CLINICAL STUDY PROTOCOL

OMNIA-1, A Phase 1/2 Study of ANV419 as Monotherapy or in Combination With Anti-PD-1 or Anti-CTLA-4 Antibody Following Anti-PD-1/Anti-PD-L1 Antibody Treatment in Patients With Unresectable or Metastatic Cutaneous Melanoma

Investigational Product: ANV419
Protocol Number: ANV419-101
EudraCT Number: 2021-006711-29

Sponsor:
Anaveon AG
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Hochbergerstrasse 60C
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Version Number: 4.0
Date: 07 March 2023

SIGNATURE PAGE

STUDY TITLE: A Phase 1/2 Study of ANV419 as Monotherapy or in Combination With Anti-PD-1 or Anti-CTLA-4 Antibody Following Anti-PD-1/Anti-PD-L1 Antibody Treatment in Patients With Unresectable or Metastatic Cutaneous Melanoma

We, the undersigned, have read this protocol and agree that it contains all necessary information required to conduct the study.

Signature	Date
[redacted]	07 MAR-2023
	07-MAR-2023
	07-Ma-23

INVESTIGATOR AGREEMENT

By signing below, I agree that:

I have read this protocol. I approve this document and I agree that it contains all necessary details for carrying out the study as described. I will conduct this study in accordance with the design and specific provision of this protocol and will make a reasonable effort to complete the study within the time designated. I will provide copies of this protocol and access to all information furnished by Anaveon AG to study personnel under my supervision. I will discuss this material with them to ensure they are fully informed about the study product and study procedures. I will let them know that this information is confidential and proprietary to Anaveon AG and that it may not be further disclosed to third parties. I understand that the study may be terminated or enrollment suspended at any time by Anaveon AG, with or without cause, or by me if it becomes necessary to protect the best interests of the study patients.

I agree to conduct this study in full accordance with Food and Drug Administration Regulations, Institutional Review Board/Ethic Committee Regulations and International Council for Harmonisation Guidelines for Good Clinical Practices.

_____ _____

Investigator's Signature Date

_____

Investigator's Printed Name

SYNOPSIS

TITLE: A Phase 1/2 Study of ANV419 as Monotherapy or in Combination With Anti-PD-1 or Anti-CTLA-4 Antibody Following Anti-PD-1/Anti-PD-L1 Antibody Treatment in Patients With Unresectable or Metastatic Cutaneous Melanoma

PROTOCOL NUMBER: ANV419-101

INVESTIGATIONAL PRODUCT: ANV419

PHASE: 1/2

INDICATIONS: ANV419 is being developed for treatment of unresectable or metastatic cutaneous melanoma (CM) following at least 1 line of standard of care immunotherapy including an anti-programmed death-1 [PD-1] and/or anti-programmed death-ligand 1 [PD-L1] antibody.

OBJECTIVES AND ENDPOINTS:

The study objectives and endpoints for Part 1: Monotherapy Dose Expansion, Part 2: Combination Dose Finding, and Part 3: Combination Dose Expansion are provided in Table TS1, Table TS2, and Table TS3.

Table TS1. Study Objectives and Endpoints for Part 1: Monotherapy Dose Expansion

Part 1: Monotherapy Dose Expansion – Arms A1 and A2	
Primary Objectives	**Primary Endpoints**
Evaluate the efficacy of ANV419	ORR (CR + PR), as defined by RECIST v1.1 (hereinafter, RECIST).
Secondary Objectives	**Secondary Endpoints**
To characterize the tumor response according to modified RECIST v1.1 criteria for immune-based therapeutics (iRECIST)	Tumor response in terms of objective response rate (ORR: CR + PR) assessed by iRECIST
Expand evaluation of efficacy of ANV419	- DOR (per RECIST) and iDOR (per iRECIST[0]) measured from first response until disease progression; - DCR (DCR = CR + PR + SD), iDCR (iDCR = iCR + iPR + iSD), PFS, iPFS, and OS; - Median TTR; and - Median iTTR.
Evaluate the safety of ANV419	Incidence, frequency, and severity of AEs including the following: - SAEs; - irAEs; - AESIs; - AEs leading to discontinuation of the study; and - Changes from baseline in laboratory parameters, vital signs, ECGs, and physical examination.
Explore immunogenicity after exposure to ANV419	Incidence of immunogenicity as indicated by ADA.

Table TS1. Study Objectives and Endpoints for Part 1: Monotherapy Dose Expansion (Continued)

Part 1: Monotherapy Dose Expansion – Arms A1 and A2	
Exploratory Objectives	**Exploratory Endpoints**
Explore the changes in the tumor microenvironment before and after adding ANV419 as monotherapy	Changes in immunological biomarker expression from baseline and post treatment tumor and liquid biopsies, including: - Immune cell counts, immunophenotyping (including, but not limited to, CD3, CD4, CD8, CD56, CD16, CD25, FoxP3, CD279, and CD366); - Cytokine production (including, but not limited to, IFNγ, IL-2, TNF, IL-6, IL-10); and - Immunohistochemistry (including, but not limited to, CD8, CD4, Ki67).
	Analysis of mutations in the tumor and analysis of tumor mutational burden.
	Analysis of changes in baseline ctDNA and at specified timepoints on therapy and after therapy.
	Analysis of single nucleotide polymorphisms, germline DNA for genome-wide association studies, analysis of T cell receptor repertoire, epigenetic markers, soluble CD25, and soluble PD-1/PD-L1.

Seymour L, Bogaerts J, Perrone A, et al. iRECIST: guidelines for the response criteria for use in trials testing immunotherapeutics. *Lancet Oncol*. 2017;18(3):e143-e152.
AE = adverse event; AESI = adverse event of special interest; CD = cluster of differentiation; CR = complete response; ctDNA = circulating tumor deoxyribonucleic acid; DCR = disease control rate; DNA = deoxyribonucleic acid; DOR = duration of response; ECG = electrocardiogram; FoxP3 = Forkhead box P3; iCR = immune complete response; iDCR = immune disease control rate; iDOR = immune duration of response; IFNγ = interferon gamma; IL = interleukin; iPFS = immune progression-free survival; iPR = immune partial response; irAE = immune-related adverse event; iRECIST = immune Response Evaluation Criteria in Solid Tumors; iSD = immune stable disease; iTTR = immune time to response; ORR = objective response rate; OS = overall survival; PD-1 = programmed death-1; PD-L1 = programmed death-ligand 1; PFS = progression-free survival; PR = partial response; RECIST = Response Evaluation Criteria in Solid Tumors; SAE = serious adverse event; SD = stable disease; T cell = thymus lymphocyte cell; TNF = tumor necrosis factor; TTR = time to response; v1.1 = version 1.1.

Table TS2. Study Objectives and Endpoints for Part 2: Combination Dose Finding

Part 2: Combination Dose Finding – Combination Therapy Arms (Arms B and C)	
Primary Objectives	**Primary Endpoints**
Evaluate the safety and tolerability and determine the RP2D of ANV419 in combination with pembrolizumab	Incidence, frequency, and severity of AEs including the following: - SAEs; - TEAEs; - DLTs; - AESIs; - irAEs; - AEs leading to discontinuation of the study; and - Changes from baseline in laboratory parameters, vital signs, ECGs, and physical examinations.
Evaluate the safety and tolerability and determine the RP2D of ANV419 in combination with ipilimumab	
Secondary Objectives	**Secondary Endpoints**
Evaluate PK and PD of ANV419 in combination with pembrolizumab or ipilimumab	PK endpoints in serum: - CL of ANV419; - V_{ss} of ANV419; - AUC of ANV419; and - C_{max} of ANV419. PD endpoints in peripheral blood: including, but not limited to, CD3, CD4, CD8, CD56, CD16, CD25, FoxP3, CD279, and CD366.

Table TS2. Study Objectives and Endpoints for Part 2: Combination Dose Finding (Continued)

Part 2: Combination Dose Finding – Combination Therapy Arms (Arms B and C)	
Secondary Objectives	**Secondary Endpoints**
Explore immunogenicity after exposure to ANV419 in combination with pembrolizumab or ipilimumab	Incidence of immunogenicity as indicated by ADA.
Evaluate the efficacy of ANV419 in combination with pembrolizumab or ipilimumab	ORR (CR + PR), as defined by RECIST.
Expand evaluation of efficacy of ANV419 in combination with pembrolizumab or ipilimumab	DOR (per RECIST) and iDOR (per iRECIST[1]) measured from first response until disease progression; PFS, iPFS, and OS; DCR (DCR = CR + PR + SD), iDCR (iDCR = iCR + iPR + iSD), Median TTR; and Median iTTR.
Evaluate clinical benefit in quality of life after exposure to ANV419 in combination with pembrolizumab or ipilimumab	Change in QoL at baseline and every 12 weeks while receiving ANV419 via QoL evaluations: - EQ-5D-5L; and - QLQ-C30.
Exploratory Objectives	**Exploratory Endpoints**
Explore the changes in the tumor microenvironment before and after adding ANV419 as monotherapy and in combination with pembrolizumab or ipilimumab	Changes in immunological biomarker expression from baseline and post treatment tumor and liquid biopsies, including: - Immune cell counts, immunophenotyping (including, but not limited to, CD3, CD4, CD8, CD56, CD16, CD25, FoxP3, CD279, and CD366); - Cytokine production (including, but not limited to, IFNγ, IL-2, TNF, IL-6, IL-10); and - Immunohistochemistry (including, but not limited to, CD8, CD4, Ki67).
	Analysis of mutations in the tumor and analysis of tumor mutational burden.
	Analysis of changes in baseline ctDNA and at specified timepoints on therapy and after therapy.
	Analysis of single nucleotide polymorphisms, germline DNA for genome-wide association studies, analysis of T cell receptor repertoire, epigenetic markers, soluble CD25, and soluble PD-1/PD-L1.

ADA = anti-drug antibodies; AE = adverse event; AESI = adverse event of special interest; AUC = area under the concentration-time curve; CD = cluster of differentiation; CL = systemic clearance; C_{max} = maximum observed serum concentration; CR = complete response; ctDNA = circulating tumor deoxyribonucleic acid; DLT = dose-limiting toxicity; ECG = electrocardiogram; EQ-5D-5L = Euro-QoL 5 dimension 5 level; FoxP3 = Forkhead box P3; IFNγ = interferon gamma; IL = interleukin; irAE = immune-related adverse event; ORR = objective response rate; PD = pharmacodynamic(s); PD-1 = programmed death-1; PD-L1 = programmed death-ligand 1; PK = pharmacokinetic(s); PR = partial response; QLQ-C30 = quality of life core 30; QoL = quality of life; RECIST = Response Evaluation Criteria in Solid Tumors; RP2D = recommended Phase 2 dose; SAE = serious adverse event; T cell = thymus lymphocyte cell; TEAE = treatment-emergent adverse event; TNF = tumor necrosis factor; V_{ss} = volume of distribution at steady state.

Table TS3. Study Objectives and Endpoints for Part 3: Combination Dose Expansion

Part 3: Combination Dose Expansion – Combination Therapy Arms (Arms B and C)	
Primary Objectives	**Primary Endpoints**
Evaluate the efficacy of ANV419 in combination with pembrolizumab or ipilimumab	ORR (CR + PR), as defined by RECIST.

Table TS3. Study Objectives and Endpoints for Part 3: Combination Dose Expansion (Continued)

Part 3: Combination Dose Expansion – Combination Therapy Arms (Arms B and C)	
Secondary Objectives	**Secondary Endpoints**
Expand evaluation of efficacy of ANV419 in combination with pembrolizumab or ipilimumab	- DOR (per RECIST) and iDOR (per iRECIST[1]) measured from first response until disease progression; - DCR (DCR = CR + PR + SD), iDCR (iDCR = iCR + iPR + iSD), PFS, iPFS, and OS; - Median TTR; and - Median iTTR.
Evaluate the safety of ANV419 in combination with pembrolizumab or ipilimumab	Incidence, frequency, and severity of AEs including the following: - SAEs; - irAEs; - AESIs; - AEs leading to discontinuation of the study; and - Changes from baseline in laboratory parameters, vital signs, ECGs, and physical examination.
Evaluate clinical benefit in quality of life after exposure to ANV419 in combination with pembrolizumab or ipilimumab	Change in QoL at baseline and every 12 weeks while receiving ANV419 via QoL evaluations: - EQ-5D-5L; and - QLQ-C30.
Explore immunogenicity after exposure to ANV419 in combination with pembrolizumab or ipilimumab	Incidence of immunogenicity as indicated by ADA.
Exploratory Objectives	**Exploratory Endpoints**
Explore the changes in the tumor microenvironment before and after adding ANV419 in combination with pembrolizumab or ipilimumab	Changes in immunological biomarker expression from baseline and post treatment tumor and liquid biopsies, including: - Immune cell counts, immunophenotyping (including, but not limited to, CD3, CD4, CD8, CD56, CD16, CD25, FoxP3, CD279, and CD366); - Cytokine production (including, but not limited to, IFNγ, IL-2, TNF, IL-6, IL-10); and - Immunohistochemistry (including, but not limited to, CD8, CD4, Ki67).
	Analysis of mutations in the tumor and analysis of tumor mutational burden.
	Analysis of changes in baseline ctDNA and at specified timepoints on therapy and after therapy.
	Analysis of single nucleotide polymorphisms, germline DNA for genome-wide association studies, analysis of T cell receptor repertoire, epigenetic markers, soluble CD25, and soluble PD-1/PD-L1.

1. Seymour L, Bogaerts J, Perrone A, et al. iRECIST: guidelines for the response criteria for use in trials testing immunotherapeutics. *Lancet Oncol*. 2017;18(3):e143-e152.

AE = adverse event; AESI = adverse event of special interest; CD = cluster of differentiation; CR = complete response; ctDNA = circulating tumor deoxyribonucleic acid; DCR = disease control rate; DOR = duration of response; ECG = electrocardiogram; EQ-5D-5L = Euro-QoL 5 dimension 5 level; FoxP3 = Forkhead box P3; iCR = immune complete response; iDCR = immune disease control rate; iDOR = immune duration of response; IFNγ = interferon gamma; IL = interleukin; iPFS = immune progression-free survival; iPR = immune partial response; irAE = immune-related adverse event; iRECIST = immune Response Evaluation Criteria in Solid Tumors; iSD = immune stable disease; iTTR = immune time to response; ORR = objective response rate; OS = overall survival; PD-1 = programmed death-1; PD-L1 = programmed death-ligand 1; PFS = progression-free survival; PR = partial response; QLQ-C30 = quality of life core 30; QoL = quality of life; RECIST = Response Evaluation Criteria in Solid Tumors; SAE = serious adverse event; SD = stable disease; T cell = thymus lymphocyte cell; TNF = tumor necrosis factor; TTR = time to response.

POPULATION:

Patients with unresectable or metastatic cutaneus melanoma with measurable disease, whose disease has progressed following at least 1 line of standard of care immunotherapy including an anti-PD-1/ anti-PD-L1 antibody.

Inclusion criteria

Patients who meet all of the following criteria will be eligible to participate in the study:

1. Must provide written informed consent for the study;
2. Must be able to comply with the Protocol as judged by the Investigator;
3. Are ≥18 years of age on day of signing informed consent;
4. Have histologically confirmed Stage 3 (unresectable) or Stage 4 (metastatic) CM, as per the American Joint Committee on Cancer staging system, eighth edition;
5. Have documented radiological progression on prior systemic therapy;
6. Have previously received anti-PD-1/L1 as monotherapy or in combination. A maximum of 2 prior lines of systemic therapy is allowed for BRAF wild-type disease and a maximum of 3 prior lines of systemic therapy is allowed for BRAFV600 positive disease;

   Note: Adjuvant treatment is considered as a line of therapy only if patient experienced relapse/ progression on therapy or within 6 months from adjuvant therapy completion;
7. Have measurable disease based on Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 (hereinafter, RECIST);
8. Have a performance status of 0 or 1 on the Eastern Cooperative Oncology Group (ECOG) Performance Status;
9. Have adequate organ functions as defined in Table TS4:

Table TS4. Adequate Organ Function Laboratory Values

System	Laboratory Value
Hematological	
ANC	≥1500/µL
Platelets	≥100,000/µL
Hemoglobin	≥9 g/dL or ≥4.96 mmol/L
Renal	
Measured or calculated[1] CrCl (GFR can also be used in place of CrCl)	≥30 mL/min
Hepatic	
Serum total bilirubin OR direct bilirubin	≤1.5 × ULN OR ≤1.5 × ULN for patients with total bilirubin levels >1.5 × ULN; direct bilirubin ≤1.5 × ULN for patients with Gilbert's syndrome
AST (SGOT) or ALT (SGPT)	≤2.5 × ULN OR ≤5 × ULN for patients with liver metastases
Albumin	>2.5 g/dL

Table TS4. Adequate Organ Function Laboratory Values (Continued)

1. CrCl should be calculated per Cockcroft-Gault equation.

ALT = alanine aminotransferase; ANC = absolute neutrophil count; AST = aspartate aminotransferase; CrCl = creatinine clearance; GFR = glomerular filtration rate; SGOT = serum glutamic oxalacetic transaminase; SGPT = serum glutamic pyruvic transaminase; ULN = upper limit of normal.

10. Female patients of childbearing potential must have a negative serum pregnancy test at the Screening Visit and a negative (urine or serum) pregnancy test within 72 hours prior to study Day 1. If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required and must be negative for the patient to be eligible;
11. Female patients who are not postmenopausal, and who have not undergone surgical sterilization, must agree to use highly effective methods of contraception during the treatment period and for 6 months after the last dose of study drug. They must also agree not to donate eggs (ova, oocytes) during the same timeframe; and
12. Male patients with partners of childbearing potential must agree to use highly effective methods of contraception and barrier contraception (condom) during the treatment period and for 6 months after the last dose of study drug. They must also agree not to donate sperm during the same timeframe.

Exclusion criteria

Patients who meet any of the following criteria will be excluded from participation in the study:

1. Have received investigational agent (including investigational device) within 4 weeks or an interval of 5 half-lives of the respective investigational agent prior to study Day 1, whichever is longer, with the exclusion of an anti-PD-1/anti-PD-L1 antibody given as either a single agent or non-CTLA-4 antibody containing combination (eg, anti-lymphocyte-activation gene 3 antibody);

2. Have a known hypersensitivity to ANV419 or to any of the excipients, such as sucrose, histidine or polysorbate 80. For combination arms only: Have hypersensitivity to pembrolizumab or ipilimumab or any of their excipients;

3. For combination arms only: Have previously discontinued ipilimumab, pembrolizumab, or any other PD-1/PD-L1 inhibitors due to unacceptable drug-related toxicity (defined as toxicities that required second line immunosuppression, ie, not controlled by steroids alone);

4. Have a lactate dehydrogenase level of ≥2 × upper limit of normal;

5. Have not recovered (ie, ≤Grade 1 or at baseline with the exception of alopecia or fatigue [up to Grade 2 allowed]) from adverse events (AEs) resulting from prior immunotherapies. Patients who have autoimmune AEs controlled by replacement therapy (ie, hypothyroidism) due to previous treatment are eligible provided replacement therapy has been initiated and toxicity has returned to Grade 1;

6. Have not recovered (ie, ≤Grade 1 or at baseline) from toxicities due to a previously administered chemotherapy, targeted small molecule therapy, or radiation therapy;

Note: If the patient received major surgery, they must have recovered adequately from the toxicity and/or complications from the intervention prior to starting study drug. Major surgery is defined as any surgery requiring entrance into a body cavity (eg, chest, abdomen, or brain), organ removal, normal anatomy alteration, or joint replacement. Minor surgery is defined as

any surgery in which skin, mucosa, or connective tissue sections are altered (eg, biopsy, cataract, endoscopic procedures, etc).

7. Have been diagnosed with uveal/ocular or mucosal melanoma;

8. Have a known additional malignancy (including all in-situ carcinoma) that is progressing or required active treatment within ≤2 years prior to enrollment. Exceptions include basal cell carcinoma of the skin or squamous cell carcinoma of the skin that have undergone potentially curative therapy or in situ cervical cancer or patients who completed cancer-directed and have no evidence of disease;

9 Have active central nervous system metastases and/or carcinomatous meningitis. Patients with previously treated brain metastases may participate provided they are stable (without evidence of progression by imaging for at least 4 weeks prior to study Day 1, and any neurologic symptoms have returned to baseline or have been stable for at least 7 days), have no evidence of new or enlarging brain metastases, and are not using steroids for at least 7 days prior to study drug. This exception does not include carcinomatous meningitis which is excluded regardless of clinical stability;

10. Have a diagnosis of immunodeficiency or is receiving immunosuppressive therapy within 7 days prior to study Day 1;

11. Are receiving systemic steroid >10 mg of prednisone daily or equivalent or any other immunosuppressive medication at any dose level. Local steroid therapies (eg, otic, ophthalmic, intra-articular, or inhaled medications) are acceptable;

12. Have an active autoimmune disease that has required systemic treatment in the past 2 years (ie, with use of disease modifying agents, corticosteroids, or immunosuppressive drugs). Replacement therapy (eg, thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency, etc) is not considered a form of systemic treatment;

13. Have evidence of active, non-infectious pneumonitis;

14. Have active (measurable) and uncontrolled (unresponsive to current therapy) infectious disease (bacterial, fungal, viral, protozoic);

15. Have a history of an acute coronary event (eg, myocardial infarction) within 3 months prior to study Day 1, uncontrolled and symptomatic coronary artery disease or congestive heart failure New York Heart Association Class III/IV;

16. Have an average QTcF interval >470 msec at Screening;

17. Have a history or current evidence of any condition, therapy, or laboratory abnormality that might confound the results of the study, interfere with the patient's participation for the full duration of the study, or it is not in the best interest of the patient to participate, in the opinion of the treating Investigator;

18. Have known psychiatric or substance abuse disorders that would interfere with cooperation with the requirements of the study;

19. Are pregnant or breastfeeding, or expecting to conceive or father children within the projected duration of the study, starting with the Screening Visit through 6 months after the last dose of study drug;

20. Are known to be human immunodeficiency virus (HIV) positive (or tests positive for HIV 1 or 2 at Screening), unless the following criteria are met:
    a. Cluster of differentiation (CD)4+ lymphocyte count >350 µL;
    b. Had no history of acquired immunodeficiency syndrome (AIDS)-defining opportunistic infections within the past 12 months;
    c. Have been on established anti-retroviral therapy for at least 4 weeks; and
    d. Have an HIV viral load of <400 copies/mL prior to study Day 1.

    Note: Patients on strong cytochrome P450 (CYP)3A4 inhibitors or strong CYP3A4 inducers must be switched to an alternate effective anti-retroviral therapy regimen prior to study treatment or are excluded if regimen prior to study Day 1 cannot be altered.
21. Have uncontrolled hepatitis B infection or hepatitis C infection;

    Note: Patients with hepatitis B (positive hepatitis B surface antigen) who have controlled infection (serum hepatitis B virus DNA by polymerase chain reaction that is below the limit of detection and receiving anti-viral therapy for hepatitis B) are permitted. Patients with controlled infections must undergo periodic monitoring of hepatitis B virus DNA.

    Note: Patients with hepatitis C (positive hepatitis C virus antibody) who have controlled infection (undetectable hepatitis C virus RNA by polymerase chain reaction either spontaneously or in response to a successful prior course of anti-hepatitis C virus therapy) are permitted.
22. Have received a live vaccine within 30 days of study Day 1; or

    Note: Seasonal influenza vaccines for injection are generally inactivated flu vaccines and are allowed; however, intranasal influenza vaccines (eg, Flu-Mist®) are live attenuated vaccines, and are not allowed.
23. For combination arms only: Have received solid organ or hematopoietic stem cell transplant.

STUDY DESIGN AND DURATION:

This is a multi-site, open label, randomized, parallel arm, Phase 1/2 adaptive study to evaluate the efficacy and safety of ANV419 as a monotherapy and in combination with pembrolizumab or ipilimumab in patients aged 18 years or older with advanced CM who have previously been treated with at least 1 line of standard of care immunotherapy, including an anti-PD-1/ anti-PDL1 antibody.

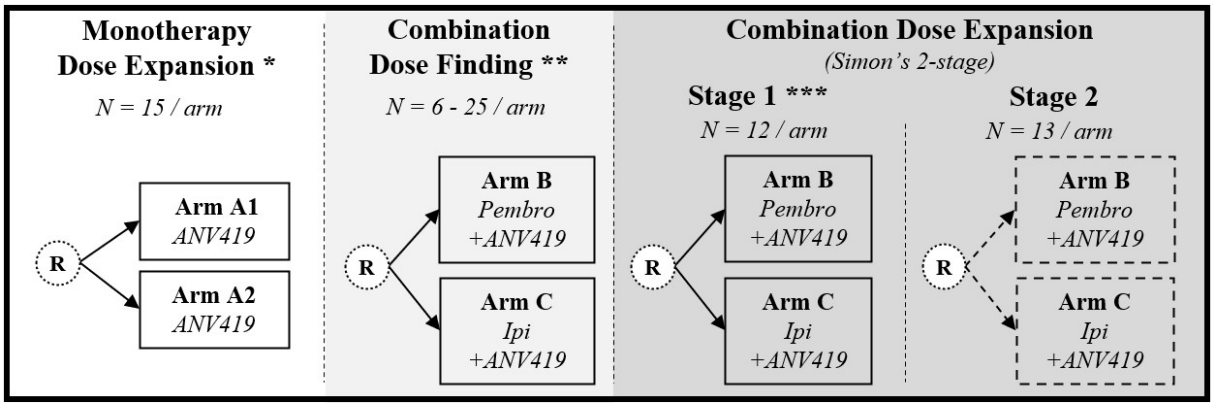
The 4 following treatment arms will be included in this study:

- Arm A1: ANV419 ([redacted]);
- Arm A2: ANV419 ([redacted]);
- Arm B: ANV419 ([redacted]) in combination with pembrolizumab (Keytruda®); and
- Arm C: ANV419 ([redacted])in combination with ipilimumab (Yervoy®).

There will be up to 3 separate parts in this study: Part 1: Monotherapy Dose Expansion with patients randomized to receive infusion of ANV419 ([redacted]. If Part 1 is successful, Part 2: Combination Dose Finding with patients randomized to Arms B and C with infusion of ANV419 [redacted], and finally, Part 3: Combination Dose Expansion with patients randomized to Arms B and C (see Figure FS1). A total of up to 130 patients are planned to be enrolled in the study: a maximum of 30 patients in the Monotherapy Dose Expansion part, a maximum of 50 patients in the Combination Dose Finding part, and a maximum of 50 patients in the Combination Dose Expansion part. Randomization in the Monotherapy Dose Expansion part and Combination Dose Expansion part will be stratified by BRAF mutation status.

In the Combination Dose Expansion part, the number of patients within each arm will be determined by pre-defined decision rules presented in Table TS6.

Figure FS1. Study Design



* = If ANV419 monotherapy is successful, the combination portion will be initiated.
** = Dose escalation increment is decided by the SRC until RP2D of ANV419 per arm is identified.
*** = Arm not meeting pre-specified ORR criteria may be stopped early after Stage 1.
In the Combination Dose Finding part, patients will be manually randomized to Arm B or Arm C. In the Monotherapy Dose Expansion part and the Combination Dose Expansion part, patients will be randomized by IRT into Arms A1 or A2 and Arms B or C, respectively.
Ipi = ipilimumab; IRT = Interactive Response Technology; ORR = objective response rate; Pembro = pembrolizumab; R = randomization; RP2D = recommended Phase 2 dose; SRC = Safety Review Committee.

All patients will be assessed for response using RECIST and computed tomography imaging, which will occur every [redacted], using the same modality as used for baseline imaging until progressive disease per RECIST and immune RECIST, withdrawal of consent, or initiation of a new anticancer therapy. Treatment decision will be based on local assessment. All images will be collected and stored centrally for potential central analysis. [redacted] The study will also assess other clinical parameters including progression-free survival (PFS) and will provide the opportunity to explore blood- and tumor-based markers that may predict response to ANV419 as monotherapy or in combination with anti-PD-1 or anti-CTLA-4 antibodies.

Part 1: Monotherapy Dose Expansion

The Monotherapy Dose Expansion part (Arms A1 and A2) will be a parallel group part with a Bayesian sequential monitoring analysis[a] and up to 15 patients per arm. This part will establish the efficacy and safety of ANV419 as monotherapy.

Initially, two doses of ANV419 will be explored: [redacted] based on data collected in the ongoing Phase 1 ANV419-001 study [redacted]. An additional dose of ANV419 may be explored once the final results of ANV419-001 Study will be available. Treatment with ANV419 as a monotherapy can continue for up to [redacted].

Decision making on whether to continue the study beyond the Monotherapy Dose Expansion part, and the total number of patients recruited to this part, will be based on Bayesian sequential monitoring. The study will be stopped at the end of this part in the case of an unfavorable risk/benefit profile for ANV419 monotherapy. This includes observing a total of 0 of 30 responses from the 2 monotherapy arms combined (a strong signal that ANV419 does not induce a response) and/or report of any safety issues that might stop the trial. There is 95% certainty that the true objective response rate (ORR) is greater than 10% if we observe any 1 of the following:

- 2 responses in 3 to 7 patients;
- 3 responses in 8 to 13 patients;
- 4 responses in 14 to 19 patients; or
- 5 responses in 20 to 27 patients.

Response (complete response [CR] or partial response [PR]) will be assessed at each disease evaluation by the Investigator.

Part 2: Combination Dose Finding

This part will only be initiated following approval of a substantial amendment supporting the ANV419 starting dose in the combination part. The submission will include data from ANV419-001 Study and from Part 1 of this trial, and occur at any time when at least 2 responses have been observed in the Monotherapy Dose Expansion part. The Combination Dose Finding part will be comprised of 2 arms (Arms B and C) that will identify a recommended Phase 2 dose (RP2D) for ANV419 in each arm when administered in combination with pembrolizumab (Arm B) or ipilimumab (Arm C) at the prescribed dosing. The number of patients recruited to each arm will be between 6 and 25 patients depending on the number of dose increments possible. A minimum of 6 patients will be treated at RP2D. The patients from the Combination Dose Finding part will not be randomized into the Combination Dose Expansion part.

Dosing of ANV419 when administered in combination with pembrolizumab (Arm B) or ipilimumab (Arm C) will occur as shown in Table TS5, with a dose of ANV419 currently planned to start at [redacted]. Patients in the Combination Dose Finding part will be treated with a minimum of 24 hours interval between patients to allow for monitoring of acute toxicities. Dose level 1, as shown in Table TS5, will be reviewed by the Safety Review Committee

a. Thall PF, Simon R. Practical Bayesian guidelines for phase IIB clinical trials. *Biometrics*. 1994;50(2):337-349.

(SRC) per the safety evaluations and the SRC will make dose increment recommendations at each dose level, not exceeding 3-fold increment from one dose level to the next. The maximum dose level explored will not exceed the Q3W dose of ANV419 monotherapy studied in the ongoing ANV419-001 study. The dose-limiting toxicity (DLT) period for the Combination Dose Finding part will last for [redacted]. For details on the DLT criteria for the Combination Dose Finding part of this study, see the section below labeled "Dose-limiting toxicity criteria (applicable to Combination Dose Finding part only)."

Table TS5. ANV419 Dose Escalation Plan for Combination Dose Finding Part (Pembrolizumab or Ipilimumab)

Dose Level	ANV419 Dose	Pembrolizumab Dose or Ipilimumab Dose	Frequency
1	[redacted]		
2			
3			
4			
5			

Note: ANV419 will be administered by IV infusion over 15 minutes (+5 minutes).
Dose increments will be determined by the SRC based on a synthesis of all relevant data available from all dose levels evaluated in this study, not exceeding a 3-fold increment from one dose level to the next. The maximum dose level explored will not exceed the [redacted] studied in the ongoing ANV419-001 study.
IV = intravenous(ly); [redacted]; SRC = Safety Review Committee; TBD = to be determined.

Dose escalation in the Combination Dose Finding part will follow the Bayesian optimal interval (BOIN)[a] design to find the maximum tolerated doses (MTDs)/RP2D of ANV419 when administered in combination with pembrolizumab or ipilimumab at the prescribed dose. Dose escalation decisions will be based on a synthesis of all relevant data available from all dose levels evaluated in the ongoing Combination Dose Finding part of the study.

Part 3: Combination Dose Expansion

The Combination Dose Expansion part of the study will be separate from the Combination Dose Finding part and will further evaluate the safety and efficacy of ANV419 in combination with pembrolizumab (Arm B) or ipilimumab (Arm C). This Combination Dose Expansion part will consist of 2 stages. In Stage 1, 12 patients will be randomized by interactive response technology (IRT) into each arm. At the end of this stage, an interim analysis will be performed to assess continuation of treatment arms into Stage 2 (see Table TS6). In Stage 2, eligible patients will be randomized to the remaining treatment arms, determined at the interim analysis. Recruitment will continue until 25 patients have been randomized to a treatment arm.

Table TS6. Continuation Decision Rules for Combination Dose Expansion Part

Treatment Arm Accrual	Discontinue if the Number of Responses is	Discontinue Criterion in Terms of ORR	Continue if the Number of Responses is at Least
Stage 1 (n=12)	≤2	Observed ORR <20%	3

ORR = objective response rate.

Dosing for ANV419 in the combination arms (Arms B and C) in the Combination Dose Expansion part will be based on the RP2Ds for ANV419 determined in the Combination Dose Finding part,

a. Liu S, Yuan Y. Bayesian optimal interval designs for phase I clinical trials. *J R Stat Soc Ser C Appl Stat*. 2015;64(3):507-523.

ie, the RP2D for ANV419 when administered in combination with pembrolizumab (hereinafter, RP2D[p]) and the RP2D for ANV419 when administered in combination with ipilimumab (hereinafter, RP2D[i]).

Treatment with ANV419 in combination with pembrolizumab can continue for 24 months within the current Protocol in the absence of disease progression or unacceptable toxicity.

Treatment with ANV419 in combination with ipilimumab can continue up to a maximum of 4 cycles, per the approved label (United States Prescribing Information and Summary of Product Characteristics). If ipilimumab-related AEs occur, ipilimumab can be discontinued at any time. Once a patient has completed the maximum of 4 [redacted].

Dose-limiting toxicity criteria (applicable to Combination Dose Finding part only)

A DLT is defined as any of the treatment-emergent AEs (TEAEs) listed below, as defined by the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 5.0, occurring during the DLT period ([redacted]) and the AE is not reasonably attributed to the patient's underlying disease, other medical conditions, or concomitant medications. To be DLT evaluable, the patient must complete [redacted] or reasons other than DLT or any event that renders the patient non evaluable for DLT will be replaced. Patient who experience a delay of Cycle 2 dosing longer than 7 days for toxicity reasons will be considered as having experienced DLT. The DLT definitions are the following:

[redacted]

[redacted]

An SRC will be convened, comprised of enrolling study Investigators, Medical Monitor, and the Sponsor Medical Director or designee. All potentials DLTs will be reviewed by the SRC for a final determination and for the SRC to make recommendations regarding the study. The SRC will also consider AEs, particularly high-grade toxicities that may have occurred in patients in any treatment arm (even beyond the DLT period), when making decisions/recommendations to proceed with the study. The SRC will provide recommendations for study drug dosing and alternative dosing regimens as appropriate, not exceeding a 3-fold increment from one dose level to the next. The maximum dose level explored will not exceed [redacted]. Near the end of dose escalation, the statistician will also contribute to dose escalation recommendation, using the BOIN design, to select the MTD/RP2D.

After completion of the [redacted] DLT period for each cohort, intra-patient dose escalation is permitted with approval of the Investigator and provided the following criteria have been met:

- The patient has completed at least 1 treatment cycle;
- The DLT assessment of the dose level to which the patient will be dose-escalated is complete and determined to be safe by the SRC;
- The patient did not experience any AEs related to study drug(s) >Grade 1 at the dose level prior to escalation; and
- The patient has not required any dose reduction.

DOSAGE FORMS AND ROUTE OF ADMINISTRATION:

Patients will receive ANV419 as monotherapy (Arms A1 and A2) or in combination with pembrolizumab (Arm B) or ipilimumab (Arm C) after all Screening procedures have been completed and eligibility has been confirmed by the Investigator. Only patients enrolled in the study may receive the study drug(s). Under no circumstances will the study drug(s) be used other than as directed within this Protocol. The 3 study drugs and the administration of each are described in Table TS7.

Table TS7. Study Drug Administration

Treatment	Study Part	Arm	Dose/ Potency	Dose Frequency	Route of Administration/Duration	Regimen/ Treatment Period
ANV419	[redacted]					

Pembro	[redacted]
Ipi [6,7]	

1. Acetaminophen 1 g may be given to the patients as pre-medication or following the ANV419 infusion and can be used every 8 hours based on the symptoms experienced by the patient.
2. Hydration prior to and following ANV419 infusion is to be administered according to institutional guidelines.
3. Dose increments will be determined by the SRC based on a synthesis of all relevant data available from all dose levels evaluated in this study.
4. For the combination arms (Arm B and Arm C) of the study, pembrolizumab or ipilimumab will be administered first. Patients can receive the ANV419 infusion approximately 30 minutes after they have received the entire infusion of pembrolizumab or ipilimumab.
5. In Arms B and C of the Dose Expansion part of the study, ANV419 will be administered at the RP2D(p) or RP2D(i), respectively, identified in the Combination Dose Finding part.
6. Sites should make every effort to target infusion timing to be as close to 30 minutes (for pembrolizumab) or 90 minutes (for ipilimumab) as possible from treatment start; however, given the variability of infusion pumps from site to site, a window of ±5 minutes is permitted.
7. Ipilimumab dosing will end after [redacted]. Ipilimumab should be permanently discontinued for patients who fail to complete the full treatment course w[redacted] from administration of first dose.
8. Patients being treated on combination therapy with ANV419 plus ipilimumab who require discontinuation of ipilimumab due to toxicity may continue treatment with ANV419 after approval from the Sponsor. The reason for discontinuation must be recorded.

Ipi = ipilimumab; IV = intravenous(ly); Pembro = pembrolizumab; [redacted];
RP2D(i) = recommended Phase 2 dose for ANV419 when administered with ipilimumab; RP2D(p) = recommended Phase 2 dose for ANV419 when administered with pembrolizumab; SRC = Safety Review Committee.

Except during Cycles 1 and 2 in Arms B and C, study drug(s) may be administered up to 3 days before or after the scheduled Day 1 of each cycle due to administrative reasons.

Except during the DLT assessment period, if a dose cannot be administered at the foreseen [redacted] due to intercurrent medical issues unrelated to any study drug, dosing may be delayed for [redacted]. The [redacted] cycle will be resumed according to the re-start date.

Post-infusion observation – Monotherapy Dose Expansion part

In both arms of the Monotherapy Dose Expansion part (Arms A1 and A2), all patients will be monitored for 90 minutes post end of infusion from Cycle 1. Patients will be monitored per individual site institutional standard during administration of ANV419 as monotherapy. In addition:

- Vital signs will be monitored every 2 hours for the first 8 hours, for the first 2 cycles;
- After Cycle 2, the observation period will lessen to 90 minutes post end of infusion, provided no additional safety concerns have been identified;
- Patients may require observation beyond 23 hours if ≥Grade 3 AE and/or requires medical intervention and prolonged medical observation.

Note: It is optionally recommended (not mandatory) that patients stay in close proximity (as defined by the Investigator) to the site and are accompanied by a caregiver when possible, for whom accommodations will be provided.

Post-infusion observation – Combination Dose Finding part

At the end of study drug(s) infusion in Cycles 1 and 2 (only) of the Combination Dose Finding part, **all patients** will undergo a 23-hour observation period. Clinical monitoring will be conducted per individual site institutional standards within the framework of observation required for this Protocol, as follows:

- Vital signs will be monitored every 2 hours for the first 8 hours, and 20 hours post end of infusion;
- After Cycle 2, the observation period will lessen to 90 minutes post end of infusion, provided no additional safety concerns have been identified;
- Patients may require observation beyond 23 hours if ≥Grade 3 AE and/or requires medical intervention and prolonged medical observation.

Post-infusion observation – Combination Dose Expansion part

In both arms of the Combination Dose Expansion part (Arms B and C), all patients will be monitored for 90 minutes or longer post end of infusion in Cycle 1, depending on whether additional safety concerns have been identified in Part 2. Patients will be monitored per individual site institutional standard during administration of ANV419 in combination with pembrolizumab or ipilimumab.

Note: It is optionally recommended (not mandatory) that patients stay in close proximity (as defined by the Investigator) to the site and are accompanied by a caregiver when possible, for whom accommodations will be provided.

SAFETY VARIABLES:

The safety of ANV419 as monotherapy and in combination with pembrolizumab or ipilimumab will be assessed by monitoring AEs (including TEAEs, DLTs [Combination Dose Finding part only], AEs of special interest, serious AEs, immune-related AEs, and AEs leading to discontinuation of the study), physical examination findings (including ECOG performance status), clinical laboratory assessments, vital signs measurements, and electrocardiograms. AEs will be coded using the Medical Dictionary for Regulatory Activities and graded according to NCI CTCAE version 5.0.

STATISTICAL ANALYSES:

The Safety Population will consist of all patients who receive at least 1 dose (or partial dose) of study drug(s). The Safety Population will be used for safety analyses including DLT assessment(s).

The Efficacy Population will consist of all patients who receive at least 1 dose of study drug, have at least 1 post-baseline tumor assessment, and who are part of the Monotherapy Dose Expansion part, Combination Dose Finding part, or the Combination Dose Expansion part. The Efficacy Population will be used for efficacy analyses.

The Pharmacokinetic (PK) Population will consist of all patients who receive at least 1 dose of study drug and have at least 1 measured concentration for at least 1 of the analytes. The PK Population will be used for PK analyses.

The Pharmacodynamic (PD) Population will consist of all patients who receive at least 1 dose of study drug and have at least 1 evaluable PD sample. The PD Population will be used for PD endpoint analyses.

Interim analysis of efficacy

In Arm B or C, an interim analysis of the primary outcome will be performed at the end of Stage 1 of the Combination Dose Expansion part of the study (once 12 evaluable patients have completed at least 1 disease evaluation or have discontinued from the study). Any treatment arm with an ORR <20% per RECIST (ie, treatment arms with no more than 2 complete or partial responses) will be discontinued.

Final analysis of efficacy

Efficacy analysis will be conducted using the Efficacy Population. The primary outcome (ORR per RECIST) will be presented together with a 95% confidence interval (CI) for each treatment arm. Treatment arms with an observed ORR 95% CI with a lower limit above 20% and an upper limit above 40% will be considered for future study. All other outcomes measures will be summarized with the appropriate descriptive statistics.

Analysis of safety

In general, all safety analyses will be descriptive and presented in tabular format with appropriate summary statistics for the Safety Population. The impact of possible anti-ANV419 antibodies on safety of ANV419 will be assessed.

Analysis of pharmacokinetics

Plasma concentrations of ANV419 will be determined with a validated bioanalytical assay. Selected parameters will be calculated from plasma concentrations using noncompartmental analyses. Summary statistics will be generated by treatment arm as appropriate.

PK parameters to be analyzed:

- Systemic clearance of ANV419;
- Volume of distribution at steady state of ANV419;
- Area under the concentration-time curve of ANV419; and
- Maximum observed serum concentration of ANV419.

Analysis of pharmacodynamics

The result, change, percent change, and maximum percent change in immunologic changes to selected serum cytokines and immune cell subsets in the blood and tumor microenvironment will be summarized descriptively.

PD parameters to be analyzed (including, but not limited to):

- CD3, CD4, CD8, CD56, CD16, CD25, FoxP3, CD279, and CD366.

Other analysis

Clinical benefit assessment Quality of Life evaluation will be summarized using descriptive statistics.

SAMPLE SIZE DETERMINATION:

Monotherapy Dose Expansion part

This part of the study will use Bayesian sequential monitoring. A maximum of 15 patients will be enrolled and treated at each dose level arm. Arms A1 and A2 (monotherapy) will be analyzed as independent experiments, and also overall, and the following assumptions are made:

- Nothing is known *a priori*: assume a uniform prior, ie, the true ORR could be any value between 0% and 100%;
- A true ORR <6% indicates treatment failure; and
- A true ORR >10% indicates treatment success.

With a maximum of 15 patients in each arm, if no responses were observed, then the estimated true ORR would be 5.9%, with 90% CI (0.3%, 17.1%). This would be sufficient evidence to suggest that the treatment is unlikely to be successful. With a maximum of 30 patients overall, if no responses were observed, then the estimated true ORR would be 3.1%, with 90% CI (0.2%, 9.2%). This would be sufficient evidence to suggest that the treatment at either dose is unlikely to be successful.

There is 95% certainty that the true ORR is greater than 10% if any 1 of the following are observed:

- 2 responses in 3 to 7 patients;
- 3 responses in 8 to 13 patients;
- 4 responses in 14 to 19 patients; or
- 5 responses in 20 to 27 patients.

Combination Dose Finding part

The Combination Dose Finding part will employ BOIN[a] to find the MTD/RP2D of Arm B (ANV419 in combination with pembrolizumab) and Arm C (ANV419 in combination with ipilimumab). For each arm, the following assumptions have been predefined for the dose escalation:

- Target DLT rate of 25%;
- Maximum of 25 patients;
- Maximum of 9 patients treated at the same dose level; and
- Maximum of 5 dose levels defined in TS5 to be tested.

Patients will be enrolled and treated in cohorts of 3 patients (at least). Up to 50 patients in total will be enrolled for the Combination Dose Finding part.

Combination Dose Expansion part (efficacy analysis)

The sample size calculation is based on a Simon's 2-stage[a] design and ensures that under all possible distributions of patients to the 2 treatment arms, there is at least 80% power to correctly detect an ORR >40% and at most a Type I error rate of 10% of rejecting a null hypothesis that ORR <20%. This results in a sample size of 12 patients randomized to each treatment arm in

Stage 1, followed by 13 additional patients randomized during Stage 2: a total of 25 patients per arm at the end of Stage 2.

SITES: Approximately 30 sites in the United States of America and Europe

SPONSOR:

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a. Simon R. Optimal two-stage designs for phase II clinical trials. *Control Clin Trials*. 1989;10(1):1-10.

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation	Definition
α	Alpha
β	Beta
γ	Gamma
ADA	Anti-drug antibodies
AE	Adverse event
AESI	Adverse event of special interest
AIDS	Acquired immunodeficiency syndrome
AUC	Area under the concentration-time curve
BOIN	Bayesian optimal interval
BRAF	B-type Raf proto-oncogene
CD	Cluster of differentiation
CFR	Code of Federal Regulations
CI	Confidence interval
CL	Systemic clearance
CM	Cutaneous melanoma
C_{max}	Maximum observed serum concentration
CR	Complete response
CRA	Clinical Research Associate
CRF	Case Report Form
CRP	C-reactive protein
CRS	Cytokine release syndrome
CT	Computed tomography
CTA	Clinical trial authorization
ctDNA	Circulating tumor deoxyribonucleic acid
CTLA-4	Cytotoxic T-lymphocyte antigen-4
CYP	Cytochrome P450
DCR	Disease control rate
DLT	Dose-limiting toxicity
DNA	Deoxyribonucleic acid
DOR	Duration of response
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
EDC	Electronic data capture
EIU	Exposure In Utero
FDA	Food and Drug Administration
FoxP3	Forkhead box P3

Abbreviation	Definition
GCP	Good Clinical Practice
GLP	Good Laboratory Practices
HIV	Human immunodeficiency virus
ICANS	Immune effector cell-associated neurotoxicity syndrome
ICF	Informed consent form
ICH	International Council for Harmonisation
iCR	Immune complete response
iDCR	Immune disease control rate
iDOR	Immune duration of response
IEC	Independent Ethics Committee
IL	Interleukin
IL-2R	Interleukin-2 receptor
IMP	Investigational medical product
iPFS	Immune progression-free survival
iPR	Immune partial response
irAE	Immune-related adverse event
IRB	Institutional Review Board
iRECIST	Immune Response Evaluation Criteria in Solid Tumors
IRR	Infusion-related reaction
IRT	Interactive Response Technology
iSD	Immune stable disease
iTTR	Immune Time to Response
IV	Intravenous(ly)
LDH	Lactate dehydrogenase
mAb	Monoclonal antibody
MEK	Mitogen-activated protein kinase kinase enzyme
MTD	Maximum tolerated dose
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NIMP	Non-investigational medical product
NK	Natural killer
ORR	Objective response rate
OS	Overall survival
PBMC	Peripheral blood mononuclear cell
PD	Pharmacodynamic(s)
PD-1	Programmed death-1
PD-L1	Programmed death-ligand 1
PEG	Polyethylene glycol
PFS	Progression-free survival
PK	Pharmacokinetic(s)

Abbreviation	Definition
PR	Partial response
[redacted]	[redacted]
[redacted]	[redacted]
QTcF	Heart rate-corrected QT interval using Fridericia's formula
RECIST	Response Evaluation Criteria in Solid Tumors
RNA	Ribonucleic acid
RP2D	Recommended Phase 2 dose
RP2D(i)	Recommended Phase 2 dose for ANV419 when administered in combination with ipilimumab
RP2D(p)	Recommended Phase 2 dose for ANV419 when administered in combination with pembrolizumab
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SD	Stable disease
SRC	Safety Review Committee
SUSAR	Suspected Unexpected Serious Adverse Reaction
T cell	Thymus lymphocyte cell
TEAE	Treatment-emergent adverse event
Treg	Regulatory T cell
TTR	Time to Response
USA	United States of America
V_{ss}	Volume of distribution at steady state

1 INTRODUCTION AND BACKGROUND INFORMATION

1.1 Immunotherapy

Activating the immune system produces durable responses in a subset of human cancers. Recombinant interleukin (IL)-2 (Aldesleukin),[2] by directly stimulating innate and adaptive effector lymphocytes, is approved for the treatment of metastatic melanoma and renal cell carcinoma and induces durable responses and cures cancer in a significant proportion (approximately 10%) of patients.[3,4] More recently, checkpoint inhibition has been successfully introduced into clinical oncology and has produced clinically impressive durable response rates and significant survival benefits in melanoma, renal cell carcinoma, non-small cell lung cancer and other tumors.[5,6,7] Despite this breakthrough success of checkpoint blockade, most patients with advanced cancer still relapse and eventually succumb to the disease and further therapy improvement is therefore needed.

The current armamentarium of immuno-stimulators is rapidly growing beyond checkpoint inhibitors, including novel IL-2-like therapies. The clinical usefulness of recombinant IL-2 (Aldesleukin) has been limited because of important safety, efficacy, and logistic limitations. In brief, the safety profile among 525 patients treated for malignant melanoma and renal cell carcinoma reported hypotension (71% overall; 3% Grade 4), vomiting (50%; 1% Grade 4), diarrhea (65%; 2% Grade 4), thrombocytopenia (37% 1% Grade 4), bilirubinemia (40%; 2% Grade 4), and oliguria (63%; 6% Grade 4). Of note, serious manifestations of eosinophilia involving eosinophilic infiltration of cardiac and pulmonary tissues can occur following use of aldesleukin.[2] Six of 8 deaths during treatment of 270 patients were attributed to IL-2 (2.2%).[8] In all, this has led to a black box warning for capillary leak syndrome, which is characterized by a loss of vascular tone and extravasation of plasma proteins and fluid into the extravascular space and may be associated with cardiac arrhythmias (supraventricular and ventricular), angina, myocardial infarction, respiratory insufficiency requiring intubation, gastrointestinal bleeding or infarction, renal insufficiency, edema, and mental status changes. Therefore, IL-2 should be administered in a hospital with an intensive care facility and specialists skilled in cardiopulmonary or intensive care medicine available.

The non-selective stimulation of anti-cancer effector cells (ie, cluster of differentiation [CD]8+ thymus lymphocyte cells (T cells) and natural killer [NK] cells) and immune suppressing regulatory T cells (Tregs) is believed to limit efficacy of Aldesleukin. The short half-life of IL-2 requires dosing via continuous infusion or at least 3 times per day dosing for 5 to 8 days, further restricting its use and overall clinical usefulness.

1.2 Cutaneous Melanoma

Worldwide, about 232,100 (1.7%) cases of all newly diagnosed primary malignant cancers (excluding non-melanoma skin cancer) are cases of cutaneous melanoma (CM), and about 55,500 cancer deaths (0.7% of all cancer deaths) are due to CM annually. Of the 10 leading cancer types (excluding basal-cell and squamous-cell carcinoma of the skin), CM was the fifth most common malignancy in men and the sixth most common in women in the United States of America (USA) in 2017. The incidence of CM has increased since the early 1970s in predominantly fair-skinned populations.[9]

Historically, the median survival for patients with metastatic CM has been under 1 year. Treatment options for metastatic CM have traditionally been limited to chemotherapeutic agents such as dacarbazine and high-dose IL-2 immunotherapy in a small percentage of patients. In the past decade there has been steady progress in the development of targeted therapy and immunotherapy for metastatic CM.[10] Using programmed death-1 (PD-1)-based treatment algorithms and targeted agents in B-type Raf proto-oncogene (BRAF) V600-mutant melanoma, 5-year overall survival (OS) rates for metastatic melanoma have increased substantially from less than 10% to up to 40% to 50% today in countries that have access to these innovations. However, patients with high tumor burden, brain metastasis, and elevated lactate dehydrogenase (LDH) still have a very poor prognosis (3-year survival <10%).[9]

Approximately 40% of melanomas harbor the BRAF V600 mutation, leading to constitutive activation of the mitogen activation protein kinase signaling pathway. Dual inhibition of this pathway in patients with unresectable BRAFV600-mutated melanoma, using combination therapy with BRAF and mitogen-activated protein kinase kinase (MEK) inhibitors, confers high response rates and survival benefit, although efficacy, in metastatic patients, is often limited by development of resistance. Three combinations of targeted therapy with BRAF/MEK inhibitors have received Food and Drug Administration (FDA) approval in the unresectable setting (dabrafenib and trametinib, vemurafenib and cobimetinib, encorafenib and binimetinib), while dabrafenib and trametinib are also approved as adjuvant therapy following the resection of stage 3/4 melanoma. The oncolytic herpes virus talimogene laherparepvec is also FDA approved for the local treatment of unresectable cutaneous, subcutaneous, and nodal lesions in patients with melanoma recurrent after initial surgery.[11]

In 2020, the first triple-therapy combining BRAF/MEK targeted and anti-programmed death-ligand 1 (PD-L1) immunotherapy with atezolizumab, vemurafenib and cobimetinib (IMspire150 study) was approved for unresectable or metastatic BRAF V600-mutated melanoma,[12] while another trial investigating triple therapy (spartalizumab, dabrafenib and trametinib) missed its endpoint.[13] However, toxicity was remarkable, with 79% of patients experiencing severe side effects and treatment discontinuation in 45%. In the adjuvant setting, updated data continue to support the use of either anti-PD-1 antibodies and BRAF/MEK inhibitors.[11]

Pembrolizumab has shown clinical activity in several cancers with response rates and disease control rates previously not observed in immunotherapy. While impressive as a single agent in melanoma, with a response rate of 38% demonstrated in the Phase 1 experience,[14] those patients that do not achieve response continue to have poor outcomes. In this context, there continues to be an area of unmet need in this non-responding melanoma patient population. The T cell-inflamed tumor microenvironment may be a predictive biomarker for response to multiple immunotherapies

including therapeutic vaccines, cytokines and anti-cytotoxic T-lymphocyte antigen-4 (CTLA-4) antibodies.[15,16,17,18]

A systemic treatment that can drive a T cell response into the tumors may be CTLA-4 blocking antibodies. Phase 3 clinical studies evaluating the anti-CTLA-4 antibodies tremelimumab and ipilimumab have documented single agent response rates on the order of 10%.[19,20] For both tremelimumab and ipilimumab, pre- and post-treatment biopsies have demonstrated a significant increase in CD8+ tumor-infiltrating lymphocytes in tumor lesions after anti-CTLA-4 antibody treatment.[21,22] In some studies,[23] there is also indication of modulation with the intra-tumoral Forkhead box P3 (FoxP3)+ Treg population; however, this has not been seen uniformly.

In spite of these newly approved therapies, overall outlook for patients with metastatic CM remains dismal and the development of new effective and tolerable therapy is still needed. More specifically, an estimated 30% to 70% of patients do not respond to initial anti-programmed death 1/ligand 1 (PD-1/L1) therapy, and approximately 25% eventually progress.[24,25,26,27] Thus, there remains a high unmet need for safe novel treatment modalities that are able to produce durable and deeper responses, as well as increased survival, in a greater percentage of eligible CM patients.

1.3 ANV419

ANV419 is being developed by Anaveon AG for the treatment of multiple advanced solid tumors and multiple myeloma as a single agent and in combination with other immunostimulatory approaches. ANV419 is a stable fusion protein comprised of IL-2 fused to an anti-IL-2 monoclonal antibody (mAb) that sterically blocks the binding of the IL-2 to IL-2R alpha (α) chain. As a result, ANV419 is a high molecular weight IL-2 agonist which signals through the IL-2R β/γ present on NK cells and CD8+ T cells but shows markedly reduced signaling through the IL-2R α/β/γ present on Tregs. ANV419 has a longer half-life relative to IL-2, shows good selectivity towards the expansion of NK and CD8+ T cells over Tregs, in the ongoing ANV419-001 Phase 1 study. In addition, the covalent linkage to IgG prolongs the half-life of ANV419, leaving target mediated disposition as the major driver of clearance. Compared with other novel IL-2 agents, the molecular characteristics of ANV419 aim to enable delivery of a higher molar equivalent of IL-2, with improved tolerability and safety profile, combined with a long duration of action, resulting in effective therapy in an outpatient setting.

Available data for ANV419 support the hypothesis that it may potentially provide a favorable risk/benefit profile for patients with cancer, who can benefit from immunotherapy.

1.3.1 Nonclinical Pharmacology

The pharmacology of ANV419 was characterized pre-clinically in protein and cell-based assays as well as in murine and cynomolgus monkey pharmacodynamic (PD) studies. Affinity measurements confirmed binding of ANV419 to the IL-2R β subunit with a dissociation constant comparable to recombinant IL-2 and showed absence of ANV419 binding to the IL-2R α subunit. In peripheral blood mononuclear cell (PBMC) in vitro stimulation experiments, this selective IL-2R chain binding profile translated into strongly reduced IL-2R signaling potency in Tregs

while comparable potency to recombinant IL-2 was maintained for CD8+ T and NK cells. Accordingly, in both mice and monkeys, IV bolus administration of ANV419 led to a preferential proliferation and expansion of CD8+ T and NK cells over Tregs in a dose-dependent manner. As a monotherapy, ANV419 inhibited tumor growth in well-established syngeneic mouse tumor models. ANV419 combination with checkpoint inhibition showed improved efficacy compared with single compound efficacy.

1.3.2 Nonclinical Pharmacokinetics

The pharmacokinetic (PK) behavior of ANV419 was characterized in cynomolgus monkeys following IV bolus administration and the serum concentration-time profiles were analyzed using population PK modeling. A non-linear and faster apparent elimination of ANV419 from serum at lower doses/concentrations was observed, consistently with a target-mediated drug disposition phenomenon. [redacted].

1.3.3 Toxicology

ANV419 administered IV to CD-1® International Genetic Standard mice [redacted].

The Good Laboratory Practices (GLP) and non-GLP studies in cynomolgus monkeys showed consistent findings, all related to the pharmacological effects of ANV419 as an agonistic IL-2 fusion protein. T[redacted]

No significant differences in the cytokine release potency in whole human blood were observed between ANV419 and recombinant IL-2. The maximal cytokine secretion levels as well as the responder frequencies at related doses were similar for both compounds for all cytokines.

In summary, the nonclinical data support the design of ANV419 as a uniquely engineered “not-α” IL-2R agonist. No unexpected effects were observed in either mice or cynomolgus monkeys and all findings were related to the expected pharmacology of ANV419.

For more details on the non-clinical studies and toxicology of ANV419, please see the Investigator’s Brochure.

1.3.4 Clinical Experience

In the ANV419-001 (NCT04855929) Phase 1 dose finding study of ANV419, 34 patients with Eastern Cooperative Oncology Group (ECOG) Performance Status 0 or 1 and a range of primary tumor types with multiple previous lines of therapy, including immunotherapy, targeted therapy, and chemotherapy, have been enrolled and treated as of 07 November 2022.

The doses of ANV419 investigated ranged from [redacted]

Preliminary Safety profile

ANV419 was generally well tolerated across multiple cycles, with no dose-limiting toxicities (DLTs) [redacted] The main safety findings detected in treated patients (N=34) were generally low grade, transient and self-limiting. As expected with IL-2 class agents, all patients experienced chills and fever which were predominantly of low grade. The most frequent drug related TEAEs (≥10% of patients) regardless of Grade and ANV419 dose level were: Pyrexia (74%), chills (62%), vomiting (35%), nausea (32%), cytokine release syndrome (CRS) (24%), asthenia (21%), decreased appetite (21%), ALT increased (18%), AST increased (18%), blood bilirubin increased (18%), fatigue (18%), diarrhea (12%), hypotension (12%), myalgia (12%) and maculopapular rash (12%). Transient and self-limiting lymphopenias (up to Grade 4), resulting from mode of action related lymphocyte sequestration, were observed in all patients, however considered as non-clinically significant in most instances. All related events were generally responsive to supportive care therapy and reversible.

Ten of 34 subjects (29%) had Grade 3 or higher drug related TEAE. The most frequent ≥Grade 3 drug related TEAE (≥5% of subjects) were, AST increase (6%), blood creatinine increase (6%), lymphopenia (9%) and nausea (6%).

At the dose [redacted].

Table 1 Study ANV419-001: Grade 3 or Higher Drug Related Treatment-Emergent Adverse Events

System Organ Class	Preferred Term	No Subjects (%) N=34
Blood and lymphatic system disorders	Lymphopenia	3 (9%)
Investigations	ALT increase	1 (3%)
	AST increase	2 (6%)
	Blood bilirubin increase	1 (3%)
	Blood creatinine increase	2 (6%)
	Platelet count decrease	1 (3%)
Gastrointestinal disorders	Nausea	2 (6%)
	Diarrhea	1 (3%)

Skin and subcutaneous tissue disorders	Pemphigoid	1 (3%)
Immune system disorders	Cytokine Release Syndrome	1 (3%)
General disorders and administration site conditions	Pyrexia	1 (3%)
	Asthenia	1 (3%)

All drug related SAEs at doses of [redacted] (MTD) were of low grade; 5 CRS (4 Grade 1 and 1 Grade 2) and one pyrexia (Grade 1). All these events met SAE criteria as they required either hospitalization or prolongation of an existing hospitalization.

At doses of [redacted] and higher, an increasing inflammatory response was observed when compared to lower ANV419 doses with patients experiencing higher fever (with chills, CRP, LFT elevation and clinically non-significant drop in platelet counts, as expected with IL-2 class agents, although with a better tolerability compared to recombinant IL-2.

At dose of [redacted], lymphopenia, resulting from lymphocyte sequestration, increased in duration [redacted] with a more pronounced rebound and increased lymphocyte count at day 8 at subsequent cycles. This observation is reminiscent of the PD effect described with recombinant high dose IL-2[45] given three times a day for a total of 6-9 administrations (Figure 1).

Figure 1. ANV419 Effect on Lymphocyte Count over Treatment Cycles

[redacted]

A comprehensive summary of all drugs related TEAEs reported in the ongoing ANV419-001 study is presented in Appendix F.

Pharmacodynamic Effect

Pharmacodynamic markers of target engagement have been investigated at each dose of ANV419 and up to [redacted]

[redacted]

Figure 2. ANV419 and Preferential Proliferation of CD8+ and NK Cells

CD = cluster of differentiation; NK = natural killer; Treg = regulatory T cell.

Preliminary Efficacy

Among the 34 patients treated, 33 patients were evaluable for tumor response using RECIST v1.1

Twenty patients (61%) achieved SD or better (19 SD, 1 confirmed PR). [redacted] 14/20 patients (70%) achieved SD (13 SD, 1 confirmed PR).

1.4 Rationale

Checkpoint inhibitors have demonstrated durable response rates and significant survival benefit in melanoma, renal cell carcinoma, non-small cell lung cancer,[5,6,7] and other tumors. Despite this, many patients experience resistance to checkpoint inhibitors and/or are unable to tolerate therapy. Ultimately, most patients with advanced cancer relapse and eventually succumb to the disease. Additional therapeutic options are needed.

In the current study, Anaveon AG proposes to test the hypothesis that the administration of ANV419 as monotherapy or in combination with anti-PD-1 antibody (pembrolizumab) or anti-CTLA-4 antibody (ipilimumab) will generate clinical responses in patients with CM whose disease has progressed on anti-PD-1/anti-PD-L1 antibody or in combination (eg, anti-CTLA-4 antibody). The study will also provide the opportunity to explore blood and tumor-based markers that may predict response to ANV419 as monotherapy or in combination with anti-PD-1 antibody or anti-CTLA-4 antibody.

1.5 Risk/Benefit

Patients with CM, and particularly those with unresectable or metastatic CM following anti-PD-1/anti-PD-L1 antibody treatment represent populations with high unmet need. As discussed in Section 1.2, an estimated 30% to 70% of patients do not respond to initial anti-PD-1/anti-PD-L1 therapy and approximately 25% of patients eventually progress and may have no other therapeutic options. Therefore, there is an urgent need to identify new targeted therapies and/or combination therapies to overcome current IL-2 limitations that contribute to significant toxicity.

The available clinical data for ANV419 suggest ANV419 may have a favorable risk/benefit profile for patients with melanoma and this will be further explored in the ANV419-101 study.

The preclinical data demonstrate that ANV419 is a uniquely engineered "not-α" IL-2R agonist that signals preferentially through the intermediate affinity IL-2R β/γ and thus strongly stimulates proliferation of CD8+ T cells and NK cells while avoiding proliferation of immunosuppressive Tregs.

Since ANV419 is an experimental medicine, it is possible that unforeseen, unknown, or unanticipated drug reactions and toxicities may occur. However, as detailed below, this Protocol is designed to mitigate risks to patients through a detailed plan for careful safety monitoring, systemic review of AEs, SAEs, and active pharmacovigilance review to assess for safety signals or trends.

2 STUDY OBJECTIVES AND ENDPOINTS

The study objectives and endpoints for Part 1: Monotherapy Dose Expansion, Part 2: Combination Dose Finding, and Part 3: Combination Dose Expansion are provided in Table 2, Table 3, and Table 4.

Table 2. Study Objectives and Endpoints for Part 1: Monotherapy Dose Expansion

Part 1: Monotherapy Dose Expansion – Arms A1 and A2	
Primary Objectives	**Primary Endpoints**
Evaluate the efficacy of ANV419	ORR (CR + PR), as defined by RECIST v1.1 (hereinafter, RECIST).
Secondary Objectives	**Secondary Endpoints**
To characterize the tumor response according to modified RECIST v1.1 criteria for immune-based therapeutics (iRECIST)	Tumor response in terms of objective response rate (ORR: CR + PR) assessed by iRECIST
Expand evaluation of efficacy of ANV419	- DOR (per RECIST) and iDOR (per iRECIST[1]) measured from first response until disease progression; - DCR (DCR = CR + PR + SD), iDCR (iDCR = iCR + iPR + iSD), PFS, iPFS, and OS; - Median TTR; and - Median iTTR.
Evaluate the safety of ANV419	Incidence, frequency, and severity of AEs including the following: - SAEs; - irAEs; - AESIs; - AEs leading to discontinuation of the study; and - Changes from baseline in laboratory parameters, vital signs, ECGs, and physical examination.
Explore immunogenicity after exposure to ANV419	Incidence of immunogenicity as indicated by ADA.
Exploratory Objectives	**Exploratory Endpoints**
Explore the changes in the tumor microenvironment before and after adding ANV419 as monotherapy	Changes in immunological biomarker expression from baseline and post treatment tumor and liquid biopsies, including: - Immune cell counts, immunophenotyping (including, but not limited to, CD3, CD4, CD8, CD56, CD16, CD25, FoxP3, CD279, and CD366); - Cytokine production (including, but not limited to, IFNγ, IL-2, TNF, IL-6, IL-10); and - Immunohistochemistry (including, but not limited to, CD8, CD4, Ki67).
	Analysis of mutations in the tumor and analysis of tumor mutational burden.
	Analysis of changes in baseline ctDNA and at specified timepoints on therapy and after therapy.
	Analysis of single nucleotide polymorphisms, germline DNA for genome-wide association studies, analysis of T cell receptor repertoire, epigenetic markers, soluble CD25, and soluble PD-1/PD-L1.

1. Seymour L, Bogaerts J, Perrone A, et al. iRECIST: guidelines for the response criteria for use in trials testing immunotherapeutics. *Lancet Oncol*. 2017;18(3):e143-e152.

AE = adverse event; AESI = adverse event of special interest; CD = cluster of differentiation; CR = complete response; ctDNA = circulating tumor deoxyribonucleic acid; DCR = disease control rate; DOR = duration of response; ECG = electrocardiogram; FoxP3 = Forkhead box P3; iCR = immune complete response; iDCR = immune disease control rate; iDOR = immune duration of response; IFNγ = interferon gamma; IL = interleukin; iPFS = immune progression-free survival; iPR = immune partial response; irAE = immune-related adverse event; iRECIST = immune Response Evaluation Criteria in Solid Tumors; iSD = immune stable disease; iTTR = immune time to response; ORR = objective response rate; OS = overall survival; PD-1 = programmed death-1; PD-L1 = programmed death-ligand 1; PFS = progression-free survival; PR = partial response; RECIST = Response Evaluation Criteria in Solid Tumors; SAE = serious adverse event; SD = stable disease; T cell = thymus lymphocyte cell; TNF = tumor necrosis factor; TTR = time to response; v1.1 = version 1.1.

Table 3. Study Objectives and Endpoints for Part 2: Combination Dose Finding

Combination Dose Finding – Combination Therapy Arms (Arms B and C)	
Primary Objectives	**Primary Endpoints**
Evaluate the safety and tolerability and determine the RP2D of ANV419 in combination with pembrolizumab Evaluate the safety and tolerability and determine the RP2D of ANV419 in combination with ipilimumab	Incidence, frequency, and severity of AEs including the following: - SAEs; - TEAEs; - DLTs; - AESIs; - irAEs; - AEs leading to discontinuation of the study; and - Changes from baseline in laboratory parameters, vital signs, ECGs, and physical examinations.
Secondary Objectives	**Secondary Endpoints**
Evaluate PK and PD of ANV419 in combination with pembrolizumab or ipilimumab	PK endpoints in serum: - CL of ANV419; - V_{ss} of ANV419; - AUC of ANV419; and - C_{max} of ANV419. PD endpoints in peripheral blood: including, but not limited to, CD3, CD4, CD8, CD56, CD16, CD25, FoxP3, CD279, and CD366.
Explore immunogenicity after exposure to ANV419 in combination with pembrolizumab or ipilimumab	Incidence of immunogenicity as indicated by ADA.
Evaluate the efficacy of ANV419 in combination with pembrolizumab or ipilimumab	ORR (CR + PR), as defined by RECIST.
Expand evaluation of efficacy of ANV419 in combination with pembrolizumab or ipilimumab	DOR (per RECIST) and iDOR (per iRECIST[1]) measured from first response until disease progression; PFS, iPFS, and OS; DCR (DCR = CR + PR + SD), iDCR (iDCR = iCR + iPR + iSD), Median TTR; and Median iTTR.
Evaluate clinical benefit in quality of life after exposure to ANV419 in combination with pembrolizumab or ipilimumab	Change in QoL at baseline and every 12 weeks while receiving ANV419 via QoL evaluations: - EQ-5D-5L; and - QLQ-C30.
Exploratory Objectives	**Exploratory Endpoints**
Explore the changes in the tumor microenvironment before and after adding ANV419 as monotherapy and in combination with pembrolizumab or ipilimumab	Changes in immunological biomarker expression from baseline and post treatment tumor and liquid biopsies, including: - Immune cell counts, immunophenotyping (including, but not limited to, CD3, CD4, CD8, CD56, CD16, CD25, FoxP3, CD279, and CD366); - Cytokine production (including, but not limited to, IFNγ, IL-2, TNF, IL-6, IL-10); and Immunohistochemistry (including, but not limited to, CD8, CD4, Ki67).
	Analysis of mutations in the tumor and analysis of tumor mutational burden.
	Analysis of changes in baseline ctDNA and at specified timepoints on therapy and after therapy.

	Analysis of single nucleotide polymorphisms, germline DNA for genome-wide association studies, analysis of T cell receptor repertoire, epigenetic markers, soluble CD25, and soluble PD-1/PD-L1.

Table 3. Study Objectives and Endpoints for Part 2: Combination Dose Finding (Continued)

ADA = anti-drug antibodies; AE = adverse event; AESI = adverse event of special interest; AUC = area under the concentration-time curve; CD = cluster of differentiation; CL = systemic clearance; C_{max} = maximum observed serum concentration; CR = complete response; ctDNA = circulating tumor deoxyribonucleic acid; DLT = dose-limiting toxicity; ECG = electrocardiogram; EQ-5D-5L = Euro-QoL 5 dimension 5 level; FoxP3 = Forkhead box P3; IFNγ = interferon gamma; IL = interleukin; irAE = immune-related adverse event; ORR = objective response rate; PD = pharmacodynamic(s); PD-1 = programmed death-1; PD-L1 = programmed death-ligand 1; PK = pharmacokinetic(s); PR = partial response; QLQ-C30 = quality of life core 30; QoL = quality of life; RECIST = Response Evaluation Criteria in Solid Tumors; RP2D = recommended Phase 2 dose; SAE = serious adverse event; T cell = thymus lymphocyte cell; TEAE = treatment-emergent adverse event; TNF = tumor necrosis factor; V_{ss} = volume of distribution at steady state.

Table 4. Study Objectives and Endpoints for Part 3: Combination Dose Expansion

Part 3: Combination Dose Expansion – Combination Therapy Arms (Arms B and C)	
Primary Objectives	**Primary Endpoints**
Evaluate the efficacy of ANV419 in combination with pembrolizumab or ipilimumab	ORR (CR + PR), as defined by RECIST.
Secondary Objectives	**Secondary Endpoints**
Expand evaluation of efficacy of ANV419 in combination with pembrolizumab or ipilimumab	- DOR (per RECIST) and iDOR (per iRECIST[0]) measured from first response until disease progression; - DCR (DCR = CR + PR + SD), iDCR (iDCR = iCR + iPR + iSD), PFS, iPFS, and OS; - Median TTR; and - Median iTTR.
Part 3: Combination Dose Expansion – Combination Therapy Arms (Arms B and C)	
Secondary Objectives	**Secondary Endpoints**
Evaluate the safety of ANV419 in combination with pembrolizumab or ipilimumab	Incidence, frequency, and severity of AEs including the following: - SAEs; - irAEs; - AESIs; - AEs leading to discontinuation of the study; and - Changes from baseline in laboratory parameters, vital signs, ECGs, and physical examination.
Evaluate clinical benefit in quality of life after exposure to ANV419 in combination with pembrolizumab or ipilimumab	Change in QoL at baseline and every 12 weeks while receiving ANV419 via QoL evaluations: - EQ-5D-5L; and - QLQ-C30.
Explore immunogenicity after exposure to ANV419 in combination with pembrolizumab or ipilimumab	Incidence of immunogenicity as indicated by ADA.
Exploratory Objectives	**Exploratory Endpoints**
Explore the changes in the tumor microenvironment before and after adding ANV419 in combination with pembrolizumab or ipilimumab	Changes in immunological biomarker expression from baseline and post treatment tumor and liquid biopsies, including: - Immune cell counts, immunophenotyping (including, but not limited to, CD3, CD4, CD8, CD56, CD16, CD25, FoxP3, CD279, and CD366); - Cytokine production (including, but not limited to, IFNγ, IL-2, TNF, IL-6, IL-10); and - Immunohistochemistry (including, but not limited to, CD8, CD4, Ki67).
	Analysis of mutations in the tumor and analysis of tumor mutational burden.

	Analysis of changes in baseline ctDNA and at specified timepoints on therapy and after therapy.
	Analysis of single nucleotide polymorphisms, germline DNA for genome-wide association studies, analysis of T cell receptor repertoire, epigenetic markers, soluble CD25, and soluble PD-1/PD-L1.

Table 4. Study Objectives and Endpoints for Part 3: Combination Dose Expansion (Continued)

Seymour L, Bogaerts J, Perrone A, et al. iRECIST: guidelines for the response criteria for use in trials testing immunotherapeutics. *Lancet Oncol*. 2017;18(3):e143-e152.

AE = adverse event; AESI = adverse event of special interest; CD = cluster of differentiation; CR = complete response; ctDNA = circulating tumor deoxyribonucleic acid; DCR = disease control rate; DOR = duration of response; ECG = electrocardiogram; EQ-5D-5L = Euro-QoL 5 dimension 5 level; FoxP3 = Forkhead box P3; iCR = immune complete response; iDCR = immune disease control rate; iDOR = immune duration of response; IFNγ = interferon gamma; IL = interleukin; iPFS = immune progression-free survival; iPR = immune partial response; irAE = immune-related adverse event; iRECIST = immune Response Evaluation Criteria in Solid Tumors; iSD = immune stable disease; iTTR = immune time to response; ORR = objective response rate; OS = overall survival; PD-1 = programmed death-1; PD-L1 = programmed death-ligand 1; PFS = progression-free survival; PR = partial response; QLQ-C30 = quality of life core 30; QoL = quality of life; RECIST = Response Evaluation Criteria in Solid Tumors; SAE = serious adverse event; SD = stable disease; T cell = thymus lymphocyte cell; TNF = tumor necrosis factor; TTR = time to response.

3 STUDY DESCRIPTION

3.1 Summary of Study Design

This is a multi-site, open-label, randomized, parallel arm, Phase 1/2 adaptive study to evaluate the efficacy and safety of ANV419 as a monotherapy and in combination with pembrolizumab or ipilimumab in patients aged 18 years or older with advanced CM who have previously been treated with at least 1 line of standard of care immunotherapy, including an anti-PD-1/anti-PD-L1 antibody.

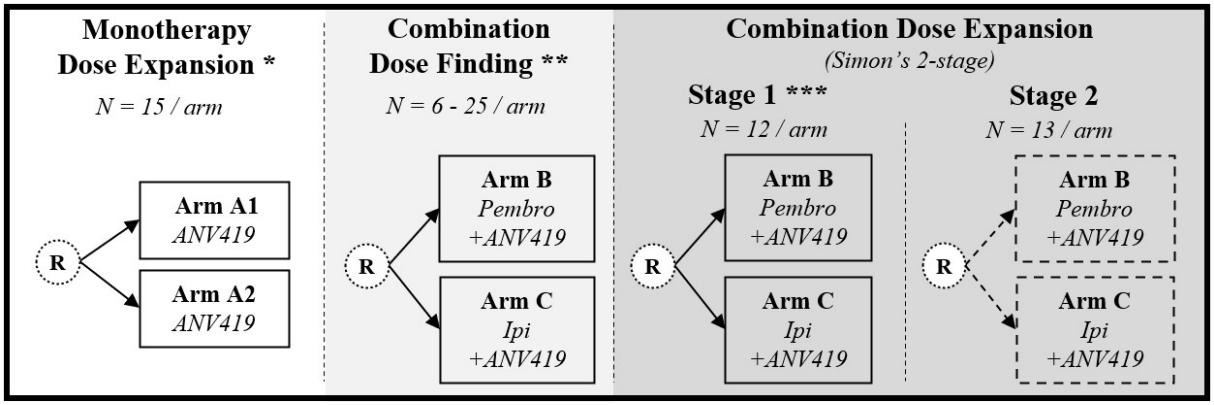
The 4 following treatment arms will be included in this study:

- Arm A1: [redacted]
- Arm A2: [redacted]
- Arm B: [redacted] in combination with pembrolizumab (Keytruda®); and
- Arm C: [redacted] in combination with ipilimumab (Yervoy®).

There will be up to 3 separate parts in this study: Part 1: Monotherapy Dose Expansion with patients randomized to receive infusion of ANV419 ([redacted] If Part 1 is successful, Part 2: Combination Dose Finding with patients randomized to Arms B and C with infusion of ANV419 [redacted] and finally, Part 3: Combination Dose Expansion with patients randomized to Arms B and C (see Figure 3). A total of up to 130 patients are planned to be enrolled in the study: a maximum of 30 patients in the Monotherapy Dose Expansion part, a maximum of 50 patients in the Combination Dose Finding part, and a maximum of 50 patients in the Combination Dose Expansion part. Randomization in the Monotherapy Dose Expansion part and Combination Dose Expansion part will be stratified by BRAF mutation status.

In the Combination Dose Expansion part, the number of patients within each arm will be determined by pre-defined decision rules presented in Table 5.

Figure 3. Study Design



* = If ANV419 monotherapy is successful, the combination portion will be initiated.
** = Dose escalation increment is decided by the SRC until RP2D of ANV419 per arm is identified.
*** = Arm not meeting pre-specified ORR criteria may be stopped early after Stage 1.
In the Combination Dose Finding part, patients will be manually randomized to Arm B or Arm C. In the Monotherapy Dose Expansion part and the Combination Dose Expansion part, patients will be randomized by IRT into Arms A1 or A2 and Arms B or C, respectively.

Ipi = ipilimumab; IRT = Interactive Response Technology; ORR = objective response rate; Pembro = pembrolizumab; R = randomization; RP2D = recommended Phase 2 dose; SRC = Safety Review Committee.

All patients will be assessed for response using Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 (hereinafter, RECIST) and computed tomography (CT) imaging, which will occur every [redacted], using the same modality as used for baseline imaging until progressive disease per RECIST and immune RECIST (iRECIST), withdrawal of consent, or initiation of a new anticancer therapy. Treatment decision will be based on local assessment. All images will be collected and stored centrally for potential central analysis. [redacted]

The study will also assess other clinical parameters including progression free survival (PFS) and will provide the opportunity to explore blood- and tumor based markers that may predict response to ANV419 as monotherapy or in combination with anti-PD-1 or anti CTLA-4 antibodies.

3.1.1 Part 1: Monotherapy Dose Expansion

The Monotherapy Dose Expansion part (Arms A1 and A2) will be a parallel group part with a Bayesian sequential monitoring analysis[28] and up to 15 patients per arm. This part will establish the efficacy and safety of ANV419 as monotherapy.

Two doses of ANV419 will be explored: [redacted] based on data collected in the ongoing Phase 1 ANV419-001 study at a frequency of [redacted]. Treatment with ANV419 as a monotherapy can continue for [redacted] within the current Protocol in the absence of disease progression or unacceptable toxicity and in the absence of data from Arms A1 and A2 showing an unfavorable risk/benefit profile for patients on ANV419 monotherapy.

Decision making on whether to continue the study beyond the Monotherapy Dose Expansion part, and the total number of patients recruited to this part, will be based on Bayesian sequential monitoring. The study will be stopped at the end of this part in the case of an unfavorable risk/benefit profile for ANV419 monotherapy. This includes observing a total of 0 of 30 responses from the 2 monotherapy arms combined (a strong signal that ANV419 does not induce a response) and/or report of any safety issues that might stop the trial. There is 95% certainty that the true objective response rate (ORR) is greater than 10% if we observe any 1 of the following:

- 2 responses in 3 to 7 patients;
- 3 responses in 8 to 13 patients;
- 4 responses in 14 to 19 patients; or
- 5 responses in 20 to 27 patients.

Response (complete response [CR] or partial response [PR]) will be assessed locally at each disease evaluation.

3.1.2 Part 2: Combination Dose Finding

This part will only be initiated following approval of a substantial amendment supporting the ANV419 starting dose in the combination part. The submission will include data from ANV419-001 Study and from Part 1 of this trial, and occurat any time when at least 2 responses have been observed in the Monotherapy Dose Expansion part.

The Combination Dose Finding part will be comprised of 2 arms (Arms B and C) that will identify a recommended Phase 2 dose (RP2D) for ANV419 in each arm when administered in combination with pembrolizumab (Arm B) or ipilimumab (Arm C) at the prescribed dosing. The number of patients recruited to each arm will be between 6 and 25 patients depending on the number of dose increments possible. A minimum of 6 patients will be treated at RP2D. The patients from the Combination Dose Finding part will not be randomized into the Combination Dose Expansion part.

Dosing of ANV419 when administered in combination with pembrolizumab (Arm B) or ipilimumab (Arm C) will occur as shown in Table 5, with a dose of ANV419 currently planned to start at [redacted]. Patients in the Combination Dose Finding part will be treated with a minimum of 24 hours interval between patients to allow for monitoring of acute toxicities. Dose level 1, as shown in Table 5, will be reviewed by the Safety Review Committee (SRC) per the safety evaluations and the SRC will make dose increment recommendations at each dose level, not exceeding 3-fold increment from on dose level to the next. The maximum dose level explored will not exceed the [redacted]

Table 5. ANV419 Dose Escalation Plan for Combination Dose Finding Part (Pembrolizumab or Ipilimumab)

Dose Level	ANV419 Dose	Pembrolizumab Dose or Ipilimumab Dose	Frequency
1	[redacted]		
2			
3			
4			
5			

Note: ANV419 will be administered by IV infusion over 15 minutes (+5 minutes).
1. Dose increments will be determined by the SRC based on a synthesis of all relevant data available from all dose levels evaluated in this study, not exceeding a 3-fold increment from one dose level to the next. The maximum dose level explored will not exceed the [redacted] dose of ANV419 monotherapy studied in the ongoing ANV419-001 study.

IV = intravenous(ly); [redacted] SRC = Safety Review Committee; TBD = to be determined.

3.1.2.1 Bayesian optimal interval dose escalation guidelines

In the Combination Dose Finding part, dose escalation will follow the Bayesian optimal interval (BOIN)[29] design with the following predefined rules to find the MTDs/RP2Ds of ANV419 in combination with pembrolizumab or ipilimumab to be used in the efficacy analysis:

- Target DLT rate of 25%;
- Maximum of 25 patients;
- Maximum of 9 patients treated at the same dose level; and
- Maximum of 5 dose levels defined in Table 5 to be tested.

As shown in Figure 4, the BOIN[29] design uses the following rules, optimized to minimize the probability of incorrect dose assignment, to guide dose escalation/de-escalation:

- If the observed DLT rate at the current dose is ≤[redacted], escalate the dose to the next higher dose level;
- If the observed DLT rate at the current dose is >[redacted], de-escalate the dose to the next lower dose level; and
- Otherwise, stay at the current dose.

The steps to implement the BOIN design are described as follows:

1. Patients in the first cohort with a cohort size of 3 patients are treated at dose level 1;
2. To assign a dose to the next cohort of patients, conduct dose escalation/de-escalation according to the rule displayed in Table 6; and

   Note: If none of the actions (ie, escalation or de-escalation) is triggered, treat the new patients at the current dose.
3. Repeat step 2 until the maximum sample size of 25 is reached or a stopping rule is met, or if the number of evaluable patients treated at the current dose reaches 9 and the decision according to Table 6 is to stay at the current dose.

After the study is completed, the MTD will be selected based on isotonic regression as specified by Liu and Yuan.[29] Specifically, the MTD will be selected as the dose for which the isotonic estimate of the toxicity rate is closest to the target toxicity rate. If there are ties, select the higher dose level when the isotonic estimate is lower than the target toxicity rate and select the lower dose level when the isotonic estimate is greater than or equal to the target toxicity rate.

Table 6. Dose Escalation/De-Escalation Rule for the BOIN Design

[redacted]

Figure 4. Flowchart for Trial Conduct Using the BOIN Design

BOIN = Bayesian optimal interval; DLT = dose-limiting toxicity; MTD = maximum tolerated dose.

Operation characteristics

Table 7 shows the operating characteristics of the trial design and based on 1000 simulations of the trial using R package "BOIN" (BOIN v2.7.0.0).[30] The operating characteristics show that the design selects the true MTD, if any, with high probability and allocates more patients to the dose levels with DLT rate closest to the target of [redacted]

Table 7. Operating Characteristics of the BOIN Design

3.1.3 Part 3: Combination Dose Expansion

The Combination Dose Expansion part of the study will be separate from the Combination Dose Finding part and will evaluate the safety and efficacy of ANV419 in combination with pembrolizumab (Arm B) or ipilimumab (Arm C). This Combination Dose Expansion part will consist of 2 stages. In Stage 1, 12 patients will be randomized by interactive response technology (IRT) into each arm. At the end of this stage, an interim analysis will be performed to assess continuation of treatment arms into Stage 2 (see Table 8). In Stage 2, eligible patients will be randomized to the remaining treatment arms, determined at the interim analysis. Recruitment will continue until 25 patients have been randomized to a treatment arm.

Table 8. Continuation Decision Rules for Combination Dose Expansion Part

Treatment Arm Accrual	Discontinue if the Number of Responses is	Discontinue Criterion in Terms of ORR	Continue if the Number of Responses is at Least
Stage 1 (n=12)	≤2	Observed ORR <20%	3
ORR = objective response rate.			

Dosing for ANV419 in the combination arms (Arms B and C) in the Combination Dose Expansion part will be based on the RP2Ds for ANV419 determined in the Combination Dose Finding part, ie, the RP2D for ANV419 when administered in combination with pembrolizumab (hereinafter, RP2D[p]) and the RP2D for ANV419 when administered in combination with ipilimumab (hereinafter, RP2D[i]).

Treatment with ANV419 in combination with pembrolizumab can continue for 24 months within the current Protocol in the absence of disease progression or unacceptable toxicity.

Treatment with ANV419 in combination with ipilimumab can continue up to a maximum of 4 cycles, per the approved label (United States Prescribing Information and Summary of Product Characteristics). If ipilimumab-related AEs occur, ipilimumab can be discontinued at any time. Once a patient has completed the maximum of 4 [redacted]

3.1.4 Dose-Limiting Toxicity Criteria (Applicable to Combination Dose Finding Part Only)

A DLT is defined as any of the treatment-emergent AEs (TEAEs) listed below, as defined by the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 5.0, occurring during the DLT period ([redacted]) and the AE is not reasonably attributed to the patient's underlying disease, other medical conditions, or concomitant medications. To be DLT evaluable, the patient must complete [redacted]. The DLT definitions are the following:

[redacted]

An SRC will be convened, comprised of enrolling study Investigators, Medical Monitor, and the Sponsor Medical Director or designee. All potentials DLTs will be reviewed by the SRC for a final determination and for the SRC to make recommendations regarding the study. The SRC will also

consider AEs, particularly high-grade toxicities that may have occurred in patients in any treatment arm (even beyond the DLT period), when making decisions/recommendations to proceed with the study. The SRC will provide recommendations for study drug dosing and alternative dosing regimens as appropriate, not exceeding a 3-fold increment from one dose level to the next. The maximum dose level explored will not exceed the [redacted] dose of ANV419 monotherapy studied in the ongoing ANV419-001 study. Near the end of dose escalation, the statistician will also contribute to dose escalation recommendation, using the BOIN design, to select the MTD/RP2D.

After completion of the [redacted] DLT period for each cohort, intra-patient dose escalation is permitted with approval of the Investigator and provided the following criteria have been met:

- The patient has completed at least 1 treatment cycle;
- The DLT assessment of the dose level to which the patient will be dose-escalated is complete and determined to be safe by the SRC;
- The patient did not experience any AEs related to study drug(s) >Grade 1 at the dose level prior to escalation; and
- The patient has not required any dose reduction.

3.2 Stopping Rules

Treatment of individual patients may be stopped under defined circumstances as outlined in Section 4.4.

3.3 Safety Review Committee

An SRC will be established to monitor safety aspects of the trial and make recommendations to Anaveon and Medpace about trial conduct to ensure patient safety and scientific validity.

The SRC Charter will further describe membership and responsibilities of the SRC.

3.4 Study Indication(s)

ANV419 is being developed for treatment of unresectable or metastatic CM following at least 1 line of standard of care immunotherapy, including an anti-PD-1 and/or anti-PD-L1 antibody.

4 SELECTION AND WITHDRAWAL OF PATIENTS

Population

Patients with unresectable or metastatic CM with measurable disease, whose disease has progressed following or on at least 1 line of standard of care immunotherapy (on anti-PD-1, anti-PD-L1, and/or CTLA-4 antibody treatment).

4.1 Inclusion Criteria

Patients who meet all of the following criteria will be eligible to participate in the study:

1. Must provide written informed consent for the study;
2. Must be able to comply with the Protocol as judged by the Investigator;
3. Are ≥18 years of age on day of signing informed consent;
4. Have histologically confirmed Stage 3 (unresectable) or Stage 4 (metastatic) CM, as per the American Joint Committee on Cancer staging system, eighth edition;
5. Have documented radiological progression on prior systemic therapy;
6. Have previously received anti-PD-1/L1 as monotherapy or in combination. A maximum of 2 prior lines of systemic therapy is allowed for BRAF wild-type disease and a maximum of 3 prior lines of systemic therapy is allowed for BRAFV600 positive disease;

   Note: Adjuvant treatment is considered as a line of therapy only if patient experienced relapse/ progression on therapy or within 6 months from adjuvant therapy completion;
7. Have measurable disease based on RECIST;
8. Have a performance status of 0 or 1 on the ECOG Performance Status;
9. Have adequate organ functions as defined in Table 9:

Table 9. Adequate Organ Function Laboratory Values

System	Laboratory Value
Hematological	
ANC	≥1500/µL
Platelets	≥100,000/µL
Hemoglobin	≥9 g/dL or ≥4.96 mmol/L
Renal	
Measured or calculated[1] CrCl (GFR can also be used in place of CrCl)	≥30 mL/min
Hepatic	
Serum total bilirubin OR direct bilirubin	≤1.5 × ULN OR ≤1.5 × ULN for patients with total bilirubin levels >1.5 × ULN; direct bilirubin ≤1.5 × ULN for patients with Gilbert's syndrome
AST (SGOT) or ALT (SGPT)	≤2.5 × ULN OR ≤5 × ULN for patients with liver metastases
Albumin	>2.5 g/dL

1. CrCl should be calculated per Cockcroft-Gault equation.
ALT = alanine aminotransferase; ANC = absolute neutrophil count; AST = aspartate aminotransferase; CrCl = creatinine clearance; GFR = glomerular filtration rate; SGOT = serum glutamic oxalacetic transaminase; SGPT = serum glutamic pyruvic transaminase; ULN = upper limit of normal.

10. Female patients of childbearing potential must have a negative serum pregnancy test at the Screening Visit and a negative (urine or serum) pregnancy test within 72 hours prior to study Day 1. If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required and must be negative for the patient to be eligible;
11. Female patients who are not postmenopausal, and who have not undergone surgical sterilization, must agree to use highly effective methods of contraception during the treatment period and for 6 months after the last dose of study drug. They must also agree not to donate eggs (ova, oocytes) during the same timeframe; and
12. Male patients with partners of childbearing potential must agree to use highly effective methods of contraception and barrier contraception (condom) during the treatment period and for 6 months after the last dose of study drug. They must also agree not to donate sperm during the same timeframe.

4.2 Exclusion Criteria

Patients who meet any of the following criteria will be excluded from participation in the study:

1. Have received investigational agent (including investigational device) within 4 weeks or an interval of 5 half-lives of the respective investigational agent prior to study Day 1, whichever is longer, with the exclusion of an anti-PD-1/anti-PD-L1 antibody given as either a single agent or non-CTLA-4 antibody containing combination (eg, anti-lymphocyte-activation gene 3 antibody);
2. Have a known hypersensitivity to ANV419 or to any of the excipients, such as sucrose, histidine or polysorbate 80. For combination arms only: Have hypersensitivity to pembrolizumab or ipilimumab or any of their excipients;
3. For combination arms only: Have previously discontinued ipilimumab, pembrolizumab, or any other PD-1/PD-L1 inhibitors due to unacceptable drug-related toxicity (defined as toxicities that required second line immunosuppression, ie, not controlled by steroids alone);
4. Have an LDH level of ≥2 × upper limit of normal;
5. Have not recovered (ie, ≤Grade 1 or at baseline with the exception of alopecia or fatigue [up to Grade 2 allowed]) from AEs resulting from prior immunotherapies. Patients who have autoimmune AEs controlled by replacement therapy (ie, hypothyroidism) due to previous treatment are eligible provided replacement therapy has been initiated and toxicity has returned to Grade 1;
6. Have not recovered (ie, ≤Grade 1 or at baseline) from toxicities due to a previously administered prior chemotherapy, targeted small molecule therapy, or radiation therapy;

   Note: If the patient received major surgery, they must have recovered adequately from the toxicity and/or complications from the intervention prior to starting study drug. Major surgery is defined as any surgery requiring entrance into a body cavity (eg, chest, abdomen, or brain), organ removal, normal anatomy alteration, or joint replacement. Minor surgery is defined as any surgery in which skin, mucosa, or connective tissue sections are altered (eg, biopsy, cataract, endoscopic procedures, etc).
7. Have been diagnosed with uveal/ocular or mucosal melanoma;

8. Have a known additional malignancy (including all in-situ carcinoma) that is progressing or requires active treatment within ≤2 years prior to enrollment. Exceptions include basal cell carcinoma of the skin or squamous cell carcinoma of the skin that have undergone potentially curative therapy or in situ cervical cancer or patients who completed cancer-directed therapy and have no evidence of disease;
9. Have active central nervous system metastases and/or carcinomatous meningitis. Patients with previously treated brain metastases may participate provided they are stable (without evidence of progression by imaging for at least 4 weeks prior to study Day 1 and any neurologic symptoms have returned to baseline or have been stable for at least 7 days), have no evidence of new or enlarging brain metastases, and are not using steroids for at least 7 days prior to study drug. This exception does not include carcinomatous meningitis which is excluded regardless of clinical stability;
10. Have a diagnosis of immunodeficiency or is receiving immunosuppressive therapy within 7 days prior to study Day 1;
11. Are receiving systemic steroid >10 mg of prednisone daily or equivalent or any other immunosuppressive medication at any dose level. Local steroid therapies (eg, otic, ophthalmic, intra-articular, or inhaled medications) are acceptable;
12. Have an active autoimmune disease that has required systemic treatment in the past 2 years (ie, with use of disease modifying agents, corticosteroids, or immunosuppressive drugs). Replacement therapy (eg, thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency, etc) is not considered a form of systemic treatment;
13. Have evidence of active, non-infectious pneumonitis;
14. Have active (measurable) and uncontrolled (unresponsive to current therapy) infectious disease (bacterial, fungal, viral, or protozoic);
15. Have a history of an acute coronary event (eg, myocardial infarction) within 3 months prior to study Day 1, uncontrolled and symptomatic coronary artery disease or congestive heart failure New York Heart Association Class III/IV;
16. Have an average QTcF interval >470 msec at Screening;
17. Have a history or current evidence of any condition, therapy, or laboratory abnormality that might confound the results of the study, interfere with the patient's participation for the full duration of the study, or it is not in the best interest of the patient to participate, in the opinion of the treating Investigator;
18. Have known psychiatric or substance abuse disorders that would interfere with cooperation with the requirements of the study;
19. Are pregnant or breastfeeding, or expecting to conceive or father children within the projected duration of the study, starting with the Screening Visit through 6 months after the last dose of study drug;
20. Are known to be human immunodeficiency virus (HIV) positive (or tests positive for HIV 1 or 2 at Screening), unless the following criteria are met:
    a. CD4+ lymphocyte count >350 µL;

b. Had no history of acquired immunodeficiency syndrome (AIDS)-defining opportunistic infections within the past 12 months;

c. Have been on established anti-retroviral therapy for at least 4 weeks; and

d. Have an HIV viral load of <400 copies/mL prior to study Day 1.

Note: Patients on strong cytochrome P450 (CYP)3A4 inhibitors or strong CYP3A4 inducers must be switched to an alternate effective anti-retroviral therapy regimen prior to study treatment or are excluded if regimen prior to study Day 1 cannot be altered.

21. Have uncontrolled hepatitis B infection or hepatitis C infection;

Note: Patients with hepatitis B (positive hepatitis B surface antigen) who have controlled infection (serum hepatitis B virus DNA by polymerase chain reaction that is below the limit of detection and receiving anti-viral therapy for hepatitis B) are permitted. Patients with controlled infections must undergo periodic monitoring of hepatitis B virus DNA.

Note: Patients with hepatitis C (positive hepatitis C virus antibody) who have controlled infection (undetectable hepatitis C virus RNA by polymerase chain reaction either spontaneously or in response to a successful prior course of anti-hepatitis C virus therapy) are permitted.

22. Have received a live vaccine within 30 days of study Day 1; or

Note: Seasonal influenza vaccines for injection are generally inactivated flu vaccines and are allowed; however, intranasal influenza vaccines (eg, Flu-Mist®) are live attenuated vaccines, and are not allowed.

23. For combination arms only: Have received solid organ or hematopoietic stem cell transplant.

4.3 Suspension of enrollment

Adverse events and serious adverse events (SAEs) are expected to occur frequently in this study based on the patient population being accrued and the nature of the advanced malignancy. As a result, there is no specific incidence rate of SAEs that will define a stopping rule. Instead, regular systematic review of SAEs will serve as the basis for enrolment suspension or prematurely stopping of the study.

4.3.1 Criteria for suspension of enrollment

In any case, the study will be paused and the Investigators, Institutional Review Board (IRB)/Independent Ethics Committee (IEC), regulatory agencies, and SRC will be promptly informed if any patient develops, in the dose expansion parts (Part 1 and Part 3), any of the following events assessed to be related to study drug by the Investigator and/or SRC:

- Life-threatening (Grade 4) toxicity that is unexpected and/or unmanageable (ie, does not resolve to Grade 3 or lower within 7 days)
- Death

The SRC will be urgently convened to review the safety data and make recommendations for potential changes in the study conduct (e.g. permanent discontinuation, dose reduction of a treatment in the combination arm or adaptation of the safety monitoring measures). If enrollment suspension is triggered due to an AE suspected to be related to ANV419, the enrollment in the

study will be paused. However, if the enrollment suspension is triggered due to a known toxicity of pembrolizumab or ipilimumab, or suspected synergistic toxicity in only one of the tested combination therapy arm, the monotherapy arm and the other combination therapy arm will still proceed if toxicity is not observed.

Should enrollment in the study or in one treatment arm be suspended, the study will not be restarted until all parties (SRC and Sponsor) have agreed to the course of action to be taken and the IRBs/IECs have been notified.

4.4 Discontinuation of study treatment

Discontinuation of a patient from study treatment may occurfor any of the following reasons:

- The patient or legal representative (such as a parent or legal guardian) withdraws consent;
- Confirmed radiographic disease progression;

  Note: A patient may be granted an exception to continue on treatment with confirmed radiographic disease progression if clinically stable or clinically improved. Such cases should be discussed by the Investigator or treating physician with the Sponsor.

  Note: In certain circumstances, a patient experiencing disease progression per RECIST without clinical deterioration may be allowed to continue on treatment if the Investigator considers it in the patient's best interest and in agreement between the Investigator and Sponsor. If repeated tumor assessment within 4 to 8 weeks confirms progressive disease, the patient will need to be discontinued permanently from treatment.
- Occurrence of any medical condition or circumstance that exposes the patient to substantial risk and/or does not allow the patient to adhere to the requirements of the Protocol;
- Any SAE, clinically significant AE, DLT, severe laboratory abnormality, intercurrent illness, or other medical condition which indicates to the Investigator that continued participation is not in the best interest of the patient;
- Patients who meet Hy's law will be discontinued from treatment;
- Pregnancy;
- Requirement of prohibited concomitant medication;
- Patient failure to comply with Protocol requirements or study-related procedures;
- The patient is lost to follow-up; or
- Termination of the study by the Sponsor or the regulatory authority.

Patients who discontinue for reasons noted above other than progressive disease will have post-treatment follow-up for disease status until disease progression, initiation of a non-study cancer treatment, withdrawal of consent, or lost to follow-up. In addition, each patient, irrespective of disease progression, will be followed for survival by telephone (or public records when allowed as per local regulation) until death or study termination whichever occurs first. Study staff should make every effort to complete the full panel of assessments scheduled for the End of Study Visit in addition to disease evaluation as noted above ([redacted] OR ≤30 days since last

dose of study drug). The reason for patient withdrawal must be documented in the electronic case report form (eCRF).

In the case of patients lost to follow-up, attempts to contact the patient must be made and documented in the patient's medical records.

Any patient in the Combination Dose Finding part that does not complete the DLT period for reason other than DLT or that is not DLT evaluable will be replaced.

4.5 Reasons for End of Study and withdrawal from study

Patients may withdraw consent at any time for any reason or be dropped from the study at the discretion of the Investigator should any untoward effect occur. In addition, a patient may be withdrawn by the Investigator or the Sponsor if enrollment into the study is inappropriate, the study plan is violated, or for administrative and/or other safety reasons.

Reasons for end of study and patient withdrawal from the study could be any of the following:

- Withdrawal of consent by the patient;
- Lost to follow-up;
- Death; or
- Study termination by Sponsor.

The study will be discontinued or terminated in case of an unacceptable risk, any relevant toxicity, or a negative change in the risk/benefit assessment. This might include the occurrence of AEs for which the character, severity, or frequency is new in comparison to the existing risk profile. In addition, any data deriving from other clinical studies or toxicology studies which negatively influence the risk/benefit assessment might cause discontinuation or termination of the study.

4.6 Patients of Reproductive Potential

Pregnancy and breastfeeding are exclusion criteria for this study. It is important that female patients and the female partners of male patients do not become pregnant during the study and for a recommended period of 6 months following the last dose of ANV419. Pregnancy tests for all female patients of childbearing potential will be performed as shown in the Schedule of Procedures (Appendix A). If a planned pregnancy test reveals a start of pregnancy, the patient will be withdrawn from the study.

A female patient of childbearing or reproductive potential is defined as any female who has experienced menarche and who has not undergone successful surgical sterilization (hysterectomy, bilateral salpingectomy, or bilateral oophorectomy) or is not postmenopausal (defined as amenorrhea for at least 12 consecutive months with an appropriate clinical profile at the appropriate age; eg, greater than 45 years).

Female patients of childbearing potential must agree to use highly effective methods of contraception during the treatment period and for 6 months after the last dose of study drug. They must also agree not to donate eggs (ova, oocytes) during the same timeframe.

Male patients with partners of childbearing potential must agree to use highly effective methods of contraception and barrier contraception (condom) during the treatment period and for 6 months after the last dose of study drug. They must also agree not to donate sperm during the same timeframe.

A highly effective method of contraception is defined as a method that can achieve a failure rate of less than 1% per year when used consistently and correctly, and that is considered to be a highly effective birth control method. Such methods include:

- Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation (oral, intravaginal, or transdermal);
- Progestogen-only hormonal contraception associated with inhibition of ovulation (oral, injectable, or implantable);[a]
- Intrauterine device[a] intrauterine hormone-releasing system[a] and bilateral tubal occlusion;[a]
- Vasectomized partner;[a,b] and
- Sexual abstinence.[c]

The double-barrier method (synthetic condoms; diaphragm; or cervical cap with spermicidal foam, cream or gel), periodic abstinence (such as calendar, symptothermal, or post-ovulation), withdrawal (coitus interruptus), lactational amenorrhea method, and spermicide only are NOT acceptable as highly effective methods of contraception.

Female patients of childbearing potential and contraception methods are defined per the 2020 Clinical Trial Facilitation Group recommendations.[31]

Female patients who become pregnant must report to the Investigator and be removed from the study immediately. Male patients whose female partners become pregnant will not be removed from the study but must report to the Investigator. The Sponsor or Investigator will follow-up on the pregnancy until 8 weeks after delivery to assess for congenital defects.

a. Contraception methods that in the context of the 2020 Clinical Trial Facilitation Groups recommendations are considered to have low user dependency.
b. A vasectomized partner is a highly effective birth control method provided that the vasectomized partner is the sole sexual partner of the female patient of childbearing potential study participant and that the vasectomized partner has received medical assessment of the surgical success.
c. In the context of the 2020 Clinical Trial Facilitation Group recommendations, sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical study and the preferred and usual lifestyle of the patient.

5 STUDY TREATMENTS

5.1 Treatment Groups

The 4 following treatment arms will be included in this study:

- Arm A1: [redacted]
- Arm A2: [redacted]
- Arm B: [redacted]
- Arm C: [redacted]

5.2 Rationale for Dosing

5.2.1 Rationale for ANV419 Dosing

[redacted]

[redacted]

5.2.2 Rationale for Pembrolizumab Dosing

The dose amount for pembrolizumab will be based on the approved package insert per United States Prescribing Information and Summary of Product Characteristics[32] and the European Medicines Agency-approved label; 200 mg IV Q3W.

5.2.3 Rationale for Ipilimumab Dosing

The dose amount required to prepare ipilimumab will be determined based on the patient's weight in kilograms and per the approved package insert[33] and the European Medicines Agency-approved label; 3 mg/kg IV Q3W.

5.3 Randomization and Blinding

Patients enrolled in the Monotherapy Dose Expansion part will be randomized by IRT and stratified by BRAF mutation status into Arms A1 or A2 on Cycle 1 Day 1.

Patients enrolled in the Combination Dose Finding part will be manually randomized into Arm B or Arm C on Cycle 1 Day 1. Steps for assigning the randomization number are as follows: The Clinical Operations team/trained individuals will use the pre-generated randomization number lists to find the next available randomization number and assign it to the patient. The team will then use the randomization number to obtain the treatment assignment from the pre-generated randomization scheme provided by the Biostatistics team. The Clinical Operations team will maintain and complete the randomization schemes throughout the course of study.

Patients enrolled in the Combination Dose Expansion part will be randomized by IRT and stratified by BRAF mutation status into Arms B or C on Cycle 1 Day 1.

For the Combination Dose Expansion part, following the interim analysis at the end of Stage 1, if 1 treatment arm is removed from Stage 2 (leaving only 1 treatment arm open for enrollment), randomization by IRT will no longer be required and eligible patients will be enrolled into the remaining treatment arm, provided there are sufficient slots remaining.

This is an open-label study. No blinding is required.

5.4 Drug Supplies

5.4.1 Formulation and Packaging

ANV419 is a stable fusion protein comprised of IL-2 fused to an anti-IL-2 mAb that sterically blocks the binding of the IL-2 to IL-2R-alpha (CD25). The ANV419 investigation product is a liquid, colorless, clear formulation with no visible particles, containing 2.5 mg/mL ANV419 protein, 20 mM histidine, 8% (w/v) sucrose, and 0.02% (w/v) PS80, pH 6.0. ANV419 is stored at -20°C (±5°C) and thawed by leaving at room temperature (15°C to 25°C) for approximately 1 hour and then further diluted into normal saline.

All ANV419 vials should be visually inspected for particulate matter and discoloration prior to preparation. Vials should not be used if the solution is cloudy, discolored, or contains extraneous or considerable particulate matter.

For formulation and packaging information on pembrolizumab and ipilimumab, please refer to the Pharmacy Manual and package inserts.[32,33]

5.4.2 Study Drug Preparation and Dispensing

Instructions for the preparation and dispensation of ANV419, pembrolizumab, and ipilimumab are described in the Pharmacy Manual.

5.4.3 Study Drug Administration

Patients will receive ANV419 as monotherapy (Arms A1 and A2) or in combination with pembrolizumab (Arm B) or ipilimumab (Arm C) after all Screening procedures have been completed and eligibility has been confirmed by the Investigator. Only patients enrolled in the study may receive the study drug(s). Under no circumstances will the study drug(s) be used other than as directed within this Protocol.

The 3 study drugs and the administration of each are described in Table 10.

Table 10. Study Drug Administration

Treatment	Study Part	Arm	Dose/ Potency	Dose Frequency	Route of Administration/Duration	Regimen/ Treatment Period
ANV419	[redacted]					
Pembro						
Ipi[6,7]						

1. Acetaminophen 1 g may be given to the patients as pre-medication or following the ANV419 infusion and can be used every 8 hours based on the symptoms experienced by the patient. Hydration prior to and following ANV419 infusion is to be administered according to institutional guidelines.
2. Dose increments will be determined by the SRC based on a synthesis of all relevant data available from all dose levels evaluated in this study.
3. For the combination arms (Arm B and Arm C) of the study, pembrolizumab or ipilimumab will be administered first. Patients can receive the ANV419 infusion approximately 30 minutes after they have received the entire infusion of pembrolizumab or ipilimumab.
4. In Arms B and C of the Combination Dose Expansion part of the study, ANV419 will be administered at the RP2D(p) or RP2D(i), respectively, identified in the Combination Dose Finding part.
5. Sites should make every effort to target infusion timing to be as close to 30 minutes (for pembrolizumab) or 90 minutes (for ipilimumab) as possible from treatment start; however, given the variability of infusion pumps from site to site, a window of ±5 minutes is permitted.
6. Ipilimumab dosing will end after [redacted].
7. Patients being treated on combination therapy with ANV419 plus ipilimumab who require discontinuation of ipilimumab due to toxicity may continue treatment with ANV419 after approval from the Sponsor. The reason for discontinuation must be recorded.

Ipi = ipilimumab; IV = intravenous(ly); Pembro = pembrolizumab; [redacted]
RP2D(i) = recommended Phase 2 dose for ANV419 when administered with ipilimumab; RP2D(p) = recommended Phase 2 dose for ANV419 when administered with pembrolizumab; SRC = Safety Review Committee.

Except during Cycles 1 and 2 in Arms B and C, study drug(s) may be administered up to 3 days before or after the scheduled Day 1 of each cycle due to administrative reasons.

Except during the DLT assessment period, if a dose cannot be administered at the foreseen [redacted] interval due to intercurrent medical issues unrelated to any study drug, dosing may be delayed for up to [redacted]. The [redacted] will be resumed according to the re-start date.

5.4.3.1 Post-infusion observation – Monotherapy Dose Expansion part

In both arms of the Monotherapy Dose Expansion part (Arms A1 and A2), all patients will be monitored for 90 minutes post end of infusion from Cycle 1. Patients will be monitored per individual site institutional standard during administration of ANV419 as monotherapy. In addition:

- Vital signs will be monitored every 2 hours for the first 8 hours, for the first 2 cycles
- After Cycle 2, the observation period will lessen to 90 minutes post end of infusion, provided no additional safety concerns have been identified;
- Patients may require observation beyond 23 hours if ≥Grade 3 AE and/or requires medical intervention and prolonged medical observation.

Note: It is optionally recommended (not mandatory) that patients stay in close proximity (as defined by the Investigator) to the site and are accompanied by a caregiver when possible, for whom accommodations will be provided.

Based on emerging data, the SRC may still decide that it is in the best interest of the patients to add or remove monitoring measures or observation durations, or mandate hospitalization.

5.4.3.2 Post-infusion observation – Combination Dose Finding part

At the end of study drug(s) infusion in Cycles 1 and 2 (only) of the Combination Dose Finding part, all patients will undergo a 23-hour observation period. Clinical monitoring will be conducted per individual site institutional standards within the framework of observation required for this Protocol, as follows:

- Vital signs will be monitored every 2 hours for the first 8 hours, and 20 hours post end of infusion;
- After Cycle 2, the observation period will lessen to 90 minutes post end of infusion, provided no additional safety concerns have been identified;
- Patients may require observation beyond 23 hours if ≥Grade 3 AE and/or requires medical intervention and prolonged medical observation.

5.4.3.3 Post-infusion observation – Combination Dose Expansion part

In both arms of the Combination Dose Expansion part (Arms B and C), all patients will be monitored for 90 minutes or longer post end of infusion from Cycle 1, depending on whether additional safety concerns have been idenfitied in Part 2. Patients will be monitored per individual site institutional standard during administration of ANV419 in combination with pembrolizumab or ipilimumab.

Note: It is optionally recommended (not mandatory) that patients stay in close proximity (as defined by the Investigator) to the site and are accompanied by a caregiver when possible, for whom accommodations will be provided.

5.4.4 Management of Infusion-Related Reactions in the Monotherapy Arm

Acute or delayed infusion-related reactions (IRRs) may occur with any IV administered antibody and may therefore be seen with ANV419. Patients must be monitored for any acute reaction during ANV419 administration. Following study drug infusion, patients in both arms of the Monotherapy Dose Expansion part (Arms A1 and A2) and Combination Dose Expansion part (Arms B and C) will be monitored for 90 minutes or longer post end of infusion from Cycle 1. Patients will be monitored per individual site institutional standard during administration of ANV419. IRRs may initially manifest as erythema, pruritus, fever, or chills and progress to an anaphylactic-type reaction. It is recommended to interrupt the infusion if there are any early signs of an immune-related reaction and assess the patient. If symptoms resolve without treatment, the infusion may resume at half the rate and continue if no further reaction. For ≥Grade 3 reactions, the infusion must stop, and the event discussed with the study Medical Monitor or designee. The Investigator should also discuss premedication with Medical Monitor or designee.

Symptoms of any IRRs that occur during the observation period after completion of the infusion should be reported in the eCRF and treated according to guidelines listed in Table 11. Any immune-related reaction ≥Grade 1 will be evaluated by the SRC and guidance for the subsequent treatment regimen of the individual patient (eg, inclusion of premedication, interruption, or discontinuation of dosing schedule) and current and subsequent dosing cohort will be discussed with the Investigators and implemented as per SRC recommendation.

Allergic (hypersensitivity) reactions that occur during or after study drug administration should be treated according to the guidelines listed in Table 11.

Table 11. Management of Allergic Reactions

Grade of Allergic Reaction	Treatment
Grade 1 Transient flushing or rash, drug fever <38°C (<100°F)	Remain at bedside and monitor patient until recovery of symptoms.
Grade 2 Intervention and infusion interruption indicated; responds promptly to symptomatic treatment (eg, antihistamines, NSAIDs, narcotics); prophylactic medications indicated for ≤24 hours.	- Stop the ANV419 infusion. - Begin an IV infusion of normal saline and treat the patient with diphenhydramine 50 mg IV (or equivalent) and/or acetaminophen 500 to 1000 mg PO. - Remain at bedside and monitor patient until resolution of symptoms. Corticosteroid therapy may also be administered as appropriate. If the infusion is interrupted: - Restart the infusion at half the rate when symptoms resolve; if no further complications ensue after 30 minutes, the rate may be increased to 100% of the original infusion rate. - Monitor patient closely. If symptoms recur: - The infusion should be discontinued and no further ANV419 will be administered at that visit. Administer diphenhydramine 50 mg IV and remain at bedside and monitor the patient until resolution of symptoms. - Premedication will be instituted in patients who experience an allergic reaction to study drug.
Grade 3 Prolonged (eg, not rapidly responsive to symptomatic treatment and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for clinical sequelae (eg, renal impairment, pulmonary infiltrates). Grade 4 Life-threatening consequences; urgent intervention indicated.	- Immediately discontinue infusion of ANV419. Begin an IV infusion of normal saline, and treat the patient as follows: - Recommend bronchodilators, epinephrine 0.2 to 1 mg of a 1:1000 solution for subcutaneous administration or 0.1 to 0.25 mg of a 1:10,000 solution injected slowly for IV administration, and/or diphenhydramine 50 mg IV with methylprednisolone 100 mg IV (or equivalent), as needed. - Patient should be monitored until the Investigator is comfortable that the symptoms will not recur. For Grade 3 or any Grade 4 allergic reaction: - ANV419 will be permanently discontinued for prolonged Grade 3 or any Grade 4 allergic reaction. - Patients may not continue to receive reference therapy in the absence of disease progression and/or intolerable AEs. - Investigators should follow their institutional guidelines for the treatment of anaphylaxis. Remain at bedside and monitor patient until recovery from symptoms.

AE = adverse event; IV = intravenous(ly); NSAID = nonsteroidal anti-inflammatory drug; PO = orally.

5.4.5 Dose Modification Guidelines

AEs (both serious and non-serious) potentially related to ANV419, pembrolizumab, or ipilimumab may represent an immunologic etiology. These AEs may occur shortly after the first dose or several months after the last dose.

If a patient experiences TEAEs that may be related to ANV419 alone or in combination with pembrolizumab or ipilimumab, ANV419 doses might be reduced if applicable, interrupted, or permanently discontinued and all changes must be reported in the Case Report Form (CRF). All ≥Grade 3 AEs considered possibly, probably, or definitely related to study drug(s) must be

discussed with the Investigator and Sponsor. During Cycle 1, dose interruption should be avoided if a patient has not experienced a ≥Grade 2 TEAE related to study drug. In subsequent cycles, dose interruptions and/or discontinuation are permissible following discussion between the Investigator and the Sponsor or designee.

5.4.5.1 Dose Modification and Management Guidelines for adverse events related to ANV419 in Monotherapy Arms

General principles

Common adverse events that have been reported with ANV419 include, but are not limited to pyrexia, liver enzyme elevations, lymphopenia, nausea/vomiting, and low-grade CRS. Appropriate supportive care or pre-medication is recommended to manage ANV419 related side effects, and to maintain ANV419 dose-intensity.

For patients enrolled in Arm A1 ([redacted]), dose reduction is not permitted but modification of infusion rate and/or dose delay is allowed in the event of ANV419 related toxicities. For patients enrolled in Arm A2 ([redacted]), dose reduction to [redacted] is permitted in addition to modification of infusion rate and/or dose delay. Dose re-escalation of ANV419 to the randomized dose can be considered for AEs that are self-limiting and under close monitoring. If re-escalation is not tolerated, then ANV419 should be reinstated at reduced dose.

Treatment may be delayed for up to [redacted] to allow for resolution of ANV419 related toxicities and for up to [redacted] for non-ANV419 related/unexpected toxicities (i.e., hip fracture). If treatment cannot be resumed within this time frame, the patient will be permanently discontinued from study.

The section below provides specific guidelines for the management of related ANV419 toxicities. The recommendations are not intended to serve as rigid guidelines or to replace clinical judgement.

Pyrexia

Episodes including recurring episodes of pyrexia are observed in patients receiving ANV419. Pyrexia may be accompanied with chills. Pyrexia typically presents 4 to 6 hours post ANV419 infusion and lasts between 1 and 4 days. Some patients are experiencing pyrexia on each cycle, others only on one cycle, not necessarily the first one. Pyrexia and chills typically resolve with standard supportive treatment.

To minimize the pyrexia in patients with ANV419, anti-pyretic treatment (e.g., paracetamol or acetaminophen) should be administered shortly after ANV419 infusion or as pre-medication and repeated every 8 hours as needed.

Table 12: Management guidelines for pyrexia related to ANV419

Pyrexia	Recommended management	Dose modification
First occurrence, or recurrent pyrexia	• Consider premedication with paracetamol/acetaminophen if not implemented • Exclude other reasons for pyrexia • Administer anti-pyretic treatment with NSAID and/or acetaminophen/paracetamol • Encourage oral hydration	Withhold ANV419 until < Grade 1; continue at same dose
Recalcitrant (refractory) pyrexia	• Consider adding oral corticosteroids	If pyrexia cannot be successfully managed to a tolerable level: permanently discontinue if [redacted]

Cytokine release syndrome

For management guidelines of cytokine release syndrome (CRS), refer to Table 17 further below.

Lymphopenia

ANV419 induces transient lymphopenia assumed related to lymphocyte redistribution and sequestration from the peripheral blood. This is an expected pharmacodynamic effect of ANV419 and was not associated with any increase in infection, or other clinical sequalae. In all cases, the observed lymphopenia was self-limiting with lymphocyte count rebounding around [redacted] and a dose dependent increase of lymphocyte expansion over time. Patients with prolonged or persistent lymphopenia should be thoroughly investigated for alternative etiologies than ANV419 related.

Table 13: Management guidelines for lymphopenia related to ANV419

CTCAE v5.0	Recommended management	Dose modification
Any grade	None	No dose modification
Note: for prolonged or persistent lymphopenia, alternative etiologies of lymphopenia should be excluded		

AST and/or ALT elevations with early onset (Cycle 1-2)

Transient elevation of hepatic transaminases are observed with ANV419 and are considered to occur in the context of IL-2 mediated AEs. The transient elevations are usually asymptomatic, mild or moderate in severity, typically not associated with increased total bilirubin and alkaline phosphatase, resolve spontaneously without treatment, and are predominantly occurring in the first two cycles. For AST and/or ALT elevations beyond cycle 2, and for AST/ALT elevations in the

context of total bilirubin increase, follow the adverse event management guidance for hepatitis (Table 15).

Table 14: Management guidelines for AST and/or ALT elevations with early onset related to ANV419

	Recommended management	**Dose modification**
AST or ALT > 3 but ≤ 5 × ULN	• LFT monitoring: Repeat lab every 3 days • If no improvement within 7 days, initiate treatment with steroids • Consider imaging for obstruction • Exclude non-inflammatory etiologies	Withhold ANV419 until ≤ Grade 1 or baseline; continue at same dose
AST or ALT > 5 × but ≤ 8 × ULN	• LFT monitoring: Repeat lab every 3 days • If no improvement within 7 days, initiate treatment with steroids • Consider adding non-corticosteroid immunotherapy	Withhold ANV419 until ≤ Grade 1 or baseline; continue at same dose
AST or ALT > 8 × ULN	• LFT monitoring: Repeat lab every 1-2 days • If no improvement within 7 days, initiate treatment with steroids • Consider adding non-corticosteroid immunotherapy • Consult gastroenterologist	Consider permanent discontinuation of ANV419

Hepatitis

Table 15: Management guidelines for hepatitis related to ANV419

(adapted from the ASCO management guidelines for Immune-Related Adverse Events; J Clin Oncol2021:36 4073-4126).

CTCAE v5.0	**Recommended management**	**Dose modification**
Grade 1 Asymptomatic (AST or ALT > ULN to 3.0 × ULN and/or total bilirubin > ULN to 1.5 × ULN	• Close monitoring (1-2 × weekly) • Exclude alternate etiologies (e.g., viral hepatitis, alcohol hepatitis)	Continue ANV419 at same dose

Grade 2 Asymptomatic (AST or ALT > 3.0 to ≤ 5.0 × ULN and/or total bilirubin > 1.5 to ≤ 3.0 × ULN)	• Stop unnecessary medication and any potential hepatotoxic drugs • Consider administration of steroids if no improvement in 3-5 days • Increase monitoring frequency to every 3 days • Consider adding mycophenolate mofetil if no improvement after 3 days • Consider hepatology consult for Grade 2 and above	Withhold ANV419 until ≤ Grade 1; continue at same dose
Grade 3 AST or ALT 5.0-20.0 × ULN and/or total bilirubin 3-10 × ULN, OR symptomatic liver dysfunction; fibrosis by biopsy; compensated cirrhosis; and reactivation of chronic hepatitis	• Start steroids 1-2 mg/kg methylprednisolone or equivalents • Consider liver biopsy • Monitor labs daily	Permanently discontinue ANV419
Grade 4 AST or ALT > 20.0 × ULN and/or total bilirubin > 10 × ULN OR decompensated liver function	• Consider adding methylprednisolone 2 mg/kg/d equivalents	Permanently discontinue ANV419

Note: Combination of AEs suggestive of drug induced liver injury (DILI), with hepatocellular injury (AST or ALT > 3.0 × ULN) accompanied by evidence of impaired hepatic function (total bilirubin elevation > 2 × ULN), in the absence of evidence of initial biliary obstruction (i.e., significant elevation of ALP) or some other explanation of the injury (e.g., viral hepatitis, alcohol hepatitis), see FDA guidance, should lead to permanent discontinuation from treatment.

Other adverse events

For other adverse events deemed as clinically significant and for which no specific guidelines are provided, the following dose modifications should be followed (Table 16).

Table 16: Management guidelines for "other" ANV419 related adverse events

CTCAE v5.0	Dose modification
Grade 1	Continue at the same dose of ANV419
Grade 2	If tolerable: Continue at the same dose of ANV419; If intolerable: withhold ANV419 until ≤ Grade 1 or baseline; reinstate ANV419 at the same dose
Grade 3	Withhold ANV419 until ≤ Grade 1 or baseline; 1st occurrence: reinstate ANV419 at the same dose 2nd occurrence or if not manageable: permanently discontinue if [redacted] 3rd occurrence: permanently discontinue ANV419
Grade 4	Permanently discontinue ANV419

5.4.5.2 Management of adverse immune-related adverse events in monotherapy arms

Investigators should monitor patients for potential irAEs. Once an AE is detected, it should be followed until resolution. An irAE can occur shortly after the first dose of ANV419 or several months after the last dose. For clinical management of irAEs, Investigators should follow the consensus guidelines provided by National Comprehensive Cancer Network®,[34] American Society of Clinical Oncology®,[35] and European Society for Medical Oncology[36,37] .

5.4.5.3 Management of cytokine release syndrome in monotherapy and combination therapy arms

CRS clinically manifests when large numbers of lymphocytes (B lymphocyte cells, T cells, and/or NK cells) and/or myeloid cells (macrophages, dendritic cells, and monocytes) become activated and release inflammatory cytokines. CRS has classically been associated with therapeutic mAb infusions, most notably anti-CD3 (OKT3), anti-CD52 (alemtuzumab), anti-CD20 (rituximab), and the CD28 super-agonist, TGN1412. In these settings, symptom onset typically occurs within minutes to hours after the infusion begins. CRS has also been reported following administration of bi-specific antibodies for leukemia, infusion of haploidentical mononuclear cells to patients with refractory leukemia, and adoptive immunotherapies for cancer, most notably T cells engineered to express chimeric antigen receptors.[38]

It is important to distinguish CRS from infection, tumor lysis syndrome, primary phagocyte lymphohistiocytosis/macrophage activation syndrome, hypersensitivity/allergic reaction(s), or other inflammatory disorders. Additional tests such as autoimmune serology may be used to determine a possible immunogenic etiology.

The study will be conducted in sites experienced in immune-oncology clinical studies including the management of CRS. Patients will be monitored for signs and symptoms of CRS for all cycles of treatment with ANV419. Following study drug(s) infusion during dose escalation (the Combination Dose Finding part), all patients will undergo a 23-hour observation period. Clinical monitoring will be conducted per individual sites institutional standards within the framework of observation required for this Protocol, including monitoring of vital signs every 2 hours for the first 8 hours, and 20 hours post end of infusion in Cycles 1 and 2 (only). After Cycle 2, the observation period will lessen to 90 minutes post end of infusion, provided no additional safety concerns have been identified. Safety observation measures may be added or removed, at the discretion of the SRC, upon review of all safety data for the study. Patients may require observation beyond 23 hours if ≥Grade 3 AE and/or requires medical intervention and prolonged medical observation. In both arms of the Monotherapy Dose Expansion part (Arms A1 and A2) and Combination Dose Expansion part (Arms B and C), all patients will be monitored for 90 minutes or longer post end of infusion from Cycle 1, depending on whether additional safety concerns have been identified in Part 2 . Patients will be monitored per individual site institutional standard during administration of ANV419 in combination with pembrolizumab or ipilimumab. It is optionally recommended (not mandatory) that patients stay in close proximity to the site and are accompanied by a caregiver when possible, for whom accommodations will be provided. Based on emerging data, the SRC may still decide that it is in the best interest of the patients to increase monitoring or observation durations, or mandate hospitalization.

Grading of CRS should follow the criteria specified in Table 17.

Table 17: Management of CRS per NCI CTCAE Version 5.0

Grade	Treatment
Grade 1: Fever with or without constitutional symptoms	- Vigilant supportive care. - Additional diagnostic testing should be performed to rule out differential diagnoses. If an infection cannot be ruled out with certainty, start of an empiric antibiotic therapy should be considered. - Treat fever and neutropenia if present, monitor fluid balance, administer anti-pyretics and analgesics as needed. - All patients with early signs of CRS should be regularly evaluated for signs of further deterioration. - No actions or hold ANV419 treatment until symptoms subside.
Grade 2: -Hypotension responding to fluids -Hypoxia responding to <40% O_2	- Vigilant supportive care. - Hold study drug(s). Restart once CRS resolves to Grade ≤1. - For subsequent infusions, increase infusion duration and consider premedication with antihistamines such as Benadryl® and an H_2 blocker. Hypoxia: - Supplemental oxygen. - Tocilizumab or siltuximab ± corticosteroids and supportive care, as recommended for the management of hypotension. Hypotension: - IV fluid bolus of 500 to 1000 mL of normal saline. - Can give a second IV fluid bolus if SBP remains <90 mmHg. - Tocilizumab 8 mg/kg IV or siltuximab 11 mg/kg IV for the treatment of hypotension that is refractory to fluid boluses; tocilizumab can be repeated after 6 hours if needed. If hypotension persists after 2 fluid boluses and anti-IL-6 therapy: - Start vasopressors, consider hospitalization, obtain echocardiogram, and initiate other methods of hemodynamic monitoring. - In patients at high-risk or if hypotension persists after 1 to 2 doses of antiIL6 therapy, dexamethasone can be used at 10 mg IV every 6 hours. - Manage fever and constitutional symptoms as in Grade 1. Organ toxicity: - Symptomatic management of organ toxicities, as per standard guidelines. - Consider tocilizumab or siltuximab ± corticosteroids and supportive care, as indicated for hypotension.
Grade 3: -Hypotension managed with 1 pressor -Hypoxia requiring ≥40% O_2	- Vigilant supportive care. - Permanently discontinue study drugs(s) treatment. - Patient should be hospitalized for a minimum of a 24-hour observation period. Hypoxia: - Supplemental oxygen including high-flow oxygen delivery and non-invasive positive pressure ventilation. - Tocilizumab or siltuximab ± corticosteroids and supportive care, as described above. Hypotension: - IV fluid boluses as needed, as recommended for the treatment of Grade 2 CRS. - Tocilizumab and siltuximab as recommended for Grade 2 CRS, if not administered previously. - Vasopressors as needed. - Consider transfer to ICU, obtain echocardiogram, and perform hemodynamic monitoring as in the management of Grade 2 CRS. - Dexamethasone 10 mg IV every 6 hours; if refractory, increase to 20 mg IV every 6 hours. - Manage fever and constitutional symptoms as indicated for Grade 1 CRS.

Table 17: Management of CRS per NCI CTCAE Version 5.0 (Continued)

Grade	Treatment
Grade 3 (Continued): -Hypotension managed with 1 pressor -Hypoxia requiring ≥40% O_2	Organ toxicity: - Symptomatic management of organ toxicities, as per standard guidelines. - Tocilizumab or siltuximab ± corticosteroids and supportive care, as described above.
Grade 4: -Life-threatening consequences -Urgent intervention indicated	- Vigilant supportive care. - Permanently discontinue study drug(s) treatment. - Patient should be hospitalized for a minimum of a 24-hour observation period. Hypoxia: - Mechanical ventilation. - Tocilizumab or siltuximab ± corticosteroids and supportive care, as described above. Hypotension: - IV fluids, anti-IL-6 therapy, vasopressors, and hemodynamic monitoring as defined for the management of Grade 3 CRS. - Methylprednisolone 1 to 2 g/day IV. - Manage fever and constitutional symptoms as indicated for Grade 1 CRS. Organ toxicity: - Symptomatic management of organ toxicities, as per standard guidelines. - Tocilizumab or siltuximab ± corticosteroids and supportive care, as described above. - In cases where neither tocilizumab, siltuximab, nor glucocorticoids are effective, other immunosuppressants such as the T cell-depleting antibody therapies, including alemtuzumab and ATG, IL1R-based inhibitors (anakinra) or cyclophosphamide might be of benefit.

ATG = antithymocyte globulin; CRS = cytokine release syndrome; H_2 = histamine; ICU = intensive care unit; IL = interleukin; IV = intravenous(ly); NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events; O_2 = oxygen; SBP = systolic blood pressure; T cell = thymus lymphocyte cell.
Source: U.S. Department of Health and Human Services. National Institutes of Health. National Cancer Institute. Common Terminology Criteria for Adverse Events (CTCAE). Version 5.0. 27 November 2017

5.4.5.4 Management of adverse events in combination arms

AEs associated with pembrolizumab or ipilimumab exposure may represent an immunologic etiology. These irAEs may occur shortly after the first dose or several months after the last dose of pembrolizumab/ipilimumab treatment and may affect more than 1 body system simultaneously. Therefore, early recognition and initiation of treatment is critical to reduce complications. Based on existing clinical study data, most irAEs were reversible and could be managed with interruptions of pembrolizumab or ipilimumab, administration of corticosteroids, and/or other supportive care. For suspected irAEs, ensure adequate evaluation to confirm etiology or exclude other causes. Additional procedures or tests such as bronchoscopy, endoscopy, or skin biopsy may be included as part of the evaluation. Based on the severity of irAEs, withhold or permanently discontinue pembrolizumab/ipilimumab, and administer corticosteroids. Consultation with disease-specific specialists should be considered. Dose modification and toxicity management guidelines for irAEs associated with pembrolizumab and ipilimumab are provided in Table 18 and Table 19, respectively.

Attribution of toxicity and holding study drugs

When study drugs are administered in combination, attribution of an AE to a single component is likely to be difficult. Therefore, while the Investigator may attribute a toxicity event to the combination, to ANV419 alone, to pembrolizumab alone, or to ipilimumab alone, for AEs listed in Table 18 and Table 19, both interventions must be held according to the criteria in Table 18 and Table 19.

For AEs that occur with the combination of ANV419 and pembrolizumab or ANV419 and ipilimumab that clearly can be attributed to ANV419, please refer to Section 5.4.5 for management guidelines and recommended dose modifications to be taken for ANV419.

For combination arms of this study, both drugs should be held until the attribution of an irAEs can be fully analyzed and has resolved to baseline or ≤Grade 1. In general, ≥Grade 3 TEAEs in the combination treatment arms will result in discontinuation of both ANV419 and pembrolizumab or ANV419 and ipilimumab, but, in rare instances, continuing either ANV419, pembrolizumab, or ipilimumab may be allowed where clinical benefit can be documented after resolution of toxicity to baseline or ≤Grade 1. In the event that a toxicity results in holding ANV419, pembrolizumab, ipilimumab, or the combination of ANV419 and pembrolizumab or the combination of ANV419 and ipilimumab for >42 days, the drugs should be permanently discontinued for that patient.

Table 18. Dose Modification for ANV419 in Combination With Pembrolizumab

irAEs	Grade (NCI CTCAE Version 5.0)	Action with ANV419	Action with Pembrolizumab	Corticosteroid and/or Other Therapies	Monitoring and Follow-Up
Pneumonitis	Grade 2	Withhold. Upon resolution to ≤Grade 1, may resume study treatment.	Withhold. Upon resolution to ≤Grade 1, may resume study treatment.	Administer corticosteroids (initial dose of 1 to 2 mg/kg prednisone or equivalent) followed by taper. Add prophylactic antibiotics for opportunistic infections.	Monitor participants for continuing signs and symptoms of pneumonitis. Evaluate participants with radiographic imaging.
	Recurrent Grade 2, Grade 3 or 4	Withhold study treatment. Upon resolution to ≤Grade 1, may resume study treatment 1 dose level lower.	Permanently discontinue.		
Diarrhea/colitis	Grade 2 or 3	Withhold. Upon resolution to ≤Grade 1, may resume study treatment.	Withhold. Upon resolution to ≤Grade 1, may resume study treatment.	Administer corticosteroids (initial dose of 1 to 2 mg/kg prednisone or equivalent) followed by taper.	Monitor participants for continuing signs and symptoms of enterocolitis (ie, diarrhea, abdominal pain, blood or mucus in stool with or without fever) and of bowel perforation (ie, peritoneal signs and ileus). Participants with ≥Grade 2 diarrhea suspected colitis should consider GI consultation and performing endoscopy to rule out colitis. Participants with diarrhea/colitis should be advised to drink liberal quantities of clear fluids. If sufficient oral fluid intake is not feasible, fluid and electrolytes should be substituted via IV infusion.
	Recurrent Grade 3 or Grade 4	Permanently discontinue.	Permanently discontinue.		

Table 18. Dose Modification for ANV419 in Combination With Pembrolizumab (Continued)

irAEs	Grade (NCI CTCAE Version 5.0)	Action with ANV419	Action with Pembrolizumab	Corticosteroid and/or Other Therapies	Monitoring and Follow-Up
AST or ALT elevation or increased bilirubin	Grade 2[0]	Withhold. Upon resolution to ≤Grade 1, may resume study treatment.	Withhold. Upon resolution to ≤Grade 1, may resume study treatment.	Administer corticosteroids (initial dose of 0.5 to 1 mg/kg prednisone or equivalent) followed by taper.	Monitor with liver function tests (consider weekly or more frequently until liver enzyme value returned to baseline or is stable).
	Grade 3[0] or 4[0]	Permanently discontinue.	Permanently discontinue.	Administer corticosteroids (initial dose of 1 to 2 mg/kg prednisone or equivalent) followed by taper.	
T1DM or hyperglycemia	New onset T1DM or Grade 3 or 4 hyperglycemia associated with evidence of β-cell failure	Withhold. Upon resolution to ≤Grade 1, may resume study treatment.	Withhold.[0]	Initiate insulin replacement therapy for participants with T1DM. Administer antihyperglycemic in participants with hyperglycemia.	Monitor participants for hyperglycemia or other signs and symptoms of diabetes.
Hypophysitis	Grade 2	Withhold. Upon resolution to ≤Grade 1, may resume study treatment.	Withhold. Upon resolution to ≤Grade 1, may resume study treatment.	Administer corticosteroids and initiate hormonal replacements as clinically indicated.	Monitor for signs and symptoms of hypophysitis (including hypopituitarism and adrenal insufficiency).
	Grade 3 or 4	Withhold or permanently discontinue.[0]	Withhold or permanently discontinue.[0]		
Hyperthyroidism	Grade 2	Continue.	Continue.	Treat with nonselective beta-blockers (eg, propranolol) or thionamides as appropriate.	Monitor for signs and symptoms of thyroid disorders.
	Grade 3 or 4	Withhold or permanently discontinue.[0]	Withhold or permanently discontinue.[0]		
Hypothyroidism	Grade 2, 3 or 4	Continue.	Continue.	Initiate thyroid replacement hormones (eg, levothyroxine or liothyronine) per Standard of Care.	Monitor for signs and symptoms of thyroid disorders.

Table 18. Dose Modification for ANV419 in Combination With Pembrolizumab (Continued)

irAEs	Grade (NCI CTCAE Version 5.0)	Action with ANV419	Action with Pembrolizumab	Corticosteroid and/or Other Therapies	Monitoring and Follow-Up
Nephritis: grading according to increased creatinine or acute kidney injury	Grade 2	Withhold. Upon resolution to ≤Grade 1, may resume study treatment.	Withhold. Upon resolution to ≤Grade 1, may resume study treatment.	Administer corticosteroids (prednisone 1 to 2 mg/kg or equivalent) followed by taper.	Monitor changes of renal function.
	Grade 3 or 4	Permanently discontinue.	Permanently discontinue.		
Neurological toxicities	Grade 2	Withhold. Upon resolution to ≤Grade 1, may resume study treatment.	Withhold. Upon resolution to ≤Grade 1, may resume study treatment.	Based on severity of AE, administer corticosteroids.	Ensure adequate evaluation to confirm etiology and/or exclude other causes.
	Grade 3 or 4	Permanently discontinue.	Permanently discontinue.		
Myocarditis	Grade 2, 3 or 4	Permanently discontinue.	Permanently discontinue.	Based on severity of AE, administer corticosteroids.	Ensure adequate evaluation to confirm etiology and/or exclude other causes.
Exfoliative dermatologic conditions	Suspected SJS, TEN, or DRESS	Withhold.	Withhold.	Based on severity of AE, administer corticosteroids.	Ensure adequate evaluation to confirm etiology or exclude other causes.
	Confirmed SJS, TEN, or DRESS	Permanently discontinue.	Permanently discontinue.		
All other irAEs	Persistent Grade 2	Withhold. Upon	Withhold. Upon resolution to	Based on severity of AE, administer	Ensure adequate evaluation to

		resolution to ≤Grade 1, may resume study treatment.	≤Grade 1, may resume study treatment.	corticosteroids.	confirm etiology or exclude other causes.
	Grade 3	Withhold or discontinue based on the event.[0]	Withhold or discontinue based on the event.[0]		
	Recurrent Grade 3 or Grade 4	Permanently discontinue.	Permanently discontinue.		

Table 18. Dose Modification for ANV419 in Combination With Pembrolizumab (Continued)

Note: Non-irAEs will be managed as appropriate, following clinical practice recommendations. AST/ALT = >3 to 5 × ULN if baseline is normal; >3 to 5 × baseline, if baseline is abnormal; bilirubin: >1.5 to 3 × ULN if baseline is normal; >1.5 to 3 × baseline if baseline is abnormal. AST/ALT: >5 to 20 × ULN if baseline is normal; >5 to 20 × baseline, if baseline is abnormal; bilirubin: >3 to 10 × ULN if baseline is normal; >3 to 10 × baseline if baseline is abnormal. AST/ALT: >20 × ULN if baseline is normal; >20 × baseline, if baseline is abnormal; bilirubin: >10 × ULN if baseline is normal; >10 × baseline if baseline is abnormal. The decision to withhold or permanently discontinue pembrolizumab is at the discretion of the Investigator or treating physician. If control is achieved or resolution to ≤Grade 2, pembrolizumab may be resumed. Events that require discontinuation include, but are not limited to, encephalitis and other clinically important irAEs (eg, vasculitis and sclerosing cholangitis). AE = adverse event; ALT = alanine aminotransferase; AST = aspartate aminotransferase; DRESS = drug reaction with eosinophilia and systemic symptoms; GI = gastrointestinal; irAE = immune-related adverse event; IV = intravenous(ly); NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events; SJS = Stevens-Johnson syndrome; T1DM = type 1 diabetes mellitus; TEN = toxic epidermal necrolysis; ULN = upper limit of normal. Source: Keytruda®. Package Insert. Merck Sharp & Dohme Corp; 2014

Table 19. Dose Modification for ANV419 in Combination With Ipilimumab

irAEs	Grade (NCI CTCAE Version 5.0)	Action with ANV419	Action with Ipilimumab	Corticosteroid and/or Other Therapies	Monitoring and Follow-Up
Pneumonitis	Grade 2	Withhold. Upon resolution to ≤Grade 1, may resume study treatment.	Withhold. Upon resolution to ≤Grade 1, may resume study treatment.	Administer corticosteroids (initial dose of 1 to 2 mg/kg prednisone or equivalent) followed by taper. Add prophylactic antibiotics for opportunistic infections.	Monitor participants for continuing signs and symptoms of pneumonitis. Evaluate participants with radiographic imaging.
	Recurrent Grade 2, Grade 3 or 4	Withhold study treatment. Upon resolution to ≤Grade 1, may resume study treatment 1 dose level lower.	Permanently discontinue.		

Table 19. Dose Modification for ANV419 in Combination With Ipilimumab (Continued)

irAEs	Grade (NCI CTCAE Version 5.0)	Action with ANV419	Action with Ipilimumab	Corticosteroid and/or Other Therapies	Monitoring and Follow-Up
Diarrhea/colitis	Grade 2	Withhold. Upon resolution to ≤Grade 1, may resume study treatment.	Withhold. Upon resolution to ≤Grade 1, may resume study treatment.	Administer corticosteroids (initial dose of 1 to 2 mg/kg prednisone or equivalent) followed by taper.	Monitor participants for continuing signs and symptoms of enterocolitis (ie, diarrhea, abdominal pain, blood or mucus in stool with or without fever) and of bowel perforation (ie, peritoneal signs and ileus). Participants with ≥Grade 2 diarrhea suspected colitis should consider GI consultation and performing endoscopy to rule out colitis. Participants with diarrhea/colitis should be advised to drink liberal quantities of clear fluids. If sufficient oral fluid intake is not feasible, fluid and electrolytes should be substituted via IV infusion.
	Recurrent Grade 3 or Grade 4	Permanently discontinue.	Permanently discontinue.		
AST or ALT elevation or increased bilirubin	AST/ALT >3 to 5 × ULN or total bilirubin is more than 1.5 × and up to 3 × ULN	Withhold. Upon resolution to ≤Grade 1, may resume study treatment.	Withhold. Upon resolution to ≤Grade 1, may resume study treatment.	Administer corticosteroids (initial dose of 0.5 to 1 mg/kg prednisone or equivalent) followed by taper.	Monitor with liver function tests (consider weekly or more frequently until liver enzyme value returned to baseline or is stable).
	AST/ALT >5 × ULN or total bilirubin is more than 3 × ULN	Permanently discontinue.	Permanently discontinue.	Administer corticosteroids (initial dose of 1 to 2 mg/kg prednisone or equivalent) followed by taper.	

Table 19. Dose Modification for ANV419 in Combination With Ipilimumab (Continued)

irAEs	Grade (NCI CTCAE Version 5.0)	Action with ANV419	Action with Ipilimumab	Corticosteroid and/or Other Therapies	Monitoring and Follow-Up
Endocrinopathies	Grade 2, 3, or 4	Withhold. Upon resolution to ≤Grade 1, may resume study treatment.	Withhold if not clinically stable.	Treatment with replacement or interventions as appropriate.	Monitor for signs and symptoms of endocrinopathies.
Hypophysitis[1]	Grade 2, 3, or 4	Withhold. Upon resolution to ≤Grade 1, may resume study treatment.	Withhold. Resume when acute symptoms have resolved.	Administer corticosteroids and initiate hormonal replacements as clinically indicated.	Monitor for signs and symptoms of hypophysitis (including hypopituitarism and adrenal insufficiency).
Nephritis: with renal dysfunction	Grade 2 or 3 increased blood creatinine	Withhold. Upon resolution to ≤Grade 1, may resume study treatment.	Withhold. Upon resolution to ≤Grade 1, may resume study treatment.	Administer corticosteroids (prednisone 1 to 2 mg/kg or equivalent) followed by taper.	Monitor changes of renal function.
	Grade 3 or 4	Permanently discontinue.	Permanently discontinue.		
Neurological toxicities[2]	Grade 2	Withhold. Upon resolution to ≤Grade 1, may resume study treatment.	Withhold. Upon resolution to ≤Grade 1, may resume study treatment.	Based on severity of AE, administer corticosteroids.	Ensure adequate evaluation to confirm etiology and/or exclude other causes.
	Grade 3 or 4	Permanently discontinue.	Permanently discontinue.		
Myocarditis	Grade 2	Withhold. Upon resolution to ≤Grade 1, may resume study treatment.	Withhold. Upon resolution to ≤Grade 1, may resume study treatment.	Based on severity of AE, administer corticosteroids.	Ensure adequate evaluation to confirm etiology and/or exclude other causes.
	Grade 3 or 4	Permanently discontinue.	Permanently discontinue.		
Exfoliative or bullous dermatologic conditions	Grade 2	Withhold until specialist assessment.	Withhold until specialist assessment.	Based on severity of AE, administer corticosteroids.	Ensure adequate evaluation to confirm etiology or exclude other causes.
	Grade 3 or 4	Permanently discontinue.	Permanently discontinue.		

Table 19. Dose Modification for ANV419 in Combination With Ipilimumab (Continued)

irAEs	Grade (NCI CTCAE Version 5.0)	Action with ANV419	Action with Ipilimumab	Corticosteroid and/or Other Therapies	Monitoring and Follow-Up
Ophthalmologic	Grade 2, 3, or 4 that does not improve to Grade 1 within 2 weeks while receiving topical therapy or that requires treatment	Withhold or discontinue based on the event.	Permanently discontinue.	Based on recommendation by ophthalmologist.	Ensure evaluation by ophthalmologist and continue to follow up as clinical indicated.
All other irAEs	Persistent Grade 2	Withhold. Upon resolution to ≤Grade 1, may resume study treatment.	Withhold. Upon resolution to ≤Grade 1, may resume study treatment.	Based on severity of AE, administer corticosteroids.	Ensure adequate evaluation to confirm etiology or exclude other causes.
	Grade 3	Withhold or discontinue based on the event.	Withhold or discontinue based on the event.		
	Recurrent Grade 3 or Grade 4	Permanently discontinue.	Permanently discontinue.		

Note: Non-irAEs will be managed as appropriate, following clinical practice recommendations.
1. Signs of mass effect, including headache, photophobia, or visual field cuts.
2. Permanently discontinue ipilimumab if signs of encephalitis or respiratory insufficiency due to neurological toxicity regardless of grade.

AE = adverse event; ALT = alanine aminotransferase; AST = aspartate aminotransferase; GI = gastrointestinal; irAE = immune-related adverse event; IV = intravenous(ly); NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events; ULN = upper limit of normal.
Source: Yervoy®. Package Insert. Bristol-Myers Squibb Company; 2011

5.4.5.5 Management of infusion-related reactions for combination therapy arms

Pembrolizumab

Pembrolizumab may cause severe or life-threatening infusion-reactions, including severe hypersensitivity or anaphylaxis. Signs and symptoms usually develop during or shortly after drug infusion and generally resolve completely within 24 hours of completion of infusion. For ≤Grade 2 IRRs, interrupt or slow the rate of infusion.[32] For ≥Grade 3 IRRs, stop infusion and permanently discontinue pembrolizumab.[32]

Ipilimumab

Severe infusion reactions can occur with ipilimumab. For ≤Grade 2 IRRs, interrupt or slow the rate of infusion.[33] For ≥Grade 3 IRRs, stop infusion and permanently discontinue ipilimumab.[33]

5.4.6 Treatment Compliance

The Investigator or other study site personnel under the direction of the Investigator will be responsible for study drug administration and recording dosing information in source documents.

Patient compliance will be assessed by the site using drug dispensing and infusion logs, and progress notes about dose reductions/interruptions. The CRF will capture infusion details and reasons for changes in dose level (eg, a new record completed each time dose level changes, including periods where no dose was taken, and the reason for a dose level change).

5.4.7 Storage and Accountability

ANV419 will be sent at -20°C under a temperature-controlled shipment and stored in a secure, limited access storage area at -20°C (±5°C) until use. The assigned personnel should ensure that the study drug is stored in accordance with the environmental conditions (temperature, light, humidity) as determined by the Sponsor. If concerns regarding the quality or appearance of the study drug arise, the study drug should not be dispensed and the Sponsor or designee should be contacted immediately.

For details regarding the storage of pembrolizumab and ipilimumab, please see the approved package insert of each.

Records will be maintained indicating the receipt and dispensation of all study drug supplies. At the conclusion of the study, the clinical site will be responsible for final drug accountability and destruction.

5.5 Prior and Concomitant Medications and/or Procedures

5.5.1 Excluded Medications and/or Procedures

The following medications and procedures are prohibited during the Screening and study:

- Any investigational agent (including investigational device) other than ANV419, pembrolizumab, and ipilimumab;
- Antineoplastic systemic chemotherapy or biological therapy;
- Immunotherapy not specified in this Protocol;
- Radiation therapy;

  Note: Radiation therapy to a symptomatic solitary lesion or to the brain may be allowed after discussion between the Investigator and Sponsor.
- Systemic glucocorticoids for any purpose other than to modulate symptoms from an event of clinical interest of suspected immunologic etiology;

  Note: The use of physiologic doses of corticosteroids may be approved after consultation with the Sponsor.
- Live vaccines administered within 30 days of planned start of study drug; and

  Note: Seasonal influenza vaccines for injection are generally inactivated flu vaccines and are permitted; however, intranasal influenza vaccines (eg, Flu-Mist) are live attenuated vaccines and are prohibited.
- Local surgery resulting from disease progression is prohibited; however, if indicated for palliative measure and after Investigator approval, local surgery may be permitted after the [redacted]. Patients who, in the opinion of the Investigator, require the use of any aforementioned treatments for clinical management should be removed from the study.

5.5.2 Allowed Medications and/or Procedures

All treatments that the Investigator considers necessary for a patient's welfare may be administered at the discretion of the Investigator in keeping with the community standards of medical care.

Drug-drug interaction studies have not been conducted with ANV419; however, ANV419 may cause the release of cytokines that may suppress CYP450 enzymes. If a patient is using any concomitant medications known to be sensitive substrates of CYP450 in this study, safety events should be closely monitored. See Appendix E for examples of sensitive clinical substrates for CYP450-mediated metabolism.

5.5.3 Documentation of Prior and Concomitant Medication Use

The use of prior or concomitant medications will be recorded from 28 days prior to Cycle 1 Day 1 to the Safety Follow-Up Visit up to 90 days after last dose of study drug or the start date of a new cancer regimen, whichever is shorter, except for concomitant medications related to cancer treatment, for which lifetime history prior to entering the study will be recorded.

6 STUDY PROCEDURES

All study procedures will follow the Schedule of Procedures, see Appendix A .

6.1 Tumor Measurements

Tumor measurements will be performed as indicated in Appendix A .

Tumors will be assessed based on RECIST (see Appendix C) and iRECIST (see Appendix D).

Baseline disease assessment will include radiographic tumor measurements using CT imaging of the chest, abdomen, pelvis, or any other areas with suspected disease involvement and CT or magnetic resonance imaging of the brain during Screening.

On-study scans should be performed [redacted] using the same modality as used for baseline imaging until progressive disease per RECIST and iRECIST, withdrawal of consent, or initiation of a new anticancer therapy. Brain imaging is only to be repeated for patients with history, ongoing, or suspicion of central nervous system involvement.

[redacted]

6.2 Eastern Cooperative Oncology Group Performance Status

ECOG Performance Status will be assessed as indicated in Appendix A using the ECOG scale (see Appendix G).

6.3 Quality of Life Evaluation

Quality of Life (QoL) evaluations (EQ-5D-5L and QLQ-C30) are to be performed for clinical benefit assessment at baseline and every 12 weeks after Cycle 1 Day 1 in combination arms (Arms B and C).

6.4 Optional Tissue Biopsies

For patients consenting to biopsy, fresh tumor tissue will be collected at screening and then on-study within ±3 days of the imaging assessment and 7 days of the start of the next dosing cycle. Biopsy will be performed if the procedure is considered at low risk for the patient, clinically feasible and if the tumor is of sufficient size to be biopsied, otherwise, for baseline specimens, archived biopsy might be used if not older than 3 months at time of ICF signature. Any tissue that is suspected to contain tumor, including lymph nodes, may be biopsied.

Available archived biopsies will be collected in patients who do not consent to on study biopsy, provided the tumor tissue is not older than 3 months at time of ICF signature.

6.5 Pharmacokinetic Analyses

Serum samples for PK will be drawn as indicated in Appendix A.

If warranted for additional safety assessments, additional samples can be collected by the Investigator after discussion with the Sponsor. All samples will be sent to the central laboratory. Please refer to the laboratory manual for details.

PK parameters to be analyzed:

- Systemic clearance (CL) of ANV419;
- Volume of distribution at steady state (V_{ss}) of ANV419;
- Area under the concentration-time curve (AUC) of ANV419; and
- Maximum observed serum concentration (C_{max}) of ANV419.

6.6 Pharmacodynamic Analyses (Immuno-Profiling and Ki67 Analysis)

Blood samples for PD will be drawn as indicated in Appendix A**.**

All samples will be sent to the central laboratory. Please refer to the laboratory manual for details.

Immunophenotyping using flow cytometry has become the method of choice in identifying cells within blood samples and can therefore be used to monitor the mode of action of ANV419 as monotherapy or in combination with other treatments. Potential predictive markers of efficacy will also be explored.

Immunophenotyping markers may include, but will not be limited to, CD3, CD4, CD8, CD25, FoxP3, CD56, CD16, CD279, CD366, and Ki67.

6.7 Exploratory Serum Biomarker Analyses

Serum samples for biomarkers will be drawn as indicated in Appendix A.

If warranted for an additional PD assessment or if a PD visit is missed, an additional blood sample can be collected by the Investigator at a later visit after discussion with the Sponsor. All samples will be sent to the central laboratory. Please refer to the laboratory manual for details.

6.8 Peripheral Blood Mononuclear Cell and Cytokine Production Analyses

PBMC samples will be collected for all patients in the Monotherapy Dose Expansion part and Combination Dose Finding part. Samples will be drawn as indicated in Appendix A.

All samples will be sent to the central laboratory. Please refer to the laboratory manual for details.

The analysis of cytokines derived from peripheral blood stimulated immune cells will provide direct evidence about their functionality and potential for cytotoxic cell killing and ultimately reduction of tumor growth. The following markers will be analyzed in PBMC samples using flow cytometry or using the Isoplexis system, potentially after magnetic isolation of different cell populations and stimulation: cytokines including, but not limited to, Interferon γ, Tumor Necrosis Factor, IL-6, IL-2, and IL-10.

6.9 Tumor Mutational Burden and Circulating Tumor DNA Analyses

Sampling for circulating tumor DNA (ctDNA) analyses will occur for patients that agree to perform tumor biopsies at the timepoints indicated in Appendix A.

All samples will be sent to the central laboratory. Please refer to the laboratory manual for details.

In recent years, the analysis of tumor mutational burden was shown to correlate with higher immunogenicity of tumors, and a correlation with response to checkpoint inhibitor treatment has been proposed. ctDNA has been recently described as a predictive biomarker for pembrolizumab as a single agent in 25 different cancers and has been shown to identify patients with highly favorable survival.[39] Therefore, tumor mutational burden may be monitored through defined

commercial panels or through whole exome sequencing, and ctDNA in the blood may be analyzed for specific mutations defined in tumor biopsies.

6.10 Other Exploratory Biomarkers

Other potential exploratory biomarkers that may be measured include the following:

- Density and/or percentage of cell populations determined by immunohistochemistry (examples may include, but are not limited to, CD8, CD366 (TIM-3), CD19, CD45, Ki67, CD56, Immunoglobulin G1, FoxP3, CD3, CD127, CD25, CD279 (PD-1), CD4, NKG2D, CD16, Perforin, CD20, and tumor specific markers);
- Concentration of peripheral blood soluble biomarkers (examples include, but are not limited to, soluble CD25, soluble PD-1/PD-L1, and IL-6);
- Protein and RNA expression patterns in target cell populations and tissues outlined above using, but not limited to, CyTOF® and/or gene expression methods;
- Single nucleotide polymorphisms;
- T cell receptor repertoire;
- Epigenetic markers; and
- Isolated immune cells from patient PBMCs analyzed via functional assays.

While the goal of the biomarker assessments is to provide supportive data for the clinical study, there may be circumstances when a decision is made to stop a collection, or to not perform or discontinue an analysis due to either practical or strategic reasons (eg, inadequate sample number, issues related to the quality of the sample, issues related to the assay that preclude analysis, or impossibility to perform correlative analyses, etc). Therefore, depending on the results obtained during the study, sample collection and/or analysis may be omitted at the discretion of Sponsor.

6.11 Immunogenicity Analyses

Blood samples for anti-drug antibodies (ADA) will be drawn as indicated in Appendix A and analyzed at a central laboratory. Please refer to the laboratory manual for details. Additional samples will be taken in the case of an IRR or irAE to rule out involvement of ADA. ADA samples will be analyzed for anti-ANV419 antibodies, their cross-reactivity to human IL-2, and their capacity to neutralize ANV419 function in a cell-based assay. In case of a Grade 3 or higher IRR, irAE, or any other AE deemed clinically suspicious of an irAE as judged relevant by the SRC, all available ADA samples from the respective patient will be analyzed immediately.

The probability of inducing a clinically relevant anti-ANV419 immune response is considered to be moderate. The most important potential risk associated with an anti-ANV419 humoral immune response is neutralization of endogenous IL-2, as this might result in systemic activation of immune effector cells. However, no such response was observed to aldesleukin, and therefore, this risk for severe consequences is considered low. In conclusion, the overall immunogenicity risk in the context of oncology indications is considered low to moderate as the probability of an ADA response is moderate while the severity of possible consequences is considered to be low.

6.12 Serology

Serology assessments will be performed as indicated in Appendix A and will include the analytes presented in Appendix B.

6.13 Sample Labeling and Storage

Details regarding sample collection, preparation, handling, storage, and shipping instructions are provided in the Laboratory Manual.

6.13.1 Sample Labeling

Each sample will be clearly labeled with the following information:

- Protocol number;
- Subject ID;
- Visit;
- Sample name;
- Sampling time; and
- Scheduled sampling time point.

6.13.2 Sample Storage

Procedures for storage and shipment will be followed according to the Laboratory Manual. The samples can be destroyed by specific authorization from the Sponsor.

7 SAFETY ASSESSMENTS

7.1 Adverse Events

An AE is defined as any untoward medical occurrence in a clinical investigation patient administered a pharmaceutical product, which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and/or unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational medicinal product, whether or not related to the investigational medicinal product. All Aes, including observed or volunteered problems, complaints, or symptoms, are to be recorded on the appropriate eCRF.

Aes, which include clinical laboratory test variables, will be monitored and documented in accordance with NCI CTCAE version 5.0 from signing of informed consent until the Safety Follow-Up Visit up to 90 days after the last dose of study drug or the start of a new cancer regimen, whichever is shorter. Patients should be instructed to report any AE that they experience to the Investigator, whether or not they think the event is due to study drug. Beginning at signing of informed consent, Investigators should make an assessment for Aes at each visit and record the event on the appropriate AE eCRF.

Wherever possible, a specific disease or syndrome rather than individual associated signs and symptoms should be identified by the Investigator and recorded on the eCRF. However, if an observed or reported sign or symptom is not considered a component of a specific disease or syndrome by the Investigator, it should be recorded as a separate AE on the eCRF. Additionally, the condition that led to a medical or surgical procedure (eg, surgery, endoscopy, tooth extraction, or transfusion) should be recorded as an AE, not the procedure itself.

A complete medical history will be compiled for each patient. Any medical condition already present at Screening should be recorded as medical history and not be reported as an AE unless the medical condition or signs or symptoms present at baseline changes in severity, frequency, or seriousness at any time during the study. In this case, it should be reported as an AE.

Clinically significant abnormal laboratory or other examination (eg, electrocardiogram [ECG]) findings that are detected during the study or are present at the signing of informed consent and significantly worsen during the study should be reported as Aes, as described below. The Investigator will exercise his or her medical and scientific judgment in deciding whether an abnormal laboratory finding or other abnormal assessment is clinically significant. Clinically significant abnormal laboratory values occurring during the clinical study will be followed until repeat tests return to normal, stabilize, or are no longer clinically significant. Abnormal test results that are determined to be an error should not be reported as an AE. Laboratory abnormalities or other abnormal clinical findings (eg, ECG abnormalities) should be reported as an AE if any of the following are applicable:

- If an intervention is required as a result of the abnormality;
- If action taken with the study drug is required as a result of the abnormality; or
- Based on the clinical judgment of the Investigator.

7.1.1 Adverse (Drug) Reaction

All noxious and unintended responses to a medicinal product related to any dose should be considered an adverse drug reaction. “Responses” to a medicinal product means that a causal relationship between a medicinal product and an AE is at least a reasonable possibility, ie, the relationship cannot be ruled out.

7.1.2 Unexpected Adverse Drug Reaction

An Unexpected Adverse Drug Reaction is defined as an adverse reaction, the nature or severity of which is not consistent with the applicable product information. For ANV419, pembrolizumab, and ipilimumab, the reference safety information is included in Section 6 of the Investigator’s Brochure currently in force. The reference safety information for ANV419 will be reviewed yearly and the periodicity of the review will be harmonized with the reporting period of the Development Safety Update Report where possible.

7.1.3 Assessment of Adverse Events by the Investigator

The severity of all Aes should be graded according to the NCI CTCAE version 5.0. For those AE terms not listed in the CTCAE, the following grading system should be used:

- CTCAE Grade 1: Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated;
- CTCAE Grade 2: Moderate; minimal local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living;
- CTCAE Grade 3: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care activities of daily living;
- CTCAE Grade 4: Life threatening consequences; urgent intervention indicated; and
- CTCAE Grade 5: Death related to the AE.

Causality assessment

The relationship of an AE to the administration of the study drug is to be assessed according to the following definitions:

No (unrelated, not related, unlikely to be related) – The time course between the administration of study drug and the occurrence or worsening of the AE rules out a causal relationship and another cause (concomitant drugs, therapies, complications, etc) is suspected; and

Yes (possibly, probably, or definitely related) – The time course between the administration of study drug and the occurrence or worsening of the AE is consistent with a causal relationship and no other cause (concomitant drugs, therapies, complications, etc) can be identified.

The definition implies a reasonable possibility of a causal relationship between the event and the study drug. This means that there are facts (evidence) or arguments to suggest a causal relationship.

The following factors should also be considered:

- The temporal sequence from study drug administration-

  The event should occur after the study drug is given. The length of time from study drug exposure to event should be evaluated in the clinical context of the event.

- Underlying, concomitant, intercurrent diseases-

  Each report should be evaluated in the context of the natural history and course of the disease being treated and any other disease the patient may have.

- Concomitant drug-

  The other drugs the patient is taking or the treatment the patient receives should be examined to determine whether any of them might be recognized to cause the event in question.

- Known response pattern for this class of study drug-

  Clinical and/or preclinical data may indicate whether a particular response is likely to be a class effect.

- Exposure to physical and/or mental stresses-

  The exposure to stress might induce adverse changes in the recipient and provide a logical and better explanation for the event.

- The pharmacology and pharmacokinetics of the study drug-

  The known pharmacologic properties (absorption, distribution, metabolism, and excretion) of the study drug should be considered.

7.1.4 Adverse Events of Special Interest

The Investigator will monitor each patient for clinical and laboratory evidence for pre-defined (per the results of the ongoing Phase 1 ANV419-001 study) Aes of special interest (AESIs) throughout the patient's participation in this study.

The Investigator will assess and record any additional information on the AESI in detail on an AE form which must be submitted within 24 hours of awareness of the event.

For this study, AESIs include the following:

- Grade 3 and Grade 4 CRS;
- Grade 3 and Grade 4 IRR;
- Grade 3 and Grade 4 capillary leak syndrome; and
- Grade 3 and Grade 4 immune effector cell-associated neurotoxicity syndrome (ICANS) as per the American Society for Transplantation and Cellular Therapy and National Comprehensive Cancer Network guidelines for ICANS.[34,38]

During the course of the study, additional AESIs may be identified by the Sponsor.

AESIs must be recorded in the eCRF.

7.2 Serious Adverse Events

An AE or adverse reaction is considered serious if, in the view of either the Investigator or Sponsor, it results in any of the following outcomes:

- Death;
- A life-threatening AE;

  Note: An AE or adverse reaction is considered "life-threatening" if, in view of either the Investigator or Sponsor, its occurrence places the patient at immediate risk of death. It does not include an event that, had it occurred in a more severe form, might have caused death.

- Requires hospitalization or prolongation of existing hospitalizations;

  Note: Any hospital admission with at least 1 overnight stay will be considered an inpatient hospitalization. An emergency room or urgent care visit without hospital admission will not be recorded as a SAE under this criterion, nor will hospitalization for a procedure scheduled or planned before signing of informed consent, or elective treatment of a pre-existing condition that did not worsen from Baseline Visit. However, unexpected complications and/or prolongation of hospitalization that occur during elective surgery should be recorded as Aes and assessed for seriousness. Admission to the hospital for social or situational reasons (ie, no place to stay, live too far away to come for hospital visits, respite care) will not be considered inpatient hospitalizations.

- A persistent or significant disability/incapacity or substantial disruption of the ability to conduct normal life functions;
- A congenital anomaly/birth defect; or
- An important medical event.

  Note: Important medical events that do not meet any of the above criteria may be considered an SAE when, based upon appropriate medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed above. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalizations, or the development of drug dependency.

Note: Events of progression of a patient's underlying cancer, as well as, events clearly related to the progression of a patient's cancer (signs/symptoms of progression) should not be reported as an SAE unless the outcome is fatal during the study or within the safety reporting period. If the event has a fatal outcome during that timeframe, the event of Progression of "Type of Cancer" must be recorded as an SAE with NCI CTCAE Grade 5 (fatal) outcome indicated. Diagnosis of progression of disease or hospitalization due to signs and symptoms of disease progression alone should not be reported as an SAE.

7.3 Serious Adverse Event Reporting – Procedures for Investigators

Initial reports

All SAEs occurring from signing of informed consent until the Safety Follow-Up Visit up to 90 days after the last dose of study drug, or the start of a new cancer regimen, whichever is shorter, must be reported to Medpace Clinical Safety within 24 hours of the knowledge of the occurrence.

After the reporting window, any SAE that the Investigator considers related to study drug must be reported to the Medpace Clinical Safety or the Sponsor/designee.

To report the SAE, complete the SAE form electronically in the electronic data capture (EDC) system for the study. When the form is completed, Medpace Safety personnel will be notified electronically by the EDC system and will retrieve the form. If the event meets serious criteria and it is not possible to access the EDC system, send an email to Medpace Safety at medpace-safetynotification@medpace.com or call the Medpace SAE reporting line (phone number listed below), and fax/email the completed paper SAE form to Medpace (contact information listed in Section 7.6) within 24 hours of awareness. When the EDC system becomes available, the SAE information must be entered within 24 hours of the system becoming available.

Follow-up reports

The Investigator must continue to follow the patient until the SAE has subsided or until the condition becomes chronic in nature, stabilizes (in the case of persistent impairment), or the patient dies or is considered lost to follow-up.

Within 24 hours of receipt of follow-up information, the Investigator must update the SAE form electronically in the EDC system for the study and submit any supporting documentation (eg, patient discharge summary or autopsy reports) to Medpace Clinical Safety via fax or email. If it is not possible to access the EDC system, refer to the procedures outlined above for initial reporting of SAEs.

7.4 Pregnancy Reporting

If a patient becomes pregnant after the start of study drug or within6 months after the last dose of study drug, the Investigator is to stop dosing with study drug(s) immediately if applicable and the patient should be withdrawn from the study. End of Study procedures should be implemented at that time.

A pregnancy is not considered to be an AE or SAE; however, it must be reported to Medpace Clinical Safety within 24 hours of knowledge of the event. Medpace Clinical Safety will then provide the Investigator/site the Exposure In Utero (EIU) form for completion. The Investigator/site must complete the EIU form and fax/email it back to Medpace Clinical Safety.

If the female partner of a male patient becomes pregnant while the patient is receiving study drug or6 months after the last dose of study drug, the Investigator should notify Medpace Clinical Safety as described above.

The pregnancy should be followed until the outcome of the pregnancy, whenever possible, and until 8 weeks after delivery to assess for congenital defects. Once the outcome of the pregnancy is known, the EIU form should be completed and faxed/emailed to Medpace Clinical Safety. If the outcome of the pregnancy meets the criteria for immediate classification as an SAE (ie, postpartum complication, spontaneous abortion, stillbirth, neonatal death, or congenital anomaly), the Investigator should follow the procedures for reporting an SAE.

7.5 Expedited Reporting

The Sponsor/designee will report all relevant information about Suspected Unexpected Serious Adverse Reactions (SUSARs) that are fatal or life-threatening as soon as possible to the FDA, applicable competent authorities in all the Member States concerned, and to the Central Ethics Committee, and in any case no later than 7 days after knowledge by the Sponsor/designee of such

a case. Relevant follow-up information will subsequently be communicated within an additional 8 days.

All other SUSARs will be reported to the FDA, applicable competent authorities concerned and to the Central Ethics Committee concerned as soon as possible but within a maximum of 15 days of first knowledge by the Sponsor/designee.

The Sponsor/designee will also report any additional expedited safety reports required in accordance with the timelines outlined in country-specific legislation.

The Sponsor/designee will also inform all Investigators as required per local regulation.

The requirements above refer to the requirements relating to investigational medicinal product.

Expedited reporting of SUSARs related to all investigational medical products (IMPs), (ie, ANV419, pembrolizumab, and ipilimumab) is required. Expedited reporting of SUSARs, related to non-IMPs (NIMPs) is not required. Listings of cases related to NIMPs will be included in the Development Safety Update Report.

7.6 Special Situation Reports

Special situation reports include reports of overdose, misuse, abuse, medication error, and reports of adverse reactions associated with product complaints.

- **Overdose:** Refers to the administration of a quantity of a medicinal product given per administration or cumulatively (accidentally or intentionally), which is above the maximum recommended dose according to the Protocol. Clinical judgment should always be applied. In cases of a discrepancy in the drug accountability, overdose will be established only when it is clear that the patient has taken additional dose(s) or the Investigator has reason to suspect that the patient has taken additional dose(s).
- **Misuse:** Refers to situations where the medicinal product is intentionally and inappropriately used not in a way that is not in accordance with the Protocol instructions or local prescribing information and may be accompanied by harmful physical and/or psychological effects.
- **Abuse:** Is defined as persistent or sporadic, intentional excessive use of a medicinal product, which is accompanied by harmful physical or psychological effects.
- **Medication error:** Is any unintentional error in the prescribing, dispensing, or administration of a medicinal product by a healthcare professional, patient, or consumer, respectively. The administration or consumption of the unassigned treatment and administration of an expired product are always reportable as medication errors, cases of patients missing doses of investigational product are not considered reportable as medication error.
- **Product complaint:** Is defined as any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, durability, reliability, safety, effectiveness, or performance of a drug or device after it is released for distribution. A special situations form will only be completed if a complaint is associated with an adverse drug reaction.

All special situation events as described above must be reported on the Special Situations Report form and faxed/emailed to Medpace Clinical Safety (contact information listed below) within 24 hours of knowledge of the event. All Aes associated with these Special Situation reports should be reported as Aes or SAEs as well as recorded on the AE eCRF and/or the SAE report form.

Details of the symptoms and signs, clinical management, and outcome should be provided, when available.

Safety Contact Information: Medpace Clinical Safety
[redacted]

Medpace SAE reporting line – Europe:
[redacted]

7.7 Clinical Laboratory Assessments

Clinical laboratory assessments (urinalysis, coagulation, chemistry, serology, endocrinology, and hematology) will be performed locally as indicated in Appendix A and will include the laboratory analytes presented in Appendix B. Patients found to have treatment-emergent laboratory toxicity of Grades 3 or 4 will be monitored at least weekly until resolution. Urinalysis may be done by dipstick or microscopy.

If applicable for logistical reason, clinical laboratory assessments can be performed within 24 hours from ANV419 administration.

7.8 Vital Signs

Vital signs will be measured as indicated in the Appendix A and will include measurements of systolic and diastolic blood pressure, heart rate, respiratory rate, and body temperature.

7.9 Electrocardiograms

Electrocardiograms will be performed as indicated in Appendix A. Twelve-lead ECGs will be performed locally and should be collected in triplicate, separated by approximately 5 minutes. When ECG measurements coincide with blood sample draws for PK, PD, or ADA sampling, the ECG measurement should be timed sufficiently prior to blood sample collection without impacting the sample collection time. Additional triplicate ECGs may be performed as clinically indicated. The patient should be relaxed and in a recumbent or semi-recumbent position at least 5 minutes before recording an ECG. ECGs will be reviewed locally by the site and parameters will be entered into the EDC.

7.10 Physical Examinations

Physical examinations will be performed as indicated in Appendix A.

A full physical examination and review of relevant systems, including height, will occur at the [redacted] Height will be measured at baseline only. Symptom-directed physical examination measurements are to be performed at all other visits and as clinically indicated.

8 STATISTICS

A Statistical Analysis Plan (SAP) will be prepared as a separate document. The SAP will include a more technical and detailed description of the planned statistical summaries and will be finalized prior to any interim analysis.

8.1 Analysis Populations

The Safety Population will consist of all patients who receive at least 1 dose (or partial dose) of study drug(s). The Safety Population will be used for safety analyses including DLT assessments.

The Efficacy Population will consist of all patients who receive at least 1 dose of study drug, have at least 1 post-baseline tumor assessment, and who are part of the Monotherapy Dose Expansion part, Combination Dose Finding part, or the Combination Dose Expansion part. The Efficacy Population will be used for efficacy analyses.

The PK Population will consist of all patients who receive at least 1 dose of study drug and have at least 1 measured concentration for at least 1 of the analytes. The PK Population will be used for PK analyses.

The PD Population will consist of all patients who receive at least 1 dose of study drug and have at least 1 evaluable pharmacodynamic sample. The PD Population will be used for PD endpoint analyses.

8.2 Statistical Methods

8.2.1 Sample Size Determination

Monotherapy Dose Expansion part

This part of the study will use Bayesian sequential monitoring. A maximum of 15 patients will be enrolled and treated at each dose level arm. A1and A2 monotherapy arms will be analyzed as independent experiments, and also overall, and the following assumptions are made:

- Nothing is known *a priori*: assume a uniform prior, ie, the true ORR could be any value between 0% and 100%;
- A true ORR <6% indicates treatment failure; and
- A true ORR >10% indicates treatment success.

With a maximum of 15 patients in an arm, if no responses were observed, then the estimated true ORR would be 5.9%, with 90% confidence interval (CI) (0.3%, 17.1%). This would be sufficient evidence to suggest that the treatment is unlikely to be successful. With a maximum of 30 patients overall, if no responses were observed, then the estimated true ORR would be 3.1%, with 90% CI (0.2%, 9.2%). This would be sufficient evidence to suggest that the treatment at either dose is unlikely to be successful.

There is 95% certainty that the true ORR is greater than 10% if any 1 of the following are observed:

- 2 responses in 3 to 7 patients;
- 3 responses in 8 to 13 patients;
- 4 responses in 14 to 19 patients; or

- 5 responses in 20 to 27 patients.

Combination Dose Finding part

The Combination Dose Finding part will employ BOIN[29] to find the MTD/RP2D of Arm B (ANV419 in combination with pembrolizumab) and Arm C (ANV419 in combination with ipilimumab). For each arm, the following assumptions have been predefined for the dose escalation:

- Target DLT rate of 25%;
- Maximum of 25 patients;
- Maximum of 9 patients treated at the same dose level; and
- Maximum of 5 dose levels defined in Table 5 to be tested.

Patients will be enrolled and treated in cohorts of 3 patients (at least). Up to 50 patients in total will be enrolled for the Combination Dose Finding part, with a minimum of 6 patients treated at RP2D.

Combination Dose Expansion part (efficacy analysis)

The sample size calculation is based on a Simon's 2-stage[40] design and ensures that under all possible distributions of patients to the 2 treatment arms, there is at least 80% power to correctly detect an ORR >40% and at most a Type I error rate of 10% of rejecting a null hypothesis that ORR <20%. This results in a sample size of 12 patients randomized to each treatment arm in Stage 1, followed by 13 additional patients randomized during Stage 2: a total of 25 patients per arm at the end of Stage 2.

8.2.2 Baseline Characteristics

Demographics (ie, date of birth, race, ethnicity, and sex of the patient as allowed per local guidelines), and patients' baseline clinical characteristics will be summarized for each arm by dose level in the Combination Dose Finding part of the study and by treatment arm in the Monotherapy Dose Expansion part and Combination Dose Expansion part and overall using descriptive statistics.

8.2.3 Interim Efficacy Analysis

In Arm B or C, an interim analysis of the primary outcome will be performed at the end of Stage 1 of the Combination Dose Expansion part of the study (once 12 evaluable patients have completed at least 1 disease evaluation or have discontinued from the study). Any treatment arm with an ORR <20% per RECIST (ie, treatment arms with no more than 2 complete or partial responses) will be discontinued.

8.2.4 Final Analysis of Efficacy

Efficacy analysis will be conducted using the Efficacy Population. The primary outcome (ORR per RECIST) will be presented together with a 95% CI for each treatment arm. Treatment arms with an observed ORR 95% CI with a lower limit above 20% and an upper limit above 40% will be considered for future study. All other outcomes measures will be summarized with the appropriate descriptive statistics.

Additional detail regarding derivation and analysis of efficacy outcomes are provided below:

- ORR per RECIST is defined as the proportion of patients whose best overall response is CR or PR;
- ORR per iRECIST is defined as the proportion of patients whose best overall response is immune CR (iCR) or immune PR (iPR);
- Duration of response (DOR) per RECIST will be calculated for patients with CR or PR as the best overall response. DOR is defined as the number of weeks from the start of the first response (CR or PR) to the first date of progressive disease per RECIST, clinical progression, or death due to any cause. DOR will be summarized descriptively using the Kaplan-Meier method;
- Immune DOR (iDOR) per iRECIST will be calculated for patients with iCR or iPR as the best overall response. iDOR is defined as the number of weeks from the start of the first response (iCR or iPR) to the first date of progressive disease per iRECIST, clinical progression, or death due to any cause. iDOR will be summarized descriptively using the Kaplan-Meier method;
- Disease control rate (DCR) per RECIST is defined as the proportion of patients whose best overall response is CR, PR, or SD; (DCR = CR + PR + SD). DCR will be summarized descriptively;
- Immune DCR (iDCR) per iRECIST defined as the proportion of patients whose best overall response is iCR or iPR or immune SD (iSD) per iRECIST; (iDCR = iCR + iPR + iSD). iDCR will be summarized descriptively;
- PFS is defined as the time from the initiation of study treatment to the first occurrence of disease progression per RECIST or death from any cause, whichever occurs first. PFS will be summarized descriptively using the Kaplan-Meier method;
- Immune PFS (iPFS) is defined as the time from the initiation of study treatment to the first occurrence of disease progression per iRECIST or death from any cause, whichever occurs first. iPFS will be summarized descriptively using the Kaplan-Meier method;
- OS is defined as the time from the initiation of study treatment to death from any cause and will be summarized descriptively using the Kaplan-Meier method;
- Time to response (TTR) per RECIST will be calculated for patients with CR or PR as the best overall response. TTR is defined as the time from first dose date to the start of the response (CR or PR) per RECIST. TTR will be summarized descriptively using the KaplanMeier method; and
- Immune TTR (iTTR) per iRECIST will be calculated for patients with iCR or iPR as the best overall response. iTTR is defined as the time from first dose date to the start of the first response (iCR or iPR) per iRECIST. iTTR will be summarized descriptively using the Kaplan-Meier method.

8.2.5 Analysis of Immunogenicity

The impact of pre-existing, treatment-emergent, and treatment-boosted ADA on PK, safety, and efficacy read-outs will be evaluated by descriptive statistics and summarized in the Clinical Study Report.

8.2.6 Analysis of Safety

In general, all safety analyses will be descriptive and presented in tabular format with appropriate summary statistics for the Safety Population.

The safety of ANV419 as monotherapy and in combination with pembrolizumab or ipilimumab will be assessed by monitoring Aes (including TEAEs, DLTs [Combination Dose Finding part only], AESIs, SAEs, irAEs, and Aes leading to discontinuation of the study), physical examination findings (including ECOG performance status), clinical laboratory assessments, vital signs measurements, and ECGs. Aes will be coded using the Medical Dictionary for Regulatory Activities and graded according to NCI CTCAE version 5.0.

TEAEs will be summarized by System Organ Class and Preferred Term and further by grade according to NCI CTCAE version 5.0 and relationship to study drug.

The impact of possible anti-ANV419 antibodies on safety of ANV419 will be assessed.

8.2.7 Analysis of Pharmacokinetics

Plasma concentrations of ANV419 will be determined with a validated bioanalytical assay. Selected PK parameters will be calculated from plasma concentrations using noncompartmental analyses. Summary statistics will be generated by treatment arm as appropriate.

PK parameters to be analyzed:

- CL of ANV419;
- V_{ss} of ANV419;
- AUC of ANV419; and
- C_{max} of ANV419.

8.2.8 Analysis of Pharmacodynamics

The result, change, percent change, and maximum percent change in immunologic changes to selected serum cytokines and immune cell subsets in the blood and tumor microenvironment will be summarized descriptively.

PD parameters to be analyzed (including, but not limited to):

- CD3, CD4, CD8, CD56, CD16, CD25, FoxP3, CD279, and CD366.

8.2.9 Other Analysis

Clinical benefit assessment Quality of Life evaluation will be summarized using descriptive statistics.

9 DATA MANAGEMENT AND RECORD KEEPING

9.1 Data Management

9.1.1 Data Handling

Data will be recorded at the site on eCRFs and reviewed by the Clinical Research Associate (CRA) during monitoring visits. The CRAs will verify data recorded in the EDC system with source documents. All corrections or changes made to any study data must be appropriately tracked in an audit trail in the EDC system. An eCRF will be considered complete when all missing, incorrect, and/or inconsistent data have been accounted for.

9.1.2 Computer Systems

Data will be processed using a validated computer system conforming to regulatory requirements.

9.1.3 Data Entry

Data must be recorded using the EDC system as the study is in progress. All site personnel must log into the system using their secure username and password in order to enter, review, or correct study data. These procedures must comply with Title 21 of the Code of Federal Regulations (CFR) (21 CFR Part 11) and other appropriate international regulations. All passwords will be strictly confidential.

9.1.4 Medical Information Coding

For medical information, the following thesauri will be used:

- Medical Dictionary for Regulatory Activities (latest) for medical history and Aes; and
- World Health Organization Drug Dictionary for prior and concomitant medications.

9.1.5 Data Validation

Validation checks programmed within the EDC system, as well as supplemental validation performed via review of the downloaded data, will be applied to the data in order to ensure accurate, consistent, and reliable data. Data identified as erroneous, or data that are missing, will be referred to the investigative site for resolution through data queries.

The eCRFs must be reviewed and electronically signed by the Investigator.

9.2 Record Keeping

Records of patients, source documents, monitoring visit logs, eCRFs, inventory of study product, regulatory documents, and other Sponsor correspondence pertaining to the study must be kept in the appropriate study files at the site. Source data is defined as all information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical study necessary for the evaluation and reconstruction of the clinical study. Source data are contained in source documents (original records or certified copies). These records will be retained in a secure file for the period as set forth in the Clinical Study Agreement. Prior to transfer or destruction of these records, the Sponsor must be notified in writing and be given the opportunity to further store such records.

9.3 End of Study

The end of the study (study completion) is defined as the date of the final statistical analysis. At this time, patients who are still receiving ANV419 and continue to demonstrate clinical benefit may enter a long-term extension study to continue ANV419 treatment.

10 INVESTIGATOR REQUIREMENTS AND QUALITY CONTROL

10.1 Ethical Conduct of the Study

Good Clinical Practice (GCP) is an international ethical and scientific quality standard for designing, conducting, recording, and reporting studies that involve human patients. Compliance with this standard provides public assurance that the rights, safety, and wellbeing of study patients are protected, consistent with the principles that have their origin in the Declaration of Helsinki, and that the clinical study data are credible.

10.2 Institutional Review Board/Independent Ethics Committee

The Institutional Review Board (IRB)/Independent Ethics Committee (IEC) will review all appropriate study documentation in order to safeguard the rights, safety, and well-being of patients. The study will only be conducted at sites where IRB/IEC approval has been obtained. The Protocol, Investigator's Brochure, informed consent form (ICF), advertisements (if applicable), written information given to the patients, safety updates, annual progress reports, and any revisions to these documents will be provided to the IRB/IEC by the Investigator.

Federal regulations and International Council for Harmonisation (ICH) Guidelines require that approval be obtained from an IRB/IEC prior to participation of patients in research studies. Prior to study onset, the Protocol, any Protocol amendments, ICFs, advertisements to be used for patient recruitment, and any other written information regarding this study to be provided to a patient or patient's legal guardian must be approved by the IRB/IEC.

No drug will be released to the site for dosing until written IRB/IEC authorization has been received by the Sponsor.

10.3 Informed Consent

The ICF and any changes to the ICF made during the course of the study must be agreed to by the Sponsor or designee and the IRB/IEC prior to its use and must be in compliance with all ICH GCP, local regulatory requirements, and legal requirements.

The Investigator must ensure that each study patient is fully informed about the nature and objectives of the study and possible risks associated with participation and must ensure that the patient has been informed of his/her rights to privacy. The Investigator will obtain written informed consent from each patient before any study-specific activity is performed and should document in the source documentation that consent was obtained prior to enrollment in the study. The original signed copy of the ICF must be maintained by the Investigator and is subject to inspection by a representative of the Sponsor, their representatives, auditors, the IRB/IEC and/or regulatory agencies. A copy of the signed ICF will be given to the patient.

10.4 Future Use of Biological Samples

In order to be able to address future scientific questions, patients will be asked to allow biospecimen collection, cryopreservation, and banking. If the patient agrees, banked samples may be used for future exploratory biomarker research and drug development projects; eg, to identify patients who are more likely to benefit from a treatment or experience an AE, or to gain a mechanistic or genetic understanding of drug effects.

Biobanking will only occur after informed consent has been given in accordance with local ethical and regulatory requirements.

Blood and tissue samples for future research studies will be cryopreserved and stored for patients who have consented. It is the responsibility of the Investigator or designee (if acceptable under local regulations), to obtain written informed consent from each individual who has consented to have his/her samples stored for future research in a contract laboratory facility under the responsibility of the Sponsor and its potential partners after adequate explanation of the aims, methods, objectives, and potential hazards. Patients must receive an explanation that they are completely free to refuse long-term storage of their samples for future research and may withdraw consent at any time and for any reason during the storage period of the specimen(s), and that refusal of long-term storage does not preclude participation in the study.

Patient samples and information will be stored in a secure storage area and will be identified only by a coded patient identification number. Patient samples will be kept for a maximum of 5 years, after which the samples will be destroyed according to the standard procedures of the laboratory.

At any time, if informed consent is withdrawn, no new data will be added to the study database. Data already obtained from the samples will continue to be kept and used. Patients have the right to request their identifiable samples be destroyed at any time and to be informed of any plans for new analyses on the retained samples.

All samples will be stored at an external biobanking facility contracted by Anaveon AG. Measures are in place to comply with the applicable rules for the collection, cryopreservation, biobanking, and future use of biological samples and clinical data, including the following:

- Sample and data usage must be in accordance with the ICF;
- The facilities storing biological samples from clinical study participants are qualified for the storage of biological samples collected in clinical studies;
- An appropriate sample and data management system is in place, including audit trails for clinical data and/or samples, and the ability to identify and destroy such samples according to the ICF; and
- Data and/or samples may be transferred to third parties and other countries as specified in the ICF.

10.5 Patient Emergency Study Contact Card

On enrollment in the study, the patient will receive a patient card to be carried at all times. The patient card will state that the patient is participating in a clinical research study, type of treatment, number of treatment packs received, and contact details in case of an SAE.

10.6 Study Monitoring Requirements

It is the responsibility of the Investigator to ensure that the study is conducted in accordance with the Protocol, ICH GCP, Directive 2001/20/EC, applicable regulatory requirements, and the Declaration of Helsinki and that valid data are entered into the eCRFs.

To achieve this objective, the monitor's duties are to aid the Investigator and, at the same time, the Sponsor in the maintenance of complete, legible, well organized and easily retrievable data. Before the enrollment of any patient in this study, the Sponsor or their designee will review with the Investigator and site personnel the following documents: Protocol, Investigator's Brochure, eCRFs and procedures for their completion, informed consent process, and the procedure for reporting SAEs.

The Investigator will permit the Sponsor or their designee to monitor the study as frequently as deemed necessary to determine that data recording and Protocol adherence are satisfactory. During the monitoring visits, information recorded on the eCRFs will be verified against source documents and requests for clarification or correction may be made. After the eCRF data are entered by the site, the CRA will review the data for safety information, completeness, accuracy, and logical consistency. Computer programs that identify data inconsistencies may be used to help monitor the clinical study. If necessary, requests for clarification or correction will be sent to Investigators. The Investigator and his/her staff will be expected to cooperate with the monitor and provide any missing information, whenever possible.

All monitoring activities will be reported and archived. In addition, monitoring visits will be documented at the investigational site by signature and date on the study-specific monitoring log.

10.7 Disclosure of Data

Data generated by this study must be available for inspection by the FDA, the Sponsor or their designee, applicable foreign health authorities, and the IRB/IEC as appropriate. Patients or their legal representatives may request their medical information be given to their personal physician or other appropriate medical personnel responsible for their welfare.

Patient medical information obtained during the study is confidential and disclosure to third parties other than those noted above is prohibited.

10.8 Retention of Records

To enable evaluations and/or audits from regulatory authorities or the Sponsor, the Investigator will keep records, including the identity of all participating patients (sufficient information to link records, eg, eCRFs and hospital records), all original signed ICFs, copies of all eCRFs, SAE forms, source documents, and detailed records of treatment disposition. The records should be retained by the Investigator according to specifications in the ICH guidelines, local regulations, or as specified in the Clinical Study Agreement, whichever is longer. The Investigator must obtain written permission from the Sponsor before disposing of any records, even if retention requirements have been met.

If the Investigator relocates, retires, or for any reason withdraws from the study, the Sponsor should be prospectively notified. The study records must be transferred to an acceptable designee, such as another Investigator, another institution, or to the Sponsor.

10.9 Publication Policy

Following completion of the study, the data may be considered for publication in a scientific journal or for reporting at a scientific meeting. Each Investigator is obligated to keep data pertaining to the study confidential. The Investigator must consult with the Sponsor before any study data are submitted for publication. The Sponsor reserves the right to deny publication rights until mutual agreement on the content, format, interpretation of data in the manuscript, and journal selected for publication are achieved.

10.10 Insurance and Indemnity

In accordance with the relevant national regulations, the Sponsor has taken out patient liability insurance for all patients who have given their consent to the clinical study. This cover is designed for the event that a fatality, physical injury, or damage to health occurs during the clinical study's execution.

10.11 Legal Aspects

The clinical study is submitted to the relevant national competent authorities in all participating countries to achieve a clinical trial authorization (CTA).

The study will commence (ie, initiation of study centers) when the CTA and favorable Ethics opinion have been received.

11 STUDY ADMINISTRATIVE INFORMATION

11.1 Protocol Amendments

Any amendments to the study Protocol will be communicated to the Investigators by Medpace or the Sponsor. All Protocol amendments will undergo the same review and approval process as the original Protocol. A Protocol amendment may be implemented after it has been approved by all regulatory bodies, including the IRB/IEC, unless immediate implementation of the change is necessary for patient safety. In this case, the situation must be documented and reported to the IRB/IEC within 5 working days.

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APPENDIX A: SCHEDULE OF PROCEDURES

Table 20 . Schedule of Procedures for Patients Enrolled in Arms A1 or A2 (Monotherapy)

Week	-4 to -1		1			2	3		5	7	9		11	13	14-23	24-52	53-105	EOS [b]	SFU Visit [c,d]	Survival FU (Q12W) [d]
Cycle	SCR[a]	BL[a]	C1				C2		C3	C4	C5		C6	C7	C8 to C12	C13-C26	C27-C53			
Day [e]	-28 to -3	-3 to -1	D1	[redacted]																
Informed consent	X																			
Eligibility criteria	X	X	X																	
Demographic information[f]	X	X																		
Medical/ surgical history	X	X																		
Histology report (mutation status)	X																			
Vital signs[g]		[redacted]																		
Physical examination[j]																				
Body weight (kg)																				
ECOG PS	X																			
12-lead ECG[n]	X																			
Safety laboratory (local)[o, p]	X																			
Viral Serology[q]	X																			
Thyroid hormones[r]	X																			
Randomization																				

Week	-4 to -1		1			2	3		5	7	9		11	13	14-23	24-52	53-105	EOS [b]	SFU Visit [c,d]	Survival FU (Q12W) [d]
Cycle	SCR[a]	BL[a]	C1				C2		C3	C4	C5		C6	C7	C8 to C12	C13-C26	C27-C53			
Day [e]	-28 to -3	-3 to -1	D1	[redacted]																
Pregnancy test[t]	X	X							X		X			X	X[t]	X[t]	X[t]	X	X	
CT scan[u]	X[u]	[redacted]																		
Disease evaluation (RECIST) [u]																				
Cytokine sampling[w]																				
PBMC sampling																				
PK sampling[w]																				
ADA sampling[ee]																				
Biomarker sampling																				
Immune-profile sampling [ff]																				
ctDNA sampling																				
Tumor biopsy[hh]	X																			
ANV419 infusion[ii, jj]																				
Post infusion monitoring (90 minutes) [kk]																				
Aes[ll]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Prior/ concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Survival																				X

a. If Screening assessments were performed within 72 hours of Cycle 1 Day 1 (C1D1), it can be combined with baseline visit and the assessments will only be done once. The baseline visit is to be conducted within 3 days from dosing unless otherwise specified.

b. The EOS Visit is 730 days [redacted] after C1D1 OR ≤30 days since last dose of study drug. This will also be the same visit with the same assessments for patients who discontinue the study early.
c. A SFU visit will be made ≤90 days since the last dose of study drug for safety purposes .
d. Patients who discontinue for reasons listed in Section 4.4 other than progressive disease will have post-treatment follow-up for disease status until disease progression, initiation of a non-study cancer treatment, withdrawal of consent, or lost to follow-up. In addition, each patient, irrespective of disease progression, will be followed for survival by telephone (or public records when allowed as per local regulation) until death or study termination whichever occurs first.
e. The visit window is ±3 days. For visits occurring on [redacted] no visit window apply.
f. Demographics will include date of birth (month and year), race, ethnicity, and sex as allowed per local guidelines.
g. Vital signs will include measurements of systolic and diastolic blood pressure, heart rate, respiratory rate, and body temperature.
h. Vital signs will be collected pre-dose and then every 2 hours (±30 minutes) for the first 8 hours post end of infusion.
i. Vital signs will occur approximately 24 hours (±4 hours) after end of infusion and then ad-hoc as clinically indicated.
.
j. From C12, a physical examination will occur at every other visit.
k. A full physical examination and review of relevant systems will occur at this visit, including height. Height to be measured at baseline only.
l. Symptom-directed physical examination is to be performed as clinically indicated.
m. ECOG Performance Status will be assessed using the ECOG scale (see Appendix G). [redacted].
n. Twelve-lead ECGs will be performed locally and should be collected in triplicate, separated by approximately 5 minutes. ECGs will be performed at screening, baseline and within 2 hours pre-dose and 1 hour post-dose on dosing days until [redacted]
o. Clinical laboratory assessments will be performed locally. Urinalysis, coagulation, chemistry, and hematology will include the laboratory analytes presented in Appendix B. Patients found to have treatment-emergent laboratory toxicity of Grades 3 or 4 will be monitored at least weekly until resolution.
p. Urinalysis may be done by dipstick or microscopy.
q. Including HBV, HCV, HIV1, and HIV2.
r. Including T3, T4, and TSH. [redacted].
s. Patients enrolled in the Monotherapy Dose Expansion part will be randomized by IRT and stratified by BRAF mutation status into Arms A1 or A2 on C1D1 (-3 days).
t. Female patients of childbearing potential must have a negative serum pregnancy test at the Screening Visit and negative (urine or serum) pregnancy test within 72 hours prior to study Day 1. If the urine test is positive or cannot be confirmed negative, a serum pregnancy test will be required and must be negative for the patient to be eligible. [redacted].
u. Imaging performed prior to signing consent can be used for screening purposes if done within 8 weeks from signing consent. Baseline disease assessment using CT imaging (including brain assessment) is to be performed within 21 days of baseline. [redacted]
v. CT scan is not required at EOS if available within 4 weeks prior to the EOS Visit.
w. If warranted for additional safety assessments, additional samples can be collected by the Investigator after discussion with the Sponsor. For patients who discontinue for reasons other than progressive disease, PK/ADA samples will be collected during post-treatment follow-up disease status until disease progression.
x. To be collected pre-dose and then 2 (±30 minutes) and 4 hours (±1 hour) post end of infusion of ANV419.
y. PK samples to be drawn pre-dose and then 15 minutes (±5 minute), 1 hour (±30 minutes), 2 hours (±30 minutes), 4 hours (±1 hour), and 8 hours (±1 hour) post end of infusion.

z. PK samples to be drawn 24 hours (±1 hour) post end of infusion.
aa. PK samples to be drawn 72 hours (±1 hour) post end of infusion.
bb. PK samples to be drawn pre-dose and then 1 hour (±30 minutes), and 2 hours (±30 minutes) post end of infusion.
cc. Samples to be drawn pre-dose.
dd. [redacted]
ee. All ADA samples to be taken pre-dose. Additional samples will be taken in the case of an IRR or irAE to rule out involvement of ADA. [redacted].
ff. If warranted for an additional PD assessment or if a PD visit is missed, an additional blood sample can be collected by the Investigator at a later visit after discussion with the Sponsor.
gg. To be drawn [redacted].
hh. Tumor biopsies for research purpose may be performed within ±3 days of the imaging assessment and within 7 days of the start of the dosing cycle if deemed safe and clinically feasible . Any tissue that is suspected to contain tumor, including lymph nodes, may be biopsied. All biopsies are optional.
ii. Acetaminophen 1 g may be given to the patients as pre-medication or following the ANV419 infusion and can be used every 8 hours as needed.
jj. A treatment interval of at least 12 days is required.
kk. Patients will be monitored for 90 minutes post end of infusion from C1 per individual site institutional standard.
ll. Aes and SAEs should be recorded from signing of informed consent until the SFU Visit up to 90 days (±7 days) after last dose of study drug or the start date of the next cancer regimen, whichever occurs first.
mm. [redacted]

ADA = anti-drug antibodies; AE = adverse event; BL = baseline; C = Cycle; CT = computed tomography; ctDNA = circulating tumor deoxyribonucleic acid; D = Day; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; EOS = End of Study; HBV = hepatitis B virus; HCV = hepatitis C virus; HIV = human immunodeficiency virus; irAE = immune-related adverse events; IRR = infusion-related reaction; PBMC = peripheral blood mononuclear cell; PD = pharmacodynamic(s); PK = pharmacokinetic(s); [redacted] RECIST = Response Evaluation Criteria in Solid Tumors; SAE = serious adverse event; SCR = Screening Visit; SFU = Safety Follow-Up; T3 = triiodothyronine; T4 = thyroxine; TSH = thyroid-stimulating hormone.

Table 21. Schedule of Procedures for Patients Enrolled in Arm B and Arm C (Combination Therapy)

Week	-4 to -1		1	2	3	4	5	7	10	13	16	19	22 to 34	35+ Q6W			Survival FU (Q12W)[d]
Cycle	SCR[a]	BL[a]	C1			C2		C3	C4	C5	C6	C7	C8 to C12	C13+ Q2C	EOS[b]	SFU Visit[c,d]	
Day [e]	-28 to -3	-3 to -1	D1	[redacted]													
Informed consent	X																
Eligibility criteria	X	X	X														
Demographic information[f]	X	X															
Medical/ surgical history	X	X															
Histology report (mutation status)	X																
Vital signs[g]		[redacted]															
Physical examination[k]																	
Body weight(kg)																	
ECOG PS[n]	X																
12-lead ECG[o]	X																
Safety laboratory (local)s[q,r]	X																
Viral Serology[s]	X																
Thyroid hormones[t]	X																
Randomization																	
Pregnancy test[v]	X																
CT scan[x]	X[x]																

Week	-4 to -1		1			2	3	4	5	7	10		13	16	19	22 to 34	35+ Q6W			Survival FU (Q12W)[d]
Cycle	SCR[a]	BL[a]	C1					C2		C3	C4		C5	C6	C7	C8 to C12	C13+ Q2C	EOS[b]	SFU Visit[c,d]	
Day [e]	-28 to -3	-3 to -1	D1	D2	D4	D8	D15	D1	D8	D1	D1	D4	D1	D1	D1	D1				
Disease evaluation (RECIST)[x]																				
Cytokine sampling[z]																				
PBMC sampling[bb]																				
PK sampling[z]																				
ADA sampling[ii]																				
Biomarker sampling																				
Immune-profile sampling [kk]																				
ctDNA sampling																				
SNP sampling (Arm C only)																				
Tumor biopsy[mm]	X																			
QoL evaluation (EQ-5D-5L and QLQ-C30)[nn]																				
ANV419 infusion[oo,pp,qq]																				
Pembrolizumab infusion (Arm B only)[qq,rr]																				

Week	-4 to -1		1			2	3	4	5	7	10		13	16	19	22 to 34	35+ Q6W	EOS[b]	SFU Visit[c,d]	Survival FU (Q12W)[d]
Cycle	SCR[a]	BL[a]	C1					C2		C3	C4		C5	C6	C7	C8 to C12	C13+ Q2C			
Day [e]	-28 to -3	-3 to -1	D1	D2	D4	D8	D15	D1	D8	D1	D1	D4	D1	D1	D1	D1				
Ipilimumab infusion (Arm C only)[qq,rr]			[redacted]																	
Post-infusion observation (23h)[uu,vv]																				
Post-infusion monitoring (90mn)[ww]																				
AEs[zz]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[j]	X	X	
Prior/ concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[j]	X	X	
Survival																				X

a. If Screening assessments were performed within 72 hours of Cycle 1 Day 1 (C1D1) it can be combined with baseline visit and the assessments will only be done once. The baseline window is to be conducted within 3 days from dosing unless otherwise specified.
b. The EOS Visit is [redacted] after C1D1 OR ≤30 days since last dose of study drug. This will also be the same visit with the same assessments for patients who discontinue the study early.
c. A SFU visit will be made ≤90 days since the last dose of study drug for safety purposes .
d. Patients who discontinue for reasons listed in Section 4.4 other than progressive disease will have post-treatment follow-up for disease status until disease progression, initiation of a non-study cancer treatment, withdrawal of consent, or lost to follow-up. In addition, each patient, irrespective of disease progression, will be followed for survival by telephone (or public records when allowed as per local regulation) until death or study termination whichever occurs first.
e. The visit window will be ±3 days, except for [redacted]y
f. Demographics will include date of birth (month and year), race, ethnicity, and sex as allowed per local guidelines.
g. Vital signs will include measurements of systolic and diastolic blood pressure, heart rate, respiratory rate, and body temperature.
h. Vital signs to be collected pre-dose and then every 2 hours (±30 minutes) for the first 8 hours post end of ANV419 infusion.
i. Vital signs will occur approximately 20 hours (±3 hours) after end of infusion for Combination Dose Finding patients or approximately 24 hours (±4 hours) post end of infusion for Combination Dose Expansion patients, and then ad-hoc as clinically indicated.
j. To occur every cycle following [redacted]
k. From [redacted].

l. A full physical examination and review of relevant systems will occur at this visit, including height. Height tobe measured at baseline only.
m. Symptom-directed physical examination isto be performed as clinically indicated.
n. ECOG Performance Status will be assessed using the ECOG scale (see Appendix G). ECOG [redacted]
o. Twelve-lead ECGs will be performed locally and should be collected in triplicate, separated by approximately 5 minutes. [redacted]
p. ECGs [redacted]
q. Clinical laboratory assessments will be performed locally. Urinalysis, coagulation, chemistry, and hematology will include the laboratory analytes presented in Appendix B. Patients found to have treatment-emergent laboratory toxicity of Grades 3 or 4 will be monitored at least weekly until resolution.
r. Urinalysis may be done by dipstick or microscopy.
s. Including HBV, HCV, HIV1, and HIV2.
t. Including T3, T4, and TSH. From C5, thyroid hormones should be measured [redacted].
u. Patients enrolled in the Combination Dose Finding part will be manually randomized to Arm B or Arm C on C1D1 (-3 days). Patients enrolled in the Combination Dose Expansion part will be randomized by IRT and stratified by BRAF mutation status into Arm B or Arm C on C1D1 (-3 days).
v. Female patients of childbearing potential must have a negative serum pregnancy test at the Screening Visit and negative (urine or serum) pregnancy test within 72 hours prior to study Day 1. If the urine test is positive or cannot be confirmed negative, a serum pregnancy test will be required and must be negative for the patient to be eligible.
w. To occur pre-dose every cycle from previous assessment and at EOS.
x. Imaging performed prior to signing consent can be used for screening purposes if done within 8 weeks from signing consent. [redacted]
y. [redacted]
z. If warranted for additional safety assessments, additional samples can be collected by the Investigator after discussion with the Sponsor.
aa. To be collected pre-dose and then 2 hours (±30 minutes) and 4 hours (±1 hour) post end of infusion of ANV419.
bb. PBMC samples will be collected for all patients in the Combination Dose Finding part only (and no patients in Combination Dose Expansion part).
cc. PK samples to be drawn pre-dose and then 15 minutes (±5 minute), 1 hour (±30 minutes), 2 hours (±30 minutes), 4 hours (±1 hour), and 8 hours (±1 hour) post end of infusion.
dd. PK samples to be drawn 24 hours (±1 hour) post end of infusion.
ee. PK samples to be drawn 72 hours (±1 hour) post end of infusion.
ff. PK samples to be drawn pre-dose and then 1 hour (±30 minutes), and 2 hours (±30 minutes) post end of infusion.
gg. Samples to be drawn pre-dose.
hh. To be drawn pre-dose every [redacted].
ii. All ADA samples to be taken pre-dose. Additional samples will be taken in the case of an IRR or irAE to rule out involvement of ADA. From C5, ADA samples to be taken [redacted]
jj. To be drawn [redacted] from the previous assessment. To occur pre-dose on days where study drug is administered.
kk. If warranted for an additional PD assessment or if a PD visit is missed, an additional blood sample can be collected by the Investigator at a later visit after discussion with the Sponsor.
ll. To be drawn [redacted]
mm. Tumor biopsies for research purpose may be performed within ±3 days of the imaging assessment and within 7 days of the start of the dosing cycle if deemed safe and clinically feasible. Any tissue that is suspected to contain tumor, including lymph nodes, may be biopsied. All biopsies are optional.

nn. QoL evaluations (EQ-5D-5L and QLQ-C30) are to be performed for clinical benefit assessment at baseline and [redacted].
oo. Acetaminophen 1 g may be given to the patients as pre-medication or following the ANV419 infusion and can be used every 8 hours as needed.
pp. A treatment interval of [redacted].
qq. Pembrolizumab or ipilimumab will be administered first. Patients can receive the ANV419 infusion approximately 30 minutes after they have received the entire infusion of pembrolizumab or ipilimumab.
rr. Sites should make every effort to target infusion timing to be as close to 30 minutes (for pembrolizumab) or 90 minutes (for ipilimumab) as possible; however, given the variability of infusion pumps from site to site, a window of ±5 minutes is permitted.
ss. Ipilimumab dosing will end after [redacted]
tt. Patients being treated on combination therapy with ANV419 plus ipilimumab who require discontinuation of ipilimumab due to toxicity may continue treatment with ANV419 after approval from the Sponsor. The reason for discontinuation must be recorded.
uu. At the end of study drug(s) infusion in C1 and C2 (only) of the Combination Dose Finding part, all patients will undergo a 23-hour observation period. Clinical monitoring will be conducted per individual sites institutional standards within the framework of observation required for this Protocol, with vital signs monitored every 8 hours for the first 23 hours post end of ANV419 infusion. After C2, the observation will lessen to 90 minutes post end of infusion, provided no additional safety concerns have been identified.
vv. Combination Dose Finding part patients only.
ww. Patients will be monitored for 90 minutes or longer post end of ANV419 infusion from C1 per individual site institutional standard.
xx. Combination Dose Expansion part patients only.
yy. All patients in Combination Dose Finding part and Combination Dose Expansion part, provided no additional safety concerns have been identified.
zz. AEs and SAEs should be recorded from signing of informed consent until the SFU Visit up to 90 days (±7 days) after last dose of study drug or the start date of the next cancer regimen, whichever occurs first.

ADA = anti-drug antibodies; AE = adverse event; BL = baseline; BRAF = B-type Raf proto-oncogene; C = Cycle; CT = computed tomography; ctDNA = circulating tumor deoxyribonucleic acid; D = Day; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; EOS = End of Study; EQ-5D-5L= Euro-QoL 5 dimension 5 level; HBV = hepatitis B virus; HCV = hepatitis C virus; HIV = human immunodeficiency virus; irAE = immune-related adverse events; IRR = infusion-related reaction; IRT = interactive response technology; PBMC = peripheral blood mononuclear cell; PD = pharmacodynamic(s); PK = pharmacokinetic(s); [redacted] QLQ-C30 = quality of life core 30; QoL = quality of life; RECIST = Response Evaluation Criteria in Solid Tumors; SAE = serious adverse event; SCR = Screening Visit; SFU = Safety Follow-Up; SNP = single nucleotide polymorphism; T3 = triiodothyronine; T4 = thyroxine; TSH = thyroid-stimulating hormone.

APPENDIX B: CLINICAL LABORATORY ANALYTES

Standard Safety Chemistry Panel

Alanine aminotransferase	Albumin
Alkaline phosphatase	Amylase
Aspartate aminotransferase	Blood urea nitrogen
Calcium	Chloride
Creatine kinase	Creatinine
Estimated glomerular filtration rate	Gamma-glutamyl transferase
Glucose	Inorganic phosphorus
Lactate dehydrogenase	Lipase
Potassium	Sodium
Total protein	Total and Direct bilirubin
Urea (where blood urea nitrogen is not tested)	Uric acid

Additional Chemistry Parameters

C-reactive protein	Cholesterol
Triglycerides	

Endocrinology

Thyroid-stimulating hormone	T3
T4	

T3 = triiodothyronine; T4 = thyroxine.

Hematology

Absolute basophil value	Absolute eosinophil value
Absolute monocyte count	Absolute neutrophil count
Hematocrit	Hemoglobin
Lymphocyte count	Platelets
Red blood cell count	White blood cell count and differential [1]

1. Manual microscopic review is performed only if white blood cell count and/or differential values are out of reference range.

Coagulation

D-dimer	International normalized ratio [1]
Prothrombin ratio	Prothrombin time

1. Prothrombin time/international normalized ratio should be measured daily for any patient experiencing alanine aminotransferase or aspartate aminotransferase elevations ≥3 × upper limit of normal with concomitant elevation in bilirubin ≥2 × upper limit of normal until resolution to baseline of the liver function test abnormality.

Urinalysis

Bilirubin	Blood
Glucose	Ketones
Leukocyte esterase	Microscopy [1]
Nitrite	pH
Protein	Specific gravity
Urobilinogen	

1. Urinalysis may be done by dipstick or microscopy.

Serology

Hepatitis B surface antigen	Hepatitis B virus DNA [1]
Hepatitis C virus antibody	Hepatitis C virus RNA [2]
Human immunodeficiency virus 1	Human immunodeficiency virus 2

1. Hepatitis B virus DNA will be tested by PCR in patients with positive hepatitis B surface antigen.
2. Hepatitis C virus RNA will be tested by PCR in patients with positive hepatitis C virus antibody.

DNA = deoxyribonucleic acid; PCR = polymerase chain reaction; RNA = ribonucleic acid.

APPENDIX C: TUMOR MEASUREMENTS AND ASSESSMENT OF DISEASE RESPONSE USING RESPONSE EVALUABLE CRITERIA IN SOLID TUMORS (RECIST) 1.1

Tumor measurements are to be performed for all patients during Screening as follows:

- Baseline disease assessment: radiographic tumor measurements using computed tomography (CT) imaging of the chest, abdomen, pelvis, or any other areas with suspected disease involvement, and CT or magnetic resonance (MR) imaging of the brain during Screening. For brain imaging, MR imaging without and with contrast is preferred and CT with contrast is acceptable if MR imaging is medically contraindicated. For each modality, intravenous (IV) and oral contrast should be utilized (chest CT does not require IV contrast) where applicable unless medically contraindicated.

Thereafter, tumor measurements and disease response assessments are to be performed as follows:

Radiographic disease assessment: [redacted]

Anatomical measurements (summed across target lesions) will be documented during Screening and each subsequent evaluation. When possible, the same qualified physician will interpret results to reduce variability. Test results and Investigator's findings will be filed in the patient's source documents.

During Screening, tumor lesions are to be categorized as measurable versus nonmeasurable and target versus nontarget, as follows:

Measurable versus nonmeasurable

- Measurable: Lesions that could accurately be measured in at least 1 dimension, the longest diameter in the plane of measurement to be recorded as:
    - Tumor lesions: ≥10 mm by CT scan;
    - Malignant lymph nodes: To be considered pathologically enlarged and measurable, the node must be ≥15 mm in short axis when assessed by CT scan. At baseline and in follow-up, only the short axis will be measured and followed. Nodes that have a short axis <10 mm are considered nonpathological and should not be recorded or followed.
- Nonmeasurable: All other lesions, including small lesions (longest diameter <10 mm or pathological lymph nodes with ≥10 to <15 mm short axis), and truly nonmeasurable lesions.

Target versus nontarget

- Target: All measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, representative of all involved organs, are to be identified as target lesions and measured and

recorded at Screening. Target lesions are to be selected on the basis of their size (ie, those with the longest diameter) and suitability for accurate repeated measurement. Lymph nodes may be selected as target lesions; they must be defined as measurable and only the short axis of the node will contribute to the baseline sum. All other pathologic nodes with short axis ≥10 mm but <15 mm should be considered nontarget lesions.

- Nontarget: All other lesions not classified as target lesions (or sites of disease) are to be identified as nontarget lesions and are to be recorded in the electronic Case Report Form (eCRF). Measurement of nontarget lesions is not required.

The sum of diameters (longest for non-nodal lesions and short axis for nodal lesions) for all target lesions is to be calculated and recorded in the eCRF as the baseline sum diameters.

Disease response in target and nontarget lesions will be assessed by the Investigator using RECIST 1.1, according to the categories and criteria described in Table 22 below. The best overall response for each patient will be reported as the best response documented over the sequence of objective statuses recorded using the categories and criteria in Table 22.

Table 22. Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 Guidelines for Tumor Response

Disease Response Criteria for Target and Non-Target Lesions	
Evaluation of target lesions	
Complete response	Disappearance of all target lesions. Any pathologic nodes (whether target or nontarget lesions) must have a reduction in SAD to <10 mm.
Partial response	At least a 30% decrease in the SOD (LD for non-nodal lesions and SAD for nodal lesions) of target lesions, taking as reference the baseline sum LD.
Stable disease	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for progressive disease, taking as reference the smallest sum LD since the treatment started.
Progressive disease	At least a 20% increase in the SOD of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest sum on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm (Note: The appearance of 1 or more new lesions is also considered progression).
Evaluation of non-target lesions	
Complete response	Disappearance of all nontarget lesions and normalization of tumor marker level.
Incomplete response/Stable disease	Persistence of 1 or more nontarget lesion(s) and/or maintenance of tumor marker level above the normal limits.
Progressive disease	Appearance of 1 or more new lesions and/or unequivocal progression of existing nontarget lesions.
LD = longest diameter; PR = partial response; SAD = short axis diameters; SOD = sum of the diameters. Source: Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). *Eur J Cancer*. 2009;45(2):228-247	

APPENDIX D: MODIFIED RESPONSE EVALUATION CRITERIA IN SOLID TUMORS 1.1 FOR IMMUNE-BASED THERAPEUTICS (IRECIST) QUICK REFERENCE

The principles used to establish objective tumor response are largely unchanged from Response Evaluation Criteria in Solid Tumors (RECIST) 1.1, but the major change for immune-RECIST (iRECIST) (ie, Modified Response Evaluation Criteria in Solid Tumors 1.1 for immune-based therapeutics) is the concept of resetting the bar if RECIST 1.1 progression is followed at the next assessment by tumor shrinkage. iRECIST define immune-unconfirmed progressive disease (iUPD) on the basis of RECIST 1.1 principles; however, iUPD requires confirmation, which is done on the basis of observing either a further increase in size (or in the number of new lesions) in the lesion category in which progression was first identified in (ie, target or nontarget disease), or progression (defined by RECIST 1.1) in lesion categories that had not previously met RECIST 1.1 progression criteria. However, if progression is not confirmed but instead tumor shrinkage occurs (compared with baseline), which meets the criteria of immune-complete response, immune-partial response, or immune-stable disease, then the bar is reset so that iUPD needs to occur again (compared with nadir values) and then be confirmed (by further growth) at the next assessment for immune-confirmed progressive disease to be assigned. If no change in tumor size or extent from iUPD occurs, then the time point response would again be iUPD. This approach allows atypical responses, such as delayed responses that occur after pseudo-progression, to be identified, further understood, and better characterized.

See Table 23 for a comparison between RECIST 1.1 and iRECIST.

Table 23 Comparison Between RECIST 1.1 and iRECIST

	RECIST 1.1	iRECIST
Definition of measurable and nonmeasurable disease; numbers and site of target disease	Measurable lesions are ≥10 mm in diameter (≥15 mm for nodal lesions); maximum of 5 lesions (2 per organ); all other disease is considered nontarget (must be ≥10 mm in short axis for nodal disease).	No change from RECIST 1.1; however, new lesions are assessed as per RECIST 1.1 but are recorded separately on the case report form (but not included in the sum of lesions for target lesions identified at baseline).
CR, PR, or SD	Cannot have met criteria for progression before CR, PR, or SD.	Can have had iUPD (1 or more instances), but not iCPD, before iCR, iPR, or iSD.
Confirmation of SD	Not required.	Not required.

Table 23Table 23 Comparison Between RECIST 1.1 and iRECIST (Continued)

	RECIST 1.1	iRECIST
New lesions	Result in progression; recorded but not measured.	New lesions should be assessed and categorized as measurable or nonmeasurable using RECIST 1.1. New lesions result in iUPD, but iCPD is only assigned on the basis of this category if at the next assessment, additional new lesions appear or an increase in size of new lesions is seen (≥5 mm for the sum of new lesion target or any increase in new lesion nontarget); the appearance of new lesions, when none have previously been recorded, can also confirm iCPD.
Confirmation of progression	Not required (unless equivocal).	The next imaging assessment should be performed at ≥4 weeks but ≤8 weeks after iUPD. Progression is confirmed if the next imaging assessment confirms a further increase in size of at least 5 mm in the lesion category in which progression was first identified, or progression in a lesion category that had not previously met RECIST 1.1 progression criteria, or development of new lesions. However, the criteria for iCPD (after iUPD) are not considered to have been met if iCR, iPR, or iSD criteria (compared with baseline and as defined by RECIST 1.1) are met at the next assessment after iUPD. The status is then reset and iCR, iPR, or iSD should be documented.
Consideration of clinical status	Not included in assessment.	Clinical stability is considered when deciding whether treatment is continued after iUPD.

CR = complete response; iCPD = immune-confirmed progressive disease; iCR = immune-complete response; iPR = immune-partial response; iRECIST = immune-Response Evaluation Criteria in Solid Tumors; iSD = immune-stable disease; iUPD = immune-unconfirmed progressive disease; PR = partial response; RECIST = Response Evaluation Criteria in Solid Tumors; SD = stable disease.

APPENDIX E: EXAMPLES OF SENSITIVE CLINICAL SUBSTRATES FOR P450-MEDIATED METABOLISM (FOR CONCOMITANT USE IN CLINICAL DDI STUDIES AND/OR LABELING)

Table 24. Examples of Sensitive Clinical Substrates for P450-Mediated Metabolism

	Sensitive Substrates
CYP1A2	alosetron, caffeine, duloxetine, melatonin, ramelteon, tasimelteon, tizanidine
CYP2B6	bupropion[aaa]
CYP2C8	repaglinide[bbb]
CYP2C9	celecoxib[ccc]
CYP2C19	S-mephenytoin, omeprazole
CYP2D6	atomoxetine, desipramine, dextromethorphan, eliglustat,[ddd] nebivolol, nortriptyline, perphenazine, tolterodine, R-venlafaxine
CYP3A	alfentanil, avanafil, buspirone, conivaptan, darifenacin, darunavir[eee], ebastine, everolimus, ibrutinib, lomitapide, lovastatin[fff], midazolam, naloxegol, nisoldipine, saquinavir[eee], simvastatin[fff], sirolimus, tacrolimus, tipranavir[eee], triazolam, vardenafil
	budesonide, dasatinib, dronedarone, eletriptan, eplerenone, felodipine, indinavir[eee], lurasidone, maraviroc, quetiapine, sildenafil, ticagrelor, tolvaptan

Note: Sensitive substrates are drugs that demonstrate an increase in AUC of ≥5-fold with strong index inhibitors of a given metabolic pathway in clinical DDI studies. Sensitive substrates of CYP3A with ≥10-fold increase in AUC by co-administration of strong index inhibitors are shown. Other elimination pathways may also contribute to the elimination of the substrates listed in the table above and should be considered when assessing the drug interaction potential.
This table was prepared to provide examples of clinical substrates and not intended to be an exhaustive list. DDI data were collected based on a search of the University of Washington Metabolism and Transport Drug Interaction Database (Source: Hachad H, Ragueneau-Mejlessi I, Levy RH, et al. A useful tool for drug interaction evaluation: the University of Washington Metabolism and Transport Drug Interaction Database. *Hum Genomics*. 2010;5[1]:1-12).
aaa. Listed based on an in vivo induction study and the observed effect might be partly attributable to induction of other pathway(s).
bbb. OATP1B1 substrate.
ccc. Listed based on pharmacogenetic studies.
ddd. Sensitive substrate of CYP2D6 and moderate sensitive substrate of CYP3A.
eee. Usually administered to patients in combination with ritonavir or cobicistat, strong CYP3A inhibitors.
fff. Acid form is an OATP1B1 substrate.
AUC = area under the concentration versus time curve; CYP = cytochrome P450; DDI = drug-drug interaction; OATP1B1 = organic anion transporting polypeptide 1B1.
Source: https://www.fda.gov/drugs/drug-interactions-labeling/drug-development-and-drug-interactions-table-substrates-inhibitors-and-inducers#table3-1

APPENDIX F: ANV419 SAFETY EVENTS

Table 25. Study ANV419-001: Drug Related Treatment Emergent Adverse Events

System Organ Class		Preferred Term	No Patients (%) N=34
		Any TEAE related to ANV419	**33 (97%)**
General Disorders and administration site conditions		**Pyrexia**	**25 (74%)**
		Chills	**21 (62%)**
		Asthenia	**7 (21%)**
		Fatigue	**6 (18%)**
		Malaise	**3 (9%)**
		Hot flush	**1 (3%)**
		Lethargy	**1 (3%)**
		Oedema peripheral	**1 (3%)**
		Temperature regulation disorder	**1 (3%)**
Gastrointestinal disorders		**Vomiting**	**12 (35%)**
		Nausea	**11 (32%)**
		Diarrhea	**4 (12%)**
		Abdominal discomfort	**1 (3%)**
		Abdominal pain	**1 (3%)**
		Abdominal pain upper	**1 (3%)**
		Colitis	**1 (3%)**
		Dyspepsia	**1 (3%)**
		Dysphagia	**1 (3%)**
		Flatulence	**1 (3%)**
		Gastro-esophageal reflux disease	**1 (3%)**
Investigations		**Alanine aminotransferase increased**	**6 (18%)**
		Aspartate aminotransferase increased	**6 (18%)**
		Blood bilirubin increased	**6 (18%)**
		Blood creatinine increased	**2 (6%)**
		Blood alkaline phosphatase increased	**1 (3%)**
		C-reactive protein increased	**1 (3%)**
		Gamma-glutamyl transferase increased	**1 (3%)**
		Platelet count decreased	**1 (3%)**
		Decreased appetite	**7 (21%)**

Metabolism and nutrition disorders		**Hyponatremia**	**1 (3%)**
		Dehydration	**1 (3%)**
		Hypocalcemia	**1 (3%)**
Skin and subcutaneous tissue disorders		**Rash maculo-papular**	**4 (12%)**
		Pemphigoid	**1 (3%)**
		Hyperhidrosis	**1 (3%)**
		Rash	**1 (3%)**
Immune system disorders		**Cytokine release syndrome**	**8 (24%)**
Blood and lymphatic system disorders		**Lymphopenia**	**3 (9%)**
		Anemia	**2 (6%)**
		Thrombocytopenia	**2 (6%)**
		Neutropenia	**1 (3%)**
Musculoskeletal and connective tissue disorders		**Myalgia**	**4 (12%)**
		Back pain	**1 (3%)**
		Pain in extremity	**1 (3%)**
Renal and urinary disorders		**Cystitis noninfective**	**2 (6%)**
		Dysuria	**1 (3%)**
Vascular disorders		**Hypotension**	**4 (12%)**
Infections and infestations		**Rash pustular**	**2 (6%)**
Nervous system disorders		**Hypoesthesia**	**1 (3%)**
		Peripheral sensory neuropathy	**1 (3%)**
Respiratory, thoracic and mediastinal disorders		**Dyspnea**	**1 (3%)**
		Pleural effusion	**1 (3%)**

APPENDIX G: EASTERN COOPERATIVE ONCOLOGY GROUP PERFORMANCE STATUS

Table 26. ECOG Performance Status

Grade	Descriptions
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light sedentary nature (eg, light housework, office work).
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead.

ECOG = Eastern Cooperative Oncology Group.
Source: Oken MM, Creech RH, Tormey DC, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. *Am J Clin Oncol*. 1982;5(6):649-655