TARGETING EZH2 WITH TAZEMETOSTAT IN FOLLICULAR LYMPHOMA

VINCENT RIBRAG

Chairman hematological multidisciplinary committee Ditep (chief molecular therapeutics in hematological early drug development)

Bologna Lymphoma meeting, May 2017

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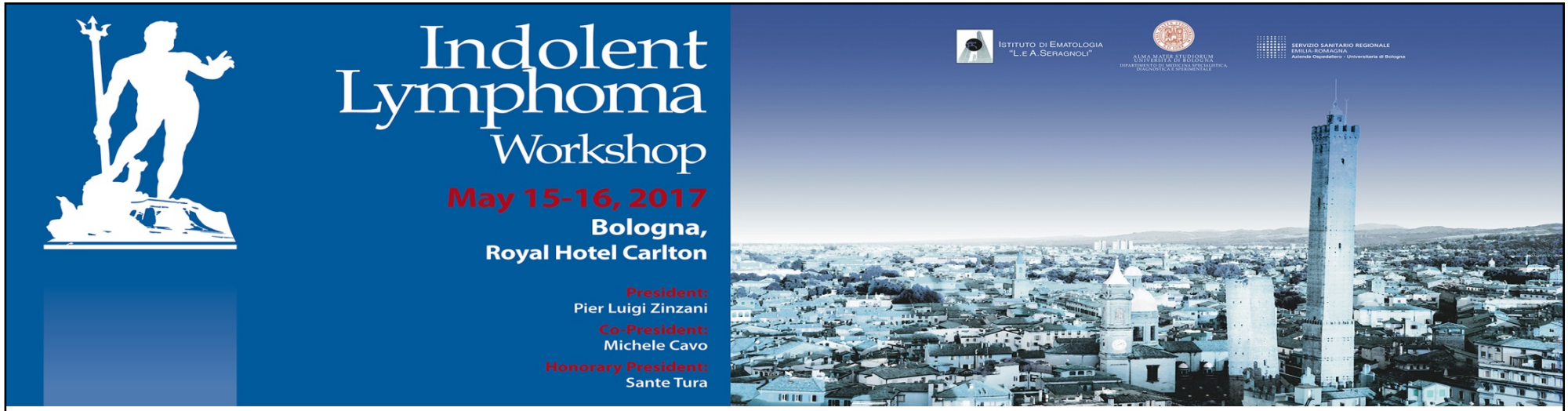
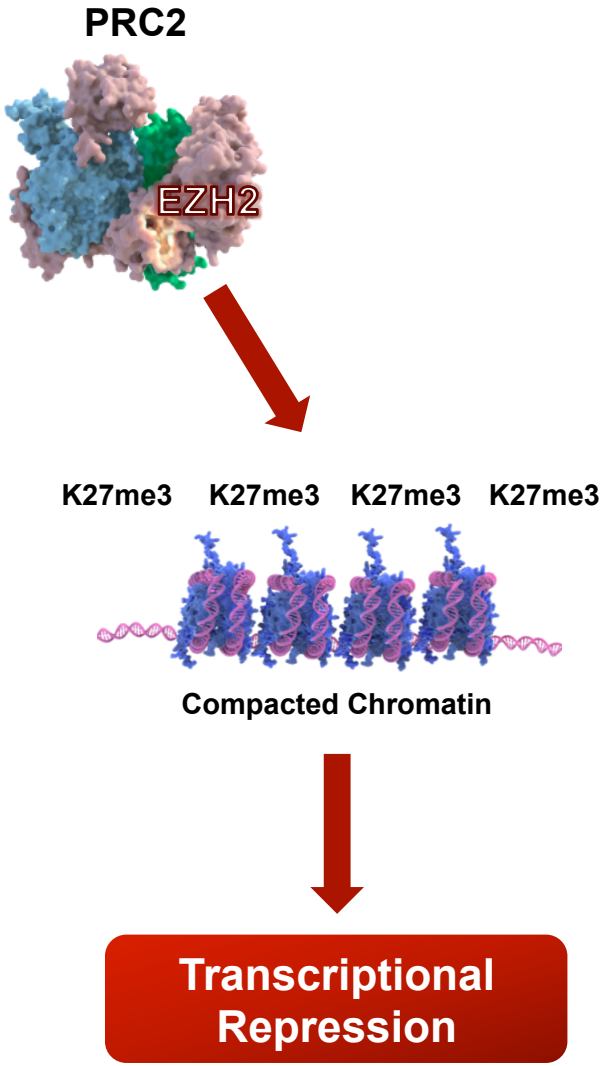


Disclosures of Ribrag Vincent

Company name	Research support	Employee	Consultant	Speakers bureau	Advisory board
Servier			X		
Argen X	X				
Epizyme	X				X
Incyte, Roche					X
Esai, Gilead					X
Nanostring					X
BMS, MSD					X
Infinity					X

Tazemetostat, Mechanism of Action

- EZH2 is the catalytic subunit of the multi-protein PRC2 (Polycomb Repressive Complex 2), which generates mono-, di- and tri-methylation of H3K27.
  - H3K27me3 is a transcriptionally repressive histone mark, and H3K27 is the only significant substrate for PRC2
- Aberrant trimethylation of H3K27 is oncogenic in a broad spectrum of human cancers, such as B-cell NHL.
- Mutations in other proteins that affect H3K27 and chromatin accessibility in general are prevalent across almost all cancer types.
- Tazemetostat (EPZ-6438) is a potent and highly selective EZH2 inhibitor with antitumor activity in a variety of hematologic malignancies and solid tumors models, including FL and DLBCL.



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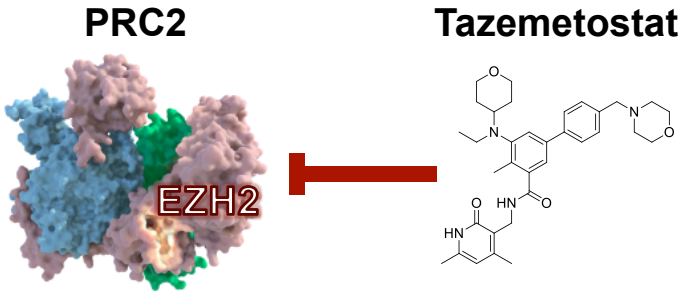
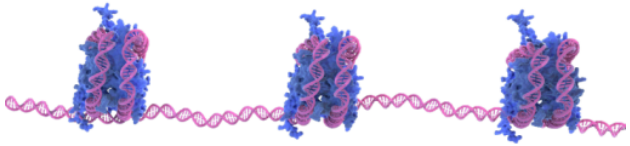
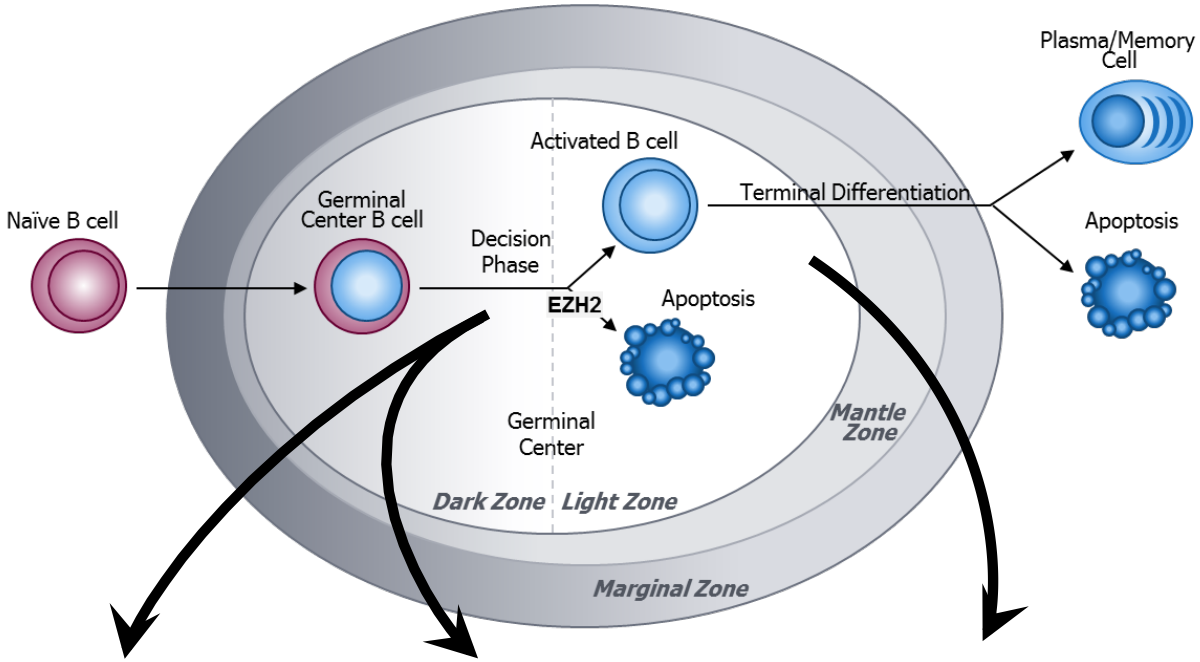




Transcriptionally Permissive Chromatin

Transcriptional Activation

EZH2 Activating Mutations and Other Genetic Lesions in Follicular Lymphoma and DLBCL



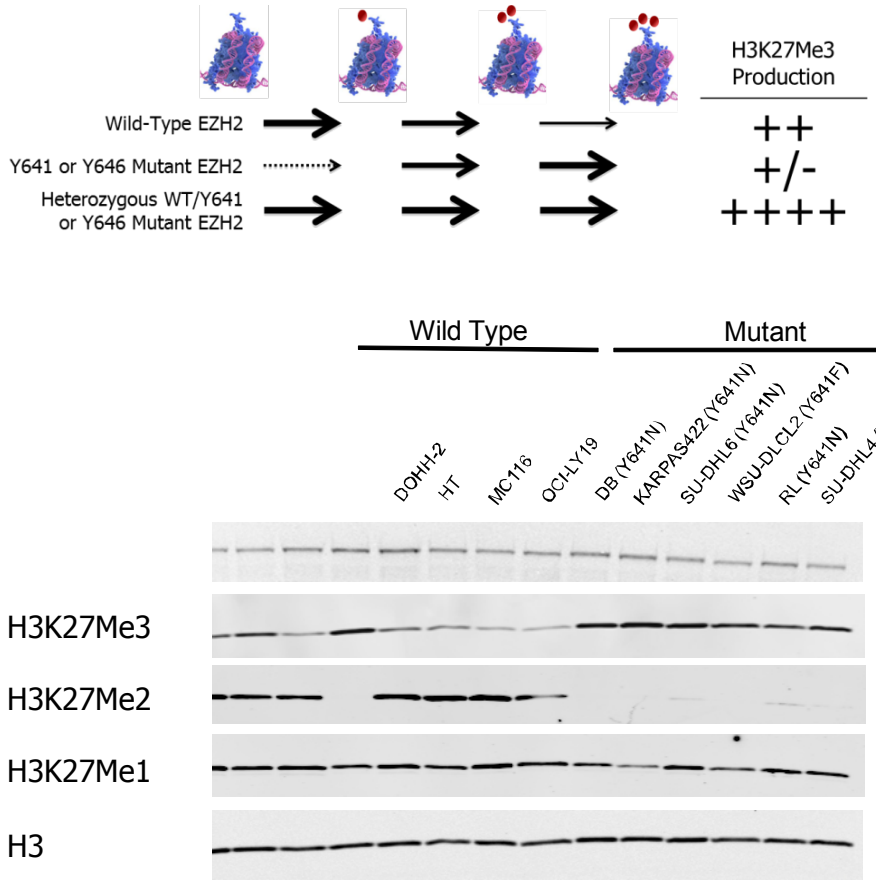
Follicular lymphoma	GC B cell-like (GCB) DLBCL	Activated B cell-like (ABC) DLBCL
• **EZH2 activation** • MLL2 inactivation	• **EZH2 activation** • Gα13 pathway inactivation • Ectopic expression of BCL2 and/or MYC	• Constitutive NF-κB activation • PRDM1 inactivation

- CREBBP or EP300 inactivation
- MLL2 inactivation
- Constitutive BCL6 expression
- Immune escape

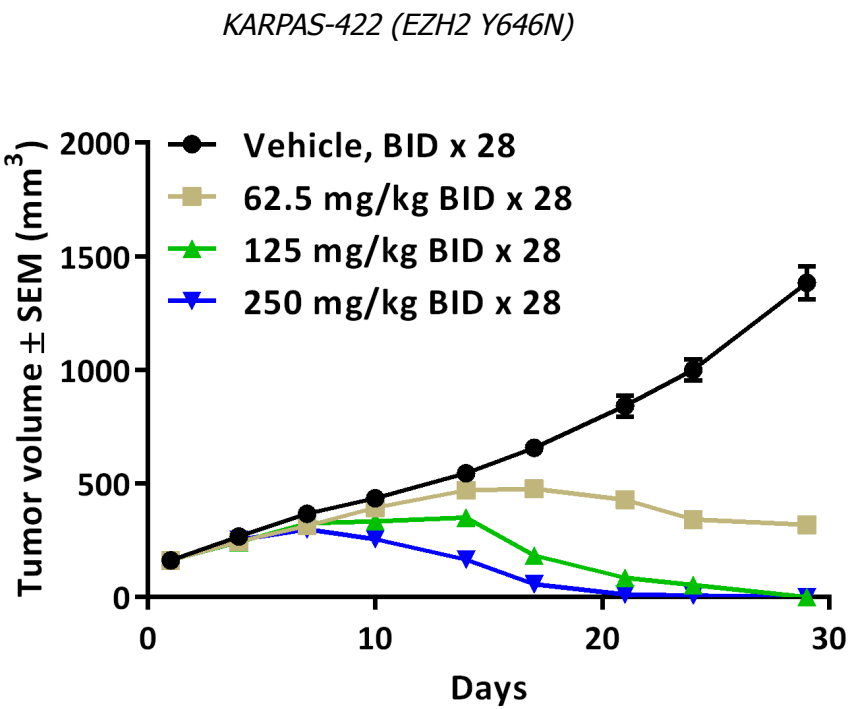
Adapted from Basso et al, NRI, 2015

EZH2 Activating Mutations Cause Elevated H3K27me3 Levels and are Dependent on EZH2 Activity

H3K27me3 hypertrimethylation in cells containing EZH2 activating mutations

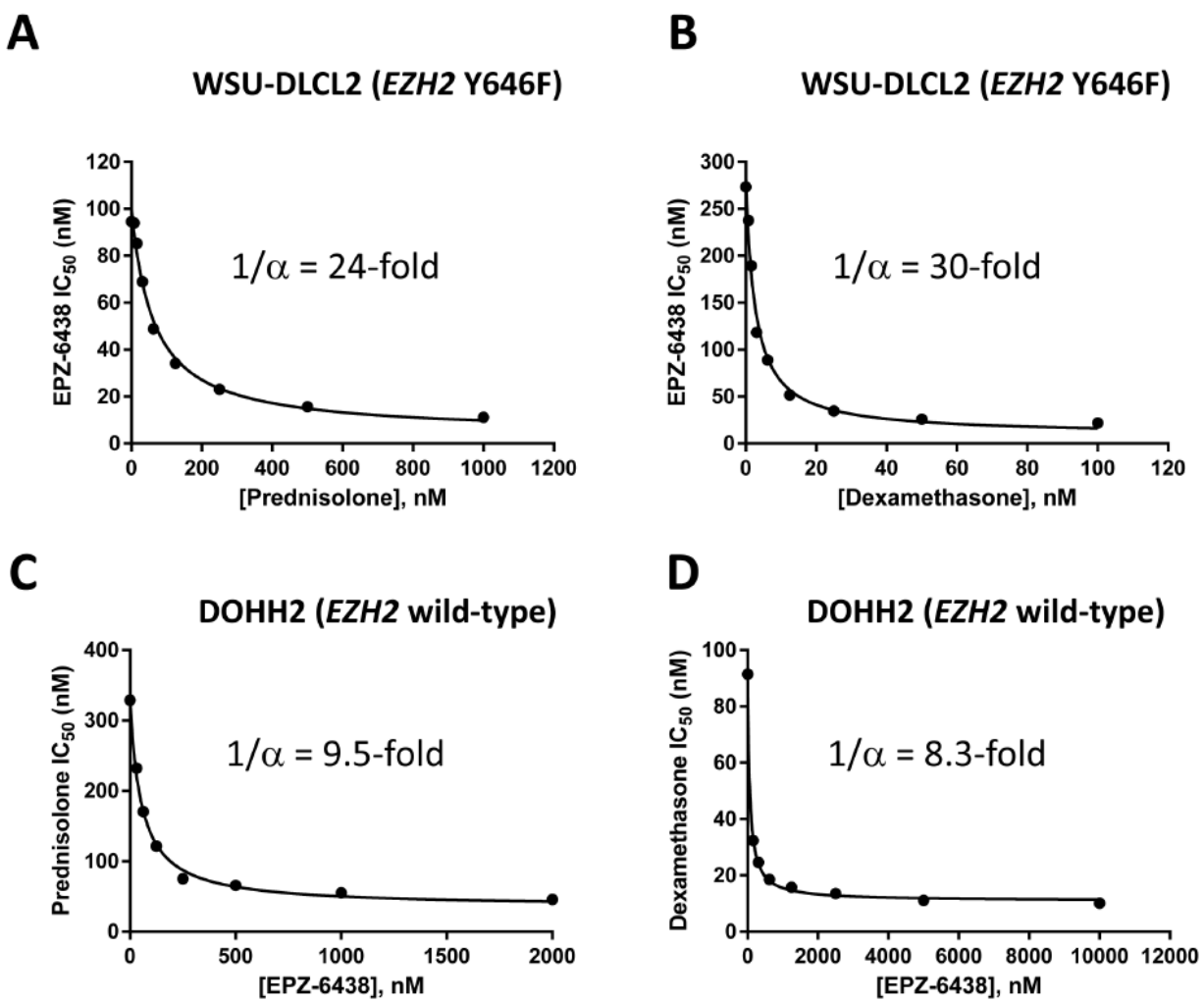


Tazemetostat induces robust tumor regressions in *in vivo* xenografts containing EZH2 activating mutations



Sneeringer et al, PNAS, 2010
Knutson et al., Mol. Cancer Therapeutics, 2014

Anti-proliferative Synergy of Tazemetostat and Corticosteroids



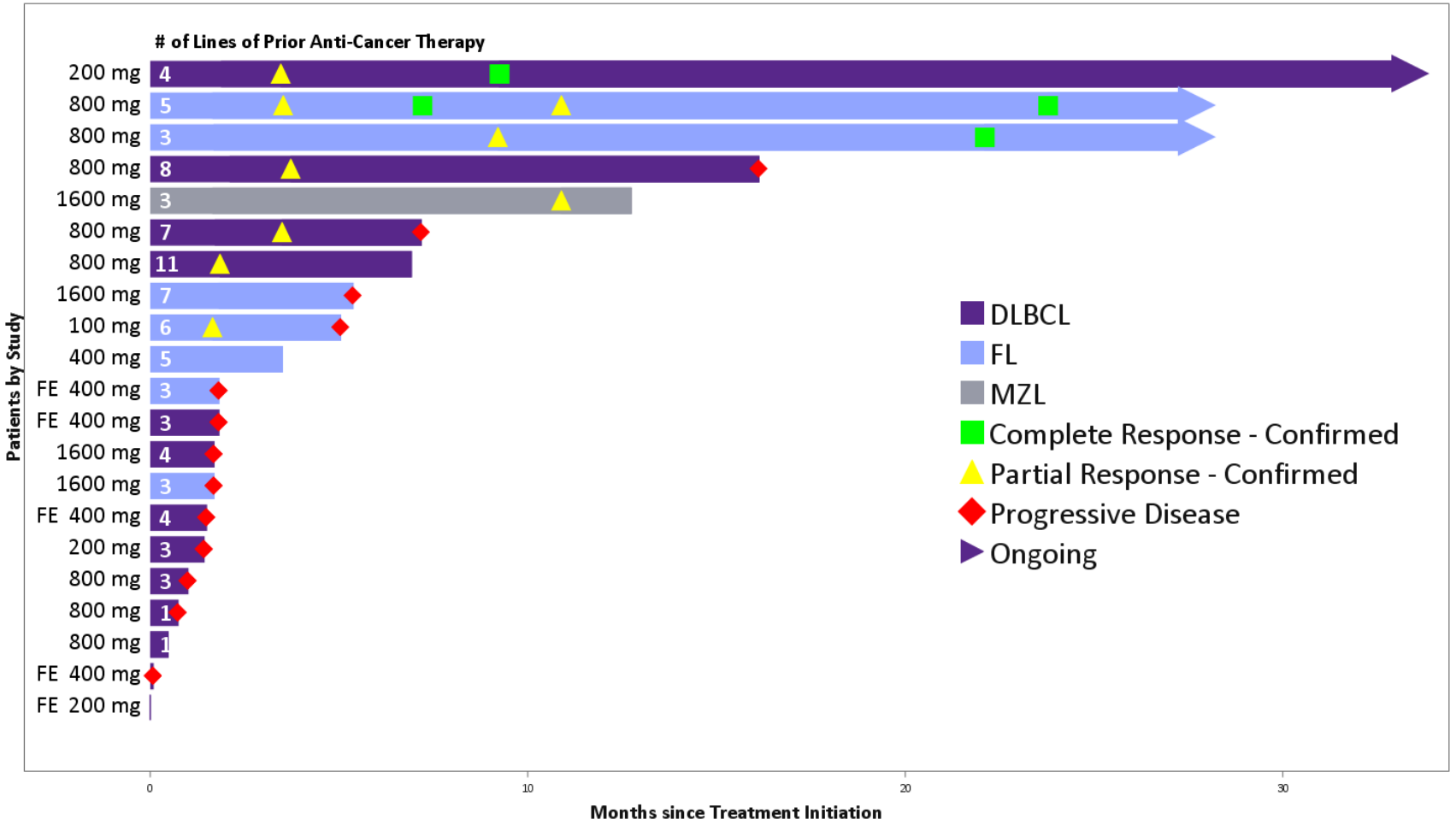
Knutson et al. PLoS One. 2014

Preclinical observation builds the foundation for clinical development strategies

Tazemetostat Clinical Experience: phase 1

- RP2D has been selected as 800 mg BID based on safety, efficacy, PK, and PD
  - MTD not reached across doses explored
    - 100 – 1600 mg BID PO
    - 1 DLT observed (grade 4 thrombocytopenia) at 1600 mg BID
  - Safety, broadly tolerable mainly constitutional AE's
  - PK parameters (C_{max} and $AUC_{0\text{-}12h}$) dose proportional at steady state through 1600 mg dose
  - Evidence of target inhibition (reduction in H3K27me3 staining) in post dose tumor biopsies at 800 and 1600 mg BID
  - PK-PD relationship explored in pre- and post dose skin biopsies across full dose range explored
    - Reductions in post dose H3K27me3 dependent on dose of tazemetostat and skin layer analyzed
    - Reduction in post dose H3K27me3 comparable for 800 and 1600 mg doses

Tazemetostat Phase 1, clinical activity

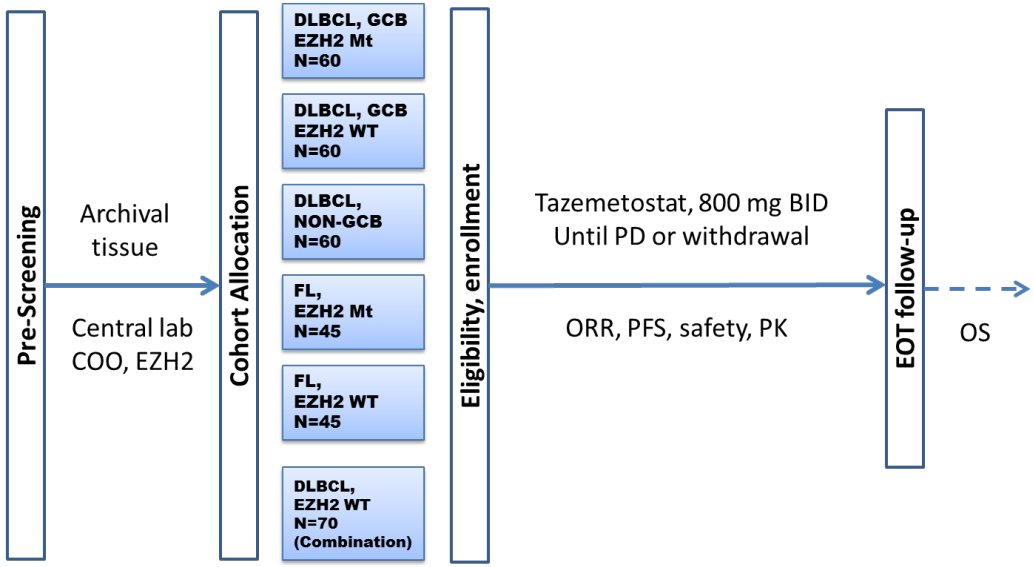


Ribrag, et al. ASH Lymphoma Biology 2016

Tazemetostat Ongoing Phase 2 NHL Study Design

Study designed to assess clinical activity and safety of tazemetostat in five NHL subtypes and determine potential registration path for each subtype

- Global, multi-center, open-label study in 6 cohorts of patients with R/R DLBCL or FL Patient stratification based on EZH2 mutational status and cell of origin
  - All patients treated with ≥ 2 prior therapies
- Primary endpoint: overall response rate
  - Secondary endpoints: progression-free survival (PFS) and duration of response
- Study expanded to 340 patients total
  - 60 patients in each DLBCL cohort; 45 patients in each FL cohort for monotherapy
  - 70 patients in DLBCL cohort for combination with prednisolone



Adverse Events Led to Low Rate of Dose Reductions and Discontinuations

Patients (n=82)	**All Adverse Events (AEs)***	**Treatment-Related AEs**
Adverse Event (any)	65 (79%)	41 (50%)
Grade ≥ 3	23 (28%)	13 (16%)
Serious AE	15 (18%)	8 (10%)
AE Leading to Dose Interruption	18 (22%)	12 (15%)
AE Leading to Dose Reduction	3 (4%)	2 (2%)
AE Leading to Drug Discontinuation	5 (6%)	2 (2%)

* All treatment emergent adverse events that first appear during treatment, which were absent before or which worsen relative to the pre-treatment

Morschhauser, et al. ASH Lymphoma Biology 2016,

Data as of 5/27/16

Tazemetostat Demonstrated Favorable Safety Profile in Phase 2 Patients

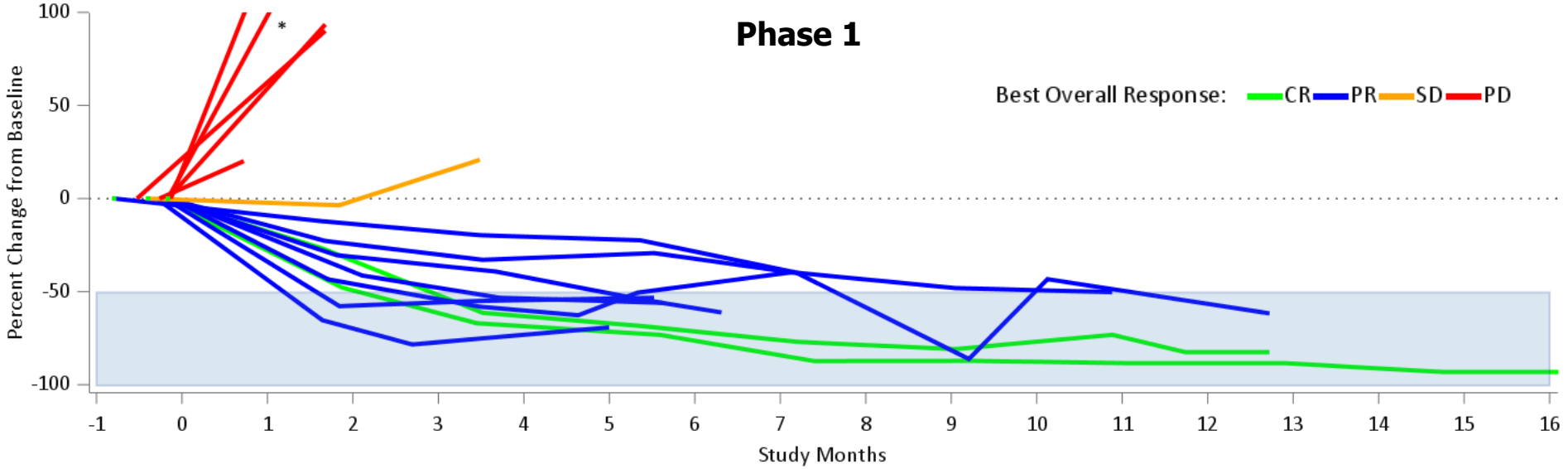
	All Adverse Events (AEs)*		Treatment-Related AEs	
Patients (n=82) with AE[1]	**All Grades**	**Grade ≥ 3**	**All Grades**	**Grade ≥ 3**
Nausea	15 (18%)	0	11 (13%)	0
Cough	11 (13%)	0	1 (1%)	0
Asthenia	9 (11%)	0	8 (10%)	0
Thrombocytopenia	9 (11%)	3 (4%)	7 (9%)	2 (2%)
Fatigue	7 (9%)	3 (4%)	4 (5%)	1 (1%)
Neutropenia	7 (9%)	5 (6%)	6 (7%)	4 (5%)
Constipation	5 (6%)	0	1 (1%)	0
Diarrhoea	5 (6%)	0	3 (4%)	0
Insomnia	5 (6%)	0	2 (2%)	0
Lung infection	5 (6%)	1 (1%)	1 (1%)	0
Vomiting	5 (6%)	0	1 (1%)	0
Hyperglycaemia	4 (5%)	1 (1%)	1 (1%)	0
Lethargy	4 (5%)	0	1 (1%)	0
Urinary tract infection	4 (5%)	0	2 (2%)	0

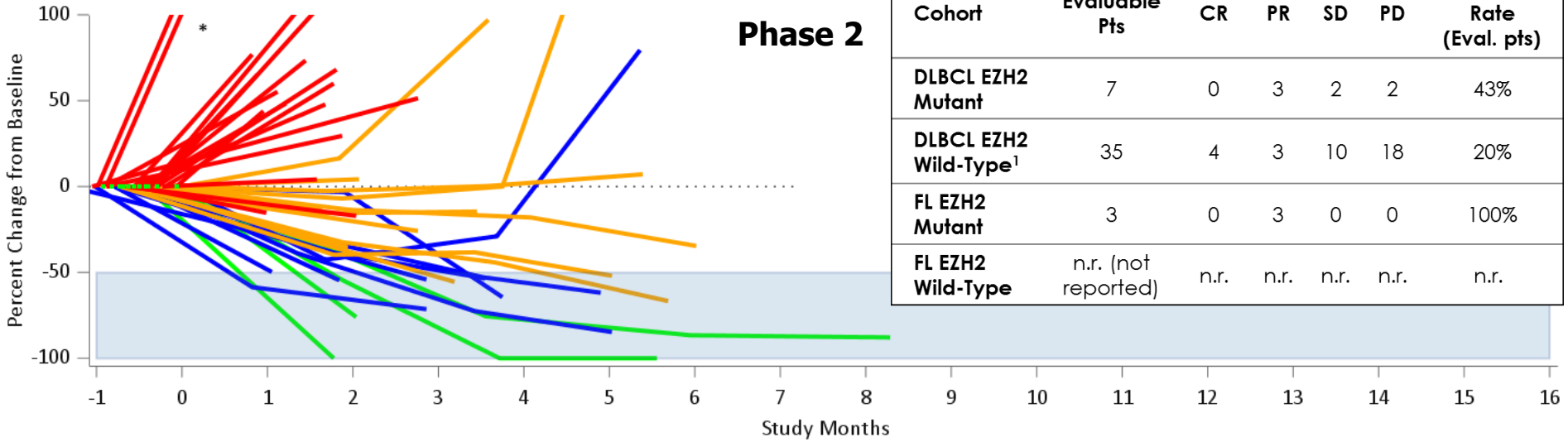
*All treatment emergent adverse events that first appear during treatment, which were absent before or which worsen relative to the pre-treatment; adverse events reported in ≥5% of patients

Morschhauser, et al. ASH Lymphoma Biology 2016,

Data as of 5/27/16

Evolution of Tumor Response and Preliminary Efficacy Assessment



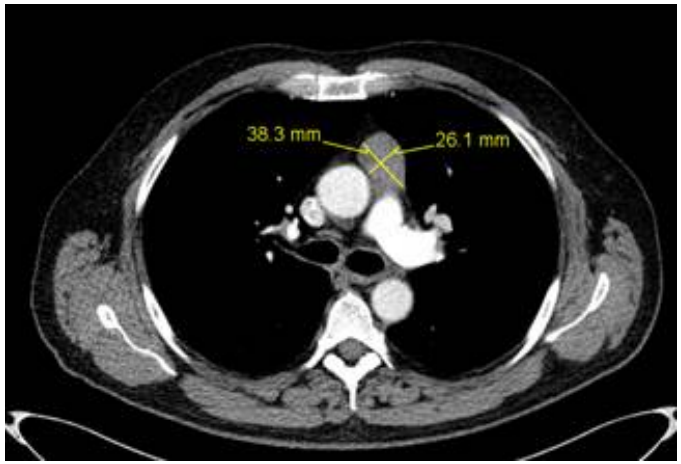


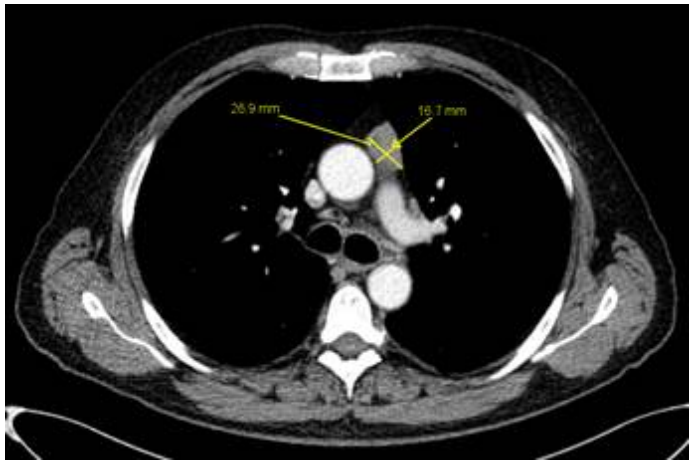
Cohort	Evaluable Pts	CR	PR	SD	PD	Response Rate (Eval. pts)
DLBCL EZH2 Mutant	7	0	3	2	2	43%
DLBCL EZH2 Wild-Type[1]	35	4	3	10	18	20%
FL EZH2 Mutant	3	0	3	0	0	100%
FL EZH2 Wild-Type	n.r. (not reported)	n.r.	n.r.	n.r.	n.r.	n.r.

Phase 1: Ribrag et al., ICML 2015; Phase 2: Morschhauser, et al. ASH Lymphoma Biology 2016

Objective Response in Follicular Lymphoma Patient with EZH2 Y646N Mutation

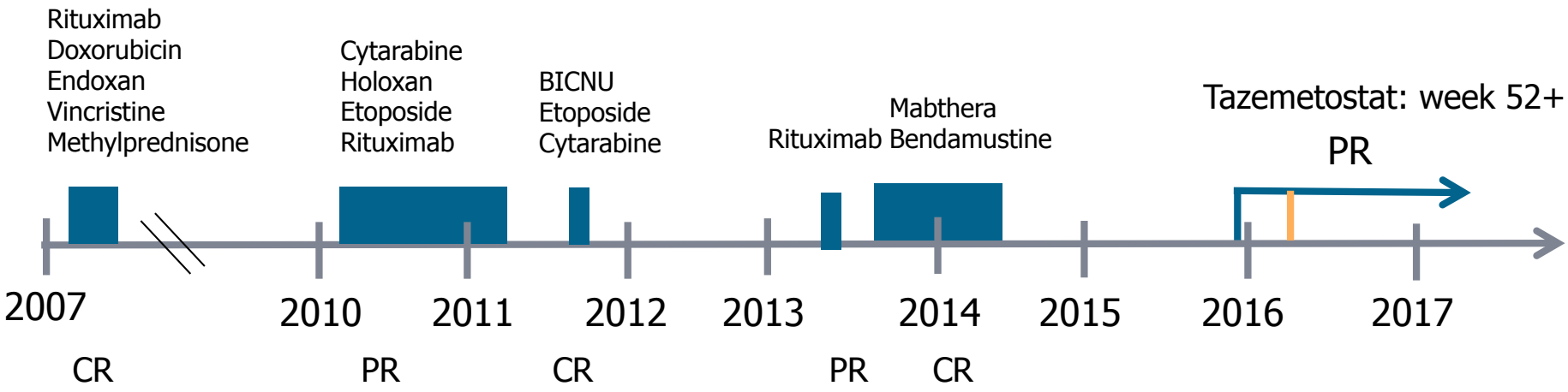
61-yr, male





Baseline: 38 x 26 = 988

Week 16: 27 x 17 = 459, -53%: PR



Morschhauser, et al. ASH Lymphoma Biology 2016, updated

Summary

- Tazemetostat is a first-in-class, potent, and specific inhibitor of EZH2
- Tazemetostat has been generally well tolerated in patients with cancer including NHL
- Encouraging clinical activity has been observed with tazemetostat monotherapy, particularly in lymphomas with activating mutations of EZH2
- Clinical investigation with tazemetostat monotherapy and combination with prednisolone and R-CHOP is ongoing.