NKP-1339: Maximum Tolerated Dose Defined for First-in-Man GRP78 targeted agent

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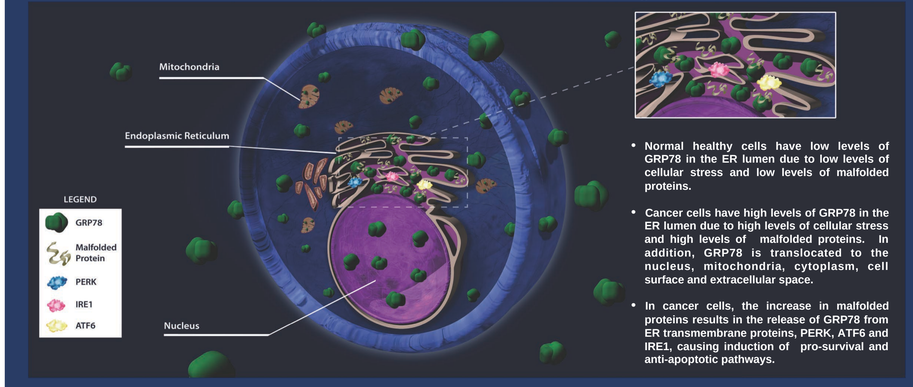
Background

NKP-1339 down-regulates GRP78 expression, a master regulator of ER stress



- Normal healthy cells have low levels of GRP78 in the ER lumen due to low levels of cellular stress and low levels of malfolded proteins.
- Cancer cells have high levels of GRP78 in the ER lumen due to high levels of cellular stress and high levels of malfolded proteins. In addition, GRP78 is translocated to the nucleus, mitochondria, cytoplasm, cell surface and extracellular space.
- In cancer cells, the increase in malfolded proteins results in the release of GRP78 from ER transmembrane proteins, PERK, ATF6 and IRE1, causing induction of pro-survival and anti-apoptotic pathways.

- Elevation of GRP78 expression levels is found in a wide variety of cancer types and correlated with tumor proliferation, metastasis, angiogenesis and tumor cell survival.
- GRP78 elevation in tumor cells has been shown to confer resistance to chemotherapeutic drugs, including cisplatin, 5-FU, paclitaxel, docetaxel, sorafenib, bortezomib, etoposide, doxorubicin, temozolomide, vinblastine and camptothecins.
- NKP-1339 is a small molecule that down-regulates the GRP78 pathway and reduces GRP78 levels in tumor cells.
  - *In vitro* preclinical studies have shown that single agent NKP-1339 is active against a broad range of tumor types including breast, colon, esophageal, gastric, osteosarcoma, liver, and lung carcinomas.
  - NKP-1339 is active in many tumor cell lines tested that are resistant to platinums, anti-metabolites, anthracyclines, vinca alkaloids and taxanes.
- The current Phase I study was initiated to determine the maximal tolerated dose of NKP-1339 when administered on a weekly schedule
- Preliminary results are presented

Study Design

Phase I study of single agent NKP-1339 infused over 60 minutes Day 1, 8 and 15 of 28-day cycle

Standard 3 + 3 design with Expanded Cohort up to 25 patients at the MTD

Major Inclusion / Exclusion Criteria:

- Patients ≥ 18 years with histologically or cytologically confirmed advanced solid tumors refractory to standard therapies
- ECOG PS 0 or 1
- Adequate hematologic, hepatic and renal function
- No symptomatic CNS metastases, no primary brain tumors
- No evidence of ischemia, recent MI, or significant abnormality on ECG
- No Peripheral neuropathy ≥ Grade 2
- Minimum life expectancy ≥ 12 weeks

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
- > 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*

Demographics

Patients enrolled to date			N = 46	
Gender	Male / Female		25 / 21	
Age, years	Median (Range)		61 years (28 - 78 years)	
Race	Caucasian / Black / Other		42 / 3 / 1	
Number of prior systemic therapies	Median (Range) Unknown		4 (0 - 8)* 14	
Tumor type	CRC	11	Thymic	1
	NSCLC	9	Sarcoma	1
	Neuroendocrine (NET)	5	SCLC	1
	H&N	4	Adrenal	1
	Breast	3	Cholangiocarcinoma	1
	Pancreatic	2	Cervical	1
	Ovarian	2	Unknown primary	1
	GE Junction	2		

*One patient with neuroendocrine tumor failed multiple local therapies

Enrollment

Dose level (mg/m²)	Patients dosed	Patients with DLT	Patients replaced in due to PD in Cycle 1
20	1		
40	1		
80	1		
160	1		
320	7	1	1
420	5		2
500	3		
625	6	1	
780	9	3	1
Expanded Cohort (625)	12	NA	

Dose Limiting Toxicity

320 mg/m² 66 year old male with transient atrial fibrillation that spontaneously reverted prior to dosing Cycle 1 Day 8. The patient had extensive tumor invasion into the mediastinum and pericardial effusion.

625 mg/m² 42 year old female had an infusion reaction consisting of fever and chills. The patient had not been premedicated with steroids.

780 mg/m² A 78 year old female had Grade 2 nausea, Grade 1 vomiting, Grade 1 fatigue following Cycle 1 Day 1 dosing associated with a Grade 2 creatinine elevation which returned to baseline within 1 week.

69 year old female had Grade 3 vomiting and Grade 3 dehydration following Cycle 1 Day 1 dosing associated with Grade 2 creatinine elevation which returned to baseline within 3 weeks.

A 53 year old male had an infusion reaction consisting of fever and chills. The patient had not been premedicated with steroids

Adverse Events

Most common adverse events (occurring in ≥ 15%) in the study population (N=46)

Event	Related		Unrelated		Total (%)
	Grade 1-2	Grade 3	Grade 1-2	Grade 3	
Fatigue	16	1	1	2	20 (43%)
Nausea	17	0	3	0	20 (43%)
Pain (general)	2	0	15	0	17 (37%)
Vomiting	11	1	4	0	16 (35%)
Diarrhea	4	0	6	0	10 (22%)
Abdominal pain	4	0	5	1	10 (22%)
Anemia	5	2	2	0	9 (20%)
Constipation	0	0	9	0	9 (20%)
Chills	9	0	0	0	9 (20%)
Dehydration	1	2	4	0	7 (15%)
Weakness	1	0	4	2	7 (15%)

- There were no Grade 4 events
- Decadron premedication prevents Infusion reactions (fever and chills)
- Fatigue is not dose related
- In the 780 mg/m² dose group, nausea and vomiting has a higher incidence and severity, and it was sometimes associated with dehydration
- In most cases, pain and weakness were attributed to the underlying malignancy
- Hematologic toxicity was infrequent: Anemia with one CTCAE Grade decrease in hemoglobin; no neutropenia has been observed to date. Thrombocytopenia was rare (I pt at 780 mg/m²; 2 pts with bone / bone marrow metastases
- Grade 1 transient hypercreatininemia in 4 pts at 780 mg/m²; Grade 2 in 1 pt treated 100 + weeks
- Mild albumin decrease from Day 1 to Day 22 with partial recovery before next cycle, while total protein levels remain stable and no edema or clinical symptoms
- Elevations of transaminases and/or bilirubin generally occurred only in patients with progression of hepatobiliary disease
- QTc prolongation has not been demonstrated

Pharmacodynamics

Baseline Plasma GPR78 levels were run for the first 12 enrolled patients:

Tumor type	Prior systemic therapies	GRP78 level (ng/ml)	Tumor type	Prior systemic therapies	GRP78 level (ng/ml)
Ovarian	6	18	Pancreatic	3	814
NSCLC	5	31	NET	3	39
NET	4	8	NSCLC	6	31
CRC	4	4120	NSCLC	4	94
CRC	4	10	NSCLC	4	17
NSCLC	4	82	H&N	4	16

Plasma GRP78 is not detectable in normal subjects. These preliminary results show that Plasma GRP78 levels are measurable in all patients tested to date

- Could be used as a marker for NKP-1339 therapy
- Paired pre- and post-therapy plasma GRP78 levels are being performed

Tumor staining for GRP78 and assessment of GRP78 polymorphism to be performed

Efficacy

36 pts completed ≥ one cycle of therapy and are evaluable to assess antitumor efficacy. In this heavily pretreated population, efficacy was assessed by partial response or stable disease for ≥ 12 weeks. All patients had PD at study entry.

Dose level (mg/m²)	Diagnosis	Prior systemic therapies	Response	Duration of therapy
320	NET	3	PR	100+ weeks
780*	NET	1	SD	27+ weeks
420	NET	0**	SD	24 weeks
500	Unknown primary	2	SD	22 weeks
320	NSCLC	4	SD	16 weeks
320	NSCLC	7	SD	16 weeks
780*	Sarcoma	3	SD	16 weeks
625	CRC	3	SD	12 weeks
625	GE Junction	3	SD	12 + weeks

*Dose reduced to 625 mg/m² when MTD determined
**Failed 4 prior chemo- and Yttrium-embolization procedures

All enrolled patients with NET had documented disease progression at study entry:

Dose Level (mg/m²)	Histology	Sites of Disease	NKP-1339 Best Response	Tumor assessment		NKP-1339 Duration of Therapy
				Target lesion	Non-target	
320	Carcinoid	Lung, liver, nodes	PR	-30%	present	100+ wks
780*	Carcinoid	Small bowel, nodes	SD	-10%	present	27+ wks
420	Gastrinoma	Liver only	SD	0	present	24 wks
320	Large Cell	Liver, bone	PD	+2%	PD	8 wks
780	Carcinoid	Liver, bone	Not evaluable	--	--	DLT

*Dose reduced to 625 mg/m² when MTD determined

Conclusions

- NKP-1339 is a small molecule targeting the GRP78 pathway
- The MTD of single agent NKP-1339 is 625 mg/m² days 1, 8, 15 Q 28 d
- NKP-1339 is generally well tolerated
  - DLT are nausea, vomiting, dehydration and reversible creatinine elevation
  - At the MTD, the most common NKP-1339 attributed adverse events are nausea, vomiting and fatigue
  - Infusion reactions can be prevented with decadron premedication, as utilized in standard 5-HT antagonist antiemetic regimens
  - Hematologic, hepatic, cardiac, neurologic, dermatologic adverse events are rare and generally not NKP-1339 related
- NKP-1339 has demonstrated activity in patients across tumor types, including neuroendocrine tumors (NET) and NSCLC
- Plasma GRP78 may be evaluated as marker for in NKP-1339 therapy
- Phase II trials in NET and Phase I combination chemotherapy trials are in development

For more information, visit www.niikipharma.com