Initial results of a phase 1a/1b study of NGM120, a first-in-class anti-GDNF family receptor alpha like (GFRAL) antibody in patients with advanced solid tumors

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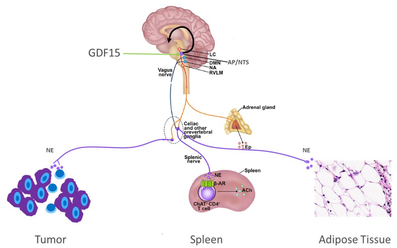
NGMBio

ePoster 550P

Background

Growth Differentiation Factor 15 (GDF15) has been shown to have both immune suppressive and pro-cachectic effects[1]. NGM120 is a novel, 1st-in class, humanized monoclonal antibody that inhibits GFRAL (the receptor for GDF15) resulting both in anti-tumor and anti-cachexia effects in preclinical animal models. In a healthy volunteer study, NGM120 (10-400 mg) was well tolerated with a favorable safety profile. We present the data from Ph1a/1b dose finding study (NCT04068896) of NGM120 and NGM120 + gemcitabine (Gem)/Nab-paclitaxel (Nab-P) in advanced cancer patients.

A model for GDF15/GFRAL's engagement of autonomic nervous system for its peripheral effects in addition to its central emergency circuit (black arrow).



Modified from Chavan SS et al, *Immunity*, 2017 and Qiao G et al, *Front Immunol*, 2018

Trial Design

Ph1a	Dose Finding Dose Expansion
Ph1b	Dose Finding
Ph2a	Placebo Controlled Dose Expansion

Phase 1a – Monotherapy (20 subjects)

- Dose-finding (NGM120 30 mg and 100 mg, Q3W, SC) followed by pharmacodynamic dose expansion for both doses
- Patients with advanced solid tumors in 10 select cancer types with median age of 64 years, 94% previously received >3 lines of therapies, median GDF15 of 2290 pg/ml (1290-59600)

Ph1b: Dose Finding in 1L metastatic pancreatic cancer patients (8 subjects)

- Dose-finding (NGM120 30 mg and 100 mg, Q4W, SC) in combination with gemcitabine + Nab-paclitaxel
- Patients with median age of 67 years and median GDF15 of 1740 pg/ml (1350-3540)

Objectives

- Safety, PK and tolerability of NGM120 in subjects with advanced solid tumors and metastatic pancreatic cancer
- Potential proof of concept for anti-tumor and/or anti-cachexia activity

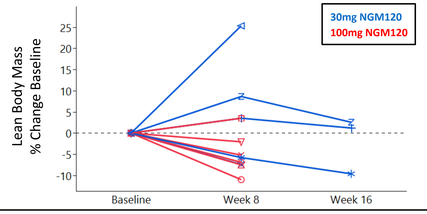
Phase 1a – Monotherapy in Advanced Solid Tumors

NGM120 Safety Profile

- No dose-limiting toxicities observed and maximal tolerated dose not reached
- Most AEs were Grade 1-2 and not attributed to NGM120, with fatigue (30%), insomnia (25%), GGT increase (20%), and nausea (20%) being most frequent
- Seven subjects experienced 11 SAE events, none of which were attributed to NGM120, but to the underlying diseases

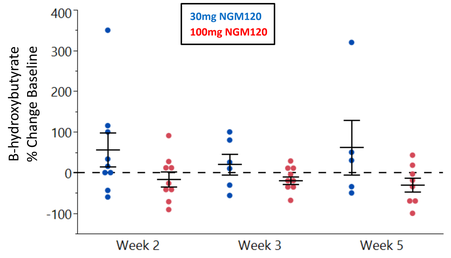
Anti-cachexia and Anti-tumor Assessments

- Four patients showed >3.5% increased lean body mass at Week 8 among the evaluable patients (see below)
- Three subjects (30%) in the 30 mg cohort and two subjects (20%) in the 100 mg cohort had stable disease based on their best response according to RECIST 1.1 criteria, although no objective response was observed



A Trend of Dose-dependent Reduction in β-hydroxybutyrate

- β-hydroxybutyrate is a form of ketone bodies, which are proportional to the extent of lipolysis induced by GDF15, therefore, a PD biomarker for pathway inhibition



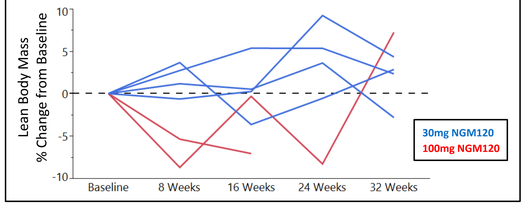
Phase 1b – Chemotherapy Combination in Pancreatic Cancer

Safety Profile Consistent with Gem + Nab-P Treatment

- No dose-limiting toxicities observed and maximal tolerated dose not reached
- Most AEs were not attributed to NGM120, with Grades 1-3 diarrhea (50%), nausea (50%), and fatigue (50%) being most frequent, which are commonly seen in the context of Gem/Nab-P therapy
- Five subjects experienced 10 SAE events; however, none of them were related to NGM120, but to the chemotherapy and/or underlying diseases

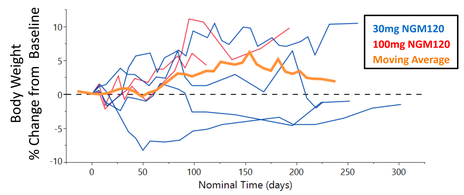
Six CT-evaluable Patients Exhibit a 4% Average Maximal Increase in Lean Body Mass

- 4/6 individuals have increased LBM after 32 weeks of treatment, although with dynamic changes in the course of their treatment

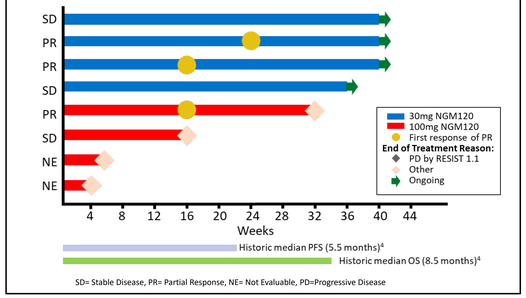


4/6 CT-evaluable Patients Exhibit >5% Maximum Body Weight Gain

- Average maximum body weight gain of 6.2% across all 6 CT-evaluable subjects



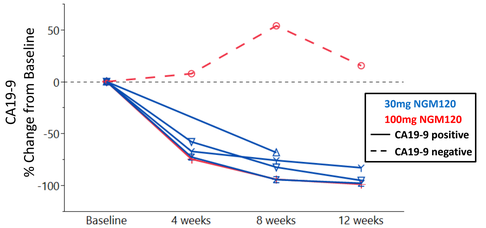
All Four 30 mg Patients Exhibit SD/PR Beyond 36 Weeks



SD= Stable Disease, PR= Partial Response, NE= Not Evaluable, PD=Progressive Disease

Substantial Reduction in Tumor Biomarker CA19-9 by NGM120 + Gem/Nab-P

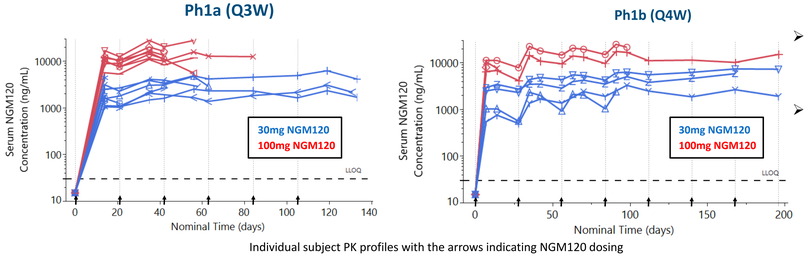
- 3 subjects (3/5, 60%) with CA19-9 positive tumors show more than 90% reduction from their baseline levels at Week 12



CA19-9 negative defined as blood levels within the normal range (<37U/mL)

Pharmacokinetics

PK Exposure Increased with Dose



Individual subject PK profiles with the arrows indicating NGM120 dosing

- The half-life in healthy volunteers is 28-40 days (NCT03392116, unpublished data)
- Accumulation ratios for Ph1a and Ph1b are 1.33-1.64 and 1.17-2.32, respectively, based on the trough concentrations following the 2nd dose (Ph1a) and the 3rd dose (Ph1b)

CONCLUSION

- Treatment with NGM120 is well tolerated, exhibiting no dose-limiting toxicities as monotherapy or in combination with Gem/Nab-P
- PK exposure increased with dose
- Increases in lean body mass and body weight were observed in a subset of the patients in both the monotherapy and combination settings
- Five SDs (5/20, 25%) were observed in the monotherapy cohorts in advanced solid tumors, but no objective responses were observed
- All six CT-evaluable pancreatic cancer patients treated with NGM120 in combination with Gem/Nab-P demonstrated disease control at 16 weeks, with three PRs and three SDs, five of whom extending to at least 32 weeks
- A randomized, placebo-controlled, single-blind Phase 2a study is ongoing to further evaluate NGM120 in the 1st line setting of pancreatic cancer in combination with Gem/Nab-P.

References:

1. Breit SN et al, *Growth Factors*, 2011
2. Chavan SS et al, *Immunity*, 2017
3. Qiao G et al, *Frontier in Immunology*, 2018
4. Von Hoff DD, et al. *N Engl J Med.* 2013

Acknowledgements

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DISCLOSURES

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