A PHASE 2 STUDY OF COMBINATION THERAPY WITH AN IL-15 SUPERAGONIST (N-803), OFF-THE-SHELF CD16-TARGETED NATURAL KILLER CELLS (HANK), AND AVELUMAB WITHOUT CYTOTOXIC CHEMOTHERAPY IN SUBJECTS WITH MERKEL CELL CARCINOMA (MCC) THAT HAS PROGRESSED ON OR AFTER TREATMENT WITH A CHECKPOINT INHIBITOR

Study Number:	**QUILT-3.063**
IND Sponsor:	NantKwest, Inc. 9920 Jefferson Blvd Culver City, CA 90232
Sponsor Contact: **(For medical questions/emergencies)**	John H. Lee, MD Senior Vice President Adult Medical Affairs, NantKwest Inc. 9920 Jefferson Blvd Culver City, CA 90232 Email: John.Lee@Nantkwest.com Cell Phone: +1-605-610-6391

Protocol Version	**Date**
Version 1	30 November 2018

STATEMENT OF COMPLIANCE

This trial will be conducted in accordance with Good Clinical Practice (GCP) as described in the International Conference on Harmonization Guideline ICH GCP E6 (R2) and in accordance with United States (US) Code of Federal Regulations (CFR) applicable to clinical studies (45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, and 21 CFR Part 312) and the general ethical principles outlined in the Declaration of Helsinki. The study will receive approval from an Institutional Review Board (IRB) prior to commencement. The Principal Investigator will assure that no deviation from or changes to the protocol will take place without prior agreement from NantKwest and documented approval from the IRB, except where necessary to eliminate an immediate hazard(s) to the trial participants.

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

Principal Investigator:

Signed: _____ Date: _____

PROTOCOL SYNOPSIS

Name of Sponsor/Company:
NantKwest, Inc.

Name of Investigational Products:

1. haNK™, NK-92 [CD16.158V, ER IL-2], Suspension for Infusion (haNK™ for Infusion)
2. N-803 (also known as ALT-803; recombinant human superagonist interleukin-15 (IL-15) complex [also known as IL-15N72D:IL-15RαSu/IgG1 Fc complex])

Name of Approved Products:

3. Avelumab (BAVENCIO® injection, for intravenous [IV] use)

Name of Active Ingredients:

Investigational Products

1. NK-92 [CD16.158V, ER IL2] cells
2. N-803, recombinant human superagonist IL-15 complex (also known as IL-15N72D: IL-15RαSu/IgG1 Fc complex)

Approved Products

3. Avelumab

Title of Study:
A phase 2 study of combination therapy with an IL-15 superagonist (N-803), off-the-shelf CD16-targeted natural killer cells (haNK), and avelumab without cytotoxic chemotherapy in subjects with Merkel cell carcinoma (MCC) that has progressed on or after treatment with a checkpoint inhibitor.

Study Number:
QUILT-3.063

Study Phase:
Phase 2

Study Objectives:

- The primary objective is to determine the efficacy of the combination treatment of avelumab, haNK, and N-803 in subjects with MCC that has progressed on or after checkpoint inhibitor therapy by objective response rate (ORR) using Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST 1.1) based on Blinded Independent Central Review (BICR).
- Secondary objectives are to obtain additional measures of efficacy by progression-free survival (PFS), overall survival (OS), disease-specific survival (DSS), duration of response (DOR), disease control rate (DCR), and quality of life (QoL) by patient-reported outcomes (PROs), and to obtain measures of safety.
- Exploratory objectives include the assessment of the pharmacokinetic (PK) and immunogenicity profiles of N-803 in combination with haNK and avelumab.
- Additional exploratory objectives include the assessment of tumor molecular profiles (genomics, transcriptomics, and proteomics), therapy-induced changes in immune responses, and molecular changes in cell-free circulating DNA (cfDNA) and RNA (cfRNA); and their correlations with subject outcomes.

Study Design:

This is a phase 2 study to evaluate the efficacy of the combination therapy of avelumab, haNK, and N-803 in subjects with MCC that has progressed on or after checkpoint inhibitor therapy as assessed by ORR. Subjects must have progressed on or within 6 months of completing treatment with single-agent avelumab or pembrolizumab, as per FDA indication. Combination therapy will be administered as follows:

Day 1, every 2 weeks:

- Avelumab (10 mg/kg IV)
- haNK (2×10^9 cells/dose IV)

Day 1, every 3 weeks:

- N-803 (15 μg/kg subcutaneous [SC] injection)

Subjects will continue to receive treatment for up to 2 years. Treatment in the study will be discontinued if the subject experiences confirmed progressive disease (PD) or unacceptable toxicity (not corrected with dose reduction), withdraws consent, or if the Investigator feels it is no longer in the subject's best interest to continue treatment.

Tumors will be assessed at screening, and tumor response will be assessed every 8 weeks in the first year, and every 12 weeks thereafter by computed tomography (CT) or magnetic resonance imaging (MRI) of target and non-target lesions in accordance with RECIST 1.1 and immune-related RECIST (irRECIST). Unscheduled tumor assessments should be carried out if the Investigator observes any signs or symptoms of PD. When disease progression per RECIST 1.1 is initially observed, experimental treatment may continue and an imaging assessment should be done 4–6 weeks after the initial PD assessment to rule out tumor pseudoprogression. If pseudoprogression is observed, the subject is allowed to continue experimental treatment and response assessments will continue every 8 or 12 weeks and will be evaluated per irRECIST. For responding subjects (partial response [PR] or complete response [CR]), a confirmatory response assessment should be done 4–6 weeks after the initial response.

N-803 immunogenicity and pharmacokinetic testing will be conducted on pre-dose blood samples collected prior to treatment on this study, weekly for the first 3 weeks, during week 7, every 3 weeks thereafter during subsequent treatment, at the end-of-treatment (EOT) visit, and 6 weeks after the last treatment, as described in Section 6.4.1 and Section 6.4.2.

Exploratory tumor molecular profiling will be conducted on samples collected prior to treatment on this study, and 8 weeks after the start of treatment, as described in Section 6.4.3. Separate blood tubes will be collected every 8 weeks in the treatment phase during routine blood draws for exploratory immunology and cfDNA/cfRNA analyses, as described in Section 6.4.4 and Section 6.4.5, respectively.

Primary Efficacy Endpoint:

- ORR by RECIST 1.1 based on BICR.

Key Secondary Efficacy Endpoint:

- DOR by RECIST 1.1 based on BICR.

Other Secondary Efficacy Endpoints:

- ORR and DOR by irRECIST based on BICR.
- PFS by RECIST 1.1 and irRECIST based on BICR.
- OS.
- DSS.
- DCR (confirmed CR, PR, or stable disease [SD] lasting for ≥ 8 weeks) by RECIST 1.1 and irRECIST based on BICR.
- QoL.

Safety Endpoints:

- Adverse events (AEs) and serious AEs (SAEs), graded using the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0.
- Laboratory tests.
- Physical examinations.
- Electrocardiograms (ECGs).
- Vital signs.

Exploratory Endpoints:

- PK profile of N-803 in combination with avelumab and haNK.
- Immunogenicity profile of N-803 in combination with avelumab and haNK.
- Tumor molecular profiles and correlations with subject outcomes.
- Therapy-induced changes in immune responses and correlations with subject outcomes.
- Molecular changes in cfDNA and cfRNA and correlations with subject outcomes.

Enrollment (planned):

This is a single-arm study and enrollment will utilize Simon's two-stage optimal design for the primary efficacy endpoint, ORR, evaluated using RECIST 1.1 based on BICR. A clinically meaningful ORR for this indication is an ORR >10% and the optimal ORR is 25%. Initially, 18 subjects will be enrolled in the study. If ≤ 2 subjects have a confirmed response, study enrollment will be terminated; otherwise, an additional 25 subjects will be enrolled in the second stage, for a total of 43 subjects in the study.

Eligibility Criteria

Inclusion Criteria:

1. Age ≥ 18 years on day of signing informed consent.
2. Able to understand and provide a signed informed consent that fulfills the relevant IRB or Independent Ethics Committee (IEC) guidelines.
3. Histologically-confirmed metastatic MCC that has progressed during treatment or within 6 months after completing treatment with single-agent avelumab or pembrolizumab therapy, as per FDA indication.
4. Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 2.
5. Have at least 1 measurable lesion of ≥ 1.0 cm.
6. Must have a recent formalin-fixed, paraffin-embedded (FFPE) tumor biopsy specimen following the conclusion of the most recent anticancer treatment and be willing to release the specimen for exploratory tumor molecular profiling. If an historic specimen is not available, the subject must be willing to undergo a biopsy during the screening period, if considered safe by the Investigator. If safety concerns preclude collection of a biopsy during the screening period, a tumor biopsy specimen collected prior to the conclusion of the most recent anticancer treatment may be used.
7. Must be willing to provide blood samples prior to the start of treatment on this study for exploratory analyses.
8. Must be willing to provide a tumor biopsy specimen 8 weeks after the start of treatment for exploratory analyses, if considered safe by the Investigator.
9. Ability to attend required study visits and return for adequate follow-up, as required by this protocol.
10. Agreement to practice effective contraception for female subjects of child-bearing potential and non-sterile males. Female subjects of child-bearing potential must agree to use effective contraception for up to 1 year after completion of therapy, and non-sterile male subjects must agree to use a condom for up to 4 months after treatment. Effective contraception includes surgical sterilization (eg, vasectomy, tubal ligation), two forms of barrier methods (eg, condom, diaphragm) used with spermicide, intrauterine devices (IUDs), and abstinence.

Exclusion Criteria:

1. Serious uncontrolled concomitant disease that would contraindicate the use of the investigational drug used in this study or that would put the subject at high risk for treatment-related complications.
2. Systemic autoimmune disease (eg, lupus erythematosus, rheumatoid arthritis, Addison's disease, or autoimmune disease associated with lymphoma).
3. History of organ transplant requiring immunosuppression.
4. History of or active inflammatory bowel disease (eg, Crohn's disease, ulcerative colitis).
5. Inadequate organ function, evidenced by the following laboratory results:
   a. Absolute neutrophil count (ANC) < 900 cells/mm^3.
   b. Platelet count < 75,000 cells/mm^3.
   c. Total bilirubin greater than twice the upper limit of normal (ULN; unless the subject has documented Gilbert's syndrome).
   d. Aspartate aminotransferase (AST [SGOT]) or alanine aminotransferase (ALT [SGPT]) > 2.5 × ULN (> 5 × ULN in subjects with liver metastases).
   e. Alkaline phosphatase (ALP) levels > 2.5 × ULN (> 5 × ULN in subjects with liver metastases, or >10 × ULN in subjects with bone metastases).
6. Uncontrolled hypertension (systolic > 160 mm Hg and/or diastolic > 110 mm Hg) or clinically significant (ie, active) cardiovascular disease, cerebrovascular accident/stroke, or myocardial infarction within 6 months prior to first study medication; unstable angina; congestive heart failure of New York Heart Association grade 2 or higher; or serious cardiac arrhythmia requiring medication.
7. Dyspnea at rest due to complications of advanced malignancy or other disease requiring continuous oxygen therapy.
8. Positive results of screening test for human immunodeficiency virus (HIV).
9. Current chronic daily treatment (continuous for > 3 months) with systemic corticosteroids (dose equivalent to or greater than 10 mg/day methylprednisolone), excluding inhaled steroids. Short-term steroid use to prevent intravenous (IV) contrast allergic reaction or anaphylaxis in subjects who have known contrast allergies is allowed.
10. Known hypersensitivity to any component of the study medication(s).
11. Subjects taking any medication(s) (herbal or prescribed) known to have an adverse drug reaction with any of the study medications.
12. Participation in an investigational drug study or history of receiving any investigational treatment within 14 days prior to screening for this study, except for testosterone-lowering therapy in men with prostate cancer.
13. Assessed by the Investigator to be unable or unwilling to comply with the requirements of the protocol.
14. Concurrent participation in any interventional clinical trial.
15. Pregnant and nursing women.

Products, Dosage, and Mode of Administration:		
Investigational Products	**Dosage**	**Mode of Administration**
haNK	2×10^9 cells/dose	IV
N-803	15 µg/kg	SC
Approved Products	**Dosage**	**Mode of Administration**
Avelumab	10 mg/kg	IV

Duration of Treatment:

Subjects will be treated for up to 2 years or until they experience PD, unacceptable toxicity (not correctable with dose modification), withdraw consent, or if the Investigator feels it is no longer in their best interest to continue treatment.

Duration of Follow-up:

Subjects who discontinue study treatment should remain in the study and continue to be followed for:

- CT or MRI imaging and response assessments (see Section 6.1.2)
- Collection of vital status every 90 days (± 14 days)

Subjects will be followed until either death (any cause) or for a minimum of 18 months past administration of the first dose of study drug.

Reference Therapy, Dosage, and Mode of Administration:

Not applicable.

Evaluation of Endpoints:

Safety:

Safety endpoints include assessments of treatment-emergent AEs, SAEs, and clinically significant changes in safety laboratory tests, physical examinations, ECGs, and vital signs. All subjects will be evaluable for toxicity from the time of their first study treatment. Toxicities will be graded using the NCI CTCAE Version 5.0.

Efficacy:

ORR, DOR, and PFS will be assessed by CT or MRI of target and non-target lesions every 8 weeks during the first year and every 12 weeks thereafter, and will be evaluated in accordance with RECIST 1.1 and irRECIST. In order to document PD, unscheduled tumor assessments should be done if the Investigator observes any signs and symptoms of PD. Experimental treatment may continue and an imaging assessment should be done 4–6 weeks after the initial PD assessment to rule out tumor pseudoprogression. If pseudoprogression is observed, the subject is allowed to continue experimental treatment and response assessments will continue every 8 or 12 weeks and will be evaluated per irRECIST. For responding subjects (PR or CR), a confirmatory response assessment should be done 4-6 weeks after the initial response. OS, DSS, and DCR will also be assessed.

An assessment of QoL will be conducted via PROs using the Functional Assessment of Cancer Therapy-Melanoma (FACT-M) instrument on study day 1 and every 12 weeks during therapy, and at the EOT visit.

Exploratory Analyses:

N-803 Immunogenicity Analysis: Immunogenicity testing for N-803 antibodies in subject serum samples will be conducted using a direct sandwich enzyme-linked immunosorbent assay (ELISA) with plates coated with N-803. Biotinylated N-803 will be used for detection with standard HRP-labeled streptavidin reagents. Anti-IL-15 antibody will serve as a reference standard and serum from N-803-immunized mice will serve as a positive control. Anti-N-803 antibody levels in subject samples will be determined based on comparison to pretreatment samples. Concentration of N-803 will be determined in all immunogenicity samples.

N-803 Pharmacokinetic Analysis: Pharmacokinetic testing for N-803 in subject serum samples will be conducted using a validated ELISA method. An IL-15-specific antibody will be used as a capture antibody. Samples will be applied and allowed to bind. After the appropriate wash conditions, labeled human IL-15 or IgG1-specific antibodies will be used for detection with colorimetric ELISA substrates. For analysis of clinical samples, purified N-803 reference standards and control human serum containing high and low levels of added N-803 will be included, and the level of N-803 in patient samples will be determined based on the N-803 standard curve.

Tumor Molecular Profiling: Genomic sequencing of tumor cells from tissue relative to non-tumor cells from whole blood will be conducted to identify tumor-specific genomic variances that may contribute to disease progression and/or response to treatment. RNA sequencing will be conducted to provide expression data and give relevance to DNA mutations. Quantitative proteomics analysis will be conducted to determine the absolute amounts of specific proteins, to confirm expression of genes that are correlative of disease progression and/or response, and to determine the cutoff values for response.

Immunologic Analysis: Immune responses to the therapy regimen will be evaluated by standard immune assays. Correlations between therapy-induced immune changes and subject outcomes will be assessed.

cfDNA/cfRNA Analysis: cfDNA and cfRNA will be extracted from plasma obtained from whole blood. Expression levels of specific tumor- and immune-related analytes will be assessed by quantitative real-time polymerase chain reaction (qPCR) and possibly other methods (eg, DNA/RNA sequencing) and analyzed for correlations with subject outcomes.

Statistical Methods:

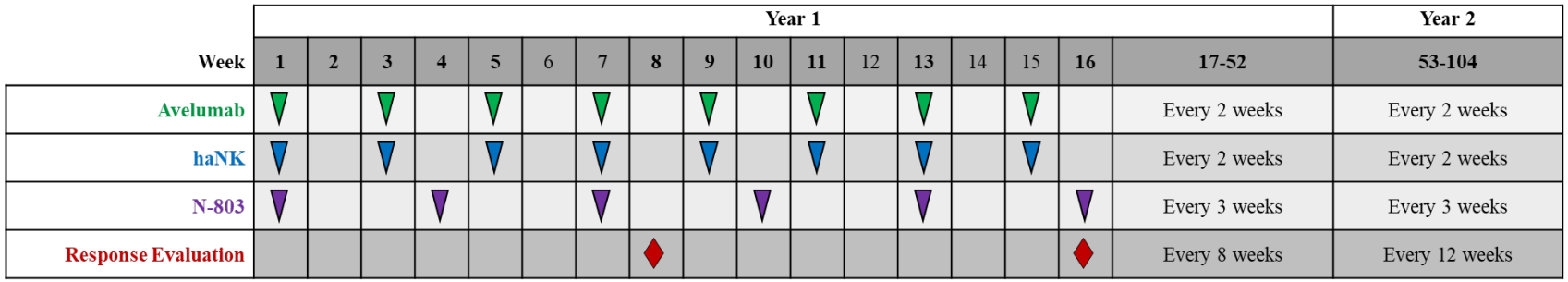
The primary efficacy endpoint, ORR, will be evaluated using RECIST 1.1 based on BICR. ORR will be analyzed using a two-sided exact 95% confidence interval (CI) derived from the Clopper-Pearson method. A clinically meaningful ORR for this indication is an ORR >10%. If the lower bound of the 95% CI for ORR is greater >10% then the combination therapy of avelumab, haNK, and N-803 in subjects with MCC who have progressed on or after checkpoint inhibitor therapy will be considered effective.

DOR, PFS, OS, and DSS will be analyzed using Kaplan-Meier methods. Descriptive statistics of PROs will be presented.

Overall safety will be assessed by descriptive analyses using tabulated frequencies of AEs by grade using CTCAE Version 5.0 in terms of treatment-emergent AEs, SAEs, and clinically significant changes in safety laboratory tests, physical examinations, ECGs, and vital signs.

Correlations of tumor molecular profiles, therapy-induced changes in immune responses, and molecular changes in cfDNA and cfRNA with subject outcomes will be explored.

Figure 1: Study Treatment Schema



APPENDIX 1. SPONSOR SIGNATURE

Study Title:	A phase 2 study of combination therapy with an IL-15 superagonist (N-803), off-the-shelf CD16-targeted natural killer cells (haNK), and avelumab without cytotoxic chemotherapy in subjects with Merkel cell carcinoma (MCC) that has progressed on or after treatment with a checkpoint inhibitor.
Study Number:	QUILT-3.063
Version Number:	1
Final Date:	30 November 2018

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

Signed: _____ Date: 12-4-18

John H. Lee, MD
Senior Vice President Adult Medical Affairs,
NantKwest Inc.
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A PHASE 2 STUDY OF COMBINATION THERAPY WITH AN IL-15 SUPERAGONIST (N-803), OFF-THE-SHELF CD16-TARGETED NATURAL KILLER CELLS (HANK), AND AVELUMAB WITHOUT CYTOTOXIC CHEMOTHERAPY IN SUBJECTS WITH MERKEL CELL CARCINOMA (MCC) THAT HAS PROGRESSED ON OR AFTER TREATMENT WITH A CHECKPOINT INHIBITOR

Study Number:	**QUILT-3.063**
IND Sponsor:	NantKwest, Inc. 9920 Jefferson Blvd Culver City, CA 90232
Sponsor Contact: **(For medical questions/emergencies)**	John H. Lee, MD Senior Vice President Adult Medical Affairs, NantKwest Inc. 9920 Jefferson Blvd Culver City, CA 90232 Email: John.Lee@Nantkwest.com Cell Phone: +1-605-610-6391

Protocol Version	**Date**
Version 1	30 November 2018
Version 2	25 February 2019

STATEMENT OF COMPLIANCE

This trial will be conducted in accordance with Good Clinical Practice (GCP) as described in the International Conference on Harmonization Guideline ICH GCP E6 (R2) and in accordance with United States (US) Code of Federal Regulations (CFR) applicable to clinical studies (45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, and 21 CFR Part 312) and the general ethical principles outlined in the Declaration of Helsinki. The study will receive approval from an Institutional Review Board (IRB) prior to commencement. The Principal Investigator will assure that no deviation from or changes to the protocol will take place without prior agreement from NantKwest and documented approval from the IRB, except where necessary to eliminate an immediate hazard(s) to the trial participants.

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

Principal Investigator:

Signed: _____ Date: _____

PROTOCOL SYNOPSIS

Name of Sponsor/Company:
NantKwest, Inc.

Name of Investigational Products:

1. haNK™, NK-92 [CD16.158V, ER IL-2], Suspension for Infusion (haNK™ for Infusion)
2. N-803 (also known as ALT-803; recombinant human superagonist interleukin-15 (IL-15) complex [also known as IL-15N72D:IL-15RαSu/IgG1 Fc complex])

Name of Approved Products:

3. Avelumab (BAVENCIO® injection, for intravenous [IV] use)

Name of Active Ingredients:

Investigational Products

1. NK-92 [CD16.158V, ER IL2] cells
2. N-803, recombinant human superagonist IL-15 complex (also known as IL-15N72D: IL-15RαSu/IgG1 Fc complex)

Approved Products

3. Avelumab

Title of Study:
A phase 2 study of combination therapy with an IL-15 superagonist (N-803), off-the-shelf CD16-targeted natural killer cells (haNK), and avelumab without cytotoxic chemotherapy in subjects with Merkel cell carcinoma (MCC) that has progressed on or after treatment with a checkpoint inhibitor.

Study Number:
QUILT-3.063

Study Phase:
Phase 2

Study Objectives:

Primary Objectives

- Evaluate the safety of the combination treatment of avelumab, haNK, and N-803 in subjects with MCC that has progressed on or after checkpoint inhibitor therapy.
- Determine the efficacy of the combination treatment of avelumab, haNK, and N-803 in subjects with MCC that has progressed on or after checkpoint inhibitor therapy by objective response rate (ORR) using Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST 1.1) based on Blinded Independent Central Review (BICR).

Secondary Objective

- Obtain additional measures of efficacy by progression-free survival (PFS), overall survival (OS), disease-specific survival (DSS), duration of response (DOR), disease control rate (DCR), and quality of life (QoL) by patient-reported outcomes (PROs).

Exploratory Objectives

- Assess the pharmacokinetic (PK) and immunogenicity profiles of N-803 in combination with haNK and avelumab.
- Assess tumor molecular profiles (genomics, transcriptomics, and proteomics) and their correlations with subject outcomes.

Study Design:

This is a phase 2 study to evaluate the safety and efficacy of the combination therapy of avelumab, haNK, and N-803 in subjects with MCC that has progressed on or after checkpoint inhibitor therapy as assessed by ORR. Subjects must have progressed on or within 6 months of completing treatment with single-agent avelumab or pembrolizumab, as per FDA indication. Combination therapy will be administered as follows:

Day 1, every 2 weeks:

- Avelumab (10 mg/kg IV)
- haNK (2×10^9 cells/dose IV)

Day 1, every 3 weeks:

- N-803 (15 μg/kg subcutaneous [SC] injection)

The initial 3 subjects will be enrolled in a staggered fashion, with a 14-day interval between each subject to enable the capture and monitoring of any acute and subacute toxicities. Preliminary assessment of the safety of the treatment regimen will occur by the NantKwest Safety Review Committee (SRC) after the third subject has completed 14 days of treatment. Enrollment will continue if data from the initial 3 subjects suggest that the combination is tolerable.

Subjects will continue to receive treatment for up to 2 years. Treatment in the study will be discontinued if the subject experiences confirmed progressive disease (PD) or unacceptable toxicity (not corrected with dose reduction), withdraws consent, or if the Investigator feels it is no longer in the subject's best interest to continue treatment.

Tumors will be assessed at screening, and tumor response will be assessed every 8 weeks in the first year, and every 12 weeks thereafter by computed tomography (CT) or magnetic resonance imaging (MRI) of target and non-target lesions in accordance with RECIST 1.1 and immune-related RECIST (irRECIST). Unscheduled tumor assessments should be carried out if the Investigator observes any signs or symptoms of PD. When disease progression per RECIST 1.1 is initially observed, experimental treatment may continue and an imaging assessment should be done 4–6 weeks after the initial PD assessment to rule out tumor pseudoprogression. If pseudoprogression is observed, the subject is allowed to continue experimental treatment and response assessments will continue every 8 or 12 weeks and will be evaluated per irRECIST. For responding subjects (partial response [PR] or complete response [CR]), a confirmatory response assessment should be done 4–6 weeks after the initial response.

N-803 immunogenicity and PK testing will be conducted on pre-dose blood samples collected prior to treatment on this study, weekly for the first 3 weeks, during week 7, every 3 weeks thereafter during subsequent treatment, at the end-of-treatment (EOT) visit, and 6 weeks after the last treatment, as described in Section 6.4.1 and Section 6.4.2.

Exploratory tumor molecular profiling will be conducted on samples collected prior to treatment on this study, and 8 weeks after the start of treatment, as described in Section 6.4.3.

Primary Efficacy Endpoint:

- ORR by RECIST 1.1 based on BICR.

Key Secondary Efficacy Endpoint:

- DOR by RECIST 1.1 based on BICR.

Other Secondary Efficacy Endpoints:

- ORR and DOR by irRECIST based on BICR.
- PFS by RECIST 1.1 and irRECIST based on BICR.
- OS.
- DSS.
- DCR (confirmed CR, PR, or stable disease [SD] lasting for ≥ 8 weeks) by RECIST 1.1 and irRECIST based on BICR.
- QoL.

Safety Endpoints:

- Adverse events (AEs) and serious AEs (SAEs), graded using the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0.
- Laboratory tests.
- Physical examinations.
- Electrocardiograms (ECGs).
- Vital signs.

Exploratory Endpoints:

- PK profile of N-803 in combination with avelumab and haNK.
- Immunogenicity profile of N-803 in combination with avelumab and haNK.
- Tumor molecular profiles and correlations with subject outcomes.

Enrollment (planned):

This is a single-arm study and enrollment will utilize Simon's two-stage optimal design for the primary efficacy endpoint, ORR, evaluated using RECIST 1.1 based on BICR. A clinically meaningful ORR for this indication is an ORR >10% and the optimal ORR is 25%. Initially, 18 subjects will be enrolled in the study. If ≤ 2 subjects have a confirmed response, study enrollment will be terminated; otherwise, an additional 25 subjects will be enrolled in the second stage, for a total of 43 subjects in the study. The initial 3 subjects will be enrolled in a staggered fashion, with a 14-day interval between each subject.

Eligibility Criteria

Inclusion Criteria:

1. Age ≥ 18 years on day of signing informed consent.
2. Able to understand and provide a signed informed consent that fulfills the relevant IRB or Independent Ethics Committee (IEC) guidelines. If a subject lacks the capacity to consent on their own behalf, a Legally Authorized Representative may consent on behalf of the prospective subject to the subject's participation in the clinical trial.
3. Histologically-confirmed metastatic MCC that has progressed during treatment or within 6 months after completing treatment with single-agent avelumab or pembrolizumab therapy, as per FDA indication.
4. Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 2.
5. Have at least 1 measurable lesion of ≥ 1.0 cm.
6. Must have a recent formalin-fixed, paraffin-embedded (FFPE) tumor biopsy specimen following the conclusion of the most recent anticancer treatment and be willing to release the specimen for exploratory tumor molecular profiling. If an historic specimen is not available, the subject must be willing to undergo a biopsy during the screening period, if considered safe by the Investigator. If safety concerns preclude collection of a biopsy during the screening period, a tumor biopsy specimen collected prior to the conclusion of the most recent anticancer treatment may be used.
7. Must be willing to provide blood samples prior to the start of treatment on this study for exploratory analyses.
8. Must be willing to provide a tumor biopsy specimen 8 weeks after the start of treatment for exploratory analyses, if considered safe by the Investigator.
9. Ability to attend required study visits and return for adequate follow-up, as required by this protocol.

10. Agreement to practice effective contraception for female subjects of child-bearing potential and non-sterile males. Female subjects of child-bearing potential must agree to use effective contraception for up to 1 year after completion of therapy, and non-sterile male subjects must agree to use a condom for up to 4 months after treatment. Effective contraception includes surgical sterilization (eg, vasectomy, tubal ligation), two forms of barrier methods (eg, condom, diaphragm) used with spermicide, intrauterine devices (IUDs), and abstinence.

Exclusion Criteria:

1. Serious uncontrolled concomitant disease that would contraindicate the use of the investigational drug used in this study or that would put the subject at high risk for treatment-related complications.
2. Systemic autoimmune disease (eg, lupus erythematosus, rheumatoid arthritis, Addison's disease, or autoimmune disease associated with lymphoma).
3. History of organ transplant requiring immunosuppression.
4. History of or active inflammatory bowel disease (eg, Crohn's disease, ulcerative colitis).
5. Inadequate organ function, evidenced by the following laboratory results:
    a. Absolute neutrophil count (ANC) < 900 cells/mm^3.
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    c. Total bilirubin greater than twice the upper limit of normal (ULN; unless the subject has documented Gilbert's syndrome).
    d. Aspartate aminotransferase (AST [SGOT]) or alanine aminotransferase (ALT [SGPT]) > 2.5 × ULN (> 5 × ULN in subjects with liver metastases).
    e. Alkaline phosphatase (ALP) levels > 2.5 × ULN (> 5 × ULN in subjects with liver metastases, or >10 × ULN in subjects with bone metastases).
6. Uncontrolled hypertension (systolic > 160 mm Hg and/or diastolic > 110 mm Hg) or clinically significant (ie, active) cardiovascular disease, cerebrovascular accident/stroke, or myocardial infarction within 6 months prior to first study medication; unstable angina; congestive heart failure of New York Heart Association grade 2 or higher; or serious cardiac arrhythmia requiring medication.
7. Dyspnea at rest due to complications of advanced malignancy or other disease requiring continuous oxygen therapy.
8. Positive results of screening test for human immunodeficiency virus (HIV).
9. Current chronic daily treatment (continuous for > 3 months) with systemic corticosteroids (dose equivalent to or greater than 10 mg/day methylprednisolone), excluding inhaled steroids. Short-term steroid use to prevent intravenous (IV) contrast allergic reaction or anaphylaxis in subjects who have known contrast allergies is allowed.
10. Known hypersensitivity to any component of the study medication(s).
11. Subjects taking any medication(s) (herbal or prescribed) known to have an adverse drug reaction with any of the study medications.

12. Participation in an investigational drug study or history of receiving any investigational treatment within 14 days prior to screening for this study, except for testosterone-lowering therapy in men with prostate cancer.
13. Assessed by the Investigator to be unable or unwilling to comply with the requirements of the protocol.
14. Concurrent participation in any interventional clinical trial.
15. Pregnant and nursing women.

Products, Dosage, and Mode of Administration:

Investigational Products	**Dosage**	**Mode of Administration**
haNK	2×10^9 cells/dose	IV
N-803	15 µg/kg	SC
Approved Products	**Dosage**	**Mode of Administration**
Avelumab	10 mg/kg	IV

Duration of Treatment:

Subjects will be treated for up to 2 years or until they experience PD, unacceptable toxicity (not correctable with dose modification), withdraw consent, or if the Investigator feels it is no longer in their best interest to continue treatment.

Duration of Follow-up:

Subjects who discontinue study treatment should remain in the study and continue to be followed for:

- CT or MRI imaging and response assessments (see Section 6.1.2)
- Collection of vital status every 90 days (± 14 days)

Subjects will be followed until either death (any cause) or for a minimum of 18 months past administration of the first dose of study drug.

Reference Therapy, Dosage, and Mode of Administration:

Not applicable.

Evaluation of Endpoints:

Safety:

Safety endpoints include assessments of treatment-emergent AEs, SAEs, and clinically significant changes in safety laboratory tests, physical examinations, ECGs, and vital signs. All subjects will be evaluable for toxicity from the time of their first study treatment. Toxicities will be graded using the NCI CTCAE Version 5.0.

Efficacy:

ORR, DOR, and PFS will be assessed by CT or MRI of target and non-target lesions every 8 weeks during the first year and every 12 weeks thereafter, and will be evaluated in accordance with RECIST 1.1 and irRECIST. In order to document PD, unscheduled tumor assessments should be done if the Investigator observes any signs and symptoms of PD. Experimental treatment may continue and an imaging assessment should be done 4–6 weeks after the initial PD assessment to rule out tumor pseudoprogression. If pseudoprogression is observed, the subject is allowed to continue experimental treatment and response assessments will continue every 8 or 12 weeks and will be evaluated per irRECIST. For responding subjects (PR or CR), a confirmatory response assessment should be done 4-6 weeks after the initial response. OS, DSS, and DCR will also be assessed.

An assessment of QoL will be conducted via PROs using the Functional Assessment of Cancer Therapy-Melanoma (FACT-M) instrument on study day 1 and every 12 weeks during therapy, and at the EOT visit.

Exploratory Analyses:

N-803 Immunogenicity Analysis: Immunogenicity testing for N-803 antibodies in subject serum samples will be conducted using a direct sandwich enzyme-linked immunosorbent assay (ELISA) with plates coated with N-803. Biotinylated N-803 will be used for detection with standard HRP-labeled streptavidin reagents. Anti-IL-15 antibody will serve as a reference standard and serum from N-803-immunized mice will serve as a positive control. Anti-N-803 antibody levels in subject samples will be determined based on comparison to pretreatment samples. Concentration of N-803 will be determined in all immunogenicity samples.

N-803 Pharmacokinetic Analysis: Pharmacokinetic testing for N-803 in subject serum samples will be conducted using a validated ELISA method. An IL-15-specific antibody will be used as a capture antibody. Samples will be applied and allowed to bind. After the appropriate wash conditions, labeled human IL-15 or IgG1-specific antibodies will be used for detection with colorimetric ELISA substrates. For analysis of clinical samples, purified N-803 reference standards and control human serum containing high and low levels of added N-803 will be included, and the level of N-803 in patient samples will be determined based on the N-803 standard curve.

Tumor Molecular Profiling: Genomic sequencing of tumor cells from tissue relative to non-tumor cells from whole blood will be conducted to identify tumor-specific genomic variances that may contribute to disease progression and/or response to treatment. RNA sequencing will be conducted to provide expression data and give relevance to DNA mutations. Quantitative proteomics analysis will be conducted to determine the absolute amounts of specific proteins, to confirm expression of genes that are correlative of disease progression and/or response, and to determine the cutoff values for response.

Statistical Methods:

The primary efficacy endpoint, ORR, will be evaluated using RECIST 1.1 based on BICR. ORR will be analyzed using a two-sided exact 95% confidence interval (CI) derived from the Clopper-Pearson method. A clinically meaningful ORR for this indication is an ORR >10%. If the lower bound of the 95% CI for ORR is >10% then the combination therapy of avelumab, haNK, and N-803 in subjects with MCC who have progressed on or after checkpoint inhibitor therapy will be considered effective.

DOR, PFS, OS, and DSS will be analyzed using Kaplan-Meier methods. Descriptive statistics of PROs will be presented.

Overall safety will be assessed by descriptive analyses using tabulated frequencies of AEs by grade using CTCAE Version 5.0 in terms of treatment-emergent AEs, SAEs, and clinically significant changes in safety laboratory tests, physical examinations, ECGs, and vital signs.

Correlations of tumor molecular profiles with subject outcomes will be explored.

Figure 1: Study Treatment Schema

	Year 1																Year 2
Week	**1**	2	**3**	**4**	**5**	6	**7**	**8**	**9**	**10**	**11**	12	**13**	14	**15**	**16**	**17-52**	**53-104**
Avelumab	▼		▼		▼		▼		▼		▼		▼		▼		Every 2 weeks	Every 2 weeks
haNK	▼		▼		▼		▼		▼		▼		▼		▼		Every 2 weeks	Every 2 weeks
N-803	▼			▼			▼			▼			▼			▼	Every 3 weeks	Every 3 weeks
Response Evaluation								◆								◆	Every 8 weeks	Every 12 weeks

APPENDIX 1. SPONSOR SIGNATURE

Study Title:	A phase 2 study of combination therapy with an IL-15 superagonist (N-803), off-the-shelf CD16-targeted natural killer cells (haNK), and avelumab without cytotoxic chemotherapy in subjects with Merkel cell carcinoma (MCC) that has progressed on or after treatment with a checkpoint inhibitor.
Study Number:	QUILT-3.063
Version Number:	2
Final Date:	25 February 2019

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

Signed: _____ Date: Feb 27 2019

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A PHASE 2 STUDY OF COMBINATION THERAPY WITH AN IL-15 SUPERAGONIST (N-803), OFF-THE-SHELF CD16-TARGETED NATURAL KILLER CELLS (haNK), AND AVELUMAB WITHOUT CYTOTOXIC CHEMOTHERAPY IN SUBJECTS WITH MERKEL CELL CARCINOMA (MCC) THAT HAS PROGRESSED ON OR AFTER TREATMENT WITH A CHECKPOINT INHIBITOR

Study Number:	**QUILT-3.063**
IND Sponsor:	NantKwest, Inc. 9920 Jefferson Blvd Culver City, CA 90232
Sponsor Contact: **(For medical questions/emergencies)**	John H. Lee, MD Senior Vice President Adult Medical Affairs, NantKwest Inc. 9920 Jefferson Blvd Culver City, CA 90232 Email: John.Lee@Nantkwest.com Cell Phone: +1-605-610-6391

Protocol Version	**Date**
Version 1	30 November 2018
Version 2	25 February 2019
Version 3	25 February 2020

STATEMENT OF COMPLIANCE

This trial will be conducted in accordance with Good Clinical Practice (GCP) as described in the International Conference on Harmonization Guideline ICH GCP E6 (R2) and in accordance with United States (US) Code of Federal Regulations (CFR) applicable to clinical studies (45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, and 21 CFR Part 312) and the general ethical principles outlined in the Declaration of Helsinki. The study will receive approval from an Institutional Review Board (IRB) prior to commencement. The Principal Investigator will assure that no deviation from or changes to the protocol will take place without prior agreement from NantKwest and documented approval from the IRB, except where necessary to eliminate an immediate hazard(s) to the trial participants.

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

Principal Investigator:

Signed: _____ Date: _____

PROTOCOL SYNOPSIS

Name of Sponsor/Company: NantKwest, Inc.
Name of Investigational Products: 1. haNK™, NK-92 [CD16.158V, ER IL-2], Suspension for Infusion (haNK™ for Infusion) 2. N-803 (also known as ALT-803; recombinant human superagonist interleukin-15 (IL-15) complex [also known as IL-15N72D:IL-15RαSu/IgG1 Fc complex]) **Name of Approved Products:** 3. Avelumab (BAVENCIO® injection, for intravenous [IV] use)
Name of Active Ingredients: **Investigational Products:** 1. NK-92 [CD16.158V, ER IL2] cells 2. N-803, recombinant human superagonist IL-15 complex (also known as IL-15N72D: IL-15RαSu/IgG1 Fc complex) **Approved Products:** 3. Avelumab
Title of Study: A phase 2 study of combination therapy with an IL-15 superagonist (N-803), off-the-shelf CD16-targeted natural killer cells (haNK), and avelumab without cytotoxic chemotherapy in subjects with Merkel cell carcinoma (MCC) that has progressed on or after treatment with a checkpoint inhibitor.
Study Number: QUILT-3.063
Study Phase: Phase 2

Study Objectives:

Primary Objectives

- Evaluate the safety of the combination treatment of avelumab, haNK, and N-803 in subjects with MCC that has progressed on or after checkpoint inhibitor therapy.
- Determine the efficacy of the combination treatment of avelumab, haNK, and N-803 in subjects with MCC that has progressed on or after checkpoint inhibitor therapy by objective response rate (ORR) using Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST 1.1) based on Blinded Independent Central Review (BICR).

Secondary Objective

- Obtain additional measures of efficacy by progression-free survival (PFS), overall survival (OS), disease-specific survival (DSS), duration of response (DOR), disease control rate (DCR), and quality of life (QoL) by patient-reported outcomes (PROs).

Exploratory Objectives

- Assess the pharmacokinetic (PK) and immunogenicity profiles of N-803 in combination with haNK and avelumab.
- Assess tumor molecular profiles (genomics and transcriptomics) and their correlations with subject outcomes.

Study Design:

This is an open-label, phase 2, single-arm study to evaluate the safety and efficacy by ORR of combination therapy with avelumab, haNK, and N-803 in subjects with MCC that has progressed on or after checkpoint inhibitor therapy. Subjects must have progressed on or within 6 months of completing treatment with single-agent avelumab or pembrolizumab, as per FDA indication. Combination therapy will be administered as follows:

Every 2 weeks:

- Avelumab (800 mg IV)
- haNK (2×10^9 cells/dose IV)

Every 3 weeks:

- N-803 (15 μg/kg subcutaneous [SC] injection)

The initial 3 subjects will be dosed in a staggered fashion, with a 14-day interval between each subject to enable the capture and monitoring of any acute and subacute toxicities. Preliminary assessment of the safety of the treatment regimen will occur by the NantKwest Safety Review Committee (SRC) after the third subject has completed 14 days of treatment. Enrollment will continue if data from the initial 3 subjects suggest that the combination is tolerable.

Subjects will continue to receive treatment for up to 2 years. Treatment in the study will be discontinued if the subject experiences confirmed PD by modified RECIST guidelines for immunotherapy trials (iRECIST), unacceptable toxicity (not corrected with dose reduction), withdraws consent, or if the Investigator feels it is no longer in the subject's best interest to continue treatment.

Tumors will be assessed at screening, and tumor response will be assessed every 8 weeks in the first year and every 12 weeks thereafter by computed tomography (CT) or magnetic resonance imaging (MRI) of target and non-target lesions in accordance with RECIST 1.1 and iRECIST. Unscheduled tumor assessments should be carried out if the Investigator observes any signs or symptoms of PD. When disease progression per RECIST 1.1 is initially observed, experimental treatment may continue and an imaging assessment should be done 4–8 weeks after the initial PD assessment to rule out tumor pseudoprogression. If pseudoprogression is observed, the subject is allowed to continue experimental treatment and response assessments will continue every 8 or 12 weeks and will be evaluated per iRECIST. For responding subjects (partial response [PR] or complete response [CR]), a confirmatory response assessment should be done 4–8 weeks after the initial response.

N-803 immunogenicity and PK testing will be conducted on blood samples collected before the first treatment on this study, prior to dosing on weeks 1, 3, and 7 and every 3 weeks thereafter during the treatment period, and at the end-of-treatment (EOT) visit, as described in Section 6.3.1 and Section 6.3.2.

Exploratory tumor molecular profiling will be conducted on samples collected prior to treatment on this study, and 8 weeks after the start of treatment, as described in Section 6.3.3.

Primary Efficacy Endpoint:

- ORR by RECIST 1.1 based on BICR.

Key Secondary Efficacy Endpoint:

- DOR by RECIST 1.1 based on BICR.

Other Secondary Efficacy Endpoints:

- ORR and DOR by iRECIST based on BICR.
- PFS by RECIST 1.1 and iRECIST based on BICR.
- OS.
- DSS.
- DCR (confirmed CR, PR, or stable disease [SD] lasting for ≥ 8 weeks) by RECIST 1.1 and iRECIST based on BICR.
- QoL.

Safety Endpoints:

- Adverse events (AEs) and serious AEs (SAEs), graded using the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0.
- Laboratory tests.
- Physical examinations.
- Electrocardiograms (ECGs).
- Vital signs.

Exploratory Endpoints:

- PK profile of N-803 in combination with avelumab and haNK.

- Immunogenicity profile of N-803 in combination with avelumab and haNK.
- Tumor molecular profiles and correlations with subject outcomes.

Enrollment (planned):

This is a single-arm study and enrollment will utilize Simon's two-stage optimal design for the primary efficacy endpoint, ORR, evaluated using RECIST 1.1 based on BICR. A clinically meaningful ORR for this indication is an ORR >10% and the optimal ORR is 25%. Initially, 18 subjects will be enrolled in the study. If ≤ 2 subjects have a confirmed response, study enrollment will be terminated; otherwise, an additional 25 subjects will be enrolled in the second stage, for a total of 43 subjects enrolled in the study. The initial 3 subjects will be dosed in a staggered fashion, with a 14-day interval between each subject.

Eligibility Criteria

Inclusion Criteria:

1. Age ≥ 18 years on day of signing informed consent.
2. Able to understand and provide a signed informed consent that fulfills the relevant IRB or Independent Ethics Committee (IEC) guidelines. If a subject lacks the capacity to consent on their own behalf, a Legally Authorized Representative may consent on behalf of the prospective subject to the subject's participation in the clinical trial.
3. Histologically-confirmed metastatic MCC that has progressed during treatment or within 6 months after completing treatment with single-agent avelumab or pembrolizumab therapy, as per FDA indication.
4. Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 2.
5. Have at least 1 measurable lesion of ≥ 1.0 cm.
6. Must have a recent formalin-fixed, paraffin-embedded (FFPE) tumor biopsy specimen following the conclusion of the most recent anticancer treatment and be willing to release the specimen for exploratory tumor molecular profiling. If an historic specimen is not available, the subject must be willing to undergo a biopsy during the screening period, if considered safe by the Investigator. If safety concerns preclude collection of a biopsy during the screening period, a tumor biopsy specimen collected prior to the conclusion of the most recent anticancer treatment may be used.
7. Must be willing to provide blood samples for exploratory analyses.
8. Must be willing to provide a tumor biopsy specimen 8 weeks after the start of treatment for exploratory analyses, if considered safe by the Investigator.
9. Ability to attend required study visits and return for adequate follow-up, as required by this protocol.

10. Agreement to practice effective contraception for female subjects of child-bearing potential and non-sterile males. Female subjects of child-bearing potential must agree to use effective contraception for up to 1 year after completion of therapy, and non-sterile male subjects must agree to use a condom for up to 4 months after treatment. Effective contraception includes surgical sterilization (eg, vasectomy, tubal ligation), two forms of barrier methods (eg, condom, diaphragm) used with spermicide, intrauterine devices (IUDs), and abstinence.

Exclusion Criteria:

1. Serious uncontrolled concomitant disease that would contraindicate the use of the investigational drug used in this study or that would put the subject at high risk for treatment-related complications.
2. Systemic autoimmune disease (eg, lupus erythematosus, rheumatoid arthritis [subjects with mild rheumatoid arthritis that aren't currently receiving treatment for their disease are eligible for enrollment], Addison's disease, or autoimmune disease associated with lymphoma).
3. History of organ transplant requiring immunosuppression.
4. History of or active inflammatory bowel disease (eg, Crohn's disease, ulcerative colitis).
5. Inadequate organ function, evidenced by the following laboratory results:
   a. Absolute neutrophil count (ANC) < 900 cells/mm^3.
   b. Platelet count < 75,000 cells/mm^3.
   c. Total bilirubin greater than twice the upper limit of normal (ULN; unless the subject has documented Gilbert's syndrome).
   d. Aspartate aminotransferase (AST [SGOT]) or alanine aminotransferase (ALT [SGPT]) > 2.5 × ULN (> 5 × ULN in subjects with liver metastases).
   e. Alkaline phosphatase (ALP) levels > 2.5 × ULN (> 5 × ULN in subjects with liver metastases, or >10 × ULN in subjects with bone metastases).

   Each study site should use its institutional ULN to determine eligibility.
6. Uncontrolled hypertension (systolic > 160 mm Hg and/or diastolic > 110 mm Hg) or clinically significant (ie, active) cardiovascular disease, cerebrovascular accident/stroke, or myocardial infarction within 6 months prior to first study medication; unstable angina; congestive heart failure of New York Heart Association grade 2 or higher; or serious cardiac arrhythmia requiring medication.
7. Dyspnea at rest due to complications of advanced malignancy or other disease requiring continuous oxygen therapy.
8. Current chronic daily treatment (continuous for > 3 months) with systemic corticosteroids (dose equivalent to or greater than 10 mg/day methylprednisolone), excluding inhaled steroids. Short-term steroid use to prevent intravenous (IV) contrast allergic reaction or anaphylaxis in subjects who have known contrast allergies is allowed.
9. Known hypersensitivity to any component of the study medication(s), including anaphylactic reaction to sulfur-containing medications.
10. Subjects taking any medication(s) (herbal or prescribed) known to have an adverse drug reaction with any of the study medications.

11. Participation in an investigational drug study or history of receiving any investigational treatment within 14 days prior to the start of treatment on this study, except for testosterone-lowering therapy in men with prostate cancer.
12. Assessed by the Investigator to be unable or unwilling to comply with the requirements of the protocol.
13. Concurrent participation in any interventional clinical trial.
14. Pregnant and nursing women.

Products, Dosage, and Mode of Administration:

Investigational Products	**Dosage**	**Mode of Administration**
haNK	2×10^9 cells/dose	IV
N-803	15 µg/kg	SC
Approved Products	**Dosage**	**Mode of Administration**
Avelumab	800 mg	IV

Duration of Treatment:

Subjects will be treated for up to 2 years or until they experience confirmed PD by iRECIST, unacceptable toxicity (not correctable with dose modification), withdraw consent, or if the Investigator feels it is no longer in their best interest to continue treatment.

Duration of Follow-up:

Subjects who discontinue study treatment should remain in the study and continue to be followed for:

- CT or MRI imaging and response assessments (see Section 6.1.2)
- Collection of vital status every 90 days (± 14 days)
- Resolution of any SAEs attributed to treatment.

Each subject will be followed until either death (any cause) or for a minimum of 18 months past administration of the first dose of study drug.

Reference Therapy, Dosage, and Mode of Administration:

Not applicable.

Evaluation of Endpoints:

Safety:

Safety endpoints include assessments of treatment-emergent AEs, SAEs, and clinically significant changes in safety laboratory tests, physical examinations, ECGs, and vital signs. All subjects will be evaluable for toxicity from the time of their first study treatment. Toxicities will be graded using the NCI CTCAE Version 5.0.

Efficacy:

ORR, DOR, and PFS will be assessed by CT or MRI of target and non-target lesions every 8 weeks during the first year and every 12 weeks thereafter, and will be evaluated in accordance with RECIST 1.1 and iRECIST. In order to document PD, unscheduled tumor assessments should be done if the Investigator observes any signs and symptoms of PD. Experimental treatment may continue and an imaging assessment should be done 4–8 weeks after the initial PD assessment to rule out tumor pseudoprogression. If pseudoprogression is observed, the subject is allowed to continue experimental treatment and response assessments will continue every 8 or 12 weeks and will be evaluated per iRECIST. For responding subjects (PR or CR), a confirmatory response assessment should be done 4-8 weeks after the initial response. OS, DSS, and DCR will also be assessed.

An assessment of QoL will be conducted via PROs using the Functional Assessment of Cancer Therapy-Melanoma (FACT-M) instrument on study day 1 and every 12 weeks during therapy, and at the EOT visit.

Exploratory Analyses:

N-803 Immunogenicity Analysis: Immunogenicity testing for N-803 antibodies in subject serum samples will be conducted using a direct sandwich enzyme-linked immunosorbent assay (ELISA).

N-803 Pharmacokinetic Analysis: Pharmacokinetic testing for N-803 in subject serum samples will be conducted using a validated ELISA method.

Tumor Molecular Profiling: Genomic sequencing of tumor cells from tissue relative to non-tumor cells from whole blood will be conducted to identify tumor-specific genomic variances that may contribute to disease progression and/or response to treatment. RNA sequencing will be conducted to provide expression data and give relevance to DNA mutations.

Statistical Methods:

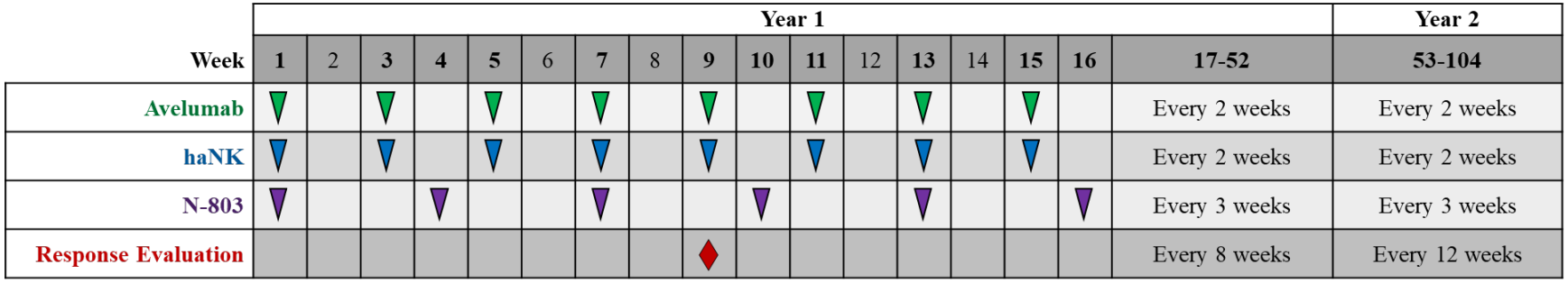
The primary efficacy endpoint, ORR, will be evaluated using RECIST 1.1 based on BICR. ORR will be analyzed using a two-sided exact 95% confidence interval (CI) derived from the Clopper-Pearson method. A clinically meaningful ORR for this indication is an ORR > 10%. If the lower bound of the 95% CI for ORR is > 10% then the combination therapy of avelumab, haNK, and N-803 in subjects with MCC who have progressed on or after checkpoint inhibitor therapy will be considered effective.

DOR, PFS, OS, and DSS will be analyzed using Kaplan-Meier methods. Descriptive statistics of PROs will be presented.

Overall safety will be assessed by descriptive analyses using tabulated frequencies of AEs by grade using CTCAE Version 5.0 in terms of treatment-emergent AEs, SAEs, and clinically significant changes in safety laboratory tests, physical examinations, ECGs, and vital signs.

Correlations of tumor molecular profiles with subject outcomes will be explored.

Figure 1: Study Treatment Schema



APPENDIX 1. SPONSOR SIGNATURE

Study Title:	A phase 2 study of combination therapy with an IL-15 superagonist (N-803), off-the-shelf CD16-targeted natural killer cells (haNK), and avelumab without cytotoxic chemotherapy in subjects with Merkel cell carcinoma (MCC) that has progressed on or after treatment with a checkpoint inhibitor.
Study Number:	QUILT-3.063
Version Number:	3
Final Date:	25 February 2020

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

Signed: _____ Date: 2-27-2020

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A PHASE 2 STUDY OF COMBINATION THERAPY WITH AN IL-15 SUPERAGONIST (N-803), OFF-THE-SHELF CD16-TARGETED NATURAL KILLER CELLS (haNK), AND AVELUMAB WITHOUT CYTOTOXIC CHEMOTHERAPY IN SUBJECTS WITH MERKEL CELL CARCINOMA (MCC) THAT HAS PROGRESSED ON OR AFTER TREATMENT WITH A CHECKPOINT INHIBITOR

Study Number:	**QUILT-3.063**
IND Sponsor:	ImmunityBio, Inc. 9920 Jefferson Blvd Culver City, CA 90232
Sponsor Contact: **(For medical questions/emergencies)**	Lennie Sender, MD Chief Operating Officer ImmunityBio, Inc. 9920 Jefferson Blvd Culver City, CA 90232 Email: Lennie.Sender@ImmunityBio.com Mobile Phone: +1-714-615-2350

Protocol Version	**Date**
Version 1	30 November 2018
Version 2	25 February 2019
Version 3	25 February 2020
Version 4	17 June 2021

STATEMENT OF COMPLIANCE

This trial will be conducted in accordance with Good Clinical Practice (GCP) as described in the International Conference on Harmonization Guideline ICH GCP E6 (R2) and in accordance with United States (US) Code of Federal Regulations (CFR) applicable to clinical studies (45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, and 21 CFR Part 312) and the general ethical principles outlined in the Declaration of Helsinki. The study will receive approval from an Institutional Review Board (IRB) prior to commencement. The Principal Investigator will assure that no deviation from or changes to the protocol will take place without prior agreement from ImmunityBio and documented approval from the IRB, except where necessary to eliminate an immediate hazard(s) to the trial participants.

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

Principal Investigator:

Signed: _____ Date: _____

PROTOCOL SYNOPSIS

Name of Sponsor/Company:
ImmunityBio, Inc.

Name of Investigational Products:

1. haNK™, NK-92 [CD16.158V, ER IL-2], Suspension for Infusion (haNK™ for Infusion)
2. N-803 (also known as ALT-803; recombinant human superagonist interleukin-15 (IL-15) complex [also known as IL-15N72D:IL-15RαSu/IgG1 Fc complex])

Name of Approved Products:

3. Avelumab (BAVENCIO® injection, for intravenous [IV] use)

Name of Active Ingredients:
Investigational Products:

1. NK-92 [CD16.158V, ER IL2] cells
2. N-803, recombinant human superagonist IL-15 complex (also known as IL-15N72D: IL-15RαSu/IgG1 Fc complex)

Approved Products:

3. Avelumab

Title of Study:
A phase 2 study of combination therapy with an IL-15 superagonist (N-803), off-the-shelf CD16-targeted natural killer cells (haNK), and avelumab without cytotoxic chemotherapy in subjects with Merkel cell carcinoma (MCC) that has progressed on or after treatment with a checkpoint inhibitor.

Study Number:
QUILT-3.063

Study Phase:
Phase 2

Study Objectives:

Primary Objectives

- Evaluate the safety of the combination treatment of avelumab, haNK, and N-803 in subjects with MCC that has progressed on or after checkpoint inhibitor therapy.
- Determine the efficacy of the combination treatment of avelumab, haNK, and N-803 in subjects with MCC that has progressed on or after checkpoint inhibitor therapy by objective response rate (ORR) using Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST 1.1) based on Blinded Independent Central Review (BICR).

Secondary Objective

- Obtain additional measures of efficacy by progression-free survival (PFS), overall survival (OS), disease-specific survival (DSS), duration of response (DOR), disease control rate (DCR), and quality of life (QoL) by patient-reported outcomes (PROs).

Exploratory Objectives

- Assess the pharmacokinetic (PK) and immunogenicity profiles of N-803 in combination with haNK and avelumab.
- Assess tumor molecular profiles (genomics and transcriptomics) and their correlations with subject outcomes.

Study Design:

This is an open-label, phase 2, single-arm study to evaluate the safety and efficacy by ORR of combination therapy with avelumab, haNK, and N-803 in subjects with MCC that has progressed on or after checkpoint inhibitor therapy. Subjects must have progressed on or within 6 months of completing treatment with single-agent avelumab or pembrolizumab, as per FDA indication. Combination therapy will be administered as follows:

Every 2 weeks:

- Avelumab (800 mg IV)
- haNK (2×10^9 cells/dose IV)

Every 3 weeks:

- N-803 (15 μg/kg subcutaneous [SC] injection)

The initial 3 subjects will be dosed in a staggered fashion, with a 14-day interval between each subject to enable the capture and monitoring of any acute and subacute toxicities. Preliminary assessment of the safety of the treatment regimen will occur by the ImmunityBio Safety Review Committee (SRC) after the third subject has completed 14 days of treatment. Enrollment will continue if data from the initial 3 subjects suggest that the combination is tolerable.

Subjects will continue to receive treatment for up to 2 years. Treatment in the study will be discontinued if the subject experiences confirmed PD by modified RECIST guidelines for immunotherapy trials (iRECIST), unacceptable toxicity (not corrected with dose reduction), withdraws consent, or if the Investigator feels it is no longer in the subject's best interest to continue treatment.

Tumors will be assessed at screening, and tumor response will be assessed every 8 weeks in the first year and every 12 weeks thereafter by computed tomography (CT) or magnetic resonance imaging (MRI) of target and non-target lesions in accordance with RECIST 1.1 and iRECIST. Unscheduled tumor assessments should be carried out if the Investigator observes any signs or symptoms of PD. When disease progression per RECIST 1.1 is initially observed, experimental treatment may continue and an imaging assessment should be done 4–8 weeks after the initial PD assessment to rule out tumor pseudoprogression. If pseudoprogression is observed, the subject is allowed to continue experimental treatment and response assessments will continue every 8 or 12 weeks and will be evaluated per iRECIST. For responding subjects (partial response [PR] or complete response [CR]), a confirmatory response assessment should be done 4–8 weeks after the initial response.

N-803 immunogenicity and PK testing will be conducted on blood samples collected before the first treatment on this study, prior to dosing on weeks 1, 3, and 7 and every 3 weeks thereafter during the treatment period, and at the end-of-treatment (EOT) visit, as described in Section 6.3.1 and Section 6.3.2.

Exploratory tumor molecular profiling will be conducted on samples collected prior to treatment on this study, and 8 weeks after the start of treatment, as described in Section 6.3.3.

Primary Efficacy Endpoint:

- ORR by RECIST 1.1 based on BICR.

Key Secondary Efficacy Endpoint:

- DOR by RECIST 1.1 based on BICR.

Other Secondary Efficacy Endpoints:

- ORR and DOR by iRECIST based on BICR.
- PFS by RECIST 1.1 and iRECIST based on BICR.
- OS.
- DSS.
- DCR (confirmed CR, PR, or stable disease [SD] lasting for ≥ 8 weeks) by RECIST 1.1 and iRECIST based on BICR.
- QoL.

Safety Endpoints:

- Adverse events (AEs) and serious AEs (SAEs), graded using the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0.
- Laboratory tests.
- Physical examinations.
- Electrocardiograms (ECGs).
- Vital signs.

Exploratory Endpoints:

- PK profile of N-803 in combination with avelumab and haNK.

- Immunogenicity profile of N-803 in combination with avelumab and haNK.
- Tumor molecular profiles and correlations with subject outcomes.

Enrollment (planned):

This is a single-arm study and enrollment will utilize Simon's two-stage optimal design for the primary efficacy endpoint, ORR, evaluated using RECIST 1.1 based on BICR. A clinically meaningful ORR for this indication is an ORR >10% and the optimal ORR is 25%. Initially, 18 subjects will be enrolled in the study. If ≤ 2 subjects have a confirmed response, study enrollment will be terminated; otherwise, an additional 25 subjects will be enrolled in the second stage, for a total of 43 subjects enrolled in the study. The initial 3 subjects will be dosed in a staggered fashion, with a 14-day interval between each subject.

Eligibility Criteria

Inclusion Criteria:

1. Age ≥ 18 years on day of signing informed consent.
2. Able to understand and provide a signed informed consent that fulfills the relevant IRB or Independent Ethics Committee (IEC) guidelines. If a subject lacks the capacity to consent on their own behalf, a Legally Authorized Representative may consent on behalf of the prospective subject to the subject's participation in the clinical trial.
3. Histologically-confirmed metastatic MCC that has progressed during treatment or within 6 months after completing treatment with single-agent avelumab or pembrolizumab therapy, as per FDA indication.
4. Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 2.
5. Have at least 1 measurable lesion of ≥ 1.0 cm.
6. Must have a recent formalin-fixed, paraffin-embedded (FFPE) tumor biopsy specimen following the conclusion of the most recent anticancer treatment and be willing to release the specimen for exploratory tumor molecular profiling. If an historic specimen is not available, the subject must be willing to undergo a biopsy during the screening period, if considered safe by the Investigator. If safety concerns preclude collection of a biopsy during the screening period, a tumor biopsy specimen collected prior to the conclusion of the most recent anticancer treatment may be used.
7. Must be willing to provide blood samples for exploratory analyses.
8. Must be willing to provide a tumor biopsy specimen 8 weeks after the start of treatment for exploratory analyses, if considered safe by the Investigator.
9. Ability to attend required study visits and return for adequate follow-up, as required by this protocol.
10. Agreement to practice effective contraception for female subjects of child-bearing potential and non-sterile males. Female subjects of child-bearing potential must agree to use effective contraception for up to 1 year after completion of therapy, and non-sterile male subjects must agree to use a condom for up to 4 months after treatment. Effective contraception includes

surgical sterilization (eg, vasectomy, tubal ligation), two forms of barrier methods (eg, condom, diaphragm) used with spermicide, intrauterine devices (IUDs), and abstinence.

Exclusion Criteria:

1. Serious uncontrolled concomitant disease that would contraindicate the use of the investigational drug used in this study or that would put the subject at high risk for treatment-related complications.
2. Systemic autoimmune disease (eg, lupus erythematosus, rheumatoid arthritis [subjects with mild rheumatoid arthritis that aren't currently receiving treatment for their disease are eligible for enrollment], Addison's disease, or autoimmune disease associated with lymphoma).
3. History of organ transplant requiring immunosuppression.
4. History of or active inflammatory bowel disease (eg, Crohn's disease, ulcerative colitis).
5. Inadequate organ function, evidenced by the following laboratory results:
   a. Absolute neutrophil count (ANC) < 900 cells/mm^3.
   b. Platelet count < 75,000 cells/mm^3.
   c. Total bilirubin greater than twice the upper limit of normal (ULN; unless the subject has documented Gilbert's syndrome).
   d. Aspartate aminotransferase (AST [SGOT]) or alanine aminotransferase (ALT [SGPT]) > 2.5 × ULN (> 5 × ULN in subjects with liver metastases).
   e. Alkaline phosphatase (ALP) levels > 2.5 × ULN (> 5 × ULN in subjects with liver metastases, or >10 × ULN in subjects with bone metastases).

   Each study site should use its institutional ULN to determine eligibility.
6. Uncontrolled hypertension (systolic > 160 mm Hg and/or diastolic > 110 mm Hg) or clinically significant (ie, active) cardiovascular disease, cerebrovascular accident/stroke, or myocardial infarction within 6 months prior to first study medication; unstable angina; congestive heart failure of New York Heart Association grade 2 or higher; or serious cardiac arrhythmia requiring medication.
7. Dyspnea at rest due to complications of advanced malignancy or other disease requiring continuous oxygen therapy.
8. Current chronic daily treatment (continuous for > 3 months) with systemic corticosteroids (dose equivalent to or greater than 10 mg/day methylprednisolone), excluding inhaled steroids. Short-term steroid use to prevent intravenous (IV) contrast allergic reaction or anaphylaxis in subjects who have known contrast allergies is allowed.
9. Known hypersensitivity to any component of the study medication(s), including anaphylactic reaction to sulfur-containing medications.
10. Subjects taking any medication(s) (herbal or prescribed) known to have an adverse drug reaction with any of the study medications.
11. Participation in an investigational drug study or history of receiving any investigational treatment within 14 days prior to the start of treatment on this study, except for testosterone-lowering therapy in men with prostate cancer.

12. Assessed by the Investigator to be unable or unwilling to comply with the requirements of the protocol.
13. Concurrent participation in any interventional clinical trial.
14. Pregnant and nursing women.

Products, Dosage, and Mode of Administration:

Investigational Products	**Dosage**	**Mode of Administration**
haNK	2×10^9 cells/dose	IV
N-803	15 µg/kg	SC
Approved Products	**Dosage**	**Mode of Administration**
Avelumab	800 mg	IV

Duration of Treatment:

Subjects will be treated for up to 2 years or until they experience confirmed PD by iRECIST, unacceptable toxicity (not correctable with dose modification), withdraw consent, or if the Investigator feels it is no longer in their best interest to continue treatment.

Duration of Follow-up:

Subjects who discontinue study treatment should remain in the study and continue to be followed for:

- CT or MRI imaging and response assessments (see Section 6.1.2)
- Collection of vital status every 90 days (± 14 days)
- Resolution of any SAEs attributed to treatment.

Each subject will be followed until either death (any cause) or for a minimum of 18 months past administration of the first dose of study drug.

Reference Therapy, Dosage, and Mode of Administration:

Not applicable.

Evaluation of Endpoints:

Safety:

Safety endpoints include assessments of treatment-emergent AEs, SAEs, and clinically significant changes in safety laboratory tests, physical examinations, ECGs, and vital signs. All subjects will be evaluable for toxicity from the time of their first study treatment. Toxicities will be graded using the NCI CTCAE Version 5.0.

Efficacy:

ORR, DOR, and PFS will be assessed by CT or MRI of target and non-target lesions every 8 weeks during the first year and every 12 weeks thereafter, and will be evaluated in accordance with RECIST 1.1 and iRECIST. In order to document PD, unscheduled tumor assessments should be done if the Investigator observes any signs and symptoms of PD. Experimental treatment may continue and an imaging assessment should be done 4–8 weeks after the initial PD assessment to rule out tumor pseudoprogression. If pseudoprogression is observed, the subject is allowed to continue experimental treatment and response assessments will continue every 8 or 12 weeks and will be evaluated per iRECIST. For responding subjects (PR or CR), a confirmatory response assessment should be done 4-8 weeks after the initial response. OS, DSS, and DCR will also be assessed.

An assessment of QoL will be conducted via PROs using the Functional Assessment of Cancer Therapy-Melanoma (FACT-M) instrument on study day 1 and every 12 weeks during therapy, and at the EOT visit.

Exploratory Analyses:

N-803 Immunogenicity Analysis: Immunogenicity testing for N-803 antibodies in subject serum samples will be conducted using a direct sandwich enzyme-linked immunosorbent assay (ELISA).

N-803 Pharmacokinetic Analysis: Pharmacokinetic testing for N-803 in subject serum samples will be conducted using a validated ELISA method.

Tumor Molecular Profiling: Genomic sequencing of tumor cells from tissue relative to non-tumor cells from whole blood will be conducted to identify tumor-specific genomic variances that may contribute to disease progression and/or response to treatment. RNA sequencing will be conducted to provide expression data and give relevance to DNA mutations.

Statistical Methods:

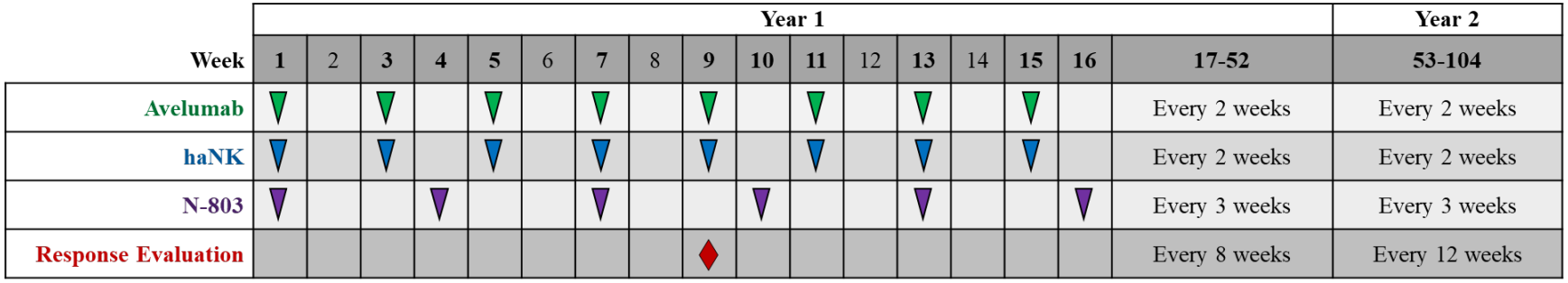
The primary efficacy endpoint, ORR, will be evaluated using RECIST 1.1 based on BICR. ORR will be analyzed using a two-sided exact 95% confidence interval (CI) derived from the Clopper-Pearson method. A clinically meaningful ORR for this indication is an ORR > 10%. If the lower bound of the 95% CI for ORR is > 10% then the combination therapy of avelumab, haNK, and N-803 in subjects with MCC who have progressed on or after checkpoint inhibitor therapy will be considered effective.

DOR, PFS, OS, and DSS will be analyzed using Kaplan-Meier methods. Descriptive statistics of PROs will be presented.

Overall safety will be assessed by descriptive analyses using tabulated frequencies of AEs by grade using CTCAE Version 5.0 in terms of treatment-emergent AEs, SAEs, and clinically significant changes in safety laboratory tests, physical examinations, ECGs, and vital signs.

Correlations of tumor molecular profiles with subject outcomes will be explored.

Figure 1: Study Treatment Schema



APPENDIX 1. SPONSOR SIGNATURE

Study Title:	A phase 2 study of combination therapy with an IL-15 superagonist (N-803), off-the-shelf CD16-targeted natural killer cells (haNK), and avelumab without cytotoxic chemotherapy in subjects with Merkel cell carcinoma (MCC) that has progressed on or after treatment with a checkpoint inhibitor.
Study Number:	QUILT-3.063
Version Number:	4
Final Date:	17 June 2021

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

Signed: Leonard Sender Date: 06-18-2021

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