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 biochemically 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 1 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 1.5, 2 mg/kg IV every two weeks. All fifteen subjects (10 colorectal, 5 pancreatic) have completed the study. 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.

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.

Background
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 vaccines.

In Vitro Data
• FACS analysis demonstrated 60-95% staining of colorectal and 50-55% colorectal pancreatic cancer cell lines with NPC-1C.
• 50-60% of colorectal and pancreatic tumor 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.

Clinical Observations
• 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.

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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

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.
• No prior adjuvant chemotherapy.
• No prior monoclonal antibody therapy.

RESULTS

Conclusions:
• NPC-1C is tolerated well at the current dose level of 1.5 mg/kg every two 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

Pharmacokinetic Data

Adverse Events

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
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Results: 3 subjects enrolled and evaluated 2 subjects (1=colorectal; 1=pancreatic) with SD after Course 1
Reversible hemolysis NOT requiring intervention identified in 3 subjects

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