Identification of a First-In-Class PRMT5 Inhibitor with Potent *In Vitro* and *In Vivo* Activity in Preclinical Models of Mantle Cell Lymphoma

Elayne Penebre, Kristy G Kuplast, Christina R Majer, P Ann Boriak-Sjodin, Tim J Wigle, L Danielle Johnston, Nathalie Rioux, Michael J Munchhof, Lei Jin, Suzanne L Jacques, Kip A West, Trupti Lingaraj, Kimberly Stickland, Scott A Ribich, Alejandra Raimondi, Margaret Porter-Scott, Nigel J Waters, Roy M Pollock, Jesse J Smith, Melissa Pappalardi, Olena Barbash, Ryan Kruger, Mikel P Moyer, Robert A Copeland, Richard Chesworth, Kenneth W Duncan

8 December 2014

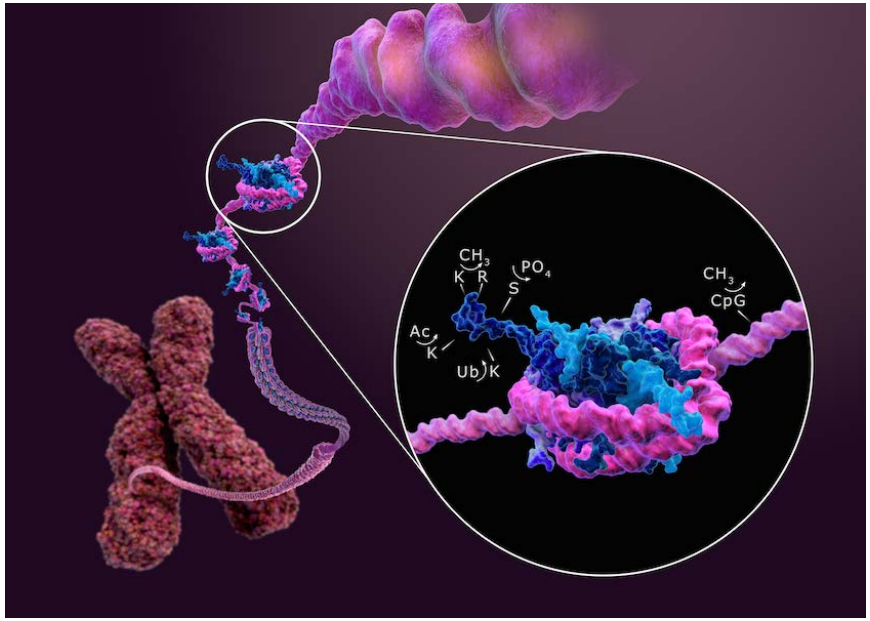
Disclosures

Disclosure Information
ASH Meeting
8 December 2014
Elayne Penebre

I have the following financial relationships to disclose:

- Grant/Research support from: LLS, MMRF, GSK, Eisai & Celgene
- Stockholder in and Employee of: Epizyme, Inc.

PMTome Target Class



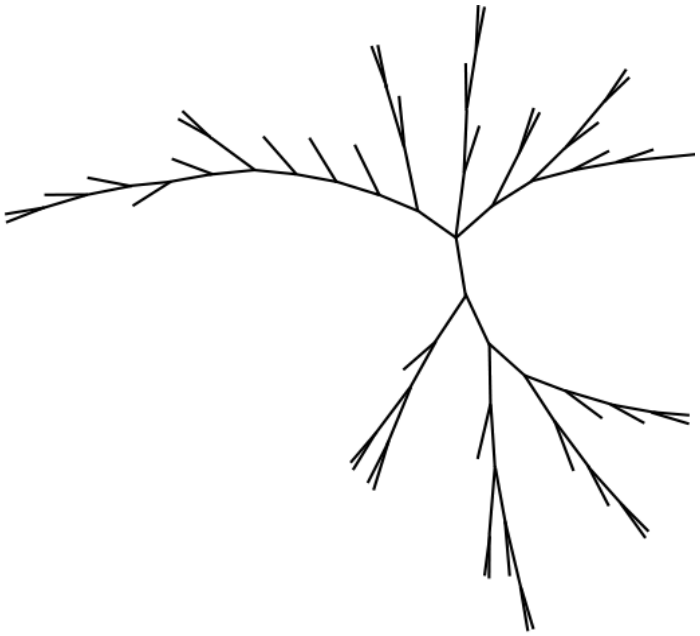
Oncogenic PMT → **Disease**

Misregulated gene expression

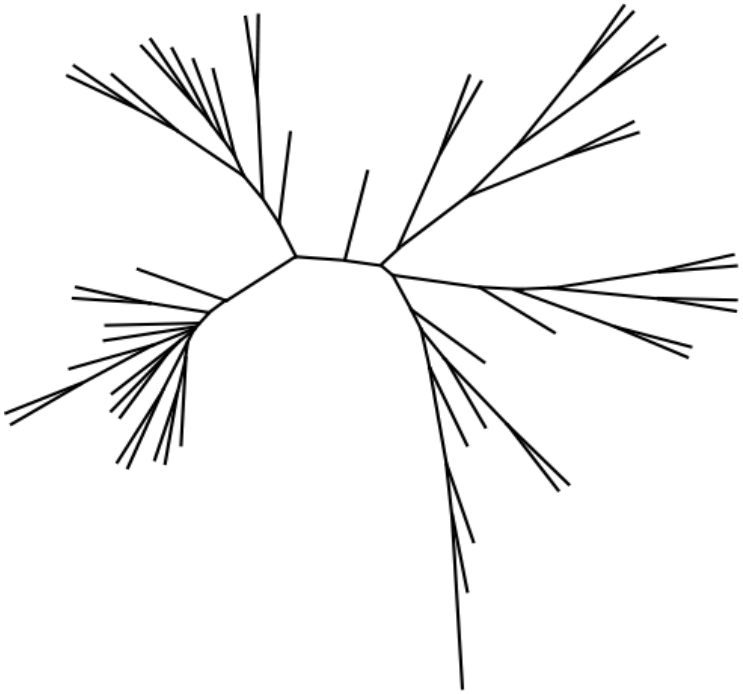
- **Protein methyltransferase (PMTs)** are part of a regulatory system that **controls gene expression**, called **epigenetics**
- PMTs **regulate** gene expression by placing **methyl marks on nuclear and cytoplasmic substrates**
- **Genetic alterations** can alter PMT activity making them **oncogenic** due to misregulated gene expression
- 96-member target class, **20 prioritized** based on oncogenic mechanism

PMTs – Equally Divided Between KMTs and RMTs

Arginine Methyl Transferases (RMTs)



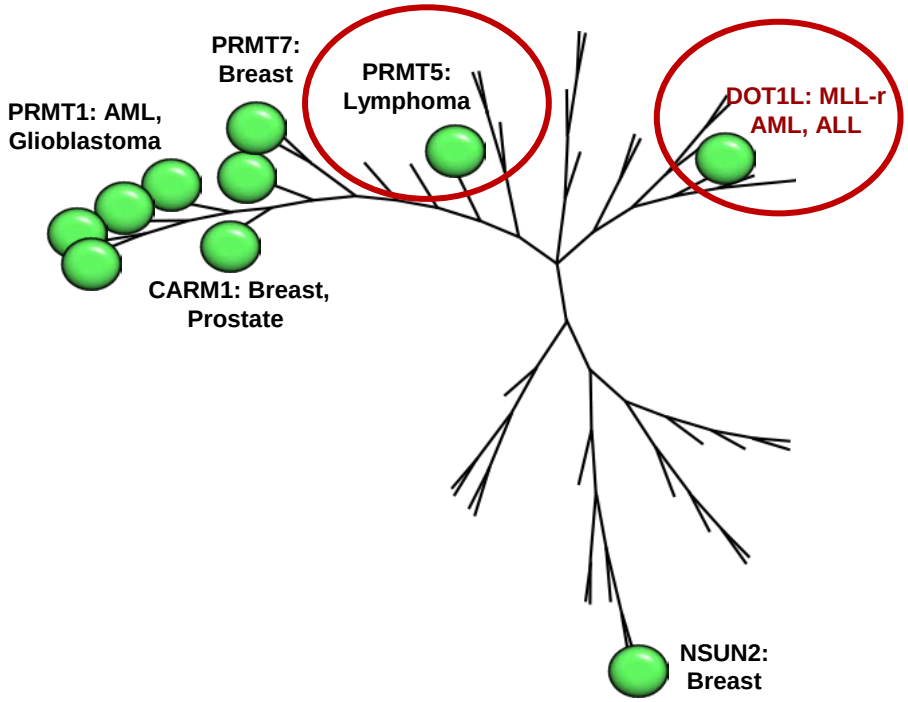
Lysine Methyl Transferases (KMTs)



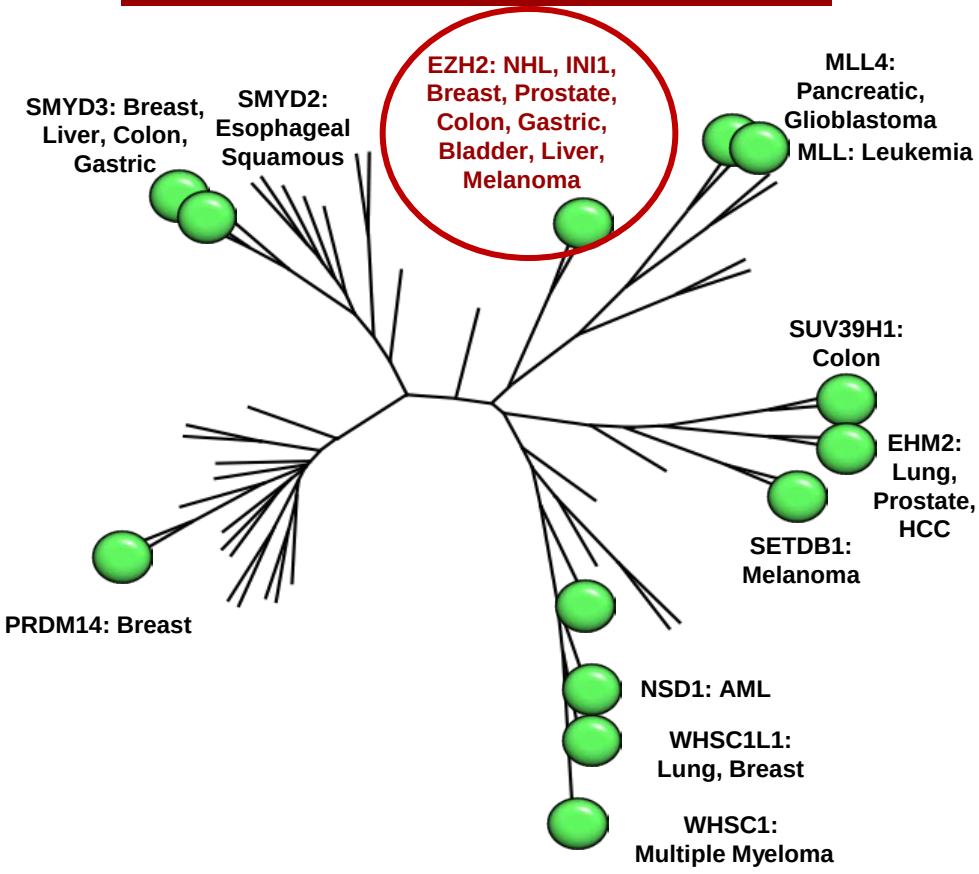
Richon et al. 2011 *Chem. Biol. Drug Design*
Modified from: Copeland 2011 *Drug Discov. Today Ther. Strat.*
Copeland 2013 *Clinical Cancer Research*

PMTs as Drivers of Cancer

Arginine Methyl Transferases (RMTs)



Lysine Methyl Transferases (KMTs)



Richon et al. 2011 *Chem. Biol. Drug Design*
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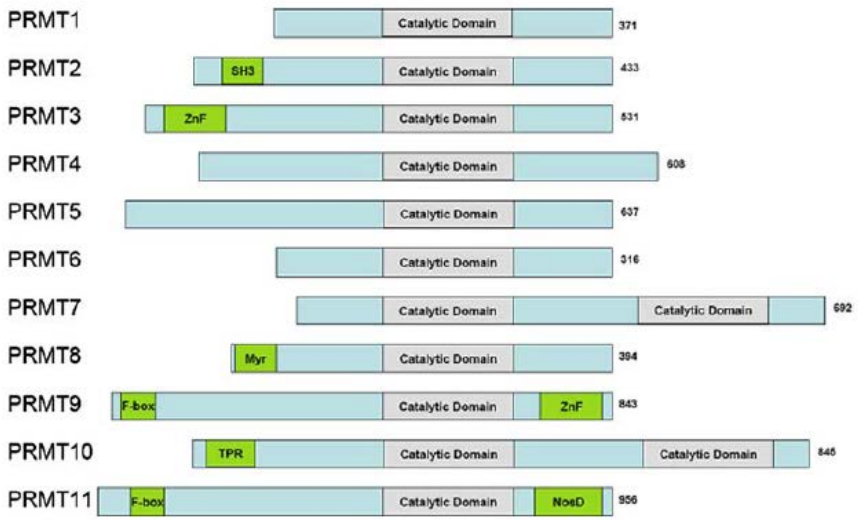
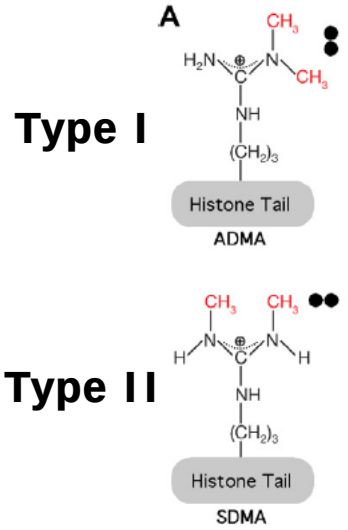
PRMT5 is a Type II Arginine Methyltransferase



Wolf 2009, *Cell and Mol Life Sci*

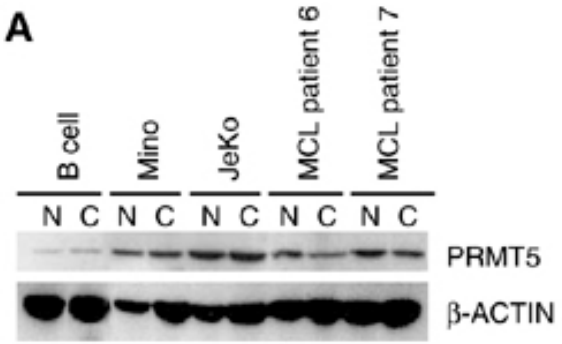


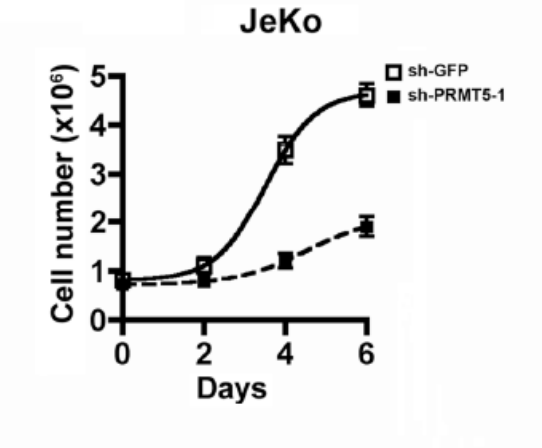
Di Lorenzo, Bedford, 2010, *FEBS Let.*

- The mammalian family of Arginine Methyltransferases (RMTs) contains 11 members
- PRMT5 is the pre-dominant Type II RMT that is responsible for the symmetric dimethylation of arginine residues
- PRMT5 has been shown to methylate numerous nuclear and cytoplasmic substrates; some of which are postulated to drive tumorigenesis
- PRMT5 has been shown to be upregulated in several human malignancies including lymphomas

PRMT5 Overexpression in Mantle Cell Lymphoma (MCL)

- PRMT5 Overexpression identified in Mantle Cell Lymphoma (MCL)
- Anti-proliferative effects observed upon PRMT5 KD in Jeko-1, a MCL cell line
- MCL is one of the rarest forms of non-Hodgkin's lymphomas (NHLs) representing ~6% of NHL cases or ~4000 new cases per year in the United States
- MCL is defined by the t(11;14) translocation resulting in overexpression of cyclin D1

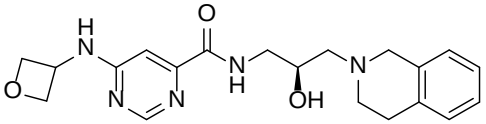




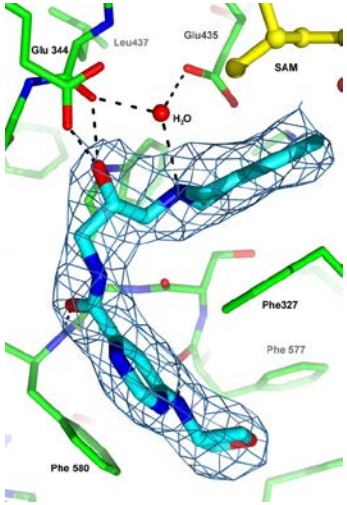
Pal et al. 2007 *EMBO*
Chung et al. 2013 *JBC*

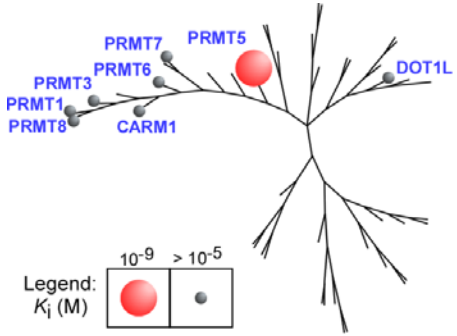
EPZ015666 – First-in-class PRMT5 Inhibitor

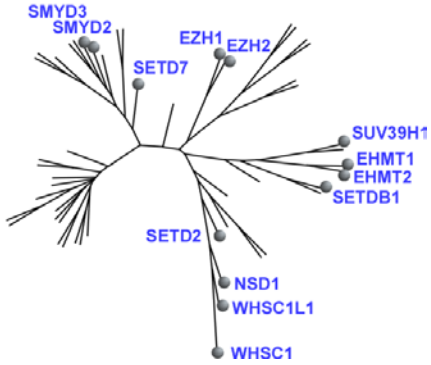
- **Potent** inhibition of PRMT5:MEP50 complex
  - SAM uncompetitive, peptide competitive inhibition
- Highly **selective** vs. other PMTs
  - Biochemical – >20,000-fold by K_i
  - Biochemical K_i : 5 nM
  - Cell Biochemical (In-Cell-Western) IC50 : 8 nM
- **Orally bioavailable**
- Potent **methyl mark inhibition** with excellent correlation to killing of cells *in vitro*
- Potent ***in vivo* efficacy** in animal models of MCL following inhibition of target methyl mark



EPZ015666
K_i = 5 nM





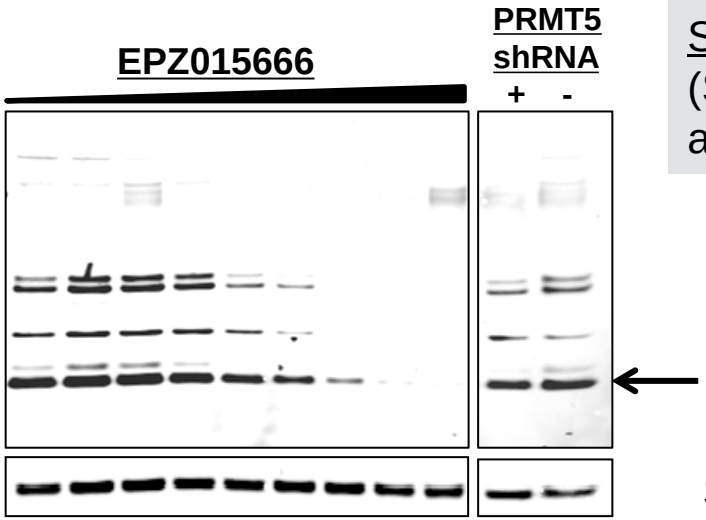


Penebre et al. submitted

EPZ015666 Inhibits Symmetric Arginine Di-methylation in a Dose-Dependent Manner

Symmetric Di-Methyl Arginine (SDMA) is a pan-dimethyl arginine antibody (motif Ab)

SDMA Motif Ab, full gel



- **On target inhibition of EPZ015666 demonstrated by strong correlations between biochemical, cell biochemical, and phenotypic IC50s**

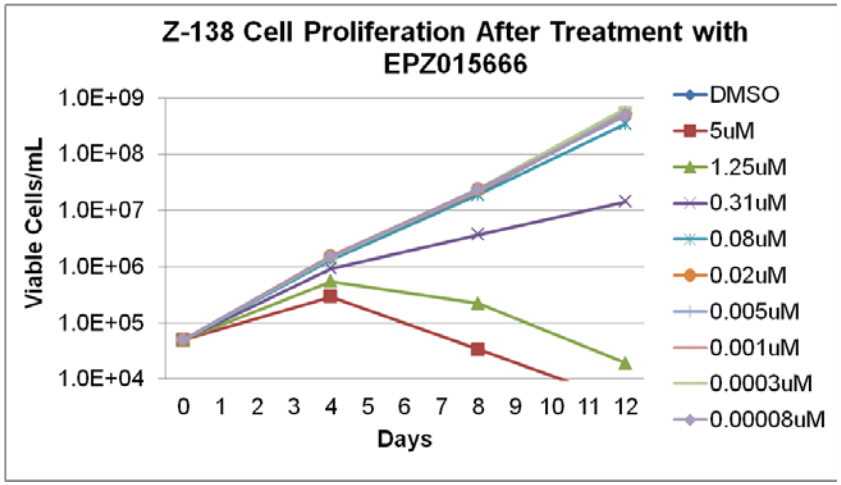
Biochemical IC_{50} (nM)

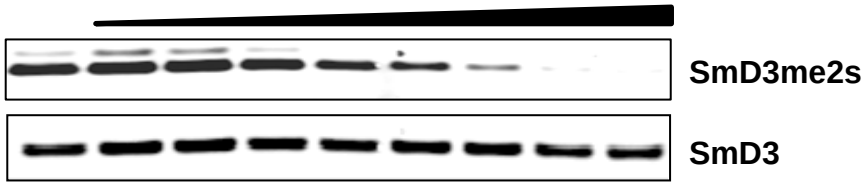
HT Proliferation IC_{50} (nM)

Penebre et al. submitted

MCL Cell Lines are Sensitive to EPZ015666 Treatment

Z-138





Methylation Day 4 IC_{50} = 44 nM

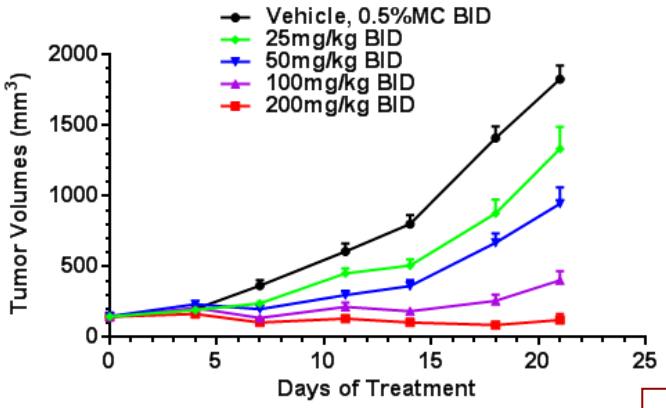
MCL Cell Line	Day 12 Proliferation IC_{50} (nM)	SDMA Western Blot IC_{50} (nM)
Z-138	96	44
Granta-519	61	4
Maver-1	450	42
Mino	103	78
Jeko-1	904	347

Penebre et al. submitted

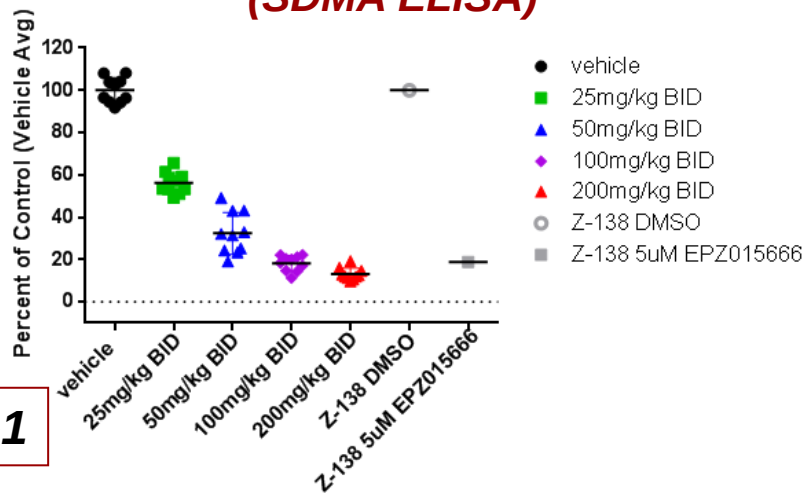
Z-138 Xenografts Are Highly Sensitive to Orally Dosed EPZ015666

Z-138

21-day Efficacy Study

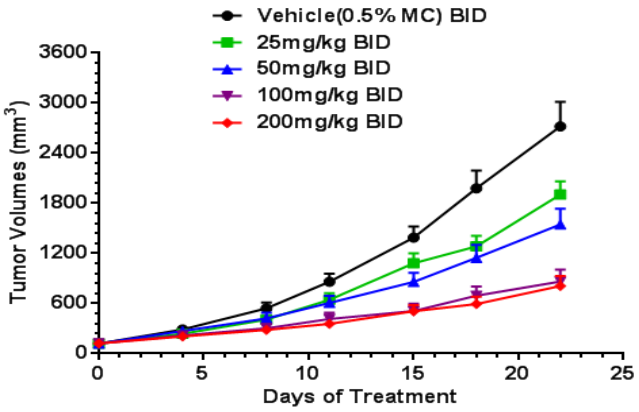


Target Inhibition in Day 21 Tumors (SDMA ELISA)

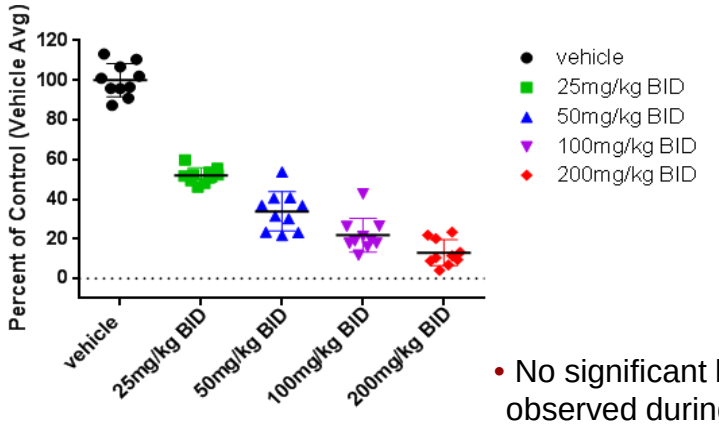


Maver-1

22-day Efficacy Study



Target Inhibition in Day 22 Tumors (SDMA ELISA)



- No significant body weight loss observed during the studies

Penebre et al. submitted

EPZ015666: First RMT Inhibitor Showing *In Vitro* and *In Vivo* Activity in Pre-clinical Models of MCL

- EPZ015666 is a potent, selective and orally bioavailable inhibitor of PRMT5
- EPZ015666 demonstrated potent cellular activity as measured by its ability to block symmetric dimethylation of SmD3 and inhibit proliferation of MCL cell lines
- EPZ015666 displays robust anti-tumor activity as a single agent in MCL xenograft animal models
- Pre-clinical studies of the effects of PRMT5 inhibition in other cancer indications is currently being studied

EPZ015666: Acknowledgements

We would like to thank the principal investigators and their institutions, the employees of Epizyme and GSK.