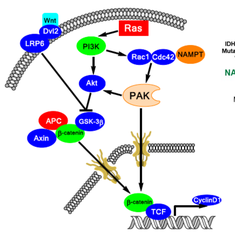
A First in Human Phase 1 Study of KPT-9274, a First in Class Dual Inhibitor of PAK4 and NAMPT, in Patients with Advanced Solid Malignancies or NHL

Aung Naing[1], Stephen Leong[2], Michael J. Pishvaian[3], Albiruni Razak[4], Amit Mahipal[5], Jordan D. Berlin[6], Daniel C. Cho[7], William Senapedis[8], Sharon Shacham[8], Michael G. Kauffman[8], Joel Ellis[8], Julie Meade[8], and Erkan Baloglu[8]

(1) University of Texas, MD Anderson Cancer Center, Houston, TX, USA, (2) University of Colorado Cancer Center, Aurora, CO, USA, (3) Georgetown University, Lombardi Comprehensive Cancer Center, Washington, DC, USA, (4) UHN Princess Margaret Cancer Centre, Toronto, ON, Canada, (5) Mayo Clinic, Rochester, MN, USA, (6) Vanderbilt University Medical Center, Nashville, TN, USA, (7) NYU Langone Medical Center, New York, NY, USA,(8) Karyopharm Therapeutics Inc, Newton, MA, USA

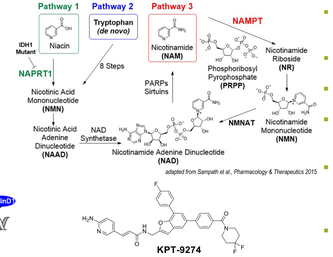
KPT-9274 Mechanism of Action

Mechanism of Action of PAK4 Modulation



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

Mechanism of Action of NAMPT Inhibition

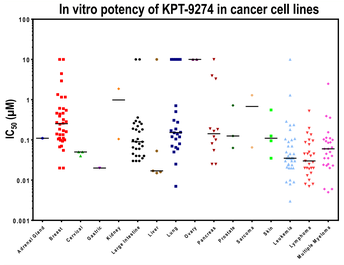


Mechanism of Action of KPT-9274

- 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

In vitro potency of KPT-9274 in cancer cell lines



Anti-tumor activity of oral KPT-9274 in a variety of mouse xenografts models

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 efficacy of KPT-9274, a 1st in Class dual inhibitor of PAK4 and NAMPT in patients with advanced solid malignancies or NHL

Dose Escalation

Part A	Part B
KPT-9274 Single Agent To determine the RP2D or MTD of KPT-9274	**KPT-9274 + Niacin ER** To determine the RP2D or MTD of KPT-9274 + Niacin ER

Expansion

KPT-9274 ± Niacin ER

1. NAPRT1+ (N ~ 10)
2. NAPRT1- (N ~ 10)
3. NAPRT1 +/- (N ~ 10)
4. IDH1 mutant (N ~ 15)

- **Primary Objectives**
  - Determine the MTD and RP2D for KPT-9274 administered alone (Part A) or in combination with Niacin ER (Part B)
  - Evaluate the safety / tolerability including DLT of KPT-9274 +/- Niacin ER and the dosing schedule
- **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 and meets the following criteria:
    - Gr ≥3 nausea/vomiting, dehydration or diarrhea while taking optimal supportive medications or
    - Gr 4 neutropenia lasting > 5 days; febrile neutropenia (ANC<1E9/L, fever>38.5 ºC); Gr 4 thrombocytopenia or Gr 3 thrombocytopenia with bleeding, or any requirement for platelet transfusion or Gr 4 anemia, unexplained by underlying disease or
    - Any other Gr ≥3 non-hematological toxicity except alopecia or electrolyte abnormalities correctable with supportive therapy

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)

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%

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	3

Human Pharmacokinetic (PK) Profile of KPT-9274

PK Parameters – Day 1

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

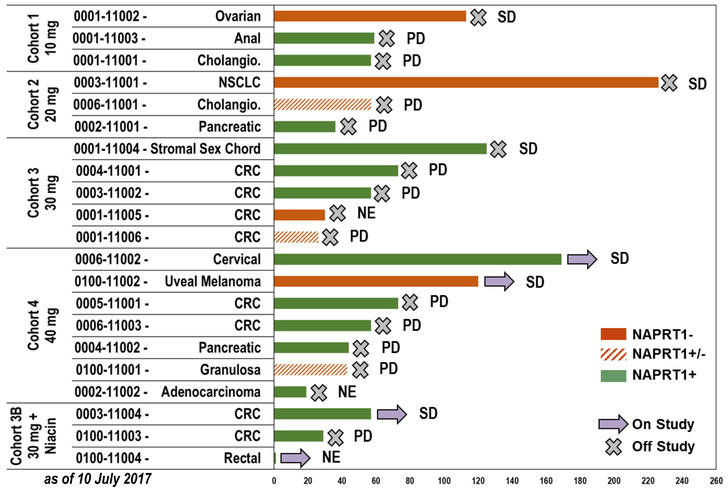
PK Parameters – Day 24

Dose (mg)	C_{max} (ng/mL)	T_{max} (h)	$AUC_{0\text{-}inf}$ (ng*h/mL)
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

Time on Study, Disease, and Response



Related Adverse Events in ≥ 3 Patients

Adverse Events	All Dose Levels (N=21)			
	G1/2	G3	G4	Total
Anemia	5 (24%)	7 (33%)	1 (5%)	13 (62%)
Arthralgia / Arthritis	9 (43%)			9 (43%)
Fatigue	5 (24%)	1 (5%)		6 (29%)
Diarrhea	4 (19%)			4 (19%)
Myalgia	4 (19%)			4 (19%)
ALT increased	3 (14%)			3 (14%)
Edema	3 (14%)			3 (14%)
Dizziness	3 (14%)			3 (14%)
Flushing*	3 (14%)			3 (14%)
Dyspnea	3 (14%)			3 (14%)

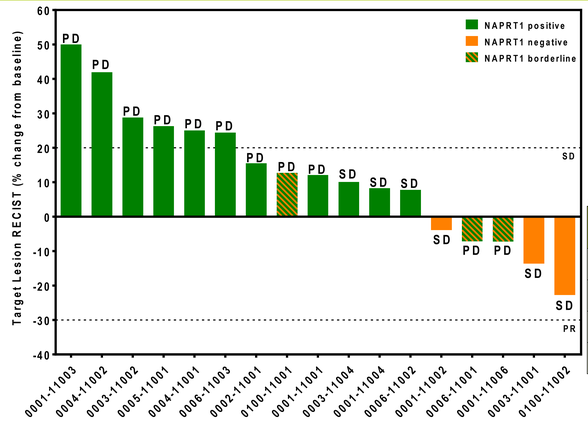
	10 mg (N=3)	20 mg (N=3)		30 mg (N=5)		40 mg (N=7)			30 mg + Niacin (N=3)
	All	G1/2	G3	G1/2	G3	G1/2	G3	G4	G1/2
No Events		1	1	1	2	2	4	1	1
				3		5			1
				1	1	3			1
				1		2			1
				2		1			1
				2					1
		1		1		1			
						1			2
						1			2
						2			1

* Pts receiving Niacin

Adverse Events (AEs) Summary (*as of 10 July 2017*)

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

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	-	NE
0002-11002	+	NE
0100-11003	+	PD
0100-11004	+	Pending

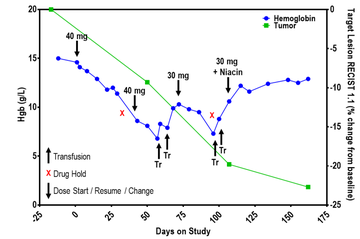
as of 10 July 2017

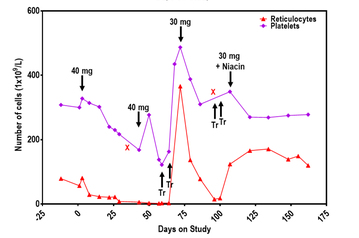
Case Study – Patient 0100-11002

- 56 year old man diagnosed with intraocular (uveal) melanoma (2009) metastatic to the liver and lungs (2016), GNAQ mutated, NAPRT1-,
- Comorbidities: Controlled atrial fibrillation and arthritis.
- Joined the study in March, 2017 (single agent KPT-9274; 3 prior chemotherapy regimens).
- Dose interruption/reduction due to anemia/fatigue, recovered with niacin supplementation, continuing active daily life.
- On study (>175 days; last seen on 22 Aug 2017; SD (-22.6%).

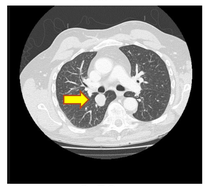
Prior Therapies

Regimen	Treatment	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

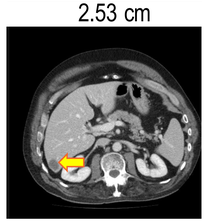




Feb 17

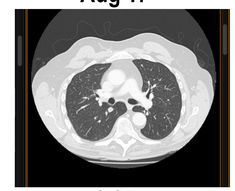


2.53 cm

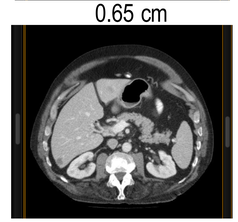


2.54 cm

Aug 17



0.65 cm



1.34 cm

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 to date
- The most common AEs are anemia, arthralgia, and fatigue
- GI related AEs are infrequent and low grade
- Niacin can safely be given with KPT-9274 and may improve KPT-9274 tolerability
- NAPRT1 status may predict response to KPT-9274 ± Niacin

Contact Information: Aung Naing, MD (anaing@mdanderson.org)
Erkan Baloglu, PhD, MBA (ebaloglu@karyopharm.com)