A phase 1/2, open-label, dose-escalation, safety, and tolerability study of NC762 in subjects with advanced or metastatic solid tumors

NextCure

Abstract #748

Emese Zsiros[1], Satish Shah[2], Martin Gutierrez[3], Megan Nelson[4], Stephanie Kordahi[4], Nadia Myrthil[4], Aaron Morawski[4], Alina Barbu[4], Jahangheer Shaik[4], Chelsea Zhou[4], Chrysi Kanellopoulou[4], Daniel Fitzgerald[4], Dallas B Flies[4], Zac Cusumano[4], Sol Langermann[4], Han Myint[4], Pat LoRusso[5], Kunle Odunsi[6]

1. Roswell Park Comprehensive Cancer Center, Buffalo, NY, 2. Pennsylvania Cancer Specialists, Gettysburg, PA; 3. Hackensack University Medical Center, Hackensack, NJ; 4. NextCure Inc., Beltsville, MD; 5. Yale Cancer Center, New Haven, CT; 6. University of Chicago Comprehensive Cancer Center, Chicago, IL

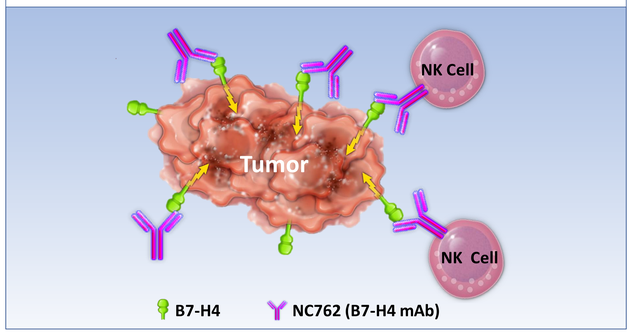
Background

B7-H4 (B7 homolog 4) is a transmembrane protein, associated with the B7 family of molecules known for their immunomodulatory functions. While limited expression is observed on healthy tissue (Sica et al., 2003[1]), B7-H4 is commonly expressed by several tumor types including ovarian, lung, renal, melanoma, prostate, pancreatic, and breast cancers (Choi et al., 2003[2]; Salceda et al., 2005[3]), and is often correlated with poor clinical outcome. Given differential expression of B7-H4 in healthy and cancerous tissues, B7-H4 presents itself as an attractive candidate for a targeted therapeutic monoclonal antibody (mAb) for oncology.

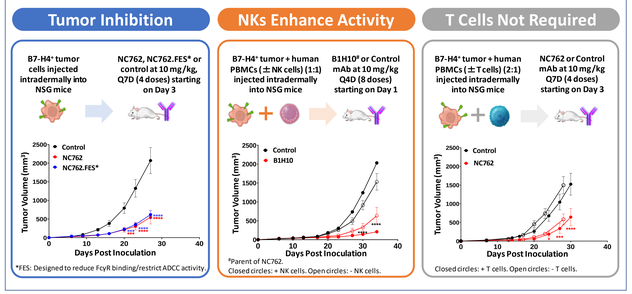
NC762 is a humanized IgG1κ monoclonal antibody that targets human B7-H4. Preclinical data demonstrated that binding of NC762 to tumors expressing B7-H4 results in inhibition of tumor growth *in vivo*. The inhibitory effect on tumor growth is not dependent on T cells and does not appear to be a predominant antibody-dependent cellular cytotoxicity (ADCC) mechanism. However, NC762 has been Fc engineered to enhance binding to CD16A and does demonstrate increased anti-tumor activity in the presence of NK cells.

NC762 is currently being evaluated in a multi-center, first in human, phase 1/2, open-label, single-armed study for multiple solid tumors.

NC762: Mechanism of Action



NC762 Inhibits Human Tumor Growth *In Vivo*



1. Sica et al., *Immunity*. 2003; 18:849-8612011.
2. Choi et al., *J. Immunology*. 2003; 171:4650-4654.
3. Salceda et al., *Exp. Cell Res*. 2005; 306:128-141.

NC762 Study Schema & Demographics

Phase 1a: Dose Escalation

- Locally advanced or metastatic solid tumors
- 3+3 design
- Dosing every 2 weeks

Cohort 1: 0.5 mg/kg
Cohort 2: 1.5 mg/kg
Cohort 3: 5.0 mg/kg
Cohort 4: 10 mg/kg
Cohort 5: 20 mg/kg

Phase 1b: Safety Dose Expansion

- B7H4+ Tumors
- Confirm PK and PD
- Biopsy analysis
- Determine RP2D

Characteristic	All Dose Escalation Subjects (N= 18)
Age, years	
Median (range)	72 (45 – 86)
Sex, n (%)	
Female	8 (44.4%)
Male	10 (55.6%)
ECOG performance status, n (%)	
0	7 (38.9%)
1	11 (61.1%)
Prior systemic anti-cancer regimens	
Median (range)	4 (1 – 7)[a]
Prior Immunotherapy, n (%)	4 (26.7%)[a]
Tumor Types, n	
Colorectal Cancer	5
Lung Cancer	2
Ovarian Cancer[b]	4
Prostate Cancer	4
Pancreatic Cancer	3

a. Calculated with n = 15 due to 3 subjects without prior systemic anti-cancer regimens documented.
b. Inclusive of Mullerian Peritoneal and Primary Peritoneal subjects.

Key Inclusion Criteria

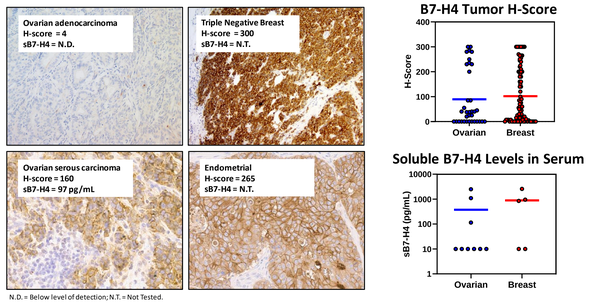
- Men and women aged 18 or older.
- ECOG performance status 0 to 1.
- Phase 1a: Locally advanced or metastatic solid tumors.
- Phase 1b & 2: Subjects with B7-H4+ non-small cell lung (squamous), breast, endometrial, hepatocellular, and ovarian cancer. These proposed indications may change based on emerging data.
- Presence of measurable disease based on RECIST v1.1.

Key Exclusion Criteria

- Active autoimmune disease that required systemic treatment in the past.
- Known active CNS metastases and/or carcinomatous meningitis.
- Known concurrent malignancy that is progressing or requires active treatment, or history of other malignancy within 2 years of study entry.
- Evidence of active, noninfectious pneumonitis or history of interstitial lung disease.
- Documented known activating or driver mutations (i.e., EGFR mutations/ amplification, BRAF mutations, ALK alterations, etc.) which have not been previously treated with a standard of care targeted therapy.
- Subjects with screening QTc interval > 470 milliseconds (corrected by Fridericia) are excluded.
- Active infection requiring systemic therapy.
- Evidence of hepatitis B virus (HBV) or hepatitis C virus (HCV), unless the hepatitis is considered to be cured.

NC762 Biomarker Strategy

Evaluating B7-H4 Tumor Expression & Soluble B7-H4 in Cancer Patients



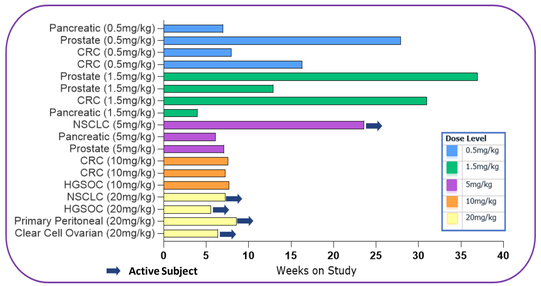
N.D. = Below level of detection; N.T. = Not Tested.

- B7-H4 IHC assay was validated in CLIA laboratory and is ready for prospective screening.
- High expression was identified in women's cancers (ovarian, breast, and endometrial).
- Soluble B7-H4 was observed in patients with high B7-H4 expression on tumor membrane.

NC762 Is Safe & Well Tolerated With Early Signs Of Disease Control

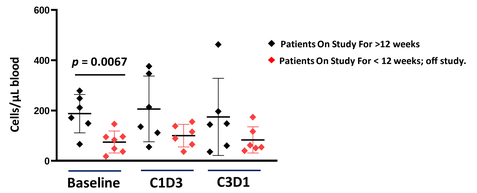
Adverse Event (AE)	0.5mg/kg (N=4) n(%)		1.5mg/kg (N=4) n(%)		5.0mg/kg (N=3) n(%)		10mg/kg (N=3) n(%)		20mg/kg (N=4) n(%)		Subjects (N=18) with AE, n(%)	
	Any Grade	Grade 3-4	Any Grade	Grade 3-4	Any Grade	Grade 3-4	Any Grade	Grade 3-4	Any Grade	Grade 3-4	Any Grade	Grade 3-4
Arthralgias	1(25)	0	0	0	1(33)	0	0	0	0	0	2(11.1)	0
Diarrhea	1(25)	0	0	0	1(33)	0	1(33)	0	0	0	3(16.7)	0
Elevation of alkaline phosphatase	0	0	1(33)	0	0	0	0	0	1(25)	0	2(11.1)	0
Elevation of lipase	1(25)	1(25)	0	0	0	0	0	0	1(25)	0	2(11.1)	1(5.6)
Fatigue	0	0	0	0	2(67)	0	1(33)	0	0	0	3(16.7)	0
Nausea	1(25)	0	0	0	1(33)	0	0	0	1(25)	0	3(16.7)	0

Swimmer Plot



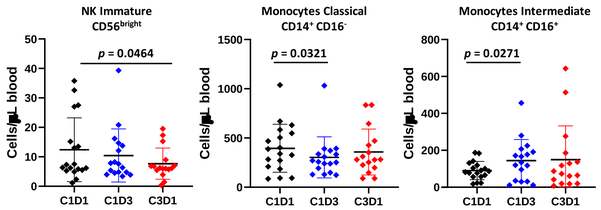
Baseline Cytotoxic NK Cells Associate With Time On Study

Baseline NK Cytotoxic Cells (NK CD56^{dim} CD16^{+})



- Patients that stay on study for > 12 weeks have an elevated number of NK cytotoxic cells (NK CD56^{dim} CD16^{+}) at baseline.

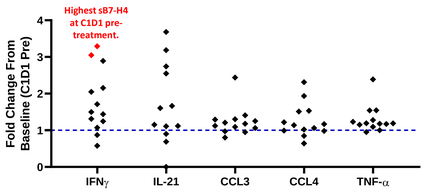
NC762 Induces Changes in NK and Myeloid Populations



- Significant changes in NK and myeloid cell subpopulations were observed at various time points after treatment.
- These changes may suggest immune activation after NC762 treatment.

NC762 Administration Elicits Cytokines & Chemokines Secretion

Cytokines Profiling 24 Hours After Treatment



- Increases in IFN-γ, IL-21, CCL3/MIP1α, CCL4/MIP1β, and TNF-α were observed 24 hours after NC762 treatment.
- Patients with the highest fold change in IFNγ also showed the highest soluble B7-H4 at baseline.

Discussion

- Preliminary analysis of this Phase 1a dose escalation study showed NC762 is safe and tolerable across all 5 Dose Levels up to 20mg/kg with no safety concerns.
- It is encouraging to observe that several subjects remained on study for > 12 weeks, even in lower dose cohorts. All subjects on study treatment in Cohort 5 (20mg/kg) are pending initial disease assessment at this time.
- The following encouraging trends in the peripheral blood biomarkers have been observed:
  - Patients who had a longer duration of time-on-study had a higher number of NK cytotoxic cells (NK CD56dim CD16+) at baseline;
  - Treatment of NC762 is associated with changes in NK and myeloid cell populations, suggesting immune activations upon treatment;
  - Patients with the highest fold change in IFNγ also showed the highest soluble B7-H4 at baseline.
- Phase 1b study is ongoing with the safety expansion, prospectively enrolling subjects with biopsy confirmed B7-H4 positive tumors (non-small cell lung (squamous), breast, endometrial, hepatocellular, and ovarian) to finalize the Recommended Phase 2 Dose.