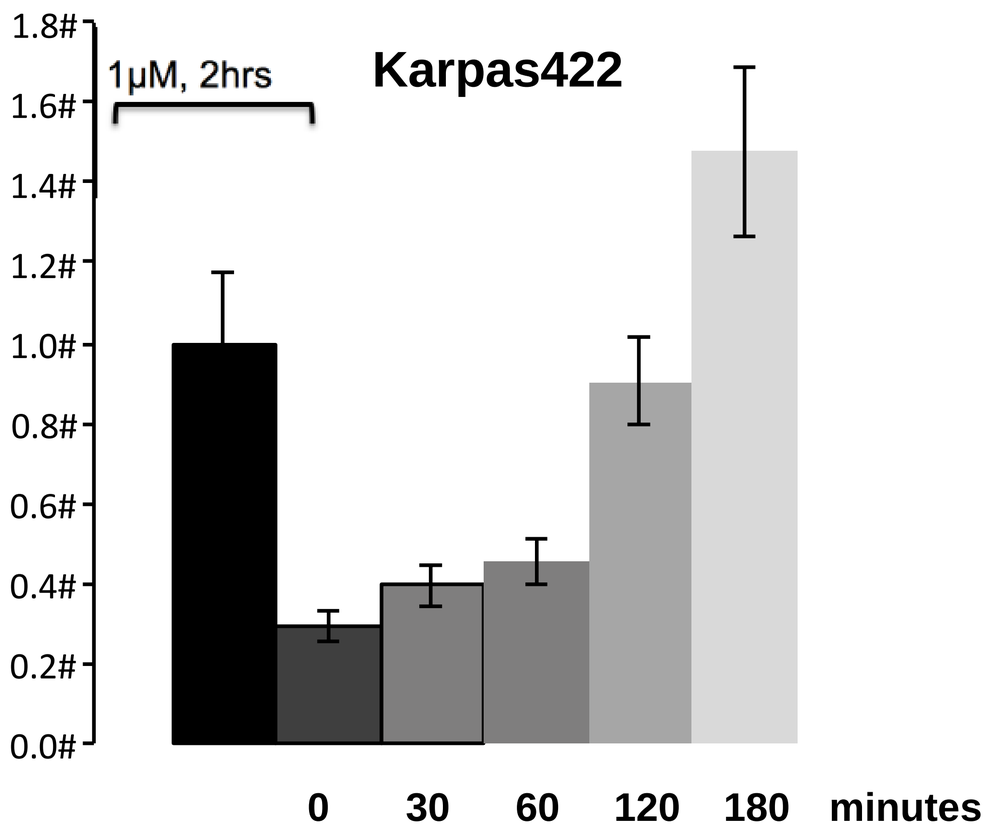


Boi, Gaudio, Bonetti, et al. Clinical Cancer Res 2015

OTX015 in lymphomas

MYC down-regulation is reversible

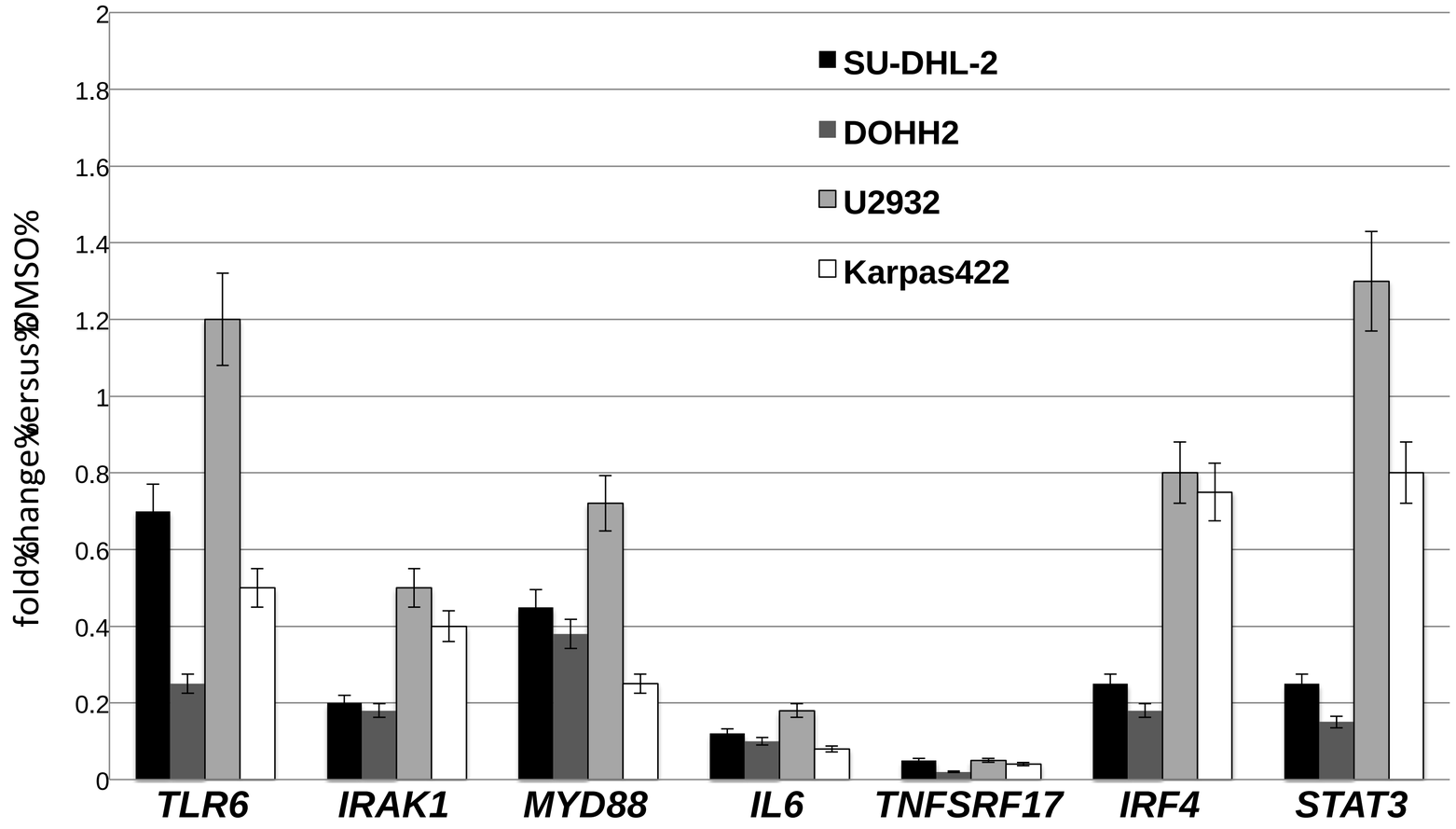




Boi, Gaudio, Bonetti, et al. Clinical Cancer Res 2015

OTX015 in lymphomas

Down-regulation of TLR/JAK/STAT/NFKB



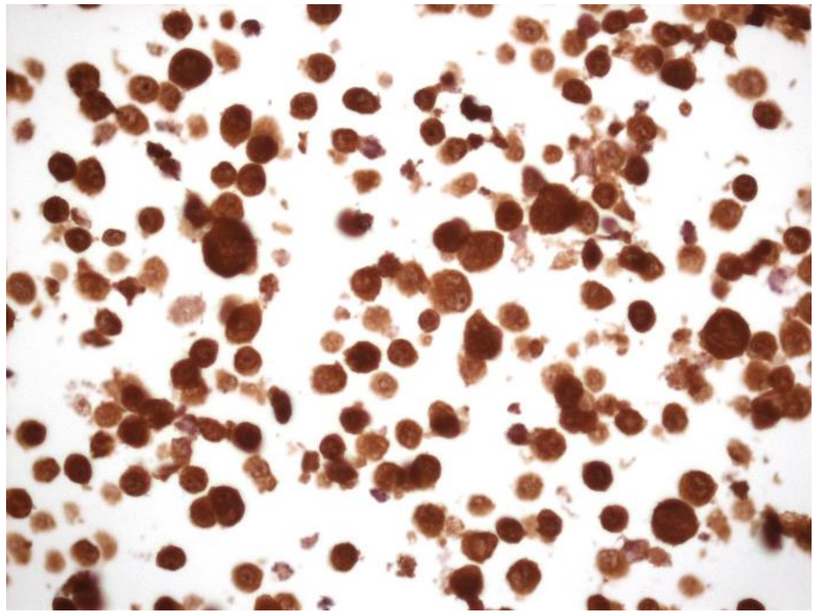
Boi, Gaudio, Bonetti, et al. Clinical Cancer Res 2015

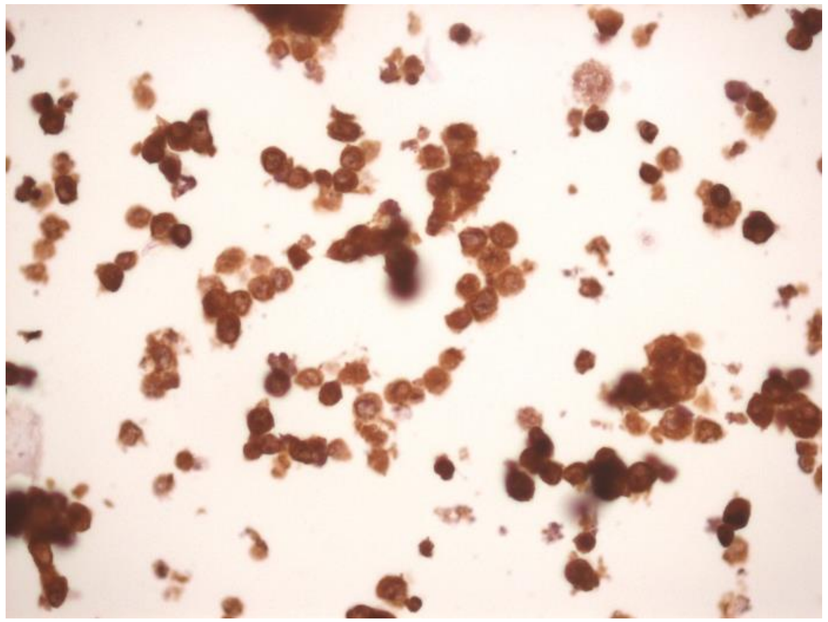
OTX015 in lymphomas

Down-regulation of active NFKB

p50 (NFKB1)

DMSO, 24hr





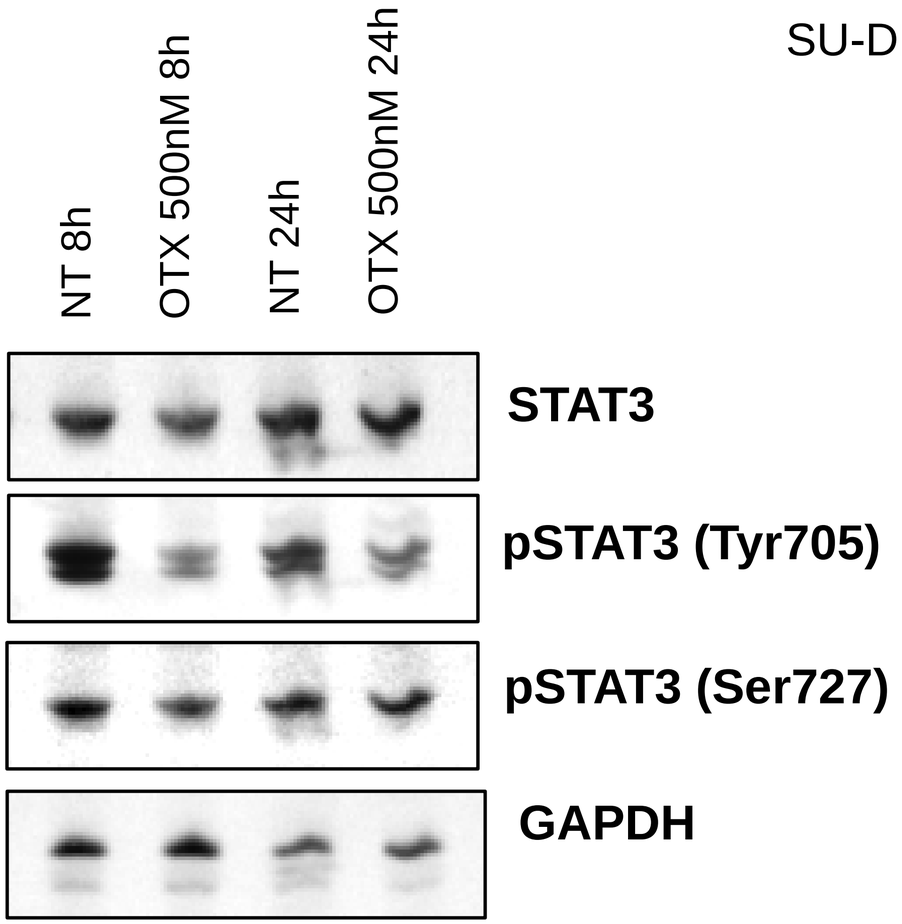
OTX015 500nM, 24hr

SU-DHL-2

Boi, Gaudio, Bonetti, et al. Clinical Cancer Res 2015

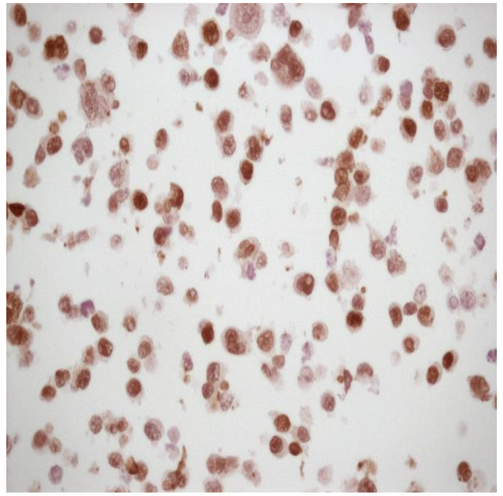
OTX015 in lymphomas

Down-regulation of active JAK/STAT3

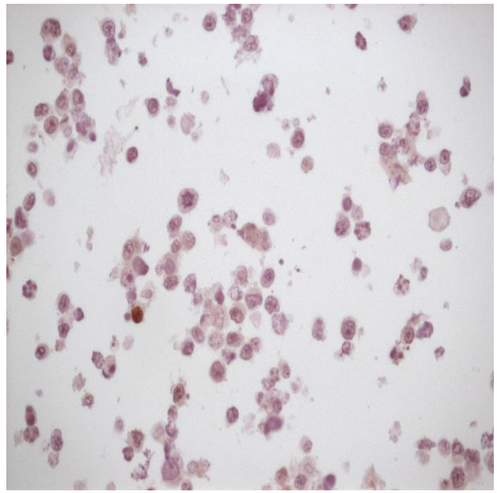


SU-DHL-2

pSTAT3 (Tyr705)



DMSO, 24hr



OTX015 500nM, 24hr

Boi, Gaudio, Bonetti, et al. Clinical Cancer Res 2015

OTX015 in lymphomas

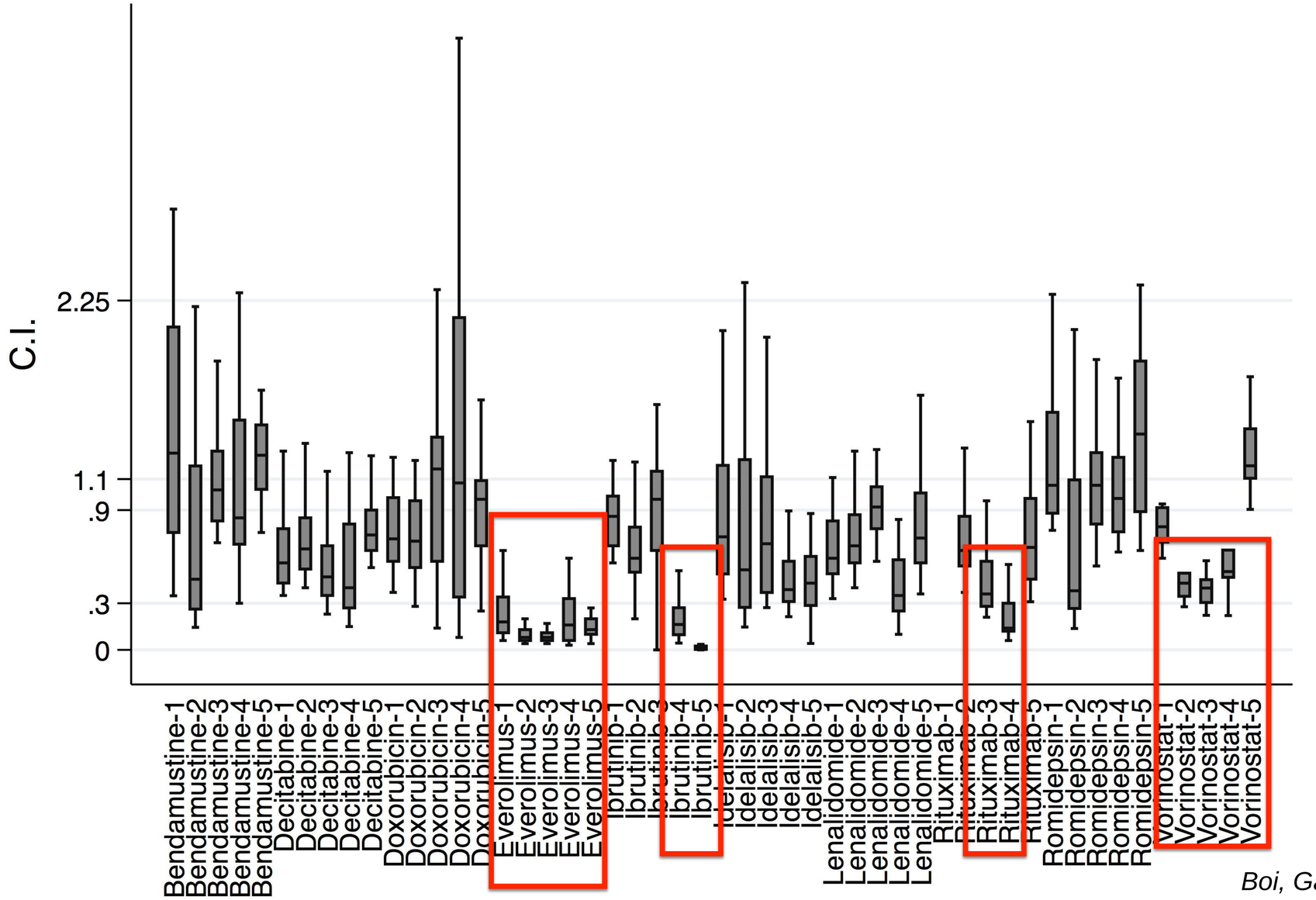
Assessment of combinations

Molecule	
Bendamustine	chemotherapy
Doxorubicin	chemotherapy
Bortezomib	Proteasome inhibitor
Ibrutinib	BTK inhibitor
Lenalidomide	Immunomodulant
Rituximab	anti-CD20 moAb
Vorinostat	HDAC inhibitor
Romidepsin	HDAC inhibitor
Decitabine	demethylating

three GCB-DLBCL
two ABC-DLBCL

Boi, Gaudio, Bonetti, et al. Clinical Cancer Res 2015

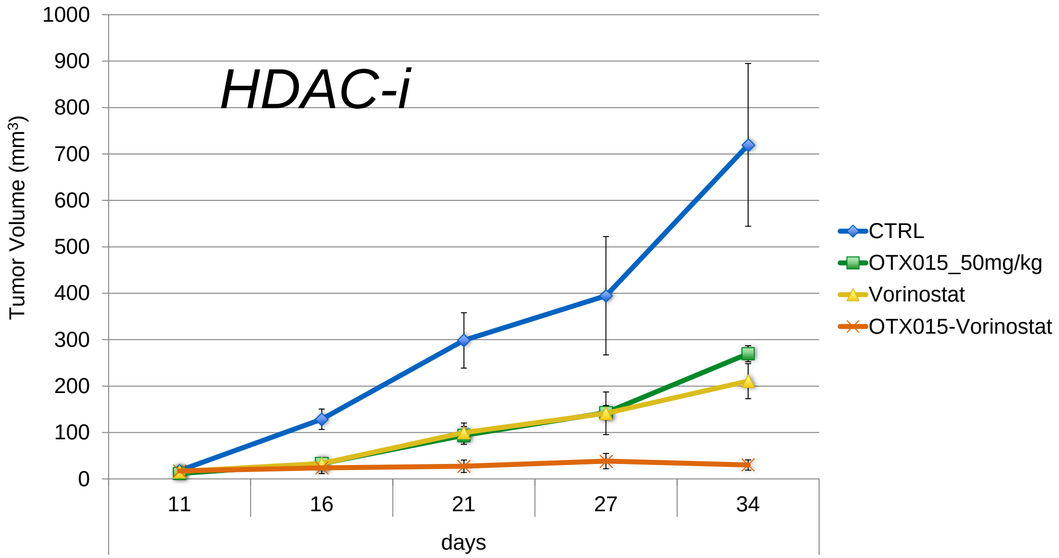
DLBCL: synergism with several anti-cancer agents

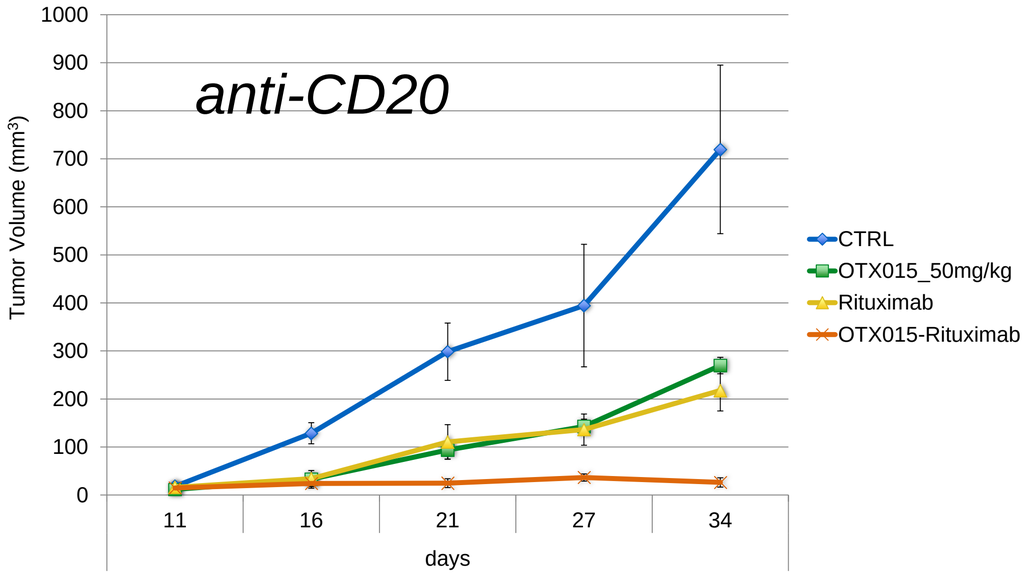


Best:
- ☑ Everolimus
- ☑ Ibrutinb
- ☑ Rituxmab
- ☑ Vorinostat

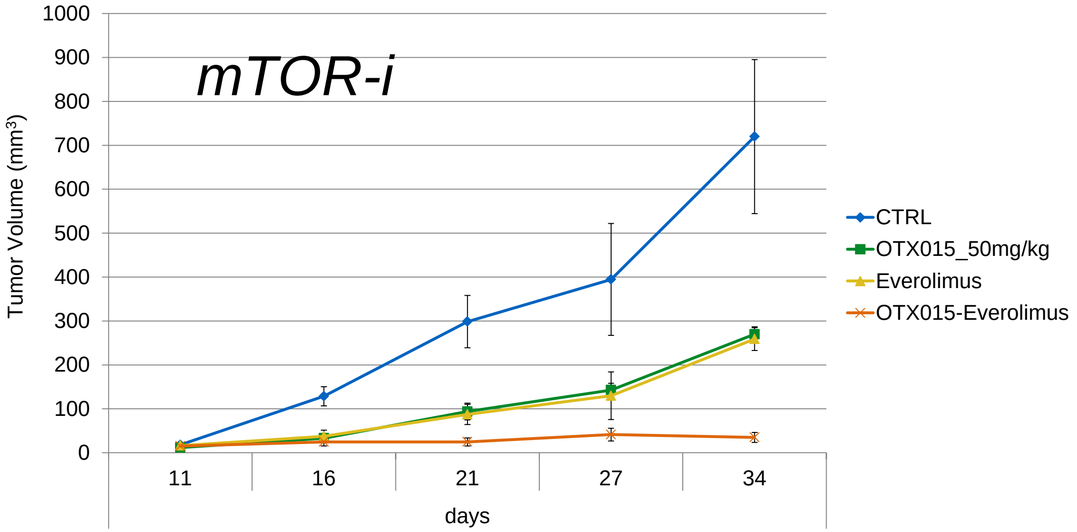
Boi, Gaudio, Bonetti, et al. Clinical Cancer Res 2015

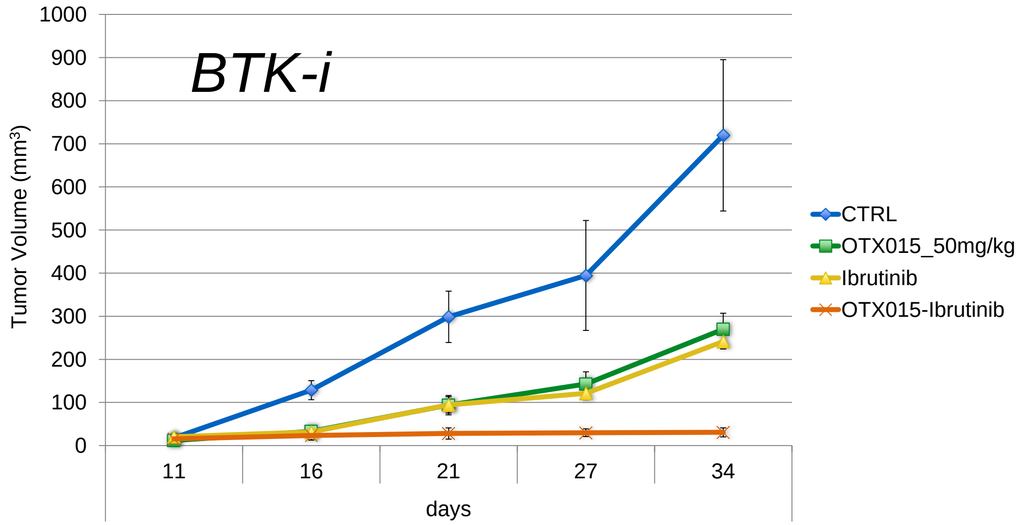
OTX015 synergises with different compounds





in vivo





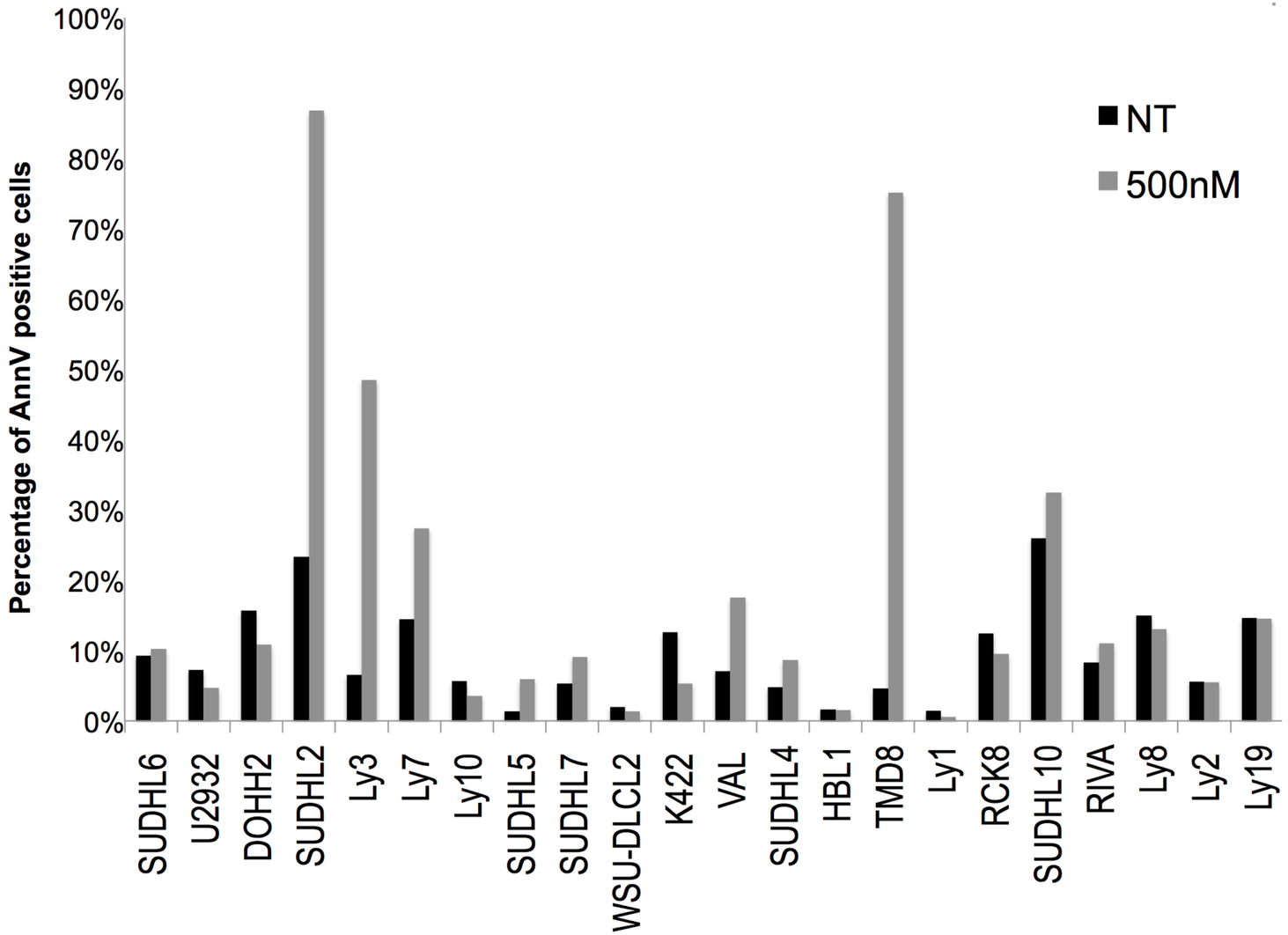
ABC-DLBCL SU-DHL-2 xenograft

Gaudio E, et al. Oncotarget 2016

Bet Bromodomain inhibitors in lymphomas

Any biomarkers?

Apoptosis limited to a genetically defined subgroup of DLBCL

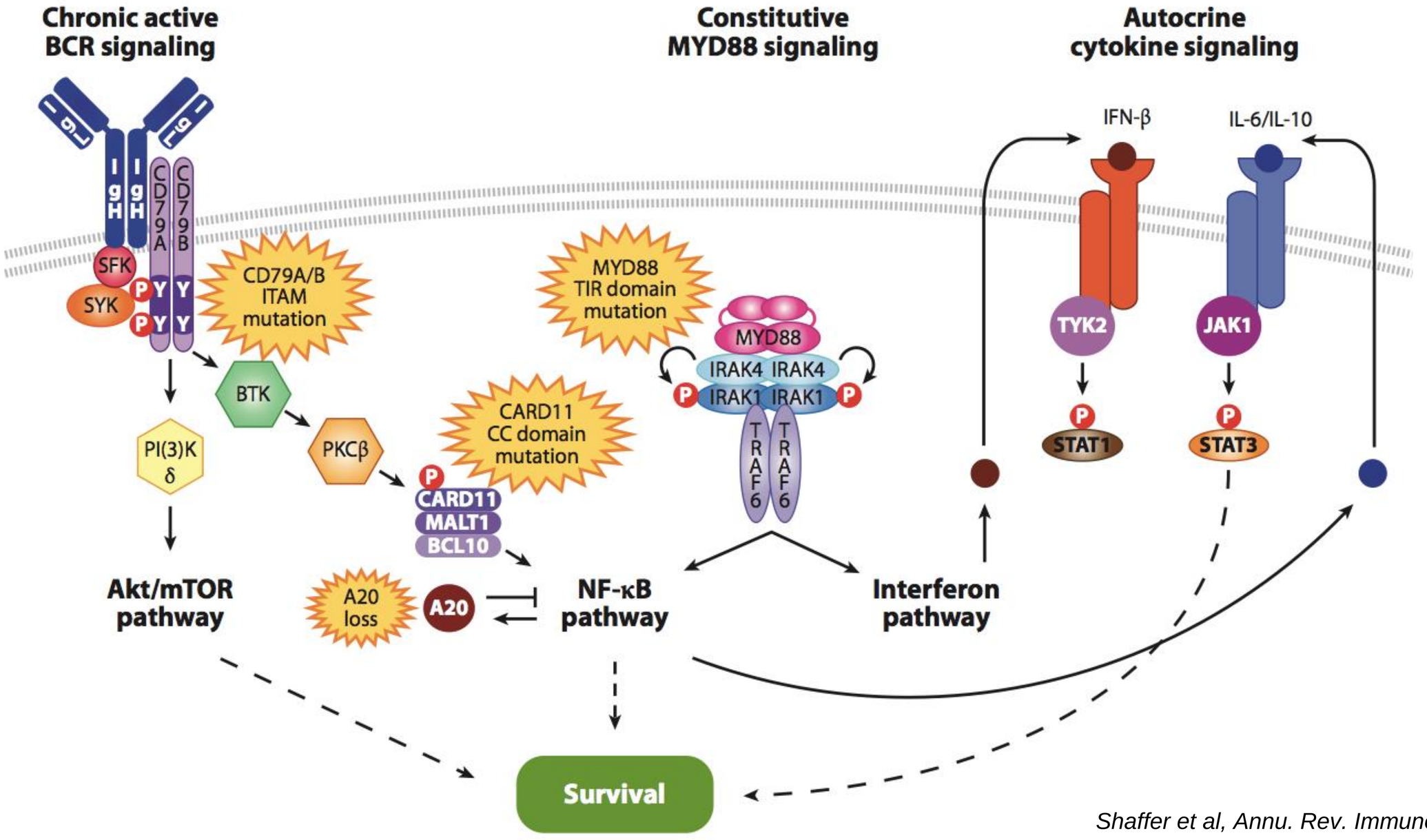


ABC-DLBCL
mut *MYD88*
mut in *CD79B* or mut *CARD11*
wt TP53

Mutations in *MYD88* and for components of the BCR signalling: significantly associated with apoptosis (P = 0.027)

Boi, Gaudio, Bonetti, et al. Clinical Cancer Res 2015

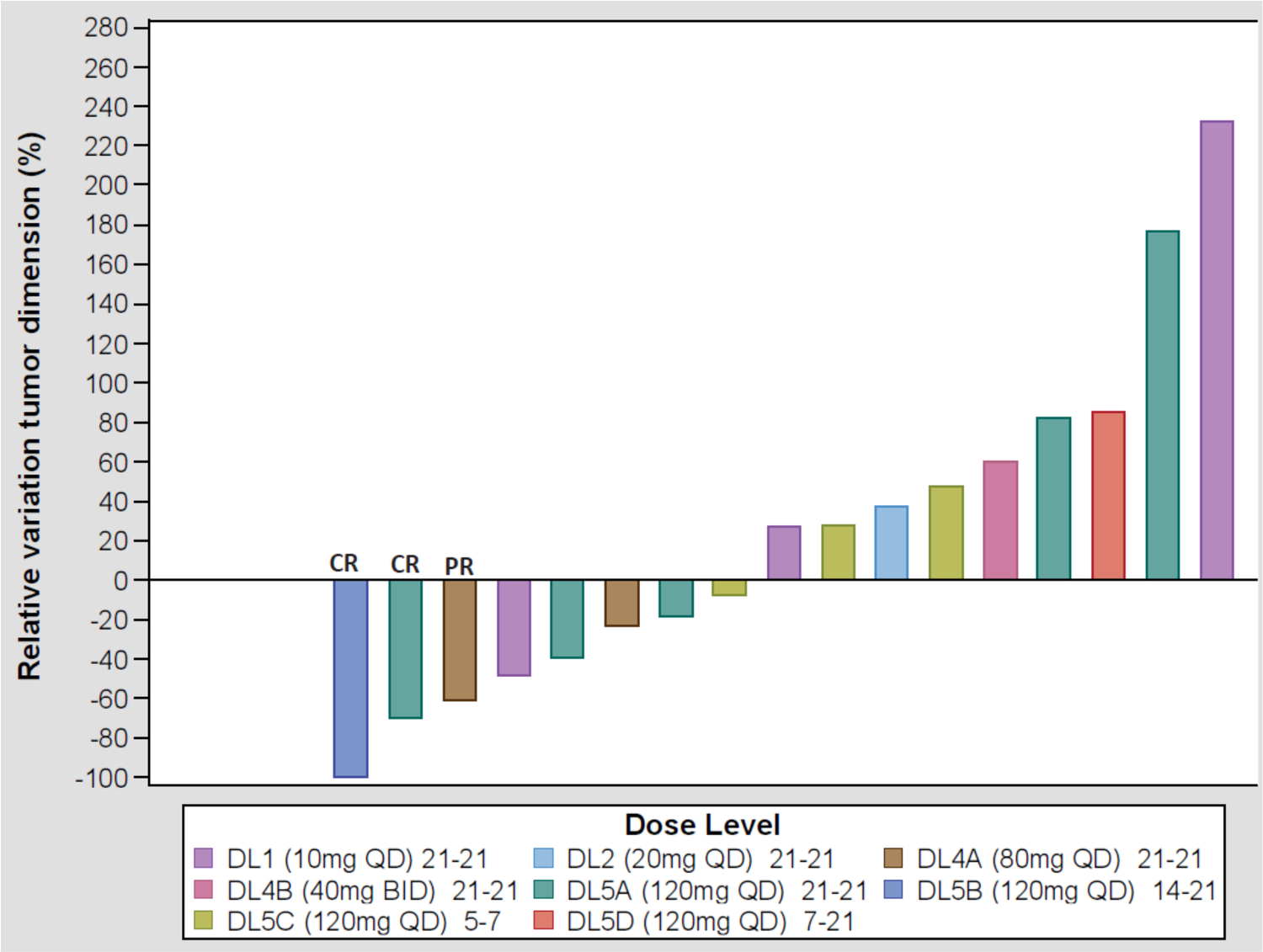
MYD88, CD79B and CARD11 act on the signalling



Shaffer et al, Annu. Rev. Immunol. 2012

OTX015 in lymphomas

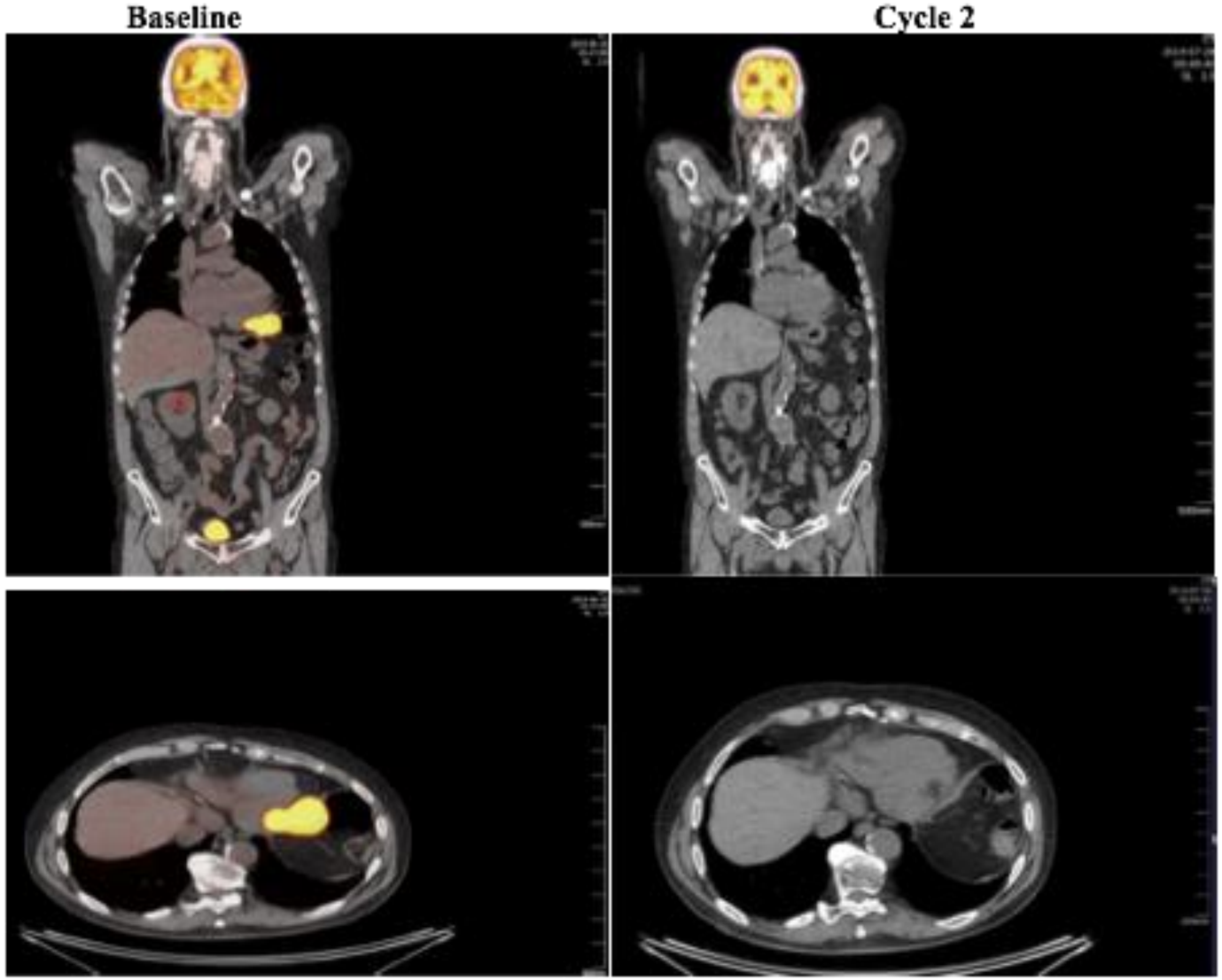
Complete responses in the Phase I



Amorim, Stathis et al. Lancet Hematology 2016

OTX015 in lymphomas

Complete responses in the Phase I



Amorim, Stathis et al. Lancet Hematology 2016

Conclusions

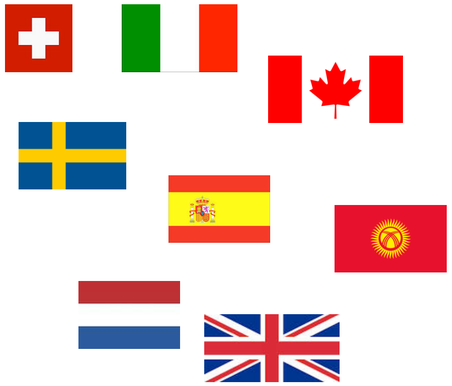
- Anti-proliferative activity in mature B-cell lymphoid tumor cell lines
- Mainly cytostatic activity, but apoptosis in genetically defined subgroups
- Down-regulation of MYC and MYC targets target genes
- Down-regulation of MYD88, JAK/STAT3 and NFKB pathways
- Synergism with different agents
- Signs of clinical activity

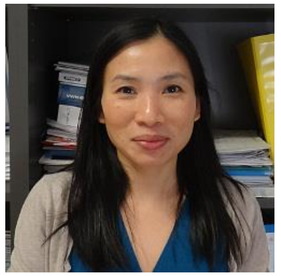
Acknowledgments

Lymphoma & Genomics Research Program









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Georg Stussi
Franco Cavalli


14-ICML
14th International Conference on Malignant Lymphoma
Palazzo dei Congressi
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www.lymphcon.ch
SAVE THE DATE: June 14-17, 2017