NEW DRUGS IN HEMATOLOGY

EZH2 INHIBITOR

TAZEMETOSTAT

VINCENT RIBRAG
DITEP-HEMATOLOGY

Bologna May 9-11, 2016

GUSTAVE ROUSSY
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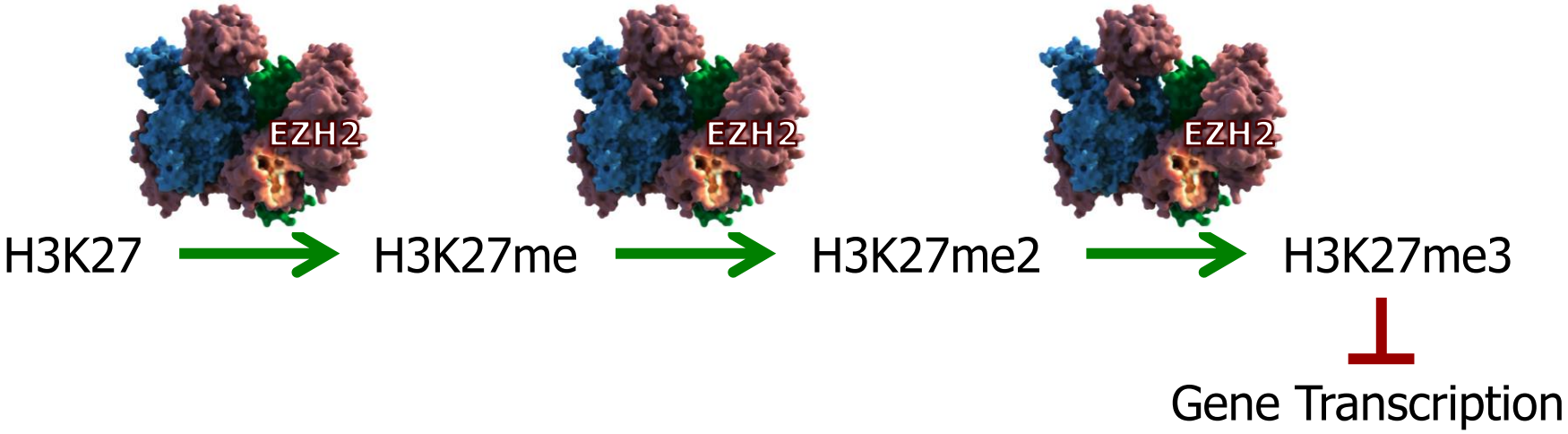
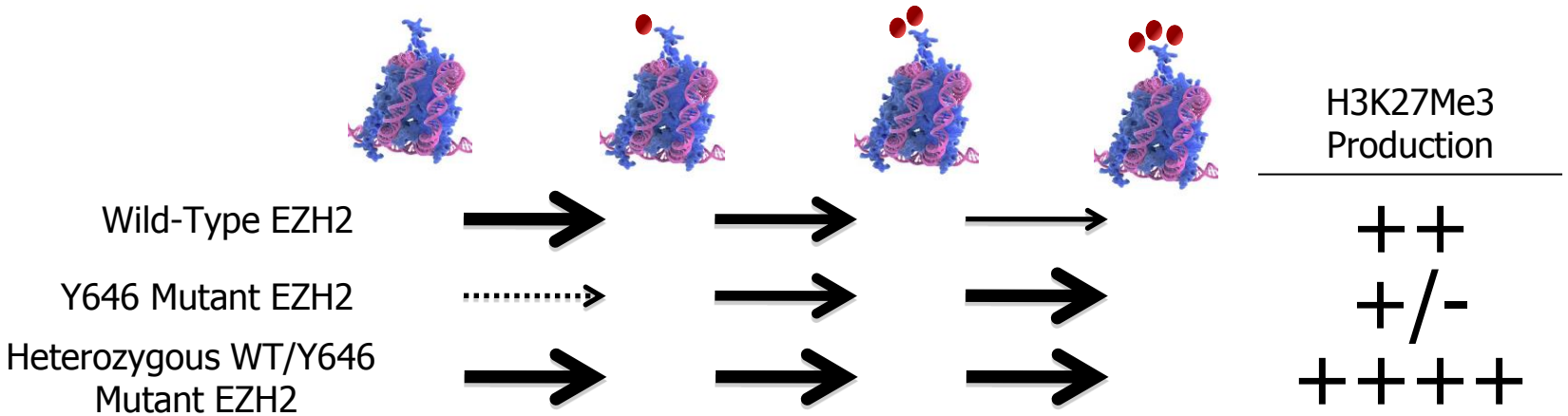
EZH2 Catalyzed Chromatin Remodeling

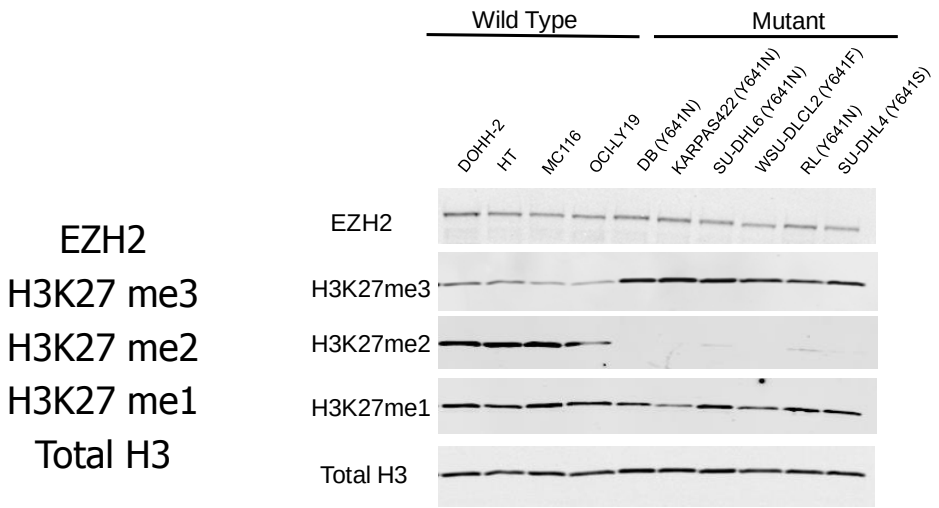
- EZH2 is the catalytic subunit of the multi-protein PRC2 (polycomb repressive complex 2)
- PRC2 is the only protein methyltransferase that can methylate H3K27
  - Catalyzes mono-, di- and tri-methylation of H3K27
  - H3K27me3 is a transcriptionally repressive histone mark
- H3K27 is the only significant substrate for PRC2
- Aberrant trimethylation of H3K27 is oncogenic in a broad spectrum of human cancers, such as B-cell NHL



Chase & Cross, Clin. Cancer Res., 2011

EZH2 Gain of Function Mutations Result in Elevated H3K27me3 Levels

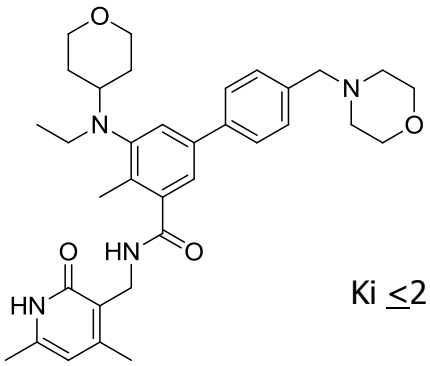




Sneeringer et al, PNAS, 2010

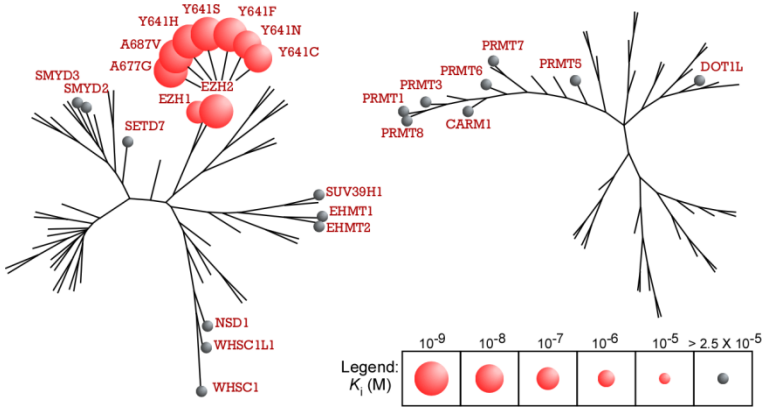
Tazemetostat (EPZ-6438): Potent and Highly Selective EZH2 Inhibitor

Novel Structure, Potent Target Inhibition



Ki ≤2.5 nM

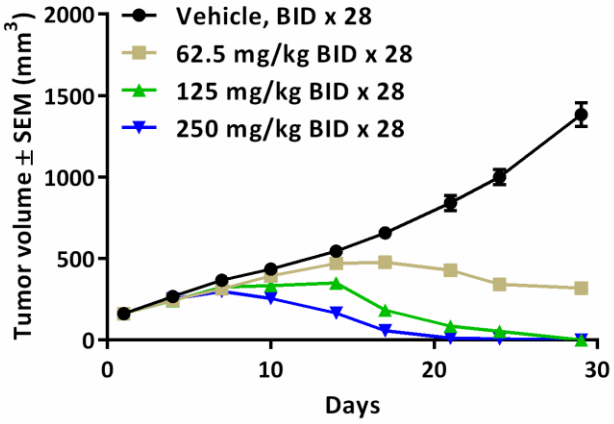
Selective for EZH2



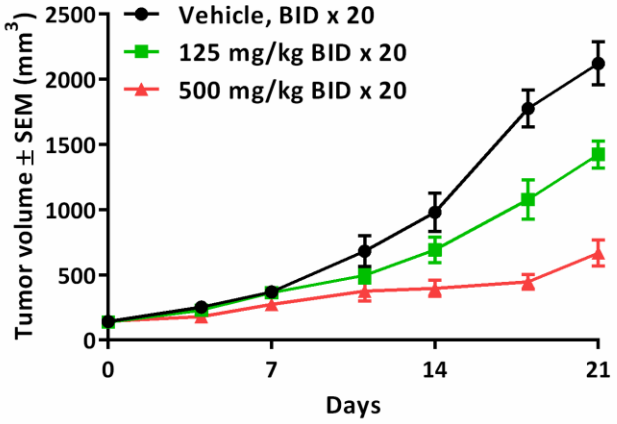
Selectivity >20,000-fold (100-fold for EZH1)

Antitumor Activity in EZH2 Mutant and WT Xenograft Models of DLBCL

KARPAS-422 (EZH2 Y646N)

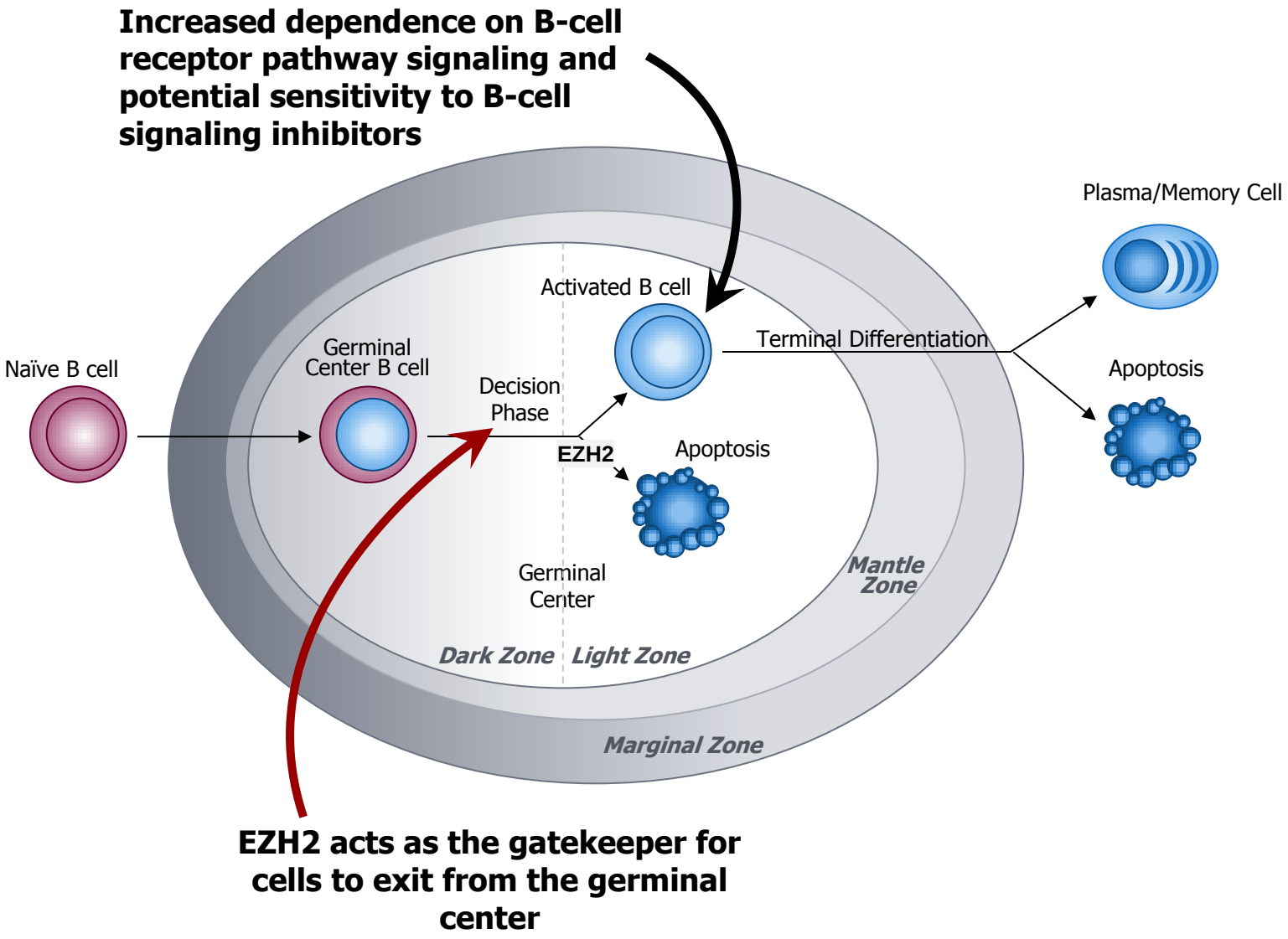


OCI-LY19 (EZH2 WT)



Knutson et al., Mol. Cancer Therapeutics, 2014
Thomenius et al. Molecular Targets Conference, 2015

Tazemetostat Drives Apoptosis or Differentiation in Lymphoma Cells Independently of EZH2 Mutation Status



Thomenius et al. Molecular Targets Conference, 2015

First-in-Human Phase 1 Trial E7438-G000-001 (NCT01897571)

- Population: relapsed or refractory B-cell lymphoma or solid tumors
- Study design: 3+3 dose-escalation completed
  - Expansion cohorts (800 mg and 1600 mg BID) completed
  - Food effect sub-study (400 mg BID) completed
  - Drug-drug interaction sub-study (800 mg BID) ongoing
- Primary endpoint: determination of RP2D/MTD
- Secondary endpoints: safety, PK, PD and tumor response (every 8 wks)
- Data cut: 7-Nov-2015

Dose (mg BID)	Patients (n=58)	Solid tumors (n=37)**	B-cell NHL (n=21)
100*	6	5	1
200	3	1	2
400	3	2	1
800	14	6	8
1600	12	8	4
Food Effect	13	8	5
Drug-Drug	7	7	0

* 2 formulations

from Ribrag et al., ASH 2015

**Solid tumor data presented by A. Italiano, ESMO/ECC 2015

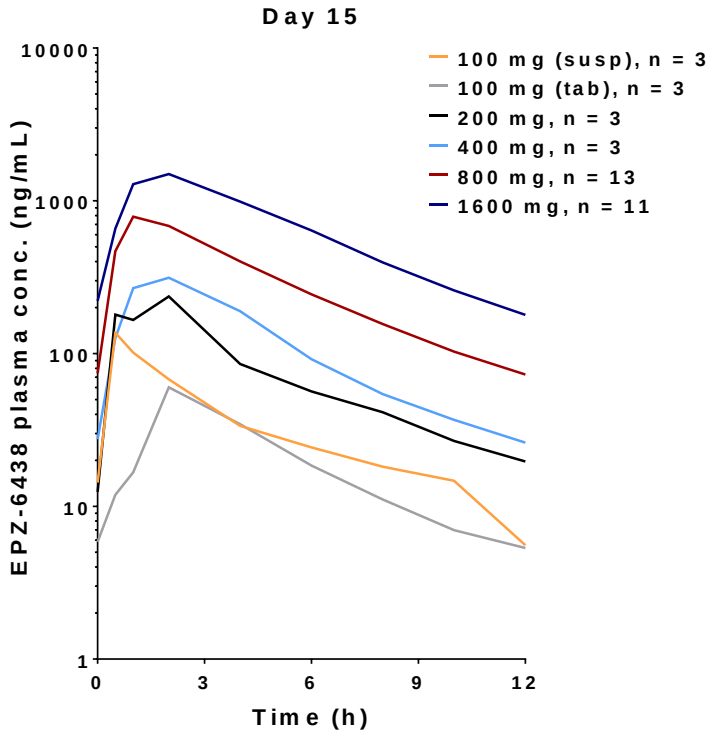
Patient Tumor Types

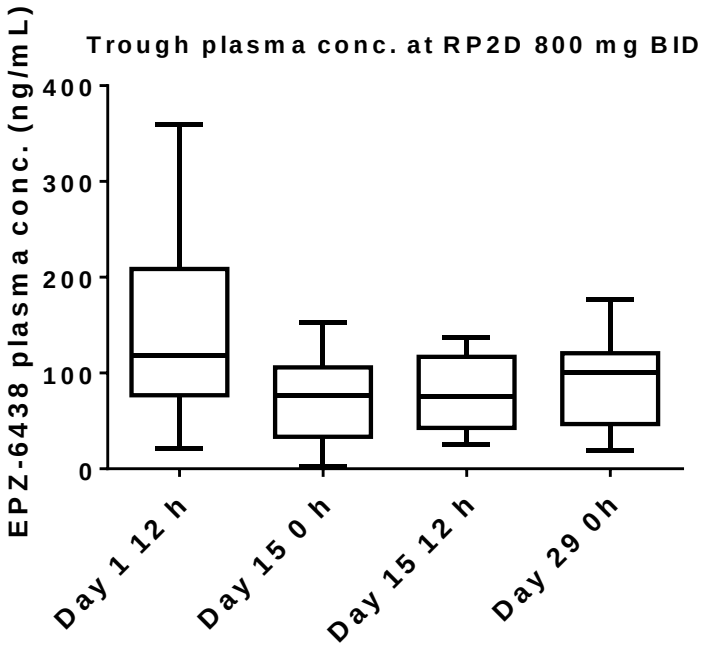
Relapsed or refractory NHL		**n=21**
Diffuse Large B cell Lymphoma (DLBCL)	GCB	5
	Non GCB	6
	undetermined	3
Follicular lymphoma (FL)		6
Marginal Zone lymphoma (MZL)		1
Relapsed or refractory solid tumors		**n=37**
INI1-deficient or negative	Malignant rhabdoid tumor	5
	Epithelioid sarcoma	3
	Synovial sarcoma	4
SMARCA4-negative tumors		3
Other solid tumors		22

2/17 NHL patients tested to date are EZH2 mutant by cobas® test (in development, Roche Molecular Systems, Inc.)

from Ribrag et al., ASH 2015

Pharmacokinetics





- Rapid absorption (t_{max} = 1-2 h) with a mean terminal $t_{1/2}$ = 3 - 5 h
- Dose-proportional C_{max} and $AUC_{0\text{-}12h}$ at steady-state (day 15) through 1600 mg BID
- Decrease in systemic exposure between day 1 and day 15 with no further reduction afterwards
  - 42% decrease in $AUC_{0\text{-}12h}$ on day 15 vs. day 1 at 800 mg BID
  - C_{trough} levels reach steady-state by day 15

from Ribrag et al., ICML 2015

Safety Profile in All Patients (n=55: 20 NHL and 35 Solid Tumors)

	All Events		All Treatment-Related	
	All Grades *	Grade ≥3	All Grades	Grade ≥3 **
Asthenia	23	0	13	0
Decreased appetite	9	1	4	0
Thrombocytopenia	8	2	7	**1**
Nausea	8	0	8	0
Constipation	7	0	2	0
Diarrhea	6	0	4	0
Vomiting	6	0	5	0
Anemia	5	0	3	0
Dry skin	5	0	4	0
Dysgeusia	5	0	5	0
Dyspnea	5	0	0	0
Muscle spasms	5	0	3	0
Abdominal pain	4	1	1	0
Hypophosphatemia	4	0	1	0
Anxiety	3	0	1	0
Depression	3	2	1	0
Hypertension	3	1	2	**1**
Insomnia	3	0	0	0
Neutropenia	3	1	3	**1**
Night sweats	3	0	3	0
Peripheral edema	3	0	2	0
Hepatocellular injury	2	1	1	**1**

* All AEs with frequency >5% regardless of attribution shown

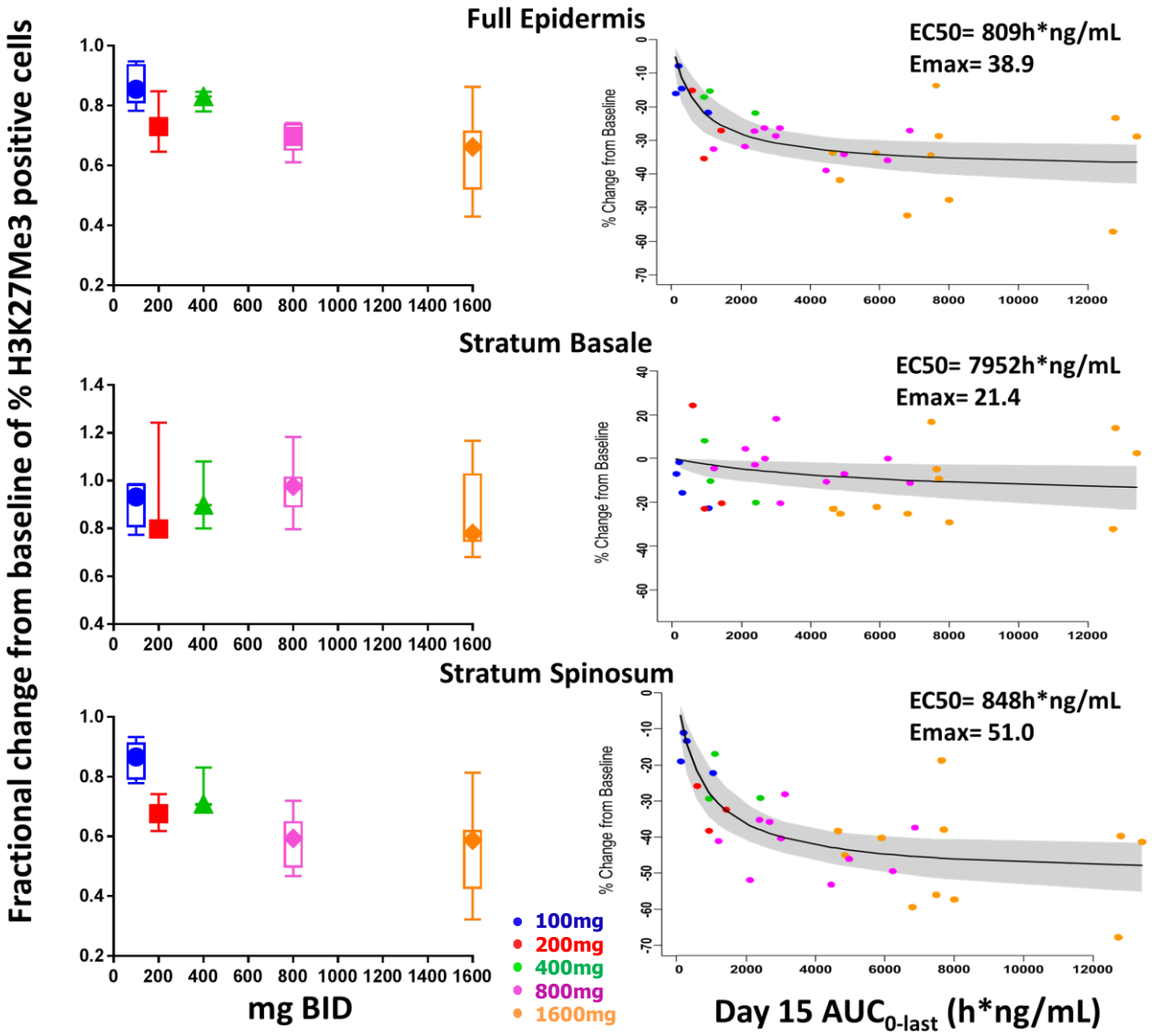
** All grade ≥3 treatment-related events shown

from Ribrag et al., ASH 2015

PK-PD: EZH2 Inhibition in Surrogate Tissue

Target inhibition in skin:

- Reduction of H3K27me3 by IHC at week 4 at all doses
- Exposure-dependent reductions in H3K27me3
- Differential effects by epithelial layer
  - Stratum basale - minimal change
  - Stratum spinosum – pronounced change
  - Full epidermis – composite signal of stratums spinosum and basale
- Reduction in H3K27me3 signal equivalent at 800 and 1600 mg BID



NHL Patient Demographics

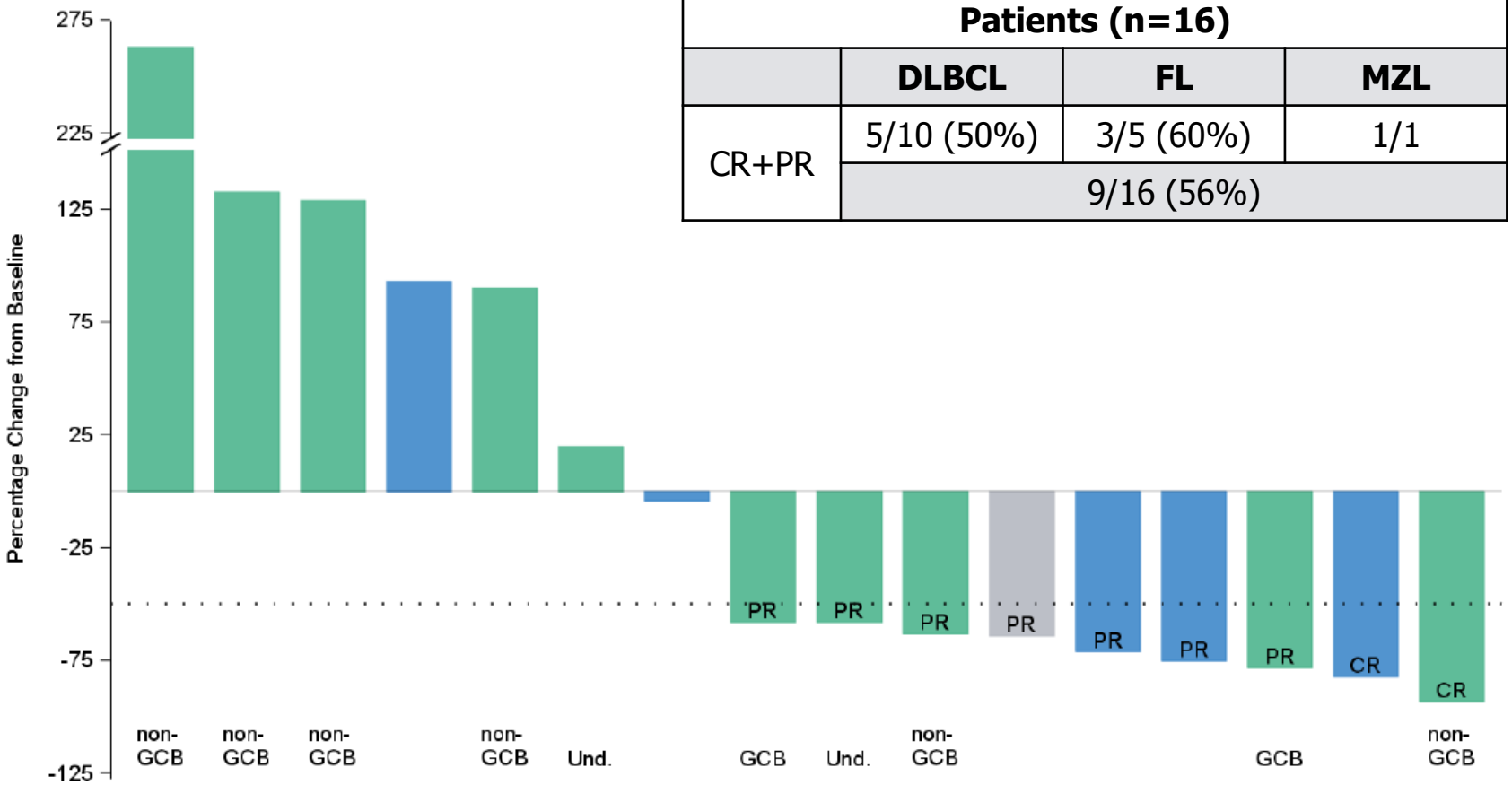
Characteristic		n=21 (%)
Median age, years [range]		63 [24-84]
Sex (M / F)		15/6
# of prior therapeutic systemic regimens	1	2 (10)
	2	1 (5)
	3	8 (38)
	4	3 (14)
	≥5	7 (33)
Prior autologous hematopoietic cell transplant		8 (38)
Prior radiotherapy		17 (57)

from Ribrag et al., ASH 2015

Waterfall Plot of Best Response in NHL

Per Protocol: Response Evaluable *

Patients (n=16)			
	DLBCL	**FL**	**MZL**
CR+PR	5/10 (50%)	3/5 (60%)	1/1
	9/16 (56%)		

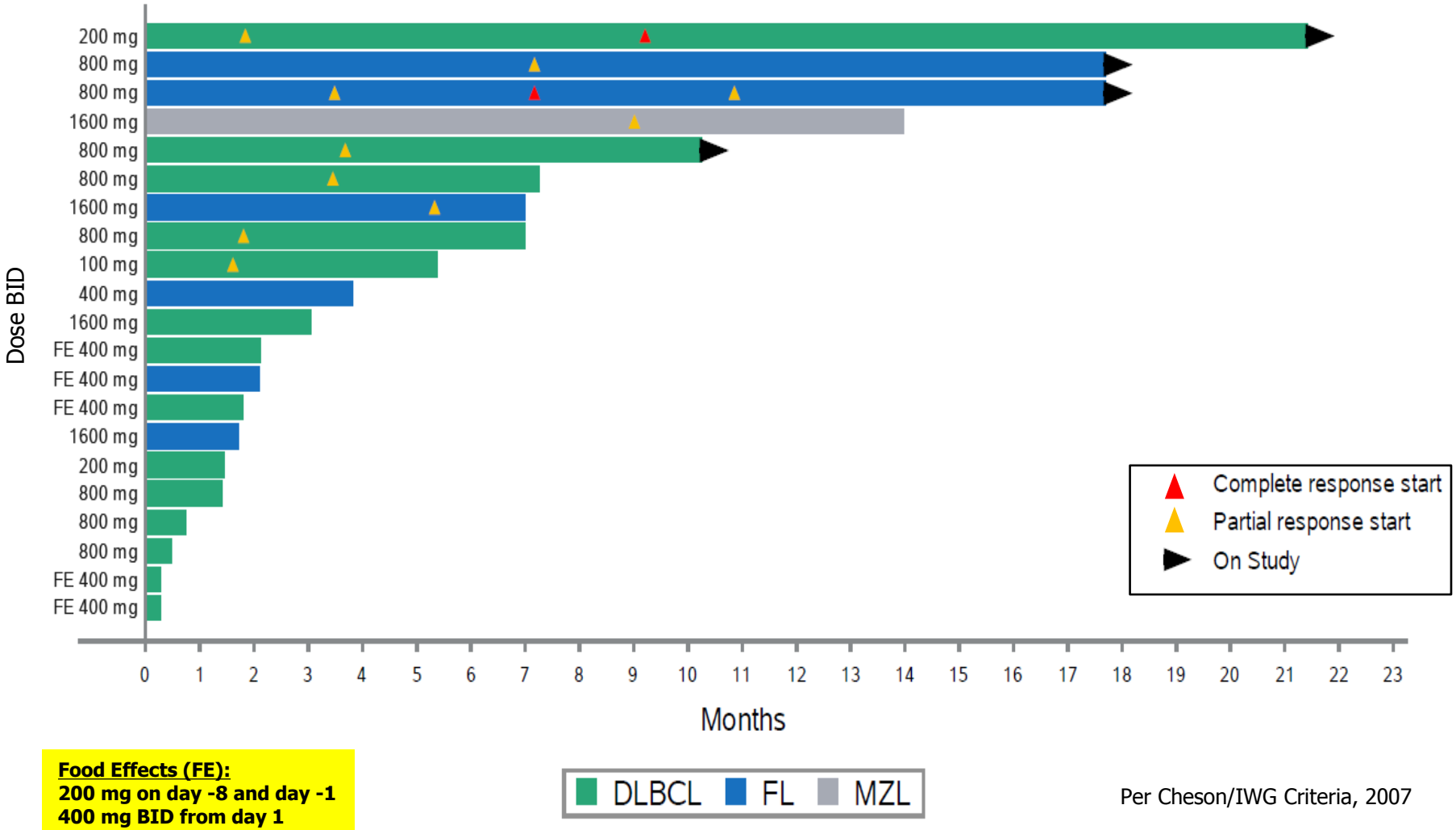


Per Cheson/IWG Criteria, 2007

* Response evaluable: Measureable disease
≥ 1 dose
≥ 1 post-baseline scan

from Ribrag et al., ASH 2015

Objective Response in NHL
All Patients (n=21)

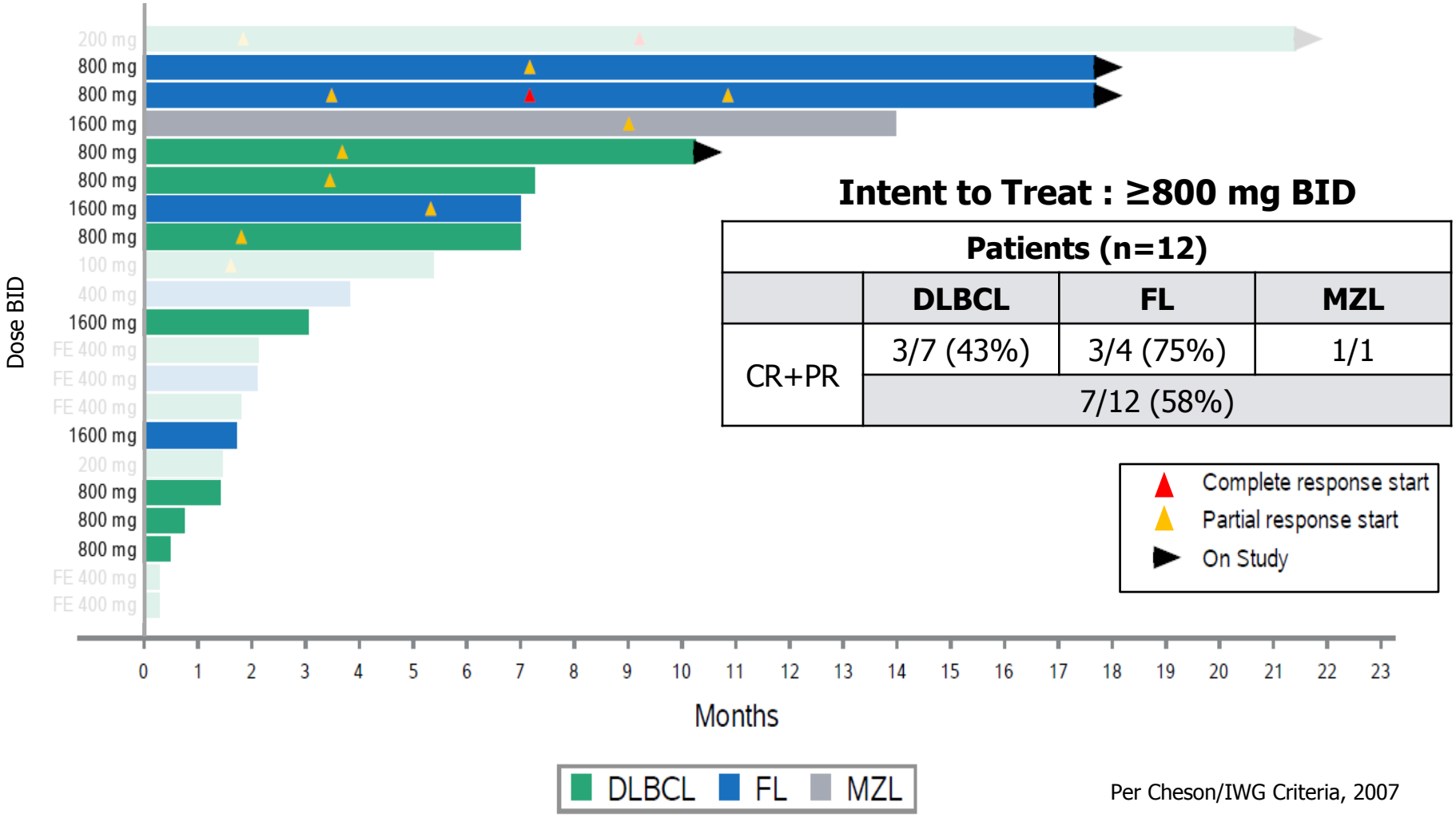


Food Effects (FE):
200 mg on day -8 and day -1
400 mg BID from day 1

Per Cheson/IWG Criteria, 2007

from Ribrag et al., ASH 2015

Objective Response in NHL
Intent to Treat Population at or above RP2D



Intent to Treat : ≥800 mg BID

Patients (n=12)			
	DLBCL	**FL**	**MZL**
CR+PR	3/7 (43%)	3/4 (75%)	1/1
	7/12 (58%)		

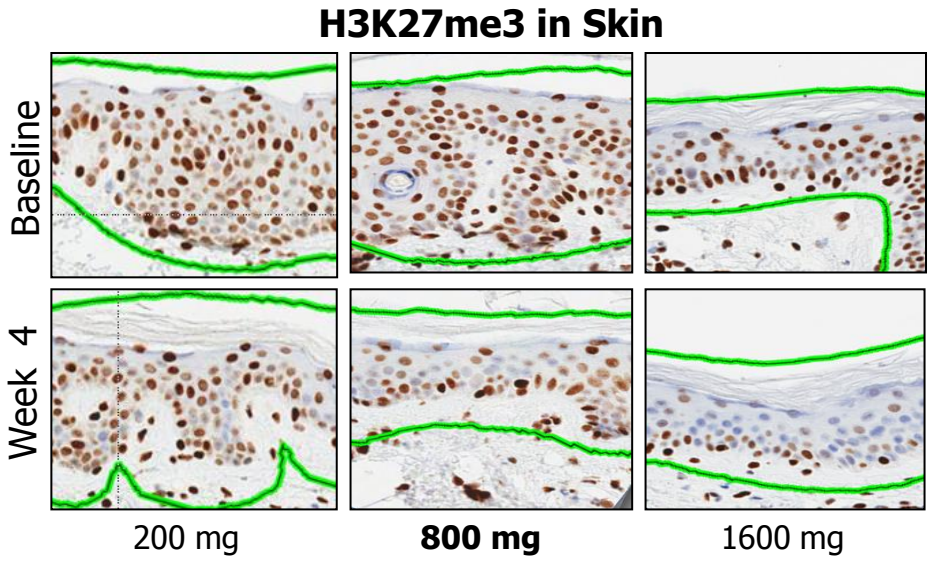
Per Cheson/IWG Criteria, 2007

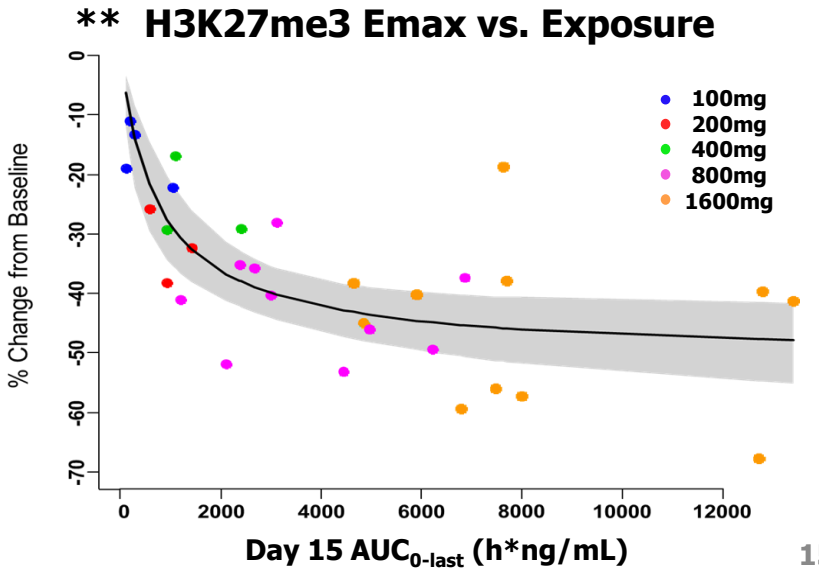
from Ribrag et al., ASH 2015

Tazemetostat Phase 2 Dose Selection

Dose BID	Efficacy	Safety	PK/PD
	Response in NHL (%)	Grade ≥3 TEAE *	H3K27me3 Inhibition Emax **
<800 mg	2/9 (22%)	7/24 (29%)	-
800 mg	5/8 (62%)	3/19 (16%)	80%
1600 mg	2/4 (50%)	4/12 (33%)	84%

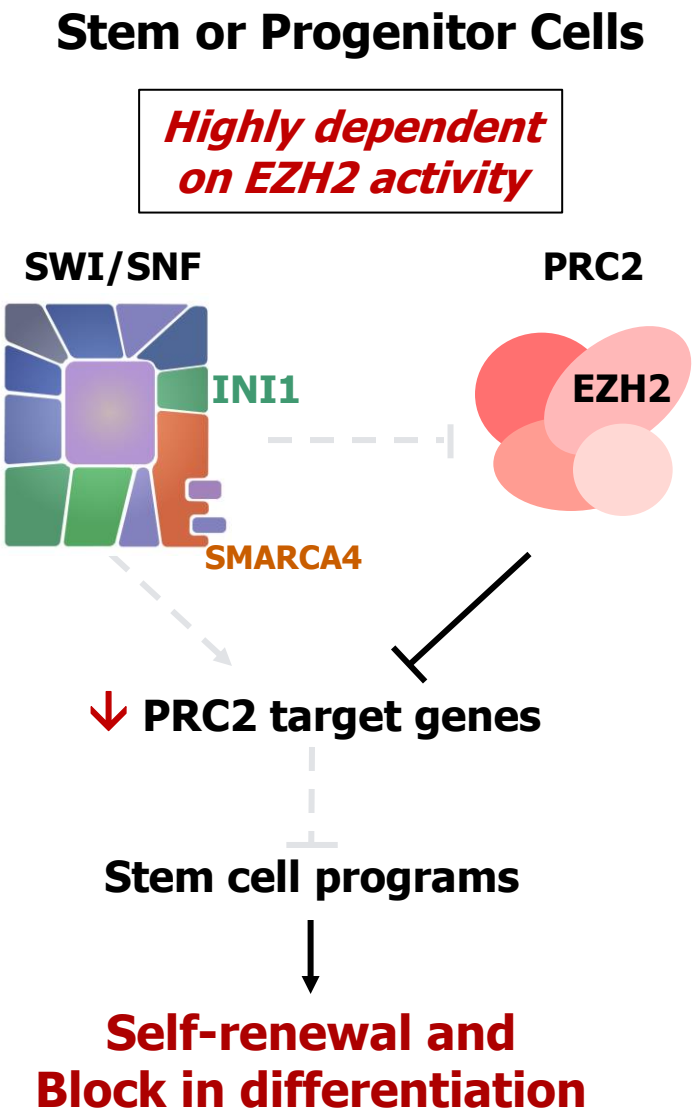
* Treatment Emergent Adverse Events in all patients (n=55)





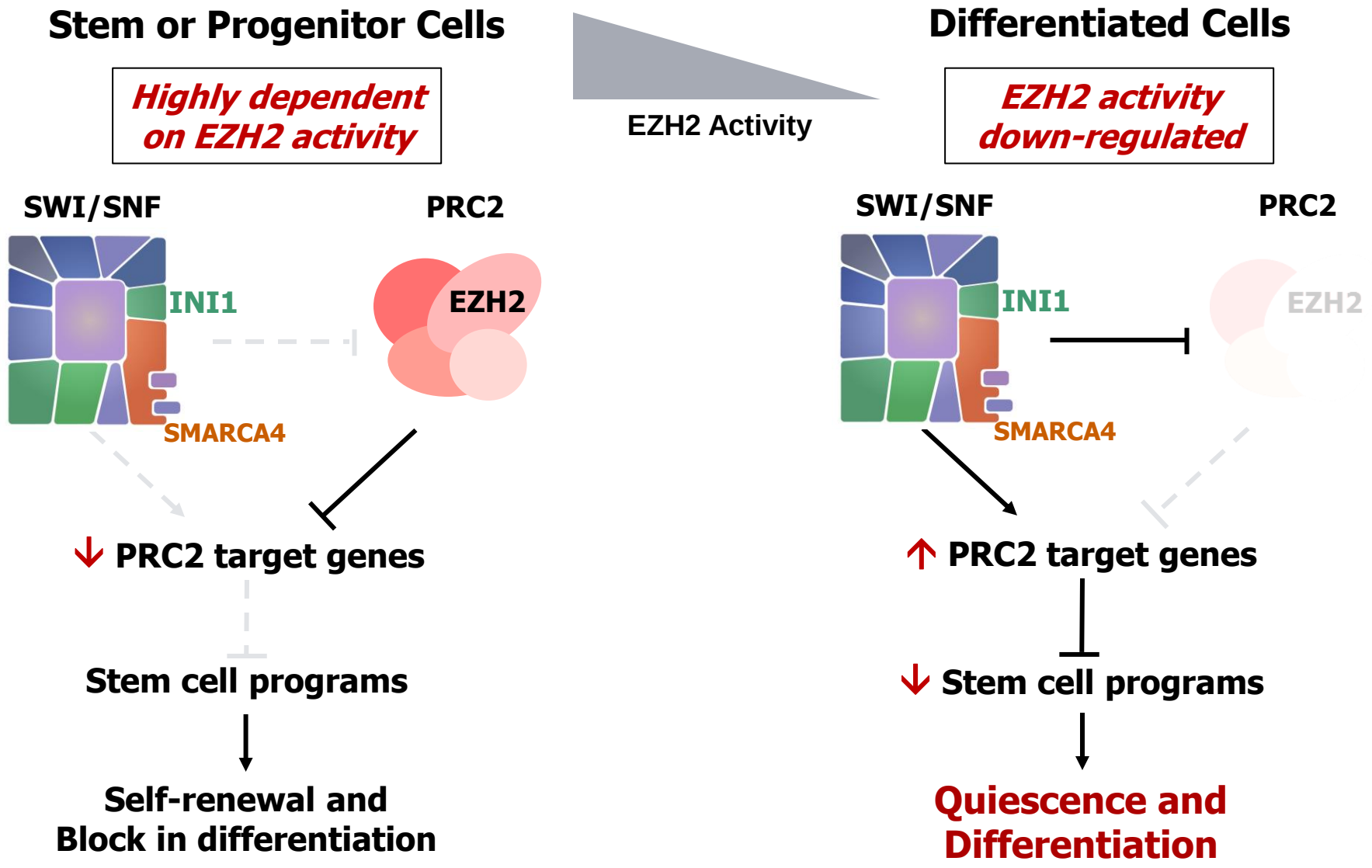
from Ribrag et al., ASH 2015

Antagonism of PRC2 and SWI/SNF-Dependent Chromatin Remodeling Regulates Pluripotency



Adapted from Wilson 2010

EZH2 Activity Is Down-regulated as Progenitor Cells Become Differentiated

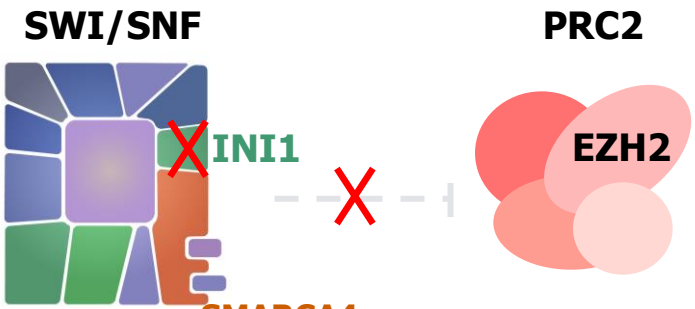


Adapted from Wilson 2010

INI1 Loss Creates an Oncogenic Dependency on EZH2 in Tumors

Stem or Progenitor Cells

Highly dependent on EZH2 activity



↓↓↓ **PRC2 target genes**

Hyper-repression of PRC2 targets

↑↑ **Stem cell programs**

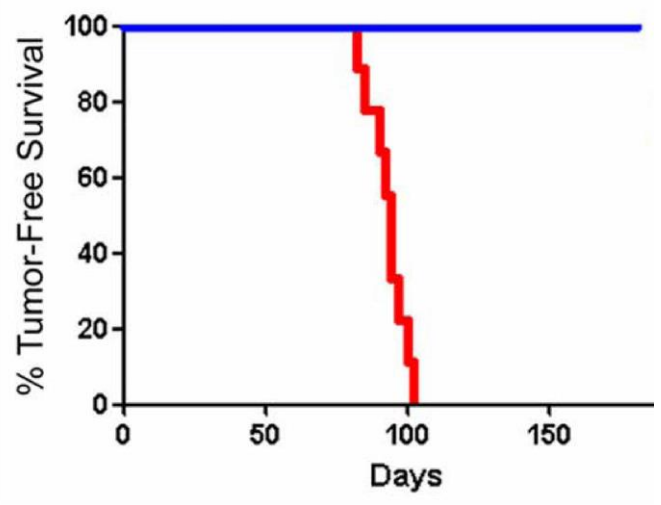
Potentiation of stem cell programs

Oncogenic Transformation

<u>INI1-negative tumors, e.g.:</u>

Malignant rhabdoid tumor (MRT)
Epithelioid sarcoma

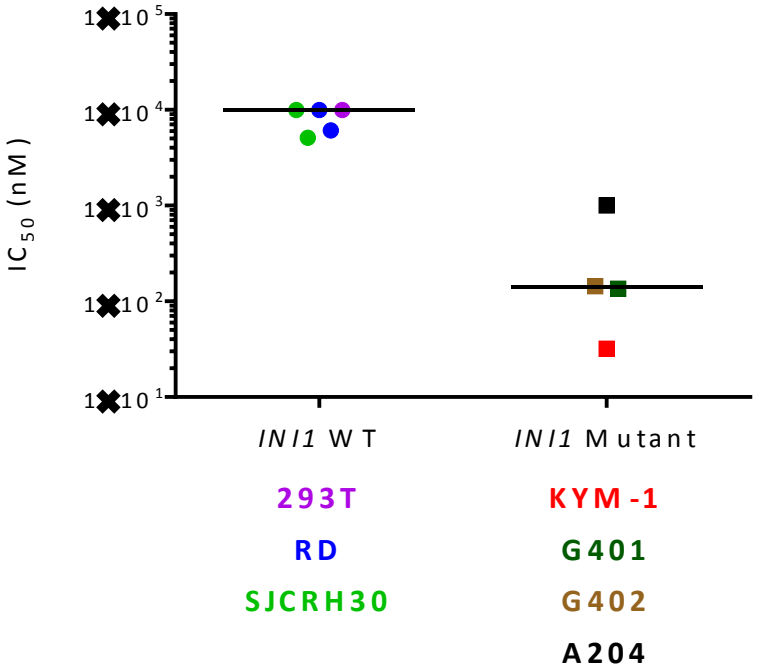
EZH2 knockout reverses oncogenesis induced by INI1 loss



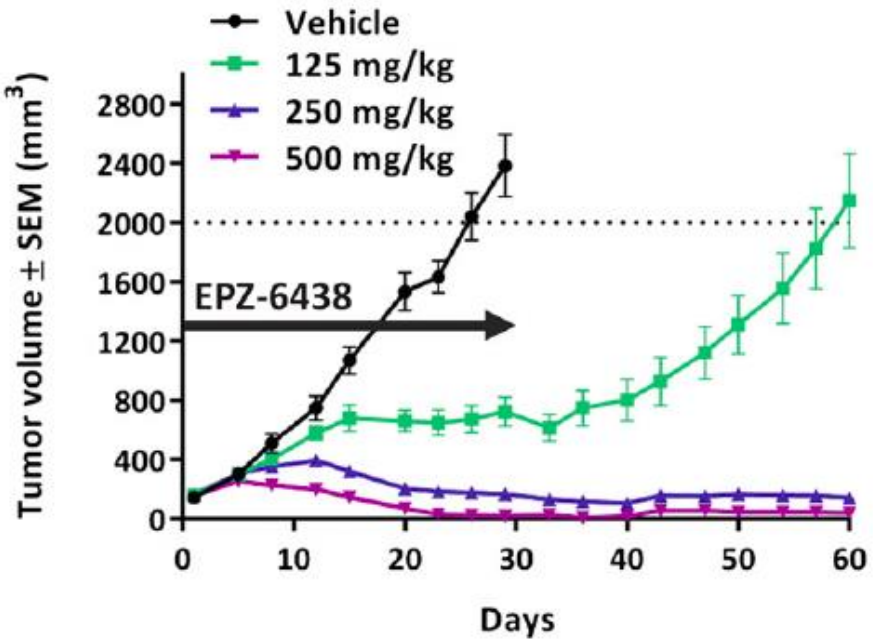
Adapted from Wilson 2010

Tazemetostat is Active in Preclinical Models of Malignant Rhabdoid Tumors

In vitro cell killing of mutant _INI1_ MRT cells

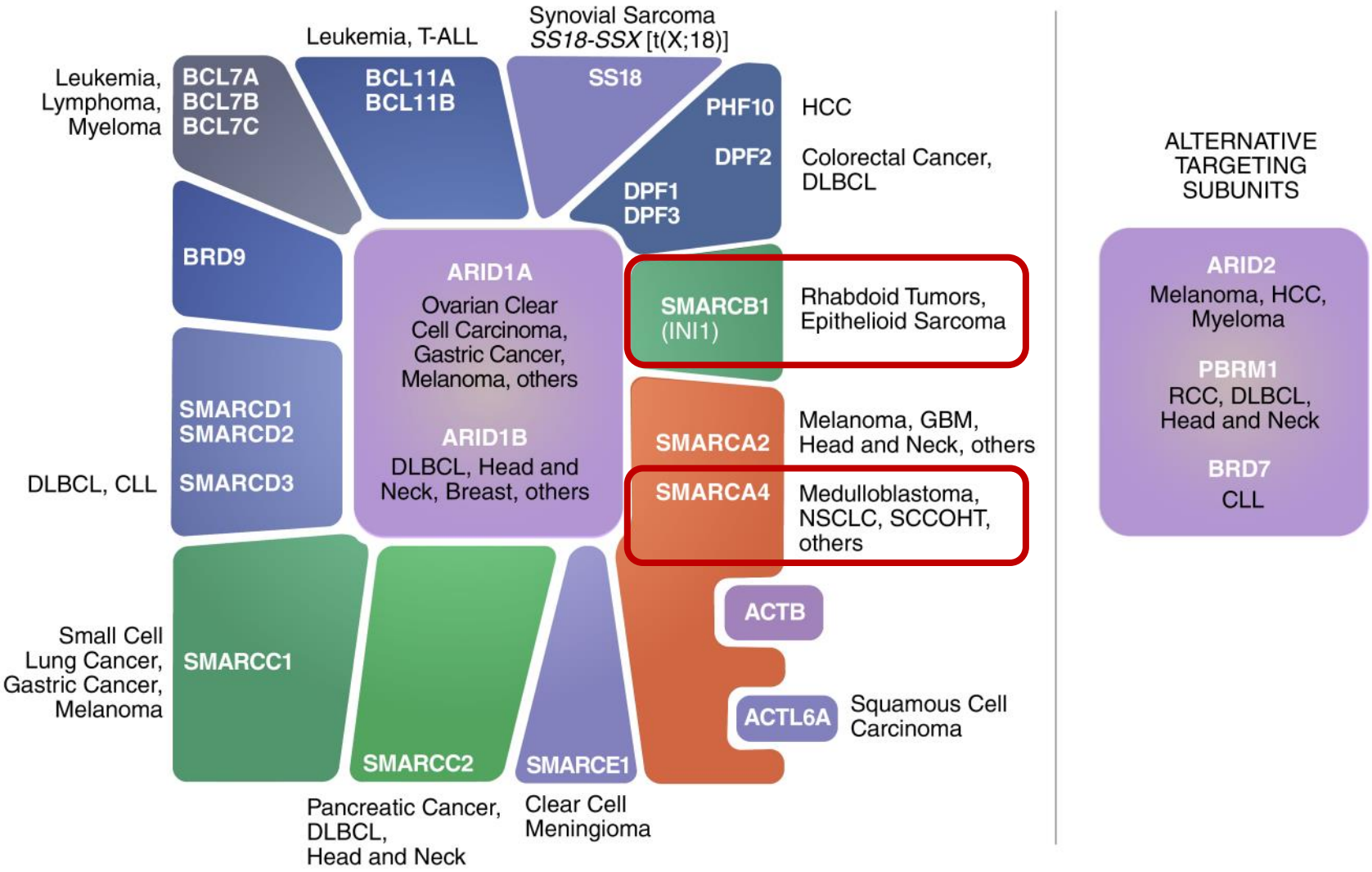


In vivo efficacy in MRT xenograft



Knutson et al. PNAS , 2013

Subunits of SWI/SNF Complexes Are Mutated Across Many Indications



Adapted from Kadoch 2015

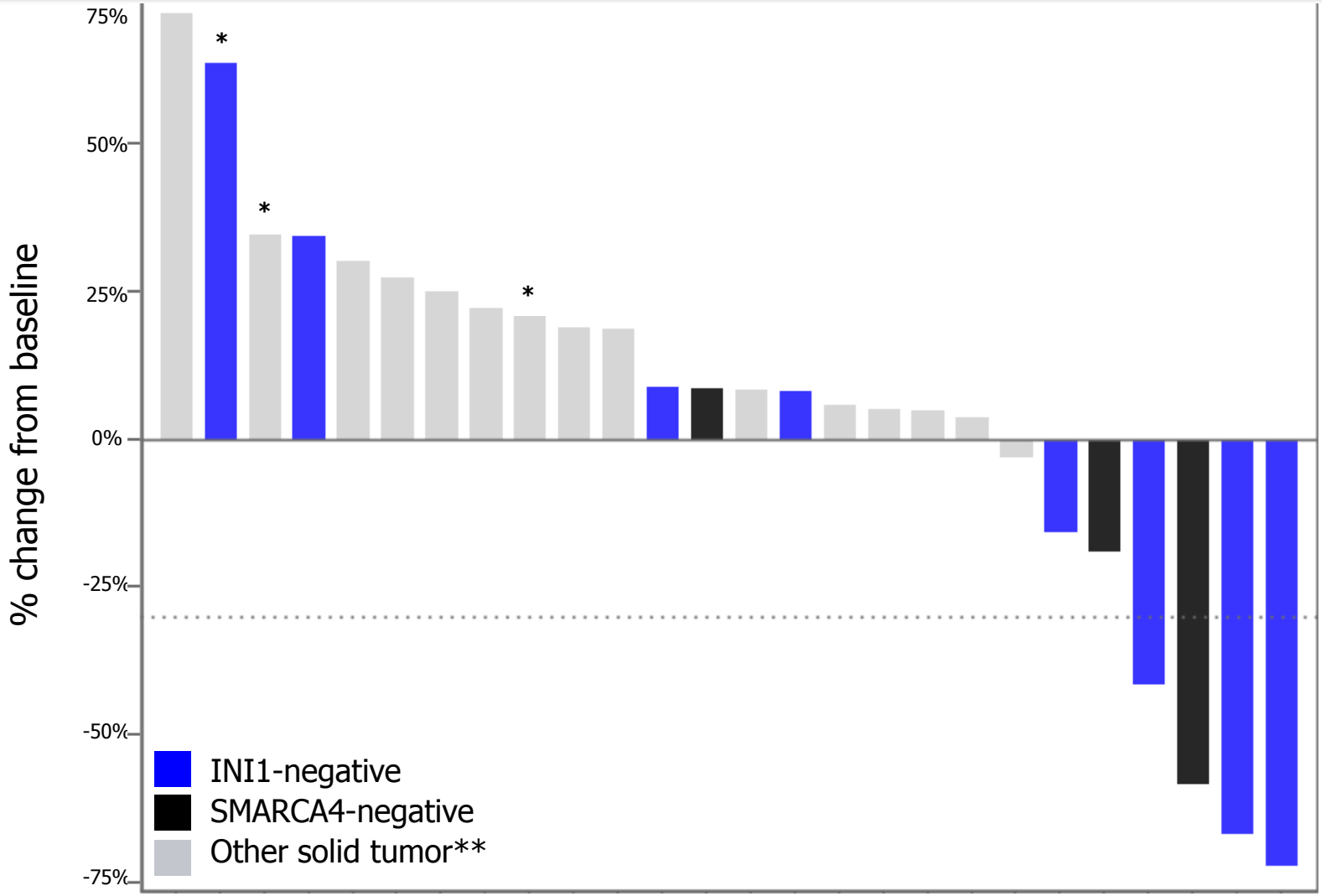
Patient Tumor Types

Relapsed or refractory solid tumor		**N=30**
INI1-negative (SMARCB1)*	Malignant rhabdoid tumor	5
	Epithelioid sarcoma	3
SMARCA4-negative*	Malignant rhabdoid tumor of ovary (SCCOHT)	2
	Thoracic sarcoma	1
Synovial sarcoma		3
GI malignancy		9
GU malignancy		2
GYN malignancy (non-SCCOHT)		2
CNS tumor/other sarcoma		3
Relapsed or refractory NHL		**N=21**

* INI1- or SMARCA4-negative by IHC

from Italiano et al., ECC 2015

Best Response in Patients with Solid Tumors



* Patients censored at time of progression

** Four additional other solid tumor patients with pending disease evaluation

from Italiano et al., ECC 2015

Phase 1 Summary

- Tazemetostat demonstrates clinical activity as monotherapy in patients with both B-cell NHL and solid tumors
- Relapsed or refractory DLBCL (both GCB and non-GCB), FL and MZL
  - Objective responses in B-cell NHL with either wild-type or mutated EZH2
  - Responses are durable – patients ongoing at 10+ to 21+ months
- Relapsed INI1- and SMARCA4-negative tumors
  - Malignant rhabdoid tumor, malignant rhabdoid tumor of ovary (SCCOHT), epithelioid sarcoma
  - Objective responses (CR and PR) and SD ≥6 months
- Pharmacodynamic inhibition of H3K27me3 demonstrated in tumor tissue and in surrogate tissue (skin)
- Safety profile as monotherapy is favorable for both monotherapy and combination development
- RP2D dose of 800 mg BID supported by safety, efficacy, PK/PD

Current Tazemetostat Development

- Non-Hodgkin Lymphoma
  - Phase 2 trial for DLBCL and FL open in France, Australia, UK, Belgium, Italy, Canada. US and additional countries to be added.
    - Five cohorts – prospectively stratified according to cell-of-origin and EZH2 mutation status
  - Phase 1/2 trial in DLBCL of tazemetostat in combination with R-CHOP in front-line elderly high-risk patients to start in 2016
- Rhabdoid and non-rhabdoid INI1-negative or SMARCA4-negative Tumors and Synovial Sarcoma
  - Phase 2 trial in adults open in US with EU and Australia to be added
  - Phase 1 trial in children (oral suspension formulation) open in US and Australia with EU to be added
- Mesothelioma
  - Phase 2 trial in mesothelioma with BAP1 loss of function to start in 2016 in US, France and UK

Acknowledgements

We thank our co-investigators and their teams and, most importantly, the patients and families who participated in the study

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Centre Régional de Lutte Contre le Cancer de Bordeaux et du Sud-Ouest

Development and application of a 62 gene panel for assessment of somatic sequence and structural variants in tumor DNA derived from non-hodgkin lymphoma patients treated in a phase 1 clinical trial with the EZH2 inhibitor tazemetostat