A First in Human Phase 1 Study of KPT-9274, a First in Class Dual Inhibitor of PAK4 and NAMPT, in Patients with Advanced Solid Malignancies or NHL

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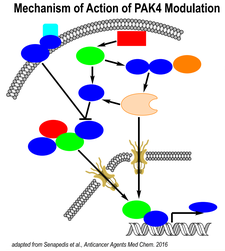
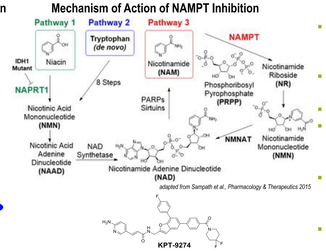
KPT-9274 Mechanism of Action

Mechanism of Action of PAK4 Modulation



adapted from Senapedis et al., Anticancer Agents Med Chem. 2016

Mechanism of Action of NAMPT Inhibition

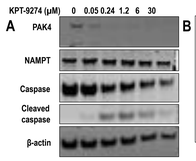


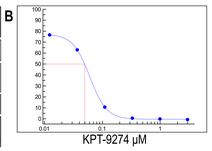
adapted from Sampath et al., Pharmacology & Therapeutics 2015

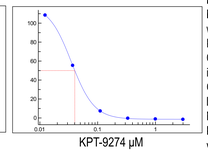
Mechanism of Action of KPT-9274

- KPT-9274 is an oral, small molecule modulator of PAK4 (p21 activated kinase) and NAMPT (nicotinamide phosphoribosyltransferase)
- PAK4 is a major player in cell morphology and WNT/β-catenin signaling
- NAMPT is the rate-limiting enzyme in NAD biosynthesis
- Co-inhibition of these targets leads to synergistic anti-tumor effects through energy depletion, inhibition of DNA repair, cell cycle arrest, and ultimately apoptosis
- Cells can utilize niacin to make NAD through an alternative pathway using NAPRT1, which is often absent in tumors making it a potential response biomarker
- KPT-9274 demonstrates potent anti-tumor activity pre-clinically and in patient dogs with cancer

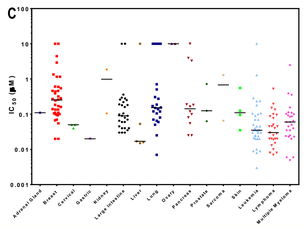
KPT-9274 Preclinical Activity







KPT-9274 downregulates PAK4 and NAMPT activity. U2OS and COLO 205 cells were treated with different concentrations of KPT-9274 for 72 hours. **(A)** Western blot of COLO 205 cells. **(B)** U2OS cells were incubated with NAD/NADH-Glo or CellTiter-Glo reagent in order to measure NAD or ATP levels, respectively. KPT-9274 reduces PAK4, NAD and ATP resulting in cancer cell death. KPT-9274 shows **(C)** *in vitro* potency across a variety of cancer cell lines and **(D)** *in vivo* anti-tumor activity in mouse xenografts



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Cancer Type	Model	Dose (mg/kg)	Regimen (per week)	Best Response
Hepatocellular carcinoma	Hep 3B	100	BIDx5	37% TGI
Renal cell carcinoma	Caki-1	100	BIDx5	46% TGI
	786-O	100	BIDx5	70% TGI
Triple negative breast cancer	MDA-MB-468	100	BIDx7	73% TGI
	MDA-MB-231	150	BIDx4	84% TGI
Non-small cell lung cancer	NCI-H520	100	BIDx5	6% TR
Colorectal carcinoma	COLO 205	100	BIDx5	41% TR
	COLO 320HSR	200	BID QoDx3	72% TGI
Esophageal Squamous	KYSE510	150	BIDx5	90% TR
Multiple myeloma	MM1.S	100	BIDx5	75% TR
T-cell acute lymphoblastic leukemia	MOLT-4	100	BIDx7	92% TR
Mantle cell lymphoma	Z-138	100	BIDx7	100% TR
	JeKo-1	200	QoDx3	93% TGI

Study Design

KCP-9274-901 is a Phase 1 open-label study of the safety, tolerability, and anti-tumor activity of KPT-9274, a 1st in Class dual inhibitor of PAK4 and NAMPT in patients with advanced solid malignancies or NHL

Dose Escalation (Phase I)

Part A
KPT-9274 Single Agent
To determine the RP2D or MTD of KPT-9274

Part B
KPT-9274 + Niacin ER
To determine the RP2D or MTD of KPT-9274 + Niacin ER

Expansion (Phase II)

KPT-9274 ± Niacin ER
~ 45 patients for safety, tolerability, and preliminary evidence of anti-tumor activity of RP2D or MTD of KPT-9274 ± Niacin ER

- **Primary Objectives - Phase I:**
  - Determine the MTD for KPT-9274 administered alone (Part A) or in combination with Niacin ER (Part B)
  - Determine the RP2D, the schedule, and evaluate the safety and tolerability, including dose-limiting toxicity for KPT-9274 +/- Niacin ER
- **Primary Objectives - Phase II:**
  - Evaluate the safety / tolerability of the RP2D or MTD for KPT-9274 +/- Niacin ER and the dosing schedule(s)
  - Determine the preliminary evidence of anti-tumor activity of KPT-9274 at the RP2D or MTD +/- Niacin ER according to RECIST (solid tumors) or Lugano Classification (NHL) Response Criteria assessed by: Overall Response Rate (**ORR**), Overall Survival (**OS**), Clinical Benefit Rate (**CBR**), Duration of Clinical Benefit, Progression-free Survival (**PFS**)
- **Dose Limiting Toxicity (DLT) Definition**
  - DLT is an AE or abnormal laboratory value (NCI CTCAE v. 4.03) that occurs within the first 28 days of treatment with KPT-9274 or
  - Grade ≥3 nausea/vomiting, dehydration or diarrhea while taking optimal supportive medications or
  - Any other Grade ≥3 non-hematological toxicity except alopecia or electrolyte abnormalities correctable with supportive therapy or
  - Grade 4 neutropenia lasting > 5 days; febrile neutropenia (ANC<1E9/L, fever>38.5 ºC); Grade 4 thrombocytopenia or Grade 3 thrombocytopenia with bleeding, or any requirement for platelet transfusion is considered a DLT or
  - Grade 4 anemia, unexplained by underlying disease

Patient Population

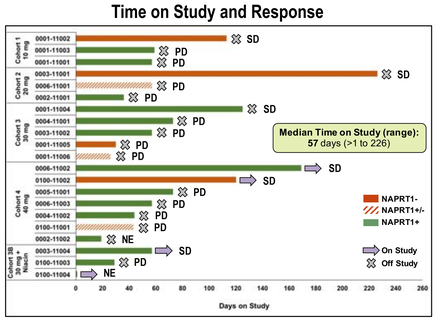
- Patients with advanced solid malignancies or NHL for which all standard therapeutic options have been exhausted
- Patients must have:
  - objective evidence of progressive disease on study entry
  - a site of disease amenable to biopsy and be a candidate for biopsy according to the treating institution's guidelines
  - adequate hematopoietic, hepatic, and renal function
  - NAPRT1 and IDH1 tumor status determined (for KPT-9274 + Niacin ER cohorts)

Patient Characteristics, Cohort, and Dosing Schedule

Cohort	Dose / Schedule	Patients Enrolled
1	10 mg / qodx3	3
2	20 mg / qodx3	3
3	30 mg / qodx3	5
4	40 mg / qodx3	7
3B	30 mg / qodx3 + 500 mg niacin ER	3

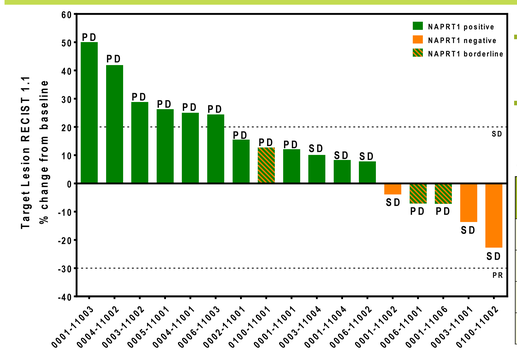
Characteristic	Dose Escalation N=21
Median Age (Range)	61 (28 – 74)
Male : Female	14 : 7
Median Prior Regimens (Range)	6 (1 – 11)
Median Days on Treatment (Range)	57 (>1 – 226)
Disease Refractory to Last Therapy %	100%

Time on Study and Response



as of 10 July 2017

Biomarker Development



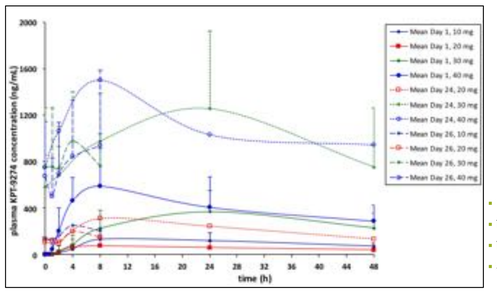
- Increased NAPRT1 promoter methylation correlates with decreased NAPRT1 expression and lack of rescue with niacin
- **25 to 30% hyper-methylation** is the cutoff for the level of methylation in normal tissue

Additional Patients with no Tumor Measurements

Patient ID	NAPRT1 Status	Disease Assessment
0001-11005	-	PD
0002-11002	+	NE
0004-11002	+	PD
0100-11003	+	PD

Human Pharmacokinetic Profile of KPT-9274

Mean ± SD Plasma KPT-9274 Concentration *vs.* Time Following Oral Administration of KPT-9274 at 10 - 40 mg to Oncology Patients, Cycle 1



PK Parameters – Day 1

Dose (mg)	C_{max} (ng/mL)	T_{max} (h)	AUC_{0-last} (ng*h/mL)	$t_{½}$ (h)
10	152	8	4,435	-
20	79.4	8	2,617	-
30	411	24	12,580	-
40	565	8	18,709	-

PK Parameters – Day 24

Dose (mg)	C_{max} (ng/mL)	T_{max} (h)	AUC_{0-tau} (ng*h/mL)	$t_{½}$ (h)
10*	256	4	1,614	-
20	319	8	10,456	-
30	1,281	19	48,146	-
40	1,550	5	53,430	-

* Day 26

- Plasma levels at 30 and 40 mg appear dose-proportional to 10 mg
- There is substantial accumulation across the 26-day dosing regimen
- The C_{max} (and accurate AUC) is likely missed; $t_{1/2}$ not determined
- Sampling adjustments to better characterize are implemented

Related Adverse Events in ≥ 5% of Patients

Group	Adverse Events	N = 21					10 mg (N=3)	20 mg (N=3)			30 mg (N=5)			40 mg (N=7)				30 mg + Niacin (N=3)	
		Gr 1	Gr 2	Gr 3	Gr 4	Total	G1-4	Gr 1	Gr 2	Gr 3	Gr 1	Gr 2	Gr 3	Gr 1	Gr 2	Gr 3	Gr 4	Gr 1	Gr 2
Hematological	Anemia	2 (9.5%)	2 (9.5%)	7 (33.3%)	1 (4.8%)	12 (57.1%)	No Events		1	1	1		2	1		4	1		1
Gastrointestinal	Diarrhea	4 (19%)				4 (19%)					1			2				1	
	Nausea	2 (9.5%)				2 (9.5%)					1								
General Disorders and Admin. Site Conditions	Fatigue	2 (9.5%)	2 (9.5%)	1 (4.8%)		5 (23.8%)						1	1	2					1
	Edema	2 (9.5%)	1 (4.8%)			3 (14.3%)		1			1			1					
	Flu-like illness		2 (9.5%)			2 (9.5%)			1			1							
Investigations	ALT increased	2 (9.5%)	1 (4.8%)			3 (14.3%)					1	1						1	
Musculoskeletal	Arthralgia	4 (19%)	4 (19%)			8 (38.1%)						2		3	2			1	
	Myalgia	1 (4.8%)	3 (14.3%)			4 (19%)						2			1			1	
	Pain in extrem.	1 (4.8%)	1 (4.8%)			2 (9.5%)		1				1							
Nervous System	Dizziness	2 (9.5%)				2 (9.5%)		1											
Renal and Urinary	Proteinuria	1 (4.8%)	1 (4.8%)			2 (9.5%)					1				1				
Respiratory	Dyspnea	2 (9.5%)				2 (9.5%)								1				1	

Adverse Events Summary

- No drug related AEs observed at 10 mg
- 1 DLT at 40 mg (G4 anemia)
- Most common AEs include anemia and arthralgia / myalgia
- Although expected, no significant GI toxicity or thrombocytopenia observed

Case Study – Patient 0100-11002

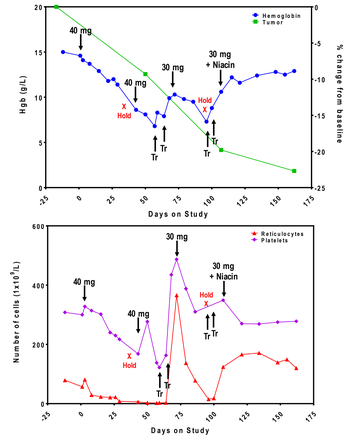
Patient Demographics

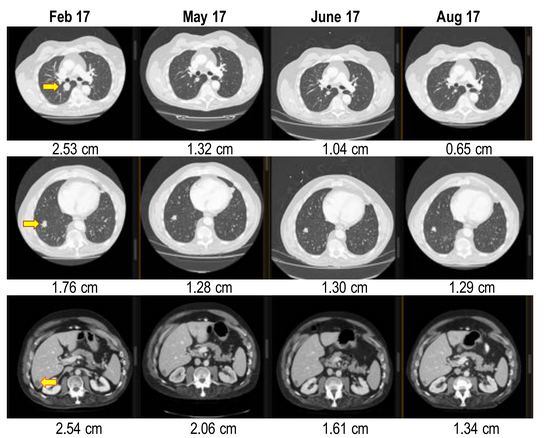
Age	56	**Current Status**	On Study
Cohort	4	**C1D1**	13 Mar 2017
Gender	Male	**Days on Study**	>175
ECOG	1	**Genetic Markers**	NAPRT1 - GNAQ (Q209L)
Diagnosis	Intraocular (Uveal) Melanoma	**Best Response**	SD (-22.6%)

Prior Therapies

Regimen	Medication	Start Date	Days on Treatment	Best Response
1	Cabozantinib	29-Feb-16	66	SD
2	Ipilimumab	31-May-16	1	Unk
3	Pembrolizumab	23-Jun-16	233	Unk
4	KPT-9274	13-Mar-17	>175	SD

- Started **KPT-9274** in Mar 2017. Last seen 22 Aug 2017, in C6. Performance Status 0-1. Full Active Daily Life / continues to work with dose reduction and niacin supplementation.
- Prior history includes controlled atrial fibrillation and arthritis.
- Patient is a farmer actively working on a farm >500 hectares (>1200 acres). He attributed this trial as one of the 'easiest' to deal with in terms of toxicities.





Summary and Conclusions

- In patients whose disease has progressed despite most available therapies, KPT-9274 induces disease stabilization
- Dose escalation is on-going in Part A (without niacin) and in Part B (with niacin)
- KPT-9274 is well tolerated across different indications; one DLT (anemia) observed
- The most common AEs are anemia, arthralgia, and myalgia
- Fatigue, nausea, and diarrhea are infrequent and low grade (one event of Grade 1 thrombocytopenia at 40 mg)
- Niacin can safely be given with KPT-9274 and may improve KPT-9274 tolerability
- NAPRT1 status may predict response to KPT-9274 ± Niacin

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