CLINICAL TRIAL PROTOCOL

Phase II Study of Neukoplast™ (NK-92) Infusions in Patients with Unresectable Stage III (IIIB) or Distant Metastatic (IV) Merkel Cell Carcinoma (MCC)

Protocol Date: October 3, 2014
Protocol Version: 1
Protocol Number: MCC-001

Study Sponsor: Conkwest, Inc.
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Disclosure Statement: This document contains information that is confidential and proprietary to Conkwest. This information is being provided to you solely for the purpose of evaluating and/or conducting a clinical trial for Conkwest. You may disclose the contents of this protocol only to study personnel under your supervision, Independent Ethics Committee/Institutional Review Board or duly authorized representatives of regulatory agencies. The foregoing shall not apply to disclosure required by any regulations; however, you will give prompt notice to Conkwest of any such disclosure.

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1.0 INVESTIGATOR AGREEMENT

I have read the attached Protocol entitled "Phase II Study of Neukoplast™ (NK-92) Infusions in Patients with Unresectable Stage III (IIIB) or Distant Metastatic (IV) Merkel Cell Carcinoma (MCC)" dated October 3, 2014. I agree to abide by all provisions set forth herein. I agree to comply with the International Conference on Harmonization Tripartite Guidelines on Good Clinical Practice, effective in the United States from 9 May 1997, and applicable United States Food and Drug Administration regulations set forth in 21 CFR §50, 54, 56, and 312. I agree to ensure that the confidential information contained in this document will not be used for any purpose other than the evaluation and conduct of the clinical investigation without the prior written consent of Conkwest, Inc.

_____ _____

Signature of Investigator Date

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Printed Name of Investigator

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Address of Investigator

_____

Phone Number of Investigator

2.0 LIST OF ABBREVIATIONS

AE	Adverse Event/Experience
ALT	Alanine transaminase
AST	Aspartate transaminase
BUN	Blood urea nitrogen
CAR	Chimeric antigen receptors
CBC	Complete blood count
CFR	Code of Federal Regulations
CRA	Clinical Research Associate
CRF	Case report form
CRO	Contract research organization
CT	Computed tomography
CTC	Common toxicity criteria
EBV	Epstein-Barr virus
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EC	Ethics Committee
GCP	Good Clinical Practice
HIV	Human immunodeficiency virus
IND	Investigational New Drug
IRB	Institutional Review Board
IV	Intravenous
LDL	Low-density lipoprotein
MCC	Merkel Cell Carcinoma
MCV	Merkel cell polyomavirus
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligram
mm	millimeter
MRI	Magnetic resonance imaging
NCI	National Cancer Institute
NK	Natural Killer
OS	Overall Survival
PFS	Progression free survival
QOL	Quality of Life
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	Serious adverse event
SCID	Severe combined immunodeficiency
SOP	Standard operating procedure
TIL	Tumor infiltrating lymphocytes
WBC	White blood cell

3.0 STUDY SYNOPSIS

Title of Study:

Phase II Study of Neukoplast™ (NK-92) Infusions in Patients with Unresectable Stage III (IIIB) or Distant Metastatic (IV) Merkel Cell Carcinoma (MCC)

Objectives:

Primary Objective:

a) Determine the effect of Neukoplast™ infusions on the 6-month (~24 weeks) progression-free survival (PFS) rate in patients with unresectable stage III (IIIB) or distant metastatic (stage IV) MCC based on Response Evaluation Criteria in Solid Tumors (RECIST) (v1.1).

Secondary Objectives:

a) Determine the overall response rate, as assessed by RECIST at week 24
b) Time to disease progression
c) Median overall survival
d) Assess the safety and toxicity of Neukoplast™
e) Quality of life assessment (FACT-G)

Study Design:

This is a multi-center, non-randomized, open-label, phase II trial to determine the effect of Neukoplast™ infusions in patients with unresectable stage III (IIIB) or distant metastatic (stage IV) MCC. The study will use an adaptive Simon optimal two-stage design. This two-stage design detects efficacy signals, allows for early assessment and avoids enrolling larger numbers of patients in case of inefficacy. In the first stage, 13 patients unresectable stage III (IIIB) or distant metastatic (stage IV) MCC will be screened in order to end up with 12 enrolled and treated. If the treatment combination can improve the 6-month progression free survival (PFS) rate from 4% to 20% [e.g. at least 1 patient out of 12 patients has PFS ≥ 24 weeks (6 months)], then the study will proceed to the second stage, in which 13 more patients will be screened in order to end up with 12 eligible who will be enrolled and treated. In addition, there will be a planned enrollment pause after the first 6 patients are enrolled, in order to assess the safety of Neukoplast™ infusions. Once the 6^h patient completes the first two infusion cycles without any serious treatment related Adverse Events, enrollment may resume (see section 10.3). Neukoplast™ will be given via IV infusion at a dose of 2×10^9 cells/m^2 on two consecutive days (= 1 cycle) every 4 weeks for a total of 6 cycles (12 infusions). If

there is evidence of disease progression, at any time point after the second cycle, the patient will be withdrawn from the trial.

Number of Patients:

Approximately 24 treated

Duration of Treatment:

The total duration of planned treatment is 5 months.

Inclusion Criteria:

1. Male or female patients 18 years of age or older.
2. Patients must have histologically confirmed inoperable Stage III (IIIB) or Stage IV MCC, as defined by the 2010 AJCC staging criteria for MCC[(2)]. Patients with stage IIIB MCC must have been evaluated by a surgical oncologist who has attested that their disease is surgically unresectable. MCC of unknown primary is allowed.
3. Up to two prior cytotoxic chemotherapies for MCC are allowed.
4. ECOG performance status of 0-2.
5. Voluntary written informed consent must be given before performance of any study-related procedure not part of normal medical care, with the understanding that consent may be withdrawn by the patient at any time without prejudice to future medical care.

Exclusion Criteria:

1. Major surgery within 30 days before study entry.
2. Any of the following clinical laboratory values within 21 days prior to enrollment:
   a. Absolute neutrophil count (ANC) < 1,000 cells/mm^3,
   b. Platelets < 50,000 x 10^9/L,
   c. Aspartate aminotransferase or alanine aminotransferase > 2 x the ULN, on condition that these abnormalities are associated with hepatic involvement by the tumor and not due to other hepatic diseases,
   d. Any abnormality of serum creatinine.
3. Liver function abnormalities as indicated by ongoing hepatic enzyme elevation (e.g. AST, ALT, gGT) > 2 times the normal range. Elevation related to direct tumor

infiltration is allowed.

4. Renal insufficiency as indicated by a creatinine level > 2 mg/dl.
5. Myocardial infarction within 6 months prior to enrollment or New York Hospital Association (NYHA) Class III or IV heart failure, uncontrolled angina, severe uncontrolled arrhythmias, or electrocardiographic evidence of acute ischemia or significant conduction system abnormalities in the opinion of the investigator. Prior to study entry any known abnormality on electrocardiogram (ECG) must be determined and documented by the investigator to be not clinically relevant to the patient participation in this study.
6. Any condition, including laboratory abnormalities, that in the opinion of the investigator places the patient at unacceptable risk if he/she were to participate in the study. This includes, but is not limited, to serious medical conditions or psychiatric illness likely to interfere with participation in this clinical study.
7. Female patients who are pregnant or breastfeeding. Female patients of childbearing potential must have a negative pregnancy test and agree to use adequate contraception for the duration of the trial.
8. Patients with other malignancies are not eligible. However, given the frequent coexistence of MCC with other malignancies, the following exceptions are allowed:
    a) If they have been continuously disease-free for any solid tumor malignancy >3 years prior to the time of randomization,
    b) Patients with basal cell carcinoma or squamous cell carcinoma
    c) Patients with prior history of *in situ* cancer (e.g. breast, melanoma, cervical),
    d) Patients with prior history of prostate that is not under active systemic treatment except hormonal therapy, but with undetectable PSA (<0.2ng/mL),
    e) Patients with chronic lymphocytic leukemia are eligible if they have isolated lymphocytosis (Rai stage O) on condition that they do not require systemic treatment for their disease [“B” symptoms, Richter’s transformation, lymphocyte doubling time (<6 months) and they do not have lymphadenopathy of hepatosplenomegaly].
    f) Patients with lymphoma of any type or hairy cell leukemia are eligible on condition that they do not receive active systemic treatment for their hematologic disease and are in complete remission as evidenced by PET/CT scans and bone marrow biopsies for at least 3 months.

Investigational Product and Administration:

Neukoplast™ (from Conkwest, Inc.) will be provided for clinical administration from a GMP contract manufacturer (CMO). The production/expansion (in vitro) of Neukoplast™ will be according to the standard operating procedures on file at GMP cell processing facility in accordance with CMO procedures and in accordance with information contained in BB-IND 8404 entitled "Natural Killer Cell Line, Neukoplast™ (NK-92), Expanded with Interleukin-2 Novartis)"; IND Sponsor: Conkwest, Inc. Cells will be shipped from the CMO to the study site according to validated procedures detailed in the IND. Cells will be washed and concentrated at the clinical site. In order to prevent Neukoplast™ cell proliferation, the Neukoplast™ cells will be irradiated with 1000 cGy prior to infusion at the study site. The cells for the second day infusion will be kept overnight in the Cell Processing facility under controlled conditions and at *room temperature.*

Efficacy Evaluation:

The 6-month PFS rate will be calculated as the number of patients alive and progression free (based on RECIST v1.1) at six months from the date of 1st infusion divided by the total number of patients. For purposes of this analysis, the 6-month PFS rate will be calculated with 6 months being based on greater than or equal to 168 days (e.g., patients alive and progression-free for at least 168 days will be counted in the numerator of the PFS rate calculation).

Safety Evaluation:

Safety and toxicity will be assessed through the analysis of AEs, ECGs, vital signs, changes on physical exams, and laboratory values. All clinically significant findings on any post-baseline tests will be reported as AEs. Adverse events will be coded using the Medical Dictionary for Regulatory Activities. Treatment-emergent AEs will be defined as those events with start dates on or after the date of the first infusion or events that were present prior to the start of treatment but worsened in severity following the first infusion.

Toxicity Stopping Rule:

To avoid exposure of patients to unnecessary toxicity, continuous toxicity monitoring will be performed throughout the study. The trial will be stopped for toxicity if the death rate

attributed to therapy (and not to the natural history of disease) significantly exceeds 5% during the first 12 weeks of treatment. Specifically, using a Pocock type stopping boundary which assumes that the death rate attributed to therapy of 0.05 is the maximum acceptable rate, the trial will be stopped if ≥2 deaths are observed in the first 6 patients or ≥3 deaths are observed in the first 9 patients. If ≥4 deaths are observed in the first cohort of 12 patients, enrollment into the second cohort will be halted. If none of the toxicity stopping rules are met, enrollment into the next cohort may be initiated.

Appendix A – Schedule of Events

Study Period	Screening	Neukoplast™ Treatment				6-Month Follow-up Visit
Study Visits	**Visit 1**	**Visit 2 Cycle 1**	**Visit 3 Cycle 2**	**Pre-Treatment Assessment Visit 4, 6, 8, 10**	**Visit 5, 7, 9, 11 Cycles 3-6**	**Visit 12**
Visit Timeframe / Window	- 21 days	Day 0 (+/- 7 days)	Week 4 (+/- 7 days)	(+/- 3 days)	Weeks 8,12, 16, and 20 (+/- 7 days)	24 weeks
Informed Consent	X					
Eligibility Criteria	X					
Medical History	X					
Physical Exam	X			X		X
Vitals	X	X[1]	X[1]	X	X[1]	X
Height and Weight	X					X
CT/MRI	X					X
12-lead ECG	X			X		X
ECOG	X			X		X
QOL Questionnaire	X			X		X
Pregnancy Test	X			X		X
Chemistries / Hematology	X			X		X
Anti-HLA Antibodies[2]			X[2]			X[2]
Urinalysis	X			X		X
Concomitant Medications	X			X		X
Adverse Events			X	X	X	X
Neukoplast™ Infusion		X	X		X	
Disease Progression [4]				X		X
Survival Status [3]						X

1 - Vital signs will be recorded at 0, 15(+/- 3 minutes), 30(+/- 3 minutes), 60(+/- 5 minutes), 90(+/- 5 minutes) and 120(+/- 5 minutes) post-infusion.

2 - The development of anti-HLA antibodies will be evaluated prior to Cycle 2 and at 6 months.

3 - Patient will be followed for survival status until death or lost to follow-up.

4 - These assessments may include bi-dimensional measurement of disease lesions by palpation, clinical exam, or radiographic imaging (x-ray, computed tomography [CT] scan, positron emission tomography [PET] scan, magnetic resonance imaging [MRI], or ultrasound). The same radiologic imaging method should be used consistently throughout the study to avoid variability in results.

CLINICAL TRIAL PROTOCOL

Phase II Study of Neukoplast™ (NK-92) Infusions in Patients with Unresectable Stage III (IIIB) or Distant Metastatic (IV) Merkel Cell Carcinoma (MCC)

Protocol Date: November 1, 2014
Amendment 1
Protocol Version: 2
Protocol Number: MCC-001

Study Sponsor: Conkwest, Inc.
2533 South Coast Highway 101
Suite 210
Cardiff-by-the-Sea, CA 92007-21333

Sponsor Contact: Karen Nichols
Vice President, Regulatory and Quality
KNichols@Conkwest.com

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1.0 INVESTIGATOR AGREEMENT

I have read the attached Protocol entitled "Phase II Study of Neukoplast™ (NK-92) Infusions in Patients with Unresectable Stage III (IIIB) or Distant Metastatic (IV) Merkel Cell Carcinoma (MCC)" dated November 1, 2014. I agree to abide by all provisions set forth herein. I agree to comply with the International Conference on Harmonization Tripartite Guidelines on Good Clinical Practice, effective in the United States from 9 May 1997, and applicable United States Food and Drug Administration regulations set forth in 21 CFR §50, 54, 56, and 312. I agree to ensure that the confidential information contained in this document will not be used for any purpose other than the evaluation and conduct of the clinical investigation without the prior written consent of Conkwest, Inc.

_____ _____

Signature of Investigator Date

_____

Printed Name of Investigator

_____

Address of Investigator

_____

Phone Number of Investigator

3.0 STUDY SYNOPSIS

Title of Study:

Phase II Study of Neukoplast™ (NK-92) Infusions in Patients with Unresectable Stage III (IIIB) or Distant Metastatic (IV) Merkel Cell Carcinoma (MCC)

Objectives:

Primary Objective:

a) Determine the effect of Neukoplast™ infusions on the 4-month (~16 weeks) progression-free survival (PFS) rate in patients with unresectable stage III (IIIB) or distant metastatic (stage IV) MCC based on Response Evaluation Criteria in Solid Tumors (RECIST) (v1.1).

Secondary Objectives:

a) Determine the overall response rate, as assessed by RECIST at week 16
b) Time to disease progression
c) Median overall survival
d) Assess the safety and toxicity of Neukoplast™
e) Quality of life assessment (FACT-G)

Study Design:

This is a multi-center, non-randomized, open-label, phase II trial to determine the effect of Neukoplast™ infusions in patients with unresectable stage III (IIIB) or distant metastatic (stage IV) MCC. The study will use an adaptive Simon optimal two-stage design. This two-stage design detects efficacy signals, allows for early assessment and avoids enrolling larger numbers of patients in case of inefficacy. In the first stage, 13 patients unresectable stage III (IIIB) or distant metastatic (stage IV) MCC will be screened in order to end up with 12 enrolled and treated. If the treatment combination can improve the 4-month progression free survival (PFS) rate from 4% to 20% [e.g. at least 1 patient out of 12 patients has PFS ≥ 16 weeks (4 months)], then the study will proceed to the second stage, in which 13 more patients will be screened in order to end up with 12 eligible who will be enrolled and treated. In addition, there will be a planned enrollment pause after the first 6 patients are enrolled, in order to assess the safety of Neukoplast™ infusions. Once the 6^h patient completes the first two infusion cycles without any serious treatment related Adverse Events, enrollment may resume (see section 10.3). Neukoplast™ will be given via IV infusion at a dose of 2×10^9 cells/m^2 on two consecutive days (= 1 cycle) every 4 weeks for a total of 4 cycles (8 infusions). If

there is evidence of disease progression believed to be unrelated to an inflammatory immune mediated response, at any time point after the second cycle, the patient will be withdrawn from the trial.

Number of Patients:

Approximately 24 treated in two cohorts of 12 patients.

Duration of Treatment:

The total duration of planned treatment is 4 months.

Inclusion Criteria:

1. Male or female patients 18 years of age or older.
2. Patients must have histologically confirmed inoperable Stage III (IIIB) or Stage IV MCC, as defined by the 2010 AJCC staging criteria for MCC[(2)]. Patients with stage IIIB MCC must have been evaluated by a surgical oncologist who has attested that their disease is surgically unresectable. MCC of unknown primary is allowed.
3. Up to two prior cytotoxic chemotherapies and/or novel immunotherapy treatments for MCC are allowed.
4. ECOG performance status of 0-2.
5. Voluntary written informed consent must be given before performance of any study-related procedure not part of normal medical care, with the understanding that consent may be withdrawn by the patient at any time without prejudice to future medical care.

Exclusion Criteria:

1. Major surgery within 30 days before study entry.
2. Any of the following clinical laboratory values at the time of enrollment:
   a. Absolute neutrophil count (ANC) < 1,000 cells/mm^3,
   b. Platelets < 50,000 x 10^9/L,
   c. Serum creatinine > 2 x the ULN
3. Liver function abnormalities as indicated by ongoing hepatic enzyme elevation (e.g. AST, ALT, gGT) > 2 times the normal range. Elevation related to direct tumor infiltration is allowed.

4. Renal insufficiency as indicated by a creatinine level > 2 x the ULN.
5. Myocardial infarction within 6 months prior to enrollment or New York Hospital Association (NYHA) Class III or IV heart failure, uncontrolled angina, severe uncontrolled arrhythmias, or electrocardiographic evidence of acute ischemia or significant conduction system abnormalities in the opinion of the investigator. Prior to study entry any known abnormality on electrocardiogram (ECG) must be determined and documented by the investigator to be not clinically relevant to the patient participation in this study.
6. Any condition, including laboratory abnormalities, that in the opinion of the investigator places the patient at unacceptable risk if he/she were to participate in the study. This includes, but is not limited, to serious medical conditions or psychiatric illness likely to interfere with participation in this clinical study.
7. Female patients who are pregnant or breastfeeding. Female patients of childbearing potential must have a negative pregnancy test and agree to use adequate contraception for the duration of the trial.
8. Patients with other malignancies are not eligible. However, given the frequent coexistence of MCC with other malignancies, the following exceptions are allowed:
    a) If they have been continuously disease-free for any solid tumor malignancy >3 years prior to the time of enrollment.
    b) Patients with basal cell carcinoma or squamous cell carcinoma
    c) Patients with prior history of *in situ* cancer (e.g. breast, melanoma, squamous cells carcinoma of the skin, cervical),
    d) Patients with prior history of prostate that is not under active systemic treatment except hormonal therapy, but with undetectable PSA (<0.2ng/mL),
    e) Patients with chronic lymphocytic leukemia are eligible if they have isolated lymphocytosis (Rai stage O) on condition that they do not require systemic treatment for their disease [“B” symptoms, Richter’s transformation, lymphocyte doubling time (<6 months) and they do not have lymphadenopathy of hepatosplenomegaly].
    f) Patients with lymphoma of any type or hairy cell leukemia are eligible on condition that they do not receive active systemic treatment for their hematologic disease and are in complete remission as evidenced by PET/CT scans and bone marrow biopsies for at least 3 months.

Investigational Product and Administration:

Neukoplast™ (from Conkwest, Inc.) will be provided for clinical administration from a GMP contract manufacturer (CMO). The production/expansion (in vitro) of Neukoplast™ will be according to the standard operating procedures on file at GMP cell processing facility in accordance with CMO procedures and in accordance with information contained in BB-IND 8404 entitled "Natural Killer Cell Line, Neukoplast™ (NK-92), Expanded with Interleukin-2 Novartis)"; IND Sponsor: Conkwest, Inc. Cells will be shipped from the CMO to the study site according to validated procedures detailed in the IND. Cells will be washed and concentrated at the clinical site. In order to prevent Neukoplast™ cell proliferation, the Neukoplast™ cells will be irradiated with 1000 cGy prior to infusion at the study site. The cells for the second day infusion will be kept overnight in the Cell Processing facility under controlled conditions and at *room temperature.*

Efficacy Evaluation:

The 4-month PFS rate will be calculated as the number of patients alive and progression free (based on RECIST v1.1) at four months from the date of 1st infusion divided by the total number of patients. For purposes of this analysis, the 4-month PFS rate will be calculated with 4 months being based on greater than or equal to 112 days (e.g., patients alive and progression-free for at least 112 days will be counted in the numerator of the PFS rate calculation).

Safety Evaluation:

Safety and toxicity will be assessed through the analysis of AEs, ECGs, vital signs, changes on physical exams, and laboratory values. All clinically significant findings on any post-baseline tests will be reported as AEs. Adverse events will be coded using the Medical Dictionary for Regulatory Activities. Treatment-emergent AEs will be defined as those events with start dates on or after the date of the first infusion or events that were present prior to the start of treatment but worsened in severity following the first infusion.

Toxicity Stopping Rule:

To avoid exposure of patients to unnecessary toxicity, continuous toxicity monitoring will be performed throughout the study. The trial will be stopped for toxicity if the death rate

attributed to therapy (and not to the natural history of disease) significantly exceeds 5% during the first 12 weeks of treatment. Specifically, using a Pocock type stopping boundary which assumes that the death rate attributed to therapy of 0.05 is the maximum acceptable rate, the trial will be stopped if ≥2 deaths are observed in the first 6 patients or ≥3 deaths are observed in the first 9 patients. If ≥4 deaths are observed in the first cohort of 12 patients, enrollment into the second cohort will be halted. If none of the toxicity stopping rules are met, enrollment into the next cohort may be initiated.

Appendix A – Schedule of Events

Study Period	Screening	Neukoplast™ Treatment				4-Month Follow-up Visit
Study Visits	**Visit 1**	**Visit 2 Cycle 1**	**Visit 3 Cycle 2**	**Pre-Treatment Assessment Visit 4, 6**	**Visit 5, 7 Cycles 3 & 4**	**Visit 8**
Visit Timeframe / Window	- 21 days	Day 0 (+/- 7 days)	Week 4 (+/- 7 days)	Within 2 weeks of next cycle	Weeks 8 &12 (+/- 7 days)	16 weeks
Informed Consent	X					
Eligibility Criteria	X					
Medical History	X					
Physical Exam	X			X		X
Vitals	X	X[1]	X[1]	X	X[1]	X
Height and Weight	X					X
CT/MRI	X					X
12-lead ECG	X			X		X
ECOG	X			X		X
QOL Questionnaire	X			X		X
Pregnancy Test	X			X		X
Chemistries / Hematology	X			X		X
Anti-HLA Antibodies[2]			X[2]			X[2]
Urinalysis	X			X		X
Concomitant Medications	X			X		X
Adverse Events			X	X	X	X
Neukoplast™ Infusion		X	X		X	
Disease Progression [4]				X		X
Survival Status [3]						X

1 - Vital signs will be recorded at 0, 15(+/- 3 minutes), 30(+/- 3 minutes), 60(+/- 5 minutes), 90(+/- 5 minutes) and 120(+/- 5 minutes) post-infusion.

2 - The development of anti-HLA antibodies will be evaluated prior to Cycle 2 and at 4 months.

3 - Patient will be followed for survival status until death or lost to follow-up.

4 - These assessments may include bi-dimensional measurement of disease lesions by palpation, clinical exam, or radiographic imaging (x-ray, computed tomography [CT] scan, positron emission tomography [PET] scan, magnetic resonance imaging [MRI], or ultrasound). The same radiologic imaging method should be used consistently throughout the study to avoid variability in results.

CLINICAL TRIAL PROTOCOL

Phase II Study of Neukoplast™ (NK-92) Infusions in Patients with Unresectable Stage III (IIIB) or Distant Metastatic (IV) Merkel Cell Carcinoma (MCC)

Protocol Date: April 1, 2015
Amendment 2
Protocol Version: 3
Protocol Number: MCC-001

Study Sponsor: Conkwest, Inc.
2533 South Coast Highway 101
Suite 210
Cardiff-by-the-Sea, CA 92007-21333

Sponsor Contact: Karen Nichols
Vice President, Regulatory and Quality
KNichols@Conkwest.com

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_____ _____

Signature of Investigator Date

_____

Printed Name of Investigator

_____

Address of Investigator

_____

Phone Number of Investigator

2.0 LIST OF ABBREVIATIONS

AE	Adverse Event/Experience
ALT	Alanine transaminase
AST	Aspartate transaminase
BUN	Blood urea nitrogen
CAR	Chimeric antigen receptors
CBC	Complete blood count
CFR	Code of Federal Regulations
CRA	Clinical Research Associate
CRF	Case report form
CRO	Contract research organization
CT	Computed tomography
CTC	Common toxicity criteria
EBV	Epstein-Barr virus
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EC	Ethics Committee
FACT-G	Functional Assessment of Cancer Therapy - General
GCP	Good Clinical Practice
HIV	Human immunodeficiency virus
HLA	Human Leukocyte Antigen
IND	Investigational New Drug
IRB	Institutional Review Board
ISF	Investigator Site File
IV	Intravenous
LDL	Low-density lipoprotein
MCC	Merkel Cell Carcinoma
MCV	Merkel cell polyomavirus
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligram
mm	millimeter
MRI	Magnetic resonance imaging
NCI	National Cancer Institute
NK	Natural Killer
OS	Overall Survival
PFS	Progression free survival
QOL	Quality of Life
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	Serious adverse event
SCID	Severe combined immunodeficiency
SOP	Standard operating procedure
TIL	Tumor infiltrating lymphocytes
TTP	Time to disease progression
WBC	White blood cell

3.0 STUDY SYNOPSIS

Title of Study:

Phase II Study of Neukoplast™ (NK-92) Infusions in Patients with Unresectable Stage III (IIIB) or Distant Metastatic (IV) Merkel Cell Carcinoma (MCC)

Objectives:

Primary Objective:

a) Determine the effect of Neukoplast™ infusions on the 4-month (~16 weeks) progression-free survival (PFS) rate in patients with unresectable stage III (IIIB) or distant metastatic (stage IV) MCC based on Response Evaluation Criteria in Solid Tumors (RECIST) (v1.1).

Secondary Objectives:

a) Determine the overall response rate, as assessed by RECIST at week 16
b) Time to disease progression
c) Median overall survival
d) Assess the safety and toxicity of Neukoplast™
e) Quality of life assessment (FACT-G)

Study Design:

This is a multi-center, non-randomized, open-label, phase II trial to determine the effect of Neukoplast™ infusions in patients with unresectable stage III (IIIB) or distant metastatic (stage IV) MCC. The study will use an adaptive Simon optimal two-stage design. This two-stage design detects efficacy signals, allows for early assessment and avoids enrolling larger numbers of patients in case of inefficacy. In the first stage, 12 patients with unresectable stage III (IIIB) or distant metastatic (stage IV) MCC will be enrolled and treated. If the treatment combination in the first stage can improve the 4-month progression free survival (PFS) rate from 4% to 20% [e.g. at least 1 patient out of 12 patients has PFS ≥ 16 weeks (4 months)], then the study will proceed to the second stage, in which 12 more patients will be enrolled and treated. In addition, there will be a planned Protocol Safety Committee meeting after the first 6 patients are enrolled in order to assess the safety of Neukoplast™ infusions (see section 10.3). Neukoplast™ will be given via IV infusion at a dose of 2 x 10^9 cells/m^2 on two consecutive days (= 1 cycle) every 4 weeks for a total of 4 cycles (8 infusions). If there is evidence of disease

progression believed to be unrelated to an inflammatory immune mediated response, at any time point after the second cycle, the patient will be withdrawn from the trial.

Number of Patients:

Approximately 24 treated in two consecutive cohorts of 12 patients.

Duration of Treatment:

The total duration of planned treatment is 4 months.

Inclusion Criteria:

1. Male or female patients 18 years of age or older.
2. Patients must have histologically confirmed Merkel Cell Carcinoma (MCC) that is inoperable Stage III (IIIB) or Stage IV, as defined by the 2010 AJCC staging criteria for MCC[(2)]. Patients with stage IIIB MCC must have been evaluated by a surgical oncologist who has documented that their disease is surgically unresectable. MCC of unknown primary is allowed.
3. Up to two prior cytotoxic chemotherapies and/or novel immunotherapy treatments for MCC are allowed.
4. ECOG performance status of 0-2.
5. Voluntary written informed consent must be given before performance of any study-related procedure not part of normal medical care, with the understanding that consent may be withdrawn by the patient at any time without prejudice to future medical care.

Exclusion Criteria:

1. Major surgery within 30 days before study entry.
2. Any of the following clinical laboratory values at the time of enrollment:
   a. Absolute neutrophil count (ANC) < 1,000 cells/mm^3,
   b. Platelets < 50,000 x 10^9/L
3. Liver function abnormalities as indicated by ongoing hepatic enzyme elevation (e.g. AST, ALT, GGT) > 2x the ULN. Elevation related to direct tumor infiltration is allowed.
4. Renal insufficiency as indicated by a creatinine level > 2 x the ULN.
5. Myocardial infarction within 6 months prior to enrollment or New York Hospital

Association (NYHA) Class III or IV heart failure, uncontrolled angina, severe uncontrolled arrhythmias, or electrocardiographic evidence of acute ischemia or significant conduction system abnormalities in the opinion of the Investigator. Prior to study entry any known abnormality on electrocardiogram (ECG) must be determined and documented by the Investigator to be not clinically significant to the patient participation in this study.

6. Any condition, including laboratory abnormalities, that in the opinion of the investigator places the patient at unacceptable risk if he/she were to participate in the study. This includes, but is not limited, to serious medical conditions or psychiatric illness likely to interfere with participation in this clinical study.
7. Female patients who are pregnant or breastfeeding. Female patients of childbearing potential must have a negative pregnancy test and agree to use adequate contraception for the duration of the trial.
8. Patients with other malignancies are not eligible. However, given the frequent coexistence of MCC with other malignancies, the following exceptions are allowed:
    a) If they have been continuously disease-free for any solid tumor malignancy >3 years prior to the time of enrollment.
    b) Patients with basal cell carcinoma or squamous cell carcinoma
    c) Patients with prior history of *in situ* cancer (e.g. breast, melanoma, squamous cells carcinoma of the skin, cervical),
    d) Patients with prior history of prostate cancer that is not under active systemic treatment except hormonal therapy, but with undetectable PSA (<0.2ng/mL),
    e) Patients with chronic lymphocytic leukemia are eligible if they have isolated lymphocytosis (Rai stage O) on the condition that they do not require systemic treatment for their disease [“B” symptoms, Richter’s transformation, lymphocyte doubling time (<6 months) and they do not have lymphadenopathy of hepatosplenomegaly].
    f) Patients with lymphoma of any type or hairy cell leukemia are eligible on the condition that they do not receive active systemic treatment for their hematologic disease and are in complete remission as evidenced by PET/CT scans and bone marrow biopsies for at least 3 months.
9. Patients on immunosuppressants, systemic corticosteroids or any other

investigational product.

Investigational Product and Administration:

Neukoplast™ (from Conkwest, Inc.) will be provided for clinical administration from a GMP contract manufacturer (CMO). The production/expansion (in vitro) of Neukoplast™ will be according to the standard operating procedures on file at the GMP cell processing facility in accordance with CMO procedures and in accordance with information contained in BB-IND 8404 entitled "Natural Killer Cell Line, Neukoplast™ (NK-92), Expanded with Interleukin-2 (Novartis)"; IND Sponsor: Conkwest, Inc. Cells will be shipped from the CMO to the study site according to validated procedures detailed in the IND. Cells will be washed and concentrated at the clinical site. In order to prevent Neukoplast™ cell proliferation, the Neukoplast™ cells will be irradiated with 1000 cGy prior to infusion at the study site. The cells for the second day infusion will be kept overnight in the Cell Processing facility under controlled cell culture incubator conditions.

Efficacy Evaluation:

The 4-month PFS rate will be calculated as the number of patients alive and progression free (based on RECIST v1.1) at four months from the date of 1st infusion divided by the total number of patients. For purposes of this analysis, the 4-month PFS rate will be calculated with 4 months being based on greater than or equal to 112 days (e.g., patients alive and progression-free for at least 112 days will be counted in the numerator of the PFS rate calculation).

Safety Evaluation:

Safety and toxicity will be assessed through the analysis of AEs, ECGs, vital signs, changes on physical exams, and laboratory values. All clinically significant findings on any post-baseline tests will be reported as AEs. Adverse events will be coded using the Medical Dictionary for Regulatory Activities. Treatment-emergent AEs will be defined as those events with start dates on or after the date of the first infusion or events that were present prior to the start of treatment but worsened in severity following the first infusion on Cycle 1/Day 1.

Toxicity Stopping Rule:

To avoid exposure of patients to unnecessary toxicity, continuous toxicity monitoring will be performed throughout the study. The trial will be stopped for toxicity if the death rate attributed to therapy (and not to the natural history of disease) significantly exceeds 5% during the first 12 weeks of treatment. Specifically, using a Pocock type stopping boundary which assumes that the death rate attributed to therapy of 0.05 is the maximum acceptable rate, the trial will be stopped if □2 deaths are observed in the first 6 patients or □3 deaths are observed in the first 9 patients. If □4 deaths are observed in the first cohort of 12 patients, enrollment into the second cohort will be halted. If none of the toxicity stopping rules are met, enrollment into the next cohort may be initiated.

Appendix A – Schedule of Events

Study Period	Screening	Neukoplast™ Treatment				4-Month Follow-up
Study Visits	**Visit 1**	**Visit 2 Cycle 1**	**Visit 3 Cycle 2**	**Pre-Infusion Assessment Visit 4, 6**	**Visit 5, 7 Cycles 3 & 4**	**Visit 8**
Visit Timeframe / Window	- 21 days	Day 0 (+/- 7 days)	Week 4 (+/- 7 days)	Within 2 weeks of next cycle	Weeks 8 &12 (+/- 7 days)	16 weeks
Informed Consent	X					
Eligibility Criteria	X					
Medical History	X					
Physical Exam	X			X		X
Vitals	X	X[1]	X[1]	X	X[1]	X
Height and Weight	X	X	X		X	X
CT/MRI	X					X
12-lead ECG	X			X		X
ECOG	X			X		X
QOL Questionnaire	X			X		X
Pregnancy Test	X			X		X
Chemistries / Hematology/UA	X			X		X
Immunologic Studies[2]	X[2]		X[2]		X[2]	X[2]
Concomitant Medications	X			X		X
Adverse Events			X	X	X	X
Tumor Biopsy (Optional)[5]		X				
Neukoplast™ Infusion		X	X		X	
Disease Progression [4]				X		X
Survival Status [3]						X

1 - Vital signs will be recorded at 0, 15(+/- 3 minutes), 30(+/- 3 minutes), 60(+/- 5 minutes), 90(+/- 5 minutes) and 120(+/- 5 minutes) from the start of the infusion..

2 - The development of NK-92-specific HLA antibodies and NK-92-specific T-Cell response will be evaluated at baseline, 4 weeks and 8 weeks post Cycle 1/Day 2. The 4-week sample will be collected prior to the administration of Cycle 2 and the 8-week sample will be collected prior to the administration of Cycle 3.

3 - Patient will be followed for survival status until death or lost to follow-up.

4 - These assessments may include bi-dimensional measurement of disease lesions by palpation, clinical exam, or radiographic imaging (x-ray, computed tomography [CT] scan, positron emission tomography [PET] scan, magnetic resonance imaging [MRI], or ultrasound). The same radiologic imaging method should be used consistently throughout the study to avoid variability in results.

5 - In order to examine possible tumor infiltration by NK-92, an *optional* biopsy will be collected approximately 5-7 days after Cycle 1 completion (Cycle 1/Day 2). This biopsy will be optional depending on the patient situation and the location of the tumor and will be collected according tot eh site's standard of care procedures (see section 8.8.2).

CLINICAL TRIAL PROTOCOL

Phase II Study of aNK (activated NK-92, formerly Neukoplast) Infusions in Patients with Unresectable Stage III (IIIB) or Distant Metastatic (IV) Merkel Cell Carcinoma (MCC)

Protocol Date: October 20, 2015
Amendment 3
Protocol Version: 4
Protocol Number: MCC-001

Study Sponsor: NantKwest, Inc.
2533 South Coast Highway 101
Suite 210
Cardiff-by-the-Sea, CA 92007-21333

Sponsor Contact: Karen Nichols
Vice President, Regulatory and Quality
Karen.Nichols@NantKwest.com

Disclosure Statement: This document contains information that is confidential and proprietary to NantKwest. This information is being provided to you solely for the purpose of evaluating and/or conducting a clinical trial for NantKwest. You may disclose the contents of this protocol only to study personnel under your supervision, Independent Ethics Committee/Institutional Review Board or duly authorized representatives of regulatory agencies. The foregoing shall not apply to disclosure required by any regulations; however, you will give prompt notice to NantKwest of any such disclosure.

1.0 INVESTIGATOR AGREEMENT

I have read the attached Protocol entitled “Phase II Study of aNK (activated NK-92, formerly Neukoplast) Infusions in Patients with Unresectable Stage III (IIIB) or Distant Metastatic (IV) Merkel Cell Carcinoma (MCC)” dated October 20, 2015. I agree to abide by all provisions set forth herein. I agree to comply with the International Conference on Harmonization Tripartite Guidelines on Good Clinical Practice, effective in the United States from May 9, 1997, and applicable United States Food and Drug Administration regulations set forth in 21 CFR §50, 54, 56, and 312. I agree to ensure that the confidential information contained in this document will not be used for any purpose other than the evaluation and conduct of the clinical investigation without the prior written consent of NantKwest, Inc.

_____ _____

Signature of Investigator Date

_____

Printed Name of Investigator

_____

Address of Investigator

_____

Phone Number of Investigator

3.0 STUDY SYNOPSIS

Title of Study:

Phase II Study of aNK (activated NK-92, formerly Neukoplast) Infusions in Patients with Unresectable Stage III (IIIB) or Distant Metastatic (IV) Merkel Cell Carcinoma (MCC)

Objectives:

Primary Objective:

Determine the effect of aNK infusions on the 4-month (~16 weeks) progression-free survival (PFS) rate in patients with unresectable stage III (IIIB) or distant metastatic (stage IV) MCC based on Response Evaluation Criteria in Solid Tumors (RECIST) (v1.1).

Secondary Objectives:

a) Determine the overall response rate, as assessed by RECIST at week 16
b) Time to disease progression
c) Median overall survival
d) Assess the safety and toxicity of aNK
e) Quality of life assessment (FACT-G)

Exploratory Objectives:

To determine the genomic and proteomic profile of subjects' tumors to identify gene mutations, gene amplifications, RNA-expression levels, and protein-expression levels. Correlations between genomic/proteomic profiles and efficacy outcomes will be assessed.

Study Design:

This is a multi-center, non-randomized, open-label, phase II trial to determine the effect of aNK infusions in patients with unresectable stage III (IIIB) or distant metastatic (stage IV) MCC. The study will use an adaptive Simon optimal two-stage design. This two-stage design detects efficacy signals, allows for early assessment and avoids enrolling larger numbers of patients in case of inefficacy. In the first stage, 12 patients with unresectable stage III (IIIB) or distant metastatic (stage IV) MCC will be enrolled and treated. If the treatment combination in the first stage can improve the 4-month progression free survival (PFS) rate from 4% to 20% [e.g. at least 1 patient out of 12 patients has PFS ≥ 16 weeks (4 months)], then the study will proceed to the second stage, in which 12 more patients will be enrolled and treated. In addition, there will be a

planned Protocol Safety Committee meeting after the first 6 patients are enrolled in order to assess the safety of aNK infusions (see section 10.3). aNK will be given via IV infusion at a dose of 2 x 10^9 cells/m^2 on two consecutive days (= 1 cycle) every 2 weeks for a total of 8 cycles (16 infusions). If there is evidence of disease progression believed to be unrelated to an inflammatory immune mediated response, at any time point after the fourth cycle, the patient will be withdrawn from the trial.

Number of Patients:

Approximately 24 treated in two consecutive cohorts of 12 patients.

Duration of Treatment:

The total duration of planned treatment is 4 months.

Inclusion Criteria:

1. Male or female patients 18 years of age or older.
2. Patients must have histologically confirmed Merkel Cell Carcinoma (MCC) that is inoperable Stage III (IIIB) or Stage IV, as defined by the 2010 AJCC staging criteria for MCC[(2)]. Patients with stage IIIB MCC must have been evaluated by a surgical oncologist who has documented that their disease is surgically unresectable. MCC of unknown primary is allowed.
3. Up to two prior systemic cytotoxic chemotherapies and/or novel immunotherapy treatments for MCC are allowed. A wash-out period of 2 weeks prior to screening is required.
4. ECOG performance status of 0-2.
5. Voluntary written informed consent must be given before performance of any study-related procedure not part of normal medical care, with the understanding that consent may be withdrawn by the patient at any time without prejudice to future medical care.

Exclusion Criteria:

1. Major surgery within 30 days before study entry.
2. Any of the following clinical laboratory values at the time of enrollment:
   a. Absolute neutrophil count (ANC) < 1,000 cells/mm^3,
   b. Platelets < 50,000 x 10^9/L

3. Liver function abnormalities as indicated by ongoing hepatic enzyme elevation (e.g. AST, ALT, GGT) > 2x the ULN. Elevation related to direct tumor infiltration is allowed.
4. Renal insufficiency as indicated by a creatinine level > 2 x the ULN.
5. Myocardial infarction within 6 months prior to enrollment or New York Hospital Association (NYHA) Class III or IV heart failure, uncontrolled angina, severe uncontrolled arrhythmias, or electrocardiographic evidence of acute ischemia or significant conduction system abnormalities in the opinion of the Investigator. Prior to study entry any known abnormality on electrocardiogram (ECG) must be determined and documented by the Investigator to be not clinically significant to the patient participation in this study.
6. Any condition, including laboratory abnormalities, that in the opinion of the investigator places the patient at unacceptable risk if he/she were to participate in the study. This includes, but is not limited, to serious medical conditions or psychiatric illness likely to interfere with participation in this clinical study.
7. Female patients who are pregnant or breastfeeding. Female patients of childbearing potential must have a negative pregnancy test and agree to use adequate contraception for the duration of the trial.
8. Patients with other malignancies, or brain metastasis, are not eligible. However, given the frequent coexistence of MCC with other malignancies, the following exceptions are allowed:
    a) If they have been continuously disease-free for any solid tumor malignancy >3 years prior to the time of enrollment.
    b) Patients with basal cell carcinoma or squamous cell carcinoma,
    c) Patients with prior history of *in situ* cancer (e.g. breast, melanoma, squamous cells carcinoma of the skin, cervical),
    d) Patients with prior history of prostate cancer that is not under active systemic treatment except hormonal therapy, but with undetectable PSA (<0.2ng/mL),
    e) Patients with chronic lymphocytic leukemia are eligible if they have isolated lymphocytosis (Rai stage O) on the condition that they do not require systemic treatment for their disease [“B” symptoms, Richter’s transformation, lymphocyte doubling time (<6 months) and they do not have lymphadenopathy of hepatosplenomegaly].

f) Patients with lymphoma of any type or hairy cell leukemia are eligible on the condition that they do not receive active systemic treatment for their hematologic disease and are in complete remission as evidenced by PET/CT scans and bone marrow biopsies for at least 3 months.

9. Patients on immunosuppressants, systemic corticosteroids or any other investigational product.

Investigational Product and Administration:

aNK (activated NK-92, formerly Neukoplast) will be provided for clinical administration from a GMP contract manufacturer (CMO). The production/expansion (in vitro) of aNK will be according to the standard operating procedures on file at the GMP cell processing facility in accordance with CMO procedures and in accordance with information contained in BB-IND 8404 entitled "Natural Killer Cell Line, aNK (activated NK-92, formerly Neukoplast), Expanded with Interleukin-2 (Novartis)"; IND Sponsor: NantKwest, Inc. Cells will be shipped from the CMO to the study site according to validated procedures detailed in the IND. Cells will be washed and concentrated at the clinical site. In order to prevent aNK cell proliferation, the aNK cells will be irradiated with 1000 cGy prior to infusion at the study site. The cells for the second day infusion will be kept overnight in the Cell Processing facility under controlled cell culture incubator conditions.

Efficacy Evaluation:

The 4-month PFS rate will be calculated as the number of patients alive and progression free (based on RECIST v1.1) at four months from the date of 1st infusion divided by the total number of patients. For purposes of this analysis, the 4-month PFS rate will be calculated with 4 months being based on greater than or equal to 112 days (e.g., patients alive and progression-free for at least 112 days will be counted in the numerator of the PFS rate calculation).

Safety Evaluation:

Safety and toxicity will be assessed through the analysis of AEs, ECGs, vital signs, changes on physical exams, and laboratory values. All clinically significant findings on any post-baseline tests will be reported as AEs. Adverse events will be coded using the Medical Dictionary for Regulatory Activities. Treatment-emergent AEs will be defined as those events with start dates on or after the date of the first infusion or events that were

present prior to the start of treatment but worsened in severity following the first infusion on Cycle 1/Day 1.

Exploratory Molecular Profiling and Analysis:

Genomic sequencing of tumor cells relative to non-tumor cells to identify the genomic variances that may contribute to response or disease progression and provide an understanding of molecular abnormalities; RNA sequencing (RNAseq) to provide expression data and give relevance to DNA mutations; and quantitative proteomics to determine the concentration of proteins and to confirm expression of genes predictive of response and disease progression.

Toxicity Stopping Rule:

To avoid exposure of patients to unnecessary toxicity, continuous toxicity monitoring will be performed throughout the study. The trial will be stopped for toxicity if the death rate attributed to therapy (and not to the natural history of disease) significantly exceeds 5% during the first 12 weeks of treatment. Specifically, using a Pocock type stopping boundary which assumes that the death rate attributed to therapy of 0.05 is the maximum acceptable rate, the trial will be stopped if $\geq$2 deaths are observed in the first 6 patients or $\geq$3 deaths are observed in the first 9 patients. If $\geq$4 deaths are observed in the first cohort of 12 patients, enrollment into the second cohort will be halted. If none of the toxicity stopping rules are met, enrollment into the next cohort may be initiated.

Appendix A – Schedule of Events

Study Period	Screening/ Baseline	Treatment Visits					4-Month Follow-up
Study Visits	**Visit 1**	**Visits 2,3,4,5 aNK Cycle 1-4**	**Visit 6 Assessment Visit**	**Visits 7,8 aNK Cycles 5-6**	**Visit 9 Assessment Visit**	**Visits 10,11 aNK Cycles 7-8**	**Visit 12**
Visit Timeframe / Window	- 21 days	Day 0 Week 2 Week 4 Week 6	Week 7	Week 8 Week 10	Week 11	Week 12 Week 14	16 weeks
Informed Consent	X						
Eligibility Criteria	X						
Medical History	X						
Physical Exam	X		X		X		X
Vitals	X	X[1]	X	X[1]	X	X[1]	X
Height and Weight	X	X	X	X	X	X	X
CT/MRI	X						X
12-lead ECG	X		X		X		X
ECOG	X		X		X		X
QOL Questionnaire	X		X		X		X
Pregnancy Test	X		X		X		X
Chemistries / Hematology / UA	X		X		X		X
Immunologic Studies[2]	X[2]	X[2]		X[2]			
Concomitant Meds	X		X		X		X
Adverse Events		X	X	X	X	X	X
Genomic/Proteomic Molecular Sampling[5]	X						
Tumor Biopsy[6]		X					
aNK Infusion		X		X		X	
Disease Progression [4]			X		X		X
Survival Status [3]							X[3]

1 - Vital signs will be recorded at 0, 15(+/- 3 minutes), 30(+/- 3 minutes), 60(+/- 5 minutes), 90(+/- 5 minutes) and 120(+/- 5 minutes) from the start of the infusion..
2 - The development of NK-92-specific HLA antibodies and NK-92-specific T-Cell response will be evaluated at baseline, 4 weeks and 8 weeks post Cycle 1/Day 2. The 4-week sample will be collected prior to the administration of Cycle 3 and the 8-week sample will be collected prior to the administration of Cycle 5.
3 - Patient will be followed for survival status until death or lost to follow-up.
4 - These assessments may include bi-dimensional measurement of disease lesions by palpation, clinical exam, or radiographic imaging (x-ray, computed tomography [CT] scan, positron emission tomography [PET] scan, magnetic resonance imaging [MRI], or ultrasound). The same radiologic imaging method should be used consistently throughout the study to avoid variability in results.
5 - Exploratory genomics and proteomics molecular profiling will be performed on formalin-fixed, paraffin embedded (FFPE) tumor tissue and whole blood (subject matched normal comparator against the tumor tissue) by next-generation sequencing and mass spectrometry-based quantitative proteomics.
6 - In order to examine possible tumor infiltration by NK-92, an *optional* biopsy will be collected within 7 days after Cycle 1 completion (Cycle 1/Day 2). This biopsy will be optional depending on the patient situation and the location of the tumor and will be collected according tot eh site's standard of care procedures (see section 8.8.2).

CLINICAL TRIAL PROTOCOL

Phase II Study of aNK (activated NK-92, formerly Neukoplast) Infusions in Patients with Unresectable Stage III (IIIB) or Distant Metastatic (IV) Merkel Cell Carcinoma (MCC)

Protocol Date: May 10, 2016
Amendment 4
Protocol Version: 5
Protocol Number: MCC-001

Study Sponsor: NantKwest, Inc.
2533 South Coast Highway 101
Suite 210
Cardiff-by-the-Sea, CA 92007-21333

Sponsor Contact: Karen Nichols
Vice President, Regulatory and Quality
Karen.Nichols@NantKwest.com

Disclosure Statement: This document contains information that is confidential and proprietary to NantKwest. This information is being provided to you solely for the purpose of evaluating and/or conducting a clinical trial for NantKwest. You may disclose the contents of this protocol only to study personnel under your supervision, Independent Ethics Committee/Institutional Review Board or duly authorized representatives of regulatory agencies. The foregoing shall not apply to disclosure required by any regulations; however, you will give prompt notice to NantKwest of any such disclosure.

SPONSOR SIGNATURE PAGE

Study Title:	Phase II Study of aNK (activated NK-92, formerly Neukoplast) Infusions in Patients with Unresectable Stage III (IIIB) or Distant Metastatic (IV) Merkel Cell Carcinoma (MCC)
Study Number:	MCC-001
Final Date:	10 May 2016

This clinical study protocol was subject to critical review and has been approved by the Sponsor.

The following personnel contributed to writing and/or approving this protocol:

Signature of Sponsor

5-10-16

Date

Andreas Niethammer, MD, PhD
Executive Director, NantKwest, Inc.
2533 S. Coast Highway, Suite 210
Cardiff-by-the-Sea, CA 92007
Office: (858) 633-0300

1.0 INVESTIGATOR AGREEMENT

I have read the attached Protocol entitled “Phase II Study of aNK (activated NK-92, formerly Neukoplast) Infusions in Patients with Unresectable Stage III (IIIB) or Distant Metastatic (IV) Merkel Cell Carcinoma (MCC)” dated May 10, 2016. I agree to abide by all provisions set forth herein. I agree to comply with the International Conference on Harmonization Tripartite Guidelines on Good Clinical Practice, effective in the United States from May 9, 1997, and applicable United States Food and Drug Administration regulations set forth in 21 CFR §50, 54, 56, and 312. I agree to ensure that the confidential information contained in this document will not be used for any purpose other than the evaluation and conduct of the clinical investigation without the prior written consent of NantKwest, Inc.

_____ _____

Signature of Investigator Date

_____

Printed Name of Investigator

_____

Address of Investigator

_____

Phone Number of Investigator

3.0 STUDY SYNOPSIS

Title of Study:

Phase II Study of aNK (activated NK-92, formerly Neukoplast) Infusions in Patients with Unresectable Stage III (IIIB) or Distant Metastatic (IV) Merkel Cell Carcinoma (MCC)

Objectives:

Primary Objective:

Determine the effect of aNK infusions on the 4-month (~16 weeks) progression-free survival (PFS) rate in patients with unresectable stage III (IIIB) or distant metastatic (stage IV) MCC based on Response Evaluation Criteria in Solid Tumors (RECIST) (v1.1).

Secondary Objectives:

a) Determine the overall response rate, as assessed by RECIST at week 16
b) Time to disease progression
c) Median overall survival
d) Assess the safety and toxicity of aNK
e) Quality of life assessment (FACT-G)

Exploratory Objectives:

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Duration of Treatment:

The total duration of planned treatment is 4 months.

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6. Any condition, including laboratory abnormalities, that in the opinion of the investigator places the patient at unacceptable risk if he/she were to participate in the study. This includes, but is not limited, to serious medical conditions or psychiatric illness likely to interfere with participation in this clinical study.
7. Female patients who are pregnant or breastfeeding. Female patients of childbearing potential must have a negative pregnancy test and agree to use adequate contraception for the duration of the trial.
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    b) Patients with basal cell carcinoma or squamous cell carcinoma,
    c) Patients with prior history of *in situ* cancer (e.g. breast, melanoma, squamous cells carcinoma of the skin, cervical),
    d) Patients with prior history of prostate cancer that is not under active systemic treatment except hormonal therapy, but with undetectable PSA (<0.2ng/mL),
    e) Patients with chronic lymphocytic leukemia are eligible if they have isolated lymphocytosis (Rai stage O) on the condition that they do not require systemic treatment for their disease [“B” symptoms, Richter’s transformation, lymphocyte doubling time (<6 months) and they do not have lymphadenopathy of hepatosplenomegaly].

f) Patients with lymphoma of any type or hairy cell leukemia are eligible on the condition that they do not receive active systemic treatment for their hematologic disease and are in complete remission as evidenced by PET/CT scans and bone marrow biopsies for at least 3 months.

9. Patients on immunosuppressants, systemic corticosteroids or any other investigational product.

Investigational Product and Administration:

aNK (activated NK-92, formerly Neukoplast) will be provided for clinical administration from a GMP contract manufacturer (CMO). The production/expansion (in vitro) of aNK will be according to the standard operating procedures on file at the GMP cell processing facility in accordance with CMO procedures and in accordance with information contained in BB-IND 8404 entitled "Natural Killer Cell Line, aNK (activated NK-92, formerly Neukoplast), Expanded with Interleukin-2 (Novartis)"; IND Sponsor: NantKwest, Inc. Cells will be shipped from the CMO to the study site according to validated procedures detailed in the IND. Cells will be washed and concentrated at the clinical site. In order to prevent aNK cell proliferation, the aNK cells will be irradiated with 1000 cGy prior to infusion at the study site. The cells for the second day infusion will be kept overnight in the Cell Processing Facility under controlled cell culture incubator conditions.

Efficacy Evaluation:

The 4-month PFS rate will be calculated as the number of patients alive and progression free (based on RECIST v1.1) at four months from the date of 1st infusion divided by the total number of patients. For purposes of this analysis, the 4-month PFS rate will be calculated with 4 months being based on greater than or equal to 112 days (e.g., patients alive and progression-free for at least 112 days will be counted in the numerator of the PFS rate calculation).

Safety Evaluation:

Safety and toxicity will be assessed through the analysis of AEs, ECGs, vital signs, changes on physical exams, and laboratory values. All clinically significant findings on any post-baseline tests will be reported as AEs. Adverse events will be coded using the Medical Dictionary for Regulatory Activities. Treatment-emergent AEs will be defined as

those events with start dates on or after the date of the first infusion or events that were present prior to the start of treatment but worsened in severity following the first infusion on Cycle 1/Day 1.
Exploratory Molecular Profiling and Analysis: Genomic sequencing of tumor cells relative to non-tumor cells to identify the genomic variances that may contribute to response or disease progression and provide an understanding of molecular abnormalities; RNA sequencing (RNAseq) to provide expression data and give relevance to DNA mutations; and quantitative proteomics to determine the concentration of proteins and to confirm expression of genes predictive of response and disease progression.
Exploratory Tumor Biopsy In order to examine possible tumor infiltration by aNK, exploratory tumor biopsies may be collected at suitable time points throughout the study in order to capture possible changes in T cell infiltration. These optional tumor biopsies may be collected at Baseline, 48-72 hours after completion of Cycle 1 and again at 4 weeks post completion of Cycle 1. A tumor biopsy may also be taken at the time of disease progression if pseudo progression needs to be excluded and biopsy analysis may guide in resulting treatment decisions. Per Investigator discretion, tissue should be obtained through either surgical or punch/core biopsy methods. Biopsies that are collected outside of a planned study visit will be captured as an unscheduled study visit. Biopsy samples should be collected and stored and shipped according to the MCC-001 Biopsy Collection Guideline.
Toxicity Stopping Rule: To avoid exposure of patients to unnecessary toxicity, continuous toxicity monitoring will be performed throughout the study. The trial will be stopped for toxicity if the death rate attributed to therapy (and not to the natural history of disease) significantly exceeds 5% during the first 12 weeks of treatment. Specifically, using a Pocock type stopping boundary which assumes that the death rate attributed to therapy of 0.05 is the maximum acceptable rate, the trial will be stopped if ≥2 deaths are observed in the first 6 patients or ≥3 deaths are observed in the first 9 patients. If ≥4 deaths are observed in the first cohort of 12 patients, enrollment into the second cohort will be halted. If none of the toxicity stopping rules are met, enrollment into the next cohort may be initiated.

Appendix A – Schedule of Events

Study Period	Screening/ Baseline	Treatment Visits					End of Study Visit
Study Visits	**Visit 1**	**Visits 2,3,4,5 aNK Cycle 1-4**	**Visit 6 Assessment Visit**	**Visits 7,8 aNK Cycles 5-6**	**Visit 9 Assessment Visit**	**Visits 10,11 aNK Cycles 7-8**	**Visit 12**
Visit Timeframe / Window	- 21 days	Day 0 Week 2 Week 4 Week 6	Week 7	Week 8 Week 10	Week 11	Week 12 Week 14	16 Weeks / End of Study
Informed Consent	X						
Eligibility Criteria	X						
Medical History	X						
Physical Exam	X		X		X		X
Vitals	X	X[1]	X	X[1]	X	X[1]	X
Height and Weight	X	X	X	X	X	X	X
CT/MRI	X						X
Digital Photography of Skin Lesions	X	X	X	X	X	X	X
12-lead ECG	X		X		X		X
ECOG	X		X		X		X
QOL Questionnaire	X		X		X		X
Pregnancy Test	X		X		X		X
Chemistries / Hematology / UA	X		X		X		X
Immunologic Studies[2]	X[2]	X[2]		X[2]			
Concomitant Meds	X		X		X		X
Adverse Events		X	X	X	X	X	X
***Optional* Genomic/ Proteomic Molecular Sampling[5]**	X						

Study Period	Screening/ Baseline	Treatment Visits					End of Study Visit
Study Visits	**Visit 1**	**Visits 2,3,4,5 aNK Cycle 1-4**	**Visit 6 Assessment Visit**	**Visits 7,8 aNK Cycles 5-6**	**Visit 9 Assessment Visit**	**Visits 10,11 aNK Cycles 7-8**	**Visit 12**
Visit Timeframe / Window	- 21 days	Day 0 Week 2 Week 4 Week 6	Week 7	Week 8 Week 10	Week 11	Week 12 Week 14	16 Weeks / End of Study
***Optional* Exploratory Tumor Biopsy**[6]	X	X	X		X		X
aNK Infusion		X		X		X	
Disease Progression /Tumor Assessment [4]			X		X		X
Survival Status [3]							X[3]

1 - Vital signs will be recorded at 0, 15(+/- 5 minutes), 30(+/- 5 minutes), 60(+/- 15 minutes), 90(+/- 15 minutes) and 120(+/- 30 minutes) from the start of the infusion.
2 - The development of aNK-specific HLA antibodies and aNK-specific T-Cell response will be evaluated at baseline, 4 weeks and 8 weeks post Cycle 1/Day 2. The 4-week sample will be collected prior to the administration of Cycle 3 and the 8-week sample will be collected prior to the administration of Cycle 5.
3 - Patient will be followed/contacted for survival status monthly until death or lost to follow-up.
4 - These assessments may include bi-dimensional measurement of disease lesions by palpation, clinical exam, digital photography, or radiographic imaging (x-ray, computed tomography [CT] scan, positron emission tomography [PET] scan, magnetic resonance imaging [MRI], or ultrasound). The same radiologic imaging method should be used consistently throughout the study to avoid variability in results.
5 – *Optional* exploratory genomics and proteomics molecular profiling will be performed on formalin-fixed, paraffin embedded (FFPE) tumor tissue and whole blood (subject matched normal comparator against the tumor tissue) by next-generation sequencing and mass spectrometry-based quantitative proteomics.
6 – *Optional* exploratory tumor biopsies may be collected at Baseline, 48-72 hours after completion of Cycle 1 and again at 4 weeks post completion of Cycle 1. A tumor biopsy may also be taken at the time of disease progression if pseudo progression needs to be excluded and biopsy analysis may guide in resulting treatment decision (see section 8.1.10).

PROTOCOL NUMBER MCC-001

PHASE II STUDY OF aNK (ACTIVATED NK-92, FORMERLY NEUKOPLAST) INFUSIONS IN PATIENTS WITH UNRESECTABLE STAGE III (IIIB) OR DISTANT METASTATIC (IV) MERKEL CELL CARCINOMA (MCC)

IND Number:	008,404
Clinical Study Sponsor:	NantKwest, Inc. 2533 South Coast Highway 101 Suite 210 Cardiff-by-the-Sea, CA 92007-21333
Sponsor Contact: **(For medical questions/emergencies)**	Andreas Niethammer, MD, PhD Chief Medical Officer Andreas.Niethammer@NantKwest.com
Sponsor Contact: **(For study administration, operations, and execution questions)**	Saundra Kirven Clinical Trial Manager Saundra.kirven@NantBio.com
SAE Reporting:	Submit SAE Reports to one (1) of the following: SAE Email: SAE.Reporting@NantBio.com Fax: 800-853-3497

Protocol Version	Date
Original Protocol MCC-001	03 October 2014
Protocol MCC-001 Amendment 1	01 November 2014
Protocol MCC-001 Amendment 2	01 April, 2015
Protocol MCC-001 Amendment 3	20 October, 2015
Protocol MCC-001 Amendment 4	10 May, 2016
Protocol MCC-001 Amendment 5	28 July 2016

PROTOCOL SYNOPSIS

Name of Sponsor/Company:

NantKwest, Inc.

Name of Investigational Product:

Activated natural killer cells (aNK cells) suspension for injection.

Name of Active Ingredient:

aNK cells

Title of Study:

Phase II Study of aNK (activated NK-92, formerly Neukoplast) Infusions in Patients with Unresectable Stage III (IIIB) or Distant Metastatic (IV) Merkel Cell Carcinoma (MCC)

Study Number:

MCC-001

Study Phase:

Phase 2

Primary Objectives:

- Determine the effect of aNK infusions on the 4-month (~16 weeks) progression-free survival (PFS) rate in patients with unresectable stage III (IIIB) or distant metastatic (stage IV) MCC based on Response Evaluation Criteria in Solid Tumors (RECIST) (v1.1).

Secondary Objectives:

- Determine overall response rate
- Determine time to disease progression
- Determine median overall survival
- Assess the safety and toxicity of aNK
- Assess quality of life (FACT-G)

Exploratory Objectives:

- To determine the genomic, transcriptomic, and proteomic profile of patients' tumors to identify gene mutations, gene amplifications, RNA-expression levels, and protein-expression levels. Correlations between genomic/transcriptomic/proteomic profiles and efficacy outcomes will be assessed.

Primary Endpoint:

- 4-month PFS rate

Secondary Endpoints:

- Overall response rate
- Time to disease progression
- Median overall survival
- Safety and toxicity of aNK
- Quality of life assessment (FACT-G)

Exploratory Endpoints:

- Genomic, transcriptomic, and proteomic profiles and correlations with efficacy
- Potential tumor infiltration by aNK

Study Design:

This is a multi-center, non-randomized, open-label, phase II trial to determine the effect of aNK infusions in patients with unresectable stage III (IIIB) or distant metastatic (stage IV) MCC. The study will use an adaptive Simon optimal two-stage design. This two-stage design detects efficacy signals, allows for early assessment and avoids enrolling larger numbers of patients in case of inefficacy. In the first stage, up to 12 patients with unresectable stage III (IIIB) or distant metastatic (stage IV) MCC were to be enrolled and treated. If the treatment in the first stage improved the 4-month progression free survival (PFS) rate from 4% to 20% [e.g. at least 1 patient out of 12 patients has PFS $\geq$ 16 weeks (4 months)], then the study would proceed to the second stage, in which 12 more patients were planned to be enrolled and treated. As of July 2016, the trial has met the required efficacy signal defined for stage 1 and will continue to enroll a planned total of 24 patients. In addition, there will be a planned Protocol Safety Committee meeting after the first 6 patients are enrolled in order to assess the safety of aNK infusions. aNK will be given via IV infusion at a dose of 2×10^9 cells/m^2 on two consecutive days (= 1 cycle) every 2 weeks for a total of 8 cycles (16 infusions). If there is evidence of disease progression believed to be unrelated to an inflammatory immune mediated response, at any time point after the fourth cycle, the patient will be withdrawn from the trial. If, at the end of the 8-cycle period, the patient does not have evidence of disease progression, unacceptable aNK-related grade 3 or grade 4 adverse events, and, in the opinion of the investigator, the patient may benefit from continued therapy, patients may continue to receive study treatment according to the dosing schedule until the patient withdraws from the study because of reasons outlined in Section 7.2. Safety and efficacy data will continue to be collected per the Schedule of Events.

Enrollment (planned):

Approximately 24 patients treated in two consecutive cohorts of 12 patients each.

Diagnosis and Main Criteria for Inclusion:

- Patients must have histologically confirmed Merkel Cell Carcinoma (MCC) that is inoperable Stage III (IIIB) or Stage IV, as defined by the 2010 AJCC staging criteria for MCC. Patients with stage IIIB MCC must have been evaluated by a surgical oncologist who has documented that their disease is surgically unresectable. MCC of unknown primary is allowed.
- Male or female patients 18 years of age or older.
- Up to two prior systemic cytotoxic chemotherapies and/or novel immunotherapy treatments for MCC are allowed. A wash-out period of 2 weeks prior to aNK treatment is required.
- ECOG performance status of 0-2.
- Voluntary written informed consent must be given before performance of any study-related procedure not part of normal medical care, with the understanding that consent may be withdrawn by the patient at any time without prejudice to future medical care.
- Adequate cardiac, liver, and kidney function.
- No major surgery within 30 days before study entry.

Investigational Product, Dosage, and Mode of Administration:

aNK cells will be provided for clinical administration from a GMP contract manufacturer (CMO). The production/expansion (in vitro) of aNK will be according to the standard operating procedures on file at the GMP cell processing facility in accordance with CMO procedures and in accordance with information contained in BB-IND 8404 entitled "Natural Killer Cell Line, aNK (activated NK-92, formerly Neukoplast), Expanded with Interleukin-2 (Novartis)"; IND Sponsor: NantKwest, Inc.

Duration of Treatment:

The total duration of planned treatment is approximately 4 months.

Reference Therapy, Dosage, and Mode of Administration:

Not applicable.

Criteria for Evaluation:

Safety:

Safety and toxicity will be assessed through the analysis of AEs, ECGs, vital signs, changes on physical exams, and laboratory values. All clinically significant findings on any postbaseline tests will be reported as AEs. AEs will be coded using the Medical Dictionary for Regulatory Activities. Treatment-emergent AEs will be defined as those events with start dates on or after the date of the first infusion or events that were present prior to the start of treatment but worsened in severity following the first infusion on Cycle 1/Day 1.

Efficacy:

The 4-month PFS rate will be calculated as the number of patients alive and progression free (based on RECIST v1.1) at four months from the date of the first infusion divided by the total number of patients. For purposes of this analysis, the 4-month PFS rate will be calculated, with 4 months based on greater than or equal to 112 days (e.g., patients alive and progression-free for at least 112 days will be counted in the numerator of the PFS rate calculation).

Exploratory Molecular Profiling and Analysis and its Rationale:

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.

Exploratory Tumor Biopsy:

To examine possible tumor infiltration by aNK, exploratory tumor biopsies may be collected at suitable time points throughout the study in order to capture possible changes in T cell infiltration. These optional tumor biopsies may be collected at Baseline, 48-72 hours after completion of Cycle 1, and again at 4 weeks post completion of Cycle 1. A tumor biopsy may also be taken at the time of disease progression if pseudo progression needs to be excluded and biopsy analysis may guide in resulting treatment decisions. If a patient decides to undergo extended treatment due to a positive clinical response, additional biopsies may be collected at the discretion of the Investigator during this period. Per Investigator discretion, tissue should be obtained through either surgical or punch/core biopsy methods. Biopsies that are collected outside of a planned study visit will be captured as an unscheduled study visit. Biopsy samples should be collected and stored and shipped according to the MCC-001 Biopsy Collection Guideline.

Statistical Methods:

Data analyses will be primarily descriptive in nature. Continuous variables will be summarized as mean, median, standard deviation, minimum and maximum; categorical variables will be summarized as the number and percentage of patients in each category.

All patients receiving one or more infusions will be included in the primary efficacy and safety analyses. Separate efficacy analyses may be performed on the evaluable population, defined as all patients receiving all planned doses (8 cycles) per protocol.

The 4-month PFS rate will be calculated as the number of patients alive and progression free (based on RECIST v1.1) at 4 months from the date of first infusion on Cycle 1/Day 1 divided by the total number of patients.

APPENDIX A. SCHEDULE OF EVENTS

Study Period	Screening/ Baseline	Treatment Visits					End of Study Visit[a]	Treatment Extension Visits
Study Visits	**Visit 1**	**Visits 2, 3, 4, 5 aNK Cycle 1-4**	**Visit 6 Assessment Visit**	**Visits 7, 8 aNK Cycles 5-6**	**Visit 9 Assessment Visit**	**Visits 10, 11 aNK Cycles 7-8**	**Visit 12**	
Visit Timeframe / Window	**-21 days**	**Day 1 and 2 Week 2 Week 4 Week 6**	**Week 7**	**Week 8 Week 10**	**Week 11**	**Week 12 Week 14**	**16 Weeks / End of Study**	**Every 2 Weeks Following Week 12**
Informed consent	X							
Eligibility criteria	X							
Medical history	X							
Physical exam	X		X		X		X	X
Vitals	X	X[b]	X	X[b]	X	X[b]	X	X[b]
Height[c] and Weight	X	X	X	X	X	X	X	X
CT/MRI	X						X	X[d]
Digital Photography of Skin Lesions	X	X	X	X	X	X	X	X
12-lead ECG	X		X		X		X	X
ECOG	X		X		X		X	X
QoL questionnaire	X		X		X		X	X
Pregnancy test	X		X		X		X	X
Chemistries / Hematology / UA	X		X		X		X	X
Immunologic studies[e]	X	X		X				

Study Period	Screening/ Baseline	Treatment Visits					End of Study Visit[a]	Treatment Extension Visits
Study Visits	**Visit 1**	**Visits 2, 3, 4, 5 aNK Cycle 1-4**	**Visit 6 Assessment Visit**	**Visits 7, 8 aNK Cycles 5-6**	**Visit 9 Assessment Visit**	**Visits 10, 11 aNK Cycles 7-8**	**Visit 12**	
Visit Timeframe / Window	**-21 days**	**Day 1 and 2 Week 2 Week 4 Week 6**	**Week 7**	**Week 8 Week 10**	**Week 11**	**Week 12 Week 14**	**16 Weeks / End of Study**	**Every 2 Weeks Following Week 12**
Concomitant meds	X		X		X		X	X
Adverse events		X	X	X	X	X	X	X
Optional genomic/transcriptomic/proteomic molecular sampling[f]	X							
Optional exploratory tumor biopsy[g]	X	X	X		X		X	X
aNK Infusion		X		X		X	X[a]	X
Disease progression /tumor assessment[h]			X		X		X	X
Survival status[i]							X	

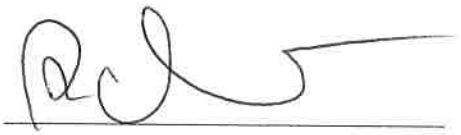
[a]Patients, who have a positive response to aNK infusions, may elect to have additional infusions after discussion with the Investigator and Medical Monitor. Patients may receive additional aNK treatment every 2 weeks, at a dose of 2 x 10^9 cells/m^2. Treatment may continue until a complete response is achieved or it is deemed appropriate by the Investigator and/or NantKwest Medical Monitor. During this extended treatment period the study assessments will be performed every 8 weeks as clinically indicated.
[b]Vital signs will be recorded at 0, 15 (±5 minutes), 30 (±5 minutes), 60 (±15 minutes), 90 (±15 minutes) and 120 (±30 minutes) from the start of the infusion.
[c]Height is recorded at screening only.
[d]CT/MRI imaging will be performed at the same intervals as the initial 8-cycle period until the patient has a confirmed CR or confirmed PD.
[e]The development of aNK-specific HLA antibodies and aNK-specific T-Cell response will be evaluated at baseline, 4 weeks and 8 weeks post Cycle 1/Day 2. The 4-week sample will be collected prior to the administration of Cycle 3 and the 8-week sample will be collected prior to the administration of Cycle 5.

[f]Optional exploratory genomic, transcriptomic, and proteomic molecular profiling will be performed on formalin-fixed, paraffin embedded (FFPE) tumor tissue and whole blood (patient matched normal comparator against the tumor tissue) by next-generation sequencing and mass spectrometry-based quantitative proteomics.
[g]Optional exploratory tumor biopsies may be collected at Baseline, 48-72 hours after completion of Cycle 1 and again at 4 weeks post completion of Cycle 1. A tumor biopsy may also be taken at the time of disease progression if pseudo progression needs to be excluded and biopsy analysis may guide in resulting treatment decision (Section 5.1.10).
[h]These assessments may include bi-dimensional measurement of disease lesions by palpation, clinical exam, digital photography, or radiographic imaging (x-ray, computed tomography [CT] scan, positron emission tomography [PET] scan, magnetic resonance imaging [MRI], or ultrasound). The same radiologic imaging method should be used consistently throughout the study to avoid variability in results.
[i]Patient will be followed/contacted for survival status monthly until death or lost to follow-up.

APPENDIX E. SPONSOR SIGNATURE

Study Title:	Phase II Study of aNK (activated aNK, formerly Neukoplast) Infusions in Patients with Unresectable Stage III (IIIB) or Distant Metastatic (IV) Merkel Cell Carcinoma (MCC)
Study Number:	MCC-001, Amendment 5
Final Date:	28 July 2016

This clinical study protocol was subject to critical review and has been approved by the Sponsor. The following personnel contributed to writing and/or approving this protocol:

Signed:  Date: _July 28 2016____

Andreas Niethammer, MD PhD
Chief Medical Officer
Andreas.Niethammer@NantKwest.com

PROTOCOL NUMBER MCC-001

PHASE 2 STUDY OF aNK (ACTIVATED NK-92, NATURAL KILLER CELLS) INFUSIONS IN COMBINATION WITH ALT-803 (IL-15) IN PATIENTS WITH STAGE III (IIIB) OR STAGE IV MERKEL CELL CARCINOMA (MCC)

IND Number:	008,404
Clinical Study Sponsor:	NantKwest, Inc. 9920 Jefferson Blvd Culver City, CA 90232
Sponsor Contact: **(For medical questions/emergencies)**	Andreas Niethammer, MD, PhD Chief Medical Officer Andreas.Niethammer@NantKwest.com
SAE Reporting:	Submit SAE Reports to one of the following: SAE Email: SAE.Reporting@NantBio.com Fax: 800-853-3497

Protocol Version	Date
Original Protocol MCC-001	03 October 2014
Protocol MCC-001 Amendment 1	01 November 2014
Protocol MCC-001 Amendment 2	01 April, 2015
Protocol MCC-001 Amendment 3	20 October, 2015
Protocol MCC-001 Amendment 4	10 May, 2016
Protocol MCC-001 Amendment 5	28 July 2016
Protocol MCC-001 Amendment 6	08 September 2016

PROTOCOL SYNOPSIS

Name of Sponsor/Company:

NantKwest, Inc.

Name of Investigational Products:

aNK™, Suspension for Intravenous Infusion (activated NK-92 cells).

ALT-803, recombinant human super agonist interleukin-15 (IL-15) complex (also known as IL 15N72D:IL-15RαSu/IgG1 Fc complex).

Name of Active Ingredient:

Activated NK-92 cells.

Recombinant human super agonist interleukin-15 (IL-15) complex.

Title of Study:

Phase 2 Study of aNK (Activated NK-92 Natural Killer Cells) Infusions in Combination With ALT-803 (IL-15) in Patients with Stage III (IIIB) or Stage IV Merkel Cell Carcinoma (MCC).

Study Number:

MCC-001

Study Phase:

Phase 2

Primary Objectives:

- Determine the effect of aNK intravenous (IV) infusions in combination with ALT-803 on the 4-month (~16 weeks) progression-free survival (PFS) rate in patients with stage III (IIIB) or stage IV MCC based on Response Evaluation Criteria in Solid Tumors (RECIST Version 1.1).

Secondary Objectives:

- Determine overall response rate (ORR).
- Determine time to disease progression (TTP).
- Determine overall survival (OS).
- Assess the safety and tolerability of the combination of aNK and ALT-803.
- Assess quality of life (FACT-G).

Exploratory Objectives:

- To determine the genomic, transcriptomic, and proteomic profile of patients' tumors to identify gene mutations, gene amplifications, RNA-expression levels, and protein-expression levels. Correlations between genomic, transcriptomic, and proteomic profiles and efficacy outcomes will be assessed.

Primary Endpoint:

- 4-month PFS rate.

Secondary Endpoints:

- ORR.
- TTP.
- OS.
- Safety and tolerability of the combination of aNK plus ALT-803.
- Quality of life assessment (FACT-G).

Exploratory Endpoints:

- Genomic, transcriptomic, and proteomic profiles and correlations with efficacy.
- Immune cell quantification in the tumor microenvironment.

Study Design:

This is a multi-center, non-randomized, open-label, phase 2 trial to determine the effects of aNK in combination with ALT-803 in patients with stage III (IIIB) or stage IV MCC. The study will use an adaptive Simon optimal two-stage design, which detects efficacy signals, allows for early assessment, and avoids enrolling larger numbers of patients in case of inefficacy.

In the original protocol, an initial cohort of up to 12 patients with stage III (IIIB) or stage IV MCC were to be enrolled and treated with aNK monotherapy (first stage). If the treatment in the first stage improved the 4-month progression free survival (PFS) rate from 4% to 20% (e.g. at least 1 patient out of 12 patients has PFS ≥ 16 weeks [4 months]), then the study would proceed to the second stage, in which 12 more patients were planned to be enrolled and treated. As of July 2016, the trial has met the required efficacy signal defined for the first stage and will continue to enroll a planned total of 24 patients who will receive the combination of aNK and ALT-803. Any patients who are already receiving aNK cells as monotherapy will receive aNK cells in combination with ALT-803 in subsequent cycles.

As of 08 September 2016, the protocol has been amended to include ALT-803 in combination with aNK. There will be a planned Safety Review Committee meeting after 6 patients have received at least 2 cycles of aNK in combination with ALT-803.

aNK will be given via IV infusion at a dose of 2×10^9 cells/m^2 on two consecutive days (= 1 cycle) every 2 weeks. In addition, ALT-803 will be administered SC at 10 µg/kg on the first day of every aNK infusion (before the aNK infusion) every 2 weeks.

If there is evidence of disease progression at any time point after the sixth cycle and it is believed to be unrelated to an inflammatory immune-mediated response, the patient will be withdrawn from the trial. If, at the end of the 8-cycle period, the patient does not have evidence of disease progression, unacceptable aNK-related and/or ALT-803-related grade 3 or grade 4 adverse events, and, in the opinion of the investigator, the patient may benefit from continued therapy, patients may continue to receive study treatment according to the dosing schedule until the patient withdraws from the study because of reasons outlined in Section 7.7. Safety and efficacy data will continue to be collected per

the Schedule of Events.
Enrollment (planned): Approximately 24 patients.
Diagnosis and Main Criteria for Inclusion: • Patients must have histologically confirmed MCC that is Stage III (IIIB) or Stage IV, as defined by the 2010 AJCC staging criteria for MCC. MCC of unknown primary is allowed. • Male or female patients 18 years of age or older. • Prior systemic cytotoxic chemotherapies and/or novel immunotherapy treatments for MCC are allowed. A wash-out period of 2 weeks prior to aNK treatment is required. • ECOG performance status of 0-2. • Voluntary written informed consent must be given before performance of any study-related procedure not part of normal medical care, with the understanding that consent may be withdrawn by the patient at any time without prejudice to future medical care. • Mandatory diagnostic biopsy and whole blood sample are required. • Adequate cardiac, liver, and kidney function. • No major surgery within 30 days before study entry.
Investigational Product, Dosage, and Mode of Administration: aNK cells will be provided for clinical administration from a GMP Contract Manufacturing Organization (CMO). The production/expansion (in vitro) of aNK will be according to the standard operating procedures on file at the GMP cell processing facility in accordance with CMO procedures and in accordance with information contained in BB-IND 8404 entitled "Natural Killer Cell Line, aNK (activated NK-92, formerly Neukoplast), Expanded with Interleukin-2 (Novartis)"; IND Sponsor: NantKwest, Inc. aNK will be given via IV infusion at a dose of 2×10^9 cells/m^2 on two consecutive days (= 1 cycle) every 2 weeks. ALT-803 will be administered SC at 10 µg/kg on the first day of every aNK infusion (before the aNK infusion) every 2 weeks. Injection sites should be rotated per institutional guidelines and each injection site separated by at least 1 inch.
Duration of Treatment: Patients will receive experimental treatment until they experience progressive disease or unacceptable toxicity, withdraw consent, or if the investigator feels it is no longer in their best interest to continue treatment. Experimental treatment will be administered for a minimum of 8 cycles, unless the patient dies or there is a clinical necessity to terminate 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 the sixth cycle and it is believed to be unrelated to an inflammatory immune-mediated response, the patient will be withdrawn from the trial.

Reference Therapy, Dosage, and Mode of Administration:

Not applicable.

Criteria for Evaluation:

Safety:

Safety and toxicity will be assessed through the analysis of AEs, ECGs, vital signs, changes on physical exams, and laboratory values. All clinically significant findings on any postbaseline tests will be reported as AEs. AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Treatment-emergent AEs will be defined as those events with start dates on or after the date of the first infusion or events that were present prior to the start of treatment but worsened in severity following the first infusion on cycle 1/day 1.

Efficacy:

The 4-month PFS rate will be calculated as the number of patients alive and progression free (based on RECIST v1.1) at four months from the date of the first infusion divided by the total number of patients. For purposes of this analysis, the 4-month PFS rate will be calculated based on 4 months being greater than or equal to 112 days (e.g., patients alive and progression-free for at least 112 days will be counted in the numerator of the PFS rate calculation). ORR, TTP, and OS will also be assessed.

Exploratory Molecular Profiling and Analysis and its Rationale:

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.

Exploratory Tumor Biopsy:

To examine possible tumor infiltration by aNK cells as well as other immune cells, including but not limited to autologous NK cells, T cells, and myeloid-derived suppressor cells, exploratory tumor biopsies may be collected at any time point as clinically indicated. Tumor biopsies may also be taken at the time of disease progression if pseudo-progression (progression on imaging due to infiltration by inflammation-related immune cells) needs to be excluded and if biopsy analysis may guide treatment decisions.

Statistical Methods:

Data analyses will be primarily descriptive in nature. Continuous variables will be summarized as mean, median, standard deviation, minimum and maximum; categorical variables will be summarized as the number and percentage of patients in each category.

All patients receiving aNK or ALT-803 will be included in the efficacy and safety analyses. Patients who only received aNK cells as monotherapy will be summarized separately from patients who

received aNK plus ALT-803 combination therapy.

The 4-month PFS rate will be calculated as the number of patients alive and progression free (based on RECIST v1.1) at 4 months from the date of first infusion on cycle 1/day 1 divided by the total number of subjects. The 95% confidence intervals for the 4-month PFS response rate will also be presented. The ORR and its 95% confidence interval will be presented. TTP and OS will be analyzed using Kaplan-Meier methods.

Table 6: Schedule of Events

Study Period	Screening/ Baseline	Treatment Visits					Week 16[a]	Treatment Extension Visits
Study Visits	**Visit 1**	**Visits 2, 3, 4, 5 aNK Cycle 1-4**	**Visit 6 Assessment Visit**	**Visits 7, 8 aNK Cycles 5-6**	**Visit 9 Assessment Visit**	**Visits 10, 11 aNK Cycles 7-8**	**Visit 12**	
Study Week	**Up to -21 Days**	**Week 0 Week 2 Week 4 Week 6**	**Week 7**	**Week 8 Week 10**	**Week 11**	**Week 12 Week 14**	**16 Weeks**	**Every 2 Weeks Following Visit 12**
Informed consent	X							
Eligibility criteria	X							
Medical history	X							
Physical exam	X		X		X		X	X
Vitals[b]	X	X	X	X	X	X	X	X
Height[c] and weight	X	X	X	X	X	X	X	X
CT/MRI[d]	X						X	X
Digital photography of skin lesions	X	X	X	X	X	X	X	X
12-lead ECG[e]	X	X	X	X	X	X	X	X
ECOG	X	X	X	X	X	X	X	X
FACT-G QoL questionnaire[e]	X		X		X		X	X
Pregnancy test (WOCBP)	X	X	X	X	X	X	X	X
Clinical laboratory tests	X	X	X	X	X	X	X	X
Immunologic studies[f]	X	X		X	X	X		

Study Period	**Screening/ Baseline**	**Treatment Visits**					**Week 16[a]**	**Treatment Extension Visits**
Study Visits	**Visit 1**	**Visits 2, 3, 4, 5 aNK Cycle 1-4**	**Visit 6 Assessment Visit**	**Visits 7, 8 aNK Cycles 5-6**	**Visit 9 Assessment Visit**	**Visits 10, 11 aNK Cycles 7-8**	**Visit 12**	
Study Week	**Up to -21 Days**	**Week 0 Week 2 Week 4 Week 6**	**Week 7**	**Week 8 Week 10**	**Week 11**	**Week 12 Week 14**	**16 Weeks**	**Every 2 Weeks Following Visit 12**
Concomitant medications	X	X	X	X	X	X	X	X
Adverse events		X	X	X	X	X	X	X
Mandatory genomic/transcriptomic/proteomic molecular sampling[g]	X							
Optional exploratory tumor biopsy[h]		X	X		X		X	X
aNK infusion[i]		X		X		X	X[a]	X
ALT-803 administration[j]		X		X		X	X	X[a]
Disease progression /tumor assessment[k]	X		X		X		X	X
Survival status[l]							X	

[a]Patients who have a positive response to treatment with aNK plus ALT-803 may be provided the opportunity to continue additional treatment after discussion with the Investigator and Sponsor Medical Monitor. Patients may receive additional aNK plus ALT-803 treatment every 2 weeks at a dose of 2×10^9 cells/m^2. Treatment may continue until a complete response is achieved or it is deemed appropriate by the Investigator and/or Sponsor Medical Monitor.
[b]Vital signs will be recorded at 0, 15 (±5 minutes), 30 (±5 minutes), 60 (±15 minutes), 90 (±15 minutes) and 120 (±30 minutes) minutes from the start of the infusion.
[c]Height is recorded at screening only.
[d]CT/MRI imaging will be performed at the same intervals as the initial 8-cycle period until the patient has a confirmed CR or confirmed PD.
[e]ECGs will be performed at 6-week intervals during treatment extension.

[f]The development of aNK-specific HLA antibodies and aNK-specific T-Cell response will be evaluated at baseline, 4 weeks, and 8, 10, 11, and 12 weeks post cycle 1/day 2. The 4-week sample will be collected prior to the administration of cycle 3, the 8-week sample will be collected prior to the administration of cycle 5, the 10-week sample will be collected prior to the administration of cycle 6, the 11-week sample will be collected during the visit 9 assessment visit, and the 12-week sample will be collected prior to the administration of cycle 7.
[g]Mandatory exploratory genomic, transcriptomic, and proteomic molecular profiling will be performed on formalin-fixed, paraffin embedded (FFPE) tumor tissue and whole blood (patient matched-normal comparator against the tumor tissue) by next-generation sequencing and mass spectrometry-based quantitative proteomics.
[h]Optional exploratory tumor biopsies may be collected at any time point as clinically indicated. A tumor biopsy may also be taken at the time of disease progression if pseudo-progression needs to be excluded and if biopsy analysis may guide in resulting treatment decision (Section 6.17).
[i]aNK cells are administered day 1 and day 2 every 2 weeks (1 cycle).
[j]ALT-803 is administered SC on each day-1 aNK infusion, before the aNK infusion, every 2 weeks.
[k]Assessments may include bi-dimensional measurement of disease lesions by palpation, clinical exam, digital photography, or radiographic imaging (x-ray, computed tomography [CT] scan, positron emission tomography [PET] scan, magnetic resonance imaging [MRI], or ultrasound). The same radiologic imaging method should be used consistently throughout the study to avoid variability in results.
[l]Patient will be contacted monthly by site staff via telephone to obtain disease progression and survival status. Contacts will be continued until death or lost to follow-up.

APPENDIX C. SPONSOR SIGNATURE

Study Title:	Phase 2 Study of aNK (Activated NK-92 Natural Killer Cells) Infusions in Combination With ALT-803 (IL-15) in Patients with Stage III (IIIB) or Stage IV Merkel Cell Carcinoma (MCC)
Study Number:	MCC-001, Amendment 6
Final Date:	08 September 2016

This clinical study protocol was subject to critical review and has been approved by the Sponsor. The following personnel contributed to writing and/or approving this protocol:

Signed: _____ Date: 8th Sept 2016

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