NGM707 in Combination With Pembrolizumab in Advanced or Metastatic Solid Tumors: Preliminary Results from Dose Escalation

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Abstract #CT099

Abstract

Background: NGM707-IO-101 (NCT04913337) is a Phase 1/2, dose escalation/expansion study evaluating NGM707, a humanized monoclonal antibody that blocks ILT2 and ILT4 receptors, as monotherapy or in combination with pembrolizumab. Here we report data from the combination Part 1b of the study.

Methods: Eligible patients (pts) with advanced/metastatic solid tumors were enrolled into escalating dose cohorts of 200-1800 mg NGM707 combined with 200 mg pembrolizumab, administered Q3W iv. Assessment of safety and tolerability and recommended expansion doses for NGM707 in combination with pembrolizumab were the primary objectives of the study. Secondary and exploratory objectives included assessment of pharmacokinetics/receptor occupancy (RO), immunogenicity, biomarkers, and preliminary antitumor activity per RECIST v1.1.

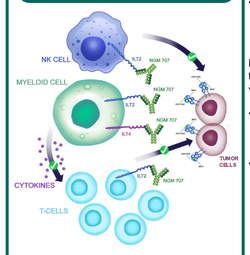
Results: As of 16 Feb 2024, 49 pts have been enrolled in the combination escalation at dose levels up to 1800 mg, which included 5 pts who crossed over from monotherapy. Median age 59 yrs [28-81]; ECOG PS 0 (18.4%), 1 (81.6%). Pts had received a median of 3 prior therapies (range 1-6) and all pts had metastatic disease. Overall, 24/49 pts had prior exposure to anti-PD1/anti-PD-L1. Treatment-related adverse events (any grade/grade ≥3) occurred in 42.9%/4.1% of pts. The most common treatment-related adverse events were fatigue (16.3%), diarrhea (8.2%) and nausea (6.1%). No dose-limiting toxicities were observed. A maximum tolerated dose was not reached, and the maximum administered dose was 1800 mg NGM707 in combination with 200 mg pembrolizumab. Peripheral immune cells showed dose-dependent RO, with doses ≥ 200 mg maintaining ILT2 and ILT4 RO for the entire dosing interval. PK of NGM707 was typical for monoclonal antibodies, with a half-life of 12.8 days. Gene expression changes associated with myeloid cell and T cell activation were observed in tumor biopsies post-treatment. Of 39 response-evaluable pts, best overall responses to date are pCR in 1 patient, PR in 4 pts, SD in 12 pts, representing a DCR of ~44%. 12 pts had reduced target lesion (TL) size with a maximum reduction of 100%. Out of the 5 patients who had pCR or PR, 4 patients were pre-treated with anti-PD1/anti-PD-L1. Two subjects with MSS CRC achieved confirmed PR, one of them with TL reduction that allowed subsequent surgical resection of all gross residual disease and confirmed pathological CR with no active tumor cells and ctDNA below detection.

Conclusions: NGM707 in combination with pembrolizumab was safe and well tolerated at all dose levels. In this advanced and metastatic solid tumor cohort, early efficacy signals have been observed. Evidence of myeloid cell reprogramming was observed in paired tumor biopsies.

Background

Figure 1: Mechanism of Action

NGM707 is a potent, first-in-class monoclonal antibody targeting the myeloid-enriched inhibitory receptors ILT2 (LILRB1) and ILT4 (LILRB2)



Dual antagonist antibody binds an epitope shared by ILT2 and ILT4: because both arms can bind ILT2 or ILT4, binding avidity is enhanced vs a bispecific antibody in which each arm can only bind a single target

- Potential to reprogram ILT4-expressing myeloid cells and stimulate the activity of ILT2-expressing myeloid and lymphoid cells

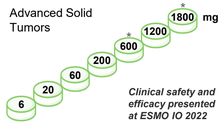
Preclinical studies of NGM707 suggest that:

- ILT4 blockade reverses myeloid cell immune suppression
- ILT2 blockade promotes tumor cell killing by NK and CD8+ T cells as well as tumor cell phagocytosis by macrophages
- Dual blockade of ILT2 and ILT4 acts additively to reverse suppression of Fc receptor signaling

First-in-human study of NGM707 ongoing as monotherapy and in combination with anti-PD1 (NCT04913337)

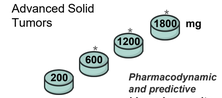
Figure 2: Dose Escalation Scheme

Part 1a: NGM707



Clinical safety and efficacy presented at ESMO IO 2022

Part 1b: NGM707 + Pembrolizumab



Pharmacodynamic and predictive biomarker results - AACR 2024 (Poster #3641)

**Includes paired biopsy cohort*

ILT2 = Immunoglobulin-like transcript 2; ILT4 = Immunoglobulin-like transcript 4; NK = Natural killer; Fc = fragment crystallizable; MHC = major histocompatibility complex

Methods And Materials

Study Design:

- Phase 1/2, dose escalation/expansion study for combination of NGM707 and pembrolizumab (200 mg) Q3W IV.
- Cohort size was 2 to 4 patients. At DLT safe levels additional patients were enrolled.
- DLT observation period was 28 days. Late-onset toxicities were taken into consideration for determination of the MTD/MAD.
- Dose escalation was guided by a Bayesian analysis of dose limiting toxicity (DLT) data for NGM707. Toxicity is modelled using 2-parameter logistic regression for the probability of a participant experiencing a DLT at the given dose.
- Patients were allowed to stay on study for treatment beyond progression as per the opinion of the treating physician.
- Safety was monitored continuously by blood tests and clinical findings. Efficacy was to be evaluated every 9 weeks.
- Periodically study data was reviewed and evaluated in Safety Monitoring Committee meetings.

Key Eligibility Criteria: Patients over 18 years old diagnosed with RCC, NSCLC, CRC, SCCHN, PDAC, Gastric, Esophageal, Ovarian, Breast, Cervical Cancer, Mesothelioma, and Melanoma. Intolerant to or progressed on all available therapies. Have at least 1 measurable lesion by CT or MRI. Adequate bone marrow, liver, renal, and heart function.

Dosing: Each patient received NGM707 (200 – 1800 mg) followed by pembrolizumab (200 mg) IVQ3W. Maximum duration of pembrolizumab was 35 cycles. Intra-patient dose escalation was allowed. Crossover was allowed after diagnosis of progressive disease.

Receptor Occupancy (RO): Measured in peripheral blood by flow cytometry with competing and non-competing fluorochrome-labeled antibodies specific for each target. In addition, monocytes were identified using antibodies specific for CD45 and CD14.

PK: Serum NGM707 concentration and PK parameters including Cmax, Tmax, AUC, CL, and Vd were estimated by non-compartmental method.

Results

Table 1: Patient Demographics/Clinical Characteristics

	NGM707 + Pembrolizumab Total N=49 n (%)
Age (yr)	
Median (Range)	59 (28-81)
Sex	
Female Male	24 (49) 25 (51)
Race	
White Black or African American Asian Not Reported/Unknown	23 (46.9) 2 (4.1) 20 (40.8) 4 (8.2)
Tumor Type	
CRC Gastric NSCLC PDAC SCCHN Melanoma Other	14 (28.6) 8 (16.3) 6 (12.2) 5 (10.2) 4 (8.2) 3 (6.1) 9 (18.3)

	NGM707 + Pembrolizumab Total N=49 n (%)
Baseline ECOG	
0 1	9 (18.4) 40 (81.6)
No of Prior Cancer Therapy	
Median (Range)	3 (1-6)
Prior anti PD1 or PD-L1 Therapy	
Received Not received	24 (49) 25 (51)
PD-L1 Expression*	
Positive CPS≥1% Negative Missing	28 (57.1) 10 (20.4) 11(22.4)

* PD-L1 was assessed centrally by 22C3 IHC pharmDx (Agilent), except for 5 subjects for whom historical local lab data was used.

Table 2: Summary of Treatment-related AEs and irAEs

	NGM707 + Pembrolizumab Total N=49, n (%)	
	Any Grade	**Grade 3-4****
Treatment-related AE	21 (42.9)	2 (4.1) [200 mg, grade 4, thrombocytopenia; and 1200 mg, grade 3, myalgia]
Treatment-related AE occurring in >5% of patients		
Fatigue	8 (16.3)	0 (0)
Diarrhea	4 (8.2)	0 (0)
Nausea	3 (6.1)	0 (0)
All irAE and infusion reactions, n (%)*		
Diarrhea	8 (16.3)	0 (0)
AST increased	5 (10.2)	2 (4.1) [600 mg, grade 4, not related; 1200mg, grade 3, related]
ALT increased	4 (8.2)	0 (0)
Blood bilirubin increased	3 (6.1)	2 (4.1) [600 mg, grade 3, not related; 1200mg, grade 3, related]
Pruritus	3 (6.1)	0 (0)
Infusion-related reaction	2 (4.1)	0 (0)
Hypothyroidism	1 (2)	0 (0)
Rash	1 (2)	0 (0)
Pneumonitis	1 (2) [1800 mg, grade 2, related]	0 (0)

None of the patients discontinued the treatment due to AE related to the study drugs

* Regardless of attribution to study treatment or immune relatedness by the investigator; ** No grade 5 AE. AE: Adverse Event; irAE: Immune-related Adverse Event; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase

Figure 3: Best Percent Change from Baseline in Target Lesion (RECIST v1.1)

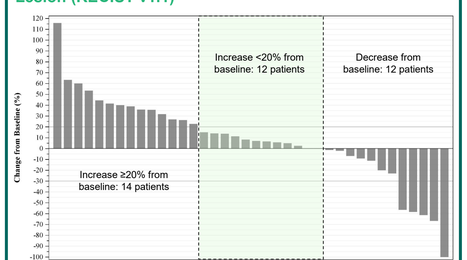
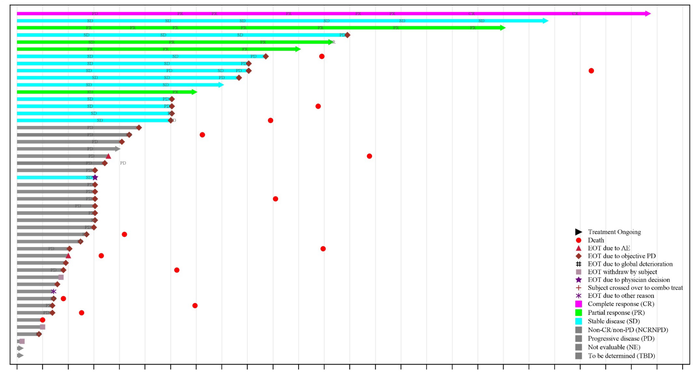


Figure 4: Swimmer Graph of Efficacy



- 49 patients treated to date (includes 5 crossed from mono), 10 ongoing
- Of 39 response-evaluable patients, best overall response (BOR):
  - 4 PR and 1 pathological CR (pCR)
  - 12 SD
- ~44% evaluable patients with SD or better BOR

Figure 5: Patient Vignette of Durable Response in MSS CRC

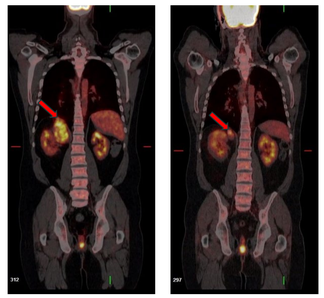
MSS CRC Patient With Pathological Complete Response

Background

- 41-year-old male receiving NGM707 (1800 mg) and pembrolizumab as 4th line therapy
- Primary tumor in colon, target lesions in liver and adrenal gland
- Prior salvage liver surgery and multiple lines of chemo (including FOLFOXIRI + bevacizumab)
- MSS, PD-L1 CPS=1, TMB low

Outcomes

- PR lasting more than 1 year
- Pathological CR after surgical resection of target lesions at 48 weeks
- Ongoing therapy

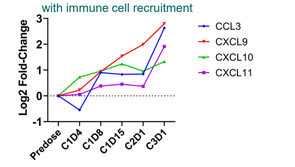


Baseline

Pre-Surgery

Peripheral Blood Biomarker Changes

Increase in chemokines associated with immune cell recruitment



Decrease in CD163 (suppressive marker) on non-classical monocytes

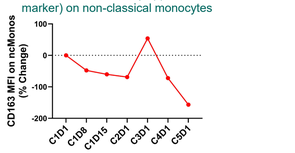
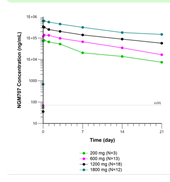
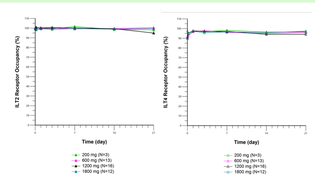


Figure 6: Pharmacokinetic (PK), Receptor Occupancy (RO) and Biomarker Evaluation

Linear PK observed at all NGM707 dose levels

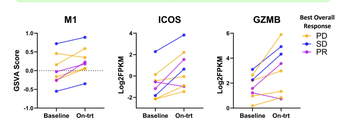


Full peripheral ILT2 and ILT4 RO was maintained throughout the entire dosing window



Monocyte profiles shown; Cycle 2 Day 1 pre-dose PK and RO data were excluded for three subjects who had delayed Day 21 pre-dose sampling (Day 26 or later)

Biomarker changes in paired biopsies in response to NGM707 and pembrolizumab



Gene expression changes associated with myeloid cell and T cell activation reflect the expected mechanism of action of NGM707 and pembrolizumab.

M1 Macrophage gene signature (Combes et al. Cell, 2022) calculated with GSVA. Inducible co-stimulator (ICOS) and Granzyme B (GZMB) are genes associated with T cell activation and tumor killing. On-treatment biopsies were collected between days 14-36 of treatment, C1D15 to C2D15.

Discussion

- Overall safety profile of NGM707 combined with pembrolizumab could provide advantage over more toxic therapies currently used to overcome resistance to anti-PD1/PDL1 therapy.
- Encouraging efficacy signals were observed in several tumor types after previous disease progression on anti-PD1/PDL1 alone or in combination with other agents.
- Durable responses per RECIST 1.1 criteria in heavily pre-treated patients, together with biomarker signaling of immune-suppressive tumor microenvironment (TME) reprogramming, suggest possible clinical opportunities for a novel treatment paradigm.
  - Case study of CR in MSS CRC patient, allowing surgical resection of residual disease with pathological CR, could open potential for perioperative therapy to effectively lower tumor staging and reduce recurrence and metastases in advanced CRC settings.
  - Better understanding of the characteristics of the TME in MSS CRC might enhance new insights into immunotherapy efficacy in advanced CRC settings.
  - Biomarker-based patient selection could enable the identification of MSS CRC patients with the highest probability of responding to NGM707 with anti-PD1; such biomarkers may include PD-L1 expression, tumor inflammation signatures, ILT2/ILT4 ligands and tumor mutational profiles.
- Further data and more mature efficacy data set will guide clinical strategy of NGM707 + anti-PD1/PDL1 future studies.

Conclusions

- NGM707 in combination with pembrolizumab was safe and well tolerated across all dose levels used in the Phase 1/2 dose escalation part of the study.
- Early efficacy signals have been observed in the advanced and metastatic solid tumor settings:
  - Best overall responses were pCR in 1 pt and PR in 4 pts and SD in 12 pts, representing DCR of ~44%
  - 12 pts had reduced target lesion size, with a max of 100%
  - 4 out of 5 patients (1 pCR and 4 PR) were pre-treated with anti-PD1/PDL1
  - 1 patient with MSS CRC achieved pCR and another MSS CRC patient achieved a PR
- Gene expression changes associated with myeloid cell and T cell activation were observed in tumor biopsies post-treatment.*
- NGM707 half-life was 12.8 days.
- Peripheral receptor saturation achieved throughout the dosing interval at doses of ≥ 200 mg Q3W IV.
- NGM707 in combination with pembrolizumab demonstrates encouraging preliminary anti-tumor activity.

* Details presented in a separate poster: AACR 2024 #3641

Acknowledgements

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The study is ongoing. Data was updated on 16 Feb 2024.

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