169 Dual HKMT inhibitors

Asset Overview

Product Type	Small molecule
Indication	Oncology
Current Stage	Lead discovery/optimization
Target(MoA)	Dual Histone Methyltransferase (HKMT) inhibitors
Brief Description	EZH2 and EHMT2 Histone Methyltransferases are essential for cancer stem cell maintenance • Existing EZH2 inhibitors have little activity in solid tumours that express wild type EZH2 EZH2 and EHMT2 show increased copy number and high expression in wide variety of epithelial tumour types • SiRNA double knock down of EZH2 and EHMT2 or pharmacological inhibition of both EZH2 and EHMT2 is more biologically effective at (Curry et al 2015)
Organization	Imperial College London

Differentiation

□ **Overview**

- Many cancers show overexpression of histone methyl transferases and aberrant silencing of gene expression while highly specific inhibitors of repressive histone methyltransferase EZH 2 show clinical promise for tumours bearing mutant EZH 2 they are far less effective in majority of tumours solely (over)expressing wild type EZH 2 A team at Imperial College, utilizing a powerful phenotypic screen, has developed a series of novel small molecules which target both HKMTs (EHMT 2 (G 9 a) and EZH 2 for treatment of solid tumours

□ **Key Features**

- Selective for a two key repressive HKMTs (EHMT 2 (G 9 a) and EZH 2 while preserving others
- Dual pharmacological inhibition of repressive HKMTs is highly effective in inducing changes in gene expression and inhibition of cell growth in breast and ovarian cancer cells expressing wild type EZH 2
- Reduces repressive chromatin marks while increasing permissive marks
- Induces apoptosis in a breast, ovarian cancer, lymphoma cell lines at low uM to high nM concentrations
- Synergistically increases drug sensitivity in combination studies with existing oncology drugs in various cancers 955 cancer cell lines tested)
- Tested in ovarian cancer xenograft model

□ **Novel drug**

- Potential to generate novel chemical matter with mechanism of action different from existing drugs
- Simpler to deliver and schedule dual inhibitor than two epigenetic drugs especially in combination studies with other therapies

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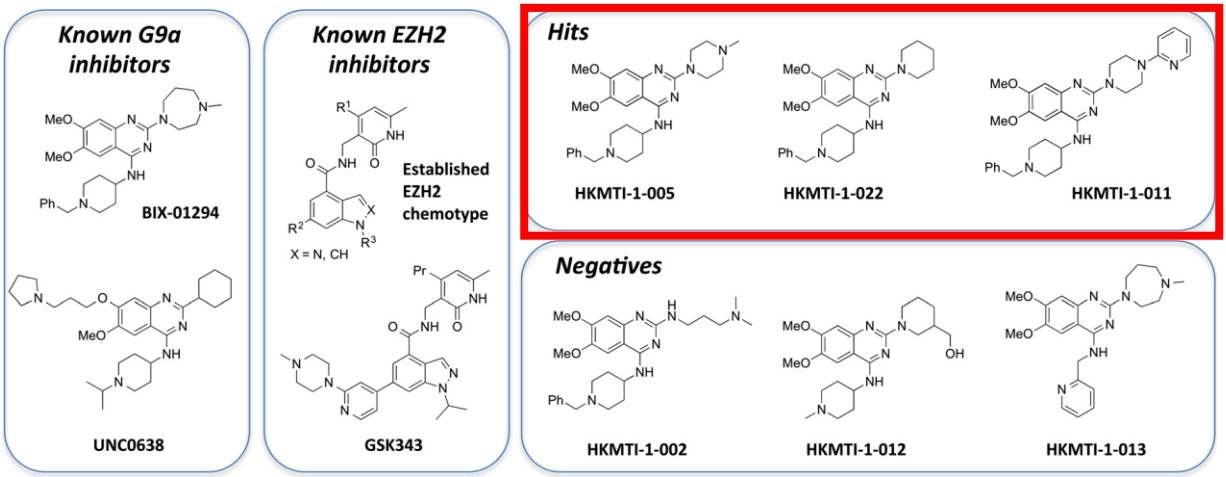
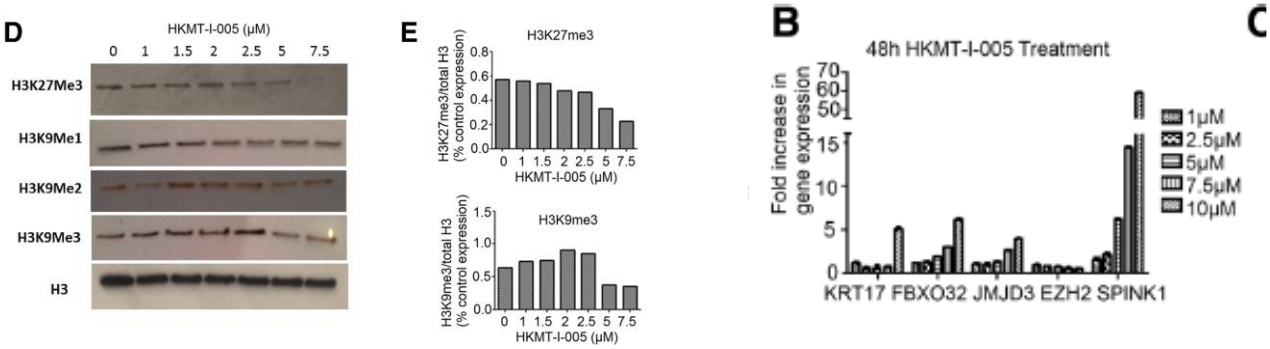
Key Data

Chemical structure of histone lysine methyltransferase inhibitors



Compound-induced upregulation of EZH2-repressed target genes



Sybr green real-time PCR mRNA level measurement of EZH2 target genes and executing enzymes following a 48-h treatment with HKMTI-1-005 at different concentrations of MDA-MB-231 cells.

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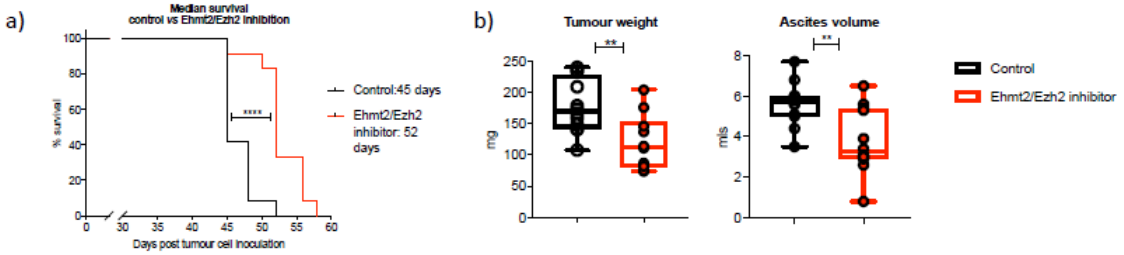
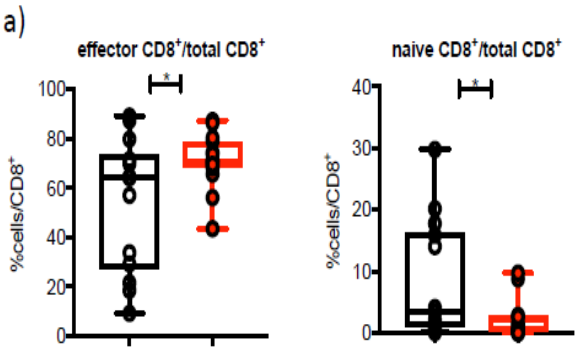
Dual Ehmt2/Ezh2 blockade confers a survival advantage



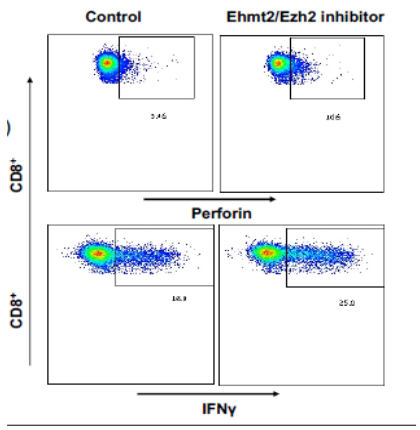
In vivo, dual Ehmt2/Ezh2 inhibition confers a survival advantage over control (52d vs 45d, p<.0001) (fig 2a). Tumour weight and ascites volume were significantly lower in the group treated with the dual inhibitor (mean 120mg vs 178mg, p=.006; 3.7ml vs 5.6ml, p=.003) compared to control (fig).

Ehmt2/Ezh2 inhibition shapes the immune microenvironment within tumour deposits



Ehmt2/Ezh2 inhibition results in an increase in effector CD8+ T cells (71.2% vs 54.4% p=.03) with a simultaneous decrease in naïve CD8+ T cells (3.44% vs 0.68%, p=.02) in the TME (fig 3a). There are significant increases in both mean fluorescence intensity (MFI) of CXCR3, the receptor involved in CXCL9/CXCL10 axis (MFI 3959 vs 1862, p<.001) and granzyme-B producing CD8+ cells (65.1% vs 27.2% p<.0001) following Ehmt2/Ezh2 inhibition (fig 3b)

Ehmt2/Ezh2 inhibition augments activation of splenic CD8+ cells



CD8+ cells derived from mice after treatment with Ehmt2/Ezh2 inhibitor demonstrate higher level of perforin (10.2% vs 5.9%, p=.004) and IFNγ (22% vs 18%, p =.01), compared to control.

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Intellectual Property

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Status	Registered
Country	US, EP, AU

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