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

N. R. Dickson[1], S. F. Jones[1], H. A. Burris III[1], R. K. Ramanathan[2], G. J. Weiss[2], J. R. Infante[1], J. C. Bendell[1], W. McCulloch[3], D. D. Von Hoff[2]

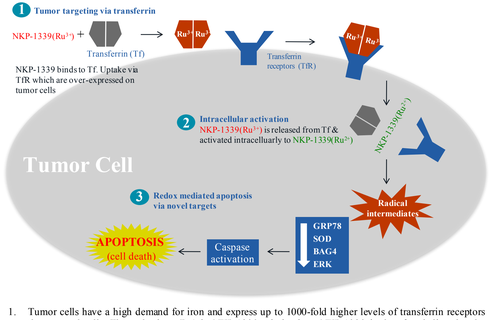
[1]Sarah Cannon Research Institute/Tennessee Oncology, Nashville, TN [2]Virginia G. Piper Cancer Center at Scottsdale Healthcare/TGen, Scottsdale, AZ [3]Niiki Pharma Inc., Hoboken, NJ

Abstract

Background: NKP-1339 is a novel transferrin targeted ruthenium based anti-cancer compound which is intravenously administered. Its intracellular targets include GRP78, a key regulator of misfolded protein processing. In nonclinical anti-tumor studies, NKP-1339 showed activity against different tumor types, including those resistant to platinum and other standard anti-cancer agents. This Phase I trial evaluates the safety, tolerability, maximum tolerated dose (MTD), pharmacokinetics (PK), and pharmacodynamics (PD) of NKP-1339. **Methods:** NKP-1339 is administered as a 30-90 minute infusion (based on volume to be infused) on days 1, 8, and 15 of a 28 day cycle. Full PK sampling in blood and urine is performed on Day 1; trough plasma and urine samples are obtained predose on Cycle 1 Day 8 and Cycle 2 Day 1. PD markers analyzed for NKP-1339 effect include transferrin, transferrin receptor, ferritin, serum iron, and TIBC. **Results:** A total of 16 patients with metastatic solid tumors have been treated at 6 different dose levels (20, 40, 80, 160, 320, and 420 mg/m^2). Tumor types represented in this population include: lung (5); neuroendocrine (3); colon (4) and 1 each of ovarian, cervical, pancreatic, and head & neck cancer. All patients have a performance score of 0 or 1. Demographics: 7 female /9 male; 14 white /2 black; median age 63.5 years (range 51 to 75). At 420 mg/m^2 an unusual finding of a transient green discoloration to the plasma in the absence of clinical jaundice or other signs/symptoms has been noted. This is probably due to the complex chemical state of ruthenium in plasma. Unrelated to the plasma discoloration, Grade 1-2 pyrexia and/or rigors has been observed in 2 of 5 patients at the 420 mg/m^2 dose level, but has been prevented in subsequent infusions with steroid-based premedications. Preliminary PK results on the patients enrolled at the 20mg/m^2 through 420mg/m^2 dose levels show dose proportionality of C_{max} and AUC $_{0\text{-}192}$ (AUC of first dosing interval). Two patients with Stage IV neuroendocrine tumors have experienced stable disease for up to 13+ cycles (52+weeks). **Conclusions:** Promising anti-cancer activity in neuroendocrine tumors has been observed with this novel ruthenium based compound. The toxicity profile is manageable and the PK profile is consistent with preclinical predictions. Dose escalation (current dose 500mg/m^2) is ongoing as MTD not reached.

NKP-1339 Mechanism of Action

NKP-1339 is a novel transferrin targeted ruthenium based anti-cancer compound. Its intracellular targets include GRP78, a key regulator of misfolded protein processing. The three key steps in NKP-1339 mechanism of tumor cell apoptosis induction are outlined in the figure below. In nonclinical anti-tumor studies, NKP-1339 showed activity against different tumor types, including those resistant to standard anti-cancer agents (e.g., platinums, vinca alkaloids, taxanes, anthracyclines).



1. Tumor cells have a high demand for iron and express up to 1000-fold higher levels of transferrin receptors than normal cells. The ruthenium (Ru) in NKP-1339 mimics iron. NKP-1339 is therefore believed to be targeted to tumor cells by specific binding to transferrin and uptake via the transferrin receptor.
2. The Ru in NKP-1339 is in the +3 oxidation state, which is not highly reactive. Intracellularly, following uptake via transferrin and cycling via the endosomes, the Ru in NKP-1339 is reduced to its reactive +2 oxidation state.
3. The reduced reactive NKP-1339 in the tumor cell is believed to initiate a redox chain reaction which generates cytosolic radical intermediates/reactive oxygen species whose targets include cytosolic proteins such as GRP78, inducing apoptosis of the tumor cell.

NKP-1339 -09-002 Study Design and Methods

Open label Phase I dose escalation

Objectives:

- Determine the safety, tolerability and maximum tolerated dose of NKP-1339
- Estimate the PK parameters of NKP-1339
- Report any responses to NKP-1339 in subjects with advanced tumors
- Explore PD endpoints

Study Population:

- Patients ≥ 18 years with histologically or cytologically confirmed advanced solid tumors refractory to standard therapies who signed an IRB approved Informed Consent Form (ICF)
- ECOG PS 0 or 1
- Adequate hematologic, hepatic and renal function
- No supplemental IRON, i.e., therapeutic or as part of a multivitamin regimen
- No chemotherapy, immunotherapy, or radiotherapy for < 4 weeks, BMTs < 9 months or major surgery < 3 weeks
- No symptomatic central nervous system metastases. No primary brain tumors or known brain metastasis unless clinically stable and on stable or reducing dose of steroids
- No evidence of ischemia, MI within the past 6 months, or other significant abnormality on ECG
- No clinically significant active infection including HIV, hepatitis B, or hepatitis C
- No peripheral neuropathy ≥ Grade 2
- Minimum life expectancy ≥ 12 weeks

Study Treatment:

- NKP-1339 infused over 30-90 minutes (dependent upon infusion volume) on Days 1, 8 and 15 of 28-day cycle.

Definition of Dose Limiting Toxicity:

- Toxicity severity graded according to the CTCAE (ver. 3.0); occurring during Cycle 1 and related to NKP-1339
- Grade 4 neutropenia for ≥ 7 days
- Febrile neutropenia
- Grade 4 thrombocytopenia or Grade 3 thrombocytopenia (< 50.0 x 10^9/L) with bleeding
- > Grade 2 neurotoxicity
- ≥ Grade 2 cardiotoxicity
- Grade 2 hypersensitivity reaction or infusion reaction
- Any other non-hematologic Grade 3 or 4 toxicity other than nausea/vomiting or alopecia
- Inability to complete the first cycle due to any toxicity *thought to be related to NKP-1339*

Patient Characteristics

DIAGNOSIS	n (%)
NSCLC	5 (31%)
Neuroendocrine	3 (19%)
Colon	3 (19%)
Other: (ovarian, pancreatic, colorectal, head & neck, cervical)	5 (31%)

PRIOR THERAPIES	
Prior Chemo, n (%)	16 (100%)
1 prior chemo regimen	1 (6%)
≥ 3 prior chemo regimen (range 3 – 9 prior regimens)	15 (94%)
Prior Radiation, n (%)	9 (56%)

DEMOGRAPHICS	(n = 16)
Age (yrs), median (range)	63.5 (51-75)
Male, n (%)	9 (56%)
Female, n (%)	7 (43%)

ECOG STATUS	n (%)
0	9 (56%)
1	7 (44%)

Dose Escalation

Single patient cohorts enrolled until ≥ Grade 2 toxicity encountered, at which time cohorts converted to a standard 3 + 3 dose escalation scheme.

COHORT	DOSE (mg/m^2)	NO. OF PATIENTS	DOSE LIMITING TOXICITY
1	20	1	0
2	40	1	0
3	80	1	0
4	160	1	0
5	320	7*	1 (atrial fibrillation)
6	420	5†	0
7	500	2	0

MTD not reached. Dose escalation ongoing at the 500 mg/m^2 dose level

*One patient was unable to complete Cycle 1 dosing due to disease progression and was replaced.

†Two patients were unable to complete Cycle 1 dosing due to disease progression and were replaced.

Safety and Tolerability

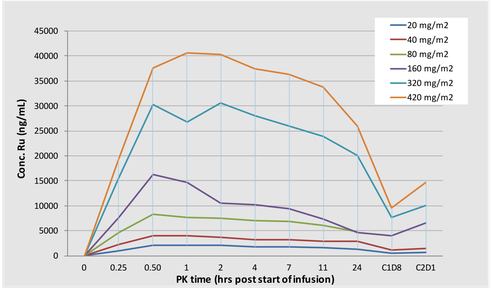
ADVERSE EVENT	NO. OF PATIENTS	GRADE
FATIGUE	6 (38%)	1, 2, 3
NAUSEA	5 (31%)	1
CHILLS	4 (25%)	1, 2
PYREXIA	3 (19%)	1, 2
VOMITING	2 (13%)	1, 2
PLASMA DISCOLORATION	3 (19%)	1
GERD	2 (13%)	1
HEADACHE	2 (13%)	1, 2
PHLEBITIS	2 (13%)	1, 2

The following adverse events were reported by one patient each (all are Grade 1 unless otherwise noted): abdominal cramping, anemia (Gr 2 and 3), atrial fibrillation (Gr 2), abnormal breath sounds, dehydration, diarrhea, indigestion, exertional dyspnea (Gr 2), eructation, hypertension (Gr 3), hyponatremia (Gr 3), infusion reaction, peripheral neuropathy, nightmares, peripheral edema, body aches (Gr 2) pleural effusion, rales, respiratory reaction and wheezing.

Unique Finding -Plasma Discoloration: The NKP-1339 parent compound is reddish-brown as a powder and the reconstituted drug is clear. Transient discoloration of plasma and urine at the 420 mg/m^2 NKP-1339 dose was noted in some patients. No skin discoloration was observed. The plasma/urine discoloration was described as green or olive-green and resolved within a few hours . The discoloration was not correlated with any other signs or symptoms and has continued to be reported at the 500mg/m^2 (current) dose level.

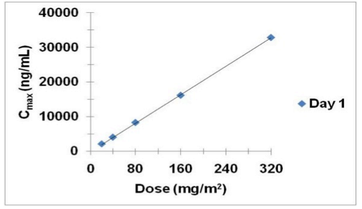
Pharmacokinetics

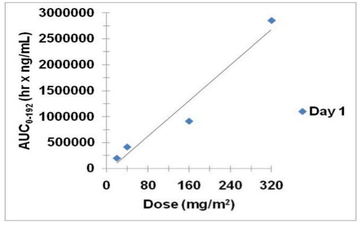
PK samples are obtained 0, 0.25, 0.5, 1, 2, 4, 6-8, 10-12, and 24 hours after the start of the infusion on Cycle 1 Day 1 as well as pre-infusion on Cycle 1 Day 8 and Cycle 2 Day 1.



Ruthenium plasma levels for the first 6 cohorts (20mg/m^2 through 420mg/m^2) and the C_{max} and AUC $_{0\text{-}192}$

NKP-1339-09-002
Dose Proportionality of C_{max} and $AUC_{0\text{-}192}$ (AUC of first dosing interval)





The C_{max} and AUC$_{0\text{-}192}$ (AUC of first dosing interval) for the first 5 cohorts show a dose proportionality for NKP-1339.

NKP-1339 Treatment Outcome

Patient No.	Dose (mg/m^2)	Tumor	No. prior chemo regimes	No. NKP-1339 cycles (1 cycle = 28 days)	Anti-tumor effect (best response)
1	20	Colon	6	2	PD
2	40	Colon	5	2	PD
3	80	Ovarian	7	1	PD
4	160	Colon	4	2	PD
5	320	SCLC	6	1	PD
6	320	NSCLC	4	4	Stable disease
7	320	Pancreatic	3	1	PD
8	320	NET Carcinoid small intestine	5	13+	Minor Response/SD Rx ONGOING
9	320	NSCLC	9	4	Stable disease
10	320	NSCLC	4	2	PD
11	320	NET secondary to prostate cancer	1	2	PD
12	420	Colorectal	4	1	PD
13	420	NSCLC	3	1	PD
14	420	NET Gastrinoma	5	6	Stable disease
15	420	Head and Neck	7	1	PD
16	420	Cervical	5	2	PD

NKP-1339 Anti-tumor Activity

1. Neuroendocrine tumors
   - Metastatic carcinoid (one patient):
     - 3 lines previous treatments (Sandostatin LAR, Xeloda, ALK inhibitor) with best recorded previous response 2-4 months stable disease
     - NKP-1339 treatment: 12 months tumor regression (minor response); NKP-1339 treatment ongoing
   - Metastatic gastrinoma (one patient):
     - 5 lines previous treatments
     - NKP-1339 treatment: 6 months stable disease
2. NSCLC
   - Metastatic non-squamous cell NSCLC (two patients)
     - 4 and 9 lines of prior chemotherapy respectively
     - NKP-1339 treatment: 4 months stable disease for each patient

Conclusions

1. NKP-1339 is a novel transferrin targeted ruthenium based agent that induces apoptosis.
2. In this Phase I study, NKP-1339 has demonstrated
   - Prolonged stable disease in neuroendocrine tumors
   - Manageable toxicity profile
   - Dose proportional PK profile
3. MTD has not been reached. Dose escalation ongoing (current dose 500mg/m^2).