A Phase I Study of NPC-1C: a novel, therapeutic antibody to treat pancreas and colorectal cancers

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Abstract

Background:
NPC-1C (NEO-101; Ensituximab) is a chimeric monoclonal antibody being developed as a novel biological treatment for pancreatic and colorectal cancers. This antibody was selected from a panel of hybridomas generated from mice immunized with semi-purified membrane-associated proteins derived from biologically screened, pooled human allogeneic colon cancer tissues. The NPC-1C target appears to be a variant of MUC5AC that is expressed specifically by human colon and pancreatic tumors with only occasional minimal cross-reactivity to certain normal GI tract tissues.
Methods:
A Phase 1 open label, multi-center dose escalation clinical trial with NPC-1C treated 15 subjects with advanced pancreatic and colorectal cancer who were refractory to standard therapy. The primary objectives of the Phase I clinical trial was safety and tolerability of escalating doses of NPC-1C and to assess pharmacokinetics (PK) and select immune responses to the antibody at each dose level. Secondary objectives evaluated for evidence of clinical benefit and to explore the immunologic correlates associated with administration of NPC-1C.
Results:
Three cohorts of subjects were treated with NPC-1C at escalating dose levels of 1, 1.5, and 2 mg/kg IV every two weeks. All fifteen subjects (10 colorectal, 5 pancreatic) have completed the study (4/15 non-evaluable). Two patients at the 1mg/kg and one patient at the 2mg/kg demonstrated stable disease at the initial restaging scans. At the 2 mg/kg dose level, at escalating rates of infusion, 3 subjects experienced mild to moderate hemolysis that resolved without intervention. Six patients received 1.5 mg/kg at a constant rate of infusion have been evaluated, with no dose limiting toxicity. One patient re-staged in the 1.5 mg/kg cohort showed stable disease. Undetectable or insignificant levels of HAMA in serum were observed in 13 patients tested. An NPC-1C specific ELISA to assess PK has been developed and qualified; analysis of subject serum samples is currently underway.
Conclusions:
NPC-1C is tolerated well at the current dose level of 1.5 mg/kg every 2 weeks with no DLT is experienced in any of the 6 evaluable subjects. Despite advanced disease for subject population, preliminary signs of activity, based on stabilization of disease, have been observed

Background

History of NPC-1C Development

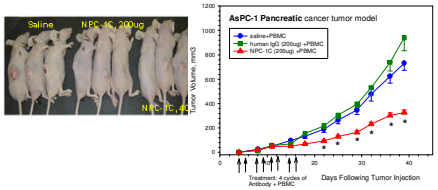
- NPC-1C was developed from a previous cancer vaccine derived from antigens isolated from pooled tumor extracts obtained from surgical samples from patients with colorectal cancer.
- Data published from these clinical studies in the 1980's demonstrated both safety and signs of efficacy of the original vaccine. *(Specific active immunotherapy in patients with adenocarcinoma of the colon utilizing tumor –associated antigens (TAA). A phase I clinical trial. Hollinshead A, Elias EG, Arlen M, et al. Cancer 56(3):480-9, 1985)*

In Vitro Data

- FACS analysis demonstrated 60-95% staining of colorectal and 50-55% pancreatic cancer cell lines with NPC-1C.
- 50-60% of colorectal and pancreatic tumors express NPC-1C antigen by IHC
- Minimal expression on normal tissue
- NPC-1C binds to a variant of MUC-5AC.
- Killing activity via ADCC ranging from 25-65% tumor cell lysis in 4 hour Cr release assay.

Pre-Clinical In Vivo Data

- Anti-tumor activity was demonstrated with NPC-1C in mice bearing established human pancreatic cell lines.
- PK testing in animals supports dosing every two weeks.
- Biodistribution studies indicate that NPC-1C can traffic to the tumor site following intravenous administration and potentially effect an anti-tumor effect.
- Animal toxicity studies did not identify toxicities associated with the administration of NPC-1C.



The Clinical Trial

A Phase 1/2A Therapeutic, Open Label, Multi-Center Clinical Trial of NPC-1C, a Chimeric Monoclonal Antibody, in Adults with Recurrent, Locally Advanced Unresectable or Metastatic Pancreatic and Colorectal Cancer after Standard Therapy

PROTOCOL

Primary Objectives

- Determine the safety and tolerability of escalating doses of NPC-1C
- Assess PK and select immune responses to the antibody.

Secondary Objectives

- Evaluate evidence of clinical benefit, as measured by RECIST criteria;
- Explore the immunologic correlates associated with administration of NPC-1C monoclonal antibody therapy.

Study Design: Phase 1

- NPC-1C administered IV every 2 weeks for 4 doses (one course); additional courses if no progression per RECIST.
- To establish safety, increasing dose levels of NPC-1C were planned to be administered to cohorts of 3-6 subjects. Each cohort to receive the same dose level; dose levels to increase with each new cohort after safety established in the preceding cohort.

Eligibility criteria of interest

- Colorectal or pancreatic cancer, unresectable or metastatic, after standard therapy
- Good end organ function and performance status
- ≥ 20% of tumor tissue staining positive for NPC-1C target antigen
- No history of hemolytic episodes

RESULTS

Clinical Observations

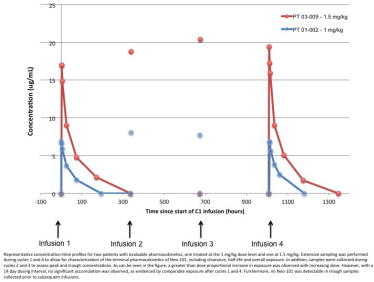
Dose cohort 1 (1 mg/kg NPC-1C per dose):
3 subjects enrolled and evaluated
2 subjects (1=colorectal; 1=pancreatic) with SD after Course 1
No DLT experienced

Dose cohort 2 (2 mg/kg NPC-1C per dose):
4 subjects enrolled (3 non-evaluable)
1 subject (colorectal) evaluated: SD after Course 1
Reversible hemolysis NOT requiring intervention identified in 3 subjects

Dose cohort 1.5 (1.5 mg/kg NPC-1C per dose):
8 subjects enrolled (2 non-evaluable)
1 (colorectal) with SD after Course 1
No DLT experienced

RESULTS

Pharmacokinetic Data



Representative concentration-time profiles for two patients with evaluable pharmacokinetics, one treated at the 1 mg/kg dose level and one at 1.5 mg/kg. Extensive sampling was performed during cycles 1 and 3 to allow for characterization of the terminal pharmacokinetics of Neo-101, including clearance, half-life and overall exposure. In addition, samples were collected during cycles 2 and 3 to assess peak and trough concentrations. As can be seen in the figure, a greater than dose proportional increase in exposure was observed with increasing dose. However, with a 14-day dosing interval, no significant accumulation was observed, as evidenced by comparable exposure after cycles 1 and 4. Furthermore, no Neo-101 was detectable in trough samples collected prior to subsequent infusions.

Adverse Events

	NPC-1C 1mg/kg (n=3)		NPC-1C 1.5mg/kg (n=5)		NPC-1C 2mg/kg (n=4)		NPC-1C Total (n=12)	
Event	All Grades	Grade 3 or 4	All Grades	Grade 3 or 4	All Grades	Grade 3 or 4	All Grades	Grade 3 or 4
Back Pain	1 (33%)	0	0	0	3 (75%)	1 (25%)	4 (33%)	1 (8%)
Hyperbilirubinemia	0	0	2 (40%)	1 (20%)	0	0	2 (17%)	1 (8%)
Fatigue	0	0	1 (20%)	1 (20%)	0	0	1 (8%)	1 (8%)
Abdominal Pain	0	0	1 (20%)	1 (20%)	0	0	1 (8%)	1 (8%)
Hypersensitivity reaction	3 (100%)	0	1 (20%)	0	3 (75%)	0	7 (58%)	0
Lymphocytes	0	0	4 (80%)	0	2 (50%)	0	6 (50%)	0
Ascites	0	0	2 (40%)	0	1 (25%)	0	3 (25%)	0
Hypoxia	0	0	0	0	1 (25%)	0	1 (8%)	0
Elevated Cr	0	0	0	0	1 (25%)	0	1 (8%)	0
Elevated LDH	0	0	0	0	1 (25%)	0	1 (8%)	0
Diaphoresis	0	0	0	0	1 (25%)	0	1 (8%)	0
Hematuria	0	0	0	0	1 (25%)	0	1 (8%)	0

Correlative Studies

- Assessment of patient PBMC's pre- and post-treatment for ADCC is underway.
- Analysis of cytokine profile by Luminex bead assay pre- and post-treatment
- Determination of correlation between clinical response and ADCC or cytokine profile

Conclusions

NPC-1C is well tolerated at the current dose level of 1.5 mg/kg every 2 weeks with no DLT experienced in any of the 6 evaluable patients. Despite advanced disease in this patient population, preliminary signs of activity based on stabilization of disease, have been observed.

Future plans

- Assessment of immune correlates of response or ADCC
- Phase 2 clinical trial