A Phase I Dose Escalation Study of NKP-1339 in Patients with Advanced Solid Tumors Refractory to Treatment

N. R. Dickson¹, S. F. Jones¹, H. A. Burris III², R. K. Ramanathan², G. J. Weiss³, J. R. Infante¹, J. C. Bendell², W. Mc Culloch³, D. D. Von Hoff⁴

¹Sarah Cannon Research Institute/Tennessee Oncology, Nashville, TN
²Virginia G. Piper Cancer Center at Scottsdale Healthcare/TGen, Scottsdale, AZ
³Níkki Pharma Inc., Hoboken, NJ

Background
NKP-1339 is a novel, undisclosed targeted radionuclide-based anticancer product which is in an early clinical development. In initial preclinical studies, NKP-1339 has significant antitumor activity against breast, ovarian, colon, and neuroendocrine tumors. Preclinical data suggest that NKP-1339 has a unique and highly specific mechanism of action, and may offer new opportunities for patients with refractory and advanced solid tumors. This Phase I study is designed to determine the maximum tolerated dose (MTD) and evaluate the safety and tolerability of NKP-1339.

NKP-1339 Mechanism of Action
NKP-1339 is a novel, undisclosed radionuclide-targeted anticancer product. It is designed to target tumors based on the expression of a specific biomarker, such as TfR, which is overexpressed in a range of solid tumors. NKP-1339 is a radiolabeled antibody that binds specifically to the biomarker, allowing for targeted delivery of radiation to the tumor site.

Objectives
• To determine the safety, tolerability, and maximum tolerated dose (MTD) of NKP-1339
• To evaluate pharmacokinetics and determine dose-limiting toxicities
• To determine the likely dose to escalate to phase 2 studies

Study Population
Patients with inoperable solid tumors will be enrolled to a 2-step design. Eligibility criteria include appropriate histology and evidence of measurable disease. Key eligibility criteria include ECOG performance status of 0-2, adequate hematologic, hepatic, and renal function, and no prior treatment with NKP-1339. Patients must have adequate organ function and be able to tolerate the study medication.

Dosage Escalation
The starting dose of NKP-1339 will be 1 mg/m² on Day 1. The dose will be increased to 4 mg/m² (6% increase) on Day 2, and then to 8 mg/m² (8% increase) on Day 3. Each dose level will be escalated by 20 mg/m² every 2 weeks until the MTD is reached. If no dose-limiting toxicities (DLTs) are observed at the MTD, the dose will be escalated further.

Pharmacokinetics
Blood samples will be obtained on Days 1, 2, and 8 after the last dose of the infusion cycle Day 1 to determine pharmacokinetics.

Safety and Tolerability
The following adverse events are expected by phase 1 trials: Grade 3–4 neutropenia, thrombocytopenia, and anemia. The study will also evaluate for other potential toxicities as determined by the study protocol. All adverse events will be evaluated using the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 5.0.

Conclusions
This Phase I study will provide important information about the safety, tolerability, and pharmacokinetics of NKP-1339, which will be used to inform future development of this novel anticancer product.

NKP-1339 Treatment Outcome

NKP-1339 Anti-tumor Activity
1. Neutropenia/tumor lysis
2. Hematologic toxicity
3. Gastrointestinal toxicity
4. Nephrotoxicity

NKP-1339 Dose Escalation

NKP-1339 -09-002 Study Design and Methods

Single patient Phase I dose escalation

Objectives
- Determine the safety, tolerability, and maximum tolerated dose (MTD) of NKP-1339
- Evaluate pharmacokinetics and determine dose-limiting toxicities
- Determine the likely dose to escalate to phase 2 studies

Study Design
- A Phase I dose escalation study
- 2-step design: starting dose of 1 mg/m² on Day 1, followed by escalation to 4 mg/m² (6% increase) on Day 2, and then to 8 mg/m² (8% increase) on Day 3
- Dose escalation by 20 mg/m² every 2 weeks until the MTD is reached
- If no dose-limiting toxicities (DLTs) are observed at the MTD, the dose will be escalated further

Dose Escalation

<table>
<thead>
<tr>
<th>CURRENT DOSE</th>
<th>NO. OF PATIENTS</th>
<th>DOSE LIMITING TOXICITY</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 mg/m²</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>4 mg/m²</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>8 mg/m²</td>
<td>1</td>
<td>0</td>
</tr>
</tbody>
</table>

Safety and Tolerability

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Dose Proportionality

The Kp is the unbound drug fraction. Kp is the drug concentration divided by the unbound drug concentration in plasma. The ratio of the maximum effect to the unbound drug fraction is called the intrinsic clearance.

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Dose Proportionality at Cmax and AUC(0-24h) of a 1st dose following 6 intervals.

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