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Protocol C-500-01

A Phase 1/2, Open-Label, Multicenter Study to Evaluate the Safety, Pharmacokinetics, and Pharmacodynamics of an Anti–CTLA-4 Human Monoclonal Antibody (AGEN1884) in Subjects with Advanced or Refractory Cancer and in Subjects who have Progressed During Treatment with a PD-1/PD-L1 Inhibitor as their Most Recent Therapy

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The study is to be conducted according to the protocol and in compliance with Good Clinical Practice (GCP) and other applicable regulatory requirements.

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SYNOPSIS

Study Title	Phase 1/2, Open-Label, Multicenter Study to Evaluate the Safety, Pharmacokinetics, and Pharmacodynamics of an Anti–CTLA-4 Human Monoclonal Antibody (AGEN1884) in Subjects with Advanced or Refractory Cancer and in Subjects who have Progressed During Treatment with a PD-1/PD-L1 Inhibitor as their Most Recent Therapy
Protocol	C-500-01
Number of Study Centers	Multicenter (US only)
Clinical Phase	Phase 1/2
Study Rationale	Cytotoxic T lymphocyte–associated protein 4 (CTLA-4) is one of various downregulators of immune response, known as an inhibitory checkpoint, and blocking it with an anti–CTLA-4 antibody has been demonstrated to enhance immune responsiveness by inhibiting downregulation of T-cell activation. An immunoglobulin G1 (IgG1) anti–CTLA-4 antibody has demonstrated robust clinical efficacy, and has received approval in the United States for the treatment of metastatic melanoma, and in Europe for previously treated metastatic melanoma. The clinical efficacy associated with blockade of CTLA-4 has also been associated with toxicity as the result of immune activation. Moreover, only a subset of patients, even among melanoma patients, will respond to CTLA-4 blockade alone. The combination of CTLA-4 blockade with blockade of the PD-1/PD-L1 (programmed cell death protein 1/programmed cell death protein 1 ligand 1) pathway was recently shown to be more effective than targeting either pathway alone, but still had substantial side effects suggestive primarily of toxicity from CTLA-4 blockade. Moreover, substantial clinical activity has been observed when PD-1/PD-L1 inhibition and CTLA-4 inhibition are combined sequentially. Although the half-life of nivolumab is 17-25 days, its occupancy of PD-1 on circulating T cells has a mean plateau of 72% for at least 59 days, with PD-1 blockade persisting even with undetectable serum nivolumab concentrations ; therefore, substantial inhibition of PD-1 would be expected to continue in the PD-l/PD-L1 cohorts at the time of AGEN1884 treatment initiation. The results of this single-agent study will inform the further development of AGEN1884. Combining a CTLA-4 inhibitor such as AGEN1884 with PD-1 blockade or other immunotherapies therefore remains an attractive goal in immuno-oncology. Alternate combination approaches to the development of AGEN1884 may ameliorate the side effects of CTLA-4 blockade while focusing immune stimulation to the benefit of patients with tumor types for which immunotherapy does not currently work, and patients with melanoma who cannot tolerate CTLA-4 blockade with the approved antibody as currently administered. The present study will seek to define the safety and maximum tolerated dose (MTD) of single-agent AGEN1884, and include expansion of enrollment at the MTD or maximum planned dose level to further explore the activity of AGEN1884 monotherapy in subjects with advanced or refractory cancer, including those who have progressed during treatment with an approved or investigational PD-1/PD-L1 inhibitor as their most recent therapy (2-6 weeks prior to first dose of study drug).

	The Phase 1 portion of the study also included expansion of enrollment at 1 mg/kg and 3 mg/kg to further explore the activity of AGEN1884 as a monotherapy. In Phase 2, subjects who have received previous treatment with immunotherapeutic agents (except those who received previous treatment with anti–CTLA-4 agents) will be allowed to enroll in order to better understand the safety of sequential treatment with AGEN1884 in what is becoming a common clinical practice due to the approval of multiple PD-1– and PD-L1–targeting agents.
Study Objectives	**Primary Objectives** • To evaluate the safety, tolerability, and dose-limiting toxicities (DLTs) of AGEN1884 in subjects with advanced or metastatic cancer (solid tumors or lymphoma), including but not limited to carcinoma, sarcoma, or melanoma (Phase 1); and to evaluate the safety and tolerability of AGEN1884 in subjects who have progressed during treatment with a PD-1/PD-L1 inhibitor as their most recent therapy (Phase 2). • To characterize AGEN1884 pharmacokinetics (PK). **Secondary Objectives** • To evaluate the preliminary efficacy of AGEN1884 by assessing objective response rate (ORR), disease control rate (DCR), and duration of response (DOR) per Response Evaluation Criteria in Solid Tumors (RECIST) Version 1.1. • To evaluate the preliminary efficacy of AGEN1884 by assessing progression-free survival (PFS) and overall survival (OS). **Exploratory Objectives** • To explore biomarkers that may predict pharmacologic activity or response to AGEN1884. • To characterize the effect of AGEN1884 on tumor tissue obtained post-treatment, if available.
Study Population	The population in this Phase 1/2 study will include subjects ≥18 years old with a histological or cytological diagnosis of relapsed or refractory lymphoma or solid cancer, including carcinoma, sarcoma, or melanoma, that is considered incurable and without therapies with established benefit. The Phase 2 population will include subjects who have progressed during treatment with an approved or investigational PD-1/PD-L1 inhibitor as their most recent therapy (2-6 weeks prior to first dose of study drug) with a subpopulation to include approximately 20 subjects with advanced hepatocellular carcinoma (HCC) and 40 non-HCC subjects. Subjects will be excluded if they have had a previous severe hypersensitivity reaction to another fully human monoclonal antibody, history of primary of secondary immunodeficiency or autoimmunity, or received anticancer medications or other investigational drugs within protocol-defined intervals before the first administration of study drug.
Number of Subjects, Accrual, and Study Duration	Overall, approximately 100 subjects will be enrolled in Phase 1 and Phase 2. In Phase 2, up to 60 of these subjects must have experienced progression with a PD-1/PD-L1 inhibitor as their most recent therapy (2-6 weeks prior to first dose of study drug). Approximately 20 subjects in Phase 2 will have advanced HCC.

	Study duration will be approximately 5 years (including enrollment and follow-up).
Study Design and Dosing	This is an open-label, Phase 1/2, multicenter study to evaluate the safety, PK, pharmacodynamics, and activity of an anti–CTLA-4 human monoclonal antibody (AGEN1884). The Phase 1 portion of the study is completed. It enrolled adult subjects with refractory, advanced cancer. The 3+3 dose escalation evaluated AGEN1884 at 0.1, 0.3, 1, 3, and 6 mg/kg dose levels. It also included an expansion phase at 1 mg/kg and 3 mg/kg. Dose levels >6 mg/kg were not planned. The biopharmacological properties of the antibody indicated that this dose escalation plan would include evaluation of doses within a safe and clinically active range. Dose escalation continued until the MTD was reached or the maximum planned dose level (6 mg/kg) was shown to be safe (i.e., passes DLT evaluation). The MTD was defined as the dose below which 2 DLTs are observed among 3 subjects treated at a given dose level. Based on data from the Phase 1 dose escalation, 1 mg/kg was chosen as the starting dose in Phase 2. Phase 2 consists of approximately 40 subjects who have progressed during treatment with an approved or investigational PD-1/PD-L1 inhibitor as their most recent therapy (2-6 weeks prior to first dose of study drug). For this phase: • Approximately 20 subjects with advanced HCC will be enrolled. • The enrollment of non-HCC will be approximately 40 subjects. Note: additional subjects may be enrolled to either the HCC or non-HCC populations as necessary to ensure that 20 subjects are evaluable for the additional PK evaluation (i.e., 3 additional timepoints, see Section 5.3). Expanded PK/anti-drug antibody (ADA) and safety data will be analyzed to plan future development of combination therapies. Subjects who have received prior therapy with cancer vaccines or oncolytic viral therapy will be allowed to enroll on this study. Subjects will be evaluated for immune correlates, PK, pharmacodynamics, disease response, and safety, as determined through adverse events, vital signs, physical examination, clinical laboratory tests, and imaging.
Study Drug	AGEN1884 is a novel, fully human monoclonal immunoglobulin G1 antibody designed to block CTLA-4.
Dosage and Administration	AGEN1884 will be administered intravenously (IV) for each cycle (3 weeks) as a 60-min (-10/+20 min) infusion. Infusions will be followed immediately by a 15-min saline flush of the IV line. In Phase 1, subjects will receive AGEN1884 at 0.1, 0.3, 1, 3, and 6 mg/kg dose levels in a 3+3 dose escalation design. Subjects in Phase 2 will begin treatment at the 1 mg/kg dose level. Duration of cycles: cycles are 3 weeks for the first 4 cycles. For the subsequent cycles (Cycle 5 and onward): At the 12-week evaluation timepoint, subjects may continue to receive AGEN1884 every 3, 6, or 12 weeks (± 7 days) for a maximum duration of 1 year of treatment, provided they were not evaluated with PD and were tolerating the study drug. The appropriate schedule will be based on discussion with the medical monitor. Subjects who

	progressed yet still have clinical benefit from treatment may continue on treatment following discussion with, and approval of, the medical monitor.

Inclusion and Exclusion Criteria	**Inclusion Criteria** Subjects must meet all of the following criteria: 1. Written informed consent. 2. ≥18 years of age. 3. Histological or cytological diagnosis of solid cancer or lymphoma that is considered incurable and without therapies with established benefit. Biopsy is not necessary for subjects with known prior diagnosis, and clinical or radiographic evidence of recurrence. – **For Phase 2 only**: Subjects PD-1/PD-L1 naïve and those who experienced documented disease progression during treatment with an approved or investigational PD-1/PD-L1 inhibitor as their most recent therapy (2-6 weeks prior to first dose of study drug). – For subjects in Phase 2 with HCC: This cohort includes subjects with histological diagnoses of HCC (not including atypical histology such as cholangiocarcinoma mix or fibrolamellar hepatocellular carcinoma) who experienced documented disease progression during treatment with an approved or investigational PD-1/PD-L1 inhibitor as their most recent therapy (2-6 weeks prior to first dose of study drug). 4. Eastern Cooperative Oncology Group (ECOG) score of 0 or 1. 5. Subjects in Phase 2 with HCC should have a Child-Pugh score of A or B7 with no encephalopathy or ascites. 6. Life expectancy ≥12 weeks. 7. Adequate cardiac function (New York Heart Association [NYHA] class ≤II). 8. Adequate organ function, defined as absolute neutrophil count (ANC) ≥1,500×10^6/L, absolute lymphocyte count ≥500/mm^3, hemoglobin ≥8.0 g/dL, and platelet count ≥100,000×10^6/mm^3 without blood growth factors or without transfusions within 1 week of first dose. **For subjects in Phase 2 with HCC**: Platelet count ≥60 ×10^6/mm^3 and ANC ≥1,000×10^6/L are acceptable provided that the principal investigator assesses these abnormalities as being due to liver disease. 9. Adequate liver function, defined as aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤2.5× institutional upper limit of normal (ULN), and bilirubin ≤1.5 ULN. **For subjects in Phase 2 with HCC:** AST and ALT ≤5 × ULN, bilirubin ≤2 × ULN, and albumin ≥ 2.8 mg/dL. 10. Adequate renal function, defined as estimated creatinine clearance ≥50 mL/min according to Cockcroft-Gault formula, or measured 24-hour creatinine clearance (or local institutional standard method). 11. Adequate coagulation defined by international normalized ratio (INR) or prothrombin time (PT) ≤ 1.5 x ULN (unless the patient is receiving anticoagulant therapy); and activated partial thromboplastin time (aPTT) ≤ 1.5 x ULN (unless the subject is receiving anticoagulant therapy). Subjects in Phase 2 with HCC can have an INR ≤2.3 x ULN.

	Note: Subjects in Phase 2 with HCC and on anticoagulant treatment would have an assigned value of 1 point when scoring PT/INR so the overall Child-Pugh score is not adversely affected. 12. Female subjects of childbearing potential and fertile male subjects must agree to use adequate contraception or abstain from sexual activity from the time of consent through 90 days after the end of study drug. Adequate contraception includes condoms with contraceptive foam; oral, implantable, or injectable contraceptives; contraceptive patch; intrauterine device; diaphragm with spermicidal gel; or a sexual partner who is surgically sterilized or postmenopausal. **Note:** Abstinence is acceptable if this is the established and preferred contraception for the subject. 13. In the expansion phase (Phase 2), all subjects must provide a sufficient and adequate formalin fixed paraffin embedded (FFPE) tumor tissue sample preferably collected after progression on the last therapy and/or collected at screening, if clinically feasible. If a recent biopsy is not available, an archival FFPE sample should be provided from a site not previously irradiated. If no tumor tissue is available, a fresh biopsy will be required, if clinically feasible. **Exclusion Criteria** 1. Other malignancies treated within the last 5 years, except *in situ* cervix carcinoma or non-melanoma skin cancer. 2. Other form(s) of antineoplastic therapy anticipated during the period of the study. 3. Previous severe hypersensitivity reaction to another fully human monoclonal antibody or severe reaction to immuno-oncology agents, such as colitis or pneumonitis requiring treatment with steroids. 4. History of interstitial lung disease. 5. Primary or secondary immunodeficiency, including immunosuppressive disease, autoimmune disease (including autoimmune endocrinopathies), or usage of immunosuppressive medications. **Note**: Subjects with diabetes type 1, vitiligo, psoriasis, hypo-, or hyperthyroid disease not requiring immunosuppressive treatment are eligible. Subjects with Type 2 diabetes mellitus are allowed. 6. Subjects with a known history of human immunodeficiency virus 1 and 2, human T lymphotropic virus 1. **Subjects in Phase 2 with HCC:** Subjects with active hepatitis B infection who are receiving effective antiviral therapy are permitted. Subjects with active hepatitis C infection are allowed (antiviral therapy not required). 7. Administration of anticancer medications or investigational drugs within the following intervals before the first administration of study drug: a) ≤14 days for chemotherapy, targeted small molecule therapy, or radiation therapy. Subjects must also not have had radiation pneumonitis as a result of treatment and cannot participate in the study if they are on chronic corticosteroids for radiation pneumonitis. A 1-

	week washout is permitted for palliative radiation to non–central nervous system (CNS) disease, with medical monitor approval. **Note**: Bisphosphonates and denosumab are permitted medications. b) ≤14 days for prior immunotherapy. Subjects in the dose escalation cohorts are excluded if they have received prior checkpoint inhibitors, costimulatory agonists, or immune modulating therapy except as described below. Once a dose level is determined to be safe by the safety review committee, subjects will be allowed to enroll in dose-level expansion cohorts if they have received other non–CTLA-4 targeting immunotherapies. c) Subjects enrolling in Phase 2 must have cancer that has progressed after prior treatment with an approved or investigational PD-1/PD-L1 inhibitor as their most recent therapy (2-6 weeks prior to first dose of study drug). The minimum requirement of 2 weeks (14 days) from prior anti–PD-1/PD-L1 therapy is to allow resolution of any lower-grades (≤2) adverse events observed with the therapy. If the investigator feels the subject has tolerated prior anti–PD-1/PD-L1 therapy well, then treatment with study agent may begin sooner. d) ≤7days for prior corticosteroid treatment, with the following exceptions: – Use of an inhaled or topical corticosteroid is permitted. – Corticosteroid premedication for radiographic imaging for dye allergies is permitted. – Use of physiologic corticosteroid replacement therapy may be approved after consultation with the medical monitor. e) ≤21 days for prior monoclonal antibody used for anticancer therapy, with the exception of denosumab. **This does not apply to subjects being enrolled in Phase 2, who have received a PD-1/PD-L1 inhibitor as their most recent therapy (2-6 weeks prior to the first dose of study drug; see above)**. f) ≤7 days for immunosuppressive-based treatment for any reason, with the exceptions noted above for prior corticosteroid treatment (exclusion criterion d). g) ≤21 days or 5 half-lives before first dose of study treatment for all other investigational study drugs or devices. For investigational agents with long half-lives (i.e., >5 days), enrollment before the fifth half-life requires medical monitor approval. h) For subjects in Phase 2 with HCC < 6 weeks for prior locoregional therapy to the liver e.g., transcatheter chemoembolization (TACE), radiation, surgery, or radioembolization. 8. Has not recovered to grade ≤1 from toxic effects of prior therapy and/or complications from prior surgical intervention before starting therapy. **Note**: Subjects with grade ≤2 neuropathy and alopecia are an exception and may enroll. 9. Uncontrolled infection or other serious medical illnesses. 10. History or presence of an abnormal electrocardiogram (ECG) that, in the investigator's opinion, is clinically meaningful.

	11. Any medical conditions that, in the opinion of the investigator, would preclude use of AGEN1884, including AGEN1884 hypersensitivity. 12. Women who are pregnant or breastfeeding. 13. Concurrent participation in other investigational drug trials. 14. Has a CNS tumor, metastasis(es), and/or carcinomatous meningitis identified either on the baseline brain imaging obtained during the screening period or identified prior to consent. **Note**: Subjects with history of brain metastases that have been treated may participate provided they show evidence of stable supra-tentorial lesions at screening (defined as 2 brain images, both of which are obtained after treatment to the brain metastases. These imaging scans should both be obtained ≥4 weeks apart). In addition, any neurologic symptoms that developed either as a result of the brain metastases or their treatment must have returned to baseline or resolved. For individuals who received steroids as part of brain metastases treatment, steroids must be discontinued ≥ 7 days prior to first dose of study drug. 15. **For subjects in Phase 2 with HCC, the following exclusions also apply**: a. Recent encephalopathy episodes in the last 6 months. b. Recent (within the last 3 months) gastro-esophageal varices bleeding c. Subject whose tumors have cardiac involvement, as determined by imaging.
Pharmacodynamics	Blood samples will be collected to measure proteins and markers of inflammation or immune modulation. Plasma will be derived from whole blood samples and used for immune cell population profiling and DNA/ribonucleic acid (RNA) sequencing.
Pharmacokinetics and Immunogenicity	AGEN1884 PK will be characterized and potential impact of ADA on PK profiles will be assessed. AGEN1884 immunogenicity will be evaluated with serum ADA monitoring.
Efficacy	Disease assessments will be performed based on RECIST Version 1.1. Disease response assessments by RECIST to be performed at Study Week 6, Week 12 and Q6w for subjects assigned to 3- or 6-w treatment schedule, or Q12w for subjects assigned to 12-w treatment schedule until off-disease response evaluation criteria are met.
Safety	Subjects will be followed for safety and adverse events for the duration of the study and for ≤90 days after the last dose of investigational agent. Safety will be evaluated through adverse events (per National Cancer Institute Common Terminology Criteria for Adverse Events v. 5), physical examinations, vital signs, 12-lead ECG, clinical laboratory assessments, and lymphocyte subset measurements.

Endpoints	**Primary Endpoints** • Safety and tolerability will be assessed by monitoring the frequency, duration, and severity of drug-related adverse events; by completing physical examinations; by evaluating changes in vital signs and ECG; through clinical evaluations; and laboratory blood and urine sample evaluations. • PK parameters to be estimated and reported may include, but may not be limited to, maximum drug concentration at steady-state (C_{max-ss}), minimum drug concentration at steady state (C_{min-ss}), area under the drug concentration-time curve within time span t1 to t2 at steady-state ($AUC_{(t1-t2)-ss}$), area under the drug concentration-time curve from time of dosing to time of last observation ($AUC_{(0-t)}$), area under the drug concentration-time curve from time of dosing extrapolated to infinity ($AUC_{(0-\infty)}$), time to reach maximum drug concentration (t_{max}), terminal elimination rate constant (λ_z), terminal elimination half-life ($t_{½}$), systemic clearance (CL), and volume of distribution (Vd). **Secondary Endpoints** • Objective response rate, (ORR), defined as the percentage of subjects having CR or PR, as determined by radiographic disease assessments per RECIST 1.1. • Disease control rate (DCR) will include subjects that have best overall response (BOR) of CR, PR and SD for at least 12 weeks. • Progression-free survival (PFS), defined as the interval from the date of first dose of investigational agent until the earliest date of disease progression (PD), as determined by investigator assessment of objective radiographic disease assessments per RECIST 1.1, or death due to any cause if occurring sooner than progression. • Duration of response, (DOR), defined as the interval from the date measurement criteria are met for CR or PR (whichever is first recorded) until the earliest date of disease progression, as determined by investigator assessment of objective radiographic disease assessments per RECIST 1.1, or death due to any cause if occurring sooner than progression. Only subjects who achieve an initial response will be evaluated for DOR. • Overall survival (OS), defined as the interval from the date of first dose of investigational agent until the date of death. • The pharmacologically active dose of AGEN1884, determined through clinical signs of drug activity, surrogate markers, or pharmacodynamic studies, including but not limited to the presence of immune-related adverse events. **Exploratory Endpoints** • Other biomarker effects and outcome predictors for AGEN1884 in peripheral blood and/or tumor tissue will be evaluated as exploratory analyses.
Statistical Considerations	Overall, there will be approximately 100 subjects enrolled in Phase 1 and Phase 2 of this study. After safety is established in the 1 mg/kg and 3 mg/kg cohorts, additional subjects will be enrolled into those dose levels to support the objectives and expand the number of correlates available for evaluation. The Phase 2 population will include up to 60 subjects who have progressed during treatment with an approved or investigational PD-1/PD-L1 inhibitor as their most recent therapy (2-6 weeks prior to first dose of study drug) with a subpopulation to include approximately 20 subjects with advanced HCC and approximately 40 non-HCC subjects.

	The sample size is not based on inferential statistics. **Statistical Analyses** Descriptive statistics of safety, efficacy, PK, and pharmacodynamic parameters will be provided by dose level, study cohort, and study phase. Both noncompartmental (NCA) and compartmental modeling (e.g., population pharmacokinetics [PopPK]) techniques will be used to analyze the PK.

LIST OF ABBREVIATIONS AND TERMS

Abbreviation	Term
ACTH	adrenocorticotropic hormone
ADA	anti-drug antibody(ies)
ADCC	antibody-dependent cellular cytotoxicity
ADL	activities of daily living
ADR	adverse drug reaction
AE	adverse event
AESI	adverse event of special interest
AFP	alpha-fetoprotein
ALT	alanine aminotransferase
ANC	absolute neutrophil count
APC	antigen-presenting cell
aPTT	partial thromboplastin time
AST	aspartate aminotransferase
AUC	area under the drug concentration-time curve
$AUC_{(0-\infty)}$	area under the drug concentration-time curve from time of dosing extrapolated to infinity
$AUC_{(0-t)}$	area under the drug concentration-time curve from time of dosing to time of last observation
$AUC_{(\tau1-\tau2)-ss}$	area under the drug concentration-time curve within time span t1 to t2 at steady-state
BOR	best overall response
C	Celsius or cycle
CA-125	cancer antigen 125
CL	systemic clearance
C_{max-ss}	maximum drug concentration at steady-state
C_{min-ss}	minimum drug concentration at steady-state
CNS	central nervous system
CR	complete response
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events Version 5
CTLA-4	cytotoxic T lymphocyte–associated protein 4

Abbreviation	Term
D	day
DCR	disease control rate
DLT	dose-limiting toxicity
DNA	deoxyribonucleic acid
DOR	duration of response
EBUS	endobronchial ultrasound
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
Fc	fragment crystallizable
FcγR	fragment-crystallizable gamma receptor
FDA	Food and Drug Administration
FFPE	formalin-fixed paraffin-embedded
GCP	Good Clinical Practice
GGT	gamma glutamyltransferase
GLP	Good Laboratory Practice
h	hour(s)
HCC	hepatocellular carcinoma
ICF	informed consent form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IgG1	immunoglobulin G1
INR	international normalized ratio
irAE	immune-related adverse event
IRB	Institutional Review Board
IV	intravenous(ly)
LFT	liver function test
LLN	lower limit of normal
λz	terminal elimination rate constant
MABEL	minimally anticipated biologic effect level
μmol	micromolar

Abbreviation	Term
MRI	magnetic resonance imaging
MRSD	maximum recommended starting dose
MTD	maximum tolerated dose
NCI	National Cancer Institute
NSAID	nonsteroidal anti-inflammatory drug
NYHA	New York Heart Association
ORR	objective response rate
OS	overall survival
PBMC	peripheral blood mononuclear cell
PD	progressive disease
PD-1	programmed cell death protein 1
PD-L1	programmed cell death protein 1 ligand 1
PET	positron emission tomography
PFS	progression-free survival
PGx	pharmacogenomics
PK	pharmacokinetic(s)
PO	*per os* (orally)
PopPK	population pharmacokinetic(s)
PR	partial response
PT	prothrombin time
Q	every
QTc	corrected QT
RECIST	Response Evaluation Criteria in Solid Tumors Version 1.1
RNA	ribonucleic acid
SAE	serious adverse event
SAP	statistical analysis plan
SD	stable disease
SRC	Safety Review Committee
$t_{1/2}$	terminal elimination half-life
T4	thyroxine
TCR	T-cell receptor

Abbreviation	Term
t_{max}	time to reach maximum drug concentration
Tregs	regulatory T cells
TSH	thyroid stimulating hormone
ULN	upper limit of normal
V_d	volume of distribution
W	week
WBC	white blood cell

1. Study Objectives

1.1 Primary Objectives

- To evaluate the safety, tolerability, and dose-limiting toxicities (DLTs) of AGEN1884 in subjects with advanced or metastatic cancer (solid tumors or lymphoma), including but not limited to carcinoma, sarcoma, or melanoma (Phase 1); and to evaluate the safety and tolerability of AGEN1884 in subjects who have progressed during treatment with a PD-1/PD-L1 (programmed cell death protein 1/PD-1 ligand 1) inhibitor as their most recent therapy (Phase 2).
- To characterize AGEN1884 pharmacokinetics (PK).

1.2 Secondary Objectives

- To evaluate the preliminary efficacy of AGEN1884 by assessing objective response rate (ORR), disease control rate (DCR), and duration of response (DOR) per Response Evaluation Criteria in Solid Tumors (RECIST) Version 1.1.
- To evaluate the preliminary efficacy of AGEN1884 by assessing progression-free survival (PFS) and overall survival (OS).

1.3 Exploratory Objectives

- To explore biomarkers that may predict pharmacologic activity or response to AGEN1884.
- To characterize the effect of AGEN1884 on tumor tissue obtained post-treatment, if available.

2. Background

2.1 Investigational Agent: AGEN1884

AGEN1884 is a novel, fully human monoclonal immunoglobulin G1 (IgG1) antibody designed to block cytotoxic T lymphocyte–associated protein 4 (CTLA-4), a key negative regulator of T-cell responses. Blocking CTLA-4 with an antibody enhances antitumor immune responsiveness by inhibiting the downregulation of T-cell activation. In this first-in-human trial, AGEN1884 will be evaluated as monotherapy in subjects with advanced and/or refractory malignancies, including those who have progressed during treatment with a PD-1/PD-L1 inhibitor as their most recent therapy.

2.1.1 Supporting Nonclinical Data

AGEN1884 selectively binds with high affinity to human CTLA-4 and cross-reacts with cynomolgus monkey (*Macaca fascicularis*) CTLA-4. However, AGEN1884 does not cross-react with rodent CTLA-4 or CTLA-4–related members of the CD28 superfamily. AGEN1884 potently blocks the interaction of CTLA-4 with CD80 and CD86, resulting in increased levels of interleukin 2 from T-cell receptor (TCR)–activated T cells cultured from peripheral blood mononuclear cells (PBMCs). By contrast, when soluble AGEN1884 is added to human PBMCs or whole blood in the absence of TCR activation, cytokines are not induced. Cytokine production in the absence of TCR stimulation would be predictive of cytokine release syndrome *in vivo*. Importantly, activated T cells cultured in the presence of AGEN1884 showed no evidence of reduced cytokine production, thereby excluding any agonistic inhibitory signals delivered by this

antibody. Consistent with its ability to engage cynomolgus monkey CTLA-4, AGEN1884 enhanced T cell–dependent antibody responses in animals immunized with a hepatitis B vaccine.

CTLA-4 is also expressed by regulatory T cells (Tregs), which can impair tumor immunity by multiple suppressive mechanisms (Wing et al., 2008; Zou, 2006). One such mechanism involves Treg-expressed CTLA-4 mediating the physical removal of CD80 and CD86 from the surface of activated antigen-presenting cells (APCs) by a process termed trans-endocytosis, which can attenuate the immune-stimulatory potential of APCs (Qureshi et al.). Emerging clinical and preclinical study data support a secondary mechanism of action for anti–CTLA-4 antagonist antibodies involving the deletion of Tregs (Bulliard et al., 2013; Marabelle et al., 2013; Romano et al., 2015; Selby et al., 2013; Simpson et al., 2013). This mechanism involves the co-binding of anti–CTLA-4 antibodies to Tregs located within the tumor and fragment-crystallizable gamma receptor (FcγR)–expressing effector cells (e.g., natural killer or myeloid cells), resulting in antibody-dependent cellular cytotoxicity (ADCC) or antibody-dependent cellular phagocytosis. The elimination of tumor-associated Tregs, which contribute to tumor immunity by dampening the activation of effector T cell to tumor-associated antigens, is considered to be a major obstacle in achieving effective antitumor immunity during immunotherapy (Zou, 2006). Consistent with an IgG1κ fragment crystallizable (Fc) region, AGEN1884 can bind to FcγRs expressed by effector immune cell populations and mediate ADCC activity against target cells expressing high levels of CTLA-4. Also consistent with its IgG1κ Fc region, AGEN1884 showed *in vitro* evidence of complement-dependent cytotoxicity toward CTLA-4–expressing target cells.

AGEN1884 PK studies have been conducted in cynomolgus monkeys following both single and repeated intravenous (IV) administration. AGEN1884 has a biphasic disposition with a terminal elimination half-life ($t_{1/2}$) of between 8 and 20 days. Exposure (maximum drug concentration at steady-state [$C_{max\text{-}ss}$] and area under the drug concentration-time curve [AUC]) increased in an approximately dosage-proportional manner. No gender difference was noted for plasma drug exposure ($C_{max\text{-}ss}$ or AUC). Accumulation was observed, as exposure was approximately twice as high after multiple weekly administrations.

Repeated-administration IV toxicology studies have been conducted in cynomolgus monkeys, including a 1-month Good Laboratory Practice (GLP) study. In both studies, AGEN1884 was administered by a slow IV bolus once weekly (days 1, 8, 15, 22, and 29) at dosages of 0 (vehicle), 5, 30, and 100 mg/kg AGEN1884. No evidence of any toxicity was observed after a thorough examination of in-life, clinical pathology (including cytokines), flow cytometry, and macroscopic and histopathological examinations. A GLP tissue cross-reactivity study with human tissues indicated binding to plasma membranes of mononuclear cells in a number of tissues.

The maximum recommended starting dose (MRSD) was based on the MRSD derived from the minimally anticipated biological effect level (MABEL). The proposed starting dose for this study is 0.1 mg/kg of AGEN1884, which is based on *in vitro* pharmacology and *in vivo* PK and toxicology studies. This dosage is higher than the calculated MABEL of 0.042 mg/kg, but is believed to represent a safe starting dosage that will provide improved opportunity for pharmacological activity in Phase 1 subjects. Please refer to the Investigator's Brochure for further details.

2.2 Rationale

CTLA-4 is one of various down regulators of the immune response, known as an inhibitory checkpoint, and blocking it with an anti–CTLA-4 antibody has been demonstrated to enhance immune responsiveness by inhibiting downregulation of T-cell activation. An IgG1 anti–CTLA-4 antibody has demonstrated robust clinical efficacy, and has received approval in the United States for the treatment of metastatic melanoma, and in Europe for previously treated metastatic melanoma (Page et al.m 2013).

The clinical efficacy associated with blockade of CTLA-4 has also been associated with toxicity as the result of immune activation. Moreover, only a select group of patients, even among melanoma patients, will respond to CTLA-4 blockade alone (Page et al., 2013). The combination of CTLA-4 blockade with PD-1 blockade was recently shown to be more effective than targeting either pathway alone, but still had substantial side effects suggestive primarily of toxicity from CTLA-4 blockade (Larkin et al., 2015). Combining a CTLA-4 inhibitor such as AGEN1884 with PD-1 blockade or other immunotherapies therefore remains an attractive goal in immuno-oncology. Alternate combination approaches to the development of AGEN1884 may ameliorate the side effects of CTLA-4 blockade while focusing immune stimulation to the benefit of patients with tumor types for which immunotherapy does not currently work, and patients with melanoma who cannot tolerate CTLA-4 blockade with the approved antibody as currently administered.

The present study will seek to define the safety and maximum tolerated dose (MTD) of single-agent AGEN1884, and include expansion of enrollment at the MTD or maximum planned dose level to further explore the activity of AGEN1884 monotherapy in subjects with advanced or refractory cancer, including those who have progressed during treatment with an approved or investigational PD-1/PD-L1 inhibitor as their most recent therapy (2-6 weeks prior to first dose of study drug). The Phase 2 portion of the study will also include expansion of enrollment at 1 mg/kg and 3 mg/kg to further explore the activity of AGEN1884 as a monotherapy. In the expansion phase, subjects who have received previous treatment with immunotherapeutic agents (except those who received previous treatment with anti–CTLA-4 agents) will be allowed to enroll in order to better understand the safety of sequential treatment with AGEN1884 in what is becoming a common clinical practice due to the approval of multiple PD-1– and PD-L1–targeting agents.

Moreover, substantial clinical activity has been observed when PD-1/PD-L1 inhibition and CTLA-4 inhibition are combined sequentially (Weber et al., 2016). Although the half-life of nivolumab is 17-25 days (Bristol-Meyers Squibb, 2013), its occupancy of PD-1 on circulating T cells has a mean plateau of 72% for at least 59 days, with PD-1 blockade persisting even with undetectable serum nivolumab concentrations (Brahmer et al., 2010); therefore, substantial inhibition of PD-1 would be expected to continue in the PD-l/PD-L1 cohorts at the time of AGEN1884 treatment initiation. The results of this single-agent study will inform the further development of AGEN1884.

3. Investigational Plan

3.1 Overall Study Design

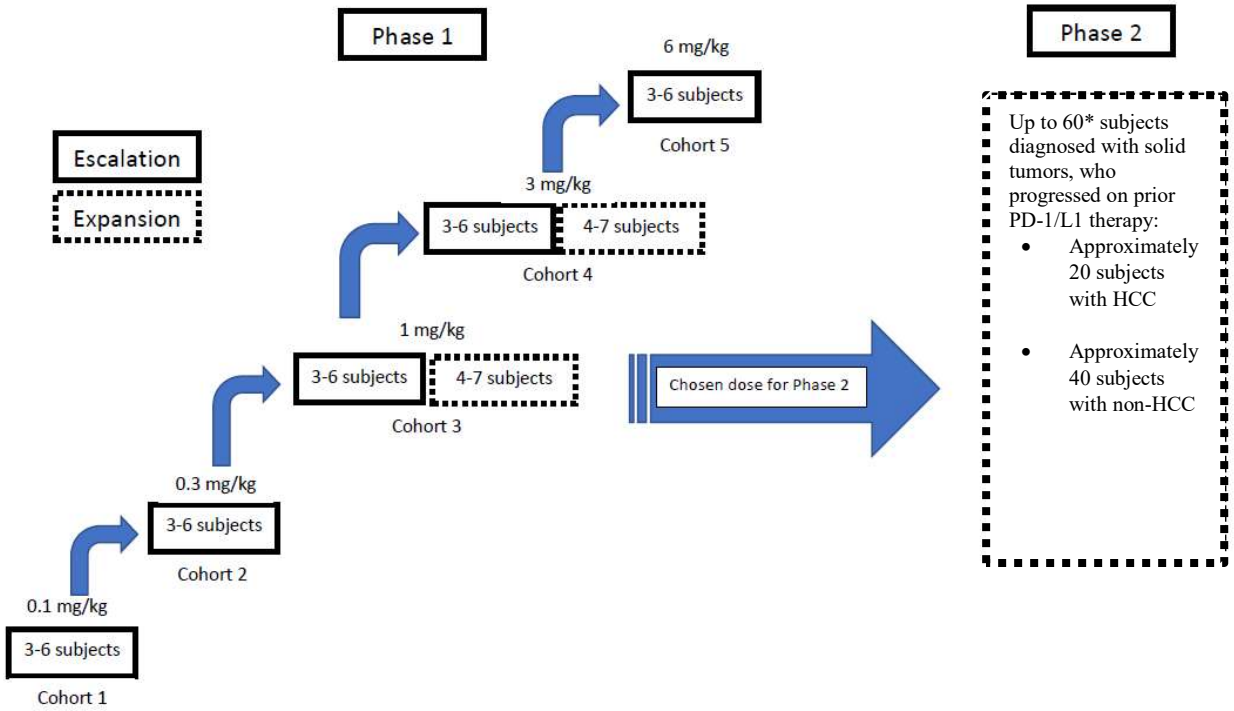
This is an open-label, Phase 1/2, multicenter study to evaluate the safety, PK, and pharmacodynamics, and activity of an anti–CTLA-4 human monoclonal antibody (AGEN1884)

in subjects with advanced or refractory cancer. The Phase 1 portion of the study has been completed and contained a 3+3 dose escalation phase evaluating AGEN1884 at 0.1, 0.3, 1, 3, and 6 mg/kg dose levels, and an expansion phase at 1 mg/kg and 3 mg/kg. Dose levels >6mg/kg were not planned.

The Phase 2 portion of the study includes subjects who have progressed during treatment with an approved or investigational PD-1/PD-L1 inhibitor as their most recent therapy (2-6 weeks prior to first dose of study drug). The dose for the Phase 2 portion of the study was based on clinical data from the Phase 1 portion evaluating AGEN1884 as monotherapy. At the time of this amendment, based on data from the Phase 1 dose escalation, 1 mg/kg was chosen as the starting dose for Phase 2.

The study design is depicted in Figure 1.

Figure 1: Study Design



* Additional subjects may be enrolled in Phase 2 to either the HCC or non-HCC populations as necessary to ensure that 20 subjects are evaluable for additional PK assessments (i.e., 3 additional timepoints, see Section 5.3).

AGEN1884 will be administered on Day 1 of each 3-week cycle for 4 cycles. At a 12-week evaluation timepoint (based on 2 scans of tumor assessment), subjects may continue to receive AGEN1884 every 3, 6, or 12 weeks (± 7-days), for a maximum duration of 1 year of treatment, provided they were not diagnosed with disease progression and were tolerating the study drug. The appropriate schedule will be based on discussion with the medical monitor. Subjects who progressed during the treatment period, yet still have clinical benefit from treatment, may continue treatment post-progression with the medical monitor's approval. The dosing schedule for these subjects should be determined based on discussion with the medical monitor.

Phase 1

The Phase 1 portion of the study was to enroll overall approximately 40 adult subjects with refractory, advanced cancer (solid tumors or lymphoma), including those who have progressed during treatment with an approved or investigational PD-1/PD-L1 inhibitor as their most recent therapy (2-6 weeks prior to first dose of study drug). The 3+3 dose escalation started at 0.1 mg/kg, as shown in Table 1. (Dose levels beyond 6 mg/kg are not currently planned.) The bio-pharmacological properties of the antibody suggested that this dose escalation plan would include evaluation of doses within a safe and clinically active range. Dose escalation continued until the MTD was reached or the maximum planned dose level (6 mg/kg) was shown to be safe after cohort expansion occurred at the 1 mg/kg and 3 mg/kg dose levels. The MTD is defined as the dose below which 2 DLTs are observed (see Section 3.1.2.2 for definition of DLTs).

The cohorts and dose levels are shown in Table 1. Information about stopping rules for toxicity is provided in Section 3.1.2.3.

Table 1: AGEN1884 Dose Levels and Cohorts

Dose Level Cohort	AGEN1884 Dose (mg/kg)	Study Phase	Number of Subjects
Phase 1			
1 (starting dose)	0.1	Dose escalation	3-6
2	0.3	Dose escalation	3-6
3	1	Dose escalation and expansion [a]	10
4	3	Dose escalation and expansion [a]	10
5	6	Dose escalation	3-6
Phase 2			
	1	Subjects who progressed on a PD-1/PD-L1 inhibitor as last prior therapy [b]	Up to 60 [c]

DLT: dose-limiting toxicity; HCC: hepatocellular carcinoma; PD-1: programmed cell death protein 1; PD-L1: ligand 1 of programmed cell death protein 1.

[a] Includes 3-6 subjects for DLT evaluation plus additional subjects to achieve up to 10 evaluable subjects in the cohort.

[b] Includes subjects who progressed during treatment with an approved or investigational PD-1/PD-L1 inhibitor as their most recent therapy (2-6 weeks prior to first dose of study drug). Includes subjects in Phase 2 with HCC who progressed during treatment with an approved or investigational PD-1/PD-L1 inhibitor as their most recent therapy (2-6 weeks prior to first dose of study drug). Of the 40 subjects in this cohort at the 1.0 mg/kg dose level: 1) Approximately 20 subjects diagnosed with HCC will be enrolled; 2) The enrollment of non-HCC will be approximately 40 subjects.

[c] Additional subjects may be enrolled to either the HCC or non-HCC populations as necessary to ensure that 20 subjects are evaluable for additional PK evaluation (i.e., 3 additional timepoints, see Section 5.3).

The DLT observation period was defined as 28 days from initial administration of AGEN1884. Based on experience with other anti–CTLA-4 antibodies, this allowed for infusion-related toxicities and other early onset immune-related toxicities, such as skin-related adverse events, to be observed during the DLT observation period without unnecessarily prolonging the observation period. Additionally, some immune-related toxicities from CTLA-4 inhibition were likely to occur later in therapy than 42 days (Weber et al., 2013), the last day before dose number 3 would be due for subjects on this study. Therefore, late toxicities were evaluated by the Safety Review Committee (SRC) per Section 3.1.1 to ensure that related toxicities are still considered in DLT review even if they fall outside of the observation period.

Once the 1 mg/kg and 3 mg/kg dosages were declared safe, these cohorts were expanded to include overall 10 evaluable subjects in each cohort before enrolling subjects into the 6 mg/kg dose cohort. Dose escalation continued until the MTD was reached, or the maximum planned dose level (6 mg/kg) was shown to be safe after cohort expansion occurred at the 1 mg/kg and 3 mg/kg dose levels. The expansion cohorts allowed collection of additional PK/anti-drug antibody (ADA) and safety data, which will be used to plan development of combination (AGEN1884 plus drug[s]) strategies. As several anti–PD-1 and anti–PD-L1 products are already commercially available, many subjects receive these therapies as standard of care, therefore subjects who previously received these therapies were allowed to enroll in these expansion cohorts to help to better understand the safety of sequential treatment with AGEN1884.

Disease response assessments by RECIST was to be performed at Study Week 6, Week 12 and Q6w for subjects assigned to 3- or 6-w treatment schedule, or Q12w for subjects assigned to 12-w treatment schedule until off-disease response evaluation criteria are met.

Phase 2

Up to 60 subjects will be enrolled at the recommended Phase 2 dose of 1.0 mg/kg. Phase 2 consists of subjects who have progressed during treatment with an approved or investigational PD-1/PD-L1 inhibitor as their most recent therapy (2-6 weeks prior to first dose of study drug). For this phase:

- Approximately 20 subjects with advanced HCC will be enrolled.
- The enrollment of non-HCC will be approximately 40 subjects.

Note: additional subjects may be enrolled to either the HCC or non-HCC populations as necessary to ensure that 20 subjects are evaluable for the purpose of the additional PK evaluation (i.e. 3 additional timepoints, see Section 5.3).

Disease response assessments by RECIST to be performed at Study Week 6, Week 12 and Q6w for subjects assigned to 3- or 6-w treatment schedule, or Q12w for subjects assigned to 12-w treatment schedule until off-disease response evaluation criteria are met.

Subjects in both phases were evaluated for PK, PD, disease response, and safety, as determined through physical examination, vital signs, 12-lead electrocardiograms (ECGs), clinical laboratory tests, cytokine and lymphocyte subset measurements, and adverse events (Table 10).

3.1.1 Safety Review Committee

Study safety review will be presided over by the SRC, composed of the clinical investigators and medical monitor/study sponsor. The SRC will be convened regularly, including at the end of a cohort, once the protocol-defined criteria for dose escalation are met, to review all available

subject safety data in advance of providing formal notification to investigators that they may proceed to enroll subjects in the escalated dose cohort. The SRC will also be convened to evaluate all subjects on study when ≥2 adverse events are noted that are possible DLTs on a dose level and/or discuss additional toxicities that may warrant dose de-escalation, as described in Section 3.1.2.3. In Phase 2, the SRC will continue to meet at a frequency specified in the Safety Review Charter.

3.1.2 Dose-Limiting Toxicity Evaluation

3.1.2.1 Dose Escalation Procedures in Phase 1

The initial starting dose was 0.1 mg/kg and the first subject was enrolled to confirm safety at this level, which is near the MABEL dose. A minimum of 3 subjects were to be enrolled in each cohort. The first 2 subjects in each dosing cohort were to be enrolled ≥24 hours apart, and enrollment of the second subject did not proceed unless the first subject tolerated the therapy without DLT within the first 24 hours following the start of the infusion of the first subject. Each subject was observed for a DLT observation period of 28 days from initiation of AGEN1884 treatment, and 3 subjects must have been able to receive and tolerate the first 2 doses of AGEN1884 without DLTs during this observation period before the next cohort began enrollment. The dose was to be escalated if 0 of the first 3 evaluable subjects enrolled had a DLT. If 1 of the first 3 evaluable subjects enrolled had a DLT, then the cohort was to be expanded to include 3 additional evaluable subjects; if no DLT occurred in the additional 3 subjects, then the dose was to be escalated. If a DLT occurred in ≥2 subjects in the total cohort, the MTD was deemed to be exceeded, and the prior dose level was evaluated to determine the MTD by increasing enrollment to 6 subjects. If the prior dose level was already deemed to be safe and enrolled 6 subjects, then it was defined as the MTD. Alternate dosing schedules of AGEN1884 could have been explored depending on PK, pharmacodynamics, and safety results.

If 0.1 mg/kg exceeded the MTD (i.e., does not pass DLT evaluation), the sponsor and investigators considered alternate dose schedules (e.g., every 4 weeks) based on available safety, PK, and pharmacodynamics data. If an alternate schedule was tested and determined to be safe, re-escalation of AGEN1884 proceeded according to Table 1.

Additional subjects were enrolled in a cohort to achieve the minimum of 3 evaluable subjects at each dose level. Subjects who dropped out or who had dose interruptions/reductions that resulted in a subject being non-evaluable for DLTs were considered non-evaluable. Dose modifications in the DLT period due to any related toxicity were considered a DLT. Subjects who experienced a DLT during the dose-escalation portion of the study were discontinued from study drug. Intrasubject dose escalation was not permitted.

When accrual for the 3 mg/kg dose cohort was paused for safety assessment and DLT observation, expansion of the 1 mg/kg cohort began to enroll a total of 10 evaluable subjects.

Once 3 mg/kg was determined to be safe by the SRC, the 3 mg/kg dose cohort was expanded to enroll a total of 10 evaluable subjects; backfilling into the 1 mg/kg dose cohort was paused during this time. If the 1 mg/kg dose cohort did not reach 10 subjects, additional subjects were enrolled in the 1 mg/kg cohort after 10 evaluable subjects were enrolled in the 3 mg/kg cohort. Once 1 mg/kg and 3 mg/kg cohorts completed expansion and had each enrolled 10 evaluable subjects, dose escalation resumed at 6 mg/kg, according to the protocol. If any of the first 3

evaluable subjects enrolled at the maximum planned dose of 6 mg/kg experienced DLT, an additional 3 subjects were enrolled for a total of 6 subjects at the maximum planned dose.

3.1.2.2 Definition of Dose-Limiting Toxicity

With exceptions discussed below, a DLT is defined as a grade ≥3 adverse drug reaction (ADR), according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) Version 5, occurring in the DLT evaluation period (i.e., 28 days after the initial administration of AGEN1884) in subjects enrolled in the phase 1 dose escalation.

The SRC recognizes that in the absence of prior human experience with AGEN1884, a conservative approach should be adopted in ascribing the relevance of the treatment-related toxicity to drug. Treatment-emergent serious adverse events (SAEs) will be ascribed as related to drug except in cases in which a clear relationship to the underlying disease or recognized comorbidities are evident. For this trial, the MTD is defined as the highest dose at which <2 of 6 subjects experience a DLT.

A DLT is specifically defined as any one of the following:

- Grade ≥2 uveitis, eye pain, or blurred vision that does not respond to topical therapy.
- Any grade ≥3 toxicity that is possibly, probably, or definitely related to AGEN1884 occurring during the DLT evaluation period (28 days after initial administration of AGEN1884), except for any of the following:
  - Grade 3 infusion-related reaction resolving within 6 hours of dosing and controlled with medical management.
  - Transient (≤6 hours) grade 3 flu-like symptoms or fever, which are controlled with medical management.
  - Transient (≤24 hours) grade 3 fatigue, local reactions, headache, nausea, or emesis that resolves to grade ≤1.
  - Grade 3 diarrhea, skin toxicity, or liver function test (LFT), (alanine aminotransferase [ALT], aspartate aminotransferase [AST], or gamma glutamyltransferase [GGT]) increase that resolves to grade ≤1 within 7 days after medical management (e.g., immunosuppressant treatment) has been initiated.
  - Single laboratory values out of normal range that are unlikely related to trial treatment according to the investigator, do not have any clinical correlate, and resolve to grade ≤1 within 7 days with adequate medical management.
  - Tumor flare phenomenon, defined as local pain, irritation, or rash localized at sites of known or suspected tumor.

Subjects who do not complete the DLT observation period and do not receive 2 doses of AGEN1884 during the DLT observation period for reasons other than a DLT will be replaced.

3.1.2.3 Stopping Rules in Phase 1 for Enrollment Based on Toxicities

- If 2 or more DLTs occur at Dose Level 1 (0.1 mg/kg), then study enrollment will stop and evaluation of biologic and clinical activity will be completed for Dose Level 1. If there is a rationale to proceed at or near Dose Level 1 based on clinical or biological activity from

enrolled subjects, then Agenus will redesign the study with new dose levels and potentially a new dose frequency, both of which would be intended to decrease the dose intensity on study, and approach the Food and Drug Administration (FDA) for guidance before activating such a redesigned study.

- The SRC will meet to review the dose cohort under evaluation as well as safety of the full cohort under evaluation. Should ≥2 subjects on any dose level experience toxicities that meet DLT criteria but occur after the DLT evaluation period, enrollment will be held and the occurrences would be thoroughly evaluated by the SRC. Should these events be consistent with DLTs, for instance, from immune-related toxicities, they will be evaluated for relatedness to AGEN1884. The SRC will evaluate the events and de-escalate the dose level due to immune-related adverse events meeting DLT criteria that occur beyond the DLT evaluation period.

3.2 Eligibility Criteria

3.2.1 Inclusion Criteria

Subjects must meet all of the following criteria:

1. Written informed consent.
2. ≥18 years of age.
3. Histological or cytological diagnosis of solid cancer or lymphoma that is considered incurable and without therapies with established benefit. Biopsy is not necessary for subjects with known prior diagnosis, and clinical or radiographic evidence of recurrence.
   - **For Phase 2 only:** Subjects PD-1/PD-L1 naïve and those who experienced documented disease progression during treatment with an approved or investigational PD-1/PD-L1 inhibitor as their most recent therapy (2-6 weeks prior to first dose of study drug).
   - **For subjects in Phase 2 with HCC:** This cohort includes subjects with histological diagnoses of HCC (not including atypical histology such as cholangiocarcinoma mix or fibrolamellar hepatocellular carcinoma) who experienced documented disease progression during treatment with an approved or investigational PD-1/PD-L1 inhibitor as their most recent therapy (2-6 weeks prior to first dose of study drug).
4. Eastern Cooperative Oncology Group (ECOG) score of 0 or 1 (Appendix C).
5. Subjects in Phase 2 with HCC should have a Child-Pugh score of A or B7 with no encephalopathy or ascites (Appendix F).
6. Life expectancy ≥12 weeks.
7. Adequate cardiac function (New York Heart Association [NYHA] class ≤II) (Appendix D).
8. Adequate organ function, defined as absolute neutrophil count (ANC) $\geq 1{,}500 \times 10^6$/L, absolute lymphocyte count ≥500/mm^3, hemoglobin ≥8.0 g/dL, and platelet count

≥100,000×10^6/mm^3 without blood growth factors or without transfusions within 1 week of first dose.

For subjects in Phase 2 with HCC: Platelet count ≥60×10^6/mm^3 and ANC ≥1,000×10^6/L are acceptable provided that the principal investigator assesses these abnormalities as due to liver disease.

9. Adequate liver function, defined as AST and ALT ≤2.5× institutional upper limit of normal (ULN), and bilirubin ≤1.5 ULN.

   For subjects in Phase 2 with HCC: AST and ALT ≤5 × ULN, bilirubin ≤2 × ULN, and albumin ≥ 2.8 mg/dL.

10. Adequate renal function, defined as estimated creatinine clearance ≥50 mL/min according to Cockcroft-Gault formula, or measured 24-hour creatinine clearance (or local institutional standard method).

11. Adequate coagulation defined by international normalized ratio (INR) or prothrombin time (PT) ≤ 1.5 x ULN (unless the patient is receiving anticoagulant therapy); and activated partial thromboplastin time (aPTT) ≤ 1.5 x ULN (unless the subject is receiving anticoagulant therapy). Subjects in Phase 2 with HCC can have an INR ≤2.3 x ULN.

    Note: Subjects in Phase 2 with HCC and on anticoagulant treatment would have an assigned value of 1 point when scoring PT/INR so the overall Child-Pugh score is not adversely affected.

12. Female subjects of childbearing potential and fertile male subjects must agree to use adequate contraception or abstain from sexual activity from the time of consent through 90 days after the end of study drug. Adequate contraception includes condoms with contraceptive foam; oral, implantable, or injectable contraceptives; contraceptive patch; intrauterine device; diaphragm with spermicidal gel; or a sexual partner who is surgically sterilized or postmenopausal. **Note:** Abstinence is acceptable if this is the established and preferred contraception for the subject.

13. In the expansion phase (Phase 2) , all subjects must provide a sufficient and adequate formalin-fixed paraffin embedded (FFPE) tumor tissue sample preferably collected after progression on the last therapy and/or collected at screening, if clinically feasible. If a recent biopsy is not available, an archival FFPE sample should be provided from a site not previously irradiated. If no tumor tissue is available, a fresh biopsy will be required if clinically feasible (See Section 5.6.1 for details).

3.2.2 Exclusion Criteria

Subjects are ineligible to enroll in this study if they fulfill any of the following exclusion criteria.

1. Other malignancies treated within the last 5 years, except *in situ* cervix carcinoma or non-melanoma skin cancer.
2. Other form(s) of antineoplastic therapy anticipated during the period of the study.
3. Previous severe hypersensitivity reaction to another fully human monoclonal antibody or severe reaction to immuno-oncology agents, such as colitis or pneumonitis requiring treatment with steroids.

4. History of interstitial lung disease.
5. Primary or secondary immunodeficiency, including immunosuppressive disease, autoimmune disease (including autoimmune endocrinopathies), or usage of immunosuppressive medications.

   Note: Subjects with diabetes type 1, vitiligo, psoriasis, hypo-, or hyperthyroid disease not requiring immunosuppressive treatment are eligible. Subjects with Type 2 diabetes mellitus are allowed.
6. Subjects with a known history of human immunodeficiency virus 1 and 2, human T lymphotropic virus 1.

   Subjects in Phase 2 with HCC: Subjects with active hepatitis B infection who are receiving effective antiviral therapy are permitted. Subjects with active hepatitis C infection are allowed (antiviral therapy not required).
7. Administration of anticancer medications or investigational drugs within the following intervals before the first administration of study drug:

   a. ≤14 days for chemotherapy, targeted small molecule therapy, or radiation therapy. Subjects must also not have had radiation pneumonitis as a result of treatment and cannot participate in the study if they are on chronic corticosteroids for radiation pneumonitis. A 1-week washout is permitted for palliative radiation to non–central nervous system (CNS) disease, with medical monitor approval.

      Note: Bisphosphonates and denosumab are permitted medications.

   b. ≤14 days for prior immunotherapy. Subjects in the dose escalation cohorts are excluded if they have received prior checkpoint inhibitors, costimulatory agonists, or immune modulating therapy except as described below. Once a dose level is determined to be safe by the SRC, subjects will be allowed to enroll in dose-level expansion cohorts if they have received other non–CTLA-4 targeting immunotherapies.

   c. Subjects enrolling in Phase 2 must have cancer that has progressed after prior treatment with an approved or investigational PD-1/PD-L1 inhibitor as their most recent therapy (2-6 weeks prior to first dose of study drug). The minimum requirement of 2 weeks (14 days) from prior anti–PD-1/PD-L1 therapy is to allow resolution of any lower-grade (≤2) adverse events observed with the therapy. If the investigator feels the subject has tolerated prior anti–PD-1/PD-L1 therapy well, then treatment with study agent may begin sooner.

   d. ≤7 days for prior corticosteroid treatment, with the following exceptions:

      – Use of an inhaled or topical corticosteroid is permitted.

      – Corticosteroid premedication for radiographic imaging for dye allergies is permitted.

      – Use of physiologic corticosteroid replacement therapy may be approved after consultation with the medical monitor.

e. ≤21 days for prior monoclonal antibody used for anticancer therapy, with the exception of denosumab. **This does not apply to subjects being enrolled in Phase 2, who have received a PD-1/PD-L1 inhibitor as their most recent therapy (2-6 weeks prior to first dose of study drug; see above).**

f. ≤7 days for immunosuppressive-based treatment for any reason, with the exceptions noted above for prior corticosteroid treatment (exclusion criterion d).

g. ≤21 days or 5 half-lives before first dose of study treatment for all other investigational study drugs or devices. For investigational agents with long half-lives (e.g., >5 days), enrollment before the fifth half-life requires medical monitor approval.

h. For subjects in Phase 2 with HCC < 6 weeks for prior locoregional therapy to the liver e.g., transcatheter chemoembolization (TACE), radiation, surgery, or radioembolization.

8. Has not recovered to grade ≤1 from toxic effects of prior therapy and/or complications from prior surgical intervention before starting therapy.

   Note: Subjects with grade ≤2 neuropathy and alopecia are an exception and may enroll.

9. Uncontrolled infection or other serious medical illnesses.

10. History or presence of an abnormal ECG that, in the investigator's opinion, is clinically meaningful.

11. Any medical conditions that, in the opinion of the investigator, would preclude use of AGEN1884, including AGEN1884 hypersensitivity.

12. Women who are pregnant or breastfeeding.

13. Concurrent participation in other investigational drug trials.

14. Has a CNS tumor, metastasis(es), and/or carcinomatous meningitis identified either on the baseline brain imaging obtained during the screening period or identified prior to consent.

    Note: Subjects with history of brain metastases that have been treated may participate provided they show evidence of stable supra-tentorial lesions at screening (defined as 2 brain images, both of which are obtained after treatment to the brain metastases. These imaging scans should both be obtained ≥4 weeks apart). In addition, any neurologic symptoms that developed either as a result of the brain metastases or their treatment must have returned to baseline or resolved. For individuals who received steroids as part of brain metastases treatment, steroids must be discontinued ≥ 7 days prior to first dose of study drug.

15. **For subjects in Phase 2 with HCC, the following exclusions also apply**:

    a. Recent encephalopathy episodes in the last 6 months.

    b. Recent (within the last 3 months) gastro-esophageal varices bleeding.

    c. Subject whose tumors have cardiac involvement, as determined by imaging.

3.3 Randomization

No randomization to treatment assignments will be performed in this study.

3.4 Blinding

The study will be open label; no blinding will be performed.

3.5 Discontinuation of Therapy

Treatment with AGEN1884 should be discontinued if 1 of the following primary reasons occur:

- Unacceptable toxicity (based on the investigator's clinical decision that the subject is unable to tolerate therapy).
- Adverse event
- Radiographic progression of disease (compared to baseline assessment). Disease progression is defined as progression confirmed by a second, consecutive assessment ≥6 weeks apart.

  Note: If subject with evaluation of disease progression is having clinical benefit despite the progression, treatment may continue following discussion with, and approval of the medical monitor.
- Investigator decision
- Clinical progression of disease
- Protocol deviation
- Subject completed treatment
- Investigator decision
- Subject noncompliance with protocol for nonmedical reasons

Subjects who discontinue therapy prior to progression should continue to be followed for response and complete disease assessments every 12 weeks according to standard of care for up to 2 years from first AGEN1884 administration. Subjects will be followed for safety ≥90 days following the last administration of investigational agent, as described in Section 5.8.

3.6 Discontinuation from Study

Subjects should be discontinued from the study for 1 of the following primary reasons:

- Withdrawal of consent
- Lost to Follow-up
- Death
- Subject noncompliance with protocol
- Administrative study closure
- Completed study

3.7 Treatment Beyond Disease Progression

Subjects will be permitted, with the Sponsor's approval, to continue with treatment beyond initial RECIST 1.1 defined PD as long as they meet the following criteria:

- Investigator-assessed clinical benefit from the treatment;
- Subject is clinically stable;
- Subject is tolerating study drug; and
- There is agreement with the sponsor.

The assessment of clinical benefit should take into account whether the subject is clinically deteriorating and unlikely to receive further benefit from continued treatment. The following criteria need to be taken into consideration:

- Absence of clinical symptoms and signs (including worsening of laboratory values) indicating disease progression.
- No decline in ECOG performance status.
- Absence of rapid progression of disease or of progressive tumor at critical anatomical sites (e.g., cord compression) requiring urgent alternative medical intervention.

Subjects should discontinue study therapy upon evidence of further progression, defined as an additional 10% or greater increase in tumor burden from time of initial progression (including all target lesions and new measurable lesions).

Imaging is required every 6 weeks (± 3 days) for those subjects with confirmed PD who remain on AGEN1884 until treatment is discontinued.

4. Investigational Agent

4.1 Description of Investigational Agent

AGEN1884 is a novel, fully human monoclonal IgG1 antibody designed to block CTLA-4. It will be supplied as 50 mg per vial. AGEN1884 should be stored in a refrigerator at 2°C to 8°C.

4.1.1 Dosage and Administration

AGEN1884 will be administered intravenously (IV) for each cycle (3 weeks) as a 60-min (-10/+20 min) infusion. Infusions will be followed immediately by a 15-min saline flush of the IV line.

Treatment will be administered every 3 weeks for the first 4 cycles.

At the 12-week evaluation timepoint, subjects may continue to receive AGEN1884 every 3, 6, or 12 weeks (± 7 days) for a maximum duration of 1 year of treatment, provided they were not diagnosed with PD and were tolerating the study drug. The appropriate schedule will be based on discussion with the medical monitor. Subjects who progressed yet still have clinical benefit from treatment may continue on treatment following discussion with, and approval of, the medical monitor. For detailed criteria and consideration for treatment post-progression, refer to Section 3.7. Dosing is described in Table 1.

Please refer to the Pharmacy Manual for further instructions on AGEN1884 dosage and administration.

4.1.2 Dosing Delay Criteria

Prior to every AGEN1884 administration, laboratory values will be reviewed. AGEN1884 administration will be delayed for the following adverse events (AEs), if the following AEs occur on the day of planned AGEN1884 dosing:

- Either febrile neutropenia or neutropenia <500 cells/mm³ for >1 week despite the use of growth factors.
- Any grade ≥2, non-skin, drug-related AE except for fatigue and laboratory abnormalities
- Any grade 3 drug-related laboratory abnormality (except lymphopenia, AST, ALT, total bilirubin, or asymptomatic lipase or amylase).
    - Grade 3 lymphopenia does not require a dose delay.
    - If the subject has a baseline AST, ALT, or total bilirubin that is within normal limits, dosing should be delayed for drug-related grade ≥2 toxicity.
    - If the subject has a baseline AST, ALT, or total bilirubin within the grade 1 toxicity range, dosing should be delayed for drug-related grade ≥3 toxicity.
    - Any grade 3 drug-related amylase or lipase abnormality that is not associated with symptoms or clinical manifestations of pancreatitis does not require dose delay.
- Any grade 3, skin, drug-related AE.
- Any AE, laboratory abnormality, or intercurrent illness that, in the judgment of the investigator, warrants delaying the dose of study medication.
- For subjects in Phase 2 with HCC and an elevated baseline liver function test:

  Dose delay for the following:

  - Baseline AST, ALT < 2 x ULN with an increase to ≥ 5 x ULN
  - Baseline AST, ALT ≥ 2 x ULN with an increase to >3 x the baseline level
  - Elevations of AST, ALT ≥500 IU/L or 20 x ULN regardless of baseline level
  - Baseline total bilirubin ≤ 1.5 x ULN and increase to ≥ 2 x ULN
  - Baseline total bilirubin >1.5 x ULN and increase to ≥ 2 x baseline level
  - Elevations of total bilirubin ≥3x ULN regardless of baseline level

  Permanently discontinue for

  - Elevations of ALT ≥20 x ULN regardless of baseline level
  - Clinical Hepatic Decompensation regardless of lab values as follows:
    - New onset clinical ascites
    - Upper gastrointestinal bleeding due to portal hypertension
    - Encephalopathy
    - Coagulopathy due to liver disease
    - Worsening Child-Pugh score to 9

Subjects in Phase 2 with HCC will be followed closely and the appropriate course of action (including but not limited to hospitalization and/or consultation with a hepatologist) will be implemented as clinically indicated. In addition, other common causes of hepatic dysfunction should be ruled out; if a diagnoses of autoimmune hepatitis (AIH) is made, see Table 6 for additional management guidelines.

4.2 Infusion Reactions

Subjects receiving AGEN1884 should be monitored for infusion reactions. This includes the measurement of vital signs for ≥1 hour after infusion, defined as 1 hour after the completion of the 60-minute infusion of AGEN1884 and the 15-minute flush that follows the infusion. Subjects will remain in the clinic under close supervision for the duration of this monitoring period. Subjects with mild or moderate infusion reactions may receive AGEN1884 with close monitoring. Premedication with an antipyretic or antihistamine may be considered. For severe infusion reactions, AGEN1884 infusion must be discontinued, and appropriate medical therapy should be administered.

Subjects who do not experience any grade ≥1 infusion-related toxicity during or after the infusion may be released from monitoring after 1 hour if they are otherwise stable. Subjects with any infusion-related toxicity must be managed as per the guidelines below, and monitoring will continue until any infusion-related toxicity has abated to grade <1 and ≥1 hour has passed from the completion of the entire infusion and flush. Before leaving the study site, all subjects will be given information on infusion-related toxicity per institutional guidelines. This will include instructions on when and how to return for immune-mediated toxicities associated with CTLA-4 blockade.

If mild or moderate infusion reaction occurs, the infusion should be interrupted, and supportive care should be administered until the symptoms resolve, per treating clinician.

Management guidelines for infusion reactions will be provided to the investigators at each site (Table 2).

Table 2: Infusion Reaction Guidelines

CTCAE Grade	Treatment	Premedication at Subsequent Dose Administration
Grade 1 Mild reaction; infusion interruption not indicated; intervention not indicated.	Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator.	None.
Grade 2 Requires infusion interruption but responds promptly to symptomatic treatment (e.g., antihistamines, nonsteroidal anti-inflammatory drugs [NSAIDs], narcotics, IV fluids); prophylactic medications indicated for ≤24 hours.	Stop infusion and monitor symptoms. Additional appropriate medical therapy may include but is not limited to the following: • IV fluids • Antihistamines • NSAIDS • Acetaminophen • Narcotics Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator. If symptoms resolve within 1 hour of stopping drug infusion, the infusion may be restarted at 50% of the original infusion rate. Otherwise, dose administration will be held until symptoms resolve, and the subject should be premedicated for the next scheduled dose. Subjects who develop grade 2 toxicity despite adequate premedication should be permanently discontinued from further study drug administration.	Subject may be premedicated 1.5 h (± 30 min) prior to infusion with the following: • Diphenhydramine 50 mg PO (or equivalent dose of antihistamine). • Acetaminophen 500-1000 mg PO (or equivalent dose of antipyretic).
Grade 3 or 4 Grade 3 Prolonged (i.e., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae (e.g., renal impairment, pulmonary infiltrates). Grade 4 Life-threatening; pressor or ventilatory support indicated.	Stop infusion. Additional appropriate medical therapy may include but is not limited to: • IV fluids • Antihistamines • NSAIDs • Acetaminophen • Narcotics • Oxygen • Pressors • Corticosteroid • Epinephrine Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator. Hospitalization may be indicated. Subject is permanently discontinued from further study drug administration.	No subsequent dosing.

CTCAE: Common Terminology Criteria for Adverse Events; h: hour; IV: intravenous; min: minute; NSAID: nonsteroidal anti-inflammatory drug, PO: orally.

4.3 Management of Immune-Related Adverse Events

Immuno-oncology agents such as AGEN1884 are associated with immune-related adverse events (irAEs). Early recognition and management of irAEs may mitigate severe toxicity. Investigators should also monitor subjects closely for potential irAEs, which may manifest after weeks of treatment, at the earliest. Such events may consist of persistent rash, diarrhea, colitis, autoimmune hepatitis, pneumonitis, encephalitis, arthritis, glomerulonephritis, cardiomyopathy, or uveitis and other inflammatory eye conditions.

Management algorithms have been developed to assist investigators in assessing and managing the following groups of irAEs: gastrointestinal, pulmonary, dermatological, renal, hepatic, neurological, and endocrine, among others.

Adverse events (both non-serious and serious) associated with drug exposure and consistent with an immune phenomenon may represent an immunologic etiology. These irAEs may be predicted based on the nature of the study drugs, their mechanism of action, and reported experience with immunotherapies that have a similar mechanism of action. An irAE can occur shortly after the first dose or several months after the last dose of treatment. Particular attention should be paid to AEs that may be suggestive of potential irAEs, as outlined below.

4.3.1 Dermatological irAEs

Rule out non-inflammatory causes. If a non-inflammatory cause is identified, treat accordingly and continue therapy per protocol (Table 3).

Table 3: Dermatological irAE Management Algorithm

Dermatological irAEs		
CTCAE Grade of Rash	**Management**	**Follow-Up**
Grade 1-2 Covering ≤30% body surface area	• Symptomatic therapy (e.g., antihistamines, topical corticosteroids). • Continue AGEN1884 therapy per protocol.	• **If persists >1 to 2 weeks or recurs**: Consider skin biopsy. • Delay AGEN1884 therapy. • Consider 0.5-1 mg/kg/day methylprednisolone IV or oral equivalent. Once improving, taper corticosteroids over ≥1 month; consider prophylactic antibiotics for opportunistic infections; and resume AGEN1884 therapy per protocol. • **If worsens**: Treat as grade 3-4.
Grade 3-4 Covering >30% body surface area; life-threatening consequences	• Delay or discontinue AGEN1884 therapy per protocol. • Consider skin biopsy. • Dermatology consult • 1-2 mg/kg/day methylprednisolone IV or IV equivalent.	• **If improves to grade 1**: Taper corticosteroids over ≥1 month; add prophylactic antibiotics for opportunistic infections. • Resume AGEN1884 therapy per protocol.

CTCAE: Common Terminology Criteria for Adverse Events; irAE: immune-related adverse event; IV: intravenous; kg: kilogram; mg: milligram

4.3.2 Gastrointestinal irAEs

Rule out non-inflammatory causes. If non-inflammatory cause is identified, treat accordingly and continue therapy. Opiates/narcotics may mask symptoms of perforation. Infliximab should not be used in cases of perforation or sepsis (Table 4).

Table 4: Gastrointestinal irAEs Management Algorithm

Gastrointestinal irAEs		
CTCAE Grade of Diarrhea/Colitis	**Management**	**Follow-Up**
Grade 1 Diarrhea: <4 stools/day over baseline. Colitis: asymptomatic.	• Continue AGEN1884 therapy per protocol. • Symptomatic treatment.	• Close monitoring for worsening symptoms. • Educate subject to report worsening immediately. • Consider symptomatic treatment including hydration, electrolyte replacement, dietary changes (e.g., American Dietetic Association colitis diet), and loperamide. • **If worsens**: Treat as grade 2 or 3-4.
Grade 2 Diarrhea: 4-6 stools per day over baseline; IV fluids indicated <24 h; not interfering with activities of daily living (ADL). Colitis: abdominal pain; blood in stool.	• Delay AGEN1884 therapy per protocol. • Symptomatic treatment.	• **If improves to grade 1**: Resume AGEN1884 therapy per protocol. • **If persists >5 to 7 days or recurs**: 0.5-1 mg/kg/day methylprednisolone or equivalent. • When symptoms improve to grade 1, taper corticosteroids over ≥1 month; consider prophylactic antibiotics for opportunistic infections; resume AGEN1884 therapy per protocol. • **If worsens or persists >3 to 5 days with oral corticosteroids**: Treat as grade 3-4.
Grade 3-4 Diarrhea (grade 3): ≥7 stools per day over baseline; incontinence; IV fluids ≥24 h; interfering with ADL. Colitis (grade 3): severe abdominal pain, medical intervention indicated, peritoneal signs. Grade 4: life-threatening, perforation	• Discontinue AGEN1884 therapy per protocol. • 1-2 mg/kg/day methylprednisolone IV or equivalent. • Add prophylactic antibiotics for opportunistic infections. • Consider lower endoscopy.	• **If improves**: Continue corticosteroids until grade 1, then taper over ≥1 month. • **If persists >3 to 5 days, or recurs after improvement**: Add infliximab 5 mg/kg (if no contraindication). • **Note**: Infliximab should not be used in cases of perforation or sepsis.

ADL: activities of daily living; CTCAE: Common Terminology Criteria for Adverse Events; h: hour; irAE: immune-related adverse event; IV: intravenous; kg: kilogram; mg: milligram.

4.3.3 Pulmonary irAEs

Rule out non-inflammatory causes. If non-inflammatory cause is identified, treat accordingly and continue therapy per protocol. Evaluate with imaging and pulmonary consultation (Table 5).

Table 5: Pulmonary irAE Management Algorithm

Pulmonary irAEs		
CTCAE Grade of Pneumonitis	**Management**	**Follow-Up**
Grade 1 Radiographic changes only.	• Consider delay of AGEN1884 therapy per protocol. • Monitor for symptoms every 2-3 days. • Consider pulmonary and infectious disease consults.	• Re-image every ≥3 weeks. • **If worsens**: Treat as grade 2 or grade 3-4.
Grade 2 Mild to moderate new symptoms	• Delay AGEN1884 therapy per protocol. • Pulmonary and infectious disease consults. • Monitor symptoms daily; consider hospitalization. • 1 mg/kg/day methylprednisolone IV or oral equivalent. • Consider bronchoscopy, lung biopsy.	• Re-image every 1-3 days. • **If improves**: When symptoms return to near baseline, taper corticosteroids over ≥1 month, then resume AGEN1884 therapy per protocol, and consider prophylactic antibiotics. • **If not improving after 2 weeks or worsening**: Treat as grade 3-4.
Grade 3-4 Severe new symptoms; new/ worsening hypoxia; life-threatening.	• Discontinue AGEN1884 therapy per protocol. • Hospitalize. • Pulmonary and infectious disease consults. • 2-4 mg/kg/day methylprednisolone IV or IV equivalent. • Add prophylactic antibiotics for opportunistic infections. • Consider bronchoscopy, lung biopsy.	• **If improves to baseline**: Taper corticosteroids over ≥6 weeks. • **If not improving after 48 hours or worsening**: Add additional immunosuppression (e.g., infliximab, cyclophosphamide, IV immunoglobulin, mycophenolate mofetil).

CTCAE: Common Terminology Criteria for Adverse Events; irAE: immune-related adverse event; IV: intravenous; kg: kilogram; mg: milligram

4.3.4 Hepatic irAEs

Rule out non-inflammatory causes (e.g., alcohol use, acute viral hepatitis, flare up from chronic hepatitis, co-infection [e.g., with hepatitis D], etc.). If a non-inflammatory cause is identified, treat accordingly and continue therapy per protocol. Consider imaging for obstruction and a hepatologist consult (Table 6).

Table 6: Hepatic irAE Management Algorithm

Hepatic irAEs		
CTCAE Grade of Liver Test Elevation	**Management**	**Follow-Up**
Grade 1 AST or ALT >ULN to 3 x ULN and/or total bilirubin >ULN to 1.5 x ULN.	• Continue AGEN1884 therapy per protocol.	• Continue liver function tests (LFT) monitoring per protocol. • **If worsens**: Treat as grade 2 or grade 3-4.
Grade 2 AST or ALT >3 to ≤5 x ULN and/or total bilirubin >1.5 to ≤3 x ULN. If subject has concurrent AST or ALT >3 x ULN **and** total bilirubin >2 x ULN, discontinue AGEN1884 therapy per protocol (Hy's Law)	• Delay AGEN1884 therapy per protocol. • Increase frequency of monitoring to every 3 days.	• **If returns to baseline**: Resume routine monitoring; resume AGEN1884 therapy per protocol. • **If elevations persist >5 to 7 days or worsen**: 0.5-1 mg/kg/day methylprednisolone IV or oral equivalent. When LFT returns to grade 1 or baseline, taper corticosteroids over ≥1 month, consider prophylactic antibiotics for opportunistic infections, and resume AGEN1884 therapy per protocol.
Grade 3-4 AST or ALT >5 x ULN and/or total bilirubin >3 x ULN.	• Permanently discontinue AGEN1884 therapy per protocol. • Increase frequency of monitoring to every 1-2 days. • 1-2 mg/kg/day methylprednisolone IV or oral equivalent.* • Add prophylactic antibiotics for opportunistic infections. • Consult gastroenterology. • Consider obtaining MRI/CT scan of liver and liver biopsy if clinically warranted.	• **If returns to grade 2**: Taper corticosteroids around 4 to 6 weeks. • **If does not improve in >3 to 5 days, worsens, or rebounds**: Add mycophenolate mofetil 1 g twice daily. If no response within an additional 3-5 days, consider other immunosuppressants per local guidelines.

Hepatic irAEs		
CTCAE Grade of Liver Test Elevation	**Management**	**Follow-Up**
For subjects in Phase 2 with HCC and elevated baseline LFT **Dose delay for the following:** Baseline AST, ALT < 2 x ULN with an increase to ≥ 5 x ULN Baseline AST, ALT ≥ 2 x ULN with an increase to >3 x the baseline level Elevations of AST, ALT ≥500 IU/L or 20 x ULN regardless of baseline level Baseline total bilirubin ≤ 1.5 x ULN and increase to ≥ 2 x ULN Baseline total bilirubin >1.5 x ULN and increase to ≥ 2 x baseline level Elevations of total bilirubin ≥3x ULN regardless of baseline level	• Dose delay or discontinue AGEN1884 therapy. • 1-2 mg/kg/day methylprednisolone IV or oral equivalent.* • Consider hepatologist consult • Increase frequency of monitoring to every 3 days	• **If returns to grade <1 or baseline level within 1 week** then taper corticosteroids over ≥ 1 month • If symptoms and laboratory resolve to grade ≤1 or baseline levels and steroids have been tapered to a prednisone level ≤ 10mg/day or equivalent for at least a week, may consider resuming AGEN1884 • **If does not improve in >3 to 5 days, worsens, or rebounds**: Add mycophenolate mofetil 1 g twice daily. If no response within an additional 3-5 days, consider other immunosuppressants per local guidelines and **hepatologist consult**. Also, permanently discontinue. • If symptoms and laboratory do not resolve to grade ≤1 or baseline levels within 3 weeks or steroids cannot be tapered to a prednisone level ≤ 10 mg/day or equivalent within 9 weeks, AGEN1884 must be permanently discontinued**.** • **All cases considered for re-treatment should be discussed with the medical monitor**

* The recommended starting dose for grade 4 hepatitis is 2 mg/kg/day methylprednisolone IV.
ALT: alanine aminotransferase; AST: aspartate aminotransferase; CT: computed tomography; CTCAE: Common Terminology Criteria for Adverse Events; HCC: hepatocellular carcinoma; irAE: immune-related adverse event; IV: intravenous; kg: kilogram; LFT: liver function test; mg: milligram; MRI: magnetic resonance imaging; ULN: upper limit of institutional normal.

4.3.5 Endocrine irAEs

Rule out non-inflammatory causes. If non-inflammatory cause is identified, treat accordingly and continue therapy per protocol. Consider visual field testing, endocrinology consultation, and imaging (Table 7).

Table 7: Endocrine irAE Management Algorithm

Endocrine irAEs		
Endocrine Disorder	**Management**	**Follow-Up**
Asymptomatic TSH abnormality	• Continue AGEN1884 therapy per protocol. • **If TSH <0.5 x lower limit of normal (LLN) or TSH >2 x ULN, or consistently out of range in 2 subsequent measurements**: Include free thyroxine (T4) at subsequent cycles as clinically indicated; consider endocrinology consult.	
Symptomatic endocrinopathy	• Evaluate endocrine function. • Consider pituitary scan. • **Symptomatic with abnormal lab/pituitary scan**: Delay AGEN1884 therapy per protocol; 1-2 mg/kg/day methylprednisolone IV or oral equivalent; initiate appropriate hormone therapy. • **No abnormal lab/pituitary MRI scan but symptoms persist**: Repeat labs in 1-3 weeks, MRI in 1 month.	• **If improves (with or without hormone replacement)**: Taper corticosteroids over ≥1 month and consider prophylactic antibiotics for opportunistic infections. • Resume AGEN1884 therapy per protocol. • Subjects with adrenal insufficiency may need to continue corticosteroids with mineralocorticoid component.
Suspicion of adrenal crisis (e.g., severe dehydration, hypotension, shock out of proportion to current illness)	• Delay or discontinue AGEN1884 therapy per protocol. • Rule out sepsis. • Stress dose of IV corticosteroids with mineralocorticoid activity. • IV fluids. • Consult endocrinologist. • If adrenal crisis ruled out, treat as above for symptomatic endocrinopathy.	

irAE: immune-related adverse event; IV: intravenous; kg: kilogram; LLN: lower limit of normal; mg: milligram; MRI: magnetic resonance imaging; TSH: thyroid stimulating hormone; ULN: upper limit of normal.

4.3.6 Renal irAEs

Rule out non-inflammatory causes. If non-inflammatory cause is identified, treat accordingly and continue therapy per protocol (Table 8).

Table 8: Renal irAE Management Algorithm

Renal irAEs		
CTCAE Grade of Creatinine Elevation	**Management**	**Follow-Up**
Grade 1 Creatinine >ULN and >baseline but ≤1.5 x baseline	• Continue AGEN1884 therapy per protocol. • Monitor creatinine weekly.	• **If returns to baseline**: Resume routine creatinine monitoring per protocol. • **If worsens**: Treat as grade 2 or grade 3-4.
Grade 2-3 Creatinine >1.5 x baseline to ≤6 x ULN	• Delay AGEN1884 therapy per protocol. • Monitor creatinine every 2-3 days. • 0.5-1.0 mg/kg/day methylprednisolone IV or oral equivalent. • Consider renal biopsy	• **If returns to grade 1**: Taper corticosteroids over ≥1 month, consider prophylactic antibiotics for opportunistic infections, and resume AGEN1884 therapy and routine creatinine monitoring per protocol. • **If elevations persist > 7 days or worsen**: Treat as grade 4.
Grade 4 Creatinine >6 x ULN	• Discontinue AGEN1884 therapy per protocol. • Monitor creatinine daily. • 1.0-2.0 mg/kg/day methylprednisolone IV or IV equivalent. • Consult nephrologist. • Consider renal biopsy.	• **If returns to grade 1**: Taper corticosteroids over ≥1 month and add prophylactic antibiotics for opportunistic infections.

CTCAE: Common Terminology Criteria for Adverse Events; irAE: immune-related adverse event; IV: intravenous; kg: kilogram; mg: milligram; ULN: upper limit of normal.

4.3.7 Neurological irAEs

Rule out non-inflammatory causes. If a non-inflammatory cause is identified, treat accordingly and continue therapy per protocol (Table 9).

Table 9: Neurological irAE Management Algorithm

Neurological irAEs		
CTCAE Grade of Neurological Toxicity	**Management**	**Follow-Up**
Grade 1 Asymptomatic or mild symptoms; intervention not indicated.	• Continue AGEN1884 therapy per protocol.	• Continue to monitor subject. • **If worsens**: Treat as grade 2 or grade 3-4.
Grade 2 Moderate symptoms; limiting instrumental ADL.	• Delay AGEN1884 therapy per protocol. • Treat symptoms per local guidelines. • Consider 0.5-1.0 mg/kg/day methylprednisolone IV or oral equivalent.	• **If returns to baseline**: Resume AGEN1884 therapy per protocol. • **If worsens**: Treat as grade 3-4.
Grade 3-4 Severe symptoms; limiting self-care ADL; life-threatening.	• Discontinue AGEN1884 therapy per protocol. • Obtain neurology consult. • Treat symptoms per local guidelines. • 1.0-2.0 mg/kg/day methylprednisolone IV or IV equivalent. • Add prophylactic antibiotics for opportunistic infections.	• **If improves to grade 2**: Taper corticosteroids over ≥1 month. • **If worsens or atypical presentation**: Consider IV immunoglobulin or other immunosuppressive therapies per local guidelines.

ADL: activities of daily living; CTCAE: Common Terminology Criteria for Adverse Events; irAE: immune-related adverse event; IV: intravenous; kg: kilogram; mg: milligram.

4.4 Adverse Drug Reactions Requiring Treatment Discontinuation or Modifications

An ADR is defined as all noxious and unintended responses to a medicinal product, related to any dose. A causal relationship between the medicinal product and an AE is deemed at least a reasonable possibility if the relationship cannot be ruled out by another cause.

4.4.1 Dose Reductions

No dose reductions are allowed. Each subject will stay on the regimen dose levels assigned in the trial unless treatment needs to be stopped. Dose reductions or dose escalations of AGEN1884 are not permitted.

4.4.2 Permanent Treatment Discontinuation

The following ADRs require permanent treatment discontinuation of AGEN1884:

Any grade 4 ADRs except for single laboratory values out of normal range that are unlikely related to trial treatment as assessed by the investigator, do not have any clinical correlate, and resolve within 7 days with adequate medical management.

Any grade 3 ADRs except for any of the following:

- Transient (≤6 hours) grade 3 flu-like symptoms or fever, which are controlled with medical management.
- Transient (≤24 hours) grade 3 fatigue, local reactions, headache, nausea, or emesis that resolves to grade ≤1.
- Single laboratory values out of normal range (excluding grade ≤3 liver function test increase) that are unlikely related to trial treatment according to the investigator; do not have any clinical correlate; and resolve to grade ≤1 within 7 days with adequate medical management.
- Tumor flare phenomenon, defined as local pain, irritation, or rash localized at sites of known or suspected tumor.
- Any grade ≥3 drug-related amylase or lipase abnormality that is not associated with symptoms, or clinical manifestations of pancreatitis does not require dose delay. The trial medical monitor should be consulted for such grade ≥3 amylase or lipase abnormalities.
- Increases in ECOG performance status to ≥3 that do not resolve to ≤2 by Day 14 of the following cycle (infusions should not be given on the following cycle if ECOG performance status is ≥3 on day of study drug administration).

Any grade 2 ADR should be managed as follows:

- If a grade 2 ADR resolves to grade ≤1 by the last day of the current cycle, trial treatment may continue.
- If a grade 2 ADR does not resolve to grade ≤1 by the last day of the current cycle, infusions should not be administered during the following cycle. If, at the end of the following cycle, the event has not resolved to grade 1, the subject should permanently discontinue treatment with AGEN1884.
- For grade 2 ADRs related to hormone insufficiencies that can be managed by replacement therapy, up to 2 subsequent doses may be omitted.
- Upon the second occurrence of the same grade 2 ADR (except for hormone insufficiencies that can be managed by replacement therapy) in the same subject, treatment with AGEN1884 should be permanently discontinued.

Subjects who received systemic corticosteroids for management of any drug-related toxicity must be off corticosteroids or have tapered down to an equivalent dose of prednisone ≤10 mg/day for study treatment to be resumed.

All infusion-related and hypersensitivity reactions (grades 1-4) should be handled according to the guidelines in Table 2.

Subjects in Phase 2 with HCC will be discontinued for any of the following reasons:

- New onset clinical ascites
- Upper gastrointestinal bleeding due to portal hypertension
- Encephalopathy
- Coagulopathy secondary to liver disease
- Worsening Child-Pugh score to 9
- ALT, AST elevations ≥20 x ULN

4.5 Prior and Concomitant Therapy

Before first administration of study drug, subjects must not have received anticancer medications or investigational drugs within the intervals defined in Section 3.2.2, exclusion criterion #7. Subjects will not be permitted to receive any other anticancer-related therapy during the study.

4.6 Investigational Agent Accountability

International regulatory agencies require accounting for the disposition of all investigational product received by each investigative site. Information on investigational product disposition required by law consists of the date received, date administered, quantity administered, and the subject to whom the investigational product was administered. The principal investigator (or designee, as specified in the Delegation of Authority Log) is responsible for accounting for all unused investigational product and all used investigational product containers. Investigational product may not be given to non–study participants under any circumstances.

Supplies will be shipped to the investigative site at appropriate intervals, depending on subject accrual. The site will use either the Investigational Product Dispensing Form provided by Agenus or a similar standard form approved by Agenus to document investigational drug disposition. This form must be maintained either in the pharmacy or in another area approved by the Agenus monitor. The monitor will review investigational product accountability during routine monitoring visits.

At the termination of the study, a final investigational product accountability review and reconciliation must be completed, and any discrepancies must be investigated and their resolution documented.

5. Study Procedures and Assessments

5.1 Schedule of Assessments

The schedule of assessments is provided in Table 10.

Table 10: Schedule of Assessments

	Screening	Treatment and Evaluation													Disease Assessments	End of Treatment Visit	Final Safety Visit	Survival F/U
Study Week		**1**	**2**		**4**			**7**			**10**		**12**	**Q3, 6, and 12W after Week 12**	**After disc. of treatment**	**28 days after last dose**	**90 days after last dose**	**Every 12 weeks until death or for up to 2 years**
Visit Window (days)	**Within 28 d of first dose**		**± 2**		**± 3**			**± 3**			**± 7**		**± 2**	**± 7**	**± 7**	**± 7**	**± 7**	**± 14**
Assessment		**D1 C1**	**D8 C1**		**D1 C2**			**D1 C3**			**D1 C4**		**D15 C4**					
Informed consent	X																	
Review of eligibility criteria	X	X																
Medical history [a]	X																	
NYHA class evaluation	X																	
Tumor biopsies/archival tissue collection [b]	X							X										
12-lead ECG [c]	X	X			X										X	X	X	
Performance status (ECOG)	X	X			X			X			X			X	X	X	X	
Physical examination	X	X			X			X			X			X	X	X	X	
MRI or CT disease assessment by RECIST [d]	X							X					X	X [d]	X	X	X	
AGEN1884 administration [e]		X			X			X			X			X				
Serum chemistry [f]	X	X	X		X			X			X			X	X	X	X	
Endocrine function tests (free T4, TSH and ACTH) [f]	X	X	X		X			X			X			X		X		
Hematology [f]	X	X	X		X			X			X			X	X	X	X	
Tumor marker assessment [g]	X	X			X			X			X			X	X	X	X	
Urinalysis [f]	X	X	X		X			X			X			X	X	X	X	
Coagulation [f]	X	X	X		X			X			X			X	X	X	X	

	Screening	Treatment and Evaluation													Disease Assessments	End of Treatment Visit	Final Safety Visit	Survival F/U
Study Week		**1**	**2**		**4**			**7**			**10**		**12**	**Q3, 6, and 12W after Week 12**	**After disc. of treatment**	**28 days after last dose**	**90 days after last dose**	**Every 12 weeks until death or for up to 2 years**
Visit Window (days)	**Within 28 d of first dose**		**± 2**		**± 3**			**± 3**			**± 7**		**± 2**	**± 7**	**± 7**	**± 7**	**± 7**	**± 14**
Assessment		**D1 C1**	**D8 C1**		**D1 C2**			**D1 C3**			**D1 C4**		**D15 C4**					
Adverse events	X	X	X		X			X			X		X	X	X	X	X	
Pregnancy test [h]	X	X			X			X			X			X		X	X	
Concomitant medications	X	X	X		X			X			X		X	X	X	X	X	
Vital signs [i]	X	X [i]	X		X [i]			X [i]			X [i]		X	X [i]	X	X	X	
Evaluation of DLTs (phase 1 dose escalation only)		X	X		X													
PGx (whole blood) [j]	X																	
Blood sample for serum PK and/or ADA [k]		X	X		X			X			X		X			X	X	
Survival follow-up and initiation of subsequent therapy																		X

ACTH: adrenocorticotropic hormone; ADA: anti-drug antibody(ies); AFP: alpha-fetoprotein; C: cycle; CA-125: cancer antigen 125; CR: complete response; CT: computed tomography; D: day; disc: discontinuation; DLT: dose-limiting toxicity; ECG: electrocardiogram; ECOG: Eastern Cooperative Oncology Group; F/U: follow-up; FFPE: formalin-fixed paraffin-embedded; HCC: hepatocellular carcinoma; IV: intravenous; MRI: magnetic resonance imaging; NYHA: New York Heart Association; PGx: pharmacogenomics; PK: pharmacokinetic(s); PR: partial response; Q: every; RECIST: Response Evaluation Criteria in Solid Tumors Version 1.1; SD: stable disease; T4: thyroxine; TSH: thyroid stimulating hormone; W: week.

a. All prior cancer treatments collected as part of medical history.

b. Biomarker assessment will be performed on the most recent FFPE biopsy of a tumor lesion, preferably collected after progression on the last therapy and/or collected at screening, if clinically feasible. If a recent biopsy is not available, an archival FFPE sample should be provided from a site not previously irradiated. An optional tumor biopsy will be collected at Cycle 3, Day 1 (-3/+1 day), if clinically feasible, to assess pharmacodynamic effects of the drug.

c. 12-lead ECG to be recorded at screening (within 7 d of first treatment dose) any time during visit as long as within protocol window. Day 1 of Cycles 1 and 2 to be recorded 1 h ± 30 min following flush of infusion line. Other ECGs to be ordered as clinically indicated by treating physician.

d. Disease response assessments by RECIST to be performed at Study Week 6, Week 12 and Q6w for subjects assigned to 3- or 6-w treatment schedule, or Q12w for subjects assigned to 12-w treatment schedule until off-disease response evaluation criteria are met.

e. AGEN1884 to be administered IV over 60 (-10/+20) min. Subjects with SD, PR, or CR at 12-w evaluation timepoint may continue receiving AGEN1884 every 3, 6, or 12 w (± 7 d) beginning at Study Week 12 for ≤1 year provided they are tolerating study drug. The appropriate schedule will be based on discussion with medical monitor to confirm that proposed schedule is in subject's best interest.

f. For screening, laboratory assessments to be completed within 7 d prior to first AGEN1884 administration. Prior to every AGEN1884 administration, laboratory values to be reviewed (with the exception of endocrine function tests). Delay AGEN1884 if any dosing delay criteria are met according to Section 4.1.2.

g. For tumors with known markers (e.g., AFP for HCC, CA-125 for ovarian cancer, etc.), samples to evaluate tumor marker levels at sites at screening and at each tumor assessment.

h. Women of childbearing potential only. Serum pregnancy test to be performed at screening (within 7 d of first AGEN1884 treatment); urine pregnancy tests to be performed at subsequent visits.

i. Vital sign measurements to be collected within 30 min prior to administration, every 30 (± 10) min during the 60-min AGEN1884 infusion, including at end of 15-min flush of infusion line (± 15 min). This equates to 4 sets of vitals over the course of a 60-min infusion and flush, including pre-administration vitals. A final set of vitals will be collected 1 h (± 15 min) following flush of infusion line, unless otherwise indicated.

j. Blood sample for PGx is collected only if an optional PGx consent is signed.

k. For Cycles 1, 2, 3, 4, 5, 8, 12, and 16, blood samples for serum PK and ADA analyses to be collected on Day 1 predose (within 1 h predose). For Cycles 1 and 4, a blood sample for serum PK analysis is to be collected on Day 1 at 2 (±0.25) h post start of AGEN1884 infusion. The 2 h postdose PK sample should never be taken during any study drug infusion, but within 1 h following end of the infusion (for those study drug infusions that go longer than the protocol recommended durations). A blood sample for serum PK analysis will also be collected at Cycle 1 Day 8 (168 ±4 h post start of AGEN1884 infusion).Blood samples for serum PK and ADA analyses are to be collected at the End of Treatment Visit and the Final Safety Visit. See Table 11 for additional PK sampling in an approximate 20 subject subpopulation.

5.1.1 Screening

Subjects will undergo screening assessments specified in the schedule of assessments (Table 10) within 28 days prior to the first dose of AGEN1884. Laboratory assessments (including serum pregnancy) and ECG should be performed within 7 days prior to first treatment dose of AGEN1884.

Subjects who fulfill all of the inclusion criteria and none of the exclusion criteria will be enrolled into the study. Subjects who do not meet the inclusion and exclusion criteria will be considered screen fails, and their demographic information and reason for screen failure should be documented.

5.1.2 Treatment and Evaluation Period

Subjects will be treated as described in the schedule of assessments (Table 10) and evaluated for pharmacodynamics, PK, immune correlates, disease response, and safety. If a subject discontinues for reasons other than PD, tumor assessments will continue until PD occurs or other criteria for discontinuation are met.

5.1.3 End-of-Treatment Visit

The End-of-Treatment Visit should occur at the time study drug is discontinued for any reason. The End-of-Treatment Visit occurs 28 days from the last dose of study treatment.

5.1.4 Final Safety Visit

The mandatory Safety Follow-Up Visit should be conducted for all subjects approximately 90 days after the last dose of study drug or before the initiation of a new antineoplastic treatment, whichever comes first. Subjects with an AE of Grade >1 will be further followed until the resolution of the AE to Grade 0-1 or until beginning of a new antineoplastic therapy, whichever occurs first. Subjects with an ADR ongoing at the Safety Follow-up Visit must be followed up until the ADR resolves, becomes stable, or is considered not clinically significant by the investigator.

5.1.5 Survival Follow-up

Subjects who discontinue study treatment will be followed for survival by phone contact every 3 months. Survival follow-up will continue until death, for up to 2 years, or until study closure. Subjects will also be followed for initiation of another cancer therapy.

If a subject withdraws from the interventional portion of a study and does not consent to continued follow-up of associated clinical outcome information, the investigator will not access for purposes related to the study the subject's medical record or other confidential records requiring the subject's consent. However, investigators will consult public records, such as obituaries and the Social Security index to establish survival status.

5.2 Demographics and Screening Procedures

5.2.1 Demographics and Medical/Cancer History

The subject's date of birth, gender, race, and ethnicity are to be documented.

A full medical history is to be documented during the screening visit by the investigator or designated participating physician and may include medical notes documented by a referring

physician in the subject's medical record. The medical history is to include any current active diagnoses and any previously treated illnesses, including the approximate date of onset (at minimum indicate the year or approximate year) and date of resolution if applicable, and description of any prior surgeries. The body systems to be reviewed and any concurrent or past diagnoses documented include but are not limited to: eyes, ears, nose, and throat; respiratory; cardiovascular; gastrointestinal; musculoskeletal; neurological; endocrine/metabolic; hematologic/lymphatic; dermatological; genitourinary; psychiatric; and allergies.

Baseline information about the malignancy, including type of cancer, date of diagnosis, and prior treatments, will also be collected.

5.2.2 Eastern Cooperative Oncology Group Scale

Subjects will be graded according to ECOG performance status score (Appendix C).

5.2.3 New York Heart Association Class Evaluation

The NYHA class will be evaluated at screening (Appendix D).

5.2.4 Tumor Markers

For tumors with known markers (e.g., alpha-fetoprotein [AFP] for HCC, cancer antigen 125 [CA-125] for ovarian cancer, etc.), samples to evaluate levels of tumor markers will be obtained at screening and at each tumor assessment.

5.3 Pharmacokinetic Assessments

Serum AGEN1884 concentrations will be determined by validated methods. PK parameters to be estimated and reported may include, but may not be limited to, maximum observed drug concentration at steady-state ($C_{max\text{-}ss}$), minimum observed drug concentration at steady-state ($C_{min\text{-}ss}$), area under the drug concentration-time curve within time span t1 to t2 at steady-state ($AUC_{(t1\text{-}t2)\text{-}ss}$), area under the drug concentration-time curve from time of dosing to time of last observation ($AUC_{(0\text{-}t)}$), area under the drug concentration-time curve from time of dosing extrapolated to infinity ($AUC_{(0\text{-}\infty)}$), time to reach maximum drug concentration (t_{max}), terminal elimination rate constant (λ_z), terminal elimination half-life ($t_{½}$), systemic clearance (CL), and volume of distribution (Vd). PK parameters will be summarized using descriptive statistics. Individual as well as summary drug concentration-time profiles will be depicted. Unresolved missing data may be imputed when analysis integrity is affected. The conservative principle will be used for data imputation. Both noncompartmental (NCA) and compartmental modeling (e.g., population pharmacokinetics [PopPK]) techniques will be used to analyze the pharmacokinetics. Sampling times for all subjects are shown in Table 10.

In addition to the PK sampling times for the general population shown in Table 10, a subgroup of approximately 20 subjects will have samples taken at 3 additional timepoints shown in Table 11.

Table 11: Additional Pharmacokinetic Sampling Schedule in an Approximate 20 Subject Subpopulation

Cycle	Sampling Times
Cycle 1	D3 (48±4 h)
Cycle 4	D3 (48±4 h); D8 (168±4 h).

Blood samples collected Days 3 and 8 at 48±4 h and 168±4 h, respectively, after the ***start*** of the infusion.

Unresolved missing data may be imputed when analysis integrity is affected. The conservative principle will be used for data imputation.

5.4 Immunogenicity Assessments

Serum AGEN1884 ADA monitoring will be conducted via blood serum samples collected prior to drug administration, throughout the entire course of drug administration, and at the final safety visit. Sampling times are shown in Table 10.

5.5 Exploratory Biomarkers

To better understand the pharmacodynamics of AGEN1884, a correlation with additional biomarkers may be necessary, this includes but may not be limited to whole blood, plasma, and serum samples for exploratory biomarker analysis according to the schedule of assessments (Table 10) as well as tumor tissue collected at screening and an optional on-treatment biopsy.

Within this trial, additional biomarker assessments that might be correlated with safety, response, or resistance to treatment beyond those listed (e.g., monitoring inflammatory or immune markers, measuring specific cell populations, or measuring cell surface markers by flow cytometry, immunoblot, mass spectroscopy, immunoassay, tumor markers, or correlations between drug exposure and/or response including tumor mutational burden and other variations in deoxyribonucleic acid [DNA] or in ribonucleic acid [RNA] [pharmacogenomics]) may be evaluated at the discretion of the Sponsor using excess PD, PK, whole blood, plasma, serum, or biopsy samples. Participation in pharmacogenomics (PGx) studies involving the analysis of DNA and/or RNA is optional and requires separate informed consent (Section 7.1).

Ongoing research may lead to the identification of new important markers related to anti-CTLA4 therapies and/or safety in a near future; therefore, each subject will also be asked whether any remaining tumor tissue or blood-derived samples can be stored at a central repository and can be used for future exploratory research on the drug and / or disease-related aspects. A subject's consent to the use of any remaining samples for such future exploratory research shall be optional and shall not affect the subject's participation in the current trial. After analysis by the Sponsor or its designee, samples will be maintained for up to 5 years following completion of the study and will then be destroyed unless the subject withdraws consent or requests that his/her sample/results be destroyed. During this 5 year period, samples may be reanalyzed by the Sponsor or its designee, collaborator, or partner.

5.6 Pharmacodynamic Assessments and Biopsy

5.6.1 Biopsy and Tissue Collection

Tumor tissue for biomarker analysis from a biopsy of a tumor lesion not previously irradiated must be available for biomarker assessments. Biomarker assessment will be performed on the most recent FFPE biopsy of a tumor lesion, preferably collected after progression on the last therapy and/or collected at screening, if clinically feasible. If a recent biopsy is not available, an archival FFPE sample should be provided from a site not previously irradiated. An optional tumor biopsy will be collected at Cycle 3, Day 1 (-3/+1 day), if clinically feasible, to assess pharmacodynamic effects of the drug.

Tissue from needle or excisional biopsy or from resection is required.

Preferably, an FFPE tumor tissue block should be provided. If the tumor-containing FFPE tissue block is not available, 25 sections (slides) ≤ 1 month old should be provided; ≥ 15 slides are required. If no tumor tissue is available, a fresh biopsy will be required, if clinically feasible.

Fine needle aspirates, endobronchial ultrasound (EBUS) or cell blocks are not acceptable.

If a tumor biopsy was obtained from a target lesion during eligibility assessment, it is preferred to obtain a new baseline scan. Biopsy of lesions on study should be limited to non-target lesions or new lesions if their pathologic etiology is ambiguous.

Tissue processing: The cancer tissues should be fixed in 10% neutral buffered formalin, paraffin embedded, and routinely processed for histological evaluation. Formalin substitutes are not suited as fixative.

Provision of samples:

1. Priority: tumor containing FFPE tissue block;
2. Priority: if the tumor containing FFPE tissue block cannot be provided in total, sections from this block should be provided that are freshly cut (within the last month), 5 µm thick, and mounted on SuperFrost Plus microscope slides. Preferably, 25 slides should be provided; if not possible, a minimum of 15 slides are required. The SuperFrost Plus microscope slides and slide containers will be provided by the central lab.

Sample shipment: The tumor blocks and freshly prepared slides should be sent with the next shipment to the central lab.

Sample storage: At the central laboratory, the FFPE tissue blocks shall be stored at room temperature in the dark and the FFPE tumor slides shall be kept in sealed containers at 2°C to 8°C.

For additional details and instructions regarding tissue requirements, collection, storage and shipment, refer to the study Laboratory Manual.

5.6.2 Pharmacogenomics (Optional)

The sponsor may conduct research on DNA (blood) or tumor tissue specimens collected during this trial. This research may include genetic analysis (DNA) and gene expression profiling (RNA). Such research is for pharmacogenomic testing to address emergent questions not described elsewhere in the protocol (as part of the main trial) and will only be conducted on

specimens from appropriately consented subjects. The overarching goal is to develop safer, more effective drugs.

Germline (inherited) variants will be investigated in DNA extracted from the whole blood. For this purpose, an additional 4 mL of whole blood (PGx sample) will be collected at screening. Additionally, tumor biopsy samples may be used for the extraction of DNA to study tumor genetics (somatic variations). Participation is optional for subjects being recruited at sites whose IEC/IRB has approved PGx assessments and a PGx informed consent form (ICF) (optional) is signed (Section 7.1).

All samples collected during the trial will be kept confidential. For this purpose, the samples will be given a label connected with a code assigned at the start of the Main Study (coded trial subject number). Outside the study center, no one will be able to link the subject's identity to the subject number. The link between the subject's identity and the subject number will only be known by a limited number of authorized personnel. Information about race, ethnicity, sex, medical history, etc., may be available to scientists studying the PGx blood samples. Such information might be important for research or public health purposes. Genomic analysis results will not be reported back to the sites.

Participation in PGx portion of the trial is optional and requires separate informed consent. Participation in the PGx portion of the trial will not affect participation in the trial. Subjects may withdraw consent from PGx portion of the trial without withdrawing from the trial. Consent and withdrawal of consent (if applicable) for PGx assessments will be documented in the eCRF.

5.7 Tumor Assessments

5.7.1 Response Evaluation Criterion in Solid Tumors

Primary disease assessments will be performed based on RECIST Version 1.1 (Appendix E). Disease response assessments by RECIST to be performed at Study Week 6, Week 12 and Q6w for subjects assigned to 3- or 6-w treatment schedule, or Q12w for subjects assigned to 12-w treatment schedule until off-disease response evaluation criteria are met.

Assessment of tumor size (by magnetic resonance imaging [MRI] or computed tomography [CT] scan) will be performed as specified in the schedule of assessments (Table 10) until disease progression is determined by RECIST or other off–tumor evaluation criteria are met. The same modality should be used for each subject through the course of his or her disease evaluation. Treatment cycles may become out of sync with tumor assessments if a delay in therapy is indicated; however, in this event, tumor assessments will remain on the original schedule.

Subjects who discontinue study drug for a reason other than disease progression will continue to be assessed for their disease status per the schedule of events and should continue to have tumor assessments every 6 weeks, or per disease-specific schedule, until further disease progression (additional 10% from first PD observation), death, or the end of the study.

5.8 Safety Assessments

5.8.1 Physical Examination

Physical examinations are to be completed by the investigator or designated participating physician as indicated in the schedule of assessments (Table 10). The minimum body systems to be examined for any abnormalities and symptoms include: general appearance; skin; lymphatic;

head, eyes, ears, nose, throat; extremities; respiratory; cardiovascular; abdominal; musculoskeletal; and neurological.

5.8.2 Vital Signs

Vital signs will be measured at all visits indicated in the schedule of assessments (Table 10) and documented in the medical record. Measurements to be reported are temperature in Celsius or Fahrenheit, pulse (beats per minute), respiratory rate (breaths per minute), oxygen saturation, and blood pressure.

Vital sign measurements will be collected within 30 minutes prior to study drug administration, and every 30 (± 10) minutes during the 60-minute AGEN1884 infusion, including at the end of the 15-minute flush of the infusion line (± 15 minutes). This would equate to 4 sets of vitals over the course of a 60-minute infusion and flush, including the pre-administration vitals. A final set of vitals will be collected 1 hour (± 15 minutes) following the flush of the infusion line, unless otherwise indicated.

Because AGEN1884 is administered based on subject body weight, weight will be collected before each dose of AGEN1884 to confirm the administered dose. The subject's weight at the Week 1 (Cycle 1, Day 1) visit should be used for dosing calculations unless there is a >10% change in body weight. Dose adjustments for each cycle are only needed for a >10% change in weight.

5.8.3 12-Lead Electrocardiogram

A 12-lead ECG will be recorded as indicated in the schedule of assessments (Table 10). The corrected QT (QTc) interval will be calculated using Fridericia's formula.

5.8.4 Clinical Laboratory Assessments

Blood samples will be collected and submitted to the institution's local laboratory according to the institution's standard procedures.

Standard laboratory procedures and institutional guidelines will be followed to analyze and report findings for hematology, coagulation times, and serum biochemistry.

Normal ranges with the units of measure for all required parameters will be provided to the study sponsor by the local laboratory conducting the clinical laboratory analysis. All results may be reported in conventional units if this is the typical clinic report method for the local laboratory; otherwise, the International System of units may be used.

A listing of clinical laboratory assessments to be performed is provided in Table 12.

Table 12: Clinical Laboratory Assessments

Hematology	Red blood cell count Platelets Hematocrit Hemoglobin WBC count	WBC differentials and absolute counts: Neutrophils Eosinophils Basophils Lymphocytes Monocytes
Serum biochemistry	Albumin Alkaline phosphatase Aspartate amino transferase Alanine amino transferase Total bilirubin Blood urea nitrogen Glucose	Creatinine Potassium Sodium Lactate dehydrogenase
Endocrine function tests	Free thyroxine (T4) Thyroid-stimulating hormone Adrenocorticotropic hormone	
Urinalysis	Red blood cells WBCs Protein	
Coagulation	Prothrombin time INR Partial thromboplastin time	
Tumor markers	Tumors with known markers, such as alpha-fetoprotein for HCC and cancer antigen 125 for ovarian cancer	
Other	Serum and urine pregnancy tests (for women of childbearing potential only) PGx	

HCC: hepatocellular carcinoma; INR: International Normalized Ratio; PGx: pharmacogenomics; WBC: white blood cell.

5.8.5 Concomitant Medications

Concomitant medications will be recorded from date of signing of the informed consent through 90 days after the last study drug administration.

5.8.6 Adverse Events

5.8.6.1 Definitions

5.8.6.1.1 Adverse Event

An AE is defined as any untoward medical occurrence in a clinical investigation subject administered a pharmaceutical product and that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding that is deemed clinically significant), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.

Examples include:

- Any clinically significant worsening of a pre-existing condition (e.g., an increase in severity or frequency of pre-existing abnormality or disorder).
- Any illness, injury, or accident, including those that appear unrelated to study treatment.
- Extensions or exacerbations or symptomatology.
- Clinically significant abnormalities in clinical laboratory, physiological testing, or physical examination.

5.8.6.1.2 Immune-Related Adverse Events

Blocking CTLA-4 function may permit the emergence of immune-mediated AEs that result in clinical syndromes resembling autoimmunity. Rash/vitiligo, diarrhea/colitis, uveitis/episcleritis, hepatitis, and hypopituitarism were drug-related, presumptive immune-related events noted in previous studies of anti–CTLA-4 agents.

For the purposes of this study, an irAE is defined as an adverse event of unknown etiology, associated with drug exposure, and is consistent with an immune phenomenon. Efforts should be made to rule out neoplastic, infectious, metabolic, toxin, or other etiologic causes prior to labeling an adverse event an irAE. Serological, immunological, and histological (biopsy) data should be used to support the diagnosis of an immune-mediated toxicity.

5.8.6.1.3 Adverse Drug Reaction

An ADR is defined as all noxious and unintended responses to a medicinal product, related to any dose. A causal relationship between the medicinal product and an AE is at least a reasonable possibility, i.e., the relationship cannot be ruled out.

5.8.6.1.4 Unexpected Adverse Drug Reaction

An unexpected ADR is an ADR whose nature or severity is not consistent with the applicable product information (e.g., Investigator Brochure). The ADRs that are more specific or more severe than described in the Investigator Brochure should also be considered unexpected.

5.8.6.1.5 Serious Adverse Event

An SAE in a clinical trial is defined as any untoward medical occurrence that at any dose, in the view of either the investigator or sponsor:

- Results in death.
- Is life-threatening (the subject was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe).
- Requires in-patient hospitalization or prolongation of existing hospitalization.
- Results in persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions.
- Is a congenital anomaly/birth defect.
- Any event that does not meet the above criteria, but when based on appropriate medical judgment, may require medical or surgical intervention to prevent one of the outcomes listed above, e.g., allergic bronchospasm requiring intensive treatment in an emergency room or at home; blood dyscrasias or convulsions that do not result in in-patient hospitalization; development of drug abuse or drug dependency.

5.8.6.2 Recording and Reporting

5.8.6.2.1 Adverse Events

Subjects will be assessed for any AEs (non-serious or serious) from the date of consent until 90 days after the last study treatment. Any non-serious AEs identified during this time period will be followed until resolution or stabilization or only until the discontinuation from the study evaluation period if the event is not resolved at the conclusion of the study. The dates of onset and resolution for each AE will be recorded in the subject file. All AEs will be evaluated for duration, intensity, and attribution (relationship) to the investigational agent(s). All AEs (serious and non-serious) and laboratory abnormalities should be assessed for significance by the investigator, with consideration for the subject's overall medical history and concomitant medication profile.

If there is a change from baseline in a laboratory value, physical examination finding, vital sign, or medical finding, and the change is considered by the investigator to be clinically significant, the event must be recorded as an AE.

All AEs regardless of causality or seriousness must be recorded on the electronic case report form (eCRF). The frequency, grade, and nature of irAEs must be recorded.

5.8.6.2.2 Serious Adverse Events

All AEs that meet the SAE criteria, occurring from the date of consent, must be recorded on the AE pages of the eCRF and reported by facsimile to Agenus/PrimeVigilance within 24 hours of obtaining knowledge of the event. The facsimile report should include all available information requested on the SAE Report Form.

Email: [redacted]

Facsimile: [redacted]

The SAE Report Form will include data surrounding the event, e.g., the nature of the symptom(s), time of onset in relation to initiation of therapy, duration, intensity, and whether or not therapy was interrupted or discontinued. The investigator's assessment of the probable cause of the event will also be included. In addition, relevant medical history, concomitant medications, laboratory and diagnostic tests reports, and procedures, as well as all pertinent medical information related to the event, will also be collected.

PrimeVigilance will forward SAE queries directly to the investigator requesting incomplete or missing information. It is the investigator's responsibility to be diligent in providing this information back to PrimeVigilance as soon as it is available. Initial reports of SAEs should never be left on telephone voicemails. Always fax SAE Report Forms and follow up with a telephone call if needed.

If you have any safety-related questions or need to report an SAE, please email:

[redacted]

For reported deaths, the investigator should supply the sponsor and the Institutional Review Board (IRB)/Independent Ethics Committee (IEC) with any additional requested information (e.g., autopsy results, hospital discharge reports, and/or certificates of death) and should be sent as soon as they become available. Any additional information, if collected, will be reported to the sponsor as a follow-up to the initial report.

All SAEs will be followed until the event has resolved or stabilized, regardless of causality.

It is the responsibility of the principal investigator to report SAEs to their IRB. The investigator should also comply with the applicable regulatory requirement(s) related to the reporting of unexpected serious ADRs to the regulatory authority(ies) and the IRB/IEC.

Deaths occurring during the AE reportable time frame should be reported as SAEs and recorded on the eCRF. The underlying event that resulted in death should be recorded as the verbatim term, with "death" recorded as the outcome of the event.

5.8.6.3 Adverse Events of Special Interest

In the event of a non-serious adverse events of special interest (AESI), the investigator must complete the AESI report form and send it to the Sponsor/designee immediately, within 24 hours. Names, addresses, and telephone and fax numbers for AESI reporting will be included on the report form. Serious AESIs must be reported in an expedited manner as SAEs, as outlined above.

5.8.6.4 Severity of Adverse Events

Each AE is to be classified and graded according to NCI CTCAE Version 5, publication date 27 November 2017 (https://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_8.5x11.pdf).

If no CTCAE grading is applicable, the severity of an AE is graded as follows:

- **Mild (grade 1)**: The event causes discomfort without disruption of normal daily activities.
- **Moderate (grade 2)**: The event causes discomfort that affects normal daily activities.
- **Severe (grade 3)**: The event makes the subject unable to perform normal daily activities or significantly affects his/her clinical status.
- **Potentially life-threatening/life-threatening (grade 4)**: An SAE Report Form must be completed for each grade 4 AE.
- An event that results in death is considered **a grade 5 AE**, meets the definition of an SAE, and must have an SAE Report Form completed for the event.

Note: All subjects who have a grade 3 or 4 AE may be considered for discontinuation from treatment by the principal investigator and after consultation with the medical monitor.

5.9 Relationship to Study Treatment

The relationship of an AE to the investigational agent will be recorded on eCRF and defined as "unrelated," "unlikely," "possible," "probable," or "highly probable/definite."

- **Unrelated**: The event is definitely not associated with study drug administration, but is judged clearly and incontrovertibly due to causes other than the study drug.
- **Unlikely**: An event that follows such a temporal sequence from administration of the study drug that a relationship is not likely, and is likely to be due to cause such as (known characteristics of) the subject's clinical state or other treatment.

- **Possible**: An event that follows a reasonable temporal sequence from administration of the study drug, but that may be due to another cause.
- **Probable**: An event that follows a reasonable temporal sequence from administration of the study drug, and that is not easily explained by another cause such as known characteristics of the subject's clinical state or other treatment.
- **Highly probable/definite**: An event that follows an established temporal sequence from administration of the study drug, the re-challenge is positive, or there is a reoccurring pattern of characteristics during onset and cessation of event.

5.10 Pregnancy

Pregnancy, in and of itself, is not regarded as an AE unless there is suspicion that study drug may have interfered with the effectiveness of a contraceptive medication or method. When a pregnancy has been confirmed in a subject during maternal or paternal exposure to study drug, within 90 days of the last dose of study drug, the following procedures should be followed in order to ensure subject safety:

- The study drug must be discontinued immediately (female subjects only).
- The investigator must complete and submit the Agenus Clinical Trial Pregnancy form to the sponsor or its designee within **24 hours** of learning of the pregnancy.
- A serum pregnancy test must be performed to confirm the urine pregnancy test result.

  If a negative serum test does not confirm the urine pregnancy test result, then:

  - The investigator will use his or her expert judgment, based on an assessment of the potential benefit/risk to the subject, to determine whether it is in the subject's best interest to resume study drug and continue participation in the study.
  - The final safety visit evaluations must be performed.

Data on fetal outcome and breastfeeding are collected for regulatory reporting and drug safety evaluation. Follow-up should be conducted for each pregnancy to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications, by following until the first well-baby visit. Pregnancy should be recorded on a Clinical Trial Pregnancy form and reported by the investigator to the sponsor or its designee. Pregnancy follow-up information should be recorded on the same form and should include an assessment of the possible causal relationship to the sponsor's study drug to any pregnancy outcome, as well as follow-up to the first well-baby visit or the duration specified in local regulations, whichever is later. Refer to the Agenus Study Operational Guide for Completing the Clinical Trial Pregnancy Form.

Note: Any SAE occurring during pregnancy must be recorded on the SAE report form and submitted to the sponsor or designee.

5.11 Disease Progression or Secondary Cancer or Death

For the purpose of this protocol, disease progression events should not be reported as a nonserious AE or SAE unless the criteria for an SAE are met (Section 5.8.6.1.5). If the event meets SAE criteria, a specific verbatim SAE term is to be reported (e.g., brain metastases). Details of how the event manifested should be provided in a narrative format and submitted with

the Agenus SAE Report Form. An appropriate verbatim term that describes the subject diagnosis should be provided in the Agenus SAE Report form. The verbatim terms "disease progression" or "disease recurrence" should be avoided; if used, it will be queried for a request for an appropriate term with supportive details for the event.

Changes in any medical condition of a subject, including the diagnosis of a secondary cancer or a clinically significant change of medical status, should be reported as an AE on the appropriate eCRF and should be reported as an SAE only if the event meets SAE criteria.

Deaths occurring during the AE reportable time frame (within 90 days of study drug) should be reported as SAEs and recorded on the Agenus SAE Report Form. The underlying event that resulted in death should be recorded as the verbatim term, with "death" recorded as the outcome of the event.

6. Statistical Considerations

This section outlines the core elements of the planned statistical summaries and analyses for the data collected in this study. Detailed methodology for summary and statistical analyses of the data collected in this study will be documented in a statistical analysis plan (SAP), which will be maintained by the sponsor. The SAP may modify the plans outlined in the protocol; however, any major modifications of the primary endpoint definition and/or its analysis will also be reflected in a protocol amendment. If, after the data are locked, changes are made to the SAP, then these deviations to the plan will be documented, in the clinical study report.

6.1 Sample Size Considerations

Overall, approximately 90 subjects will be enrolled in Phase 1 and Phase 2 of this study. After safety is established in the 1 mg/kg and 3 mg/kg cohorts, additional subjects will be enrolled into these dose cohorts (target size of 10 subjects per cohort) to support the objectives and expand the number of correlates available for evaluation.

The Phase 2 population will include approximately 40 subjects who have progressed during treatment with an approved or investigational PD-1/PD-L1 inhibitor as their most recent therapy (2-6 weeks prior to first dose of study drug) with a subpopulation to include approximately 20 subjects with advanced HCC.

These sample sizes are not based on inferential statistics.

6.2 Endpoints

6.2.1.1 Primary Endpoints

- Safety and tolerability will be assessed by monitoring the frequency, duration, and severity of drug-related AEs; by completing physical examinations; by evaluating changes in vital signs and ECG; through clinical examinations; and laboratory blood and urine sample evaluations.
- PK parameters to be estimated and reported may include, but may not be limited to, $C_{max\text{-}ss}$, $C_{min\text{-}ss}$, $AUC_{(t1\text{-}t2)\text{-}ss}$, $AUC_{(0\text{-}t)}$, $AUC_{(0\text{-}\infty)}$, t_{max}, λz, $t_{½}$, CL, and Vd. PK parameters will be summarized using descriptive statistics. Individual as well as summary concentration-time profiles will be depicted. Both NCA and compartmental modeling (e.g., PopPK) techniques will be used to analyze the pharmacokinetics.

6.2.1.2 Secondary Endpoints

- Objective response rate, (ORR), defined as the percentage of subjects having CR or PR, as determined by radiographic disease assessments per RECIST 1.1.
- Disease control rate (DCR) will include subjects that have best overall response (BOR) of CR, PR and SD for at least 12 weeks.
- Progression-free survival (PFS), defined as the interval from the date of first dose of investigational agent until the earliest date of disease progression, as determined by investigator assessment of objective radiographic disease assessments per RECIST 1,1, or death due to any cause if occurring sooner than progression.
- Duration of response, (DOR), defined as the interval from the date measurement criteria are met for CR or PR (whichever is first recorded) until the earliest date of disease progression, as determined by investigator assessment of objective radiographic disease assessments per RECIST 1.1, or death due to any cause if occurring sooner than progression. Only subjects who achieve an initial response will be evaluated for DOR.
- Overall survival (OS), defined as the interval from the date of first dose of investigational agent until the date of death.
- The pharmacologically active dose of AGEN1884, determined through clinical signs of drug activity, surrogate markers, and pharmacodynamic studies, including but not limited to the presence of irAEs.

6.2.1.3 Exploratory Endpoints

- Other biomarker effects and outcome predictors of AGEN1884 in peripheral blood and tumor tissue will be evaluated as exploratory analyses.

6.3 Analysis Sets

The following analysis sets will be evaluated:

- DLT evaluable analysis set:
    - All subjects within the dose escalation cohorts who received ≥2 doses of AGEN1884 at their assigned dose level and completed the DLT evaluation period of 28 days, or all subjects within the dose escalation cohorts who received ≥1 dose of AGEN1884 and experienced a DLT.
- Safety analysis set:
    - All subjects who have received ≥1 dose of AGEN1884.
- Efficacy analysis set:
    - Subjects who have received ≥2 doses of AGEN1884 at the assigned dose level.

6.4 Analysis Methods

6.4.1 Safety Analysis

Descriptive statistics of safety parameters will be provided in the full safety analysis set, by dose level, and study cohort. Safety parameters include the following:

- AEs (all AEs and irAEs, subsets of related, serious, severe, and fatal events). In addition, the number and percentage of subjects who discontinue treatment due to an AE will be provided, together with the number and percentage of subjects who die due to an AE.
- Laboratory evaluations.
- Vital signs.

6.4.2 Efficacy Analysis

Efficacy endpoints will be measured in the safety analysis set. As an exploratory analysis, similar calculations will be performed on the efficacy analysis set.

6.4.2.1 Progression-Free Survival

Subjects who are alive and have not progressed at the time of analysis will be censored at the time of the last clinical assessment noted to be free of progression. The distribution of PFS times, including median PFS time and PFS rates, will be estimated in a pooled manner and by each dose level and study cohort using the Kaplan-Meier method with 95% confidence intervals. Dates of progression will be based on RECIST 1.1.

6.4.2.2 Overall Survival

Subjects who have not died at the time of analysis will be censored at the time of last known alive. The distribution of survival times, including median survival time and survival rates, will be estimated in a pooled manner and by each dose level and study cohort using the Kaplan-Meier method with 95% confidence intervals.

6.4.2.3 Objective Response Rate

Descriptive statistics (number and frequency) of response rates will be presented in a pooled manner and by dose of AGEN1884 and cohort. Disease responses will be defined based on RECIST 1.1.

6.4.2.4 Duration of Response

Descriptive statistics (median, minimum, maximum, number of applicable subjects) of disease response durations will be presented in a pooled manner and by dose of AGEN1884 and cohort. Disease responses will be defined based on RECIST 1.1.

6.5 Statistical Analysis Plan

A statistical analysis plan (SAP) for the study will be created as a separate document. General considerations with regard to statistical methods, as well as specific plans for the analysis of efficacy and safety will be detailed in the SAP.

7. Compliance with Good Clinical Practice, Ethical Considerations, and Informed Consent

7.1 Compliance with Good Clinical Practice and Ethical Considerations

This study must be conducted in compliance with the IRB/IEC informed consent regulation, and the International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) Guidelines. In addition, all local regulatory requirements will be adhered to, in particular those which afford greater protection to the safety of the trial participants.

This study will be conducted according to the current revision of the Declaration of Helsinki (Revised 64th WMA General Assembly, Fortaleza, Brazil, October 2013) and with local laws and regulations relevant to the use of new therapeutic agents in the country of conduct.

Before initiating a trial, the investigator/institution should have written and dated approval/favorable opinion from the IRB/IEC for the trial protocol/amendment(s), written ICF, subject recruitment procedures (e.g., advertisements), and written information to be provided to subjects. Subjects may also sign a separate, optional section of the ICF, related to pharmacogenomic analysis, which refers to extraction and analysis of DNA from blood and/or tumor biopsy to better understand how gene(s) may affect the efficacy of AGEN1884.

Changes to the protocol will require written IRB/IEC approval/favorable opinion prior to implementation, except when the modification is needed to eliminate an immediate hazard(s) to subjects.

The investigator, or a person designated by the investigator, will explain the benefits and risks of participation in the study to each subject or the subject's legally acceptable representative in the presence of an impartial witness and obtain written informed consent prior to the subject entering the study (before initiation of non-routine tests and administration of study drug).

Agenus will provide the site with a sample ICF, which may be modified according to local regulations or requirements. The final ICF must be agreed to by Agenus and the IRB/IEC and must contain all elements in the sample form in language readily understood by the subject. The investigator will retain each subject's original ICF, signed and dated by the subject or by the subject's legally acceptable representative, and by the person who conducted the informed consent discussion, with a copy provided to the subject.

Participation in the pharmacogenomics portion of the trial is optional. Participation in the pharmacogenomics portion of the trial will not affect participation in the trial. Subjects may withdraw consent from pharmacogenomics portion of the trial without withdrawing from the trial. The results of pharmacogenomics testing will not be made available to the subjects.

Specimens that may be used for pharmacogenomics testing include: blood and tumor specimens collected during this trial.

The investigator or qualified designee will explain the optional pharmacogenomics assessment portion of the consent to the patient, answer all his/her questions, and obtain optional written informed consent before performing any procedure related to pharmacogenomics assessment.

Whenever important new information becomes available that may be relevant to the subject's consent, the written subject information sheet and any other written information provided to subjects will be revised by the sponsor or designee and be submitted again to the IEC/IRB for review and favorable opinion. The agreed upon, revised information will be provided to each subject in the trial for signing and dating. The investigator will explain the changes to the previous version.

8. Study Management and Materials

8.1 Data Recording and Retention of Study Data

In compliance with GCP, the medical records/medical notes, etc., should be clearly marked and permit easy identification of participation by a subject in the specified clinical trial.

The investigator is to record all data with respect to protocol procedures, drug administration, laboratory data, safety data and efficacy ratings on the study eCRFs.

The principal investigator must, as a minimum, sign the final eCRF pages to attest to the accuracy and completeness of all data.

All corrections on source documents must be made in a way that does not obscure the original entry. The correct data must be inserted, dated, and initialed/authorized by study personnel. If the reason for the change is not obvious, a reason should be provided.

If the investigator relocates or retires, or otherwise withdraws his/her responsibility for maintenance and retention, Agenus must be notified (preferably in writing) so that adequate provision can be made with regard to the trial documents.

Trial documents should be retained until ≥2 years after the last approval of a marketing application in an ICH region and until there are no pending or planned marketing applications in an ICH region, or ≥2 years have elapsed since the formal discontinuation of clinical development of AGEN1884 by Agenus. These documents should be retained for a longer period, however, if required by the applicable regulatory requirements or by an agreement with Agenus. Agenus will inform the investigator in writing as to when these documents no longer need to be retained.

8.2 Monitoring, Verification of Data, Audit, and Inspection

An Agenus monitor, or appointed agent, will perform monitoring in the form of on-site visits, telephone calls, and regular review of the eCRFs at a frequency sufficient to inspect: study progress; subject enrollment/screening; compliance with protocol procedures; informed consent procedure; completeness and accuracy of data entered on the eCRFs; verification of data against original source documents; storage and accountability of investigational product; archiving of study documentation; and occurrence of AEs. Adequate time and workspace for these visits must be made available by the investigator and his/her study personnel. Periodically some/all of the facilities used in the trial (e.g., laboratory) may be reviewed or inspected by the IRB/IEC and/or regulatory authorities.

The investigator is to ensure that the trial participants are aware of and consent that personal information may be reviewed during the data verification process as part of the monitoring/auditing by properly authorized agents of Agenus or subject to inspection by regulatory authorities. In addition, participation and personal information is treated as strictly confidential to the extent the applicable law permits and not publicly available. The audit or inspection may include, for example, a review of all source documents (medical records), drug records, original clinical medical notes, and some or all of the facilities used in the trial.

The investigator agrees by written consent to this protocol to fully cooperate with compliance checks by allowing access for authorized persons to all study documents.

8.3 Study Stopping Rules

Premature termination of the clinical trial may occur because of a regulatory authority decision, change of the IRB/IEC, or drug safety problems, at the discretion of the sponsor. In addition, Agenus retains the right to discontinue development of AGEN1884.

Recruitment at a center may be stopped for reason that may include low recruitment, protocol violation, or inadequate data recording quality control and quality assurance.

9. Communication and Publication of Results

The investigators and Agenus acknowledge that this study is part of a multicenter research study. Any publication (or presentation) of the data collected from this trial will be considered a joint publication by the investigators and the appropriate Agenus personnel. Authorship will be determined by mutual agreement between Agenus personnel and the principal investigators of the study. Agenus retains the right to the initial publication or presentation of the results by the study group. Following joint publication (or at such early time as Agenus decides), each principal investigator may request, in writing, the opportunity to publish or present site-specific data in accordance with the terms set forth in the Clinical Trial Agreement between Agenus and such principal investigator.

10. References

Brahmer, J.R., Drake, C.G., Wollner, I., Powderly, J.D., Picus, J., Sharfman, W.H., Stankevich, E., Pons, A., Salay, T.M., McMiller, T.L.*, et al.* (2010). Phase I study of single-agent anti-programmed death-1 (MDX-1106) in refractory solid tumors: safety, clinical activity, pharmacodynamics, and immunologic correlates. Journal of clinical oncology : official journal of the American Society of Clinical Oncology *28*, 3167-3175.

Bristol-MeyersSquibb (2013). Investigator Brochure for nivolumab BMS-936558 MDX1106, version 12, pp. 1-131.

Bulliard, Y., Jolicoeur, R., Windman, M., Rue, S.M., Ettenberg, S., Knee, D.A., Wilson, N.S., Dranoff, G., and Brogdon, J.L. (2013). Activating Fc gamma receptors contribute to the antitumor activities of immunoregulatory receptor-targeting antibodies. J Exp Med *210*, 1685-1693.

Larkin, J., Chiarion-Sileni, V., Gonzalez, R., Grob, J.J., Cowey, C.L., Lao, C.D., Schadendorf, D., Dummer, R., Smylie, M., Rutkowski, P.*, et al.* (2015). Combined Nivolumab and Ipilimumab or Monotherapy in Untreated Melanoma. N Engl J Med *373*, 23-34.

Marabelle, A., Kohrt, H., Sagiv-Barfi, I., Ajami, B., Axtell, R.C., Zhou, G., Rajapaksa, R., Green, M.R., Torchia, J., Brody, J.*, et al.* (2013). Depleting tumor-specific Tregs at a single site eradicates disseminated tumors. J Clin Invest *123*, 2447-2463.

Page, D.B., Postow, M.A., Callahan, M.K., and Wolchok, J.D. (2013). Checkpoint modulation in melanoma: an update on ipilimumab and future directions. Curr Oncol Rep *15*, 500-508.

Qureshi, O.S., Zheng, Y., Nakamura, K., Attridge, K., Manzotti, C., Schmidt, E.M., Baker, J., Jeffery, L.E., Kaur, S., Briggs, Z.*, et al.* (2011). Trans-endocytosis of CD80 and CD86: a molecular basis for the cell-extrinsic function of CTLA-4. Science *332*, 600-603.

Romano, E., Kusio-Kobialka, M., Foukas, P.G., Baumgaertner, P., Meyer, C., Ballabeni, P., Michielin, O., Weide, B., Romero, P., and Speiser, D.E. (2015). Ipilimumab-dependent cell-mediated cytotoxicity of regulatory T cells ex vivo by nonclassical monocytes in melanoma patients. Proc Natl Acad Sci U S A *112*, 6140-6145.

Selby, M.J., Engelhardt, J.J., Quigley, M., Henning, K.A., Chen, T., Srinivasan, M., and Korman, A.J. (2013). Anti-CTLA-4 antibodies of IgG2a isotype enhance antitumor activity through reduction of intratumoral regulatory T cells. Cancer Immunol Res *1*, 32-42.

Simpson, T.R., Li, F., Montalvo-Ortiz, W., Sepulveda, M.A., Bergerhoff, K., Arce, F., Roddie, C., Henry, J.Y., Yagita, H., Wolchok, J.D.*, et al.* (2013). Fc-dependent depletion of tumor-infiltrating regulatory T cells co-defines the efficacy of anti-CTLA-4 therapy against melanoma. J Exp Med *210*, 1695-1710.

Weber, J.S., Gibney, G., Sullivan, R.J., Sosman, J.A., Slingluff, C.L., Jr., Lawrence, D.P., Logan, T.F., Schuchter, L.M., Nair, S., Fecher, L.*, et al.* (2016). Sequential administration of nivolumab and ipilimumab with a planned switch in patients with advanced melanoma (CheckMate 064): an open-label, randomised, phase 2 trial. Lancet Oncol *17*, 943-955.

Weber, J.S., Dummer, R., de Pril, V., Lebbe, C., Hodi, F.S., and Investigators, M.D.X. (2013). Patterns of onset and resolution of immune-related adverse events of special interest with

ipilimumab: detailed safety analysis from a phase 3 trial in patients with advanced melanoma. Cancer *119*, 1675-1682.

Weber, J.S., Kahler, K.C., and Hauschild, A. (2012). Management of immune-related adverse events and kinetics of response with ipilimumab. J Clin Oncol *30*, 2691-2697.

Wing, K., Onishi, Y., Prieto-Martin, P., Yamaguchi, T., Miyara, M., Fehervari, Z., Nomura, T., and Sakaguchi, S. (2008). CTLA-4 control over Foxp3+ regulatory T cell function. Science *322*, 271-275.

Zou, W. (2006). Regulatory T cells, tumour immunity and immunotherapy. Nat Rev Immunol *6*, 295-307.

Appendix A Protocol Lead Signature Page

Title	A Phase 1/2, Open-Label, Multicenter Study to Evaluate the Safety, Pharmacokinetics, and Pharmacodynamics of an Anti–CTLA-4 Human Monoclonal Antibody (AGEN1884) in Subjects with Advanced or Refractory Cancer and in Subjects who have Progressed During Treatment with a PD-1/PD-L1 Inhibitor as their Most Recent Therapy
Clinical Trial Version/Date	Amendment 9, 26 November 2019

I approve the design of the clinical trial.

_____ _____

Signature Date of Signature

Name, academic degree	[redacted]
Function	[redacted]
Institution	Agenus Inc.
Address	3 Forbes Road, Lexington, MA 02421, USA
E-mail address	[redacted]
Phone	[redacted]

Appendix B Investigator Signature Page

INVESTIGATOR SIGNATURE PAGE

Trial Title	A Phase 1/2, Open-Label, Multicenter Study to Evaluate the Safety, Pharmacokinetics, and Pharmacodynamics of an Anti–CTLA-4 Human Monoclonal Antibody (AGEN1884) in Subjects with Advanced or Refractory Cancer and in Subjects who have Progressed During Treatment with a PD-1/PD-L1 Inhibitor as their Most Recent Therapy
Clinical Trial Protocol / Date	Amendment 9, TBD 2019

No party involved in the conduct of this study will modify this protocol without obtaining Agenus' agreement. The party initiating a modification will confirm it in writing. Agenus will submit protocol amendments to the appropriate worldwide regulatory authorities.

This study will be performed in accordance with appropriate federal or national regulations and ICH-GCP guidelines.

Contact information will be provided to sites in the Investigator's Binder and site-specific documents. If necessary, contact the telephone numbers for specific adverse event reporting information in your country. The event must also be reported in writing within 48 hours of occurrence.

Institutional Review Board (IRB) and/or Independent Ethics Committee (IEC) must be notified of drug-related events according to the federal or national regulations.

I agree to conduct this study in accordance with this protocol and comply with all regulatory requirements as set forth in this protocol, appropriate federal or national regulations, and ICH-GCP guidelines. I also verify that I am the person responsible for the medical decisions at the site.

_____ _____

Principal Investigator: Name Date

_____

Principal Investigator: Signature

Appendix C Eastern Cooperative Oncology Group Score

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 or 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 working hours. Symptomatic, but in bed <50% of the day.
3	Capable of only limited self-care, confined to bed or chair more than 50% of working hours.
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead

Appendix D New York Heart Association Class

I	Patients have cardiac disease but without the resulting limitations of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea or anginal pain.
II	Patients have cardiac disease resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea or anginal pain.
III	Patients have cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary physical activity causes fatigue, palpitation, dyspnea or anginal pain.
IV	Patients have cardiac disease resulting in inability to carry on any physical activity without discomfort. Symptoms of cardiac insufficiency or of the anginal syndrome may be present even at rest. If any physical activity is undertaken, discomfort is increased.

Appendix E Response Evaluation Criteria in Solid Tumors (RECIST Version 1.1)

Measurability of tumor at baseline

Definitions: At baseline, tumor lesions/lymph nodes will be categorized measurable or non-measurable as follows:

Measurable Tumor lesions: Must be accurately measured in at least one dimension (longest diameter in the plane of measurement is to be recorded) with a minimum size of:

- 10 mm by CT scan (CT scan slice thickness no greater than 5 mm).
- 10 mm caliper measurement by clinical exam (lesions which cannot be accurately measured with calipers should be recorded as non-measurable).
- 20 mm by chest X-ray.

Malignant lymph nodes: To be considered pathologically enlarged and measurable, a lymph node must be ≥15 mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed. See also notes below on 'Baseline documentation of target and non-target lesions' for information on lymph node measurement.

Non-measurable: All other lesions, including small lesions (longest diameter <10 mm or pathological lymph nodes with ≥10 to < 15 mm short axis) as well as truly non-measurable lesions. Lesions considered truly non-measurable include: leptomeningeal disease, ascites, pleural or pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, abdominal masses/abdominal organomegaly identified by physical exam that is not measurable by reproducible imaging techniques.

Bone lesions:

- Bone scan, positron emission tomography (PET) scan or plain films are not considered adequate imaging techniques to measure bone lesions. However, these techniques can be used to confirm the presence or disappearance of bone lesions.
- Lytic bone lesions or mixed lytic-blastic lesions, with identifiable soft tissue components, that can be evaluated by cross sectional imaging techniques such as CT or MRI can be considered as measurable lesions if the soft tissue component meets the definition of measurability described above.
- Blastic bone lesions are non-measurable.

Cystic lesions:

- Lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts.
- 'Cystic lesions' thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if

noncystic lesions are present in the same subject, these are preferred for selection as target lesions.

Lesions with prior local treatment:

- Tumor lesions situated in a previously irradiated area, or in an area subjected to other loco-regional therapy, are usually not considered measurable unless there has been demonstrated progression in the lesion. Study protocols should detail the conditions under which such lesions would be considered measurable.

Baseline documentation of 'target' and 'non-target' lesions

When more than one measurable lesion is present at baseline all lesions up to a maximum of five lesions total (and a maximum of two lesions per organ) representative of all involved organs should be identified as target lesions and will be recorded and measured at baseline (this means in instances where subjects have only one or two organ sites involved a maximum of two and four lesions respectively will be recorded).

Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion which can be measured reproducibly should be selected.

Lymph nodes merit special mention since they are normal anatomical structures which may be visible by imaging even if not involved by tumor. Pathological nodes which are defined as measurable and may be identified as target lesions must meet the criterion of a short axis of ≥15 mm by CT scan. Only the short axis of these nodes will contribute to the baseline sum. The short axis of the node is the diameter normally used by radiologists to judge if a node is involved by solid tumor. Nodal size is normally reported as two dimensions in the plane in which the image is obtained (for CT scan this is almost always the axial plane; for MRI the plane of acquisition may be axial, sagittal or coronal). The smaller of these measures is the short axis. For example, an abdominal node which is reported as being 20 mm x 30 mm has a short axis of 20 mm and qualifies as a malignant, measurable node. In this example, 20 mm should be recorded as the node measurement. All other pathological nodes (those with short axis ≥10 mm but <15 mm) should be considered non-target lesions. Nodes that have a short axis <10 mm are considered non-pathological and should not be recorded or followed.

A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. If lymph nodes are to be included in the sum, then as noted above, only the short axis is added into the sum. The baseline sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

All other lesions (or sites of disease) including pathological lymph nodes should be identified as non-target lesions and should also be recorded at baseline. Measurements are not required and these lesions should be followed as 'present', 'absent', or in rare cases 'unequivocal progression' (more details to follow). In addition, it is possible to record multiple non-target lesions involving

the same organ as a single item on the case record form (e.g. 'multiple enlarged pelvic lymph nodes' or 'multiple liver metastases').

Tumor response evaluation

Evaluation of target lesions

- Complete Response (CR): Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10mm.
- Partial Response (PR): At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.
- Progressive Disease (PD): At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progression).
- Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.

Evaluation of non-target lesions

- Complete Response (CR): Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (<10mm short axis).
- Non-CR/Non-PD: Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits.
- Non-CR/Non-PD: Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits.
- Progressive Disease (PD): Unequivocal progression of existing non-target lesions. (Note: the appearance of one or more new lesions is also considered progression).

Table 1 – Time point response: patients with target (+/– non-target) disease.

Target lesions	Non-target lesions	New lesions	Overall response
CR	CR	No	CR
CR	Non-CR/non-PD	No	PR
CR	Not evaluated	No	PR
PR	Non-PD or not all evaluated	No	PR
SD	Non-PD or not all evaluated	No	SD
Not all evaluated	Non-PD	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

CR = complete response, PR = partial response, SD = stable disease, PD = progressive disease, and NE = inevaluable.

Table 2 – Time point response: patients with non-target disease only.

Non-target lesions	New lesions	Overall response
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD[a]
Not all evaluated	No	NE
Unequivocal PD	Yes or No	PD
Any	Yes	PD

CR = complete response, PD = progressive disease, and NE = inevaluable.

a 'Non-CR/non-PD' is preferred over 'stable disease' for non-target disease since SD is increasingly used as endpoint for assessment of efficacy in some trials so to assign this category when no lesions can be measured is not advised.

Appendix F Child-Pugh Score for Cirrhosis Mortality

Factor	1 point	2 points	3 points
Total bilirubin	<2 mg/dl or 34 μmol/L	2-3 mg/dl or 34-51 μmol/L	>3 mg/dl or 51 μmol/L
Serum albumin	>3.5 g/dl	2.8-3.5 g/dl	<2.8 g/dl
PT-INR	< 1.7	1.7- 2.2	>2.2
Ascites	Absent	Slight	Moderate
Hepatic encephalopathy	None	Grade 1-2	Grade 3-4
Total points	**5-6**	**7-9**	**10-15**
Class	**A**	**B**	**C**

INR: international normalized ratio; PT: prothrombin time.