CLINICAL PROTOCOL	
Title:	A PHASE 1B DOSE-ESCALATION STUDY OF CAROTUXIMAB IN COMBINATION WITH NIVOLUMAB IN PATIENTS WITH METASTATIC NON-SMALL CELL LUNG CANCER
Protocol Number:	105LC102
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Signature & Date:	Signed: _____ Print: C Theuer Dated: 17 APR 2018
Version Date:	Original Protocol: 03 May 2017 Amendment #1: 19 July 2017 Amendment #2: 05 April 2018

Statement of Confidentiality:

PROCEDURES IN CASE OF EMERGENCY

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1. SYNOPSIS

Name of Sponsor/Company: TRACON Pharmaceuticals, Inc.	
Name of Investigational Product: Carotuximab (also known as TRC105)	
Name of Active Ingredient: Carotuximab	
Title of Study: A PHASE 1B DOSE-ESCALATION STUDY OF CAROTUXIMAB IN COMBINATION WITH NIVOLUMAB IN PATIENTS WITH METASTATIC NON-SMALL CELL LUNG CANCER	
Study center(s): This study will be performed at up to 3 United States centers	
Principal Investigator: Dr. Francisco Robert	
Studied period: Date first patient enrolled: November 2017 Estimated date endpoint obtained: January 2019 Estimated date last patient completed: June 2019 Total number of estimated patients: 30-42 Estimated duration of treatment per patient: 4 months	**Phase of Development:** 1b
Rationale: Nivolumab is an antibody that binds the programmed death receptor 1 (PD-1) and promotes anti-cancer immunity by inhibiting regulatory T-cell function to sensitize tumors to immune surveillance. Nivolumab is approved for the treatment of metastatic non-small cell lung cancer (NSCLC) that has progressed following platinum-based chemotherapy, based on improved overall survival versus docetaxel in squamous cell non-small cell lung cancer (NSCLC) (median overall survival [OS] of 9.2 months versus 6.0 months, respectively) and in non-squamous NSCLC (median OS of 12.2 versus 9.4 months). The overall response rate (ORR) in this setting is 15% to 20%. Carotuximab is an investigational antibody to endoglin, a receptor expressed on proliferating endothelial cells and myeloid derived suppressor cells (MDSCs). MDSCs also inhibit anti-cancer immunity, but by a mechanism of action that is distinct from that inhibited by nivolumab. Carotuximab inhibits tumor growth in preclinical models and complements the activity of antibodies that target the PD-1 pathway. Carotuximab has been studied in more than 500 cancer patients and is tolerable as a single agent and when combined with chemotherapy or inhibitors of the vascular endothelial growth factor (VEGF) pathway. Its toxicity profile is distinct from that of nivolumab. By targeting MDSCs, carotuximab has the potential to complement nivolumab and improve clinical efficacy over that seen with single agent nivolumab.	
Objectives: <u>Primary:</u> • To evaluate safety and tolerability and determine a recommended Phase 2 dose (RP2D) for carotuximab when added to standard dose nivolumab in patients with metastatic NSCLC	

Secondary:

- To assess preliminary evidence of antitumor activity when carotuximab is added to nivolumab, by assessing response rate and progression-free survival including in patients who have not been treated previously with a PD-1/PD-L1 checkpoint inhibitor and have histological disease recurrence or progression during or after prior platinum-containing doublet chemotherapy regimen (Expansion Cohort 1) or have relapsed following prior treatment with a PD-1/PD-L1 checkpoint inhibitor (Expansion Cohort 2).
- To characterize the pharmacokinetic profile of carotuximab when given with nivolumab
- To evaluate the formation of carotuximab anti-product antibodies (APA)

Exploratory:

- To explore effects of carotuximab and nivolumab on tumor immune effector cells

Methodology:

This is a multicenter, open-label, nonrandomized, Phase 1b, dose-escalation study of carotuximab in combination with standard dose nivolumab in patients with metastatic NSCLC. Beginning with Dose Level 1, standard dose nivolumab will be given every two weeks of recurring 28 day cycles starting on Cycle 1 Day 1 (C1D1). Carotuximab will be administered weekly for 4 weeks and then given every 2 weeks, in combination with nivolumab, starting on C1D1.

Dose Level	Number of evaluable patients	Carotuximab mg/kg IV weekly[a] starting C1D1 for 4 doses and then every 2 weeks	Nivolumab IV every 2 weeks starting C1D1
-1	3-6	6 mg/kg weekly through Cycle 1 → 15 mg/kg every 2 weeks	240 mg
1 (starting dose)	3-6	8 mg/kg weekly through Cycle 1 → 15 mg/kg every 2 weeks	240 mg
2	3-6	10 mg/kg weekly through Cycle 1 → 15 mg/kg every 2 weeks	240 mg
Expansion Cohort 1[b]	Up to 12	Maximum tolerated dose (MTD)	240 mg
Expansion Cohort 2[c]	Up to 12	Maximum tolerated dose (MTD)	240 mg

[a]The first weekly carotuximab dose will be split into 2 doses whereby 3 mg/kg is administered on Cycle 1 Day 1 (C1D1) and the balance is administered on Cycle 1 Day 4.

[b]Expansion Cohort 1: Patients who have not been treated previously with a PD-1/PD-L1 checkpoint inhibitor and have histological disease recurrence or progression during or after prior platinum-containing doublet chemotherapy regimen.

[c]Expansion Cohort 2: Patients who have relapsed following prior treatment with a PD-1/PD-L1 checkpoint inhibitor without Grade 3 immune-related toxicity.

The dose-limiting toxicity (DLT) evaluation period will be the first 4 weeks (28 days) of combination therapy dosing. Each cycle will be 4 weeks (28 days) in duration.

Three patients will be initially enrolled and treated at each dose level. If none of these 3 patients experiences a DLT during the initial 28-day evaluation period of combination dosing, dose escalation will proceed following review of safety data with the study principal Investigators.

If 1 of 3 patients experiences a DLT, the dose level will be expanded to 6 patients. The maximum tolerated dose (MTD) will have been exceeded if ≥ 33% of patients experience DLT at a given dose level where at least 6 patients have been evaluated (including the expansion cohorts). DLT will have

occurred when a patient has 1 or more toxicities listed in the table below that is at least possibly related to nivolumab or carotuximab during the first 28 days of combination therapy. Patients who exit the study for reasons other than DLT prior to completion of the 28-day DLT evaluation period will be replaced to ensure an adequate safety assessment in each cohort. Patients who experience DLT who receive less than the prescribed dose of carotuximab or nivolumab due to documented toxicity during the DLT evaluation period will be considered evaluable for dose escalation purposes. A given carotuximab dose level may be reenrolled at an intermediate dose level upon agreement of study Investigators.

Toxicity Category	Drug-Related Toxicity/Grade
Hematologic	Grade 4 neutropenia for ≥5 days
	Febrile neutropenia: Grade 4 neutropenia with fever >38.5ºC both sustained over a ≥24-hour period
	Neutropenic infection: Grade ≥3 neutropenia with Grade ≥3 infection
	Grade ≥4 Anemia
	Grade ≥4 thrombocytopenia or Grade ≥3 thrombocytopenia with Grade ≥3 hemorrhage
Nonhematologic	Grade 3 or 4 nonhematologic toxicity with the following exceptions: • Asymptomatic electrolyte abnormality that is corrected to Grade 1 or better in <72 hours • Grade 3 headache lasting <48 hours
Immune related	Grade 3 pneumonitis, Grade 3 colitis, AST or ALT >5 times the upper limit of normal or total bilirubin >3 times the upper limit of normal, Grade 3 hypophysitis, Grade 3 adrenal insufficiency, serum creatinine >3 times baseline, encephalitis of any grade, type 1 diabetes mellitus with Grade 4 hyperglycemia, Grade 4 rash or suspected Stevens-Johnson syndrome or toxic epidermal necrolysis

Upon determination of the MTD, up to 24 additional patients will be enrolled (up to 12 in each cohort) into Expansion Cohorts 1 and 2.

The study will be terminated for Grade ≥ 3 infusion related reactions occurring in ≥ 33% of 6 or more patients in the expansion cohorts.

Number of Patients (planned):

Approximately 30 to 42 patients with metastatic NSCLC will be enrolled in the study.

Diagnosis and Main Criteria for Inclusion:

Inclusion Criteria:

1. Histologically confirmed metastatic non-small cell lung cancer (NSCLC) with disease recurrence or progression during or after prior platinum-containing doublet chemotherapy regimen (for dose escalation portion and, if not previously treated with a PD-1/PD-L1 checkpoint inhibitor, for Expansion Cohort 1).

2. Histologically confirmed metastatic non-small cell lung cancer (NSCLC) that has relapsed following prior PD-1/PD-L1 checkpoint inhibitor therapy without Grade 3 immune-related toxicity, which may or may not have included concurrent chemotherapy (for dose escalation and Expansion Cohort 2). Relapse following prior PD-1 checkpoint therapy is defined as confirmed progressive disease following stable disease or better (e.g., iSD, iPR, iCR) on at least 1 tumor assessment.
3. Patients with an active oncogenic driver (e.g., epidermal growth factor [EGFR], activin-receptor-like kinase 1 [ALK1], or the proto-oncogene tyrosine-protein kinase ROS-1) must have progressed on or after a US Food and Drug Administration (FDA)-approved therapy for that aberration. (Note: Previous treatment with a tyrosine kinase inhibitor and platinum-based doublets does not exclude the patient.)
4. Patients who received adjuvant or neoadjuvant platinum-doublet chemotherapy (after surgery and/or radiation therapy) and developed recurrent or metastatic disease within 6 months of completing therapy are eligible.
5. Patients with recurrent disease > 6 months after adjuvant or neoadjuvant platinum-based chemotherapy, who also subsequently progressed during or after a platinum- doublet regimen given to treat the recurrence, are eligible.
6. Formalin fixed, paraffin-embedded (FFPE) tumor tissue block that permits the preparation of 20 unstained slides of tumor sample (archival) - Biopsy must be excisional, incisional, or core. Needle aspiration is insufficient. In cases where archival tumor tissue is unavailable, tumor biopsy will be required prior to treatment initiation.
7. Programmed death ligand 1 (PD-L1) determination by validated immunohistochemistry assay (i.e., PD-L1 (SP142) CDX (Ventana) or PD-L1 IHC 22C3 PharmDx (Dako) or PD-L1 IHC 28-8 PharmDx (Dako) assay). Any PD-L1 score is acceptable including tumor proportion score (TPS) of 0.
8. Measurable disease by iRECIST
9. Age ≥ 18 years
10. Eastern Cooperative Oncology Group (ECOG) performance status ≤ 1
11. Resolution of all acute adverse events resulting from prior cancer therapies to National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) Grade ≤ 1 or baseline (except alopecia or neuropathy)
12. Adequate organ function as defined by the following criteria:

    a) Serum aspartate transaminase (AST; serum glutamic oxaloacetic transaminase [SGOT]) and serum alanine transaminase (ALT; serum glutamic pyruvic transaminase [SGPT]) ≤ 2.5 times upper limit of normal (ULN) or ≤ 5 times ULN in cases of liver metastases

    b) Total serum bilirubin ≤ 1.5 times the ULN

    c) Absolute neutrophil count (ANC) ≥ 1500/μL

    d)Platelets ≥ 100,000/μL without transfusion support within 28 days prior to study treatment

e) Hemoglobin ≥ 9.0 g/dL without transfusion support within 14 days prior to study treatment (erythropoietin or darbepoetin permitted)

f) Serum creatinine ≤ 1.5 times the ULN or creatinine clearance > 30 mL/min by Cockcroft-Gault formula

g) International normalized ratio (INR) from 0.8 to 1.2

13. Willingness and ability to consent for self to participate in study
14. Willingness and ability to comply with scheduled visits, treatment plan, laboratory tests, and other study procedures

Exclusion Criteria:

1. Autoimmune disease requiring treatment within the past twelve months (Note: Vitiligo, type 1 diabetes mellitus, residual hypothyroidism due to autoimmune thyroiditis only requiring hormone replacement, and conditions not expected to recur in the absence of an external trigger are permitted.)
2. Condition requiring systemic treatment with either corticosteroids (>10 mg daily prednisone equivalent) or other immunosuppressive medications within 14 days prior to study treatment (Note: Inhaled and topical steroids, and adrenal replacement steroid doses > 10 mg daily prednisone equivalent, are permitted in the absence of active autoimmune disease.)
3. History or active interstitial lung disease
4. Prior therapy with T-cell therapy, including an immune checkpoint inhibitor. Patients who received prior immune checkpoint inhibitor therapy are allowed in Expansion Cohort 2 in the absence of recurrent grade 2 (except skin, endocrine and constitutional symptoms), or ≥ 3 immune-related toxicity.
5. Prior treatment with carotuximab
6. Current treatment on another therapeutic clinical trial
7. Receipt of systemic anticancer therapy, including investigational agents, within 28 days prior to study treatment (Note: If anticancer therapy was given within 28 days prior to starting study treatment, patients are not excluded if ≥ 5 times the elimination half-life of the drug has elapsed.)
8. Major surgical procedure or significant traumatic injury within 4 weeks prior to study treatment, and must have fully recovered from any such procedure; and no date of surgery (if applicable) or anticipated need for a major surgical procedure planned within the next 6 months (Note: The following are not considered to be major procedures and are permitted up to 7 days prior to study treatment: Thoracentesis, paracentesis, port placement, laparoscopy, thorascopy, tube thoracostomy, bronchoscopy, endoscopic ultrasonographic procedures, mediastinoscopy, skin biopsies, incisional biopsies, imaging-guided biopsy for diagnostic purposes, and routine dental procedures.)
9. Chest radiotherapy ≤ 28 days, wide field radiotherapy ≤ 28 days (defined as > 50% of volume of pelvic bones or equivalent), or limited field radiation for palliation ≤ 14 days prior to study

treatment - Such patients must have recovered adequately from any side effects of such therapy.

10. Hypertension defined as blood pressure (BP) systolic > 150 or diastolic > 90 mm Hg (Note: Initiation or adjustment of antihypertensive medication prior to study entry is allowed provided that the average of 3 BP readings prior to study treatment is ≤150/90 mm Hg.)
11. Ascites or pericardial effusion that required intervention within 3 months prior to study treatment
12. History of brain involvement with cancer, spinal cord compression, or carcinomatous meningitis, or new evidence of brain or leptomeningeal disease (Note: Patients with radiated or resected lesions are permitted, provided the lesions are fully treated and inactive, patients are asymptomatic, and no steroids have been administered for CNS disease over the 7 days prior to study treatment)
13. Angina, myocardial infarction (MI), symptomatic congestive heart failure, cerebrovascular accident, transient ischemic attack TIA), arterial embolism, pulmonary embolism, percutaneous transluminal coronary angioplasty (PTCA), or coronary artery bypass grafting (CABG) within 6 months prior to study treatment
14. Deep venous thrombosis within 6 months prior to study treatment, unless the patient is anti-coagulated without the use of warfarin for ≥2 weeks prior to study treatment; in this situation, low molecular weight heparin is preferred
15. Active bleeding or pathologic condition that carries a high risk of bleeding (e.g., hereditary hemorrhagic telangiectasia)
16. Thrombolytic use (except to maintain IV catheters) within 10 days prior study treatment
17. Known active viral or nonviral hepatitis or cirrhosis
18. Any active infection requiring systemic treatment
19. History of hemorrhage or hemoptysis (> ½ teaspoon bright red blood) within 3 months prior to study treatment
20. History of peptic ulcer within the past 3 months prior to study treatment, unless treated for the condition and complete resolution has been documented by esophagogastroduodenoscopy (EGD) within 28 days prior to study treatment
21. History of gastrointestinal perforation or fistula in the 6 months prior to study treatment, or while previously on antiangiogenic therapy, unless underlying risk has been resolved (e.g., through surgical resection or repair)
22. Known human immunodeficiency virus (HIV) or acquired immunodeficiency syndrome (AIDS) related illness.
23. Pregnancy or breastfeeding - Female patients must be surgically sterile (i.e., ≥6 weeks following surgical bilateral oophorectomy with or without hysterectomy or tubal ligation) or be postmenopausal, or must agree to use effective contraception during the study and for 3 months following last dose of carotuximab. All female patients of reproductive potential must have a negative pregnancy test (serum or urine) within 7 days prior to study treatment.

Male patients must be surgically sterile or must agree to use effective contraception during the study and for 3 months following last dose of carotuximab. The definition of effective contraception is provided in Section 2.6.1 of this protocol.

24. Other severe acute or chronic medical or psychiatric condition or laboratory abnormality that may increase the risk associated with study participation or may interfere with the interpretation of study results and, in the judgment of the Investigator, would make the patient inappropriate for this study

Carotuximab Investigational Product Dose and Administration:

Dosing will begin at 8 mg/kg weekly for 4 doses followed by 15 mg/kg every other week (Dose Level 1) with the first dose administered on C1D1. Following the appropriate premedication regimen, the initial carotuximab dose (C1D1) will be split into 2 doses whereby 3 mg/kg is administered on C1D1 and the balance (e.g., 5 mg/kg for Dose Level 1) is administered on Cycle 1 Day 4. Beginning with Cycle 1 Day 8 and thereafter, the full (e.g., 8 mg/kg for Dose Level 1) carotuximab dose will be administered IV weekly until completion of the Cycle 1. Dosing will then transition to 15 mg/kg every 2 weeks starting with Cycle 2 Day 1 (C2D1). Dose reductions are allowed beginning in Cycle 2.

Nivolumab Dose and Administration:

Nivolumab will be administered IV at 240 mg beginning on C1D1 and every 2 weeks thereafter, in the absence of toxicity. Dose modifications are allowed according to the nivolumab package insert.

Duration of Treatment:

Patients are eligible for treatment until disease progression, unacceptable toxicity, or withdrawal of consent, or other reasons. A patient should be withdrawn from study treatment if, in the opinion of the Investigator, it is medically necessary, or if it is the wish of the patient. In addition, patients will be withdrawn from treatment in the case of:

1. iRECIST - defined disease progression
2. A need for surgery, radiation, or for other anticancer therapy not permitted by this protocol
3. Lost to follow-up or noncompliant with the protocol
4. Any carotuximab dose delay > 2 days during the 28 day DLT evaluation period (i.e., Cycle 1)
5. Dose delay such that the patient receives neither study drug for ≥ 8 consecutive weeks
6. Pregnancy - Pregnant patients should be followed for the duration of the pregnancy and the outcome of the pregnancy should be documented.
7. Arterial thrombosis of any grade (including cerebrovascular ischemia, cardiac ischemia/infarction, or peripheral or visceral arterial ischemia) or Grade 3 or 4 venous thrombosis (including pulmonary embolism)
8. Grade > 3 pneumonitis, any Grade 4 toxicity including colitis, AST or ALT > 5 times the ULN or total bilirubin > 3 times the ULN, Grade 4 hypophysitis that cannot be controlled with endocrine replacement therapy, Grade > 3 adrenal insufficiency that cannot be controlled with endocrine replacement therapy, Grade > 3 nephritis with serum creatinine > 3 times the ULN, encephalitis of any grade, type 1 diabetes mellitus with Grade 4 hyperglycemia, Grade > 3 infusion-related reactions, Grade 4 rash or suspected Stevens-Johnson syndrome or toxic epidermal necrolysis, any Grade > 3 non-hematologic treatment-related toxicity that recurs, any Grade 2 or 3 immune related toxicity that

persists despite treatment modifications or corticosteroid treatment that cannot be reduced to 10 mg of prednisone or equivalent per day within 12 weeks

Parameters to be Assessed:

Safety:

Safety assessments will include physical examinations, vital signs, ECOG performance status, laboratory tests (complete blood counts [CBC] and serum chemistry), 12-lead electrocardiograms (ECGs), and additional studies as may be clinically indicated.

Pharmacokinetics:

Serum carotuximab and nivolumab concentrations will be measured using validated methods at the time points specified in the Schedule of Events.

Immunogenicity:

Carotuximab anti-product antibodies (APA) will be measured using validated methods at time points specified in the Schedule of Events.

Exploratory Biomarkers:

Optional tumor biopsies from prior to study start and on study for PD-L1 tumor expression and T-cell and MDSC content will be assessed.

Efficacy:

iRECIST will be applied to assess response and progression.

Statistical Methods:

The study analysis population for safety and efficacy of carotuximab includes all patients receiving at least a portion of 1 dose of carotuximab.

The number of patients to be enrolled in this study will depend upon the observed safety profile, which will determine the number of patients per dose level and the number of dose escalations. It is anticipated that a total of 18 to 30 patients will be enrolled in this study.

The probability of escalation to the next higher dose for each underlying true DLT rate is shown in the table below. For example, for a toxicity that occurs in 5% of patients, there is a > 95% probability of escalating. Conversely, for a more common toxicity that occurs with a rate of 70%, the probability of escalating is < 5%.

Probability of Escalation to the Next Dose by True Underlying DLT Rate at a Dose Level

True Underlying DLT Rate	5%	10%	20%	30%	40%	50%	60%	70%	80%	90%
Probability of Escalating Dose	0.97	0.91	0.71	0.49	0.31	0.17	0.08	0.03	0.01	0.001

The probability of failing to observe a toxicity in a sample size of 3 or 6 patients given various true underlying toxicity rates in shown is the table below. For example, with 6 patients, the probability of failing to observe toxicity occurring at least 40% of the time is <5%.

Probability of Failing to Observe True Underlying DLT Rate by Sample Size

Probability of Failing to Observe Toxicity	True Underlying DLT Rate									
	5%	10%	20%	30%	40%	50%	60%	70%	80%	90%
N=3	0.86	0.73	0.51	0.34	0.22	0.13	0.006	0.027	0.008	0.001
N=6	0.74	0.53	0.26	0.12	0.05	0.016	0.004	<0.001	<0.001	<0.001

The MTD will have been exceeded if ≥ 33% of patients experience DLT at a given dose level at which ≥ 6 patients have been evaluated.

Descriptive statistics (such as means, medians, standard deviations, and ranges for continuous data and percentages for categorical data) will be used to summarize patient characteristics, treatment administration/compliance, immunogenicity, efficacy, pharmacokinetic parameters, protein biomarkers, and archival tumor tissue. Data will also be displayed graphically, where appropriate. Adverse events (AEs) and DLTs will be summarized by category (hematologic and non-hematologic) and by Medical Dictionary for Regulatory Activities (MedDRA) Preferred Term (PT) and System Organ Class (SOC). The number and percentage of patients with the following types of treatment-emergent AEs will be summarized: all AEs, all serious AEs, AEs related to study drug (carotuximab and nivolumab), AEs resulting in study drug discontinuation, and clinically significant laboratory abnormalities. Trough (pre-dose) serum carotuximab and nivolumab concentrations will be measured using validated methods. The carotuximab pharmacokinetic data may be assessed for potential correlations with response, progression-free survival (PFS), survival, AEs, and baseline characteristics using descriptive statistics and models as appropriate. The best response to iRECIST for each patient with measurable disease who received at least 1 dose of study drug will be listed by cohort. At least 3 responses out of 12 evaluable patients in Expansion Cohort 1 and at least 1 response out of 12 evaluable patients in Expansion Cohort 2 will be required to further evaluate the combination of TRC105 and nivolumab in these respective patient populations(s). Anti-product antibody (APA) to carotuximab concentrations will be measured at the time points specified.

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Table 2: Abbreviations and Specialist Terms

Abbreviation or Specialist Term	Explanation
ADCC	Antibody-dependent T-cell-mediated cytotoxicity
ADR	Adverse drug reaction
AE	Adverse event
AFP	Alpha fetoprotein
AIDS	Acquired immune deficiency syndrome
ALK	Activin receptor-like kinase
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
APA	Anti-product antibody
AST	Aspartate aminotransferase
BP	Blood pressure
CABG	Coronary Artery Bypass Graft
CBC	Complete blood count
CD	Cluster of differentiation antigen
iCR	Immune Complete response
CRF	Case report form
iCPD	Immune Confirmed progressive disease
CT	Computed tomography
CTA	Clinical Trials Agreement
CTCAE	Common Terminology Criteria for Adverse Events
CxDx	Cycle x Day x
DEHP	Diethylhexyl-phthalate
dL	Deciliter
DLT	Dose-limiting toxicity
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
EDTA	Ethylenediaminetetraacetic acid
EGD	Esophagogastroduodenoscopy
EGFR	Epidermal growth factor receptor
ELISA	Enzyme-linked immunosorbent assay
EOS	End of study
EOT	End of treatment
FDA	Food and Drug Administration
Fe	Iron studies
FFPE	Formalin fixed, paraffin-embedded
g	Gram
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act
HIV	Human immunodeficiency virus
HRA	Health Regulatory Authority
IB	Investigational Brochure
ICH	International Council on Harmonization
IEC	Independent ethics committee
IgG	Immunoglobulin G

IHC	Immunohistochemistry
IM	Intramuscular
INR	International normalized ratio
IRB	Institutional review board
IUD	Intra-uterine device
IV	Intravenous
kDa	KiloDalton
kg	Kilogram
L	Liter
µL	Microliter
mg	Milligram
mL	Milliliter
MDSC	Myeloid derived suppressor cell
MedDRA	Medical Dictionary for Regulatory Activities
min	Minute
mm	Millimeter
mm Hg	Millimeters of mercury
MRI	Magnetic resonance imaging
ms	Millisecond
MTD	Maximum tolerated dose
NCI	National Cancer Institute
ng	Nanogram
NSAID	Nonsteroidal anti-inflammatory drug
NSCLC	Non-small cell lung cancer
ORR	Overall response rate
OS	Overall survival
PET	Positron emission tomography
PFS	Progression-free survival
PlGF	Placental growth factor
PD-1	Programmed death receptor 1
PD-L1,PD-L2	Programmed death receptor ligands
PK	Pharmacokinetic
pM	Picomolar
PR	Partial response
PT	Preferred Term for adverse event in MedDRA
PTCA	Percutaneous transluminal coronary angioplasty
PUD	Peptic ulcer disease
QA	Quality assurance
iRECIST	Immune Response Evaluation Criteria in Solid Tumors
ROS-1	Proto-oncogene tyrosine-protein kinase
RP2D	Recommended Phase 2 dose
SAE	Serious adverse event
sCD105	Soluble CD105/endoglin
SCID	Severe combined immunodeficient
SCLC	Small cell lung cancer
iSD	Stable disease
SGOT	Serum glutamic oxaloacetic transaminase
SGPT	Serum glutamic pyruvic transaminase

SOC	Systemic Organ Class in MedDRA
SOP	Standard operating procedure
SN6j	Murine parent antibody of carotuximab (also known as TRC105)
TGF	Transforming growth factor
TIA	Transient ischemia attack
TPS	Tumor proportion score
TSH	Thyroid stimulating hormone
ULN	Upper limit of normal
UPCR	Urine protein-creatinine ratio
iUPD	Immune Unconfirmed progressive disease
US	United States of America
VEGF	Vascular endothelial growth factor

2. BACKGROUND

2.1. Non-Small Cell Lung Cancer (NSCLC)

Advanced non-small cell lung cancer (NSCLC) has been historically difficult to treat, and novel agents that are safe and effective are in dire need. Prognosis is poor, with 1-year survival rates ranging from 30% to 40%. Two-drug platinum-based chemotherapy regimens have long been the traditional treatment of choice, but a plateau effect is inevitably reached and survival is approximately 8 months regardless of regimen administered [1, 2].

The addition of bevacizumab (Avastin®), a vascular endothelial growth factor (VEGF) inhibitor, improves the overall survival (OS) of patients with non-squamous NSCLC when dosed with a platinum doublet as evidenced in a study that demonstrated an overall survival advantage of 2 months in the bevacizumab arm (12.3 months vs 10.3 months, respectively) [3]. The rates of clinically significant bleeding were slightly increased in the bevacizumab group (4.4% vs 0.7%). This trial study led to the standardization of paclitaxel, carboplatin, and bevacizumab as the preferred first-line therapy for patients with advanced non-squamous NSCLC. Subsequently, the AVAiL (Avastin in Lung) study confirmed the progression-free survival (PFS) benefit of adding bevacizumab to first-line cisplatin/gemcitabine, although an OS advantage was not demonstrated [4]. Bevacizumab is approved by the United States (US) Food and Drug Administration (FDA) for a number of indications, including NSCLC with carboplatin and paclitaxel for first-line treatment of unresectable, locally advanced, recurrent, or metastatic disease. Currently, the regimen of carboplatin, paclitaxel, and bevacizumab followed by maintenance bevacizumab remains the standard first-line therapy for patients with advanced NSCLC.

Nivolumab (Opdivo®) is an a human monoclonal antibody that binds the programmed death receptor 1 (PD-1) and blocks its interaction with its ligands, programmed death receptor ligands PD-L1 and PD-L2, promoting anti-cancer immunity by inhibiting regulatory T-cell function to sensitize tumors to immune surveillance. Nivolumab is approved by the FDA for a number of indications, including the treatment of metastatic NSCLC that has progressed following on or after platinum-based chemotherapy (patients with epidermal growth factor receptor [EGFR] or activin receptor-like kinase [ALK] genomic tumor aberrations should have had disease progression on FDA-approved therapy for these aberrations), based on improved OS versus docetaxel in squamous NSCLC (median 9.2 months versus 6.0 months) and in non-squamous NSCLC (median OS 12.2 versus 9.4 months) (nivolumab package insert). The overall response rate (ORR) in this setting is 15% to 20%.

Pembrolizumab (Keytruda®) is another human monoclonal antibody that binds PD-1 that is approved for the patients with NSCLC. Pembrolizumab is approved in three settings in NSCLC: for the first-line treatment of patients with metastatic NSCLC whose tumors have high PD-L1 expression (Tumor Proportion Score (TPS) ≥ 50%), as a single agent for the treatment of patients with metastatic NSCLC whose tumors express PD-L1 (TPS ≥ 1%) with disease progression on or after platinum-containing chemotherapy, and in combination with pemetrexed and carboplatin, as first-line treatment of patients with metastatic nonsquamous NSCLC. Patients

with EGFR or ALK genomic tumor aberrations should have disease progression on FDA-approved therapy for these aberrations prior to receiving pembrolizumab (see package insert).

2.2. Endoglin and Tumor Immunity

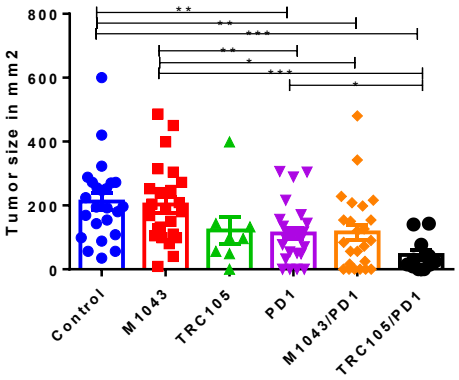
Endoglin (CD105) is a homodimeric cell membrane glycoprotein that was initially identified as a human leukemia-associated antigen [5] and later also found to be densely expressed on endothelial cells [6, 7]. Endoglin is a transforming growth factor beta (TGF-β) coreceptor that is essential for angiogenesis [8, 9] and is strongly expressed on the proliferating vascular endothelium of solid tumors [7, 10]. The essential nature of endoglin is underscored by developmental abnormalities observed in endoglin -/- homozygous mice, including absent vasculature and mortality *in utero*. Endoglin is highly expressed on angiogenic vasculature. Preclinical models of cancer indicate substantial activity for endoglin antibodies as monotherapy, in combination with cytotoxic chemotherapies, and in combination with VEGF inhibitors. Endoglin antibodies also inhibit angiogenesis in a standard murine model of choroidal neovascularization. Endoglin is also expressed on activated myeloid derived suppressor cells (MDSCs) [11], a cell type that inhibits cancer immunity by a mechanism of action that is distinct from that inhibited by immune checkpoint inhibitor nivolumab. In preclinical models, the endoglin antibody carotuximab inhibits tumor growth and complements the activity of antibody that targets the PD-1 pathway.

Carotuximab was studied in a syngeneic tumor model, wherein MC38 colorectal cancer cells were implanted orthotopically in the large intestine of mice, prior to treatment with isotype control antibody, PD-1 antibody, endoglin antibody M1043, endoglin antibody carotuximab or the combination of endoglin and PD-1 antibodies. MC38 tumors were grown in a subcutaneous donor C57/BL6 mice and then harvested, and divided into pieces of ~ 1 mm^3 that were transplanted to the cecum of recipient C57/BL6 mice. Eight days following tumor transplantation, mice were randomized based on bioluminescent signal and treatment was started and continued for 4 weeks, at which time mice were sacrificed and tumor volume was determined.

As shown in Figure 1, the combination of carotuximab and PD-1 antibody inhibited tumor growth that was statistically superior to isotype control antibody and to single-agent PD-1 antibody treatment ($p = 0.0002$ and $p = 0.025$, respectively). Notably, when combined with PD-1 antibody, the endoglin antibody carotuximab was more effective than M1043, which was consistent with the superior antibody-dependent T-cell-mediated cytotoxicity (ADCC) activity of the carotuximab towards endoglin expressing cells in this mouse model.

In clinical trials of carotuximab in bladder cancer patients as well as prostate cancer patients, carotuximab decreased T regulatory cells among CD4-positive T cells in the peripheral blood [12]. As well, carotuximab therapy increased PD-1 expression on peripheral blood CD8-postivie T cells [13] These immunomodulatory effects would be expected to complement a therapy targeting the PD-1 axis. In sum, by targeting MDSCs, carotuximab has the potential to complement nivolumab and improve clinical efficacy over that seen with single-agent nivolumab.

Figure 1: Colorectal Cancer Syngeneic Tumor Model Treated with Endoglin Antibody and PD-1 Antibody



Control vs. M1043	ns	0,1917
Control vs. TRC105	ns	0,0843
Control vs. PD1	**	0,0018
Control vs. M1043/PD1	**	0,0090
Control vs. TRC105/PD1	***	0,0002
M1043 vs. TRC105	ns	0,1165
M1043 vs. PD1	**	0,0041
M1043 vs. M1043/PD1	*	0,0170
M1043 vs. TRC105/PD1	***	0,0003
TRC105 vs. PD1	ns	0,8034
TRC105 vs. M1043/PD1	ns	0,9001
TRC105 vs. TRC105/PD1	ns	0,076
PD1 vs. M1043/PD1	ns	0,9056
PD1 vs. TRC105/PD1	*	0,0250
M1043/PD1 vs. TRC105/PD1	ns	0,0730

2.3. Carotuximab Background

Carotuximab is a genetically engineered human/murine chimeric monoclonal antibody directed against human CD105, a growth proliferation receptor found on the surface of normal and proliferating endothelial cells [7, 14, 15].

The antibody is an IgG1 kappa immunoglobulin containing murine variable region sequences and human constant region sequences [16]. Carotuximab has an approximate molecular weight of 148 kDa. Carotuximab has a binding avidity for human CD105 of approximately 5 pM. Carotuximab is formulated as 20 mM L-Histidine/L-Histidine Monohydrochloride, 240 mM Trehalose, and 0.01% Polysorbate 20 Formulation at a concentration of 25 mg/mL. The primary mechanism of action of carotuximab is the competitive inhibition of BMP9 binding to the endoglin/BMPR2/ALK1 receptor complex, which inhibits BMP9-mediated angiogenesis. This primary pharmacologic activity of carotuximab has been corroborated through multiple lines of evidence. Nonetheless, ADCC may not be completely ruled out as a contributing mechanism of action as engagement of the effector functions via the IgG1 constant regrion can mediate the low grade infusion reactions noted in the clinic [17]. Carotuximab has been studied in more than 500 cancer patients and has been generally well tolerated as a single agent and when combined with various chemotherapy agents and with inhibitors of the VEGF pathway.

2.3.1. Carotuximab Clinical Summary

Carotuximab has been studied in a total of 20 completed or ongoing clinical trials. These 20 trials have administered carotuximab to patients with hepatocellular carcinoma and glioblastoma (each 3 studies); advanced or metastatic renal cell carcinoma, metastatic or refractory choriocarcinoma, and advanced or metastatic solid tumors (each 2 studies); and metastatic breast cancer, advanced soft tissue tumors including angiosarcoma, refractory gestational trophoblastic neoplasia, non-squamous cell lung cancer, advanced or metastatic urothelial carcinoma, metastatic castration-resistant prostate cancer, and recurrent ovarian/fallopian tube/or primary peritoneal carcinoma (each 1 study). One study is a continuation clinical trial for patients from previous carotuximab studies.

Carotuximab was studied in doses ranging from 0.01 mg/kg to 15 mg/kg (every 2 weeks) and up to 15 mg/kg weekly in a first-in-human Phase 1 trial of advanced cancer patients. The recommended Phase 2 dose of carotuximab was 10 mg/kg weekly or 15 mg/kg every other week by intravenous (IV). Subsequent investigation indicated the tolerability of carotuximab dosed at 10 mg/kg weekly by IV infusion for the first month followed by 15 mg/kg by every 2 weeks thereafter, given in combination with axitinib or pazopanib. The dose-limiting toxicity observed with carotuximab dosed at 15 mg/kg weekly was anemia, characterized by a low reticulocyte production index, an on-target effect, reflecting endoglin expression on the proerythroblast, an erythrocyte precursor known to express CD105. Anemia is manageable with standard supportive measures, including growth factors and packed red blood cell transfusion, as well as carotuximab dose reduction and/or dose interruption, as appropriate.

The risk profile has also been predictable based on known attributes of the target inhibition, endoglin, the known phenotypes of the Osler-Weber-Rendu syndrome (a syndrome of endoglin heterozygosity), and in general the class effects common to immunoglobulin G Class 1 (IgG1) antibodies. The most frequently reported adverse events (AEs) have been anticipated events with regard with the biological activity of carotuximab and underlying oncologic diseases and their complications, are most commonly reported as low to moderate severity grade events, and are generally easily manageable in clinical practice.

The most common adverse reactions to carotuximab administration can be explained based on known attributes of the target inhibition of endoglin (CD105), the known phenotypes of the Osler-Weber-Rendu syndrome (a syndrome of endoglin heterozygosity), and in general the class effects common to IgG1 antibodies. Specifically, the headache and telangiectasia are known presentations of Osler-Weber-Rendu syndrome, and hemorrhagic events such as epistaxis and gingival bleeding are known consequences of the telangiectasia. The hypoproliferative, non-hemolytic anemia is believed to result from carotuximab-mediated suppression of proerythroblasts, the only cells in the marrow known to express substantial levels of CD105. As a monoclonal antibody, carotuximab, like other similar infusional agents may be associated with a risk for infusion-related reactions and their associated signs and symptoms.

Toxicities typically associated with VEGF inhibition, including hypertension, proteinuria, and thrombosis, do not appear to be prominent in patients receiving carotuximab (alone or in combination with large and small molecule VEGF inhibitors).

Although most carotuximab trials to date have not been designed to primarily assess efficacy, some patients have been observed to benefit from treatment with carotuximab. Signs of efficacy include reductions in tumor volume (including partial and complete responses by RECIST and by Choi criteria in patients with renal cell carcinoma, sarcoma, choriocarcinoma, hepatocellular cancer, colorectal cancer, glioblastoma, and ovarian cancer), serum tumor marker reductions, and reduction in pain. Based on durable complete responses in angiosarcoma patients, carotuximab in combination with pazopanib is being assessed in an ongoing Phase 3 randomized trial in angiosarcoma, a protocol that completed a Special Protocol Assessment by the US FDA.

Additional information regarding carotuximab may be found in the carotuximab Investigational Brochure (IB).

2.4. Study Rationale

Nivolumab is an antibody that binds PD-1 and promotes anti-cancer immunity by inhibiting regulatory T-cell function to sensitize tumors to immune surveillance. Nivolumab is approved by the US FDA for the treatment of metastatic non-small cell lung cancer (NSCLC) that has progressed following platinum-based chemotherapy, based on improved overall survival versus docetaxel in squamous cell non-small cell lung cancer (NSCLC) (median overall survival [OS] 9.2 months versus 6.0 months, respectively) and in non-squamous NSCLC (median OS 12.2 versus 9.4 months.

Endoglin (CD105) is expressed on activated myeloid derived suppressor cells (MDSCs) [11], a cell type that inhibits cancer immunity by a mechanism of action that is distinct from that inhibited immune checkpoint by inhibitors such as nivolumab. In preclinical models, the endoglin antibody carotuximab inhibits tumor growth and complements the activity of antibody that targets the PD-1 pathway. Nivolumab had limited activity in NSCLC following first-line treatment (15 to 20% response rate), and assessment of concurrent endoglin and PD1 blockade is of significant clinical interest.

Carotuximab is an investigational antibody to endoglin, a receptor expressed on proliferating endothelial cells and myeloid-derived suppressor cells (MDSCs). MDSCs also inhibit anti-cancer immunity, but by a mechanism of action that is distinct from that inhibited by nivolumab. Carotuximab has been studied in more than 500 cancer patients and is tolerable as a single agent and when combined with chemotherapy or inhibitors of the vascular endothelial growth factor (VEGF) pathway. Its toxicity profile is distinct from that of nivolumab. By targeting MDSCs, carotuximab has the potential to complement nivolumab and improve clinical efficacy over that seen with single-agent nivolumab.

This trial is a Phase 1b dose escalation safety study of carotuximab in combination with standard dose nivolumab with patients with metastatic NSCLC that has progressed on or after platinum-based chemotherapy or PD-1/PD-L1 checkpoint inhibition, as a single agent or with chemotherapy. A standard “3+3” dose-escalation design will be employed, followed by expansion cohorts to further assess the safety, tolerability, and preliminary efficacy of the recommended Phase 2 dose (RP2D) of carotuximab with nivolumab. The purpose of the dose escalation portion is to determine the maximum tolerated dose (MTD) of carotuximab when given in combination with nivolumab and to determine the dose-limiting toxicities (DLTs). Patients are eligible for continued therapy with nivolumab and carotuximab until disease progression, unacceptable toxicity, or withdrawal of consent, or other reasons. Patients will be scanned every 8 weeks to determine disease status.

2.5. Population to be Studied

Patients with metastatic NSCLC that has progressed on or after platinum-based chemotherapy and may have received prior targeted treatment (e.g., ALK1 inhibitor).

2.6. Potential Risks and Benefits to Human Patients

2.6.1. Potential Risks

Carotuximab

Based on an assessment across all carotuximab clinical trials, the most likely adverse reactions to carotuximab administration consist of anemia, headache, epistaxis, gingival bleeding, infusion-related reaction, telangiectasia, nausea, vomiting, decreased appetite, flushing, pyrexia, and fatigue. Other potential adverse reactions to carotuximab that are a current focus of monitoring in carotuximab studies to better understand whether there is increased risk due to carotuximab administration include infections, especially urinary tract infection, pneumothorax, hypersensitivity, and thromboembolic events including pulmonary embolism. Further details are available in the carotuximab Investigator Brochure (IB).

Nivolumab

The most commonly observed adverse reactions to single-agent nivolumab are fatigue, rash, musculoskeletal pain, pruritus, diarrhea, nausea, asthenia, cough, dyspnea, constipation, decreased appetite, back pain, arthralgia, upper respiratory tract infection, and pyrexia. Side effects of nivolumab include immune-mediated disorders, such as hepatitis, colitis, pneumonitis, endocrinopathies, nephritis and renal dysfunction, skin reactions, and encephalitis, as well as infusion reactions. The most current nivolumab package insert should be referenced for the most complete and updated information.

Computed Tomography (CT) Scans

Patients will be exposed to a relatively small amount of radiation as a result of the CT scans required in this study. This degree of exposure has not been associated with harmful health effects. In addition, the frequency of CT scans performed in this study is similar to the standard of care frequency. Patients with a medical contraindication to CT scans or known iodinated contrast allergies may instead undergo magnetic resonance imaging (MRI). There is minimal risk of MRI imaging in patients able to undergo this type of exam including very rare reports of gadolinium-induce nephrogenic systemic fibrosis in patients with poor renal function.

Venipuncture

Patients could also experience side effects from venipuncture for tests that will be done as part of this study, including pain, tenderness, and bruising at the site of collection, and rarely infection may occur at the spot where the needle is inserted.

Other Risks

This study treatment may involve risks to unborn children and therefore patients should not become pregnant or father a baby while participating in this study. Patients should not nurse (breastfeed) while on this study. Women of childbearing potential must have a negative pregnancy test before taking part in this study.

Women must be of non-childbearing potential due to surgical sterilization (i.e., at least 6 weeks following surgical bilateral oophorectomy with or without hysterectomy or tubal ligation) confirmed by medical history or menopause; or must agree to use 2 methods of effective and highly reliable methods of contraception at the same time (i.e., tubal sterilization, partner's vasectomy, intra-uterine device (IUD), male latex condom with or without spermicide, diaphragm with spermicide, cervical cap with spermicide, or vaginal sponge that contains spermicide) during study treatment (including during temporary breaks from treatment), and for at least 180 days after stopping carotuximab and at least 180 days after stopping nivolumab treatment.

Men must agree to use 2 effective and highly reliable methods of contraception at the same time (i.e., vasectomy, male latex condom with or without spermicide, partner's tubal sterilization, partner's use of an IUD, partner's use of diaphragm with spermicide, cervical cap with spermicide, or vaginal sponge that contains spermicide) during study treatment (including temporary breaks from treatment), and for at least 180 days after stopping carotuximab and at least 180 days after stopping nivolumab. The long-term risk of infertility is unknown. Ovarian failure has been observed with other antiangiogenic agents.

2.6.2. Potential Benefits

Carotuximab is an investigational product, and its efficacy has not been established. Nivolumab is approved for the treatment of appropriately selected patients who progress following treatment with chemotherapy. It is possible that the administration of carotuximab and nivolumab may result in clinical benefit (i.e., tumor response or prolonged stable disease) beyond that of treatment with nivolumab alone.

2.7. Justification of the Dose, Schedule, and Route of Administration

The dose, schedule, and route of administration of carotuximab (8 mg/kg IV weekly or 10 mg/kg weekly for 4 doses followed by 15 mg/kg every 2 weeks) was selected based on safety, pharmacokinetics, and evidence of activity in the Phase 1 study of carotuximab for patients with solid tumors (Study 105ST101) and in Phase 1b studies of carotuximab with VEGF inhibitors. Dose reduction is possible for treatment of adverse events, including anemia.

Carotuximab has not previously been dosed with a PD-1 inhibitor, but has not been associated with immune-mediated toxicity that is characteristic of nivolumab or other PD-1 inhibitors. Therefore, a carotuximab starting dose of 8 mg/kg weekly, which is 20% lower than the single-agent carotuximab MTD identified in the Phase 1 single-agent study and Phase 1b studies with bevacizumab, pazopanib, and axitinib was selected. In addition, a 6 mg/kg dose level (Dose

Level -1) has also been included and will be used should 8 mg/kg of carotuximab in combination with nivolumab exceed the MTD.

Nivolumab (Opdivo®) is an a human monoclonal PD-1 antibody that is approved by the FDA for a number of indications, including the treatment of metastatic NSCLC that has progressed following on or after platinum-based chemotherapy. This protocol is designed to administer nivolumab at the dose, schedule, and route of administration and to the target patient population per the nivolumab package insert, which for NSCLC is 240 mg IV every 2 weeks.

2.8. Study Conduct

The 105LC102 clinical trial will be conducted in compliance with the protocol, Good Clinical Practice (GCP), and the applicable regulatory requirements.

3. TRIAL OBJECTIVES AND PURPOSE

The purpose of this study is to evaluate the safety of carotuximab in combination with nivolumab.

Primary Objective:

- To evaluate safety and tolerability and determine a recommended Phase 2 dose for carotuximab when added to standard dose nivolumab in patients with metastatic NSCLC

Secondary Objectives:

- To assess preliminary evidence of antitumor activity when carotuximab is added to nivolumab, by assessing response rate and progression-free survival including in patients who have not been treated previously with a PD-1/PD-L1 checkpoint inhibitor and have histological disease recurrence or progression during or after prior platinum-containing doublet chemotherapy regimen (Expansion Cohort 1) or have relapsed following prior treatment with a PD-1/PD-L1 checkpoint inhibitor (Expansion Cohort 2).
- To characterize the pharmacokinetic profile of carotuximab when given with nivolumab
- To evaluate the formation of carotuximab anti-product antibodies

Exploratory Objective:

- To explore effects of carotuximab and nivolumab on tumor immune effector cells

4. INVESTIGATIONAL PLAN

4.1. Overall Study Design and Plan

4.1.1. Overview

This is a multi-center, open-label, nonrandomized, dose-escalation, Phase 1b study of carotuximab in combination with standard dose nivolumab in patients with NSCLC that has progressed on or after platinum-based chemotherapy or PD-1/PD-L1 checkpoint inhibition, as a single agent or with chemotherapy. The purpose of the carotuximab dose escalation portion is to determine the dose-limiting toxicities (DLTs) and maximum tolerated dose (MTD) of carotuximab when given in combination with nivolumab. A standard "3+3" dose-escalation design will be employed, followed by expansion cohorts to further assess the safety, tolerability, and preliminary efficacy of the recommended Phase 2 dose (RP2D) of carotuximab with nivolumab.

All patients must sign and date a consent form prior to undertaking any study-related procedures. Prospective patients will be screened to determine if they qualify for the study within 28 days of enrollment. Patients will receive nivolumab at 240 mg IV very 2 weeks starting on Cycle 1 Day 1 (C1D1) and will receive carotuximab starting on C1D1 at 6, 8, or 10 mg/kg weekly for 4 doses and then 15 mg/kg very 2 weeks thereafter according to the dosing schedule in Table 3 (see carotuximab Administration Section 6.1.6 and Nivolumab Administration Section 6.2.6). Intermediate carotuximab doses (below the MTD established during the trial) may be explored based upon clinical, pharmacokinetic (PK), and/or biomarker data.

Patients are eligible for continued therapy with nivolumab and carotuximab until disease progression, unacceptable toxicity, or withdrawal of consent, or other reasons. Patients will be scanned every 8 weeks to determine disease status. Adverse events will be graded according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) Version 4.03.

Table 3: Study Drug Dosing Schedule

Dose Level	Number of evaluable patients	Carotuximab mg/kg IV weekly[a] starting C1D1 for 4 doses and then every 2 weeks	Nivolumab IV every 2 weeks starting C1D1
-1	3-6	6 mg/kg weekly through Cycle 1 → 15 mg/kg every 2 weeks	240 mg
1 (starting dose)	3-6	8 mg/kg weekly through Cycle 1 → 15 mg/kg every 2 weeks	240 mg
2	3-6	10 mg/kg weekly through Cycle 1 → 15 mg/kg every 2 weeks	240 mg
Expansion Cohort 1[b]	Up to 12	Maximum tolerated dose (MTD)	240 mg
Expansion Cohort 2[c]	Up to 12	Maximum tolerated dose (MTD)	240 mg

[a]The first carotuximab dose will be split into two doses whereby 3 mg/kg is administered on cycle 1 day 1 and the balance is administered on cycle 1 day 4.
[b]Expansion Cohort 1: Patients who have not been treated previously with a PD-1/PD-L1 checkpoint inhibitor and have histological disease recurrence or progression during or after prior platinum-containing doublet chemotherapy regimen.
[c]Expansion Cohort 2: Patients who have relapsed following prior treatment with a PD-1/PD-L1 checkpoint inhibitor without Grade 3 immune-related toxicity.

Three patients will be initially enrolled and treated at each dose level. If none of these 3 patients experiences a DLT during the initial 28 days of combination therapy period, dose escalation will proceed following review of safety data with Principal Investigators at all sites. If 1 of 3 patients experiences DLT, the dose level will be expanded to 6 patients. The MTD will have been exceeded if ≥ 33% of patients experience DLT at a given dose level where at least 6 patients have been evaluated (including the expansion cohorts). DLT will have occurred when a patient has 1 or more toxicity listed in Table 4 that is at least possibly related to nivolumab or carotuximab during the first 28 days of combination therapy.

Upon determination of the MTD, up to 24 additional patients will be enrolled (up to 12 in each cohort) into Expansion Cohorts 1 and 2. The study will be terminated for grade ≥3 infusion related reactions occurring in ≥33% of 6 or more patients in the expansion cohorts.

Patients who exit the study for reasons other than DLT prior to completion of the 28-day DLT evaluation period will be replaced to ensure an adequate safety assessment in each cohort. Patients who experience DLT who receive less than the prescribed dose of carotuximab or nivolumab due to documented toxicity during the DLT evaluation period will be considered evaluable for dose escalation purposes. A given carotuximab dose level may be reenrolled at an intermediate dose level upon agreement of study Investigators.

Table 4: Dose-Limiting Toxicities

Toxicity Category	Drug-Related Toxicity/Grade
Hematologic	Grade 4 neutropenia for ≥5 days
	Febrile neutropenia: Grade 4 neutropenia with fever >38.5ºC both sustained over a ≥24-hour period
	Neutropenic infection: Grade ≥3 neutropenia with Grade ≥3 infection
	Grade ≥4 Anemia
	Grade ≥4 thrombocytopenia or Grade ≥3 thrombocytopenia with Grade ≥3 hemorrhage
Nonhematologic	Grade 3 or 4 nonhematologic toxicity with the following exceptions: • Asymptomatic electrolyte abnormality that is corrected to Grade 1 or better in <72 hours • Grade 3 headache lasting <48 hours
Immune related	Grade 3 pneumonitis, Grade 3 colitis, AST or ALT >5 times the upper limit of normal or total bilirubin >3 times the upper limit of normal, Grade 3 hypophysitis, Grade 3 adrenal insufficiency, serum creatinine >3 times baseline, encephalitis of any grade, type 1 diabetes mellitus with Grade 4 hyperglycemia, Grade 4 rash or suspected Stevens-Johnson syndrome or toxic epidermal necrolysis

4.1.2. Trial Procedures

All on-study procedures are permitted within the time window indicated in the Schedule of Assessments (Table 5).

4.1.2.1. Screening

The following screening procedures must be performed within 28 days prior to the first day of study therapy. Qualifying hematology (including iron [Fe] studies), serum chemistry (including thyroid-stimulating hormone [TSH] testing), coagulation, physical examination, ECG, pregnancy, and urinalysis collected within 7 days of Cycle 1 Day 1 (C1D1) do not need to be repeated. The following will be performed according to the Schedule of Assessments (Table 5).

- Patient signature and date on current Institutional Review Board (IRB)-approved informed consent form - Prior to undergoing any study-specific procedure, patients must read, sign, and date the current IRB)-approved informed consent form. Patients may sign consent prior to the 28-day screening period.
- Medical history, baseline signs and symptoms, prior cancer therapy, prior cancer surgery, prior radiation therapy, drug allergies, primary diagnosis, and demographics
- Physical examination, including examination of all major body systems, ECOG performance status, and vital signs - The patient's height will be obtained only at this Screening visit.

- Hematology (including serum iron, ferritin, and total iron binding capacity), coagulation (prothrombin time and INR), and serum chemistry (including liver function tests and TSH) to be performed locally
- Serum or urine pregnancy test for all females of childbearing potential to be performed locally
- Urinalysis to be performed locally - Microscopic analysis and/or urine protein-creatinine ratio (UPCR) should be performed as clinically indicated.
- CT or MRI scans of chest, abdomen, and pelvis in addition to any other applicable sites of disease
- MRI or contrast-enhanced CT scan of the brain are to be performed only if suspected brain involvement at screening.
- Bone scans are to be performed if metastases are suspected at screening.
- Single tracing 12-Lead ECG (QT, PR, and QRS intervals and heart rate will be captured)
- Assessment of concomitant medications and treatments from 28 days prior to the start of study treatment
- Optional core tumor biopsy. Tumor biopsy is required prior to treatment initiation if archival tumor tissue that permits the preparation of 20 unstained slides is unavailable.
- Archival Tumor Tissue Specimens: Archival specimens (formalin-fixed, paraffin-embedded) of the primary cancer specimen and/or metastatic cancer specimen, from the time of initial diagnosis or following prior treatment for each study participant. It is preferable that the entire paraffin block be submitted, but if this is not feasible, then at least 20 unstained slides are requested for immunohistochemical analysis (sections of ~ 5 microns are preferred). See separate laboratory guide for further collection and shipment information.

4.1.2.2. Study Drug Treatment Period

Qualifying hematology (including Fe studies), blood chemistry (including TSH testing), coagulation, urinalysis, physical examination, ECG, and pregnancy test do not need to be repeated on C1D1 if acceptable screening assessments are performed within 7 days prior to the start of study therapy. On days of dosing, all assessments should be performed prior to dosing with carotuximab unless otherwise indicated in the Schedule of Assessments (Table 5). Patients will be eligible to receive nivolumab and carotuximab until disease progression, unacceptable toxicity, withdrawal of consent, or other reasons. Each cycle is 28 days in duration. The following will be performed according to the Schedule of Assessments (Table 5).

- Physical examination including examination of all major body systems, ECOG performance status, weight, and vital signs (heart rate, temperature, blood pressure, respiratory rate)
  - Assessment of vital signs during carotuximab infusion: Vital signs are to be assessed pre-infusion (i.e., within 30 minutes of starting the infusion), every 30

minutes during the infusion (+/- 15 minutes), and at the end of the infusion (i.e., within 30 minutes after completing the infusion). Vital signs should be monitored more frequently and/or beyond the completion of the infusion if medically indicated (e.g., if the patient experiences an infusion reaction that has not yet resolved).

- Hematology, coagulation (prothrombin time and INR) and serum chemistry (including liver function tests and TSH) to be performed locally
- Single tracing 12-Lead ECG (QT, PR, and QRS intervals and heart rate will be captured)
- Urinalysis to be performed locally - Microscopic analysis and/or UPCR should be performed as clinically indicated.
- Serum or urine pregnancy test for all females of childbearing potential to be performed locally
- Blood sampling for carotuximab pharmacokinetics will include a pre-infusion trough sample to be analyzed by a third-party laboratory (see laboratory manual for specific instructions regarding collection times, procedures, processing, storage and shipment).
- Blood sampling for immunogenicity to be analyzed by a third-party laboratory (see laboratory manual for specific instructions regarding collection, processing, storage and shipment)
- Blood sampling for protein biomarker analysis by a third-party laboratory (see laboratory manual for specific instructions regarding collection processing, storage and shipment)
- CT or MRI scans of chest, abdomen, and pelvis in addition to any other applicable sites of disease - MRI or contrast-enhanced CT scan of the brain performed only if known or suspected brain involvement. Bone scans performed only if metastasis known or suspected. Scan of the chest, abdomen, and pelvis to be performed on-study as outlined in the assessment table. Known areas of disease should be consistently followed throughout the study. Assessments should be performed whenever disease progression is suspected. Allowable window for tumor imaging studies is +/- 7 days.
- Administration of carotuximab: carotuximab diluted in normal saline will be administered as a 1- to 4-hour infusion (+/- 15 minutes) on Days 1, 8, 15, and 22 of each 28-day cycle following premedication (see Section 6.1.6) for all cycles except Cycle 1. The first carotuximab dose will be split into 2 doses such that 3 mg/kg is administered on C1D1, and the balance is administered on C1D4. The entire weekly dose of carotuximab (6, 8, or 10 mg/kg) is then given on C1D8, C1D15, C1D22 and then at 15 mg/kg every 2 weeks starting with C2D1. Carotuximab will be administered IV utilizing an infusion pump. Carotuximab has been demonstrated to be compatible with polyethylene lined, non- diethylhexyl-phthalate (DEHP) infusion sets and polyvinyl chloride, non-DEHP infusion sets. Carotuximab is required to be administered with a 0.2 micron downstream filter. Duration of infusion administration may be increased as medically necessary.

- Administration of nivolumab: Administer 240 mg as an IV infusion on Days 1 and 15 of every 28-day cycle until disease progression, as described in the nivolumab package insert.
- Assessment of adverse events (AEs)
- Assessment of concomitant medications and concomitant treatments
- Optional core tumor biopsy

4.1.3. End of Study Assessments

Assessments other than carotuximab pharmacokinetics, immunogenicity, and protein biomarkers only need to be completed if they were not completed during the previous 2 weeks on study (during the last 8 weeks on study for radiologic tumor assessments). The following will be performed according to the Schedule of Assessments (Table 5).

- Physical examination including examination of all major body systems, ECOG performance status, and vital signs
- Single tracing 12-Lead ECG (QT, PR, and QRS intervals and heart rate will be captured)
- Hematology and serum chemistry (including liver function tests and TSH) to be performed locally
- Urinalysis to be performed locally. Microscopic analysis and/or UPCR should be performed as clinically indicated
- Blood sampling for carotuximab and nivolumab pharmacokinetics to be analyzed by a third-party laboratory (see laboratory manual for specific instructions regarding collection times, procedures, processing, storage and shipment)
- Blood sampling for immunogenicity to be analyzed by a third-party laboratory (see laboratory manual for specific instructions regarding collection, processing, storage, and shipment)
- Blood sampling for protein biomarker analysis by a third-party laboratory (see laboratory manual for specific instructions regarding collection processing, storage and shipment)
- CT or MRI scans of chest, abdomen, and pelvis in addition to any other applicable sites of disease - MRI or contrast-enhanced CT scan of the brain performed at only if known or suspected brain involvement. Bone scans performed only if metastasis known or suspected. Known areas of disease should be consistently followed throughout the study. Assessments should be performed whenever disease progression is suspected.
- Assessment of AEs
- Assessment of concomitant medications and concomitant treatments

4.1.4. Post-Treatment Follow-up

The following will be performed according to the Schedule of Assessments (Table 5). Samples should be collected and assessments performed even if new anti-cancer therapy commences during the follow-up period.

- Assessment of AEs: The Investigator should continue to report any study drug (carotuximab or nivolumab)-related or possibly related AEs that occur beyond the AE reporting period.
- Blood sampling for carotuximab pharmacokinetics to be analyzed by a third-party laboratory (see laboratory manual for specific instructions regarding collection, processing, storage and shipment)
- Blood sampling for immunogenicity to be analyzed by a third-party laboratory (see laboratory manual for specific instructions regarding collection, processing, storage and shipment)
- Assessment of concomitant medications and concomitant treatments
- Serum or urine pregnancy test for all females of childbearing potential to be performed locally

5.3.3.2 Clinical Protocol

Table 5: Schedule of Assessments

Protocol Activities	Screening	Cycle 1 [24]					Cycles 2+ [24]			End of Treatment (EOT)	End of Study (EOT + 28 Days) [23]
	Day -28	Day 1 [1]	Day 4 [1]	Day 8 [1]	Day 15 [1]	Day 22 [1]	Day 1 [1]	Day 15 [1]	Day 22 [1]		
Baseline Documentation											
Informed Consent [4]	X										
Medical/Oncology History [5]	X										
Baseline Signs and Symptoms [5]	X										
Physical Examination [6]	X	X					X			X	
Vital Signs [7]	X	X	X	X	X	X	X	X		X	
Laboratory Studies											
Hematology [8]	X+Fe	X			X		X			X	
Coagulation [8]	X	X									
Blood Chemistry including TSH [8]	X	X			X		X			X	
Pregnancy Test [9]	X	X					X				X
Urinalysis [10]	X	X					X			X	
Treatment with Study Drug											
Carotuximab Dosing [11]		X Split	X Split	X	X	X	X	X			
Nivolumab [12]		X			X		X	X			
Tumor Assessments											
CT or MRI Scans [13]	X								Even cycles	X	
Other Clinical Assessments											
12-Lead ECG [14]	X	X			X					X	
Concomitant Medications/Treatments [15]	X	X		X	X	X	X	X		X	X
Adverse Events [16]		X		X	X	X	X	X		X	X
Special Laboratory Assessments											
Anti-Product Antibodies (APA) [17]		X					Even cycles			X	X
Protein Biomarkers [18]		X					Cycle 2			X	
Carotuximab and nivolumab PK Pre-Dose [19]					X		Even cycles			X	X
Optional Tumor Biopsy [21]	X						≥ Cycle 2				
Archival Tumor Tissue [22]	X										

Schedule of Assessments Footnotes

1. **Days of Treatment:** All assessments should be performed prior to nivolumab or carotuximab infusion unless otherwise indicated. Each cycle is 28 days in duration.
2. **Cycle 1 Day 1 (C1D1):** Hematology (including iron studies), blood chemistry (including TSH testing), urinalysis, physical examination, ECG, and pregnancy test not required if acceptable screening assessment is performed within 7 days prior to the start of treatment on C1D1.
3. **End of Study:** The end of study visit should generally occur within 7 days (+/- 1 day) of the last dose of carotuximab or nivolumab, which occurs later. Assessments other than PK, immunogenicity, and protein biomarkers do not need to be repeated if performed within the previous 2 weeks (previous 8 weeks for radiologic tumor assessments). Follow-up visits should occur 28 days following the last dose of carotuximab or nivolumab study drug as outlined in the Schedule of Assessments.
4. **Informed Consent:** Must be obtained prior to undergoing any study specific procedure and may occur prior to the 28-day screening period.
5. **Medical and Oncologic History, Demographics, and Baseline Signs and Symptoms:** All information related to prior anticancer treatment should be recorded. Significant medical history and baseline signs and symptoms should be captured from the date of informed consent.
6. **Physical Examination:** Examination of major body systems and ECOG performance status. The patient's height will be obtained only at Screening visit.
7. **Vital Signs:** Heart rate, temperature, blood pressure, respiratory rate, and weight. Assessment during carotuximab Infusions: Vital signs are to be assessed pre-infusion (i.e., within 30 minutes of starting the infusion), every 30 minutes during the infusion (+/- 15 minutes), and at the end of the infusion (i.e., within 30 minutes after completing the infusion). Vital signs should be monitored more frequently and/or beyond the completion of the infusion if medically indicated (e.g., if the patient experiences an infusion reaction that has not yet resolved).
8. **Hematology, Chemistry (including liver function tests) & Coagulation:** Testing to be performed locally. Thyroid stimulating hormone (TSH) to be tested at screening, Day 1 of each cycle, and at the end of study visit. C1D1 assessments only need to be performed if screening assessments were performed > 7 days prior to C1D1. Iron studies (Fe) to be performed according to the schedule of assessments and as clinically indicated during the study. Lab assessments can be may be performed within 3 days prior to carotuximab dosing. In addition to the assessments scheduled for the clinical trial, patients should undergo assessment as appropriate to ensure safe treatment. See Section 8.1.1.1 for specific panel collection requirements.
9. **Pregnancy Test:** Testing to be performed locally. All female patients of childbearing potential must have a negative serum or urine pregnancy test within 7 days of C1D1, Day 1 of even cycles, and 28 days following the last dose of carotuximab or nivolumab, which occurs later.
10. **Urinalysis:** To be performed locally. C1D1 urinalysis only needs to be performed if screening urinalysis was performed more than 7 days prior to C1D1. Microscopic analysis and/or urine protein creatinine ratio (UPCR) or 24-hour urine protein collection should be performed as clinically indicated.
11. **Carotuximab Administration:** IV carotuximab diluted in normal saline will be administered every 7 days for 4 weeks. The initial weekly carotuximab dose will be given on C1D1 and split into 2 doses whereby 3 mg/kg is administered on C1D1 and the balance is administered on C1D4. The entire weekly dose of carotuximab (6, 8, or 10 mg/kg) is then given on C1D8, C1D15, and C1D22. Beginning on C2D1, carotuximab is given at 15 mg/kg every 2 weeks. See Section 6.1.6 for specific carotuximab administration guidelines.
12. **Nivolumab Dosing:** IV nivolumab at a dose of 240 mg will be administered on Days 1 and 15 of every 28-day cycle, starting on C1D1 as described in the package insert. See Section 6.2 for specific dosing guidelines.
13. **CT or MRI Tumor Imaging:** Images of the chest, abdomen, and pelvis to be performed at screening, and on-study as outlined in the assessment table. Known areas of disease should be consistently followed throughout the study. Assessments should be performed whenever disease progression is suspected. Allowable window for tumor imaging studies is +/- 7 days. MRI or contrast-enhanced CT scan of the brain to be performed at only if suspected brain involvement at screening or during study treatment. Bone scans are to be performed if metastases are suspected at screening or during study treatment.

14. **12-Lead ECG:** Single tracing 12-lead ECG will be performed at screening and at the time points indicated in the Schedule of Assessments (pre-dose). If the patient develops an arrhythmia, the ECG should be repeated on Day 1 of each subsequent cycle. For a QTc >500 ms, the ECG should be evaluated by a cardiologist at the site for confirmation. Additional ECGs may be performed on study as clinically indicated.
15. **Concomitant Medications and Treatments:** Concomitant medications and treatments will be recorded from 28 days prior to the start of study treatment and up to 28 days following the last dose of study treatment. Required carotuximab premedications should be recorded on carotuximab premedications CRF.
16. **Adverse Events:** All serious adverse events and those non-serious events assessed by the Investigator as suspected reactions (i.e., at least possibly related) to a TRACON investigational medicinal product must be followed, even after the patient's withdrawal from study, until the event is either resolved, improved to the patient's pre-treatment baseline or better, stable without anticipated future change, or the patient is lost to follow-up, or, in the case of a suspected adverse reaction, later determined to be not related to the TRACON investigational medicinal product.
17. **Anti-product antibody (APA):** 5 mL blood sample will be collected to assess anti-product antibody at the time points indicated in the Schedule of Assessments and stored at approximately -70°C to be analysed by a central laboratory. Samples will be batch shipped as indicated in the laboratory manual to a third-party laboratory. See separate laboratory guide for further collection and shipment information. Additional samples may also be collected at the time of unexpected clinical events.
18. **Protein Biomarkers:** One 10 mL purple top (K_3EDTA) tube will be collected at the time points indicated in the schedule of assessments and stored at approximately -70°C to be analysed by a central laboratory. See separate laboratory guide for further collection and shipment information.
19. **Carotuximab and Nivolumab Pharmacokinetics (PK) Trough Concentrations**: A 5 mL blood sample to be collected at the time points indicated in the Schedule of Assessments, prior to starting the either study drug infusion. Samples will be stored at approximately -70°C. Samples will be batch shipped as indicated in the laboratory manual to a third-party laboratory. See separate laboratory guide for further collection and shipment information. Additional PK samples may also be collected at the time of unexpected clinical events.
20. **Optional Tumor Biopsy:** Tumor biopsy for immune cell phenotyping prior to C1D1 and again on-study, no earlier than Cycle 2. Tumor biopsy is required if archival tumor tissue is unavailable as a formalin-fixed, paraffin embedded tumor block to permit preparation of 20 unstained slides. Tumor biopsy is required if archival tumor tissue is unavailable that permits the preparation of 20 unstained slides.
21. **Archival Tumor Tissue:** Archival specimens (formalin-fixed, paraffin-embedded) are required of the primary cancer and/or metastatic cancer specimen for each study participant. It is preferable that the entire paraffin block be submitted, but if this is not feasible, then at least 20 unstained slides are requested for immunohistochemical analysis (sections of 5 microns are preferred). Archival tumor tissue may be procured form the initial cancer diagnosis or following prior treatment, and multiple specimens may be submitted for analysis. See separate laboratory guide for further collection and shipment information.
22. **Follow-up:** The follow-up visit should occur 28 days following the last dose of carotuximab or nivolumab, whichever occurs later. The allowable visit window is +/- 7 days.
23. **Visit Windows:** Allowable window for each visit within the cycle is +/- 2 days unless otherwise stated.

5. SELECTION AND WITHDRAWAL OF PATIENTS

5.1. Patient Inclusion Criteria

1. Histologically confirmed metastatic non-small cell lung cancer (NSCLC) with disease recurrence or progression during or after prior platinum-containing doublet chemotherapy regimen (for dose escalation portion and, if not previously treated with a PD-1/PD-L1 checkpoint inhibitor, for Expansion Cohort 1).
2. Histologically confirmed metastatic non-small cell lung cancer (NSCLC) that has relapsed following prior PD-1/PD-L1 checkpoint inhibitor therapy without Grade 3 immune-related toxicity, which may or may not have included concurrent chemotherapy (for dose escalation and Expansion Cohort 2). Relapse following prior PD-1 checkpoint therapy is defined as confirmed progressive disease following stable disease or better (e.g., iSD, iPR, iCR) on at least 1 tumor assessment.
3. Patients with an active oncogenic driver (e.g., epidermal growth factor [EGFR], activin-receptor-like kinase 1 [ALK1], or the proto-oncogene tyrosine-protein kinase ROS-1) must have progressed on or after a US Food and Drug Administration (FDA)-approved therapy for that aberration (Note: Previous treatment with a tyrosine kinase inhibitor and platinum-based doublets does not exclude the patient).
4. Patients who received adjuvant or neoadjuvant platinum-doublet chemotherapy (after surgery and/or radiation therapy) and developed recurrent or metastatic disease within 6 months of completing therapy are eligible.
5. Patients with recurrent disease > 6 months after adjuvant or neoadjuvant platinum-based chemotherapy, who also subsequently progressed during or after a platinum-doublet regimen given to treat the recurrence, are eligible.
6. Formalin fixed, paraffin-embedded (FFPE) tumor tissue block that permits the preparation of 20 unstained slides of tumor sample (archival) - Biopsy must be excisional, incisional, or core. Needle aspiration is insufficient. In cases where archival tumor tissue is unavailable, tumor biopsy will be required prior to treatment initiation.
7. Programmed death ligand 1 (PD-L1) determination by validated immunohistochemistry assay (i.e., PD-L1 (SP142) CDX (Ventana) or PD-L1 IHC 22C3 PharmDx (Dako) or PD-L1 IHC 28-8 PharmDx (Dako) assay). Any PD-L1 score is acceptable including tumor proportion score (TPS) of 0.
8. Measurable disease by iRECIST
9. Age ≥ 18 years
10. Eastern Cooperative Oncology Group (ECOG) performance status ≤ 1
11. Resolution of all acute adverse events resulting from prior cancer therapies to National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) Grade ≤ 1 or baseline (except alopecia or neuropathy)
12. Adequate organ function as defined by the following criteria:

a) Serum aspartate transaminase (AST; serum glutamic oxaloacetic transaminase [SGOT]) and serum alanine transaminase (ALT; serum glutamic pyruvic transaminase [SGPT]) ≤ 2.5 times upper limit of normal (ULN) or ≤ 5 times ULN in cases of liver metastases

b) Total serum bilirubin ≤ 1.5 times the ULN

c) Absolute neutrophil count (ANC) ≥ 1500/μL

d)Platelets ≥ 100,000/μL without transfusion support within 28 days prior to study treatment

e) Hemoglobin ≥ 9.0 g/dL without transfusion support within 14 days prior to study treatment (erythropoietin or darbepoetin permitted)

f) Serum creatinine ≤ 1.5 times the ULN or creatinine clearance > 30 mL/min by Cockcroft-Gault formula

g) International normalized ratio (INR) from 0.8 to 1.2

13. Willingness and ability to consent for self to participate in study
14. Willingness and ability to comply with scheduled visits, treatment plan, laboratory tests, and other study procedures

5.2. Patient Exclusion Criteria

1. Autoimmune disease requiring treatment within the past twelve months. (Note: Vitiligo, type 1 diabetes mellitus, residual hypothyroidism due to autoimmune thyroiditis only requiring hormone replacement, and conditions not expected to recur in the absence of an external trigger are permitted.)

2. Condition requiring systemic treatment with either corticosteroids (>10 mg daily prednisone equivalent) or other immunosuppressive medications within 14 days prior to study treatment. (Note: Inhaled and topical steroids, and adrenal replacement steroid doses > 10 mg daily prednisone equivalent, are permitted in the absence of active autoimmune disease.)

3. History or active interstitial lung disease

4. Prior therapy with T-cell therapy, including an immune checkpoint inhibitor. Patients who received prior immune checkpoint inhibitor therapy are allowed in Expansion Cohort 2 in the absence of recurrent grade 2 (except skin, endocrine and constitutional symptoms), or ≥ 3 immune-related toxicity).

5. Prior treatment with carotuximab

6. Current treatment on another therapeutic clinical trial

7. Receipt of systemic anticancer therapy, including investigational agents, within 28 days prior to study treatment (Note: If anticancer therapy was given within 28 days prior to starting study treatment, patients are not excluded if ≥ 5 times the elimination half-life of the drug has elapsed.)

8. Major surgical procedure or significant traumatic injury within 4 weeks prior to study treatment, and must have fully recovered from any such procedure; and no date of surgery (if applicable) or anticipated need for a major surgical procedure planned within the next 6 months (Note: The following are not considered to be major procedures and are permitted up to 7 days prior to study treatment: Thoracentesis, paracentesis, port placement, laparoscopy, thorascopy, tube thoracostomy, bronchoscopy, endoscopic ultrasonographic procedures, mediastinoscopy, skin biopsies, incisional biopsies, imaging-guided biopsy for diagnostic purposes, and routine dental procedures.)

9. Chest radiotherapy ≤ 28 days, wide field radiotherapy ≤ 28 days (defined as > 50% of volume of pelvic bones or equivalent), or limited field radiation for palliation ≤ 14 days prior to study treatment - Such patients must have recovered adequately from any side effects of such therapy.

10. Hypertension defined as blood pressure (BP) systolic > 150 or diastolic > 90 mm Hg (Note: Initiation or adjustment of antihypertensive medication prior to study entry is allowed provided that the average of 3 BP readings prior to study treatment is ≤150/90 mm Hg.)

11. Ascites or pericardial effusion that required intervention within 3 months prior to study treatment

12. History of brain involvement with cancer, spinal cord compression, or carcinomatous meningitis, or new evidence of brain or leptomeningeal disease (Note: Patients with radiated or resected lesions are permitted, provided the lesions are fully treated and inactive, patients are asymptomatic, and no steroids have been administered for CNS disease over the 7 days prior to study treatment)

13. Angina, myocardial infarction (MI), symptomatic congestive heart failure, cerebrovascular accident, transient ischemic attack TIA), arterial embolism, pulmonary embolism, percutaneous transluminal coronary angioplasty (PTCA), or coronary artery bypass grafting (CABG) within 6 months prior to study treatment

14. Deep venous thrombosis within 6 months prior to study treatment, unless the patient is anti-coagulated without the use of warfarin for ≥2 weeks prior to study treatment; in this situation, low molecular weight heparin is preferred

15. Active bleeding or pathologic condition that carries a high risk of bleeding (e.g., hereditary hemorrhagic telangiectasia)

16. Thrombolytic use (except to maintain IV catheters) within 10 days prior study treatment

17. Known active viral or nonviral hepatitis or cirrhosis

18. Any active infection requiring systemic treatment

19. History of hemorrhage or hemoptysis (> ½ teaspoon bright red blood) within 3 months prior to study treatment

20. History of peptic ulcer within the past 3 months prior to study treatment, unless treated for the condition and complete resolution has been documented by esophagogastroduodenoscopy (EGD) within 28 days prior to study treatment

21. History of gastrointestinal perforation or fistula in the 6 months prior to study treatment, or while previously on antiangiogenic therapy, unless underlying risk has been resolved (e.g., through surgical resection or repair)

22. Known human immunodeficiency virus (HIV) or acquired immunodeficiency syndrome (AIDS) related illness

23. Pregnancy or breastfeeding - Female patients must be surgically sterile (i.e., ≥6 weeks following surgical bilateral oophorectomy with or without hysterectomy or tubal ligation) or be postmenopausal, or must agree to use effective contraception during the study and for 3 months following last dose of carotuximab. All female patients of reproductive potential must have a negative pregnancy test (serum or urine) within 7 days prior to study treatment. Male patients must be surgically sterile or must agree to use effective contraception during the study and for at least 180 days following last dose of study drug (carotuximab or nivolumab, whichever occurs later). The definition of effective contraception is provided in Section 2.6.1 of this protocol.

24. Other severe acute or chronic medical or psychiatric condition or laboratory abnormality that may increase the risk associated with study participation or may interfere with the interpretation of study results and, in the judgment of the Investigator, would make the patient inappropriate for this study.

5.3. Patient Withdrawal Criteria

A patient should be withdrawn from study treatment if, in the opinion of the Investigator, it is medically necessary, or if it is the wish of the patient. If a patient does not return for a scheduled visit, every effort should be made to contact the patient. In any circumstance, every effort should be made to document patient outcome. Data to be collected at the end of study visit are described in the Schedule of Assessments (Table 5). Patients will be followed for at least 28 days after the last dose of study drug (carotuximab or nivolumab) for AEs. If the patient withdraws consent, no further evaluations should be performed, and no attempts should be made to collect additional data. In addition, patients will be withdrawn from treatment in the case of:

1. iRECIST-defined disease progression

2. A need for surgery, radiation, or for other anticancer therapy not permitted in this protocol

3. Lost to follow-up or noncompliant with the protocol

4. Any carotuximab dose delay > 2 days during the 28 day DLT evaluation period (i.e., Cycle 1)

5. Dose delay such that a given patient is off treatment for ≥ 8 weeks for both study drugs concurrently (i.e., there is ≥ 8 weeks between doses)

6. Pregnancy - Pregnant patients should be followed for the duration of the pregnancy and the outcome of the pregnancy should be documented.

7. Arterial thrombosis of any grade (including cerebrovascular ischemia, cardiac ischemia/infarction, or peripheral or visceral arterial ischemia) or Grade 3 or 4 venous thrombosis (including pulmonary embolism)

8. Grade > 3 pneumonitis, any Grade 4 toxicity including colitis, AST or ALT > 5 times the ULN or total bilirubin > 3 times the ULN, Grade 4 hypophysitis that cannot be controlled with endocrine replacement therapy, Grade > 3 adrenal insufficiency that cannot be controlled with endocrine replacement therapy, Grade > 3 nephritis with serum creatinine > 3 times the ULN, encephalitis of any grade, type 1 diabetes mellitus with Grade 4 hyperglycemia, Grade > 3 infusion-related reactions, Grade 4 rash or suspected Stevens-Johnson syndrome or toxic epidermal necrolysis, any Grade > 3 non-hematologic treatment-related toxicity that recurs, any Grade 2 or 3 immune related toxicity that persists despite treatment modifications or corticosteroid treatment that cannot be reduced to 10 mg of prednisone or equivalent per day within 12 weeks

6. TREATMENT OF PATIENTS

6.1. Description of Carotuximab Study Drug

Carotuximab is a genetically engineered human/murine chimeric monoclonal antibody directed against human endoglin (CD105) found on the surface of proliferating endothelial cells and myeloid derived suppressor cells (MDSCs).

6.1.1. Carotuximab Composition

Carotuximab is an IgG1, kappa immunoglobulin containing murine light- and heavy-chain variable region sequences and human constant region sequences. Carotuximab has an approximate molecular weight of 148 kilo-Dalton (kDa).

6.1.2. Carotuximab Dose Levels

Each patient will be dosed with 6 (Dose Level -1), 8 (Dose Level 1) or 10 mg/kg (Dose Level 2), 4 once-weekly doses and then 15 mg/kg every 2 weeks, as shown in Table 6. The maximum weight that should be used for the purpose of dose calculation is 85 kg for women and 100 kg for men. Thus, the maximum dose that should be given to a woman at the 10 mg/kg dose is 850 mg and at the 15 mg/kg dose is 1,275 mg, and the maximum dose that should be given to a man at the 10 mg/kg dose is 1,000 mg and at the 15 mg/kg dose is 1,500 mg. Carotuximab is distributed according to lean body mass rather than overall body weight. Patients who are overweight would be at risk for high serum levels of carotuximab if the doses were not capped as specified above. Eighty-five kg for women and 100 kg for men represent accepted maximum lean body masses for the two genders.

For Dose Levels -1, 1, 2, and expansion cohorts, the first weekly carotuximab dose will be given on Cycle 1 Day 1 (C1D1) following the initial dose of nivolumab on C1D1. The carotuximab premedications will be administered immediately after the nivolumab infusion is complete and all nivolumab infusion reactions have resolved. The initial carotuximab dose will be split into 2 doses whereby 3 mg/kg will be administered on C1D1 and the balance will be administered at C1D4. The entire weekly dose of carotuximab (6, 8 or 10 mg/kg) is then given on C1D8, C1D15, and C1D22, and then 15 mg/kg of carotuximab is given every 2 weeks beginning with C2D1. Each cycle will be 28 days in duration.

Table 6: Study Drug Dosing Schedule

Dose Level	Number of evaluable patients	Carotuximab mg/kg IV weekly[a] starting C1D1 for 4 doses and then every 2 weeks	Nivolumab IV every 2 weeks starting C1D1
-1	3-6	6 mg/kg weekly through Cycle 1 → 15 mg/kg every 2 weeks	240 mg
1 (starting dose)	3-6	8 mg/kg weekly through Cycle 1 → 15 mg/kg every 2 weeks	240 mg
2	3-6	10 mg/kg weekly through Cycle 1 → 15 mg/kg every 2 weeks	240 mg
Expansion Cohort 1[b]	Up to 12	Maximum tolerated dose (MTD)	240 mg
Expansion Cohort 2[c]	Up to 12	Maximum tolerated dose (MTD)	240 mg

[a]The first weekly carotuximab dose will be split into 2 doses whereby 3 mg/kg is administered on Cycle 1 Day 1 (C1D1) and the balance is administered on Cycle 1 Day 4.
[b]Expansion Cohort 1: Patients who have not been treated previously with a PD-1/PD-L1 checkpoint inhibitor and have histological disease recurrence or progression during or after prior platinum-containing doublet chemotherapy regimen.
[c]Expansion Cohort 2: Patients who have relapsed following prior treatment with a PD-1/PD-L1 checkpoint inhibitor without Grade 3 immune-related toxicity.

6.1.3. Carotuximab Packaging and Labeling

Carotuximab will be supplied at 25 mg/mL in 20 mM L-Histidine/L-Histidine Monohydrochloride, 240 mM Trehalose, 0.01% Polysorbate 20 formulation (25 mg carotuximab in one or more of the following presentations.

200 mg Carotuximab/8 mL single-use vial

400 mg Carotuximab/16 mL single-use vial

6.1.4. Carotuximab Storage and Shipping

Carotuximab must be stored upright between 2°C and 8°C (36°F to 46°F) and protected from light.

6.1.5. Carotuximab Preparation

Carotuximab will be prepared in the pharmacy and diluted into normal saline using appropriate aseptic technique. Carotuximab must be administered using an in-line 0.2 micron filter. No incompatibilities between carotuximab and polyvinyl chloride or polyolefin bags have been observed. Multiple vials will be required for a single dose. The following formulae should be used to calculate the volume of carotuximab to be added to normal saline:

Patient weight (kg, up to a maximum 85 kg for women and 100 kg men) × dose level (mg/kg) divided by carotuximab concentration (mg/mL) = volume of carotuximab (mL) to be administered.

The volume of carotuximab that is to be administered can be rounded up or down to the nearest 1.0 mL; in the case of an increment of 0.5 mL the volume should be rounded up. **The maximum weight that should be used for dose calculation in this study is 85 kg for women and 100 kg for men (Note: there is not a weight restriction for enrollment purposes).** If the patient's weight changes by > 10% during the study, the dose of carotuximab will be recalculated. At that time a new baseline weight will be established such that subsequent weight changes by >10% from the new baseline weight would require further recalculation of the carotuximab dose. The calculated volume of carotuximab will be diluted with normal saline. Appropriate judgment should be exercised in withdrawing an adequate amount of saline necessary to permit injection of the appropriate volume of antibody into a normal saline bag in accordance with the dose needed. The final carotuximab concentration must be between 0.6 mg/mL and 10 mg/mL.

The prepared carotuximab must be gently inverted several times in order to ensure a homogeneous solution. The diluted infusion solution of carotuximab should be used within 8 hours of preparation if stored at room temperature, or within 24 hours of dilution if stored at 2° to 8°C (36º to 46ºF). The expiration time should be labeled on the bag. If the diluted infusion solution of carotuximab cannot be infused within 8 hours of preparation (i.e., the prepared infusion is at room temperature for more than 8 hours), a second bag will be

prepared that contains the balance of the planned dose that was not already delivered. The prepared solution should not be frozen.

6.1.6. Carotuximab Administration

Patients should be encouraged to drink abundant fluid (e.g., two 8 ounce glasses of water or juice) prior to the first treatment. Intravenous hydration prior to and during therapy is left to the discretion of the Investigator, but should be considered for patients that may be volume depleted.

The following carotuximab premedications should be administered, to be completed within 30 minutes to 2 hours prior to the start of each carotuximab infusion:

- Acetaminophen 650 mg PO x 1
- Methylprednisolone 100 mg IV will be given prior to the C1D1 and C1D4 infusions. In addition, methylprednisolone will be given in the case of a carotuximab dosing delay of ≥ 10 days between any 2 scheduled weekly doses or in the case of a delay of ≥ 17 days between any 2 scheduled every 2 week doses, or if the patient develops an infusion reaction ≥ Grade 2 during the immediate prior infusion.
- Cetirizine 10 mg IV or PO x 1 (or similar oral or IV antihistamine): Cetirizine (or similar oral or IV antihistimine) may be discontinued starting with C3D1, in the absence of infusion reactions with the prior dose.
- Anti-emetic treatment, while not required, may be given prior to the initial dose and subsequent doses to reduce the frequency of nausea and vomiting that may be observed during TRC105 infusions.

Carotuximab infusions will begin 2 hours to 30 minutes following the completion of the carotuximab premedication, including the methylprednisolone infusion.

Carotuximab will be administered IV utilizing an infusion pump. Carotuximab has been demonstrated to be compatible with polyethylene lined, non-DEHP infusion sets and polyvinyl chloride, non-DEHP infusion sets. Carotuximab is required to be administered with a 0.2 micron downstream filter. The attachment of the infusion pump administration set to the IV bag and transport of the carotuximab study drug to the patient will be performed as per standard study site procedures.

Following the appropriate premedication regimen, the first weekly carotuximab dose will be split into two doses whereby 3 mg/kg is administered (on cycle 1 day 1) over 4 hours (+/- 15 minutes) and the balance (e.g., 5 mg/kg for Dose Level 1) is administered on cycle 1 day 4 over 2 hours (+/- 15 minutes). Do not increase the infusion rate above 25 mg/min. Thereafter, the full (e.g., 8 mg/kg for Dose Level 1) carotuximab dose will be administered IV over 1 hour (+/- 15 minutes). Patients must complete at least one 4 hour infusion without the development of any infusion reactions, in order to reduce the subsequent carotuximab infusion to 2 hours (+/- 15 minutes) and complete a 2 hour infusion without the development of any infusion reactions in order to reduce subsequent carotuximab infusions to 1 hour (+/- 15 minutes). See Table 7 for ideal dosing schemas. Patients with infusion reactions of any kind should be managed appropriately (see Section 6.1.8) and are not permitted to reduce the duration of the next planned infusion.

The rate of carotuximab infusion must not exceed 25 mg/min. When the IV bag containing carotuximab is empty, flush the IV line with 20 mL normal saline. The dose level, time of transfer to IV bag, and the infusion start and stop times must be recorded in the source documents.

Table 7: Ideal Dosing Schema for Study Drugs and Carotuximab Premedications

Sequence	Drugs	C1D1	C1D4	C1D8	C1D15	C1D22	C2D1	C2D15
First in series of dosing	Nivolumab IV over 60 minutes (mg)	240			240		240	
Second in series of dosing								
	Methylprednisolone (mg)	100	100	0	0	0	0	0
	Cetirizine (mg)	10	10	10	10	10	10	10
	Acetaminophen (mg)	650	650	650	650	650	650	650
Third in series of dosing	Carotuximab IV (mg/kg)	3	7	10	10	10	15	15
	Carotuximab infusion duration (hours)	4	2	1	1	1	1	1

6.1.7. Carotuximab Dose Modification/Dose Delays

In Cycle 3 and beyond, carotuximab dose reductions are allowed for Grade 3 or 4 carotuximab-related AEs (including anemia) that have resolved to Grade 1 or that patient's baseline or better, as specified in Table 8. The protocol-specified withdrawal criteria include the following dosing delays:

- Any carotuximab dose delay > 2 days during the 28 day DLT evaluation period (i.e., Cycle 1).
- Dose delay such that the patient receives neither study drug for ≥ 8 consecutive weeks).

Table 8: Allowable Carotuximab Dose Modifications for Toxicity Attributed to Carotuximab

Toxicity Severity Grade	Carotuximab 15 mg/kg every 2 Weeks
Grade 1 or 2	Maintain same dose level
Grade 3 or 4	
• 1st appearance	12 mg/kg every 2 weeks
• 2nd appearance	10 mg/kg every 2 weeks
• 3rd appearance	8 mg/kg every 2 weeks
• 4th appearance	Discontinue carotuximab treatment permanently

Patients with any grade arterial thrombosis (including cerebrovascular ischemia, cardiac ischemia/infarction, or peripheral or visceral arterial ischemia) or Grade 3 or 4 venous thrombosis should be removed from study. Patients with Grade 1 or 2 venous thrombosis

who require anticoagulation will have their carotuximab therapy interrupted. Carotuximab therapy may resume once the following criteria are met:

- The patient is on a stable dose of heparin or low molecular weight heparin.
- The patient has a platelet count > 100,000/μL.
- The patient has not had a hemorrhagic event of Grade 2 or higher while on study.
- The patient does not have a pathological condition that carries a high risk of bleeding (e.g., tumor involving major vessels).
- The patient is benefiting from carotuximab therapy (no evidence of disease progression).

Patients who cannot tolerate nivolumab or carotuximab therapy and who demonstrate a response of complete response (CR), partial response (PR), or stable disease (SD) with the combination and are thought to benefit from continued single-agent therapy may continue on study on carotuximab or nivolumab alone per Section 5.3 of the protocol.

Carotuximab (and nivolumab) should be held for 2 weeks prior and for 2 weeks following major surgical procedures. However, resumption of study treatment can be shorter (but no less than 7 days) or longer than 2 weeks based on clinical judgment of adequate wound healing and recovery from the procedure. For **minor procedures** (e.g., thoracentesis, paracentesis, port placement, laparoscopy, thorascopy, tube thoracostomy, bronchoscopy, endoscopic ultrasonographic procedures, mediastinoscopy, skin biopsies, incisional biopsies, imaging-guided biopsy for diagnostic purposes, and routine dental procedures), carotuximab (and nivolumab) should be held for at least 1 week prior and for at least 1 week after (or until adequate healing).

CAROTUXIMAB PREMEDICATIONS AND SPLIT DOSING FOR CAROTUXIMAB DOSING DELAY: If a patient misses a scheduled weekly carotuximab dose and dosing is resumed ≥ 10 days after the last carotuximab dose or if a patient misses a scheduled every 2 week dose and dosing is resumed ≥ 17 days after the last carotuximab dose, carotuximab premedications (including methylprednisolone) and carotuximab are to be administered as described in Table 4. **Split dosing (2 carotuximab administrations 4 days apart) is not required.** However, it is recommended that if the patient experienced a severe headache with a previous infusion, the first carotuximab dose upon resumption should be given in 2 administrations 4 days apart as was done for the initial dose.

The schedule of assessment (Table 5) should be followed with regard to visits, labs, and any other required assessments even if carotuximab dosing is delayed.

6.1.8. Management of Carotuximab Infusion Reactions

The management of infusion-related reactions is summarized in Table 9. If a patient experiences a Grade 2 or higher adverse reaction during infusion, the infusion should be interrupted and the patient treated accordingly. Antipyretic, antihistamine, antiemetic, anti-inflammatory, and/or other symptomatic medications including epinephrine may be administered as indicated. For Grade 2 and certain Grade 3 infusion-related reactions, the infusion may be restarted at half of the previous rate and when the infusion reaction has resolved, and then increased per patient tolerance to the baseline rate and a maximum of 25 mg/min. For Grade 4 infusion reactions, the infusion should not be restarted and the patient should discontinue study drug treatment. Infusion reactions will be recorded as AEs in the

case report form (CRF). Interventions should be documented as concomitant medications or concomitant treatments, as appropriate.

Table 9: Management of Infusion Reactions

Infusion Reaction Severity	Recommended Management
Grade 1 (mild)	**1.** No intervention **2.** Continue infusion unless symptoms worsen
Grade 2 (moderate)	**1.** Interrupt infusion **2.** Treat with symptomatic medications[a] **3.** Resume infusion at half the previous rate when infusion-related symptoms improve to ≤Grade 1. Rate may be increased to 100% of previous rate after 30 minutes in the absence further complications.
Grade 3 (severe)	**1.** Interrupt infusion **2.** Treat with symptomatic medications[a] **3.** Monitor patient until infusion-related symptoms resolve, including hospitalization if necessary **4.** Discontinue study drug treatment unless other factors that contributed to the infusion reaction are identified and corrected, in which case the infusion may be resumed at half the previous rate when infusion-related symptoms improve to ≤ Grade 1. Rate may be increased to 100% of previous rate after 30 minutes in the absence further complications
Grade 4 (life-threatening)	**1.** Discontinue infusion **2.** Treat with symptomatic medications[a] **3.** Hospitalize patient **4.** Discontinue study drug treatment

[a]Symptomatic medications may include but are not limited to diphenhydramine 50 mg IV and/or hydrocortisone 100 mg IV (for fever, rash, hypoxia, or other hypersensitivity reactions), meperidine 50-100 mg IV (for shaking chills/rigors), oxygen by mask or nasal cannula (for hypoxia), epinephrine 0.5 mg intramuscular (IM) (for hypotension or bronchospasm), albuterol inhaler or nebulizer (for bronchospasm), IV fluids (for hypotension), and ondansetron 0.15 mg/kg IV (for nausea).

6.1.9. Carotuximab Drug Accountability

The Investigator must maintain an accurate accounting of carotuximab supplies. During the study, the following information must be recorded:

- Date of receipt, quantity, and lot number of the carotuximab study drug received.
- Identification number of the patient to whom the product is dispensed.
- The date(s) and quantity of the product dispensed.
- Dates and quantity of product returned, lost, or accidentally or deliberately destroyed.

Investigational Drug Accountability Logs should be maintained by the site and must be readily available for inspection.

6.1.10. Carotuximab Study Drug Handling and Disposal

Carotuximab must be stored upright between 2°C and 8°C (36°F to 46°F). The Investigator should not return clinical study materials to TRACON unless specifically instructed to do so by TRACON. Used vials do not need to be maintained. All expired vials of carotuximab should be retained until destruction is authorized by a TRACON representative. The Site Pharmacist will be responsible for documenting the destruction (according to institutional requirements) of used or expired vials.

6.2. Description of Nivolumab

See the most recent version of the nivolumab package insert.

6.2.1. Nivolumab Composition

See the most recent version of the nivolumab package insert.

6.2.2. Nivolumab Dose Level

240 mg will be administered IV every 2 weeks, starting on Cycle 1 Day 1 (C1D1), until disease progression or unacceptable toxicity.

6.2.3. Nivolumab Packaging and Labeling

See the most recent version of the nivolumab package insert.

6.2.4. Nivolumab Storage

See the most recent version of the nivolumab package insert.

6.2.5. Nivolumab Preparation

Commercially available nivolumab will be utilized in this study. Nivolumab should be prepared according to the most recent version of the package insert.

6.2.6. Nivolumab Administration

Administer nivolumab 240 mg IV over 60 minutes on Days 1 and 15 (every 2 weeks) of each 28-day cycle until progression according to the package insert, with any dose modifications done per the package insert. Nivolumab is administered before carotuximab and carotuximab premedications.

6.2.7. Nivolumab Dose Modification

Modify the nivolumab dose as may be necessary per the most recent version of the package insert.

6.2.8. Nivolumab Drug Accountability

The Investigator must maintain an accurate accounting of the nivolumab product that is used. During the study, the following information must be maintained:

- Identification number of the patient to whom the product is dispensed.
- Lot number dispensed.
- The date(s) and quantity of the product dispensed.

6.2.9. Nivolumab Drug Handling and Disposal

The Site Pharmacist will be responsible for documenting the destruction (according to institutional requirements) of used or expired vials.

6.3. Concomitant Medications

No other approved or investigational anticancer treatment will be permitted during the study period. No other investigational drug may be used during treatment on this protocol, and concurrent participation in another clinical trial is not allowed.

Patients who receive nonsteroidal anti-inflammatory drugs (NSAIDs) on study should also receive peptic ulcer disease (PUD) prophylaxis with a histamine-2 (H2) blocker or proton pump inhibitor.

Narcotic analgesics, NSAIDs, ketorolac and triptans (e.g., sumatriptan) may be offered as needed for relief of pain or headaches. Antihistamines and decongestants may be offered for the treatment of sinus congestion.

Antibiotic prophylaxis should be used for invasive dental procedures.

Packed red blood cells, colony stimulating factors, and platelet transfusions should be administered as clinically indicated.

Prophylaxis for nausea or vomiting may be offered prior to the initial infusion of carotuximab and/or nivolumab and may be used thereafter as needed.

6.4. Treatment Compliance

All carotuximab and nivolumab infusions will occur at the investigational sites under the direct supervision of the Investigator or his or her designee.

6.5. Patient Enrollment

Patients will be manually enrolled by TRACON Pharmaceuticals and assigned an 8-digit patient number. This 8-digit number will be used to identify patients throughout their participation in the trial. A regulatory binder will be provided and will include detailed instructions for the manual enrollment process.

7. ASSESSMENT OF EFFICACY

7.1. Radiologic Tumor Assessment

The primary efficacy assessment will be best overall response by iRECIST as defined in Table 10 and Seymour et al [18]. iRECIST introduces the criterion of unconfirmed progressive disease (iUPD) to prevent the discontinuation of study treatment for cases of pseudoprogression. If the criteria for iUPD have never been met, principles should follow RECIST 1.1. However, if the criteria for iUPD have been met, the next timepoint response could be:

- iUPD: no change noted in any category of lesion
- iSD, iPR, or iCR. Here, iUPD (followed by iCPD) should occur again
- iCPD, if the category in which iUPD was met at the last timepoint response shows a further increase in tumor burden as evidenced (as applicable) by a $\geq$ 5 mm increase in sum of measures of target or new target lesions, further increase in non-target or new non-target lesions, or an increase in the number of new lesions.

Investigators will make treatment decisions based on these assessments. All lesions will be classified as target or non-target lesions at the Screening visit. Each lesion designation will be maintained through the course of the study.

The same method and technique should be used to characterize each identified and reported lesion at Screening, during the study treatment period, and at the End of Study visit. Imaging-based evaluation over clinical examination is the required technique when both could be used to assess the antitumor effect of the treatment. Clinical Oncology review of all tumor measurements is desired.

Whenever possible, clinical evaluation of superficial lesions should not be used as the sole form of measurement. However, when necessary, color photograph with metric caliber is acceptable. Tumor evaluation by positron emission tomography (PET) scan or by ultrasound may not substitute for CT or MRI scans.

Radiological tumor assessments will be performed at Screening, as outlined in the Schedule of Assessments (Table 5), and whenever disease progression is suspected. Another tumor assessment will be performed at the End of Study visit if an assessment has not been performed within the prior 8 weeks. All patient files and radiological images must be available for CRF source verification.

Table 10: Assignment of Timepoint Response Using iRECIST

	Timepoint Response with no previous iUPD in any category	**Timepoint response with previous iUPD in any category**[a]
Target lesions: iCR; non-target lesions: iCR; new lesions: no	iCR	iCR
Target lesions: iCR; non-target lesions: non-iCR/non-iUPD; new lesions: no	iPR	iPR
Target lesions: iPR; non-target lesions: non-iCR/non-iUPD; new lesions: no	iPR	iPR
Target lesions: iSD; non-target lesions: non-iCR/non-iUPD; new lesions: no	iSD	iSD
Target lesions: iUPD with no change, or with a decrease from last timepoint; non-target lesions: iUPD with no change, or decrease from last timepoint; new lesions; yes	Not Applicable	New lesions confirm iCPD if new lesions were previously identified and they have increased in size (≥ 5 mm in sum of measures for new lesion target or any increase for new lesion non-target) or number; if no change is seen in new lesions (size or number) from last timepoint, assignment remains iUPD
Target lesions: iSD, iPR, iCR; non-target lesions: iUPD; new lesions: no	iUPD	Remains iUPD unless iCPD is confirmed on the basis of a further increase in the size of non-target disease (does not need to meet RECIST 1.1 criteria for unequivocal progression)
Target lesions: iUPD; non-target lesions: non-iCR/non-iUPD, or iCR; new lesions: no	iUPD	Remains iUPD unless iCPD is confirmed on the basis of a further increase in sum of measures ≥ 5mm; otherwise, assignment remains iUPD
Target lesions: iUPD; non-target lesions: iUPD; new lesions: no	iUPD	Remains iUPD unless iCPD is confirmed based on a further increase in previously identified target lesion iUPD in sum of measures ≥ 5mm or non-target lesion iUPD (previous assessment need not have shown unequivocal progression)
Target lesions: iUPD; non-target lesions: iUPD; new lesions: yes	iUPD	Remains iUPD unless iCPD is confirmed on the basis of a further increase in previously identified target lesion iUPD sum of measures ≥ 5mm, previously identified non-target lesion iUPD (does not need to be unequivocal), or an increase in the size or number of new lesions previously identified
Target lesions: non-iUPD or progression; non-target lesions: non-iUPD or progression; new lesions: yes	iUPD	Remains iUPD unless iCPD is confirmed on the basis of an increase in the size or number of new lesions previously identified

[a]Previously identified in assessment immediately before this timepoint.

Target lesions, non-target lesions, and new lesions defined according to RECIST 1.1 principles; if not pseudoprogression occurs, RECIST 1.1 and iRECIST categories for complete response, partial response, and stable disease would be the same.

8. ASSESSMENT OF SAFETY

8.1. Safety Parameters

Safety will be characterized in terms of the incidence, timing, severity graded by the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE), Version 4.03), seriousness, and drug-relatedness of adverse events (AEs) and laboratory abnormalities. In addition, physical examination, vital signs, and ECOG performance status will be serially monitored. Laboratory safety analyses will be based on the local laboratory data, and will include hematology (including iron studies at baseline), serum chemistry (including liver and kidney function, and TSH), urinalysis, serum or urine pregnancy testing, and coagulation profile (baseline only). Serum will also be assessed for immunogenicity to carotuximab (including anti-product antibody titers). In addition, single tracing 12-lead ECGs will be performed at the time points indicated in the Schedule of Assessments (Table 5). QT, PR and QRS intervals and heart rate will be captured. ECGs will also be collected as clinically indicated throughout the study.

8.1.1. Laboratory Safety Assessments

Abnormal and clinically significant laboratory tests should be recorded as adverse events. To meet the definition of clinically significant, the test result generally requires a change in medical management (e.g., new medication, unplanned treatment, additional tests, etc.).

8.1.1.1. Hematology, Serum Chemistry, Coagulation, and Pregnancy Test

Assessments will be performed at the time points indicated in the Schedule of Assessments (Table 5) and analyzed at local laboratories. Investigators may have additional blood tests performed for the purpose of planning treatment administration, or for following AEs, as clinically indicated.

- Hematology: Complete blood count (CBC) with differential and platelet count. Baseline iron studies including serum iron, ferritin, and total iron binding capacity.
- Coagulation: Prothrombin time and International Normalized Ratio (INR).
- Serum Chemistry: Total bilirubin, alanine transaminase (ALT), aspartate transaminase (AST), alkaline phosphatase, lipase, amylase, sodium, potassium, bicarbonate, chloride, calcium, phosphorus, blood urea nitrogen, creatinine, magnesium, thyroid stimulating hormone (TSH), and glucose.
- Pregnancy Test: Serum or urine pregnancy tests will be performed locally on all female patients of childbearing potential. Patients must be surgically sterile (i.e., ≥ 6 weeks following surgical bilateral oophorectomy with or without hysterectomy or tubal ligation) or be postmenopausal, or must agree to use effective contraception during the study and for ≥ 180 days following last dose of study drug (carotuximab or nivolumab, which occurs later). The definition of effective contraception is provided in Section 2.6.1 of this protocol.

8.1.1.2. Urinalysis

Urinalysis (without microscopic analysis, unless indicated) will be performed at time points indicated in the Schedule of Assessments (Table 5) and analyzed by local laboratories.

Microscopic analysis, urine protein-creatinine ratio (UPCR), and 24-hour urine collection for protein should be performed as clinically indicated.

8.1.2. Physical Examination

A physical examination including, but not limited to, general appearance, head, eyes, ears, nose, throat, neck, heart, chest, abdomen, musculoskeletal, extremities, skin, lymph nodes, neurological genitourinary (as appropriate), and rectal (as appropriate) will be assessed at time points indicated within the Schedule of Assessments (Table 5). The physical examination will include examination of known and suspected sites of disease.

8.1.3. Vital Signs

Heart rate, temperature, blood pressure, respiratory rate, and weight will be assessed at time points indicated within the Schedule of Assessments (Table 5). Height will be assessed only at the Screening visit. Heart rate, temperature, blood pressure, and respiratory rate will also be assessed during carotuximab infusions as described in Section 4.1.2.2 and the footnotes of the Schedule of Assessments (Table 5).

8.1.4. Performance Status

The ECOG scale will be used to assess performance status at Screening and at time points indicated within the Schedule of Assessments (Table 5).

8.1.5. Electrocardiogram (ECG)

A single tracing 12-lead tracing will be used for all ECGs. It is preferable that the machine used has a capacity to calculate standard intervals automatically. ECG will be performed at the time points indicated in the Schedule of Assessments (Table 5) and as clinically indicated throughout the study.

8.2. Adverse Events

All observed or volunteered AEs regardless of suspected causal relationship to study drug (carotuximab and nivolumab) will be reported as described below.

8.2.1. Definition of Adverse Event

An AE is any untoward medical occurrence in a trial patient who is administered a drug or biologic (medicinal product); the event may or may not have a causal relationship with the medicinal product. Examples of AEs include, but are not limited to the following:

- Clinically significant symptoms and signs including:
  - Worsening of signs and symptoms of the malignancy under study drug treatment
  - Signs and symptoms resulting from drug overdose, abuse, misuse, withdrawal, sensitivity, dependency, interaction, or toxicity
  - All treatment-emergent possibly related and unrelated illnesses, including the worsening of a preexisting illness
  - Injury or accidents - Note that if a medical condition is known to have caused the injury or accident (e.g., hip fracture from a fall secondary to dizziness), the

medical condition (dizziness) and a medical problem caused by the accident (hip fracture from a fall) should be reported as 2 separate AEs.

- Symptoms or signs resulting from exposure *in utero*

- Abnormalities in physiological testing or physical examination findings that require clinical intervention or further investigation (beyond ordering a repeat confirmatory test)
- Laboratory abnormalities that meet any of the following criteria (Note: Merely repeating an abnormal test, in the absence of any of the below conditions, does not constitute an AE. Any abnormal test result that is determined to be an error does not require reporting as an AE.)
  - Test result that is associated with accompanying symptoms
  - Test result that requires additional diagnostic testing or medical/surgical intervention
  - Test result that leads to a change in study drug (carotuximab or nivolumab) dosing other than protocol-stipulated dose adjustments or discontinuation from the trial, significant additional concomitant drug treatment, or other therapy
  - Test result that is considered to be an AE by the Investigator or TRACON

8.2.2. Serious Adverse Events

An AE that meets one or more of the following criteria/outcomes is classified as a serious /ae (SAE):

- Results in death
- Is life-threatening (i.e., at immediate risk of death)
- Requires in patient hospitalization or prolongation of existing hospitalization.
- Results in persistent or significant disability/incapacity
- Results in congenital anomaly/birth defect
- Other Important Medical Events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or may require medical or surgical intervention to prevent one of the outcomes listed above. Examples of such events are intensive treatment in an emergency room for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or the development of drug dependence or drug abuse.

Serious also includes any other AE that the Investigator or sponsor judges to be serious, or which is defined as serious by the Health Regulatory Authority (HRA) in the country in which the event occurred.

Progression of the malignancy under study (including signs and symptoms of progression) should be reported as an SAE if it meets criteria for serious including hospitalizations due to signs and symptoms of disease progression.

The onset date of an SAE is defined as the date on which the event initially met serious criteria (e.g., the date of admission to a hospital). The end date is the date on which the event no longer met serious criteria (e.g., the date the patient was discharged from a hospital).

8.2.2.1. Hospitalization

AEs associated with in-patient hospitalization, or prolongation of an existing hospitalization, are considered serious. Any initial admission, even if the duration is less than 24 hours, is considered serious. In addition, any transfer within the hospital to an acute/intensive care unit is considered serious (e.g., transfer from the psychiatric wing to a medical floor or transfer from a medical floor to a coronary care unit). However, the following "hospitalizations" **should not** per se constitute a serious AE:

- Rehabilitation facility admission
- Hospice facility admission
- Respite care
- Skilled nursing facility admission
- Nursing home admission
- Emergency room visit, including observation unit visit
- Outpatient same day surgery/procedure
- Hospitalization or prolongation of hospitalization in the absence of precipitating clinical adverse events as follows:
  - Admission for treatment of preexisting condition not associated with the development of a new AE or with a worsening of the preexisting condition
  - Social admission
  - Administrative admission (e.g., for yearly physical exam)
  - Protocol-specified admission during a clinical trial
  - Optional admission not associated with a precipitating clinical adverse event (e.g., for elective cosmetic surgery)
  - Preplanned treatments or surgical procedures that are not related to an SAE
- Diagnostic and therapeutic noninvasive and invasive procedures, such as surgery, should not be reported as AEs. The medical condition for which the procedure was performed should be reported if it meets the definition of an AE (e.g., acute appendicitis that begins during the AE reporting period should be reported as an AE and the appendectomy should be recorded as a concomitant treatment).

8.3. Reporting Adverse Events

8.3.1. Eliciting Adverse Event Information

The Investigator is to report all directly observed AEs and all AEs reported by the study patient using concise medical terminology. In addition, each study patient will be questioned about AEs at each clinic visit following initiation of treatment. The question asked will be, or words to the effect, "Since your last clinic visit have you had any health problems?"

8.3.2. Adverse Event Reporting Period

Safety information for each patient will be collected from the date of informed consent. AEs occurring prior to the initiation of the study treatment with nivolumab and/or carotuximab study drug will be considered "baseline-emergent adverse events," will be recorded on corresponding CRFS, and will not be retained for patients who fail screening. The AE reporting period for this study begins when the patient has received even a portion of the first dose of nivolumab or carotuximab study drug and ends 28 days after the last dose of the latest study treatment (i.e., nivolumab or carotuximab study drug) is administered.

All AEs that occur in study patients during the AE reporting period specified in the protocol must be reported to TRACON, whether or not the event is considered study treatment-related. In addition, any known untoward event that occurs beyond the AE reporting period that the Investigator assesses as related to either investigational medication/product should also be reported as an AE.

8.3.3. Reporting Requirements

Each AE is to be classified by the Investigator as SERIOUS or NONSERIOUS. This classification of the gravity of the event determines the reporting procedures to be followed. If an SAE occurs, reporting will follow local and international regulations, as appropriate.

The Investigator must notify the Sponsor of any AE that meets any one of the criteria for an SAE immediately upon learning of the event. Any subsequent revisions that are made to information pertaining to serious suspected adverse drug (carotuximab or nivolumab) reactions (e.g., change in grade, etc.), including a change in attribution to study drug from "not related" to "suspected adverse drug reaction" should also be communicated to TRACON immediately. This notification should be made to:

PRIMARY MEDICAL MONITOR

Charles Theuer, MD, PhD

TRACON Pharmaceuticals, Inc.

4350 La Jolla Village Drive, Suite 800

San Diego, California 92122

Office Phone: 1.858.550.0780 x233

Cell Phone: 1.858.344.9400

Email: ctheuer@traconpharma.com

SECONDARY MEDICAL MONITOR

James Freddo, MD

TRACON Pharmaceuticals, Inc.

4350 La Jolla Village Drive, Suite 800

San Diego, California 92122

Cell Phone: 1.858.472.2330

Email: jfreddo@traconpharma.com

Following notification, the Investigator will report the SAE via the AE CRF via the data management system. The initial AE CRF is to be updated with more detailed AE information within **5 calendar days** of the event onset.

In the rare event that the Investigator is not immediately aware of an SAE (e.g., if the study patient seeks urgent medical attention elsewhere), the Investigator is to notify the Sponsor immediately upon learning of it and document his/her first awareness.

All serious adverse events and those non-serious events assessed by the Investigator as suspected reactions (i.e., at least possibly related) to a TRACON investigational medicinal product must be followed, even after the patient's withdrawal from study, until the event is either resolved, improved to the patient's pre-treatment baseline or better, stable without anticipated future change, or the patient is lost to follow-up, or, in the case of a suspected adverse reaction, later determined to be not related to the TRACON investigational medicinal product.

SAEs that are unexpected and associated with use of the study medication will be reported to the US Food and Drug Administration (FDA) and all participating clinical sites by TRACON via MedWatch forms. For SAEs which are fatal or life-threatening, unexpected, and associated with use of the study drug (carotuximab or nivolumab), a 7-Day Alert Report will be submitted to the FDA within 7 calendar days of receipt of the SAE information. For all other SAES that are unexpected and associated with use of the study drug (carotuximab or nivolumab), a written report will be made no more than 15 calendar days from the date TRACON learns of the event. Participating clinical sites will be notified of these events in parallel with FDA notification.

All AEs, including SAEs, are to be reported on the AE CRFs.

8.3.4. Recording Adverse Events in the Case Report Forms

The Investigator is to report all directly observed AES and all AEs reported by the study patient. In addition, each study patient will be questioned about AEs. All AEs that meet the criteria specified in Section 8.2.1 are to be recorded on patient source documents and on the CRFs. AEs should be reported using concise medical terminology on the CRFs.

8.3.5. Grading of Adverse Event Severity

To report AEs on the CRFs, the Investigator will use the severity grading as described in NCI CTCAE (Version 4.03). Every effort should be made by the Investigator to assess the AE according to CTCAE criteria. If the Investigator is unable to assess severity because the term is not described in NCI CTCAE (Version 4.03), then severity of MILD, MODERATE, SEVERE, LIFE-THREATENING, or FATAL may be used to describe the maximum intensity of the AE, as guided by Table 11. Note that the selection of the most appropriate verbatim term for AEs is not restricted to only those toxicities represented in NCI CTCAE. For purposes of consistency, these intensity grades are defined as follows:

Table 11: Adverse Event Severity Grading

Grade	Non-CTCAE Severity	Definition
1	Mild	Does not interfere with patient's usual function
2	Moderate	Interferes to some extent with patient's usual function
3	Severe	Interferes significantly with patient's usual function

Grade	Non-CTCAE Severity	Definition
4	Life-Threatening	Results in immediate risk of patient's death
5	Fatal	Results in patient's death

Note the distinction between the severity and the seriousness of an AE. A severe AE is not necessarily a serious AE. For example, a headache may be severe (interferes significantly with patient's usual function) but would not be classified as serious unless it met one of the criteria for serious events.

8.3.6. Relationship to Study Drug (Carotuximab and Nivolumab)

In this study, there are 2 study drugs; the investigational drug carotuximab is given in combination with the approved drug nivolumab. The relationship of each AE to each study drug will be made independently for each of the 2 study drugs and should be guided in part by the known safety profile of each drug, including the carotuximab IB and the nivolumab package insert. The relatedness should be classified by the Investigator using the following guidelines:

- Suspected Adverse Reaction: There is a reasonable possibility that study drug caused the AE (i.e., there is evidence to suggest a causal relationship between study drug and the AE).
- Not Related: There is no reasonable possibility that the AE is associated with study drug.

AEs related to study drug are considered Adverse Drug Reactions (ADRs).

8.3.7. Expectedness

All AEs and ADRs are considered "unexpected" if not listed in the TRC150 IB for carotuximab or the package insert for nivolumab, as applicable, and not listed at the specificity or severity that has been observed in this study. For example, under this definition, hepatic necrosis would be unexpected (by virtue of greater severity) if the IB referred only to elevated hepatic enzymes or hepatitis. Similarly, cerebral thromboembolism and cerebral vasculitis would be unexpected (by virtue of greater specificity) if the IB listed only cerebral vascular accidents. "Unexpected," as used in this definition, also refers to AEs or suspected ADRs that are mentioned in the IB as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug, but are not specifically mentioned as occurring with the particular drug under investigation.

8.3.8. Exposure *in Utero*

If any study patient (or partner of a study patient) becomes or is found to be pregnant during the study or within 90 days of discontinuing the investigational medication/product, the Investigator must report the information to TRACON, or designee via the Pregnancy Notification Report Form within 24 hours of awareness of the pregnancy. This must be done irrespective of whether an AE has occurred. The information submitted should include the anticipated date of delivery.

The Investigator will follow the pregnant patient (or partner of a study patient) until completion of the pregnancy or until pregnancy termination (i.e., induced abortion) and then notify TRACON, or its designee, of the outcome within 5 days or as specified below. The

Investigator will provide this information as a follow-up to the initial report. The reason(s) for an induced abortion must be specified.

The Investigator should follow procedures for reporting an SAE if pregnancy outcome meets criteria for an SAE (e.g., spontaneous abortion, stillbirth, neonatal death, or congenital anomaly [including that in an aborted fetus]).

In the case of a live birth, the "normality" of the newborn can be assessed at the time of birth and the Pregnancy Outcome Report Form should be completed (i.e., no minimum follow-up period of a presumably normal infant must pass before a Pregnancy Outcome Report Form can be completed). The "normality" of an aborted fetus can be assessed by gross visual inspection unless pre-abortion laboratory findings are suggestive of a congenital anomaly.

Additional information about pregnancy outcomes that are classified as SAEs follows:

- "Spontaneous abortion" includes miscarriage and missed abortion.
- All neonatal deaths that occur within 1 month of birth should be reported, without regard to causality, as SAEs. In addition, any infant death after 1 month that the Investigator assesses as possibly related to the *in utero* exposure to the study drug should also be reported.

8.3.9. Follow-up of Unresolved Adverse Events

All AEs should be followed until resolved, improved to the patient's pre-treatment baseline severity or better, or the patient's participation in the study is completed, whichever occurs first. All serious adverse events and those non-serious events assessed by the Investigator as suspected reactions (i.e., at least possibly related) to a carotuximab must be followed, even after the patient's withdrawal from study, until the event is either resolved, improved to the patient's pre-treatment baseline or better, stable without anticipated future change, or the patient is lost to follow-up, or, in the case of a suspected adverse reaction, later determined to be not related to the TRACON investigational medicinal product. Any increase or decrease in AE grade should be recorded as a new adverse event. All AEs should also be documented on the AE CRF.

8.4. Safety Monitoring

The TRACON clinical team will monitor the study through periodic teleconferences with the Principal Investigators to share experiences and ensure communication. Safety of carotuximab clinical trials is monitored by an Independent Safety Advisory Committee and the TRACON Safety Monitoring Committee that each meet at least quarterly. These committees will monitor safety throughout this study and all studies of carotuximab via the following activities:

- Surveillance for SAEs according to regulatory guidelines
- Routine monitoring of non-serious AES as they are recorded in the CRFs

Carotuximab toxicity information that may affect the treatment of patients on this study will be promptly communicated in writing to all participating carotuximab clinical sites, as well as institutions participating in this clinical trial.

9. OTHER ASSESSMENTS

9.1. Other Laboratory Assessments

9.1.1. Pharmacokinetics

Samples will be sent to Fisher BioServices Inc for storage. See separate laboratory manual for specific collection, storage, and shipping information.

9.1.1.1. Carotuximab and Nivolumab Trough Concentration

A 5 mL blood sample will be collected prior to dosing with carotuximab and nivolumab on the days indicated within the Schedule of Assessments (Table 5). Samples will be separated and stored at approximately -70°C for shipment to third-party laboratory. See separate laboratory guide for further collection and shipment information.

9.1.2. Carotuximab Immunogenicity

Samples will be sent to Fisher BioServices Inc for storage. See separate laboratory manual for specific collection, storage and shipping information.

Carotuximab anti-product antibody (APA) concentrations will be measured using validated enzyme-linked immunosorbent assay (ELISA) methods at the time points specified in the Schedule of Assessments (Table 5) in all patients. APA concentrations will be evaluated in the context of pharmacokinetic parameters and AE profiles. Samples will be separated and stored at approximately -70°C for shipment to Fisher BioServices Inc. See separate laboratory guide for further collection and shipment information.

9.1.3. Protein Biomarkers

One 10 mL purple top (K_2EDTA) tube of blood will be collected on the days indicated within the Schedule of Assessments (Table 5). Samples will be stored at approximately -70°C and shipped to Fisher BioServices Inc for storage until the time of analysis. Duke University Medical Center will analyze plasma for several biomarkers including but not limited to VEGF, VEGF-R2, placental growth factor (PIGF), and sCD105. Please see the separate laboratory guide for further collection and shipment information.

9.1.4. Tumor Biopsies

Tumor biopsies will be fixed in formalin and embedded in paraffin, and immune cell markers will be assessed by immunohistochemistry and immunofluorescence, focusing on CD8+ T-cells, T regulatory cells, and MDSCs.

9.1.5. Archival Tumor Specimens

Archival specimens (formalin-fixed, paraffin-embedded) of the primary cancer and/or metastatic cancer specimen for each study participant will be obtained. It is preferable that the entire paraffin block be submitted, but if this is not feasible, then at least 20 unstained slides are requested for immunohistochemical analysis (sections of ~ 5 microns are preferred). Samples will be stored at room temperature and shipped to Fisher BioServices Inc for storage until the time of analysis. See separate laboratory guide for further collection and shipment information.

10. STATISTICS

10.1. Statistical Design/Sample Size

The number of patients to be enrolled in this study will depend upon the observed safety profile, which will determine the number of patients per dose level and the number of dose escalations. It is anticipated that approximately 18 to 30 patients will be enrolled in the study.

The probability of escalation to the next higher dose for each underlying true DLT rate is shown in Table 12. For example, at a dose level with a toxicity rate of 5% of patients, there is a greater than 95% probability of escalating. Conversely, for a dose level with a true toxicity rate of 70%, the probability of escalating is < 5%.

Table 12: Probability of Escalation to the Next Dose for Each True Underlying DLT Rate at a Dose Level

True Underlying DLT Rate	5%	10%	20%	30%	40%	50%	60%	70%	80%	90%
Probability of Escalating Dose	0.97	0.91	0.71	0.49	0.31	0.17	0.08	0.03	0.01	0.001

The probability of failing to observe DLT in a sample size of 3 or 6 patients given various true underlying toxicity rates in shown in Table 13. For example, with 6 patients, the probability of failing to observe toxicity occurring at least 40% of the time is less than 5%. The enrollment of 15 patients at a given dose level will reduce the probability of failing to observe toxicity occurring at least 30% of the time to < 5%.

Table 13: Probability of Failing to Observe True Underlying DLT Rate at a Dose Level

Probability of Failing to Observe Toxicity by Sample Size	True Underlying DLT Rate									
	5%	10%	20%	30%	40%	50%	60%	70%	80%	90%
N = 3	0.86	0.73	0.51	0.34	0.22	0.13	.0064	0.027	0.008	0.001
N = 6	0.74	0.53	0.26	0.12	0.047	0.016	0.0041	<0.001	<0.001	<0.001

10.1.1. Definition of Analyzed Study Populations

The following study populations will be considered when reporting study results:

- The study population for safety includes all patients receiving at least a portion of 1 dose of either study drug (carotuximab and nivolumab).
- The study population for PK includes also patients with adequate data for PK carotuximab or nivolumab.
- The study population for efficacy will include all safety population patients who have baseline and follow-up tumor measurements as required for assessment by iRECIST.

Patients who experience DLT who receive less than the prescribed dose of carotuximab or nivolumab due to documented toxicity in Cycle 1 will be considered evaluable for dose escalation purposes.

Only those patients who are deemed ineligible (e.g., do not satisfy eligibility criteria) or who receive no study drug (i.e., no carotuximab or nivolumab) will be eliminated from the analysis. Ineligible patients who receive therapy will not be included in the assessment of efficacy endpoints, but their data will be included in the assessment of all AE reporting.

10.2. Data Analysis

Descriptive statistics (such as means, medians, standard deviations, and ranges for continuous data and percentages for categorical data) will be used to summarize patient characteristics, treatment administration/compliance, immunogenicity, efficacy, pharmacokinetic parameters, protein biomarkers, and archival tumor tissue. Data will also be displayed graphically, where appropriate.

10.2.1. Analysis of Primary Objective

Dose-limiting toxicities (DLTs) will be summarized by category (hematologic and non-hematologic) and by Medical Dictionary for Regulatory Activities (MedDRA) Preferred Term (PT) and System Organ Class (SOC).

All AEs with an onset after initiation of treatment will be considered as treatment-emergent AEs. A preexisting condition that worsens after study drug treatment will also be considered as a treatment-emergent AE. All AEs will be coded by MedDRA SOC and PT.

The number and percentage of patients with the following types of treatment-emergent AEs will be summarized: all AEs, all SAEs, AEs related to study drug ((carotuximab) and nivolumab), AEs resulting in study drug discontinuation, and clinically significant laboratory abnormalities. Non-treatment-emergent serious AEs will be presented separately from treatment-emergent AEs. Deaths will be reported with demographic information.

10.2.2. Analysis of Pharmacokinetics

Trough (pre-dose) serum carotuximab and nivolumab concentrations will be measured using validated ELISA methods. The carotuximab pharmacokinetic data may be assessed for potential correlations with response, PFS, survival, AEs, and baseline characteristics using descriptive statistics and models as appropriate.

10.2.3. Objective Response

The best response (CR, PR, SD, or PD according to iRECIST) for each patient with measurable disease who received at least 1 dose of study drug will be listed in Expansion Cohort 1 and Expansion Cohort 2. SD will be defined as lack of tumor progression lasting for 3 cycles or longer. At least 3 of 12 evaluable patients must demonstrate a response by iRECIST (PR and CR) in Cohort 1 (PD-1 naïve patients) to justify further development of the combination of TRC105 and nivolumab in this patient population. Given a desired 30% response rate, the expectation of at least 3 responses is 75% using the binomial distribution. At least 1 of 12 evaluable patients must demonstrate a response by iRECIST (PR and CR) in Cohort 2 (PD-1 relapsed patients) to justify further development of the combination of TRC105 and nivolumab in this patient population. Given a desired 15% response rate, the expectation of at least 1 response is 86% using the binomial distribution.

10.2.4. Analysis of Protein Biomarkers

Angiogenic protein biomarker data for each patient who received at least one dose of study drug will be listed.

10.2.5. Analysis of Immunogenicity

Carotuximab anti-product antibody (APA) concentrations will be measured using validated ELISA methods at the time points specified in the Schedule of Assessments (Table 5). APA concentrations will be evaluated in the context of pharmacokinetic parameters and AE profiles.

10.2.6. Analysis of Tumor Biopsies

CD8+ T-cells, T regulatory cells, and MDSCs will be quantified for each patient who received at least 1 dose of study drug and will be listed.

10.2.7. Analysis of Archival Tumor Tissue

CD105 and PD-1/PD-L1 expression will be quantified for each patient who received at least 1 dose of study drug and will be listed. Expression will be determined by immunohistochemistry (IHC). Other markers that may relate to efficacy or toxicity of carotuximab may also be explored.

11. DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

All data entered on CRFs/electronic CRFs (eCRFs) must be verifiable within the patients' source documents (written or electronic record). The Investigator /institution guarantees TRACON representatives and appropriate regulatory authorities direct access to the original source records for the duration of the agreed study record retention period. Printouts of source records that are electronically obtained and stored will not be acceptable for audit/inspection unless provided as certified exact copies and the data remains as meaningful and useful as in its original electronic state.

Legally protected patient identification and other personal health information must be securely stored with limited access by the participating institutions. Unless secure provisions are established by the institution to allow TRACON (or designee) to perform remote monitoring of electronic source records, TRACON (or designee) will review source records/data on site and will not remove any such protected health information.

12. QUALITY CONTROL AND QUALITY ASSURANCE

Monitoring visits to clinical investigational sites will be made by TRACON or its representatives periodically during the trial to ensure that GCPs and all aspects of the protocol are being followed.

The trial site will also be subject to possible inspection by the institutional review board (IRB) or independent ethics committee (IEC) or other appropriate regulatory authority. The trial site is also subject to quality assurance audits performed by TRACON or its representatives.

It is important that the Investigator(s) and their relevant personnel are available during the monitoring visits, audits, and inspections and that sufficient attention, time, and support is devoted to the process.

TRACON and its representatives will be governed by applicable regulations, GCP standards, and internal standard operating procedures (SOPs) for the conduct of monitoring visits and quality assurance (QA) audits.

13. ETHICS

13.1. Institutional Review Board (IRB)/Independent Ethics Committee (IEC)

It is the responsibility of the Investigator to have approval of the study protocol, protocol amendments, informed consent forms, advertisements from the IRB/IEC, and any other patient-distributed materials before potential patients are consented for participation on the trial. All correspondence and other evidence of appropriate and timely communications with the IRB/IEC should be retained in the Investigator/site files. Copies of all IRB/IEC approvals should also be forwarded to TRACON.

The only circumstance in which an amendment may be initiated prior to IRB/IEC approval is where the change is necessary to eliminate apparent immediate hazards to the patients. In that event, the Investigator must notify the IRB/IEC and TRACON in writing within 5 business days after the implementation.

13.2. Ethical Conduct of the Study

The trial will be performed in accordance with the protocol, applicable local regulatory requirements and laws, and the International Council on Harmonization (ICH) Guideline on Good Clinical Practice (GCP), which supports the application of ethical principles that have their origin in the Declaration of Helsinki (see ICH E6, § 2.1).

13.3. Written Informed Consent

The informed consent form language must be agreed upon by TRACON and the IRB/IEC and must be in compliance with ICH GCP, local regulatory requirements, and legal requirements. The informed consent information must not be changed without prior approval by TRACON and the IRB/IEC. The informed consent form used in this trial, and any changes made during the course of the study, must be approved by both the IRB/IEC and TRACON, or designee, before use.

It is the responsibility of the Investigator to give each patient full and adequate verbal and written information regarding the objective and procedures of the trial and the possible risks involved. This information must be provided to the patient prior to undertaking any protocol-specified procedure. Patients must be informed about their right to withdraw from the trial at any time. Furthermore, it is the responsibility of the Investigator to ensure all patients are appropriately informed before obtaining their signed and dated consent. Signatures from the Investigator conducting the informed consent discussion should also be obtained, prior to undertaking any trial-related procedure. Consent by a legally authorized representative is not permitted. Should an impartial witness be needed, ICH E6 requirements for impartial witnesses will apply.

The Investigator will retain the original of each patient's signed consent form in the Investigator/site files.

13.4. Patient Compensation

Patients will not be compensated for participation in this study; this will be outlined in the patient informed consent form.

14. DATA HANDLING AND RECORDKEEPING

14.1. Inspection of Records

CRFs/eCRFs are required and should be completed for each patient who receives treatment with pazopanib or carotuximab. Screen failure CRF's will not be collected. Nevertheless, records of potential patients identified and screened shall be retained on site screening logs. The completed original CRFs/eCRFs are the sole property of TRACON and should not be made available in any form to third parties without written permission from TRACON (except for authorized representatives of the HRA and in accordance with Health Insurance Portability and Accountability Act [HIPAA] regulations).

It is the Investigator's responsibility to ensure completion and to review and approve all CRF data. The investigator will sign off on his/her data per patient. These signatures serve to attest that the Investigator has reviewed and approved the information contained on the CRFs and that the information is complete, accurate, and true. At all times, the Investigator has final personal responsibility for the accuracy and authenticity of all clinical and laboratory data entered on the CRFs.

The use of electronic CRFs (eCRFs) to capture study data using automated computerized data capture systems does not change the principles and requirements for collecting study data. The Investigator still retains final personal responsibility for eCRF data and any associated data pertaining to it (e.g., metadata including any record of change to the originally recorded data). The Investigator's signed approval of the eCRF data serves to attest that the electronic data and all of its associated metadata (including changes) has been reviewed and accepted as complete, accurate, and true for each patient in the study.

14.2. Retention of Records

To allow for appropriate evaluations and/or audits by regulatory authorities or TRACON, the Investigator agrees to keep records, including the identity of all participating patients (sufficient information to link records, CRFs and hospital records), all original signed informed consent forms, copies of all CRFs, source documents, and detailed records of treatment disposition. The Investigator should retain these records according to local regulations or as specified in the Clinical Trial Agreement, whichever is longer.

If the Investigator relocates, retires, or for any reason withdraws from the study, then TRACON should be prospectively notified. The study records must be transferred to an acceptable designee, such as another Investigator, another institution. The Investigator must inform TRACON of any such transfer of responsibilities and properly identify the person or institution assuming the responsibility. The responsible investigator/institution must obtain TRACON's written permission before disposing of any records.

15. DEFINITION OF END OF TRIAL

15.1. End of Trial in all Participating Countries

End of trial in all participating countries is defined as the time at which all patients enrolled in the study have completed the treatment follow-up period.

15.2. End of Trial in a Member State

End of trial in a Member State of the European Union is defined as the time at which it is deemed that sufficient patients have been recruited and completed the trial as stated in the regulatory application (e.g., the Clinical Trials Agreement [CTA]) and ethics application in the Member State. Poor recruitment is not a reason for premature termination but is considered a normal conclusion to the trial in that Member State.

15.3. TRACON Discontinuation Criteria

Premature termination of this trial may occur because of a regulatory authority decision, change in opinion of the IRB/IEC, drug safety problems, or at the discretion of TRACON. In addition, TRACON retains the right to discontinue development of carotuximab at any time.

TRACON reserves the right to discontinue the trial prior to inclusion of the intended number of patients, but intends only to exercise this right for valid scientific or administrative reasons. If a trial is prematurely terminated or discontinued, TRACON will promptly notify the Investigator. After notification, the Investigator must contact all participating patients within a 28-day time period. As directed by TRACON, all trial materials must be collected and all CRF data must be completed to the greatest extent possible.

16. PUBLICATION OF TRIAL RESULTS

Publication of trial results is discussed in the Clinical Trial Agreement.

17. FINANCING AND INSURANCE

Financing and Insurance are discussed in the Clinical Trial Agreement.

18. INVESTIGATOR PROTOCOL AGREEMENT: 105LC102

I understand that all information concerning this study supplied to me by TRACON Pharmaceuticals, Inc. is confidential information. I have read this protocol and agree to conduct the study according to all applicable regulations, Good Clinical Practice (GPS) Guidelines, and in accordance with the Clinical Trial Agreement (CTA).

I understand that this protocol and all amendments must be submitted to the appropriate IRB/IEC.

Investigator Name (PLEASE PRINT):

_____

Signature: _____Date: _____

Please sign and return this agreement to:

TRACON Pharmaceuticals, Inc.
Attn: Clinical Operations
4350 La Jolla Village Drive, Suite 800
San Diego, CA 92122

Please keep a copy for your records.

19. REFERENCES

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20. APPENDICES

20.1. Appendix 1: National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE)

The NCI CTCAE (Version 4.03) should be used to assess adverse events and may be reviewed on-line at the following NCI website:

http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf

20.2. Appendix 2: ECOG Performance Status

Grade	Performance Status
0	Fully active, able to carry on all pre-disease performance without restriction.
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work.
2	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	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead.