OPEN-LABEL, PHASE 1 STUDY OF haNK™ FOR INFUSION IN SUBJECTS WITH METASTATIC OR LOCALLY ADVANCED SOLID TUMORS

Study Number:	QUILT-3.028
Principal Investigator:	Name: William J Gradishar, FASCO FACP Address: Northwestern University Feinberg School of Medicine 303 E Chicago Ave Chicago, IL 60611 Email: wgradish@nm.org Office Phone: +1-312-695-4520
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Funded by:	NantKwest, Inc. 9920 Jefferson Blvd Culver City, CA 90232
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Protocol Version	**Date**
Version 1	12 December 2016

STATEMENT OF COMPLIANCE

This trial will be conducted in accordance with Good Clinical Practice (GCP) as described in the International Conference on Harmonization Guideline E6 (ICH E6) and in accordance with United States (US) Code of Federal Regulations (CFR) applicable to clinical studies (45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, and 21 CFR Part 312) and the general ethical principles outlined in the Declaration of Helsinki. The study will receive approval from an Institutional Review Board (IRB) prior to commencement. The Principal Investigator will assure that no deviation from, or changes to the protocol will take place without prior agreement from the sponsor and documented approval from the IRB, except where necessary to eliminate an immediate hazard(s) to the trial participants.

I agree to ensure that all staff members involved in the conduct of this study are informed about their obligations in meeting the above commitments.

Signed: _____ Date: _____

PROTOCOL SYNOPSIS

Name of Sponsor/Company:
NantKwest, Inc.

Name of Investigational Product:
NK-92 [CD16.158V, ER IL-2], Suspension for Intravenous Infusion (haNK™ for Infusion)

Name of Active Ingredient:
NK-92 [CD16.158V, ER IL-2] (high-affinity activated Natural Killer cells, [haNK™])

Title of Study:
Open-label, phase 1 study of haNK™ for Infusion in subjects with metastatic or locally advanced solid tumors.

Study Number:
QUILT-3.028

Study Phase:
Phase 1

Study Objectives:

- The primary objective of this study is to determine the dose-limiting toxicities (DLTs), maximum tolerated dose (MTD) or highest tested dose (HTD), and the overall safety profile of haNK™ for Infusion administered intravenously (IV) once per week in subjects with metastatic or locally advanced solid tumors.
- Secondary objectives are to obtain objective response rate (ORR), progression-free survival (PFS), and overall survival (OS).
- Exploratory objectives include determination of subject immune response to haNK, persistence of haNK, any tumor infiltration by haNK and immune cells, and any correlations between tumor molecular profiles and efficacy.

Study Design:
This is a phase 1 trial in subjects with metastatic or locally advanced solid tumors. The study will be conducted in two parts: part 1 will involve dose escalation using a 3 + 3 design, and part 2 will involve the expansion of the MTD or HTD to further evaluate the safety of haNK. In part 1, 3 to 6 subjects will be sequentially enrolled starting at dose cohort 1, and subjects will be assessed for DLTs.

- Cohort 1: 2×10^9 cells per infusion.
- Cohort 2: 4×10^9 cells per infusion.
- If needed, subjects will be enrolled into a dose de-escalation cohort (cohort -1): 1×10^9 cells per infusion.

In part 2, dose expansion will occur when the MTD or HTD has been determined. An additional 4 subjects may be enrolled in part 2, for a total of up to 10 subjects at the MTD or HTD.

Primary Endpoints:

- MTD or HTD and the incidence of DLTs, treatment-emergent adverse events (AEs), and serious AEs (SAEs).

Secondary Endpoints:

- ORR according to Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 and immune-related response criteria (irRC).
- PFS by RECIST and irRC.
- OS.

Exploratory Endpoints:

- Subject immune response to haNK.
- Persistence of haNK.
- Tumor infiltration by immune cells.
- Tumor infiltration by haNK cells.
- Genomic, transcriptomic, and proteomic profiles and correlations with efficacy.

Enrollment (planned):

The study is a phase 1 trial with a 3 + 3 design. Up to 16 subjects: up to 12 subjects in the dose-escalation part (part 1) and 4 subjects in the dose-expansion part (part 2) of the study.

Eligibility Criteria:

Inclusion Criteria:

- Age ≥ 18 years old.
- Able to understand and provide a signed informed consent that fulfills the relevant IRB or IEC guidelines.
- Histologically confirmed, unresectable, locally advanced or metastatic solid malignancy.
- ECOG performance status of 0 to 2.
- Have at least 1 measurable lesion and/or non-measurable disease evaluable according to RECIST Version 1.1.
- Must have an historic formalin-fixed, paraffin-embedded (FFPE) tumor biopsy specimen ≤ 6 months old and be willing to release the specimen for tumor molecular profiling analysis. If an historic specimen is not available or was taken > 6 months from the date of screening, the subject must be willing to undergo a biopsy during the screening period.
- Must be willing to provide pre- and post-infusion blood samples for exploratory analyses.
- Have received treatment with at least 1 prior line of therapy in the metastatic setting or not be a candidate for therapy of proven efficacy for their disease. Prior immune therapy is allowed.
- Resolution of all toxic side effects of prior chemotherapy, radiotherapy, or surgical procedures to CTCAE grade ≤ 1, with the exception of alopecia.
- Life expectancy ≥ 12 weeks.
- Ability to attend required study visits and return for adequate follow-up, as required by this protocol.
- Agreement to practice effective contraception (both male and female subjects, if the risk of conception exists).

Exclusion Criteria:

- History of persistent grade 2 or higher (CTCAE Version 4.03) hematological toxicity resulting from previous therapy.
- Evidence of central nervous system disease.
- History of other active malignancies or brain metastasis except: controlled basal cell carcinoma or squamous cell carcinoma; prior history of in situ cancer (eg, breast, melanoma, squamous cell carcinoma of the skin, cervical) and > 5 years without evidence of disease; prior history of prostate cancer that is not under active systemic treatment (except hormonal therapy) and with undetectable PSA (< 0.2 ng/mL).
- Serious uncontrolled concomitant disease that would contraindicate the use of the investigational drug used in this study or that would put the subject at high risk for treatment-related complications.
- Systemic autoimmune disease (eg, lupus erythematosus, rheumatoid arthritis, Addison's disease, autoimmune disease associated with lymphoma).
- History of organ transplant requiring immunosuppression.
- History of or active inflammatory bowel disease (eg, Crohn's disease, ulcerative colitis).

- Inadequate organ function, evidenced by the following laboratory results:
  - White blood cell (WBC) count < 3,500 cells/mm^3
  - Absolute neutrophil count < 1,500 cells/mm^3.
  - Platelet count < 100,000 cells/mm^3.
  - Hemoglobin < 9 g/dL.
  - Total bilirubin greater than the upper limit of normal (ULN; unless the subject has documented Gilbert's syndrome).
  - Aspartate aminotransferase (AST [SGOT]) or alanine aminotransferase (ALT [SGPT]) > 2.5 × ULN (> 5 × ULN in subjects with liver metastases).
  - Alkaline phosphatase levels > 2.5 × ULN (> 5 × ULN in subjects with liver metastases, or >10 × ULN in subjects with bone metastases).
  - Serum creatinine > 2.0 mg/dL or 177 µmol/L.
  - International normalized ratio (INR) or activated partial thromboplastin time (aPTT) or partial thromboplastin time (PTT) >1.5 × ULN (unless on therapeutic anti-coagulation).
- Uncontrolled hypertension (systolic > 150 mm Hg and/or diastolic > 100 mm Hg) or clinically significant (ie, active) cardiovascular disease, cerebrovascular accident/stroke, or myocardial infarction within 6 months prior to first study medication; unstable angina; congestive heart failure of New York Heart Association grade 2 or higher; or serious cardiac arrhythmia requiring medication.
- Dyspnea at rest due to complications of advanced malignancy or other disease requiring continuous oxygen therapy.
- Positive results of screening test for human immunodeficiency virus (HIV), hepatitis B virus (HBV), or hepatitis C virus (HCV).
- Current chronic daily treatment (continuous for > 3 months) with systemic corticosteroids (dose equivalent to or greater than 10 mg/day methylprednisolone), excluding inhaled steroids. Short-term steroid use to prevent IV contrast allergic reaction or anaphylaxis in subjects who have known contrast allergies is allowed.
- Known hypersensitivity to any component of the study medication(s).
- Participation in an investigational drug study or history of receiving any investigational treatment within 28 days prior to screening for this study, except for testosterone-lowering therapy in men with prostate cancer.
- Assessed by the investigator to be unable or unwilling to comply with the requirements of the protocol.
- Concurrent participation in any interventional clinical trial.
- Pregnant and nursing women

Investigational Product, Dosage, and Mode of Administration:

haNK™ for Infusion will be administered via IV infusion once per week. The starting dose of haNK will be a total cell count of 2 x 10^9 cells per infusion for the first 3 subjects. Further doses are dependent on the number of observed DLTs.

Duration of Treatment: Subjects will receive experimental treatment until they experience progressive disease (PD) or unacceptable toxicity, withdraw consent, or if the investigator feels it is no longer in their best interest to continue treatment. Treatment will continue for a maximum of 1 year under this protocol or until confirmed disease progression, whichever happens first. If there is evidence of disease progression at any time point after week 6 and it is believed to be unrelated to an inflammatory immune-mediated response, the patient will be withdrawn from the trial.
Duration of Follow-up: After the subject progresses, completes, or withdraws from the study, the subject will be followed every 3 months for 24 months to collect follow-up information, including survival status. Beyond 24 months, the subject will be contacted every 6 months to confirm status.
Reference Therapy, Dosage, and Mode of Administration: Not applicable.

Evaluation of Endpoints:

Safety: Safety endpoints include assessments of DLTs, MTD or HTD, treatment-emergent AEs, SAEs, and clinically significant changes in safety laboratory tests, physical examinations, ECGs, and vital signs. Toxicities will be graded using CTCAE Version 4.03.

Efficacy: ORR and PFS will be assessed by computed tomography (CT) or magnetic resonance imaging (MRI) of target and non-target lesions and will be evaluated according to RECIST Version 1.1 and irRC. OS will also be evaluated.

Exploratory Analyses:

Molecular Profiling and Analysis: Genomic sequencing of tumor cells from tissue relative to non-tumor cells from whole blood will be profiled to identify the genomic variances that may contribute to response or disease progression and provide an understanding of molecular abnormalities. RNA sequencing will be conducted to provide expression data and give relevance to DNA mutations. Quantitative proteomics analysis will be conducted to determine the exact amounts of specific proteins and to confirm expression of genes that are correlative of response and disease progression. All genomic, transcriptomic, and proteomic molecular analyses will be retrospective and exploratory.

Immune Analysis: Immune responses to haNK will be performed on serum samples from whole blood taken at screening, pre haNK infusion and 60 minutes after each haNK infusion at weeks 2, 4, 6, 8, every 4 weeks thereafter, and at the end-of-study visit. Anti-haNK antibodies will be assayed by flow cytometry. Levels of soluble cytokines (eg, interleukin [IL]-6, IL-8, IL-2) will be measured using enzyme-linked immunosorbent assay (ELISA).

haNK Cell Persistence: haNK cells will be quantified in blood by quantitative polymerase chain reaction (qPCR) in week 1, pre haNK infusion, 60 minutes post haNK infusion, and 2 days post haNK infusion; and in week 2 the same day as and before the second infusion of haNK.

Tumor Infiltration: Possible tumor infiltration by haNK and other immune cells (including autologous NK cells and CD8-positive T cells) will be assessed in exploratory tumor biopsies collected 3 to 4 days after haNK infusion. haNK cells will be detected by qPCR or major histocompatibility complex (MHC) haplotyping. Immune cells will be detected by immunohistochemistry (IHC) and fluorescence microscopy.

Tumor biopsies may also be taken at the time of disease progression if pseudo-progression (perceived progression due to inflammation) needs to be excluded and if biopsy analysis may guide treatment decisions.

Statistical Methods:

The dose-escalation part (part 1) of the trial will use a standard 3 + 3 design. In the dose-expansion part (part 2), an additional 4 subjects may be enrolled at the MTD or the HTD so that a total of up to 10 subjects will be treated at the MTD or the HTD.

The rate of DLTs and the MTD or HTD will be assessed. Overall safety will be assessed by descriptive analyses using tabulated frequencies of AEs by grade using CTCAE Version 4.03 in terms of treatment-emergent AEs, SAEs, and clinically significant changes in safety laboratory tests, physical examinations, ECGs, and vital signs. ORR will be evaluated according to RECIST Version 1.1 and irRC at the MTD or the HTD. PFS and OS will be analyzed using Kaplan-Meier methods.

Figure 1: Study Treatment Schema

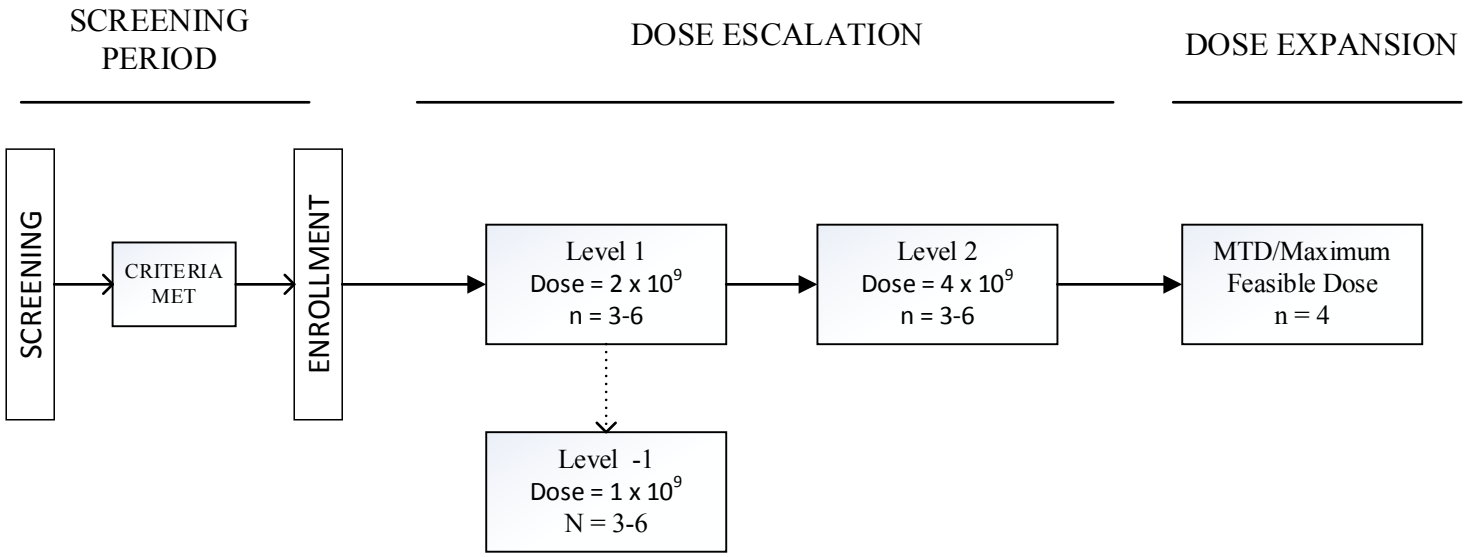

Table 11: Schedule of Events

	Screening	Treatment Period[s]													End of Study (EOS)[p]	Follow-Up[q]	Unscheduled Visit(s)[r]
Study Week		1				2			3			4[s]					
Study Day	-28 to -1	1			3	8			15			22					
		Pre	0	Post		Pre	0	Post	Pre	0	Post	Pre	0	Post			
General Assessments																	
Informed consent	X																
Inclusion/exclusion[a]	X																
Demographics	X																
Medical history[b]	X																
Confirm availability of FFPE tumor sample[c]	X																
Concomitant medications	X	X				X			X			X			X		X
Physical exam: height,[d] weight	X	X				X			X			X			X		X
Vital signs[e]	X	X				X			X			X			X		X
ECOG PS	X	X				X			X			X			X		X
12-lead ECG	X	X				X			X			X			X		
Confirm contraceptive measures	X																
haNK administration			X				X			X			X				
Adverse event collection	X	X		X		X		X	X		X	X		X	X		X
Survival status																X	

	Screening	Treatment Period[s]													End of Study (EOS)[p]	Follow-Up[q]	Unscheduled Visit(s)[r]
Study Week		1				2			3			4[s]					
Study Day	-28 to -1	1			3	8			15			22					
		Pre	0	Post		Pre	0	Post	Pre	0	Post	Pre	0	Post			
Laboratory Assessments																	
Chemistry panel[f]	X	X				X			X			X			X		
Hematology[g]	X	X				X			X			X			X		
Coagulation[h]	X	X				X			X			X			X		
Urinalysis	X	X				X			X			X			X		
Pregnancy test[i]	X	X				X			X			X			X		
Serum virology (HIV, HBV, HCV)[j]	X																
Immune analyses[k]	X					X		X				X		X	X		
Exploratory tumor molecular analysis[l]	X																
haNK cell persistence[m]		X		X	X	X											
Tumor biopsy[n]	X																
Optional tumor biopsy	May be collected at any time point, as clinically indicated.																
Tumor Imaging and Assessments																	
CT/MRI[o]	X														X		

a) Inclusion/exclusion criteria will also be evaluated at enrollment.
b) Medical history will also be evaluated at enrollment.
c) Subject's FFPE tumor tissue block must be ≤ 6 months old prior to first haNK infusion. If not available, a fresh tumor biopsy must be performed. In the event a fresh biopsy needs to be scheduled, the site may consent the subject and schedule the screening visit assessments to be performed such that all assessments fall within 28 days prior to the first dose of haNK.
d) Height required at screening visit only.

e) Vital signs of temperature, heart rate, blood pressure, and respiratory rate will be assessed at every visit. Vitals signs are to be obtained after the subject has been in a seated resting position for at least 5 minutes. Vital signs will be recorded every 15 minutes throughout the haNK infusion and every 30 minutes throughout the post-infusion hydration period.
f) Chemistry panel to include laboratory assessments noted in Table 9.
g) Hematology to include CBC with differential (5 part) and platelets with hemoglobin and hematocrit.
h) Coagulation panel to include PT, INR, and aPTT.
i) Serum pregnancy test at screening; urine dipstick pregnancy test for all other visits.
j) Virology tests include: HIV (as determined by ELISA and confirmed by western blot), HBV/HCV (as determined by HBsAg and hepatitis C serology).
k) Immune analyses via blood draws will be performed at screening, pre haNK infusion and 60 minutes post haNK infusion at weeks 2, 4, 6, and 8, every 4 weeks thereafter, and at the end-of-study visit.
l) Exploratory tumor molecular analysis to be performed at screening on the FFPE tumor block as well as a blood sample provided at the screening visit.
m) Persistence of haNK cells will be determined in whole blood taken in week 1, pre haNK infusion, 60 minutes post haNK infusion, and 2 days post haNK infusion; and in week 2 the same day as and before the second infusion of haNK.
n) Fresh tumor biopsy to be taken if subject's FFPE tumor tissue block is > 6 months old prior to first haNK infusion.
o) Tumor imaging by CT scan or MRI will be performed at screening and every 8 weeks thereafter. Evaluations may include CT or MRI scans of the chest, abdomen, pelvis (optional unless known pelvic disease is present at baseline), and brain (only as clinically warranted based on symptoms/findings). All screening tumor imaging assessments should be performed based on the subject's qualifying scan obtained within 28 days prior to the start of treatment. RECIST and irRC documentation to be completed at each assessment period. The same mode of imaging is required to be carried through each patient's respective treatment period.
p) End-of-study visit must be performed at approximately 28 days (±1 day) after the last haNK infusion.
q) Follow-up for long-term vitals/survival status every 3 months. May be via documented phone contact.
r) Additional assessments performed during an unscheduled visit are at the discretion of the PI or treating physician and must be recorded in the subject's source documents and on the Unscheduled Visit eCRF.
s) Treatment will continue once per week for a maximum of 1 year or until confirmed disease progression, whichever happens first.

APPENDIX 1. SPONSOR SIGNATURE

Study Title:	Open-label, Phase 1 Study of haNK™ for Infusion in Subjects With Metastatic or Locally Advanced Solid Tumors.
Study Number:	QUILT-3.028
Version Number	1
Date:	12 December 2016

This clinical study protocol was subject to critical review and has been approved by NantKwest, Inc.

Signed: _____ Date: 12/13/2016

Andreas Niethammer, MD, PhD
Chief Medical Officer
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Mobile Phone: +1-310-237-3052

OPEN-LABEL, PHASE 1 STUDY OF HANK™ FOR INFUSION IN SUBJECTS WITH METASTATIC OR LOCALLY ADVANCED SOLID TUMORS

Study Number:	QUILT-3.028
Principal Investigator:	Name: Lennie Sender, MD Co-Director, Chan Soon-Shiong Institute for Medicine Address: Chan Soon-Shiong Institute of Medicine Immuno-Oncology Network Mariposa 2040 E. Mariposa Avenue El Segundo, CA 90245 Email: Lennie.Sender@cssifm.com Office Phone: +1-213-266-5600
IND Sponsor:	NantKwest, Inc. 9920 Jefferson Blvd Culver City, CA 90232
Funded by:	NantKwest, Inc. 9920 Jefferson Blvd Culver City, CA 90232
Sponsor Contact: **(For medical questions/emergencies)**	John H. Lee, MD Senior Vice President Adult Medical Affairs, NantKwest Inc. Email: John.Lee@NantKwest.com Mobile Phone: +1-605-610-6391

Protocol Version	**Date**
Version 1	12 December 2016
Version 2	27 July 2017

STATEMENT OF COMPLIANCE

This trial will be conducted in accordance with Good Clinical Practice (GCP) as described in the International Conference on Harmonization Guideline E6 (ICH E6) and in accordance with United States (US) Code of Federal Regulations (CFR) applicable to clinical studies (45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, and 21 CFR Part 312) and the general ethical principles outlined in the Declaration of Helsinki. The study will receive approval from an Institutional Review Board (IRB) prior to commencement. The Principal Investigator will assure that no deviation from, or changes to the protocol will take place without prior agreement from the sponsor and documented approval from the IRB, except where necessary to eliminate an immediate hazard(s) to the trial participants.

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PROTOCOL SYNOPSIS

Name of Sponsor/Company:
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Name of Investigational Product:
NK-92 [CD16.158V, ER IL-2], Suspension for Intravenous Infusion (haNK™ for Infusion)

Name of Active Ingredient:
NK-92 [CD16.158V, ER IL-2] (high-affinity activated Natural Killer cells, [haNK™])

Title of Study:
Open-label, phase 1 study of haNK™ for Infusion in subjects with metastatic or locally advanced solid tumors.

Study Number:
QUILT-3.028

Study Phase:
Phase 1

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- The primary objective of this study is to determine the dose-limiting toxicities (DLTs), maximum tolerated dose (MTD) or highest tested dose (HTD), and the overall safety profile of haNK™ for Infusion administered intravenously (IV) once per week in subjects with metastatic or locally advanced solid tumors.
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- PFS by RECIST and irRC.
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- Subject immune response to haNK.
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- Resolution of all toxic side effects of prior chemotherapy, radiotherapy, or surgical procedures to CTCAE grade ≤ 1, with the exception of alopecia.
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Immune Analysis: Immune responses to haNK will be performed on serum samples from whole blood taken at screening, pre haNK infusion and 60 minutes after each haNK infusion at weeks 2, 4, 6, 8, every 4 weeks thereafter, and at the end-of-study visit. Anti-haNK antibodies will be assayed by flow cytometry. Levels of soluble cytokines (eg, interleukin [IL]-6, IL-8, IL-2) will be measured using enzyme-linked immunosorbent assay (ELISA).

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Tumor Infiltration: Possible tumor infiltration by haNK and other immune cells (including autologous NK cells and CD8-positive T cells) will be assessed in exploratory tumor biopsies collected 3 to 4 days after haNK infusion. haNK cells will be detected by qPCR or major histocompatibility complex (MHC) haplotyping. Immune cells will be detected by immunohistochemistry (IHC) and fluorescence microscopy.

Tumor biopsies may also be taken at the time of disease progression if pseudo-progression (perceived progression due to inflammation) needs to be excluded and if biopsy analysis may guide treatment decisions.

Statistical Methods:

The dose-escalation part (part 1) of the trial will use a standard 3 + 3 design. In the dose-expansion part (part 2), an additional 4 subjects may be enrolled at the MTD or the HTD so that a total of up to 10 subjects will be treated at the MTD or the HTD.

The rate of DLTs and the MTD or HTD will be assessed. Overall safety will be assessed by descriptive analyses using tabulated frequencies of AEs by grade using CTCAE Version 4.03 in terms of treatment-emergent AEs, SAEs, and clinically significant changes in safety laboratory tests, physical examinations, ECGs, and vital signs. ORR will be evaluated according to RECIST Version 1.1 and irRC at the MTD or the HTD. PFS and OS will be analyzed using Kaplan-Meier methods.

Figure 1: Study Treatment Schema

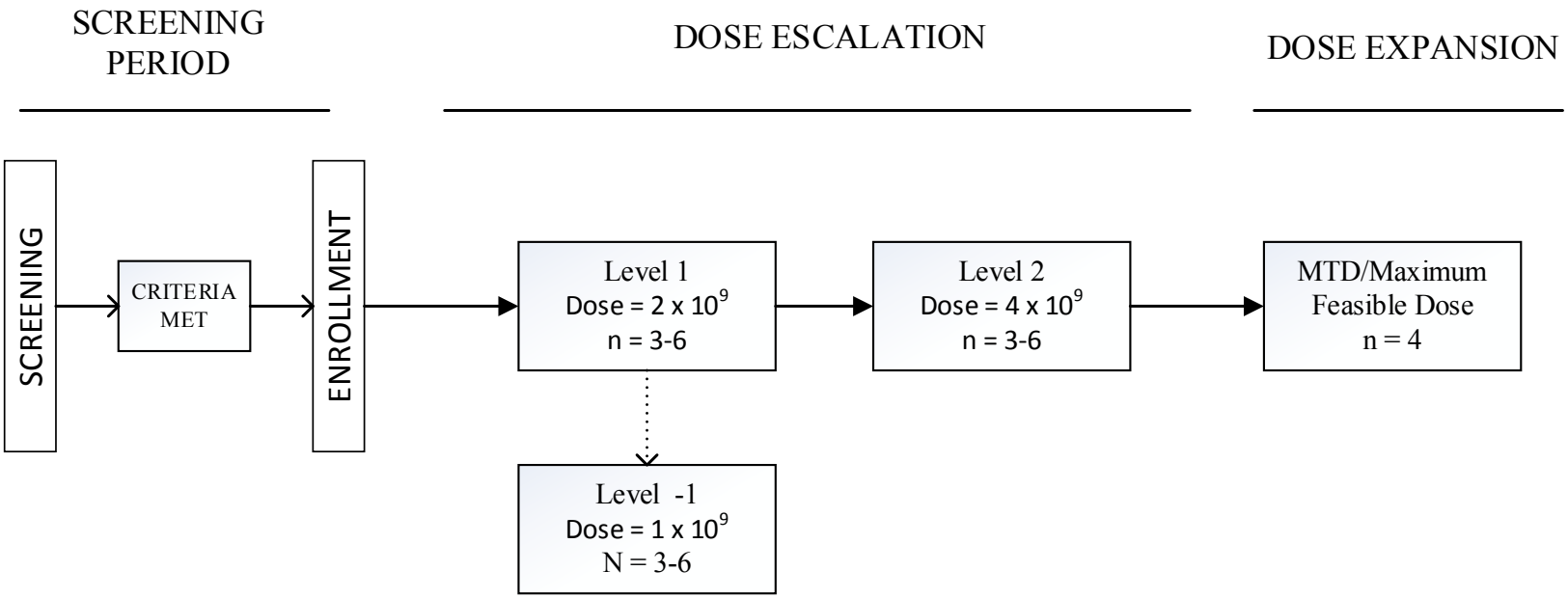

Table 11: Schedule of Events

	Screening	**Treatment Period[s]**													**End of Study (EOS)[p]**	**Follow-Up[q]**	**Unscheduled Visit(s)[r]**
Study Week		1				2			3			4[s]					
Study Day	-28 to -1	1			3	8			15			22					
		Pre	0	Post		Pre	0	Post	Pre	0	Post	Pre	0	Post			
General Assessments																	
Informed consent	X																
Inclusion/exclusion[a]	X																
Demographics	X																
Medical history[b]	X																
Confirm availability of FFPE tumor sample[c]	X																
Concomitant medications	X	X				X			X			X			X		X
Physical exam: height,[d] weight	X	X				X			X			X			X		X
Vital signs[e]	X	X				X			X			X			X		X
ECOG PS	X	X				X			X			X			X		X
12-lead ECG	X	X				X			X			X			X		
Confirm contraceptive measures	X																
haNK administration			X				X			X			X				
Adverse event collection	X	X		X		X		X	X		X	X		X	X		X

	Screening	**Treatment Period[s]**													**End of Study (EOS)[p]**	**Follow-Up[q]**	**Unscheduled Visit(s)[r]**
Study Week		1				2			3			4[s]					
Study Day	-28 to -1	1			3	8			15			22					
		Pre	0	Post		Pre	0	Post	Pre	0	Post	Pre	0	Post			
Survival status																X	
Laboratory Assessments																	
Chemistry panel[f]	X	X				X			X			X			X		
Hematology[g]	X	X				X			X			X			X		
Coagulation[h]	X	X				X			X			X			X		
Urinalysis	X	X				X			X			X			X		
Pregnancy test[i]	X	X				X			X			X			X		
Serum virology (HIV, HBV, HCV)[j]	X																
Immune analyses[k]	X					X		X				X		X	X		
Exploratory tumor molecular analysis[l]	X																
haNK cell persistence[m]		X		X	X	X											
Tumor biopsy[n]	X																
Optional tumor biopsy	May be collected at any time point, as clinically indicated.																
Tumor Imaging and Assessments																	
CT/MRI[o]	X														X		

a) Inclusion/exclusion criteria will also be evaluated at enrollment.
b) Medical history will also be evaluated at enrollment.

c) Subject's FFPE tumor tissue block must be ≤ 6 months old prior to first haNK infusion. If not available, a fresh tumor biopsy must be performed. In the event a fresh biopsy needs to be scheduled, the site may consent the subject and schedule the screening visit assessments to be performed such that all assessments fall within 28 days prior to the first dose of haNK.
d) Height required at screening visit only.
e) Vital signs of temperature, heart rate, blood pressure, respiratory rate, and oxygen saturation will be assessed at every visit. Vitals signs are to be obtained after the subject has been in a seated resting position for at least 5 minutes. Vital signs will be recorded every 15 minutes throughout the haNK infusion and every 30 minutes throughout the post-infusion monitoring period. Oxygen saturation will be measured continuously over the post-infusion monitoring period.
f) Chemistry panel to include laboratory assessments noted in Table 9.
g) Hematology to include CBC with differential (5 part) and platelets with hemoglobin and hematocrit.
h) Coagulation panel to include PT, INR, and aPTT.
i) Serum pregnancy test at screening; urine dipstick pregnancy test for all other visits.
j) Virology tests include: HIV (as determined by ELISA and confirmed by western blot), HBV/HCV (as determined by HBsAg and hepatitis C serology).
k) Immune analyses via blood draws will be performed at screening, pre haNK infusion and 60 minutes post haNK infusion at weeks 2, 4, 6, and 8, every 4 weeks thereafter, and at the end-of-study visit.
l) Exploratory tumor molecular analysis to be performed at screening on the FFPE tumor block as well as a blood sample provided at the screening visit.
m) Persistence of haNK cells will be determined in whole blood taken in week 1, pre haNK infusion, 60 minutes post haNK infusion, and 2 days post haNK infusion; and in week 2 the same day as and before the second infusion of haNK.
n) Fresh tumor biopsy to be taken if subject's FFPE tumor tissue block is > 6 months old prior to first haNK infusion.
o) Tumor imaging by CT scan or MRI will be performed at screening and every 8 weeks thereafter. Evaluations may include CT or MRI scans of the chest, abdomen, pelvis (optional unless known pelvic disease is present at baseline), and brain (only as clinically warranted based on symptoms/findings). All screening tumor imaging assessments should be performed based on the subject's qualifying scan obtained within 28 days prior to the start of treatment. RECIST and irRC documentation to be completed at each assessment period. The same mode of imaging is required to be carried through each patient's respective treatment period.
p) End-of-study visit must be performed at approximately 28 days (±1 day) after the last haNK infusion.
q) Follow-up for long-term vitals/survival status every 3 months. May be via documented phone contact.
r) Additional assessments performed during an unscheduled visit are at the discretion of the PI or treating physician and must be recorded in the subject's source documents and on the Unscheduled Visit eCRF.
s) Treatment will continue once per week for a maximum of 1 year or until confirmed disease progression, whichever happens first.

APPENDIX 1. SPONSOR SIGNATURE

Study Title:	Open-label, Phase 1 Study of haNK™ for Infusion in Subjects With Metastatic or Locally Advanced Solid Tumors.
Study Number:	QUILT-3.028
Version Number	2
Date:	27 July 2017

This clinical study protocol was subject to critical review and has been approved by NantKwest, Inc.

Signed: _____ Date: 7-26-17

John H. Lee, MD
Senior Vice President Adult Medical Affairs, NantKwest Inc.
Email: John.Lee@NantKwest.com
Mobile Phone: +1-605-610-6391

OPEN-LABEL, PHASE 1 STUDY OF HANK™ FOR INFUSION IN SUBJECTS WITH METASTATIC OR LOCALLY ADVANCED SOLID TUMORS

Study Number:	QUILT-3.028
Principal Investigator:	Name: Lennie Sender, MD Co-Director, Chan Soon-Shiong Institute for Medicine Address: Chan Soon-Shiong Institute for Medicine Immuno-Oncology Network Mariposa 2040 E. Mariposa Avenue El Segundo, CA 90245 Email: Lennie.Sender@cssifm.com Office Phone: +1-213-266-5600
IND Sponsor:	NantKwest, Inc. 9920 Jefferson Blvd Culver City, CA 90232
Funded by:	NantKwest, Inc. 9920 Jefferson Blvd Culver City, CA 90232
Sponsor Contact: **(For medical questions/emergencies)**	John H. Lee, MD Senior Vice President Adult Medical Affairs, NantKwest Inc. Email: John.Lee@NantKwest.com Mobile Phone: +1-605-610-6391

Protocol Version	**Date**
Version 1	12 December 2016
Version 2	27 July 2017
Version 3	19 September 2017

STATEMENT OF COMPLIANCE

This trial will be conducted in accordance with Good Clinical Practice (GCP) as described in the International Conference on Harmonization Guideline E6 (ICH E6) and in accordance with United States (US) Code of Federal Regulations (CFR) applicable to clinical studies (45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, and 21 CFR Part 312) and the general ethical principles outlined in the Declaration of Helsinki. The study will receive approval from an Institutional Review Board (IRB) prior to commencement. The Principal Investigator will assure that no deviation from, or changes to the protocol will take place without prior agreement from the sponsor and documented approval from the IRB, except where necessary to eliminate an immediate hazard(s) to the trial participants.

I agree to ensure that all staff members involved in the conduct of this study are informed about their obligations in meeting the above commitments.

Signed: _____ Date: _____

PROTOCOL SYNOPSIS

Name of Sponsor/Company:
NantKwest, Inc.

Name of Investigational Product:
haNK™, NK-92 [CD16.158V, ER IL-2], Suspension for Infusion (haNK™ for Infusion)

Name of Active Ingredient:
NK92 [CD16.158V, ER IL2] cells

Title of Study:
Open-label, phase 1 study of haNK™ for Infusion in subjects with metastatic or locally advanced solid tumors.

Study Number:
QUILT-3.028

Study Phase:
Phase 1

Study Objectives:

- The primary objective of this study is to determine the dose-limiting toxicities (DLTs), maximum tolerated dose (MTD) or highest tested dose (HTD), and the overall safety profile of haNK™ for Infusion administered intravenously (IV) once per week in subjects with metastatic or locally advanced solid tumors.
- Secondary objectives are to obtain objective response rate (ORR), progression-free survival (PFS), and overall survival (OS).
- Exploratory objectives include determination of subject immune response to haNK, pharmacodynamics of haNK, any tumor infiltration by haNK and immune cells, and any correlations between tumor molecular profiles and efficacy.

Study Design:
This is a phase 1 trial in subjects with metastatic or locally advanced solid tumors. The study will be conducted in two parts: part 1 will involve dose escalation using a 3 + 3 design, and part 2 will involve the expansion of the MTD or HTD to further evaluate the safety of haNK. In part 1, 3 to 6 subjects will be sequentially enrolled starting at dose cohort 1, and subjects will be assessed for DLTs.

- Cohort 1: 2×10^9 cells per infusion.
- Cohort 2: 4×10^9 cells per infusion.
- If needed, subjects will be enrolled into a dose de-escalation cohort (cohort -1): 1×10^9 cells per infusion.

In part 2, dose expansion will occur when the MTD or HTD has been determined. An additional 4 subjects may be enrolled in part 2, for a total of up to 10 subjects at the MTD or HTD.

Primary Endpoints:

- MTD or HTD and the incidence of DLTs, treatment-emergent adverse events (AEs), and serious AEs (SAEs).

Secondary Endpoints:

- ORR according to Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 and immune-related response criteria (irRC).
- PFS by RECIST and irRC.
- OS.

Exploratory Endpoints:

- Subject immune response to haNK.
- Pharmacodynamics of haNK.
- Tumor infiltration by immune cells.
- Tumor infiltration by haNK cells.
- Genomic, transcriptomic, and proteomic profiles and correlations with efficacy.

Enrollment (planned):

The study is a phase 1 trial with a 3 + 3 design. Up to 16 subjects: up to 12 subjects in the dose-escalation part (part 1) and 4 subjects in the dose-expansion part (part 2) of the study.

Eligibility Criteria:

Inclusion Criteria:

1. Age ≥ 18 years old.
2. Able to understand and provide a signed informed consent that fulfills the relevant IRB or IEC guidelines.
3. Histologically confirmed, unresectable, locally advanced or metastatic solid malignancy.
4. ECOG performance status of 0 to 2.
5. Have at least 1 measurable lesion and/or non-measurable disease evaluable according to RECIST Version 1.1.
6. Must have a recent formalin-fixed, paraffin-embedded (FFPE) tumor biopsy specimen following the conclusion of the most recent anticancer treatment and be willing to release the specimen for exploratory tumor molecular profiling. If an historic specimen is not available, the subject must be willing to undergo a biopsy during the screening period, if considered safe by the Investigator. If safety concerns preclude collection of a biopsy during the screening period, a tumor biopsy specimen collected prior to the conclusion of the most recent anticancer treatment may be used.
7. Must be willing to provide pre- and post-infusion blood samples for exploratory analyses.
8. Have received treatment with at least 1 prior line of therapy in the metastatic setting or not be a candidate for therapy of proven efficacy for their disease. Prior immune therapy is allowed.
9. Resolution of all toxic side effects of prior chemotherapy, radiotherapy, or surgical procedures to CTCAE grade ≤ 1, with the exception of alopecia.
10. Life expectancy ≥ 12 weeks.
11. Ability to attend required study visits and return for adequate follow-up, as required by this protocol.
12. Agreement to practice effective contraception for female subjects of child-bearing potential and non-sterile males. Female subjects of child-bearing potential are considered all female subjects being physiologically capable of becoming pregnant. Female subjects of child-bearing potential are usually premenopausal women or women with less than 12 months of amenorrhea post-menopause and who have not undergone surgical sterilization. Female subjects of child-bearing potential and non-sterile male subjects must agree to use effective contraception for at least 30 days after the last dose of haNK. Effective contraception includes surgical sterilization (eg, vasectomy, tubal ligation), two forms of barrier methods (eg, condom, diaphragm) used with spermicide, intrauterine devices (IUDs), and abstinence.

Exclusion Criteria:

1. History of persistent grade 2 or higher (CTCAE Version 4.03) hematological toxicity resulting from previous therapy.
2. Serious uncontrolled concomitant disease that would contraindicate the use of the investigational drug used in this study or that would put the subject at high risk for treatment-related complications.
3. Systemic autoimmune disease (eg, lupus erythematosus, rheumatoid arthritis, Addison's disease, autoimmune disease associated with lymphoma).
4. History of organ transplant requiring immunosuppression.
5. History of or active inflammatory bowel disease (eg, Crohn's disease, ulcerative colitis).

6. Inadequate organ function, evidenced by the following laboratory results:
    a. White blood cell (WBC) count < 2,500 cells/mm^3
    b. Absolute neutrophil count < 1,500 cells/mm^3.
    c. Platelet count < 100,000 cells/mm^3.
    d. Hemoglobin < 9 g/dL.
    e. Total bilirubin greater than the upper limit of normal (ULN; unless the subject has documented Gilbert's syndrome).
    f. Aspartate aminotransferase (AST [SGOT]) or alanine aminotransferase (ALT [SGPT]) > 2.5 × ULN (> 5 × ULN in subjects with liver metastases).
    g. Alkaline phosphatase levels > 2.5 × ULN (> 5 × ULN in subjects with liver metastases, or >10 × ULN in subjects with bone metastases).
    h. Serum creatinine > 2.0 mg/dL or 177 μmol/L.
7. Uncontrolled hypertension (systolic > 150 mm Hg and/or diastolic > 100 mm Hg) or clinically significant (ie, active) cardiovascular disease, cerebrovascular accident/stroke, or myocardial infarction within 6 months prior to first study medication; unstable angina; congestive heart failure of New York Heart Association grade 2 or higher; or serious cardiac arrhythmia requiring medication.
8. Dyspnea at rest due to complications of advanced malignancy or other disease requiring continuous oxygen therapy.
9. Positive results of screening test for human immunodeficiency virus (HIV).
10. Current chronic daily treatment (continuous for > 3 months) with systemic corticosteroids (dose equivalent to or greater than 10 mg/day methylprednisolone), excluding inhaled steroids. Short-term steroid use to prevent IV contrast allergic reaction or anaphylaxis in subjects who have known contrast allergies is allowed.
11. Known hypersensitivity to any component of the study medication(s).
12. Participation in an investigational drug study or history of receiving any investigational treatment within 28 days prior to screening for this study, except for testosterone-lowering therapy in men with prostate cancer.
13. Assessed by the Investigator to be unable or unwilling to comply with the requirements of the protocol.
14. Concurrent participation in any interventional clinical trial.
15. Pregnant and nursing women. A negative serum pregnancy test within 72 hours before administration of haNK must be documented before any haNK is administered to a female subject of child-bear potential.

Investigational Product, Dosage, and Mode of Administration:

haNK™ for Infusion will be administered via IV infusion once per week. The starting dose of haNK will be a total cell count of 2 x 10^9 cells per infusion for the first 3 subjects. Further doses are dependent on the number of observed DLTs.

Duration of Treatment: Subjects will receive experimental treatment until they experience progressive disease (PD) or unacceptable toxicity, withdraw consent, or if the investigator feels it is no longer in their best interest to continue treatment. Treatment will continue for a maximum of 1 year under this protocol or until confirmed disease progression, whichever happens first. If there is evidence of disease progression at any time point after week 6 and it is believed to be unrelated to an inflammatory immune-mediated response, the patient will be withdrawn from the trial.
Duration of Follow-up: After the subject progresses, completes, or withdraws from the study, the subject will be followed every 3 months for 24 months to collect follow-up information, including survival status. Beyond 24 months, the subject will be contacted every 6 months to confirm status.
Reference Therapy, Dosage, and Mode of Administration: Not applicable.

Evaluation of Endpoints:

Safety: Safety endpoints include assessments of DLTs, MTD or HTD, treatment-emergent AEs, SAEs, and clinically significant changes in safety laboratory tests, physical examinations, ECGs, and vital signs. Toxicities will be graded using CTCAE Version 4.03.

Efficacy: ORR and PFS will be assessed by computed tomography (CT) or magnetic resonance imaging (MRI) of target and non-target lesions and will be evaluated according to RECIST Version 1.1 and irRC. OS will also be evaluated.

Exploratory Analyses:

Molecular Profiling and Analysis: Genomic sequencing of tumor cells from tissue relative to non-tumor cells from whole blood will be profiled to identify the genomic variances that may contribute to response or disease progression and provide an understanding of molecular abnormalities. RNA sequencing will be conducted to provide expression data and give relevance to DNA mutations. Quantitative proteomics analysis will be conducted to determine the exact amounts of specific proteins and to confirm expression of genes that are correlative of response and disease progression. All genomic, transcriptomic, and proteomic molecular analyses will be retrospective and exploratory.

Immune Analysis: Immune responses to haNK will be performed on serum samples from whole blood taken at screening, pre haNK infusion and 60 minutes after each haNK infusion at weeks 2, 4, 6, 8, every 4 weeks thereafter, and at the end-of-study visit. Anti-haNK antibodies will be assayed by flow cytometry. Levels of soluble cytokines (eg, interleukin [IL]-6, IL-8, IL-2) will be measured using enzyme-linked immunosorbent assay (ELISA).

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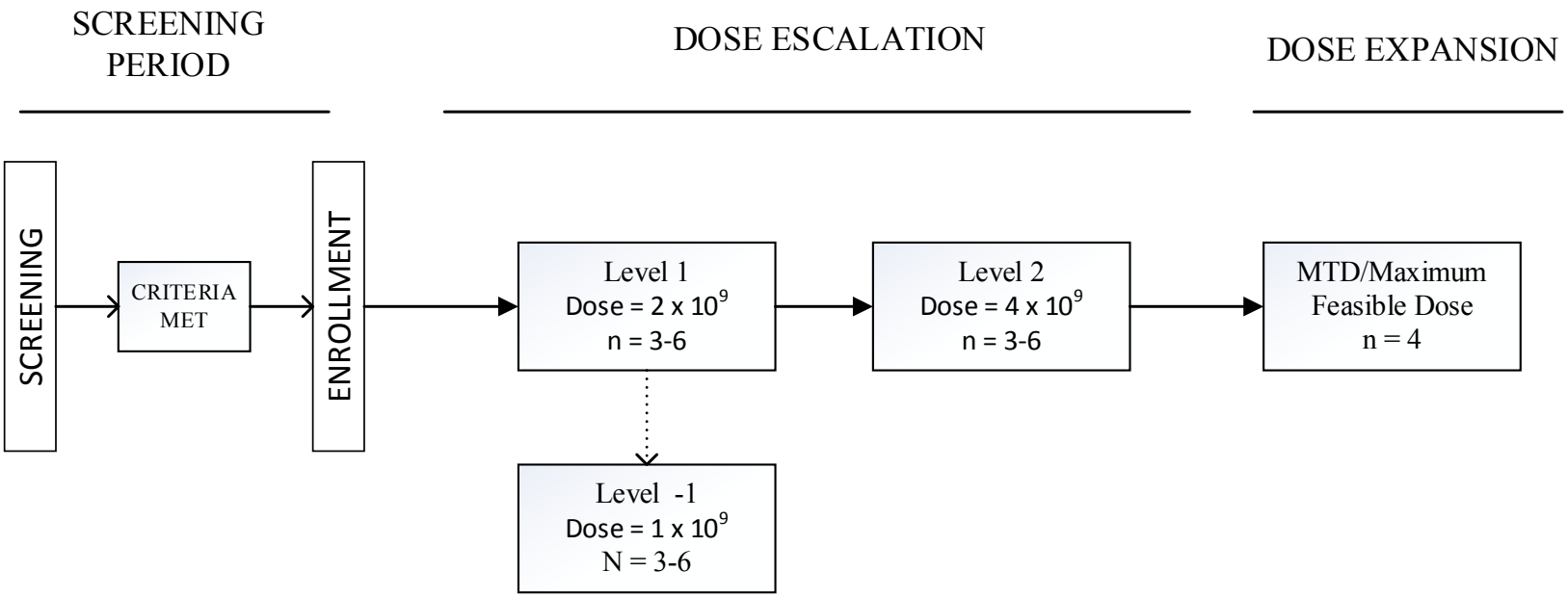

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a) Inclusion/exclusion criteria will also be evaluated at enrollment.
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concerns preclude collection of a biopsy during the screening period, a tumor biopsy specimen collected prior to the conclusion of the most recent anticancer treatment may be used.

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l) Pharmacodynamics of haNK cells will be determined in whole blood taken in week 1, pre haNK infusion, 60 minutes post haNK infusion, and 2 days post haNK infusion; and in week 2 the same day as and before the second infusion of haNK.
m) Fresh tumor biopsy to be taken if subject does not have FFPE tumor tissue block taken after most recent anticancer treatment. If safety concerns preclude collection of a biopsy during the screening period, a tumor biopsy specimen collected prior to the conclusion of the most recent anticancer treatment may be used.
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APPENDIX 1. SPONSOR SIGNATURE

Study Title:	Open-label, Phase 1 Study of haNK™ for Infusion in Subjects With Metastatic or Locally Advanced Solid Tumors.
Study Number:	QUILT-3.028
Version Number	3
Date:	19 September 2017

This clinical study protocol was subject to critical review and has been approved by NantKwest, Inc.

Signed: _____ Date: 9-19-17

John H. Lee, MD
Senior Vice President Adult Medical Affairs,
NantKwest, Inc.
Email: John.Lee@NantKwest.com
Mobile Phone: +1-605-610-6391

OPEN-LABEL, PHASE 1 STUDY OF HANK™ FOR INFUSION IN SUBJECTS WITH METASTATIC OR LOCALLY ADVANCED SOLID TUMORS

Study Number:	QUILT-3.028
Principal Investigator:	Name: Lennie Sender, MD Co-Director, Chan Soon-Shiong Institute for Medicine Address: Chan Soon-Shiong Institute for Medicine Immuno-Oncology Network Mariposa 2040 E. Mariposa Avenue El Segundo, CA 90245 Email: Lennie.Sender@cssifm.com Office Phone: +1-213-266-5600
IND Sponsor:	NantKwest, Inc. 9920 Jefferson Blvd Culver City, CA 90232
Funded by:	NantKwest, Inc. 9920 Jefferson Blvd Culver City, CA 90232
Sponsor Contact: **(For medical questions/emergencies)**	John H. Lee, MD Senior Vice President Adult Medical Affairs, NantKwest Inc. Email: John.Lee@NantKwest.com Mobile Phone: +1-605-610-6391

Protocol Version	**Date**
Version 1	12 December 2016
Version 2	27 July 2017
Version 3	19 September 2017
Version 4	07 December 2017

STATEMENT OF COMPLIANCE

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I agree to ensure that all staff members involved in the conduct of this study are informed about their obligations in meeting the above commitments.

Signed: _____ Date: _____

PROTOCOL SYNOPSIS

Name of Sponsor/Company:
NantKwest, Inc.

Name of Investigational Product:
haNK™, NK-92 [CD16.158V, ER IL-2], Suspension for Infusion (haNK™ for Infusion)

Name of Active Ingredient:
NK92 [CD16.158V, ER IL2] cells

Title of Study:
Open-label, phase 1 study of haNK™ for Infusion in subjects with metastatic or locally advanced solid tumors.

Study Number:
QUILT-3.028

Study Phase:
Phase 1

Study Objectives:

- The primary objective of this study is to determine the dose-limiting toxicities (DLTs), maximum tolerated dose (MTD) or highest tested dose (HTD), and the overall safety profile of haNK™ for Infusion administered intravenously (IV) once per week in subjects with metastatic or locally advanced solid tumors.
- Secondary objectives are to obtain objective response rate (ORR), progression-free survival (PFS), and overall survival (OS).
- Exploratory objectives include determination of subject immune response to haNK, pharmacodynamics of haNK, any tumor infiltration by haNK and immune cells, and any correlations between tumor molecular profiles and efficacy.

Study Design:
This is a phase 1 trial in subjects with metastatic or locally advanced solid tumors. The study will be conducted in two parts: part 1 will involve dose escalation using a 3 + 3 design, and part 2 will involve the expansion of the MTD or HTD to further evaluate the safety of haNK. In part 1, 3 to 6 subjects will be sequentially enrolled starting at dose cohort 1, and subjects will be assessed for DLTs.

- Cohort 1: 2×10^9 cells per infusion.
- Cohort 2: 4×10^9 cells per infusion.
- If needed, subjects will be enrolled into a dose de-escalation cohort (cohort -1): 1×10^9 cells per infusion.

In part 2, dose expansion will occur when the MTD or HTD has been determined. An additional 4 subjects may be enrolled in part 2, for a total of up to 10 subjects at the MTD or HTD.

Primary Endpoints:

- MTD or HTD and the incidence of DLTs, treatment-emergent adverse events (AEs), and serious AEs (SAEs).

Secondary Endpoints:

- ORR according to Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 and immune-related response criteria (irRC).
- PFS by RECIST and irRC.
- OS.

Exploratory Endpoints:

- Subject immune response to haNK.
- Pharmacodynamics of haNK.
- Tumor infiltration by immune cells.
- Tumor infiltration by haNK cells.
- Genomic, transcriptomic, and proteomic profiles and correlations with efficacy.

Enrollment (planned):

The study is a phase 1 trial with a 3 + 3 design. Up to 16 subjects: up to 12 subjects in the dose-escalation part (part 1) and 4 subjects in the dose-expansion part (part 2) of the study.

Eligibility Criteria:

Inclusion Criteria:

1. Age ≥ 18 years old.
2. Able to understand and provide a signed informed consent that fulfills the relevant IRB or IEC guidelines.
3. Histologically confirmed, unresectable, locally advanced or metastatic solid malignancy.
4. ECOG performance status of 0 to 2.
5. Have at least 1 measurable lesion and/or non-measurable disease evaluable according to RECIST Version 1.1.
6. Must have a recent formalin-fixed, paraffin-embedded (FFPE) tumor biopsy specimen following the conclusion of the most recent anticancer treatment and be willing to release the specimen for exploratory tumor molecular profiling. If an historic specimen is not available, the subject must be willing to undergo a biopsy during the screening period, if considered safe by the Investigator. If safety concerns preclude collection of a biopsy during the screening period, a tumor biopsy specimen collected prior to the conclusion of the most recent anticancer treatment may be used.
7. Must be willing to provide pre- and post-infusion blood samples for exploratory analyses.
8. Have received treatment with at least 1 prior line of therapy in the metastatic setting or not be a candidate for therapy of proven efficacy for their disease. Prior immune therapy is allowed.
9. Resolution of all toxic side effects of prior chemotherapy, radiotherapy, or surgical procedures to CTCAE grade ≤ 1, with the exception of alopecia.
10. Life expectancy ≥ 12 weeks.
11. Ability to attend required study visits and return for adequate follow-up, as required by this protocol.
12. Agreement to practice effective contraception for female subjects of child-bearing potential and non-sterile males. Female subjects of child-bearing potential are considered all female subjects being physiologically capable of becoming pregnant. Female subjects of child-bearing potential are usually premenopausal women or women with less than 12 months of amenorrhea post-menopause and who have not undergone surgical sterilization. Female subjects of child-bearing potential and non-sterile male subjects must agree to use effective contraception for at least 60 days (female) and 120 days (male) after the last dose of haNK. Effective contraception includes surgical sterilization (eg, vasectomy, tubal ligation), two forms of barrier methods (eg, condom, diaphragm) used with spermicide, intrauterine devices (IUDs), and abstinence.

Exclusion Criteria:

1. History of persistent grade 2 or higher (CTCAE Version 4.03) hematological toxicity resulting from previous therapy.
2. Serious uncontrolled concomitant disease that would contraindicate the use of the investigational drug used in this study or that would put the subject at high risk for treatment-related complications.
3. Systemic autoimmune disease (eg, lupus erythematosus, rheumatoid arthritis, Addison's disease, autoimmune disease associated with lymphoma).
4. History of organ transplant requiring immunosuppression.
5. History of or active inflammatory bowel disease (eg, Crohn's disease, ulcerative colitis).

6. Inadequate organ function, evidenced by the following laboratory results:
    - White blood cell (WBC) count < 2,500 cells/mm^3
    - Absolute neutrophil count < 1,500 cells/mm^3.
    - Platelet count < 100,000 cells/mm^3.
    - Hemoglobin < 9 g/dL.
    - Total bilirubin greater than the upper limit of normal (ULN; unless the subject has documented Gilbert's syndrome).
    - Aspartate aminotransferase (AST [SGOT]) or alanine aminotransferase (ALT [SGPT]) > 2.5 × ULN (> 5 × ULN in subjects with liver metastases).
    - Alkaline phosphatase levels > 2.5 × ULN (> 5 × ULN in subjects with liver metastases, or >10 × ULN in subjects with bone metastases).
    - Serum creatinine > 2.0 mg/dL or 177 μmol/L.
7. Uncontrolled hypertension (systolic > 150 mm Hg and/or diastolic > 100 mm Hg) or clinically significant (ie, active) cardiovascular disease, cerebrovascular accident/stroke, or myocardial infarction within 6 months prior to first study medication; unstable angina; congestive heart failure of New York Heart Association grade 2 or higher; or serious cardiac arrhythmia requiring medication.
8. Dyspnea at rest due to complications of advanced malignancy or other disease requiring continuous oxygen therapy.
9. Positive results of screening test for human immunodeficiency virus (HIV). However, subjects with HIV are allowed on the study if they meet the following criteria:
    - $CD4^+$ T-cell count >200 cells/mm^3.
    - Stable antiretrovital therapy for at least 12 weeks prior to entry.
    - Plasma HIV RNA levels below lower limit of quantification at screening, and no quantifiable HIV RNA levels within the 12 weeks preceding screening.
10. Current chronic daily treatment (continuous for > 3 months) with systemic corticosteroids (dose equivalent to or greater than 10 mg/day methylprednisolone), excluding inhaled steroids. Short-term steroid use to prevent IV contrast allergic reaction or anaphylaxis in subjects who have known contrast allergies is allowed.
11. Known hypersensitivity to any component of the study medication(s).
12. Participation in an investigational drug study or history of receiving any investigational treatment within 28 days prior to screening for this study, except for testosterone-lowering therapy in men with prostate cancer.
13. Assessed by the Investigator to be unable or unwilling to comply with the requirements of the protocol.
14. Concurrent participation in any interventional clinical trial.
15. Pregnant and nursing women. A negative serum pregnancy test within 72 hours before administration of haNK must be documented before any haNK is administered to a female subject of child-bear potential.

Investigational Product, Dosage, and Mode of Administration:

haNK™ for Infusion will be administered via IV infusion once per week. The starting dose of haNK will be a total cell count of 2 x 10^9 cells per infusion for the first 3 subjects. Further doses are dependent on the number of observed DLTs.

Duration of Treatment: Subjects will receive experimental treatment until they experience progressive disease (PD) or unacceptable toxicity, withdraw consent, or if the investigator feels it is no longer in their best interest to continue treatment. Treatment will continue for a maximum of 1 year under this protocol or until confirmed disease progression, whichever happens first. If there is evidence of disease progression at any time point after week 6 and it is believed to be unrelated to an inflammatory immune-mediated response, the patient will be withdrawn from the trial.
Duration of Follow-up: After the subject progresses, completes, or withdraws from the study, the subject will be followed every 3 months for 24 months to collect follow-up information, including survival status. Beyond 24 months, the subject will be contacted every 6 months to confirm status.
Reference Therapy, Dosage, and Mode of Administration: Not applicable.

Evaluation of Endpoints:

Safety: Safety endpoints include assessments of DLTs, MTD or HTD, treatment-emergent AEs, SAEs, and clinically significant changes in safety laboratory tests, physical examinations, ECGs, and vital signs. Toxicities will be graded using CTCAE Version 4.03.

Efficacy: ORR and PFS will be assessed by computed tomography (CT) or magnetic resonance imaging (MRI) of target and non-target lesions and will be evaluated according to RECIST Version 1.1 and irRC. OS will also be evaluated.

Exploratory Analyses:

Molecular Profiling and Analysis: Genomic sequencing of tumor cells from tissue relative to non-tumor cells from whole blood will be profiled to identify the genomic variances that may contribute to response or disease progression and provide an understanding of molecular abnormalities. RNA sequencing will be conducted to provide expression data and give relevance to DNA mutations. Quantitative proteomics analysis will be conducted to determine the exact amounts of specific proteins and to confirm expression of genes that are correlative of response and disease progression. All genomic, transcriptomic, and proteomic molecular analyses will be retrospective and exploratory.

Immune Analysis: Immune responses to haNK will be performed on serum samples from whole blood taken at screening, pre haNK infusion and 60 minutes after each haNK infusion at weeks 2, 4, 6, 8, every 4 weeks thereafter, and at the end-of-study visit. Anti-haNK antibodies will be assayed by flow cytometry. Levels of soluble cytokines (eg, interleukin [IL]-6, IL-8, IL-2) will be measured using enzyme-linked immunosorbent assay (ELISA).

haNK effect on HIV VL: Plasma-based HIV RNA will be quantified.

haNK Cell Pharmacodynamics: haNK cells will be quantified in blood by quantitative polymerase chain reaction (qPCR) in week 1, pre haNK infusion, 60 minutes post haNK infusion, and 2 days post haNK infusion; and in week 2 the same day as and before the second infusion of haNK.

Tumor Infiltration: Possible tumor infiltration by haNK and other immune cells (including autologous NK cells and CD8-positive T cells) will be assessed in exploratory tumor biopsies collected 3 to 4 days after haNK infusion. haNK cells will be detected by qPCR or major histocompatibility complex (MHC) haplotyping. Immune cells will be detected by immunohistochemistry (IHC) and fluorescence microscopy.

Tumor biopsies may also be taken at the time of disease progression if pseudo-progression (perceived progression due to inflammation) needs to be excluded and if biopsy analysis may guide treatment decisions.

Statistical Methods:

The dose-escalation part (part 1) of the trial will use a standard 3 + 3 design. In the dose-expansion part (part 2), an additional 4 subjects may be enrolled at the MTD or the HTD so that a total of up to 10 subjects will be treated at the MTD or the HTD.

The rate of DLTs and the MTD or HTD will be assessed. Overall safety will be assessed by descriptive analyses using tabulated frequencies of AEs by grade using CTCAE Version 4.03 in terms of treatment-emergent Aes, SAEs, and clinically significant changes in safety laboratory tests, physical examinations, ECGs, and vital signs. ORR will be evaluated according to RECIST Version 1.1 and irRC at the MTD or the HTD. PFS and OS will be analyzed using Kaplan-Meier methods.

Figure 1: Study Treatment Schema

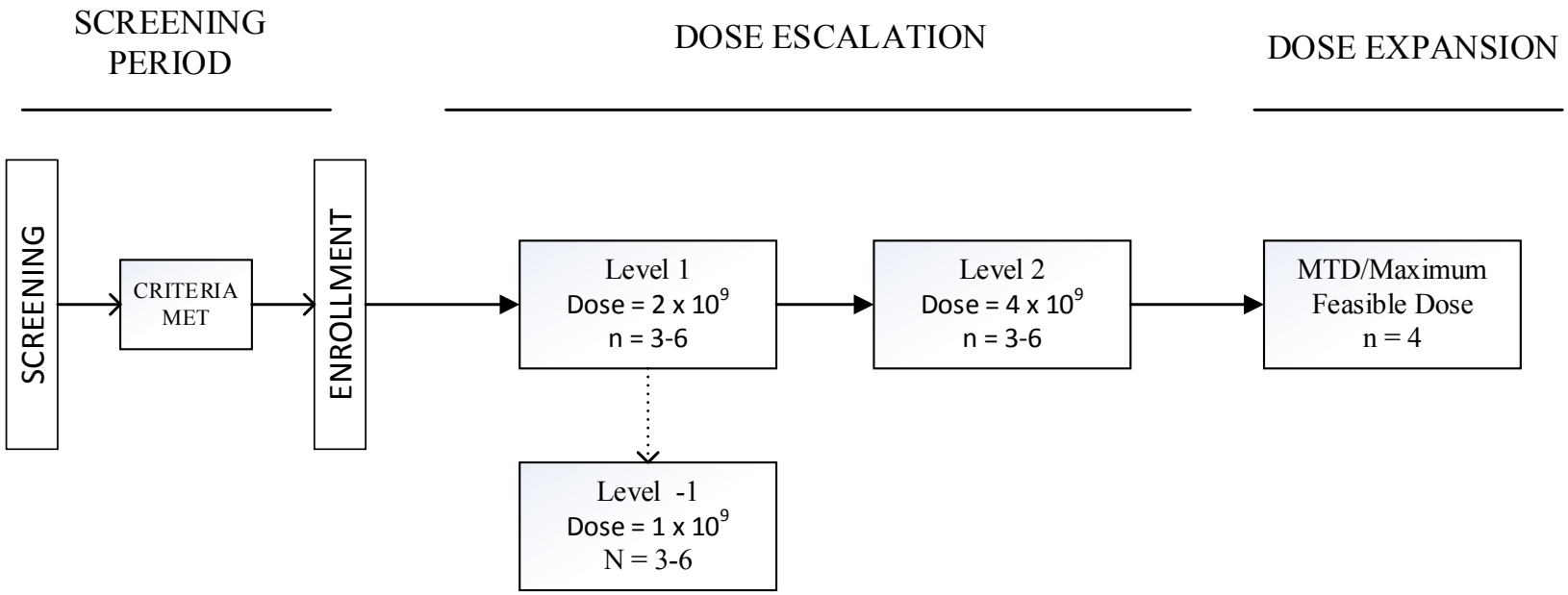

Table 11: Schedule of Events

	Screening	**Treatment Period[r]**													**End of Study (EOS)[o]**	**Follow-Up[p]**	**Unscheduled Visit(s)[q]**
Study Week		1				2			3			4[s]					
Study Day	-28 to -1	1			3	8			15			22					
		Pre	0	Post		Pre	0	Post	Pre	0	Post	Pre	0	Post			
General Assessments																	
Informed consent	X																
Inclusion/exclusion[a]	X																
Demographics	X																
Medical history[b]	X																
Confirm availability of FFPE tumor sample[c]	X																
Concomitant medications	X	X				X			X			X			X		X
Physical exam, height[d], weight	X	X				X			X			X			X		X
Vital signs[e]	X	X				X			X			X			X		X
ECOG PS	X	X				X			X			X			X		X
12-lead ECG	X	X							X						X		
Confirm contraceptive measures	X																
haNK administration			X				X			X			X				
Adverse event collection		X		X		X		X	X		X	X		X	X		X

	Screening	**Treatment Period[r]**													**End of Study (EOS)[o]**	**Follow-Up[p]**	**Unscheduled Visit(s)[q]**
Study Week		1				2			3			4[s]					
Study Day	-28 to -1	1			3	8			15			22					
		Pre	0	Post		Pre	0	Post	Pre	0	Post	Pre	0	Post			
Survival status																X	
Laboratory Assessments																	
Chemistry panel[f]	X	X				X			X			X			X		
Hematology[g]	X	X				X			X			X			X		
Urinalysis	X	X							X						X		
Pregnancy test[h]	X	X													X		
Virology (HIV)[i]	X					X						X					
Immune analyses[j]	X					X		X				X		X	X		
Exploratory tumor molecular analysis[k]	X																
haNK cell pharmacodynamics[l]		X		X	X	X											
Tumor biopsy[m]	X																
Optional tumor biopsy	May be collected at any time point, as clinically indicated.																
Tumor Imaging and Assessments																	
CT/MRI[n]	X														X		

a) Inclusion/exclusion criteria will also be evaluated at enrollment.
b) Medical history will also be evaluated at enrollment.

c) Subject's FFPE tumor tissue sample must be obtained following the conclusion of the most recent anticancer treatment and prior to first study treatment. If not available, a fresh tumor biopsy must be performed. In the event a fresh biopsy needs to be scheduled, the site may consent the subject and schedule the screening visit assessments to be performed such that all assessments fall within 28 days prior to the first dose of any study drug. If safety concerns preclude collection of a biopsy during the screening period, a tumor biopsy specimen collected prior to the conclusion of the most recent anticancer treatment may be used.
d) Height required at screening visit only.
e) Vital signs of temperature, heart rate, blood pressure, respiratory rate, and oxygen saturation will be assessed at every visit. Vitals signs are to be obtained after the subject has been in a seated resting position for at least 5 minutes. Vital signs will be recorded every 15 minutes throughout the haNK infusion and every 30 minutes throughout the post-infusion monitoring period. Oxygen saturation will be measured continuously over the post-infusion monitoring period.
f) Chemistry panel to include laboratory assessments noted in Table 9.
g) Hematology to include CBC with differential (5 part) and platelets with hemoglobin and hematocrit, as well as assessment of CD4 T cell levels.
h) Serum pregnancy test at screening; urine dipstick pregnancy test for all other visits where pregnancy testing is performed.
i) Virology tests include: HIV (as determined by ELISA and confirmed by western blot, or quantification by PCR). Viral load quantification will only be performed during treatment period if subject is determined to have HIV at screening.
j) Immune analyses via blood draws will be performed at screening, pre haNK infusion and 60 minutes post haNK infusion at weeks 2, 4, 6, and 8, every 4 weeks thereafter, and at the end-of-study visit.
k) Exploratory tumor molecular analysis to be performed at screening on the FFPE tumor block as well as a blood sample provided at the screening visit.
l) Pharmacodynamics of haNK cells will be determined in whole blood taken in week 1, pre haNK infusion, 60 minutes post haNK infusion, and 2 days post haNK infusion; and in week 2 the same day as and before the second infusion of haNK.
m) Fresh tumor biopsy to be taken if subject does not have FFPE tumor tissue block taken after most recent anticancer treatment. If safety concerns preclude collection of a biopsy during the screening period, a tumor biopsy specimen collected prior to the conclusion of the most recent anticancer treatment may be used.
n) Tumor imaging by CT scan or MRI will be performed at screening and every 8 weeks thereafter. Evaluations may include CT or MRI scans of the chest, abdomen, pelvis (optional unless known pelvic disease is present at baseline), and brain (only as clinically warranted based on symptoms/findings). All screening tumor imaging assessments should be performed based on the subject's qualifying scan obtained within 28 days prior to the start of treatment. RECIST and irRC documentation to be completed at each assessment period. The same mode of imaging is required to be carried through each patient's respective treatment period.
o) End-of-study visit must be performed at approximately 28 days (±1 day) after the last haNK infusion.
p) Follow-up for long-term vitals/survival status every 3 months. May be via documented phone contact.
q) Additional assessments performed during an unscheduled visit are at the discretion of the PI or treating physician and must be recorded in the subject's source documents and on the Unscheduled Visit eCRF.
r) Treatment will continue once per week for a maximum of 1 year or until confirmed disease progression, whichever happens first.

APPENDIX 1. SPONSOR SIGNATURE

Study Title:	Open-label, Phase 1 Study of haNK™ for Infusion in Subjects With Metastatic or Locally Advanced Solid Tumors.
Study Number:	QUILT-3.028
Version Number	4
Date:	07 December 2017

This clinical study protocol was subject to critical review and has been approved by NantKwest, Inc.

Signed: _____ Date: 12-11-17

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