NAMPT inhibitor KPT-9274 as an alternative treatment for Acute Myeloid Leukemia

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Introduction

- Acute Myeloid Leukemia (AML) is a cancer characterized by abnormal cell growth of immature myeloid cells.
- It is believed that most patients have multiple malignant clones of leukemic stem cells, each differing in their responses to treatment.
- NAMPT is a rate-limiting mechanism that produces nicotinamide adenine dinucleotide (NAD), a key metabolite essential for sustaining cellular energy metabolism.
- NAD is an important cofactor and serves as a metabolite required for a number of cellular processes such as mitochondrial function, genomic stability, DNA repair, calcium homeostasis and gene expression.
- NAMPT is over-expressed in various types of cancerous cells. They are reliant on the NAMPT salvage pathway for NAD production and do not efficiently utilize other pathways to produce NAD.
- Suppression of NAD production by inhibiting the NAMPT leads to loss of ATP, resulting in cell death without potentially toxic effects on non-cancerous cells.
- NAMPT inhibition has potential to become an alternative treatment of AML by eradicating leukemic stem cells and malignant subclones.

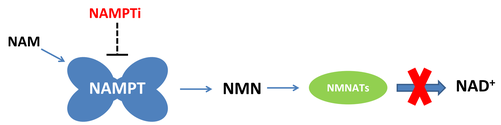

Figure 1. Schematic of NAMPT inhibition

Aim

- Previous studies have displayed anti-tumor effects of NAMPT inhibitors in tumor models *in vitro* and *in vivo*.
- The purpose of this study is to evaluate the ability of KPT-9274, a novel, potent and selective NAMPT small molecule inhibitor to decrease colony formation in AML patient samples.
- In addition, self-renewal capacity is being evaluated in AML patient samples by assessing the ability of KPT-9274 to eradicate leukemic stem cell colonies.

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Methods

- Six AML leukemic patient cells were diluted down to a specific number of cells (1,000-10,000 cells/plate) then treated with KPT-9274 or the vehicle control (DMSO).
- Cells were plated and incubated on a 6-well cell culture plate, along with a control group in a semi-solid medium.
- After two weeks, leukemic cell colonies were counted using an inverted light microscope.
- The cells were washed with 20% RPMI media, underwent a dilution process to achieve a desired amount of cells, then re-plated to assess self-renewal capacity.

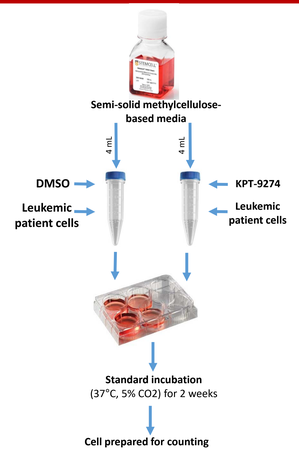

Figure 2. Experimental design

KPT-9274 Decreases Colony Formation in AML Leukemic Patient Cell Lines

A)

	Pt 0096		Pt 0597		Pt 1177		Pt 1069		Pt 1361		Pt 1363	
	KPT	Vehicle	KPT	Vehicle	KPT	Vehicle	KPT	Vehicle	KPT	Vehicle	KPT	Vehicle
Rep 1	18	18	24	29	17	33	39	141	5	21	34	53
Rep 2	4	22	8	19	21	34	39	153	10	22	20	44
Rep 3	8	10	9	20	12	20	25	134	8	17	24	44

B)

C)

	Mutational Status	Cytogenetics
Patient 1361	IDH1, NPM1, DNMT3a-R882,NRAS	NK*IDH1/2
Patient 0096	NMP1, TET2, NRAS, SRSF2	Insufficient Metaphases(46,XY[3])
Patient 0597	ASXL1, JAK2	Unknown
Patient 1177	NPM1, TET2, ASXL1	Unknown
Patient 1069	IDH2, DNMT3A-R882, SRSF2, FLT3-ITD	Unknown
Patient 1363	NRAS, IDH1, NPM1, DNMT3a-R882	NK

Figure 3. A) Patient colony counts after 2 weeks; **B)** Colony formation assay in patient 1361 after treatment with KPT-9274 and re-plating (day 26); **C)** Patient mutational status and cytogenetics.

KPT-9274 Decreases Colony Formation in AML Leukemic Patient Cell Lines

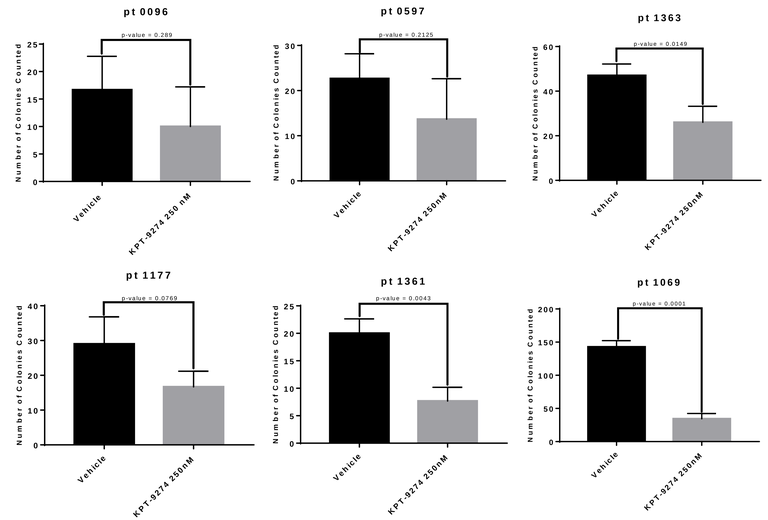

Figure 4. Treatment of AML patient cell lines with KPT-9274 shows an overall decrease in cell colonies relative to the vehicle.

Conclusion

- Inhibition of NAMPT by KPT-9274 resulted in an overall decrease in acute myeloid leukemic colonies by 39.7 to 75.9 percent.
- NAMPT inhibitors have anti-leukemic properties and have potential to be an alternative treatment for AML.
- Future considerations include assessing the self-renewal capacity of the AML patient cell lines. Regrowth of cells would indicate a resistance to the NAMPT inhibitor as a result of clonal mutations within the cell.

References

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