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

KPT-9274 is a first in class, oral, small molecule inhibitor of PAK4 (a member of the calcium/calmodulin dependent protein kinase family) and NAMPT (nicotinamide phosphoribosyltransferase). PAK4 is a major player in cell cycle and survival signaling pathways and NAMPT is the rate-limiting enzyme in NAD+ production.

The single-agent activity of these drugs leads to synergistic anti-tumor activity when given through sequential depletion of NAD+ in a cell cycle arrested state of DNA damage, cell cycle arrest, and cell line-specific apoptosis.

PAK4 and NAMPT inhibitors have demonstrated potent anti-tumor activity in preclinical and clinical trials with in patients with cancer.

KPT-9274 Preclinical Activity

In vitro potency of KPT-9274 in cancer cell lines.

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

Patient Population

- Patients with advanced solid malignancies or NHL, for which all standard treatment options have been exhausted.
- Patients must have:
  - objective evidence of progression on study entry
  - a histology of disease extant to biopsy and/or a suitable tumor biopsy according to the treating institution’s guidelines
  - adequate hematopoietic, hepatic, and renal function
  - NAPRT1 and CHR1 gene status determined (for KPT-9274, NAR-16 cohort)

Related Adverse Events in ≥3 Patients

<table>
<thead>
<tr>
<th>Adverse Events</th>
<th>Grade 1/2</th>
<th>Grade 3/4</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anemia</td>
<td>5 (24%)</td>
<td>7 (33%)</td>
<td>12 (58%)</td>
</tr>
<tr>
<td>Arthralgia/Arthritis</td>
<td>8 (42%)</td>
<td>11 (55%)</td>
<td>19 (91%)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>4 (19%)</td>
<td>6 (29%)</td>
<td>10 (48%)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>4 (19%)</td>
<td>5 (25%)</td>
<td>9 (43%)</td>
</tr>
<tr>
<td>Mucositis</td>
<td>4 (19%)</td>
<td>4 (19%)</td>
<td>8 (38%)</td>
</tr>
</tbody>
</table>
| ALA-Pred 
< 0.4 | 3 (14%) | 4 (19%) | 7 (34%) |
| Edema | 5 (24%) | 3 (14%) | 8 (38%) |
| Dyspnea | 5 (24%) | 3 (14%) | 8 (38%) |
| Hypothyroidism | 5 (24%) | 3 (14%) | 8 (38%) |

Biomarker Development

Increased NAPRT1 promoter methylation correlates with decreased NAPRT1 expression and lack of response to nicacin.

- 25 to 30% hypermethylation is the cutoff for the level of methylation in normal tissue.

NAPRT1 Expression

- Comorbidities: Controli at atrial fibrillation and anemia.
- Join the study in May 2017 (single agent KPT-9274, 3 prior chemotherapy regimens).
- Dose interruption/reduction due to anemia/fatigue, recovered with nicacin supplementation, continuing active daily life.
- 175 days; last seen on 22 Aug 2017; SD (22%).

KPT-9274 (N=21) is a Phase 1 open-label study of the safety, tolerability, and efficacy of KPT-9274, 1 hr IV Class dual inhibitor of PAK4 and NAMPT in patients with advanced solid malignancies or NHL.

PK Parameters

PK Parameters – Day 1

- Dose (mg) Cmax (ng/mL) tmax (h) AUC0-24h (ng*h/mL)
- 10 152 8 4,435
- 20 79.4 8 2,617
- 30 41.1 12 1,035
- 40 58.5 8 18,709

- Plasma levels at 30 and 40 mg appear dose-proportional to 10 mg.
- There is substantial accumulation across the 28-day dosing regimen.

PK Parameters – Day 24

- Dose (mg) Cmax (ng/mL) tmax (h) AUC0-24h (ng*h/mL)
- 10 256 4 1,614
- 20 319 8 10,406
- 30 1,265 12 18,419
- 40 1,550 5 53,430

- The Cmax (and accurate AUC) is likely missed, tmax not determined.
- Sampling adjustments to better characterize are implemented.