agenus

Clinical Trial Protocol

Clinical Trial Protocol Number	C-700-01
Title	A Phase 1/2, Open-Label, Multiple Ascending Dose Trial to Investigate the Safety, Tolerability, Pharmacokinetics, Biological, and Clinical Activity of AGEN2034 in Subjects with Metastatic or Locally Advanced Solid Tumors, with Expansion to Second Line Cervical Cancer
Short Trial Name	Phase 1/2 Study of AGEN2034 in Advanced Tumors
Trial Phase	Phase 1/2
Medical Monitor	[redacted]
Sponsor	Agenus Inc.
Original Protocol:	26 October 2016
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— Confidential —

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

The following abbreviations and specialist terms are used in this study protocol.

Abbreviation or Specialist Term	Explanation
ACTH	adrenocorticotropic hormone
ADA	anti-drug antibody; in this trial, antibody against AGEN2034
ADL	activities of daily living
ADR	adverse drug reaction
AE	adverse event
AESI	adverse event of special interest
AJCC-8	American Joint Committee on Cancer Staging Manual, 8th edition
ALT	alanine aminotransferase
ANC	absolute neutrophil count
aPTT	activated 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 (0 h) extrapolated to infinity
AUC_{0-t}	area under the drug concentration-time curve from time of dosing (0 h) to time t (typically time of last observation)
$AUC_{(t1-t2)-ss}$	area under the drug concentration-time curve within the time span t1 to time t2 at steady-state
BOR	best overall response
BUN	blood urea nitrogen
C	Celsius
CI	confidence interval
C_{max}	maximum drug concentration observed postdose
CNS	central nervous system
CR	complete response
CRO	contract research organization
CRP	C-reactive protein
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTLA-4	cytotoxic T lymphocyte antigen-4
dL	deciliter
DLT	dose-limiting toxicity
DNA	deoxyribonucleic acid
DOR	duration of response
EC_{50}	half-maximal effective concentration
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
FDA	United States Food and Drug Administration
FFPE	formalin-fixed paraffin embedded
FSH	follicle-stimulating hormone
g	gram
GCP	Good Clinical Practice
GGT	gamma-glutamyl transferase
h	hour(s)
HBV	hepatitis B virus
HCV	hepatitis C virus
HIV	human immunodeficiency virus
ICF	informed consent form

Abbreviation or Specialist Term	Explanation
ICH	International Council for Harmonisation (of Technical Requirements for Pharmaceuticals for Human Use)
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
IERC	Independent Endpoint Review Committee
IgG4	immunoglobulin G4
IgG4κ	immunoglobulin G4 antibodies with immunoglobulin kappa light chains
IL	interleukin
IMP	investigational medicinal product
INR	international normalized ratio
irAE	immune-related adverse event
IRB	Institutional Review Board
IULN	institutional upper limit of normal
IV	intravenous
kg	kilogram
L	liter
lb	pound
LDH	lactate dehydrogenase
LFT	liver function test
λ_z	terminal elimination rate constant
m	month
MCH	mean corpuscular hemoglobin
MCHC	mean corpuscular hemoglobin concentration
MCV	mean corpuscular volume
MedDRA	Medical Dictionary for Regulatory Activities
µg	microgram
mg	milligram
min	minute
mL	milliliter
mm	millimeter
mM	millimolar
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
NCI	National Cancer Institute
nM	nanomolar
NSAID	nonsteroidal anti-inflammatory drug
NSCLC	non–small-cell lung cancer
ORR	objective response rate
OS	overall survival
PBMC	peripheral blood mononuclear cell
PD	pharmacodynamic, or progressive disease
PD-1	programmed cell death protein 1
PD-L1/-L2	ligand 1 or 2 of programmed cell death protein 1
PFS	progression-free survival
PK	pharmacokinetic(s)
PO	oral, or by mouth
PR	partial response
q	each, every
Q	calendar quarter
RBC	red blood cell
RCC	renal cell carcinoma
RECIST 1.1	Response Evaluation Criteria in Solid Tumors version 1.1
RNA	ribonucleic acid

Abbreviation or Specialist Term	Explanation
SAE	serious adverse event
SAP	statistical analysis plan
SD	stable disease
SEA	*Staphylococcus* enterotoxin A
SGOT	serum glutamic oxaloacetic transaminase
SGPT	serum glutamic pyruvic transaminase
SHP-1/-2	Src homology region 2 domain–containing phosphatase 1 or 2
SMC	Safety Monitoring Committee
$t_{½}$	half-life
T4	free thyroxine
TCR	T cell receptor
TEAE	treatment-emergent adverse event
t_{max}	time to reach maximum concentration
TSH	thyroid-stimulating hormone
ULN	upper limit of normal
V	visit
wk	week(s)
WBC	white blood cell

SYNOPSIS

Trial Title	A Phase 1 / 2, Open-Label, Multiple Ascending Dose Trial to Investigate the Safety, Tolerability, Pharmacokinetics, Biological, and Clinical Activity of AGEN2034 in Subjects with Metastatic or Locally Advanced Solid Tumors, with Expansion to Second Line Cervical Cancer
Trial Number	C-700-01
Names of Trial Drug	AGEN2034
Sponsor	Agenus Inc., 3 Forbes Road, Lexington, MA 02421, USA
Phase	1 / 2
Trial Centers/ Countries	Phase 1: approximately 10-15 enrolling centers globally Phase 2: approximately 60 enrolling centers globally
Estimated Trial Period	First subject in: 2Q 2017 Last subject out: 2Q 2022
Objectives	**Phase 1:** Primary Objective • To assess the safety and tolerability of AGEN2034 in subjects with metastatic and/or locally advanced solid tumors Secondary Objectives • To characterize the AGEN2034 pharmacokinetic (PK) profile • To correlate AGEN2034 exposure with target occupancy • To evaluate the immunogenicity of AGEN2034 and correlate it to exposure Exploratory Objectives • [redacted] • To explore the association of programmed cell death protein 1 – ligand 1 (PD-L1) expression with clinical responses **Phase 2:** Primary Objective • To assess objective response rate (ORR) according to RECIST 1.1 as determined by an Independent Endpoint Review Committee (IERC) Secondary Objectives • To assess the safety and tolerability of AGEN2034 in subjects with metastatic and/or locally advanced solid tumors • To characterize the AGEN2034 PK profile • To evaluate the immunogenicity of AGEN2034 and correlate it to exposure • To assess ORR according to RECIST 1.1 as determined by investigator • To assess duration of response (DOR), disease control rate (DCR), duration of stable disease (SD), time to response, and progression-free survival (PFS) time per RECIST 1.1 • To assess overall survival (OS) rate • To assess OS time Exploratory Objectives • [redacted] • To explore the association of programmed cell death protein 1 – ligand 1 (PD-L1) expression with clinical outcomes

Endpoints	**Phase 1:** Primary Endpoints • Occurrence of dose-limiting toxicities (DLTs) in subjects in dose escalation during the first 21 days of treatment • Frequency, severity, and duration of treatment-emergent AEs (TEAEs) and laboratory abnormalities using the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) v4.03. Secondary Endpoints • AGEN2034 PK parameters which may include (but are not limited to) maximum drug concentration observed postdose at steady-state (C_{max-ss}), minimum observed 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 zero to time t ($AUC_{(0-t)}$), area under the drug concentration-time curve from time zero to infinity ($AUC_{(0-\infty)}$), time to maximum observed concentration (t_{max}), terminal disposition rate constant (λ_z), terminal elimination half-life ($t_{1/2}$), systemic clearance (CL), and volume of distribution (Vd) • Receptor occupancy on circulating T cells measured 4 hours after the 1st dose and immediately prior to the 2nd dose • Receptor occupancy saturation levels correlated with AGEN2034 PK exposure metrics • Antidrug antibody (ADA) concentrations and correlation with AGEN2034 PK exposure metrics Exploratory Endpoints • [redacted] • Baseline expression of PD-L1 **Phase 2:** Primary Endpoint • Confirmed ORR per RECIST 1.1, as determined by an IERC, in the analysis population Secondary Endpoints • Frequency, severity, and duration of TEAEs and laboratory abnormalities, using NCI CTCAE v4.03 • AGEN2034 PK parameters which may include (but are not limited to) maximum drug concentration observed postdose at steady-state (C_{max-ss}), minimum observed concentration at steady-state (C_{min-ss}), area under the drug concentration-time curve within time span t1 to t2 at steady-state ($AUC_{(\tau 1-\tau 2)-ss}$), area under the drug concentration-time curve from time zero to time t ($AUC_{(0-t)}$), area under the drug concentration-time curve from time zero to infinity ($AUC_{(0-\infty)}$), time to maximum observed concentration (t_{max}), terminal disposition rate constant (λ_z), terminal elimination half-life ($t_{1/2}$), systemic clearance (CL), and volume of distribution (Vd) • ADA concentrations and correlation with AGEN2034 PK exposure metrics • Confirmed ORR per RECIST 1.1, as determined by an investigator • DOR per RECIST 1.1, as determined by an IERC and investigator, defined as time from first observation of response to first observation of documented disease progression (or death within 12 weeks after last tumor assessment). Subjects

	without an event at analysis cutoff date will be censored on date of last tumor assessment. • DCR, defined as proportion of subjects with complete response (CR), partial response (PR), or stable disease (SD) for at least 12 weeks • Duration of SD, measured from the start of treatment until the criteria for progression are met, taking as reference the smallest measurements recorded since the treatment started, including baseline measurements • Time to response, defined as the time from the first dose date to first observation of confirmed response • PFS time, defined as time from first treatment administration to first observation of documented disease progression (or death within 12 wk after last tumor assessment), per RECIST 1.1, as determined by an IERC and investigator. Subjects without an event at analysis cutoff date will be censored on date of last tumor assessment. • Median OS and OS rate • OS time, defined as time from start of treatment to death. For subjects who are still alive at time of data cutoff for trial analysis or who are lost to follow-up, survival will be censored at the last recorded date that the subject is known to be alive as of the cutoff date for analysis <u>Exploratory Endpoints</u> • [redacted] • Baseline expression of PD-L1 association with clinical outcomes
Trial Design and Plan	This is a 2-part trial: a Phase 1, open-label, dose-escalation trial in subjects with metastatic or locally advanced solid tumors, with a consecutive Phase 2 expansion to evaluate efficacy in subjects with recurrent, unresectable, or metastatic (advanced) cervical cancer that has progressed after a platinum-based treatment regimen. **Phase 1: Dose Escalation** Phase 1 will consist of a standard 3+3 dose escalation with the following escalating dose levels and schedules: Part A1: 1, 3, and 10 mg/kg administered every 2 weeks Part A2: 6 and 10 mg/kg administered every 3 weeks Each subject will stay on the dose level and schedule assigned at trial entry. Subjects will receive AGEN2034 for a maximum of 24 months or until progression, unacceptable toxicity, or any criterion for stopping the study drug or withdrawal from the trial occurs. A Safety Monitoring Committee (SMC) will assess safety; decide on dose-escalation and opening of backfill enrollment; define the recommended Phase 2 dose (RP2D); and determine opening of the Phase 2 cohorts. In Part A1, the first subject of each cohort will be observed for 16 days (i.e., ≥ 48 hours after second dose) for occurrence of DLT before the second subject is administered trial medication. Thereafter, within each cohort, consecutively enrolled subjects may initiate treatment ≥ 48 hours after the prior enrolled subject initiated treatment. Dose escalation will continue until the maximum tolerated dose (MTD) is reached or the maximum planned dose level (10.0 mg/kg) is shown to be safe. The MTD is defined as the dose below which ≥ 2 DLTs are observed. Once Part A1 is completed, enrollment to Part A2 will begin. If < 2 DLTs are observed in Part A1 at the maximum planned dose of 10 mg/kg every 2 weeks, open enrollment to Part A2 will begin with enrollment of 10 subjects at 6 mg/kg every 3 weeks, followed

	by open enrollment of 10 subjects at 10 mg/kg every 3 weeks. If ≥ 2 DLTs are observed in Part A1, at the maximum planned dose in Part A1, the standard 3+3 dose escalation will continue with Part A2 where consecutively enrolled subjects in dose escalation may initiate treatment ≥ 48 hours after the prior enrolled subject initiated treatment. For cohorts in dose escalation, concurrent with the 3+3 dose escalation schema, additional subjects will be backfilled to lower dose levels to ensure that each cohort enrolls at least 10 subjects. Subjects enrolled to backfill cohorts may be enrolled simultaneously, without sequential dosing (i.e., not required to wait 48 hours between 2 subjects). These additional subjects at each dose level will have the purpose of generating additional safety, PK, and receptor occupancy data, and will not undergo formal DLT observation. **Phase 2: Dose Expansion** To further characterize safety and efficacy, subjects with recurrent, unresectable, or metastatic cervical cancer will be enrolled in Phase 2 and receive the RP2D of AGEN2034 (3 mg/kg every 2 weeks) for a maximum of 24 months or until progression, unacceptable toxicity, or any criterion for stopping the study drug or withdrawal from the trial occurs. An SMC will assess safety, and an Independent Data Monitoring Committee (IDMC) will evaluate safety and efficacy.
Number of Subjects (Planned)	**Phase 1 (Parts A1 and A2):** Approximately 50 subjects; final sample size may vary depending on the total number of dose levels to be tested, and subject replacement for DLT evaluation, if applicable **Phase 2:** Approximately 150 subjects with recurrent, unresectable, or metastatic cervical cancer.
Trial Eligibility	**Inclusion Criteria:** 1. Voluntarily agree to participate by giving written informed consent. Participation in pharmacogenomics testing is optional. 2. Be ≥ 18 years of age. 3. Diagnosis and prior systemic treatment: a. Phase 1: Have a histologically or cytologically confirmed diagnosis of a metastatic or locally advanced solid tumor for which no standard therapy is available or standard therapy has failed. b. Phase 2: I. Have (1) a histologically or cytologically confirmed diagnosis of squamous-cell carcinoma, adenosquamous carcinoma, or adenocarcinoma of the cervix, and (2) metastatic, locally advanced, and/or unresectable disease at the time of enrollment. Histologic confirmation of the original primary tumor is required via pathology report. **Note:** The following cervical tumors are not eligible: minimal deviation/adenoma malignum, gastric type adenocarcinoma, clear cell carcinoma, and mesonephric carcinoma. II. Has cervical cancer and has relapsed after a platinum-based treatment (first line) regimen for advanced (recurrent, unresectable, or metastatic) disease; **Note:** Subject receiving chemotherapy concurrently with primary radiation (e.g., weekly cisplatin) or subject receiving adjuvant chemotherapy following completion of radiation therapy (e.g., paclitaxel and carboplatin for ≤ 4 cycles) and progressed within 6 months after treatment completion will be eligible as this systemic therapy will be considered as first-line treatment. 4. Measurable disease – based on investigator assessment

a. Phase 1: Have objective evidence of disease; the presence of measurable disease is not required.

b. Phase 2: Have measurable disease on imaging based on RECIST version 1.1.

Note: Subjects must have at least one "target lesion" to be used to assess response, as defined by RECIST version 1.1. Tumors within a previously irradiated field will be designated as "non-target" lesions unless progression is documented or a biopsy is obtained to confirm persistence at least 90 days following completion of radiation therapy.

Note: Measurable disease by RECIST 1.1 must be confirmed by independent central radiologic review prior to first dose. Subjects without centrally confirmed measurable disease at baseline will not be eligible for this trial.

5. Have a life expectancy of at least 3 months and an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1.
6. Have adequate organ function as indicated by the following laboratory values:
   a. Adequate hematological function defined by absolute neutrophil count (ANC) $\geq 1.5 \times 10^9$/L, platelet count $\geq 100 \times 10^9$/L, and stable hemoglobin ≥ 8 g/dL (without transfusions within 1 week before first dose).
   b. Adequate hepatic function based by a total bilirubin level ≤ 1.5 x the institutional upper limit of normal (IULN), aspartate aminotransferase (AST) level ≤ 2.5 x IULN, alanine aminotransferase (ALT) level ≤ 2.5 x IULN, and alkaline phosphatase ≤ 2.5 x IULN.
   c. Adequate renal function defined as creatinine ≤ 1.5 x IULN **OR** calculated creatinine clearance ≥ 50 mL/min for subjects with creatinine levels > 1.5 x IULN (if no local guideline is available, creatinine clearance should be calculated using the Cockcroft-Gault Method).
   d. Adequate coagulation defined by international normalized ratio (INR) or prothrombin time ≤ 1.5 x IULN (unless the subject is receiving anticoagulant therapy); and activated partial thromboplastin time (aPTT) ≤ 1.5 x IULN (unless the subject is receiving anticoagulant therapy)
7. Other than the cancer for which the subject is enrolled, have no history of prior malignancy, with the exception of basal cell carcinoma of the skin, superficial bladder cancer, squamous-cell carcinoma of the skin, or has undergone potentially curative therapy with no evidence of that disease recurrence for 5 years since initiation of that therapy.
8. In Phase 2, subjects must provide a sufficient and adequate formalin-fixed paraffin embedded (FFPE) tumor tissue sample preferably from the most recent biopsy of a tumor lesion, collected either at the time of or after the diagnosis of advanced or metastatic disease has been made AND from a site not previously irradiated. If no tumor tissue is available, a fresh biopsy will be required.

   Note: Tissue from needle or excisional biopsy or from resection is required.
9. Female subjects must have a negative serum pregnancy test at screening (within 72 hours before first dose of study drug) if of childbearing potential or be of non-child bearing potential. Non-childbearing potential is defined as (by other than medical reasons):
   a. ≥ 45 years of age and has not menstruated for greater than 1 year,
   b. Amenorrheic for < 2 years without a hysterectomy and oophorectomy and a follicle-stimulating hormone (FSH) value in the postmenopausal range upon pretrial (screening) evaluation,
   c. Whose status is post hysterectomy, oophorectomy or tubal ligation.
10. If of childbearing potential, female subjects must be willing to use 2 highly effective methods (defined in the informed consent form [ICF]) throughout the

	study, starting with the screening visit through 120 days after the last dose of study drug. **Note:** Abstinence is acceptable if this is the established and preferred contraception for the subject. 11. Male subjects with a female partner(s) of child-bearing potential must agree to use 2 highly effective methods (defined in the ICF) throughout the trial starting with the screening visit through 120 days after the last dose of study drug is received. Males with pregnant partners must agree to use a condom; no additional method of contraception is required for the pregnant partner. **Note:** Abstinence is acceptable if this is the established and preferred contraception for the subject. 12. Is willing and able to comply with the requirements of the protocol. **Exclusion Criteria:** 1. Is currently participating and receiving study therapy or has participated in a study of an investigational agent and received study therapy or used an investigation device within 4 weeks before the first dose of treatment. 2. Has an inadequate washout period prior to first dose of study drug defined as: a. Received systemic cytotoxic chemotherapy or biological therapy within 3 weeks before first dose, b. Received radiation therapy within 3 weeks before first dose, or c. Had major surgery within 4 weeks before first dose. 3. Has received prior therapy with: a. Any antibody/drug targeting T-cell co-regulatory proteins (immune checkpoints) such as anti–PD-1, anti–PD-L1, or anti–cytotoxic T-lymphocyte antigen 4 (CTLA-4) antibodies b. For Phase 2: > 1 systemic treatment regimen for the advanced (recurrent, unresectable, or metastatic) cervical cancer for which the subject is considered for the study **Note:** In Phase 1, prior treatment with a CTLA-4 antibody is permissible for subjects with metastatic melanoma. 4. Has persisting toxicity related to prior therapy of NCI CTCAE Grade > 1 severity. **Note:** Sensory neuropathy or alopecia of Grade ≤ 2 is acceptable. 5. Is expected to require any other form of systemic or localized antineoplastic therapy while on trial (including maintenance therapy with another agent, radiation therapy, and/or surgical resection). 6. Has known severe hypersensitivity reactions to fully human monoclonal antibodies (NCI CTCAE version 4.03 Grade ≥ 3), any history of anaphylaxis, or uncontrolled asthma. 7. Is receiving systemic corticosteroid ≤ 7 days prior to the first dose of trial treatment or receiving any other form of systemic immunosuppressive medication (corticosteroid use on study for management of immune-related adverse events, and/or a premedication for IV contrast allergies/reactions is allowed). Subjects who are receiving daily corticosteroid replacement therapy are an exception to this rule. Examples of permitted therapy are daily prednisone at doses of 5 to 7.5 mg or equivalent hydrocortisone dose, and steroid therapy administered by topical, intraocular, intranasal, and/or inhalation routes. 8. Has a central nervous system (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 (based on 2 sets of brain images, performed ≥ 4 weeks apart, and obtained after the brain metastases treatment). In addition, any neurologic symptoms that developed either as a result of the brain metastases or their treatment must have resolved or be minimal and be expected as sequelae from treated lesions. For individuals who received steroids as part of brain metastases treatment, steroids must be discontinued ≥ 7 days prior to first dose of study drug. 9. Has active or history of autoimmune disease that has required systemic treatment within 2 years of the start of trial treatment (i.e., with use of disease modifying agents, corticosteroids or immunosuppressive drugs). Replacement therapy (i.e., thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency, etc.) is not considered a form of systemic treatment. **Note:** Subjects with diabetes type 1, vitiligo, psoriasis, hypo-, or hyperthyroid disease not requiring immunosuppressive treatment are eligible. 10. Has had an allogeneic tissue/solid organ transplant. 11. Has or had interstitial lung disease (ILD) OR has had a history of pneumonitis that has required oral or IV corticosteroids. 12. Has an active infection requiring intravenous systemic therapy. 13. Has known history of Human Immunodeficiency Virus (HIV) (HIV 1/2 antibodies). 14. Has known active Hepatitis B, Hepatitis C or tuberculosis. Active Hepatitis B is defined as a known positive HBsAg result. Active Hepatitis C is defined by a known positive Hep C Ab result and known quantitative HCV RNA results greater than the lower limits of detection of the assay. 15. Has clinically significant (i.e., active) cardiovascular disease: cerebral vascular accident/stroke or myocardial infarction within 6 months before enrollment, unstable angina, congestive heart failure (New York Heart Association class ≥ II), or serious uncontrolled cardiac arrhythmia requiring medication. 16. Has a history or current evidence of any condition, therapy, or laboratory abnormality that might confound the results of the trial, interfere with the subject's participation for the full duration of the trial, or is not in the best interest of the subject to participate, in the opinion of the treating Investigator. 17. Has known psychiatric or substance abuse disorders that would interfere with cooperation with the requirements of the trial. 18. Is, at the time of signing informed consent, a regular user (including "recreational use") of any illicit drugs or had a recent history (within the last year) of substance abuse (including alcohol). 19. Is legally incapacitated or has limited legal capacity. 20. Is pregnant or breastfeeding or expecting to conceive or father children within the projected duration of the trial, starting with the screening visit through 120 days after the last dose of study drug.
Dosage and Administration	AGEN2034 is an IgG4 antibody designed to block PD-1. **Dose Levels** Phase 1: Part A1: 1, 3, and 10 mg/kg IV every 2 weeks Part A2: 6 and 10 mg/kg IV every 3 weeks Phase 2: 3 mg/kg IV every 2 weeks **Administration** AGEN2034 will be administered IV over 60 minutes (-10/+20 min)

Planned Trial Duration	The maximum trial duration for a subject is estimated to be up to approximately 49 months. This includes a screening period, a planned treatment period of up to approximately 24 months, and a follow-up period of up to 24 months after the last dose of study treatment. The overall trial duration is expected to be approximately 63 months.
Schedule of Visits and Assessments	**Screening Period (Phase 1 and Phase 2)** Screening assessments will be conducted within 42 days prior to first treatment dose, with associated evaluations and procedures. **Treatment Phase (Phase 1 and Phase 2)** The treatment phase is divided into 2-week (Phases 1 and 2) or 3-week (Phase 1) cycles with associated evaluations and procedures that must be performed at specific time points. Each cycle begins with the administration of AGEN2034. Subjects will be treated for up to 24 months or until disease progression, unacceptable toxicity, or any criterion for stopping the study drug or withdrawal from the trial occurs. Tumor assessments will be conducted every 6 weeks from first dose until disease progression or a new line of therapy is initiated. **End-of-Treatment (Phase 1 and Phase 2)** ***Discontinuation Visit and Safety Follow-up Visit:*** All subjects who discontinue the trial treatment prematurely for an AE should have a full safety evaluation at the time of discontinuation (Discontinuation Visit). A mandatory Safety Follow-up Visit should be scheduled 4 weeks 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 adverse drug reaction (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. **Follow-up Phase (Phase 1 and Phase 2)** Subjects who discontinue treatment will be followed for up to 12 months (Phase 1) or 24 months (Phase 2) after the last dose of study drug or until death, withdrawal of consent, or becoming lost to follow-up. ***Follow-up Visits*** Visits with associated evaluations and procedures will occur every 3 months for up to 12 months following the last dose of study drug or until disease progression and/or start of a new line of therapy. Tumor assessments will continue every 6 weeks from first dose until discontinuation of study drug. ***Survival Follow-up (Phase 2 only)*** Subjects in Phase 2 who present with progressive disease and/or start a new line of therapy will be contacted by phone every 2 months to assess for survival for up to 12 months after the last dose of study drug.
Statistical Considerations:	The total sample size is expected to be approximately 200 subjects: 50 in Phase 1 and 150 in Phase 2. All data recorded will be presented in individual listings and, where appropriate, summarized in a descriptive manner. Continuous variables may be summarized using mean, standard deviation, median, and range; categorical variables will be summarized using counts and percentages. **Phase 1:** The sample size of approximately 50 subjects was determined by clinical considerations.

	Phase 2: The primary endpoint of Phase 2, ORR, will be estimated as the binomial proportion of patients with confirmed partial or complete best overall response per RECIST 1.1, as determined by an IERC, and will be reported with two-sided, 95% Wilson score confidence interval (CI). With 150 patients in the final analysis, the power to exclude an ORR of 5% by the lower limit of the 95% two-sided Wilson score CI is 92.2% and 96.2%, assuming a true ORR of 12% and 13%, respectively. The sample size will provide ≥ 77% probability to observe an AE with and underlying rate of ≥ 1%. Interim analyses will be performed to assess the safety and efficacy (using the ORR and selected secondary efficacy endpoints) when (1) data are available for approximately 30 subjects treated for at least 3 months and (2) approximately 3 months after approximately 100 patients are dosed. No early stopping for efficacy will be performed, as a more complete safety assessment and evaluation of durability of responses are necessary for determination of risks and benefits. Consequently, the interim analyses will not affect the overall type I error. A non-binding futility analysis may be performed using methods described in the statistical analysis plan. Additional interim analyses for safety and efficacy assessment may performed. Statistics for continuous variables may include means, medians, ranges, and appropriate measures of variability. Statistics for the binary endpoint will be summarized with counts and frequencies, and statistics for time-to-event data will be summarized with median, 95% CI, etc., as appropriate.

1. INTRODUCTION AND RATIONALE

In the past 2 decades, researchers have demonstrated the importance of the immune system in controlling cancer. Advances in our understanding of immuno-oncology have highlighted the dynamic interplay between host and tumor, and have shown that a tumor's ability to evade the immune system can determine outcome. This has led to the development of therapies that are changing the landscape of modern oncology. Researchers have dissected numerous regulatory pathways that are exploited by cancer to evade immune response.

The programmed cell death-1 (PD-1) and cytotoxic T lymphocyte associated antigen-4 (CTLA-4) proteins are the most extensively studied negative regulatory receptors, and whose pathways are the target of multiple therapies (Buchbinder & Desai 2016; Sharma & Allison 2015; Topalian et al 2015). Inhibition of the PD-1 and CTLA-4 pathways by blockade of receptor-ligand interactions has been demonstrated in numerous clinical trials to result in objective clinical response and increased survival in several solid tumor indications. These studies have led to a number of regulatory approvals across the globe for single agents and combinations in various indications including melanoma, non-small cell lung cancer (NSCLC), renal cell carcinoma, head and neck cancers, Hodgkin lymphoma, and micro-satellite instability-high (MSI^{HI}) cancers. This protocol will study the PD-1 antibody, AGEN2034.

The first subject enrolled in this trial in early 2017. At the time this amendment was finalized, while enrollment for Phase 1 was completed, some subjects were still participating in Parts A1 and A2. This amendment focuses primarily on changes to Phase 2 of this trial.

1.1. PD-1 Checkpoint Blockade

1.1.1. PD-1 Pathway Blockade

The importance of immune surveillance in controlling outgrowth of neoplastic transformation is well described and consistent with a correlation between prevalence of tumor-infiltrating lymphocytes in cancer tissues and favorable prognosis in various malignancies (Disis 2010). Tumors can nevertheless evade recognition and destruction by the immune system by expressing soluble and cell-expressed molecules that naturally mediate immune suppression (Topalian et al 2015). In this context, the PD-1 checkpoint inhibitor pathway has emerged as a significant mode by which tumors suppress immune control (Postow et al 2015).

PD-1, or CD279, is a member of the immunoglobulin superfamily (IgSF) that negatively regulates T-cell responses to maintain peripheral tolerance and immune homeostasis (Zha et al 2004). A range of T-cell subsets, including activated T effector cells, memory T cells, regulatory T cells, and T follicular helper cells, express PD-1. PD-1 is rapidly upregulated on T cells activated via their T-cell receptor (TCR). Under conditions of persistent antigenic exposure, such as in chronic pathogenic infections or within the tumor microenvironment, PD-1 expression can be sustained on antigen-specific T cells, leading to a state of dysfunction commonly referred to as T-cell exhaustion (Barber et al 2006).

PD-1 signaling is mediated by 2 ligands: PD-1 ligand 1 (PD-L1 or CD274) and PD-1 ligand 2 (PD- L2 or CD273) (Latchman et al 2001). PD-L1 is expressed on the cell surface of a range of immune and non-immune cell types, including antigen-presenting cells (APCs) and tumor cells. Upon binding to PD-L1 or PD-L2, PD-1 signaling in T cells can potently attenuate TCR

signaling, resulting in diminished cytokine and proliferative responses, reduced T effector cell cytolytic activity, and impaired central memory T-cell differentiation (Allie et al 2011). Proximal to ligand binding, PD-1 recruits Src homology region 2 domain–containing phosphatase (SHP)–1 and SHP-2 proteins to an immunoreceptor tyrosine-based inhibitory motif and an immunoreceptor tyrosine-based switch motif within its intracellular domain (Chemnitz et al 2004). This impairs phosphorylation of several key kinase proteins, including zeta chain–associated protein kinase 70, phosphatidylinositol 3-kinase, protein kinase B, casein kinase 2, and protein kinase C theta, thereby attenuating signaling through these gene regulatory pathways (Yokosuka et al 2012).

Inhibition of the PD-1 pathway by blockade of receptor-ligand interactions has been demonstrated to improve clinical outcome in a range of malignancies. The therapeutic benefit of such a blockade in the treatment of subjects with cervical cancer is under investigation.

1.1.2. AGEN2034

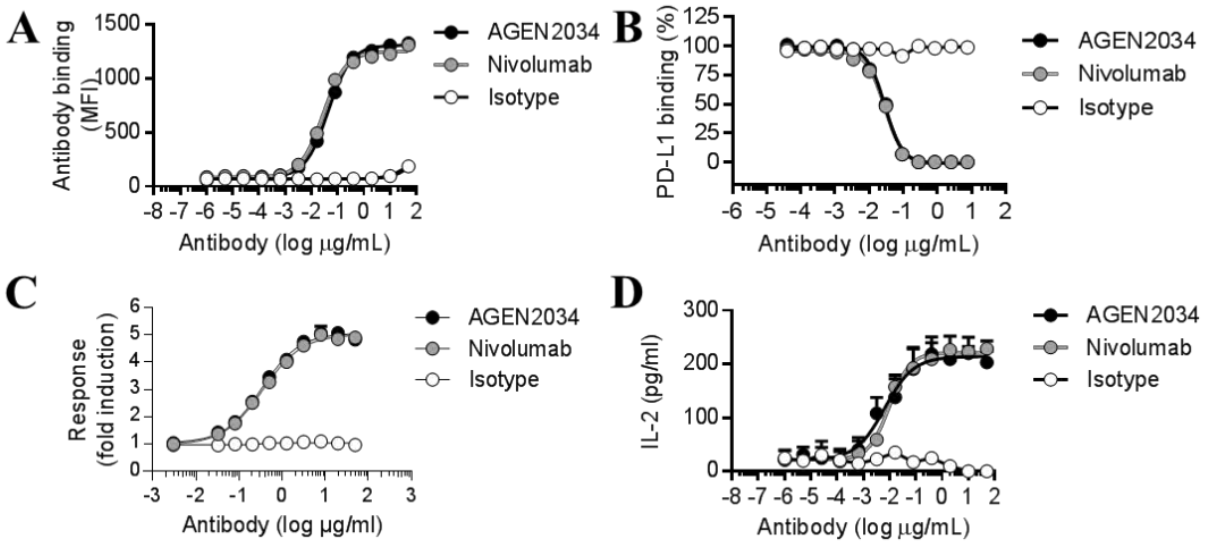
AGEN2034 is a novel, fully human monoclonal immunoglobulin G4 (IgG4) antibody, designed to block PD-1 from interacting with its ligand PD-L1 and PD-L2 in a manner comparable to nivolumab.

1.1.2.1. Summary of Preclinical Data

The utility of PD-1 as a therapeutic antibody target in human cancer has been well characterized. A human immunoglobulin G4 antibody with immunoglobulin kappa light chains (IgG4κ) monoclonal antibody directed against PD-1 (nivolumab, Opdivo®) has been evaluated in thousands of patients covering a range of IV doses, from 0.1 mg/kg to 20 mg/kg (Topalian et al, 2015). AGEN2034 is physicochemically comparable to nivolumab (anti-PD-1 specific IgG4 antibodies with Igκ light chains) and a side-by-side in vitro pharmacological characterization of AGEN2034 and nivolumab demonstrated that these two antibodies were functionally comparable. More specifically both antibodies: 1) bind human PD-1 with subnanomolar affinities (KD 0.14 nM for AGEN2034 and 0.12 nM for nivolumab) and have comparable relative cellular binding affinities to human T cells expressing PD-1 (EC_{50} 0.025 µg/mL for AGEN2034 and 0.03 µg/mL for nivolumab) (Figure 1A); 2) potently block the binding of PD-L1 to PD-1 (IC_{50} 0.03 µg/mL for both antibodies) (Figure 1B); and 3) augment the activation of recombinant PD-1 expressing and primary human T cells (Figure 1C-D).

AGEN2034 toxicity was assessed in a 4-week good laboratory practices (GLP) repeat dose study in cynomolgus monkeys and in a human tissue cross reactivity study. Details of these studies can be found in the Investigator's Brochure. Briefly, in the 4-week GLP repeat dose study, AGEN2034 was dosed by IV bolus administration of 0 (vehicle), 40 and 300 mg/kg on Study Days 1, 8, 15, 22 and 29, to 3 male and 3 female animals in the control and low dose groups and 5 male and 5 female animals in the high dose group. The dosing period was followed by a 4-week non-dosing period for 2 males and 2 females each in the vehicle and 300 mg/kg dose groups. Standard study endpoints, plus electrocardiogram (ECG), ophthalmic, and cardiovascular assessments, were included.

Figure 1: *In vitro* Comparability of AGEN2034 and Nivolumab



Head-to-head evaluation of AGEN2034 (**black**), commercial nivolumab (**gray**), or IgG4 isotype antibody (**white**) for: (A) - antibody binding to PD-1+ CD4+ T cells in cultures of *Staphylococcus* enterotoxin A (SEA)-stimulated human peripheral blood mononuclear cells (PBMCs); (B) - antibody-mediated blockade for PD-1 binding to PD-L1; (C) - inhibition of PD-1:PD-L1 signaling in a T-cell reporter assay; and (D) - T cell–induced IL-2 release in SEA-stimulated PBMC cultures. On the x-axis, log converted antibody concentration (log µg/mL) are shown. Data shown are representative of 2 independent experiments.

In this study, AGEN2034 demonstrated biphasic distribution after IV bolus dose administration and serum AGEN2034 concentrations increased in a manner commensurate with the increase in dose. There were no apparent differences in the exposure or disposition of AGEN2034 between male and female monkeys. The estimated mean half-life was 12.4 days in the recovery phase, and it is anticipated that steady-state conditions might be achieved in about 5 to 9 weeks. Anti-drug antibodies as a measure of immunogenicity of AGEN2034 in monkeys were assessed and revealed positive results at an incidence of 30 percent. Full toxicokinetic details are included in the AGEN2034 Investigator's Brochure.

The no-observed- adverse-effect level (NOAEL) of AGEN2034 from the 4-week cynomolgus monkey toxicity study is 40 mg/kg. Histopathology findings at 300 mg/kg included vascular/perivascular inflammation in a variety of tissues. The collective histology, IHC, PK and anti-drug antibody (ADA) data are consistent with an immune-mediated vasculitis caused by ADA formation in a proportion of monkeys given 300 mg/kg AGEN2034. ADA is a recognized phenomenon in non-human primate studies as it relates to the antigenicity of an administered humanized antibody and these types of events are typically not correlated with the formation of ADA in human patients (Frazier et al 2015; Ponce et al 2009; Rojko et al 2014). Other treatment-related findings in the 4-week study were consistent with pharmacodynamic effects including changes in lymphoid cellularity in the spleen (increased at ≥ 40 mg/kg) and thymus (decreased at 300 mg/kg) and an increase in mononuclear cell infiltration in the brain (≥ 40 mg/kg). These findings related to some changes in organ weights that showed a trend towards recovery following the 4-week non-dosing phase. Cytokine measurements from the 4-week toxicity study

in cynomolgus monkeys and from an in vitro cytokine release assay in human whole blood revealed no findings that are considered related to cytokine release syndrome.

A human tissue cross-reactivity GLP study was completed using cryosections from a full panel of normal human adult tissues at two concentrations (15 and 30 µg/mL AGEN2034). AGEN2034- specific membrane and/or cytoplasmic staining was observed in cells of splenic white pulp and tonsillar germinal centers. This is consistent with the expected membrane staining pattern of PD-1 on a subset of T lymphocytes.

For detailed information on preclinical characterization, manufacturing and administration of AGEN2034, please refer to the AGEN2034 Investigator's Brochure.

1.1.2.2. Summary of Clinical Data

There are no existing safety data for AGEN2034, as this study will support its first human administration.

The best indication of the safety profile of AGEN2034 is expected to be the safety profile of nivolumab (Opdivo®), as specified in its prescribing information (Opdivo® 2017).

Per Amendment 4, this study would further support safety and efficacy data utilizing the expansion cohort of subjects with cervical cancer.

1.1.3. Safety of Nivolumab

The following safety information is based on data from 7 clinical trials in which 2,166 subjects received nivolumab as a single agent for treatment of unresectable or metastatic melanoma, metastatic NSCLC, advanced renal cell carcinoma (RCC), and classical Hodgkin's lymphoma (cHL). Across all trials, nivolumab treatment was discontinued in 4% to 16% of subjects and delayed in 23% to 44% of subjects because of toxicities. Serious adverse reactions occurred in 21% to 47% of subjects. Fatal adverse reactions were also observed.

1.1.3.1. Common Adverse Reactions of Nivolumab

Adverse reactions observed in more than 20% of subjects treated with nivolumab in clinical trials included (Opdivo® 2015):

- In melanoma: Fatigue, rash, musculoskeletal pain, pruritus, diarrhea, and nausea.
- In metastatic NSCLC: Fatigue, musculoskeletal pain, decreased appetite, cough, and constipation.
- In advanced RCC: Asthenic conditions (decreased activity, fatigue, and malaise), cough, nausea, rash, dyspnea, diarrhea, constipation, decreased appetite, back pain, and arthralgia.
- In cHL: Fatigue, upper respiratory tract infection, pyrexia, diarrhea, and cough.

The most frequent severe or serious reactions, occurring in more than 2% of patients, included:

- In melanoma:
  - Pretreated (n = 268): 2%–5% abdominal pain, hyponatremia, increased aspartate aminotransferase, and increased lipase.

  - Untreated (n = 206): 2%–4% gamma-glutamyl transferase (GGT) increase, diarrhea, musculoskeletal pain, increased alanine aminotransferase (ALT), increased aspartate aminotransferase (AST), increased alkaline phosphatase, and increased bilirubin.
  - Nivolumab-only arm of combination study (n = 313): 2%–5% diarrhea, increased ALT, increased AST, hyponatremia, increased alkaline phosphatase, anemia, and lymphopenia (4.3%); and increased lipase (9%).
- In NSCLC (n = 287): >2% serious pneumonia, pulmonary embolism, dyspnea, pleural effusion, and respiratory failure.
- In RCC (n = 287): >2% serious acute kidney injury, pleural effusion, pneumonia, diarrhea, and hypercalcemia.
- In cHL (n = 263): >1% serious infusion-related reaction, pneumonia, pleural effusion, pyrexia, rash, and pneumonitis.

1.1.3.2. Notable Immune-Mediated Adverse Reactions of Nivolumab

Immune-mediated conditions are defined as adverse reactions requiring the use of corticosteroids, with no clear alternate etiology. The most common immune-mediated reactions associated with nivolumab include pneumonitis (including interstitial lung disease), colitis, hepatitis, encephalitis, nephritis and/or renal dysfunction, rash, and endocrinopathies such as hypophysitis, adrenal insufficiency, thyroid disorders, and type 1 diabetes mellitus. The majority of events were moderate or mild; however, severe events were observed, including fatal cases of pneumonitis, fatal limbic encephalitis, and toxic epidermal necrolysis. The onset time of these events is highly variable, ranging from within 1 to 2 days of first dose to more than 2 years after initiation of therapy. In many cases, the events resolved with corticosteroid treatment, and occasional event recurrence was observed after re-initiation of nivolumab therapy.

In fewer than 1% of patients, the following clinically significant immune-mediated adverse reactions occurred: uveitis, iritis, pancreatitis, facial and abducens nerve paresis, demyelination, polymyalgia rheumatica, autoimmune neuropathy, Guillain-Barré syndrome, hypopituitarism, systemic inflammatory response syndrome, gastritis, duodenitis, sarcoidosis, motor dysfunction, vasculitis, and myasthenic syndrome.

1.2. Rationale for Dose Selection

1.2.1. Starting Dose in Phase 1

The NOAEL of AGEN2034 from the 4-week cynomolgus monkey toxicity study was 40 mg/kg (see Section 1.1.2.1). This dose and serum AGEN2034 concentrations were used in the calculations below for the safe starting dose.

For the clinical trial, the starting dose of 1 mg/kg was selected based on the results of 2 complementary approaches:

- Nonclinical safety: human equivalent dose (HED) projections based on the NOAEL of 40 mg/kg from the 4-week GLP toxicity study in cynomolgus monkey

- Biological effects and efficacy: AGEN2034 is biologically active in several in vitro assays, including: 1) inhibition of PD-1 binding to PD-L1/PD-L2; 2) promotion of TCR signaling in a T cell–based reporter gene assay; 3) increase of T-cell IL-2 production; and 4) increase in T-cell proliferation under conditions of immune suppression.

Two regulatory guidelines can be used for determination of the human starting dose of AGEN2034, starting from the NOAEL:

- International Council for Harmonisation (ICH) S9 "Nonclinical Evaluation for Anticancer Pharmaceuticals" (Food and Drug Administration 2010) provides 2 methods to determine a safe starting dose:
  - HED based on average serum AGEN2034 concentrations from the cynomolgus monkey study and a 10x safety factor are derived per the guidance in Section IIIA of ICH S9.
  - The highest non-severely toxic dose (HNSTD) in mg/kg from non-rodent studies and a 6x safety factor are derived from Section V, Note 2 of ICH S9.
- In addition, the maximum recommended starting dose (MRSD), the HED based on the NOAEL dose and a 10x safety factor, is derived from the United States Food and Drug Administration (FDA) Guidance for Industry "Estimating the Maximum Safe Starting Dose in Initial Clinical Trials for Therapeutics in Adult Healthy Volunteers" (Food and Drug Administration Center for Drug Evaluation and Research 2005).
- An additional 2-fold safety factor is included in each calculation to conservatively compensate for the observed < 2-fold difference of cellular binding affinity to human PD-1 as compared to cynomolgus monkey PD-1.

Table 1: AGEN2034 Starting Dose Calculations

AGEN2034 Dose From 4-Week Cynomolgus Monkey Study[1]	HED (ICH S9 IIIA)[2]	HNSTD (ICH S9 V Note 2)[3]	MRSD (FDA VC3)[4]
40 mg/kg (NOAEL)	0.9 mg/kg	3.3 mg/kg	2.0 mg/kg
300 mg/kg	8 mg/kg	25 mg/kg	15 mg/kg

Abbreviations: FDA: Food and Drug Administration; HED: human equivalent dose; HNSTD: highest non-severely toxic dose; ICH: International Council for Harmonisation; MRSD: maximum recommended starting dose; NOAEL: no-observed-adverse-effect level.

[1] All calculations include an additional 2-fold safety factor to conservatively compensate for binding affinity difference.

[2] Based on cynomolgus monkey AGEN2034 C_{avg}: 40 mg/kg C_{avg} = 488 µg/mL; HED calculation using a 2,500 mL human blood volume and 70 kg human body weight.

[3] Based on an HNSTD value calculated as 1/6 of the mg/kg dose.

[4] Food and Drug Administration, Center for Drug Evaluation and Research, 2005.

Collectively, these guidance documents indicate a safe clinical starting dose within the 1 to 3 mg/kg range based on the NOAEL of 40 mg/kg. If the 300 mg/kg dose is considered

appropriate for human safe dose calculations, this would provide an even greater level of safety cover, between 8 to 25 mg/kg, for a clinical starting dose.

There is no cross-species reactivity to rodent PD-1 to warrant conducting rodent in vivo studies, although in vitro human data have demonstrated that AGEN2034 exhibits a pharmacological profile consistent with antagonism of the PD-1/PD-L1 interaction. These results indicate the estimated minimum anticipated biological effect level (MABEL) at EC_{10} is approximately 7.3×10^{-4} mg/kg; at EC_{50} is 6.6×10^{-3} mg/kg; and at EC_{90} is 0.17 mg/kg. It is anticipated that administration of 1 mg/kg AGEN2034 every 2 weeks will result in blood AGEN2034 concentrations that will exceed the EC_{90} throughout the duration of the administration cycle, which allows administration of an efficacious dose to subjects who are seriously ill.

Furthermore, AGEN2034 and a marketed PD-1 inhibitor, nivolumab, have comparable efficacy profiles in a number of in vitro assays. Nivolumab, as well as another marketed PD-1 inhibitor, pembrolizumab, have shown clinical activity of this class and an overall acceptable safety profile, leading to regulatory approval for these drugs as a treatment of several malignancies.

In conclusion, the proposed safe starting dose of AGEN2034 is 1 mg/kg administered every 2 weeks to subjects with advanced malignancies who have progressed after standard treatment and for which no established therapy is available.

1.2.2. Dose in Phase 2

The choice of the Phase 2 dose was based on clinical data from the Phase 1 portion of this trial, evaluating AGEN2034 as monotherapy. Supportive clinical responses are also available from publications of similar-mechanism competitor nivolumab (anti PD-1; Opdivo®) as monotherapy since AGEN2034 has been shown to be functionally comparable to nivolumab.

Dosing for Phase 1 was guided by preclinical pharmacokinetics (PK), preclinical pharmacology, and comparisons to published results of nivolumab as monotherapy.

In Phase 1, a partial response was reported (Drescher et al 2018) in the 3 mg/kg every 2 weeks (q2wk) cohort that later was designated a complete response. Preliminary PK analysis of Phase 1 data suggests an AGEN2034 terminal half-life of approximately 10 days. Therefore, dosing AGEN2034 q2wk results in only a 25% increase in accumulation ratio compared to every 3 weeks. AGEN2034 dosed at 3 and 10 mg/kg q2wk resulted in average plasma AGEN2034 concentrations (C_{avg}) of 20 and 67 µg/mL, respectively (corresponding to 1.30 and 1.80 µg/mL when log-transformed). When these log-transformed values are compared with receptor occupancy and IL-2 AGEN2034 concentration-response profiles, the AGEN2034 C_{avg} values are clearly on the flat saturated part of the dose-response curves for these key pharmacodynamic parameters. Therefore, no additional benefit is expected for AGEN2034 doses greater than 3 mg/kg q2wk.

Since limited clinical efficacy information is available from the ongoing evaluations, the primary decisions for the recommended Phase 2 dose (RP2D) of AGEN2034 were based on (1) the complete response experienced with the 3 mg/kg q2wk dose in Phase 1, and (2) favorable comparison of attained clinical C_{avg} to key preclinical pharmacodynamic evaluations. Therefore, 3 mg/kg q2wk was the dose and regimen selected as RP2D for evaluation in Phase 2 of this trial.

1.3. Rationale for Expansion Cohort

Subjects with unresectable or metastatic cervical cancer with disease progression after a platinum-based treatment regimen will be enrolled in an expansion cohort. This population has a high unmet need for effective therapy, and there is a strong rationale for the use of a PD-1 therapeutic antibody.

It is estimated that 12,800 new cases of cervical cancer will be diagnosed in the US in 2017, with 4,200 deaths attributable to this malignancy (Siegel et al 2017). More widely, cervical cancer is the 4th most common cause of cancer death for women worldwide (Torre et al 2015). Human papilloma virus (HPV) vaccination is expected to reduce the incidence of cervical cancer over time, however vaccination rates in female adolescents remain below 50% in many parts of the US (Reagan-Steiner et al 2016) and unresectable or metastatic disease is likely to remain an important health concern. The current standard of care for the first-line treatment of recurrent or metastatic cervical cancer is platinum doublet chemotherapy with or without bevacizumab (National Comprehensive Cancer Network 2016; Tewari et al 2014). While a number of agents may be utilized in clinical practice for the second-line treatment of cervical cancer currently, none can be regarded as definitive with proven survival benefit; therefore, clinical trials are often recommended for such individuals (Borcoman & Le Tourneau 2017).

The use of checkpoint protein blockade in the treatment of cervical cancer is supported by observations of high PD-L1 expression in cancers with viral etiology, including cervical cancer (Schumacher & Schreiber 2015; Mezache et al 2015). The upregulation of PD-1 and PD-L1 was also shown to correlate with impaired immunity in high-risk HPV-related cervical cancer (Yang et al 2013). Furthermore, initial trials of PD-1 therapeutic antibodies have demonstrated activity in this disease. In the KEYNOTE-028 study 24 subjects with unresectable or metastatic PD-L1 positive cervical cancer, who had failed first-line therapy, received pembrolizumab at a dose of 10 mg/kg IV every 2 weeks. Four subjects (17%) had a Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST 1.1) partial response with a median duration of response of 26 weeks (Frenel et al 2016). The safety profile of pembrolizumab was consistent with that observed in trials in other tumor types. In the KEYNOTE-158 study, a similar group of subjects with cervical cancer received pembrolizumab at a dose of 200 mg once every 3 weeks until disease progression or 2 years. In this second study, 98 subjects have been treated regardless of PD-L1 biomarker status. The ORR in the PD-L1 positive cohort (81 subjects) was 16% including 3 subjects with complete response. None of the 17 subjects with PD-L1 negative cancers responded. Again many of the responses were shown to be durable (Chung et al 2018). Pembrolizumab was approved by the US FDA in June 2018 for patients with recurrent or metastatic cervical cancer with disease progression on or after chemotherapy whose tumors express PD-L1 (CPS $\geq$ 1) as determined by an FDA-approved test (Food and Drug Administration 2018). Finally, nivolumab has been studied in a trial of subjects with virus-associated cancers including 19 subjects with cervical cancer. Nivolumab was given at a dose of 240 mg every 2 weeks. Subjects were required to have had 2 or fewer prior treatment regimens for advanced disease and were unselected for PD- L1 expression. One subject had a complete response and 4 subjects had partial response for an overall response rate of 26%. In the study population as a whole the response rate was higher in HPV positive cancers (28.6%) than in cancers with unknown HPV status (10.0%) (Hollebecque et al 2017). These findings of clinical

activity with durable responses support the study of AGEN2034 in subjects with unresectable or metastatic cervical cancer with disease progression after standard first-line therapy.

1.4. Rationale for Biomarker Assessment

1.4.1. Biomarkers in Phase 1

When the study started, due to limited understanding of the biological activities induced by AGEN2034 in cancer subjects, there was no certainty that the doses examined will be associated with relevant antitumor immune activities. As a consequence, the study will serve to: evaluate receptor occupancy at different dose levels; investigate the mechanism of action of the drug by monitoring immune cell subset activation status; and evaluate potential predictive/prognostic biomarker candidates related to the drug and/or cancer (e.g., level of PD-L1 tumor expression, HPV status).

1.4.2. Biomarkers in Phase 2

Phase 2 of the study will continue to investigate the mechanism of action of the drug by monitoring immune cell subset activation status; will monitor [redacted] as a non-invasive reflection of the tumor burden; will evaluate potential predictive/prognostic biomarker candidates related to the drug and/or cancer (e.g., level of PD-L1 tumor expression, HPV status).

1.4.3. Assessment of PD-L1 Expression in Tumors

PD-L1 expression has been associated with response to PD-1. In treatment naive NSCLC, a PD-L1 expression level of ≥ 50% tumor proportion score (TPS) as a companion diagnostic for treatment with pembrolizumab was evaluated and is now approved.

There is limited data available on PD-L1 expression in cervical cancer, particularly in subjects with metastatic disease who have relapsed after initial therapy. In a recent publication by Reddy et al (2017), 34% of subjects with cervical cancer were PD-L1 positive. On June 12, 2018, the US Food and Drug Administration approved pembrolizumab for patients with recurrent or metastatic cervical cancer with disease progression on or after chemotherapy whose tumors express PD-L1 (CPS ≥ 1) as determined by an FDA-approved test (Food and Drug Administration 2018). In KEYNOTE-158, 98 subjects have been treated regardless of PD-L1 biomarker status. The response rate in the 81 PD-L1 positive cancers was 16% including 3 subjects with complete response (Chung et al 2018).

In this study, the hypothesis is that subjects with positive PD-L1 expression may have improved anti-tumor response, therefore tumor tissue is required for subjects in trial Phase 2. This is an exploratory biomarker that, in the future, may help to determine the patients who will best respond to PD-1 inhibition.

2. OBJECTIVES, ENDPOINTS, AND BENEFIT/RISK

2.1. Objectives and Endpoints

The objectives and associated endpoints for Phase 1 and Phase 2 are shown in Section 2.1.1 and Section 2.1.2, respectively.

2.1.1. Phase 1

	Objective	Endpoint
Primary	• To assess the safety and tolerability of AGEN2034 in subjects with metastatic and/or locally advanced solid tumors	• Occurrence of DLTs in subjects in dose escalation during the first 21 days of treatment • Frequency, severity, and duration of treatment-emergent adverse events (TEAEs) and laboratory abnormalities using the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) v4.03.
Secondary	• To characterize the AGEN2034 pharmacokinetic (PK) profile	• AGEN2034 PK parameters which may include (but are not limited to) maximum drug concentration observed postdose at steady-state (C_{max-ss}), minimum observed 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 zero to time t ($AUC_{(0-t)}$), area under the drug concentration-time curve from time zero to infinity ($AUC_{(0-\infty)}$), time to maximum observed concentration (t_{max}), terminal disposition rate constant (λ_z), terminal elimination half-life ($t_{1/2}$), systemic clearance (CL), and volume of distribution (Vd)
	• To correlate AGEN2034 exposure with target occupancy	• Receptor occupancy on circulating T cells measured 4 hours after the 1st dose and immediately prior to the 2nd dose • Receptor occupancy saturation levels correlated with AGEN2034 PK exposure metrics
	• To evaluate the immunogenicity of AGEN2034 and correlate it to exposure	• Antidrug antibody (ADA) concentrations and correlation with AGEN2034 PK exposure metrics
Exploratory	[redacted]	
	• To explore the association of programmed cell death protein 1 – ligand 1 (PD-L1) expression with clinical responses	• Baseline expression of PD-L1

2.1.2. Phase 2

	Objective	Endpoint
Primary	• To assess objective response rate (ORR) according to RECIST 1.1 as determined by an Independent Endpoint Review Committee (IERC)	• Confirmed ORR per RECIST 1.1, as determined by an IERC, in the analysis population
Secondary	• To assess the safety and tolerability of AGEN2034 in subjects with metastatic and/or locally advanced solid tumors	• Frequency, severity, and duration of TEAEs and laboratory abnormalities, using NCI CTCAE v4.03.
	• To characterize the AGEN2034 PK profile	• AGEN2034 PK parameters which may include (but are not limited to) maximum drug concentration observed postdose at steady-state (C_{max-ss}), minimum observed concentration at steady-state (C_{min-ss}), area under the drug concentration-time curve within time span t1 to t2 at steady-state ($AUC_{(\tau 1-\tau 2)-ss}$), area under the drug concentration-time curve from time zero to time t ($AUC_{(0-t)}$), area under the drug concentration-time curve from time zero to infinity ($AUC_{(0-\infty)}$), time to maximum observed concentration (t_{max}), terminal disposition rate constant (λ_z), terminal elimination half-life ($t_{1/2}$), systemic clearance (CL), and volume of distribution (Vd)
	• To evaluate the immunogenicity of AGEN2034 and correlate it to exposure	• ADA concentrations and correlation with AGEN2034 PK exposure metrics
	• To assess objective response rate (ORR) according to RECIST 1.1 as determined by investigator	• Confirmed ORR per RECIST 1.1, as determined by an investigator
	• To assess duration of response (DOR), disease control rate (DCR), duration of stable disease (SD), time to response, and progression-free survival (PFS) time per RECIST 1.1	• DOR per RECIST 1.1, as determined by an IERC and investigator, defined as time from first observation of response to first observation of documented disease progression (or death within 12 weeks after last tumor assessment). Subjects without an event at analysis cutoff date will be censored on date of last tumor assessment. • DCR, defined as proportion of subjects with complete response (CR), partial response (PR), or stable disease (SD) for at least 12 weeks • Duration of SD, measured from the start of treatment until the criteria for progression are met, taking as reference the smallest measurements recorded since the treatment started, including baseline measurements. • Time to response, defined as the time from the first dose date to first observation of confirmed response.

	Objective	Endpoint
Secondary (continued)		• PFS time, defined as time from first treatment administration to first observation of documented disease progression (or death within 12 weeks after last tumor assessment), per RECIST 1.1, as determined by an IERC and investigator. Subjects without an event at analysis cutoff date will be censored on date of last tumor assessment.
	• To assess overall survival (OS) rate	• Median OS and OS rate
	• To assess OS time	• OS time, defined as time from start of treatment to death. For subjects who are still alive at time of data cutoff for trial analysis or who are lost to follow-up, survival will be censored at the last recorded date that the subject is known to be alive as of the cutoff date for analysis
Exploratory	[redacted]	
	• To explore the association of programmed cell death protein 1 – ligand 1 (PD-L1) expression with clinical outcomes	• Baseline expression of PD-L1 association with clinical outcomes

2.2. Overall Risk/Benefit Assessment

The risk-benefit relationship has been carefully considered in the planning of this trial. Based on preclinical and clinical data available to date, the conduct of the trial is considered safe and reasonable using the dose and schedule of AGEN2034 as specified for Phase 1, Cohort 1 in this clinical trial protocol.

A Safety Monitoring Committee (SMC) in Phase 1 and an Independent Data Monitoring Committee (IDMC) in Phase 2 are planned for ongoing assessment of the risk-benefit ratio. The trial shall be discontinued in the event of any new findings that indicate a relevant deterioration of the risk-benefit relationship and would render continuation of the trial unjustifiable. The risks of exposure to AGEN2034 include:

- Infusion-related reactions.
- Increase in immune-related adverse events (irAEs), which constitute a unique spectrum of AEs that occur via activation of the subject's immune system and that can sometimes lead to serious and even fatal events (Boutros et al 2016; Kumar et al 2017; Weber et al 2012).

Infusion-related reactions are a risk inherent to administration of any recombinant protein to humans. The incidence of immunogenicity and the character or severity of immunogenicity-induced side effects cannot be predicted by animal models because humanized or fully human proteins usually provoke a much stronger immune-response in rodents or non-human primates

than in humans. However, for AGEN2034, clinical signs of hypersensitivity were not observed in pilot 4-week IV repeat-dose toxicity studies conducted in cynomolgus monkeys (a primate species closer to human). There were also no findings in an in vitro cytokine release assay in human whole blood.

Immune-related AEs are events that are drug-related and can be explained by an immune phenomenon after other etiologies have been ruled out. Relevant clinical safety experience has been generated with several PD-1 pathway–blocking monoclonal antibodies and with the combination with CTLA-4 agents (Ott et al 2017; Boutros et al 2016; Kumar et al 2017).

For the reasons noted previously, it is anticipated that the safety profile of nivolumab will provide a good estimate for the safety and tolerability of AGEN2034. Overall, the safety profile for nivolumab, which blocks the PD-1/PD-L1 axis at the same level as does AGEN2034, is acceptable in the context of treatment of subjects with advanced malignancies. Nevertheless, occurrence of AEs, especially irAEs, will be carefully monitored.

A direct benefit is usually considered unlikely for participants in a Phase 1 trial, and that holds true for the current trial. However, even at the lowest dose, it is expected that the drug will be pharmacologically active, leading to blockade of PD-1 for at least part of the 14 days between each administration.

The Phase 2 portion of the study will explore the activity of the selected AGEN2034 dose in the treatment of subjects with metastatic or locally advanced, unresectable cervical cancer who have relapsed after a platinum-based treatment regimen. There is no regimen with proven clinical benefit currently available to these subjects and the treatment with PD-1 blockade provides an opportunity to improve on the response rates observed with chemotherapy.

Overall, the risk-benefit ratio of the proposed treatment with AGEN2034 is considered positive, and to further manage the potential for added risk, in this trial there will be pro-active monitoring for immunogenicity and pro-active management of immune related AEs.

3. INVESTIGATIONAL PLAN

This is a 2-part trial: a Phase 1, open-label, dose-escalation trial in subjects with metastatic or locally advanced solid tumors, with a consecutive Phase 2 expansion to evaluate efficacy in subjects with recurrent, unresectable, or metastatic (advanced) cervical cancer that has progressed after a platinum-based treatment regimen.

3.1. Phase 1 (Part A): Dose Escalation

Phase 1 (Part A) of the study will consist of a standard 3+3 dose escalation with the following escalating dose levels and schedules:

- Part A1: 1, 3, and 10 mg/kg administered every 2 weeks
- Part A2: 6 and 10 mg/kg administered every 3 weeks

In Part A1, the first subject of each cohort will be observed for 16 days (i.e., ≥ 48 hours after second dose) for occurrence of dose-limiting toxicity (DLT) before the second subject is administered trial medication. Thereafter, within each cohort in the dose escalation phase of Part A1, consecutively enrolled subjects may initiate treatment ≥ 48 hours after the prior enrolled

subject initiated treatment. Dose escalation will continue until the MTD is reached or the maximum planned dose level (10.0 mg/kg) is shown to be safe. The MTD is defined as the dose below which ≥ 2 DLTs are observed.

Once Part A1 is completed, enrollment for Part A2 will begin:

- If < 2 DLTs are observed in dose escalation at the 10 mg/kg every 2 weeks dose level in Part A1, open enrollment will begin for Part A2 at the 6 mg/kg every 3 weeks dose level; enrollment of these subjects does not to have to be sequential (that is, a wait of 48 hours between 2 subjects is not required). Once 10 subjects at the 6 mg/kg dose level have completed, open enrollment will begin for Part A2 at the 10 mg/kg every 3 weeks dose level; enrollment of these subjects does not to have to be sequential (that is, a wait of 48 hours between 2 subjects is not required).
- If ≥ 2 DLTs are observed in dose escalation at the 10 mg/kg every 2 weeks dose level in Part A1, standard 3 + 3 dose escalation will continue with Part A2. Within each dose level cohort, consecutively enrolled subjects may initiate treatment ≥ 48 hours after the prior enrolled subject initiated treatment. Dose escalation will continue until the MTD is reached or the maximum planned dose level for Part A2 (10.0 mg/kg every 3 weeks) is shown to be safe.

Each subject will stay on the dose level and schedule assigned at trial entry. Subjects will receive AGEN2034 for a maximum of 24 months or until disease progression, unacceptable toxicity, or any criterion for stopping the study drug or withdrawal from the trial occurs.

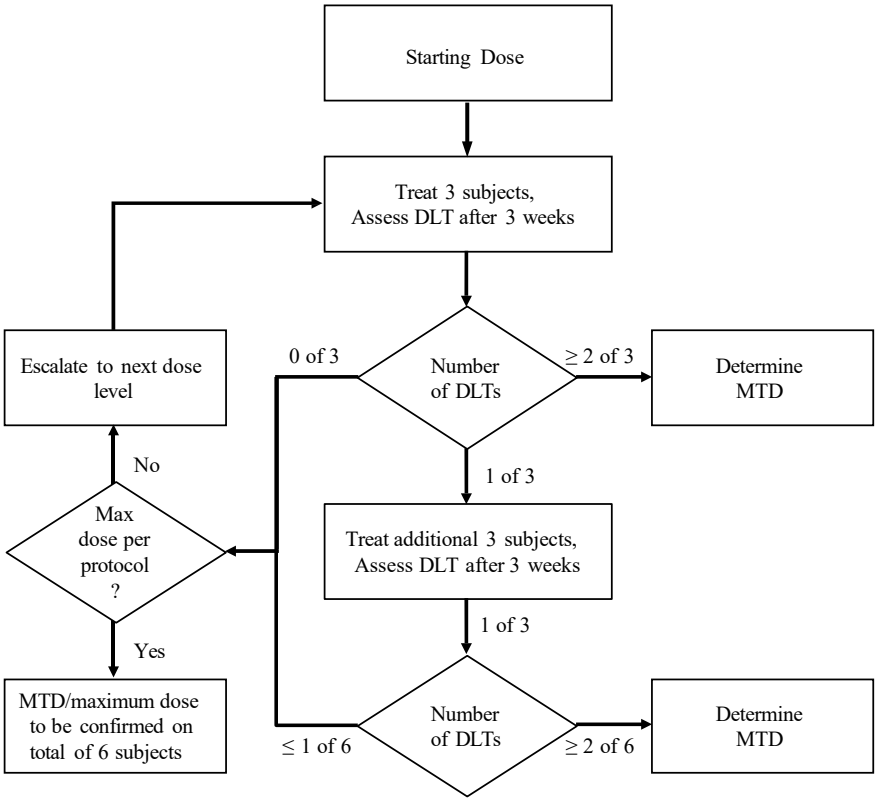
The DLT observation period for the dose escalation portion of Phase 1 (Parts A1 and A2) is the first 21 days following administration of AGEN2034. Subjects who do not complete the DLT evaluation period for reasons other than a DLT will be replaced. The decision to escalate to the next cohort will be made by the SMC, based on safety assessments after all subjects of a cohort have reached the end of the DLT evaluation period. See Section 9.1 for a description of the SMC.

The dose escalation criteria are as follows:

- For each dose level, DLTs are assessed during the first 21 days. The criteria for moving from one dose level to another do not allow escalation to the next cohort in cases in which ≥ 1 of 3 or ≥ 2 of 6 subjects in a dose-level cohort experience DLT.
- If 1 of 3 subjects in a cohort experiences a DLT, this cohort will be expanded to 6 subjects.
- The MTD is defined as the highest dose at which < 2 of 6 subjects experience a DLT. Thus, the MTD cohort should accrue a total of ≥ 6 subjects.

A schematic of dose escalation is presented in Figure 2.

Figure 2: Phase 1 Dose Escalation Schematic



DLT: dose limiting toxicity; MTD: maximum tolerated dose

It is conceptually acceptable to de-escalate to an intermediate, not pre-defined and not previously- studied dose level, if evaluation of toxicity at such a dose is desired. If this approach is taken, 3 new subjects should be enrolled at the new intermediate dose, and the aforementioned rules should be used to determine further enrollment at this dose level.

The decision to expand a cohort to 6 subjects, to de-escalate and/or to open enrollment to the Dose Expansion Phase will be made by the SMC based on safety assessments after subjects of a cohort in dose escalation have reached the end of the DLT evaluation period.

3.1.1. Dose-Limiting Toxicity

In this trial, a DLT is defined as any treatment-related toxicity that is NCI CTCAE Grade ≥ 3, confirmed by the SMC to be relevant for the study drug treatment, and that occurs during the first 3 weeks of AGEN2034 treatment in the dose escalation portion of the trial (DLT evaluation period) for all dose cohorts and for all subjects with data used for implementing the dose-escalation algorithm for determination of MTD. Additional subjects enrolled in the dose escalation phase will have AEs collected but will not have a specific DLT observation period.

The SMC recognizes that in the absence of prior human experience with AGEN2034, a conservative approach will need to be adopted in ascribing the relevance of treatment-related toxicity to drug. Treatment-related serious adverse events (SAEs) will be ascribed as related to

drug except where a clear relationship to the underlying disease or recognized co-morbidities is evident.

Exceptions to this DLT definition include:

- Grade 3 infusion-related reactions resolving within 6 hours 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 (ALT, AST, or GGT) increase that resolves to grade ≤ 1 in < 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.

Any DLT will immediately lead to permanent withdrawal of AGEN2034.

3.1.2. Stopping Rules for Toxicity

The SMC will meet to review any cohort under evaluation as well as the safety of all cohorts. Should > 33% subjects on any dose level experience toxicities that meet DLT criteria but occur after the DLT observation period or in subjects not included in the DLT analysis set, enrollment will be held and the occurrences will be thoroughly evaluated by the committee. The SMC will then make recommendations to re-open enrollment or to initiate other changes in study conduct (such as protocol amendments).

If there is a subject death within 30 days after AGEN2034 administration for reasons not related to the subject's disease progression, the trial will be put on hold to accrual and treatment held for subjects on study. The SMC will evaluate the cause of the event and recommend the appropriate change in study conduct. If the event is determined to be related to AGEN2034, then a study amendment and/or other corrective action plan will be established. If the event is determined not to be related to the AGEN2034, then the study will re-open to accrual and subjects on study will resume treatment.

3.1.3. Backfill Expansion Enrollment for Each Dose Level Cohort in the Phase 1

Concurrent with the 3+3 dose escalation schema, additional subjects will be backfilled to ensure that each combined dose level cohort enrolls at least 10 subjects:

- Part A1:
  - Once the safety of the 1 mg/kg dose is established, enrollment for the 3 mg/kg dose cohort will begin. When accrual of first 3 subjects in the 3mg/kg cohort is

paused for the 21-day safety assessment and DLT observation, enrollment of ≤ 7 subjects to backfill the 1 mg/kg cohort may begin.

– When the safety of the 3 mg/kg dose has been established, enrollment for the 10 mg/kg dose cohort will begin. When accrual for the 10 mg/kg dose cohort is paused for safety assessment and DLT observation, enrollment of ≤ 7 subjects to backfill the 3 mg/kg dose level can begin.

Note: Enrollment of 10 subjects to the 1 mg/kg dose level must be completed before additional subjects can be enrolled to backfill the 3 mg/kg dose level.

– When the safety of the 10 mg/kg dose has been established, ≤ 4 subjects may be enrolled at the same dose level, for a total of 10 subjects at 10 mg/kg.

Note: Enrollment of 10 subjects to the 1 and 3 mg/kg dose levels must be completed before additional subjects can be enrolled to backfill the 10 mg/kg dose level.

- Part A2:
  - Backfill for Part A2 will be considered if ≥ 2 DLTs are observed in dose escalation at the 10 mg/kg every 2-weeks dose level in Part A1 and dose escalation continues with Part A2. Backfill of Part A2 will proceed as follows:
  - When the safety of the 6 mg/kg dose has been established, enrollment for the 10 mg/kg dose cohort will begin. When accrual for the 10 mg/kg dose cohort is paused for safety assessment and DLT observation, enrollment of ≤ 7 subjects to backfill the 6 mg/kg dose level can begin.
  - When the safety of the 10 mg/kg dose has been established, ≤ 4 subjects may be enrolled at the same dose level, for a total of 10 subjects at 10 mg/kg.

    Note: Enrollment of 10 subjects to the 6 mg/kg dose level must be completed before additional subjects can be enrolled to backfill the 10 mg/kg dose level.

Backfill expansion enrollment of subjects for each cohort does not to have to be sequential (that is, a wait of 48 hours between 2 subjects is not required). Subjects enrolled to backfill each dose level cohort will have the purpose of generating additional safety, PK, and receptor occupancy data, and will not undergo formal DLT observation.

3.2. Phase 2: Dose Expansion Phase

There is no approved standard of care for second line treatment of advanced or metastatic cervical cancer. As such, these subjects would be eligible for the Phase 1 portion of the study; therefore, the SMC may decide to open enrollment to the expansion cohorts of this trial at a dose level that has been found to be safe and is expected to be active.

The following expansion cohort will be enrolled: recurrent, unresectable, or metastatic cervical cancer.

Enrollment of subjects for expansion cohort does not to have to be sequential (i.e., a wait of 48 hours between 2 subjects is not required). Subjects will receive AGEN2034 for a maximum of

24 months or until disease progression, unacceptable toxicity, or any criterion for stopping the study drug or withdrawal from the trial occurs.

The SMC will continue to evaluate safety on an ongoing basis for the Phase 2. Additionally, for the Phase 2 portion of the study, an IDMC will be established to evaluate safety and efficacy.

3.3. Planned Number of Subjects

3.3.1. Enrollment Targets

The planned number of subjects for this trial is:

- Phase 1 (Parts A1 and A2): approximately 50 subjects.
- Phase 2: approximately 150 subjects with recurrent, unresectable and/or metastatic cervical cancer.

The final sample size may vary depending on the total number of dose levels tested, and subject replacement for DLT evaluations.

3.3.2. Subject Replacement Strategy

In Phase 1, subjects who do not complete the DLT observation period defined in Section 3.1 for reasons other than a DLT may be replaced.

In Phase 2, no subject will be replaced.

3.4. Planned Trial Duration

The maximum trial duration for a subject is estimated to be up to approximately 49 months. This includes a screening period, a planned treatment period of up to approximately 24 months, and a follow-up period of up to 24 months after the last dose of study drug.

The overall trial duration is expected to be approximately 63 months:

- First subject in: Q2 2017
- Last subject out (after follow-up): Q2 2022

3.5. Definition of End of Trial

If the trial is not terminated for a reason provided in Section 4.4.3, the end of the trial is defined as 24 months after the last subject has received the last planned dose of study drug.

3.6. Medical Care of Subjects After End of Trial

At the end of the protocol-specified periods of active study therapy, the Sponsor will not continue to supply study drug to subjects/investigators unless the Sponsor chooses to extend the study. The investigator should ensure that the subject receives appropriate standard of care to treat the condition under study.

Upon withdrawal from trial treatment, subjects may receive the care upon which they and their physicians agree. Subjects will be followed for survival and AEs as specified in Section 6.

4. SELECTION OF TRIAL POPULATION

4.1. Target Population

Phase 1 (Parts A1 and A2):

Male and female subjects over the age of 18 years with metastatic or locally advanced solid tumors for which no standard therapy is available or standard therapy has failed.

Phase 2:

Female subjects over the age of 18 years with recurrent and/or metastatic cervical cancer who have relapsed after a platinum-based treatment regimen for advanced (recurrent, unresectable, or metastatic) disease.

After the interim analyses, subsequent enrollment of subjects may be based on biomarker enrichment (including but not limited to PD-L1 expression). In such cases, tumor tissue must be positive for the selected entry biomarker prior to subject enrollment.

4.2. Inclusion Criteria

For inclusion in the trial, **all** of the following inclusion criteria must be fulfilled as no waivers will be permitted:

1. Voluntarily agree to participate by giving written informed consent. Participation in pharmacogenomics testing is optional.
2. Be ≥ 18 years of age.
3. Diagnosis and prior systemic treatment:
    a. **Phase 1:** Have a histologically or cytologically confirmed diagnosis of a metastatic or locally advanced solid tumor for which no standard therapy is available or standard therapy has failed.
    b. **Phase 2:**
        I. Have (1) a histologically or cytologically confirmed diagnosis of squamous-cell carcinoma, adenosquamous carcinoma, or adenocarcinoma of the cervix, and (2) metastatic, locally advanced, and/or unresectable disease at the time of enrollment. Histologic confirmation of the original primary tumor is required via pathology report.

            Note: The following cervical tumors are not eligible: minimal deviation/adenoma malignum, gastric type adenocarcinoma, clear cell carcinoma, and mesonephric carcinoma.
        II. Has cervical cancer and has relapsed after a platinum-based treatment (first line) regimen for advanced (recurrent, unresectable, or metastatic) disease;

            Note: Subject receiving chemotherapy concurrently with primary radiation (e.g., weekly cisplatin) or subject receiving adjuvant chemotherapy following completion of radiation therapy (e.g., paclitaxel and carboplatin for ≤ 4 cycles) and progressed within 6 months after treatment completion will be eligible as this systemic therapy will be considered as first line treatment.

4. Measurable disease – based on investigator assessment
   a. **Phase 1:** Have objective evidence of disease; the presence of measurable disease is not required.
   b. **Phase 2:** Have measurable disease on imaging based on RECIST version 1.1.

      Note: Subjects must have at least one "target lesion" to be used to assess response, as defined by RECIST version 1.1. Tumors within a previously irradiated field will be designated as "non-target" lesions unless progression is documented or a biopsy is obtained to confirm persistence at least 90 days following completion of radiation therapy.

      Note: Measurable disease by RECIST 1.1 must be confirmed by independent central radiologic review prior to first dose. Subjects without centrally confirmed measurable disease at baseline will not be eligible for this trial.
5. Have a life expectancy of at least 3 months and an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1.
6. Have adequate organ function as indicated by the following laboratory values:
   a. Adequate hematological function defined by absolute neutrophil count (ANC) ≥ 1.5 x 10^9/L, platelet count ≥ 100 x 10^9/L, and stable hemoglobin ≥ 8 g/dL (without transfusions within 1 week before first dose).
   b. Adequate hepatic function based by a total bilirubin level ≤ 1.5 x the institutional upper limit of normal (IULN), aspartate aminotransferase (AST) level ≤ 2.5 x IULN, alanine aminotransferase (ALT) level ≤ 2.5 x IULN, and alkaline phosphatase ≤ 2.5 x IULN.
   c. Adequate renal function defined as creatinine ≤ 1.5 x IULN **OR** calculated creatinine clearance ≥ 50 mL/min for subjects with creatinine levels > 1.5 x IULN (if no local guideline is available, creatinine clearance should be calculated using the Cockcroft-Gault Method).
   d. Adequate coagulation defined by international normalized ratio (INR) or prothrombin time ≤ 1.5 x IULN (unless the subject is receiving anticoagulant therapy); and activated partial thromboplastin time (aPTT) ≤ 1.5 x IULN (unless the subject is receiving anticoagulant therapy)
7. Other than the cancer for which the subject is enrolled, have no history of prior malignancy, with the exception of basal cell carcinoma of the skin, superficial bladder cancer, squamous-cell carcinoma of the skin, or has undergone potentially curative therapy with no evidence of that disease recurrence for 5 years since initiation of that therapy.
8. In Phase 2, subjects must provide a sufficient and adequate formalin-fixed paraffin embedded (FFPE) tumor tissue sample preferably from the most recent biopsy of a tumor lesion, collected either at the time of or after the diagnosis of advanced or metastatic disease has been made AND from a site not previously irradiated. If no tumor tissue is available, a fresh biopsy will be required. (See Section 6.4.2.1 for details.)

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

9. Female subjects must have a negative serum pregnancy test at screening (within 72 hours before first dose of study drug) if of childbearing potential or be of non-child bearing potential. Non-childbearing potential is defined as (by other than medical reasons):
   a. ≥ 45 years of age and has not menstruated for greater than 1 year,
   b. Amenorrheic for < 2 years without a hysterectomy and oophorectomy and a follicle-stimulating hormone (FSH) value in the postmenopausal range upon pretrial (screening) evaluation,
   c. Whose status is post hysterectomy, oophorectomy or tubal ligation.
10. If of childbearing potential, female subjects must be willing to use 2 highly effective methods (defined in the informed consent form [ICF]) throughout the study, starting with the screening visit through 120 days after the last dose of study drug.

    Note: Abstinence is acceptable if this is the established and preferred contraception for the subject.
11. Male subjects with a female partner(s) of child-bearing potential must agree to use 2 highly effective methods (defined in the ICF) throughout the trial starting with the screening visit through 120 days after the last dose of study drug is received. Males with pregnant partners must agree to use a condom; no additional method of contraception is required for the pregnant partner.

    Note: Abstinence is acceptable if this is the established and preferred contraception for the subject.
12. Is willing and able to comply with the requirements of the protocol.

4.3. Exclusion Criteria

The subject must be excluded from participating in the trial if the subject:

1. Is currently participating and receiving study therapy or has participated in a study of an investigational agent and received study therapy or used an investigation device within 4 weeks before the first dose of treatment.
2. Has an inadequate washout period prior to first dose of study drug defined as:
   a. Received systemic cytotoxic chemotherapy or biological therapy within 3 weeks before first dose,
   b. Received radiation therapy within 3 weeks before first dose, or
   c. Had major surgery within 4 weeks before first dose.
3. Has received prior therapy with:
   a. Any antibody/drug targeting T-cell co-regulatory proteins (immune checkpoints) such as anti–PD-1, anti–PD-L1, or anti–cytotoxic T-lymphocyte antigen 4 (CTLA-4) antibodies
   b. For Phase 2: > 1 systemic treatment regimen for the advanced (recurrent, unresectable, or metastatic) cervical cancer for which the subject is considered for the study

Note: In Phase 1, prior treatment with a CTLA-4 antibody is permissible for subjects with metastatic melanoma.

4. Has persisting toxicity related to prior therapy of NCI CTCAE Grade > 1 severity.

   Note: Sensory neuropathy or alopecia of Grade ≤ 2 is acceptable.

5. Is expected to require any other form of systemic or localized antineoplastic therapy while on trial (including maintenance therapy with another agent, radiation therapy, and/or surgical resection).

6. Has known severe hypersensitivity reactions to fully human monoclonal antibodies (National Cancer Institute Common Terminology Criteria for Adverse Events version 4.03 [NCI CTCAE] Grade ≥ 3), any history of anaphylaxis, or uncontrolled asthma.

7. Is receiving systemic corticosteroid ≤ 7 days prior to the first dose of trial treatment or receiving any other form of systemic immunosuppressive medication (corticosteroid use on study for management of immune-related adverse events, and/or a premedication for IV contrast allergies/reactions is allowed). Subjects who are receiving daily corticosteroid replacement therapy are an exception to this rule. Examples of permitted therapy are daily prednisone at doses of 5 to 7.5 mg or equivalent hydrocortisone dose, and steroid therapy administered by topical, intraocular, intranasal, and/or inhalation routes.

8. Has a central nervous system (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 (based on 2 sets of brain images, performed ≥ 4 weeks apart, and obtained after the brain metastases treatment). In addition, any neurologic symptoms that developed either as a result of the brain metastases or their treatment must have resolved or be minimal and be expected as sequelae from treated lesions. For individuals who received steroids as part of brain metastases treatment, steroids must be discontinued ≥ 7 days prior to first dose of study drug.

9. Has active or history of autoimmune disease that has required systemic treatment within 2 years of the start of trial treatment (i.e., with use of disease modifying agents, corticosteroids or immunosuppressive drugs). Replacement therapy (i.e., thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency, etc.) is not considered a form of systemic treatment.

   Note: Subjects with diabetes type 1, vitiligo, psoriasis, hypo-, or hyperthyroid disease not requiring immunosuppressive treatment are eligible.

10. Has had an allogeneic tissue/solid organ transplant.

11. Has or had interstitial lung disease (ILD) OR has had a history of pneumonitis that has required oral or IV corticosteroids.

12. Has an active infection requiring intravenous systemic therapy.

13. Has known history of Human Immunodeficiency Virus (HIV) (HIV 1/2 antibodies).

14. Has known active Hepatitis B, Hepatitis C or tuberculosis. Active Hepatitis B is defined as a known positive HBsAg result. Active Hepatitis C is defined by a known positive Hep C Ab result and known quantitative HCV RNA results greater than the lower limits of detection of the assay.
15. Has clinically significant (i.e., active) cardiovascular disease: cerebral vascular accident/stroke or myocardial infarction within 6 months before enrollment, unstable angina, congestive heart failure (New York Heart Association class ≥ II), or serious uncontrolled cardiac arrhythmia requiring medication.
16. Has a history or current evidence of any condition, therapy, or laboratory abnormality that might confound the results of the trial, interfere with the subject's participation for the full duration of the trial, or is not in the best interest of the subject to participate, in the opinion of the treating Investigator.
17. Has known psychiatric or substance abuse disorders that would interfere with cooperation with the requirements of the trial.
18. Is, at the time of signing informed consent, a regular user (including "recreational use") of any illicit drugs or had a recent history (within the last year) of substance abuse (including alcohol).
19. Is legally incapacitated or has limited legal capacity.
20. Is pregnant or breastfeeding or expecting to conceive or father children within the projected duration of the trial, starting with the screening visit through 120 days after the last dose of study drug.

4.4. Criteria for Subject Withdrawal

4.4.1. Withdrawal from Treatment

The subject must be withdrawn in the event of any of the following:

- Occurrence of an event that would have been considered an exclusion criterion prior to enrollment, that is clinically relevant and affects the subject's safety, and if discontinuation is considered necessary by the investigator and/or Sponsor.

- Radiological disease progression, defined by RECIST 1.1 as defined in Section 6.4.4.3, unless the subject is considered to derive clinical benefit from the treatment by the investigator, is clinically stable and there is agreement with the Sponsor (Section 5.4.5).

  Clinical stability is defined by:

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

- Note: For Phase 2, tumor assessments should be performed every 6 weeks (± 3 days) from first treatment dose until discontinuation of treatment, regardless of reason for discontinuation. This includes patients who are being treated past disease progression. Clinical disease progression, in the absence of radiologic progression on the basis of RECIST 1.1, including 1 or more of the following:
  - signs and/or symptoms of consistent with clinically significant progression of disease, including worsening of laboratory values, appearance of new lesion/worsening of the lesion best seen clinically, etc.
  - decline in ECOG performance status
  - tumor progression at critical anatomical sites that requires urgent medical intervention (e.g., CNS metastasis with potential for cord progression)
  - initiation of chronic opiates, or initiation of chemotherapy or new antineoplastic therapy, palliative radiation therapy, or surgery
- Any Grade 2 drug-related uveitis or eye pain or blurred vision that does not respond to topical therapy and does not improve to Grade 1 severity within 2 weeks OR requires systemic treatment;
- Any Grade ≥ 2 drug-related pneumonitis or interstitial lung disease that does not resolve to dose delay and systemic corticosteroids (also see Pulmonary Immune Related Adverse Event Management Algorithm [Section 5.6.3]);
- Any Grade 2 or 3 drug-related toxicity that does not resolve in ≤ 6 weeks;
- Any Grade 3 drug-related bronchospasm, hypersensitivity reaction, or infusion-related reaction, regardless of duration; with the exception of Grade 3 infusion-related reactions resolving within 6 hours and controlled with medical management;
- Any Grade 3 non-skin, drug-related AE lasting > 7 days, with the following exceptions for uveitis, pneumonitis, bronchospasm, diarrhea, colitis, neurologic toxicity, hypersensitivity reactions, infusion reactions, endocrinopathies, and laboratory abnormalities:
  - Grade 3 drug-related uveitis, pneumonitis, bronchospasm, diarrhea, colitis, neurologic toxicity, hypersensitivity reaction, or infusion reaction of any duration requires discontinuation;
  - Grade 3 drug-related endocrinopathies adequately controlled with only physiologic hormone replacement do not require discontinuation;
  - Grade 3 drug-related laboratory abnormalities do not require treatment discontinuation except:
    - Grade 3 drug-related thrombocytopenia > 7 days or associated with bleeding requires discontinuation;
    - Any drug-related liver function test (LFT) abnormality that meets the following criteria require discontinuation (also see hepatic immune-related AE management algorithm [Table 7]):

- AST or ALT > 8 x ULN;
- Total bilirubin > 5 x ULN;
- Concurrent AST or ALT > 3 x ULN AND total bilirubin > 2 x ULN;

- Any Grade 4 drug-related AE or laboratory abnormality, except for the following events, which do not require discontinuation:
  - Grade 4 neutropenia <7 days;
  - Grade 4 lymphopenia or leukopenia;
  - Isolated Grade 4 electrolyte imbalances/abnormalities that are not associated with clinical sequelae and are corrected with supplementation/appropriate management within 72 hours after their onset;
- Any AE, laboratory abnormality, or intercurrent illness which, in the judgment of the Investigator, presents a substantial clinical risk to the subject with continued treatment;
- Tumor flare phenomenon, defined as local pain, irritation, or rash localized at sites of known or suspected tumor does not require treatment discontinuation.
- Any requirement for ≥ 10 mg per day of prednisone (or equivalent) for > 6 weeks;
- Any recurrence of a Grade 3 or 4 drug-related toxicity;
- Dose delay which results in no AGEN2034 dosing for more than 6 weeks.
- Occurrence of AEs, resulting in discontinuation of trial drug that is desired or considered necessary by the investigator and/or the subject (if applicable).
- Occurrence of pregnancy (if applicable).
- Use of a non-permitted concomitant drug, as defined in Section 5.5.2, in which the predefined consequence is withdrawal from study drug (Sponsor may be contacted to discuss whether trial treatment must be discontinued).
- Noncompliance for non-medical reasons (Section 6.4.1.11)

4.4.2. Withdrawal from the Trial

Subjects are free to discontinue the trial at any time without giving their reasons. A subject must be withdrawn in the event of any of the following:

- Withdrawal of the subject's consent.
- Participation in any other therapeutic trial during the treatment duration of this trial.

If a subject has failed to attend scheduled trial assessments, the investigator must determine the reasons and the circumstances as completely and accurately as possible.

In case of premature withdrawal from the trial, the investigations scheduled for the Discontinuation Visit should be performed (Section 6.1) if possible, with focus on the most relevant assessments. In any case, the appropriate electronic case report form (eCRF) section must be completed.

4.4.3. Premature Discontinuation of the Trial

The entire trial may be discontinued prematurely in the event of any of the following:

- New information leading to unfavorable risk-benefit judgement of AGEN2034, e.g., due to:
  - Occurrence of significant previously unknown adverse reactions, or unexpectedly high intensity or incidence of known adverse reactions.
  - Other unfavorable safety findings.

    Note: Evidence of inefficacy may arise from this trial or from other trials of AGEN2034, and unfavorable safety findings may arise from clinical or non-clinical examinations (e.g., toxicology).
- Sponsor's decision that continuation of the trial is unjustifiable for medical or ethical reasons.
- Poor enrollment of subjects, making completion of the trial within an acceptable timeframe unlikely.
- Discontinuation of development of AGEN2034.

Health authorities and Independent Ethics Committees (IECs)/Institutional Review Boards (IRBs) will be informed about trial discontinuation in accordance with applicable regulations.

The entire trial may be terminated or suspended upon request of health authorities.

5. STUDY DRUGS AND TREATMENT

5.1. Investigational Medicinal Product

The investigational medicinal product (IMP), also known as study drug, is AGEN2034, a novel, fully human monoclonal IgG4 antibody designed to block PD-1.

AGEN2034 drug product is supplied as a sterile, single-use solution for IV injection in a 2 mL or 10 mL glass vial. AGEN2034 should be stored in a refrigerator at 2°C to 8°C.

Each drug product 2 mL vial contains a withdrawable volume of 1 mL with 50 mg AGEN2034 at a nominal concentration of 50 mg/mL formulated in [redacted]. Each drug product 10 mL vial contains a withdrawable volume of 5 mL with 50 mg AGEN2034 at a nominal concentration of 10 mg/mL formulated in [redacted].

Please refer to the current version of the Investigator's Brochure and/or Pharmacy Manual for complete storage, handling, dispensing, and infusion information for AGEN2034.

5.2. Packaging and Labeling

Study drug packaging and labeling will be in accordance with applicable local regulatory requirements and applicable Good Manufacturing Practice guidelines. The following information will be pre-printed on the vial: vial contents, storage conditions, and lot number. The label will also contain a statement to conform with FDA Investigational New Drug (IND) requirements as follows:

"Caution: New Drug - Limited by federal law to investigational use."

All study drug must be kept in a secure place under appropriate storage conditions. The sponsor or its representatives must be granted access on reasonable request to check drug storage, dispensing procedures, and accountability records. Refer to the Pharmacy Manual for additional details.

5.3. Storage and Dispensing

The product storage manager should ensure that study drugs are stored in accordance with the environmental conditions (temperature, light, and humidity) as determined in the Pharmacy Manual. If concerns regarding the quality or appearance of the study drug arise, the study drug should not be dispensed and Sponsor should be contacted immediately.

Study drug documentation must be maintained including all processes required to ensure drug is accurately administered. This includes documentation of drug storage, administration and, as applicable, storage temperatures, reconstitution, and use of required processes (e.g., required diluents, administration sets).

AGEN2034 will be shipped in transport cool containers (2°C to 8°C) that are monitored with temperature control devices.

AGEN2034 drug product must be stored at 2°C to 8°C until use, with a temperature log maintained daily. All medication boxes supplied to each study center must be stored carefully, safely, and separately from other drugs.

For application in this trial, AGEN2034 drug product must be diluted with 0.9% saline solution (sodium chloride injection). Detailed information on infusion bags and medical devices to be used for preparation of dilutions and subsequent administration is provided in the Pharmacy Manual.

Once the vial is punctured, the AGEN2034 drug product must be diluted into appropriate volume of 0.9% saline solution in an infusion bag immediately. Infusion from the bag should begin within 24 hours of vial puncture when the bag is stored either at room temperature or at 5°C ± 3°C (refrigerated conditions).

Any unused portion of solution should be discarded in biohazard waste disposal, with final disposal by accepted local and national standards of incineration.

Please refer to the current version of the Investigator's Brochure and/or Pharmacy Manual for complete storage, handling, dispensing, and infusion information for AGEN2034.

5.4. Dosage and Administration

5.4.1. AGEN2034

AGEN2034 infusions should be administered within 60 minutes (-10/+20 min) using an infusion pump. A central catheter is not required for infusion; however, if a subject has a central venous catheter in place, it is recommended that it be used for the infusion. Once the infusion is completed, all remaining drug solution in the line should be administered according to institutional guidelines for saline flushing.

5.4.1.1. Treatment Regimen

In Phase 1, the dose levels and schedules shown in Table 2 will be studied.

Table 2: Phase 1 Dosing Regimens

Part and Agent	Dose	Schedule	Duration of Treatment
Part A1: Dose Level 1			
AGEN2034	1 mg/kg IV[1]	Every 2 weeks	Up to 24 months
Part A1: Dose Level 2			
AGEN2034	3 mg/kg IV[1]	Every 2 weeks	Up to 24 months
Part A1: Dose Level 3			
AGEN2034	10 mg/kg IV[1]	Every 2 weeks	Up to 24 months
Part A2: Dose Level 1			
AGEN2034	6 mg/kg IV[1]	Every 3 weeks	Up to 24 months
Part A2: Dose Level 2			
AGEN2034	10 mg/kg IV[1]	Every 3 weeks	Up to 24 months

[1] Infusion time is 60 minutes (-10/+20 min)

In Phase 2, all subjects will receive AGEN2034 at a dose of 3 mg/kg IV over 60 minutes (-10/+20 min) every 2 weeks for up to 24 months.

In both Phases, subjects will be treated for up to 24 months, regardless of dose delays, as long as the subject meets criteria to remain on therapy.

5.4.2. Premedication

Premedication should not be administered routinely prior to dosing of drugs. See Section 5.4.3 for subsequent premedication recommendations following AGEN2034-related infusion reactions.

5.4.3. Treatment of Infusion Related Reactions

Acute infusion reactions (which can include cytokine release syndrome, angioedema, or anaphylaxis) are different from allergic/hypersensitive reactions, although some of the manifestations are common to both AEs. Signs and symptoms usually develop during or shortly

after drug infusion and generally resolve completely within 24 hours of completion of infusion. Signs/symptoms may include: allergic reaction/hypersensitivity (including drug fever); arthralgia (joint pain); bronchospasm; cough; dizziness; dyspnea (shortness of breath); fatigue (asthenia, lethargy, malaise); headache; hypertension; hypotension; myalgia (muscle pain); nausea; pruritus/itching; rash/desquamation; rigors/chills; sweating (diaphoresis); tachycardia; tumor pain (onset or exacerbation of tumor pain due to treatment); urticaria (hives, welts, wheals); vomiting.

For an individual subjects, once the AGEN2034 infusion rate has been decreased by 50% or interrupted due to an infusion-related reaction, it must remain decreased for all subsequent infusions to that subject. If the subject has a second infusion-related reaction that is Grade ≥ 2 on the slower infusion rate, infusion should be stopped and the subject should discontinue treatment. If a subject experiences a Grade 3 or Grade 4 infusion-related reaction at any time, the subject must discontinue treatment. If an infusion reaction occurs, all details about drug preparation and infusion must be recorded.

Should infusion reaction be considered a significant safety issue by the SMC, the SMC might decide to recommend premedication with an antihistamine and acetaminophen approximately 30 to 60 minutes before each dose of AGEN2034 (e.g., 25–50 mg diphenhydramine, 500–650 mg paracetamol IV or oral equivalent acetaminophen). This regimen may be modified based on local treatment standards and guidelines, as appropriate.

Table 3 shows treatment guidelines for subjects who experience an infusion reaction associated with administration of AGEN2034.

Subjects receiving AGEN2034 should be monitored for infusion reactions. This includes the measurement of vital signs for at least 1 hour after 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 AGEN2034 with close monitoring. Premedication with an antipyretic or antihistamine for subsequent treatment administration may be considered. For severe infusion reactions, AGEN2034 infusion must be discontinued, and appropriate medical therapy should be administered.

Subjects who do not experience any infusion related toxicity Grade 1 or higher during or after the infusion may be released from monitoring after one hour if they are otherwise stable. Subjects with any infusion related toxicity must be managed as per the guidelines in Table 3 and monitoring will continue until any infusion related toxicity has abated to less than Grade 1 and at least one hour has passed from the completion of the entire infusion and flush. All subjects will be given information on and instructions regarding both infusion related toxicity, which is expected to be most likely in the hour after completion of the infusion, and immune related AEs, before leaving the study site. This will include instructions on when and how to return for immune mediated toxicities associated with PD-1 blockade.

Once the AGEN2034 infusion rate has been decreased by 50% or interrupted due to an infusion-related reaction, it must remain decreased for all subsequent infusions. If the subject has a second infusion-related reaction that is Grade ≥ 2 on the slower infusion rate, infusion should be stopped and the subject should discontinue treatment. If a subject experiences a Grade 3 or Grade 4 infusion-related reaction at any time, the subject must discontinue treatment. If an infusion reaction occurs, all details about drug preparation and infusion must be recorded.

Should infusion reaction be considered a significant safety issue by the SMC, the SMC might decide to recommend premedication with an antihistamine and acetaminophen approximately 30 to 60 minutes before each dose of AGEN2034 (e.g., 25-50 mg diphenhydramine, 500-650 mg paracetamol IV or oral equivalent acetaminophen). This regimen may be modified based on local treatment standards and guidelines, as appropriate.

Table 3: AGEN2034 Infusion Related Reaction Management Guidelines

CTCAE Grade	Treatment	Premedication at Subsequent Dose
Grade 1: Mild reaction; infusion interruption not indicated; intervention	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-inflammatories [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	Subject may be pre-medicated 1.5 hours (± 30 minutes) 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).
Grades 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 • Corticosteroids • 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.

5.4.4. Dose Modifications and Treatment Delay

5.4.4.1. Dose Reductions

No AGNE2034 dose reduction or escalation is allowed. Each subject will stay on the dose levels assigned in the trial unless treatment needs to be stopped.

5.4.4.2. Treatment Delay

5.4.4.2.1. Criteria for Treatment Delay

AGEN2034 administration should be delayed for the following:

- Any Grade ≥ 2 non-skin, drug-related AE with the following exceptions:
  - Do not delay treatment for Grade ≥ 2 Fatigue and laboratory abnormalities except for:
    - Delay dosing for Grade ≥ 2 serum creatinine (more than 1.5x baseline) toxicity
    - If a subject has a baseline AST, ALT, or total bilirubin that is within normal limits, delay dosing for drug-related Grade ≥ 2 toxicity;
- Any Grade ≥ 3 skin drug-related AE or suspected Stevens-Johnson syndrome (SJS) or toxic epidermal necrolysis (TEN)
- Any Grade ≥ 3 drug-related laboratory abnormality with the following exceptions for lymphopenia, AST, ALT, or total bilirubin:
  - Grade 3 lymphopenia does not require a dose delay.
  - If a subject has a baseline AST, ALT, or total bilirubin that is within normal limits, delay dosing for drug-related Grade ≥ 2 toxicity.
  - If a subject has baseline AST, ALT, or total bilirubin within the Grade 1 toxicity range, delay dosing for drug-related Grade ≥ 3 toxicity.
- Any AE, laboratory abnormality, or inter-current illness which, in the judgment of the investigator, warrants delaying the dose of study drug.

Subjects receiving AGEN2034 who have drug-related toxicities that meet the criteria for dose delay should have treatment delayed until retreatment criteria are met.

5.4.4.2.2. Criteria to Resume Treatment

Subjects may resume treatment with AGEN2034 when drug-related AE(s) resolve(s) to Grade 1 or baseline value, with the following exceptions:

- Subjects may resume treatment in the presence of Grade 2 fatigue.
- Subjects who have not experienced a Grade 3 drug-related skin AE may resume treatment in the presence of Grade 2 skin toxicity.

- Subjects with baseline Grade 1 AST/ALT or total bilirubin who require dose delays for reasons other than a 2-Grade shift in AST/ALT or total bilirubin may resume treatment in the presence of Grade 2 AST/ALT or total bilirubin.
  - Subjects with combined Grade 2 AST/ALT AND total bilirubin values meeting discontinuation parameters (Section 4.4.1) should have treatment permanently discontinued.
- Drug-related pulmonary toxicity, diarrhea, or colitis must have resolved to baseline before treatment is resumed.
- Drug-related endocrinothapies adequately controlled with only physiologic hormone replacement may resume treatment.
- 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.

5.4.5. Treatment Beyond Disease Progression

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

- Investigator-assessed clinical benefit from the treatment;
- Is clinically stable (see definition in Section 4.4.1);
- 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 PD who remain on AGEN2034 until treatment is discontinued.

At the time of initial progression, new lesions are considered measurable if the longest diameter is ≥ 10 mm (except for pathological lymph nodes, which must have a short axis of ≥ 15 mm). Any new lesion considered non-measurable at the time of initial progression may become measurable and therefore included in the tumor burden measurement if the longest diameter

increases to ≥ 10 mm (except for pathological lymph nodes, which must have an increase in short axis to ≥ 15 mm).

5.5. Concomitant Treatments

5.5.1. Acceptable Concomitant Medications

All treatments that the investigator considers necessary for a subject's welfare may be administered at the discretion of the investigator in keeping with the community standards of medical care. All concomitant medication will be recorded on the eCRF including all prescription, over-the-counter (OTC), herbal supplements, and IV medications and fluids. If changes occur during the trial period, documentation of drug dosage, frequency, route, and date will also be included on the eCRF.

Palliative and supportive care is permitted during the course of the trial for underlying medical conditions and management of symptoms.

Surgery for tumor control or symptom management is not permitted during the study. Palliative radiotherapy is permitted to a single lesion if considered medically necessary by the treating physician as long as the lesion is NOT a RECIST 1.1-defined target lesion and treatment is NOT administered for tumor control. Trial therapy should be held during the course of palliative radiotherapy and should be resumed no earlier than the next scheduled administration of trial therapy. The specifics of the radiation treatment, including the location, will be recorded.

All concomitant medications received within 30 days before the first dose of trial treatment through the Safety Follow-up Visit should be recorded.

5.5.1.1. Rescue Medications and Supportive Care

Subjects should receive appropriate supportive care measures as deemed necessary by the treating investigator including but not limited to the items outlined below.

For guidelines for continuing treatment with AGEN2034, see Section 5.4.4.2.2.

- Diarrhea: Subjects should be carefully monitored for signs and symptoms of enterocolitis (such as diarrhea, abdominal pain, blood or mucus in stool, with or without fever) and of bowel perforation (such as peritoneal signs and ileus). In symptomatic subjects, infectious etiologies should be ruled out, and if symptoms are persistent and/or severe, endoscopic evaluation should be considered. All subjects who experience diarrhea should be advised to drink liberal quantities of clear fluids. If sufficient oral fluid intake is not feasible, fluid and electrolytes should be substituted via IV infusion.
- Anemia: Transfusions and/or erythropoietin may be utilized as clinically indicated for the treatment of anemia, but should be clearly noted as concurrent medications. Consider a potential immunologic etiology.
- Neutropenia: Prophylactic use of colony-stimulating factors including Granulocyte Colony- Stimulating Factor (G-CSF), PEGylated G-CSF or Granulocyte Macrophage Colony- Stimulating Factor GM CSF is not allowed in this trial. Therapeutic use of

G-CSF is allowed in subjects with Grade 3-4 febrile neutropenia. Consider a potential immunologic etiology.

- Thrombocytopenia: Transfusion of platelets may be used if clinically indicated. Immune thrombocytopenia purpura (ITP) should be ruled out before initiation of platelet transfusion.
- Anti-infectives: Subjects with a documented infectious complication should receive oral or IV antibiotics or other anti-infective agents as considered appropriate by the treating Investigator for a given infectious condition, according to standard institutional practice.
- Adverse event with a potential immunologic etiology (irAE): identification, evaluation and management of adverse experiences of a potential immunologic etiology. Depending on the type and severity of an irAE, oral or intravenous treatment with a corticosteroid should be considered, in addition to appropriate symptomatic treatment of a given condition (see Section 5.6 for management algorithms). These are also considered AEs of special interest (AESI) and should be reported to the Sponsor per Section 7.2.2.2.

5.5.2. Prohibited and/or Restricted Treatments

As stated in the exclusion criteria (Section 4.3), subjects must not have had chemotherapy, radiotherapy (other than palliative bone-directed radiotherapy, as described in Section 5.5.1), major surgery, or received another investigational agent within 28 days before the start of study treatment.

Subjects are prohibited from receiving the following therapies and treatments during the Screening and Treatment periods of this trial:

- Immunotherapy not specified in this protocol.
- Chemotherapy.
- Investigational agents other than AGEN2034.
- Surgery for symptom management or tumor control.
- Growth factors (granulocyte colony-stimulating factor or granulocyte macrophage colony- stimulating factor). Exception: Erythropoietin and darbepoietin alpha may be prescribed at the investigator's discretion. Therapeutic use of G-CSF is allowed in subjects with Grade 3 or 4 febrile neutropenia.
- Radiation therapy for tumor control.
- Glucocorticoids for any purpose other than to modulate symptoms from an irAE, or for use as a pre-medication in subjects with a known history of an IV contrast allergy administered as part of computed tomography (CT) radiography.

Note: Replacement doses of corticosteroids (for example, prednisone 5-7.5 mg daily) are permitted while on study.

Note: Use of inhaled or topical corticosteroid is permitted.

- Bisphosphonates and/or receptor activator of nuclear factor kappa-B ligand (RANKL) inhibitor therapies cannot be initiated after informed consent has been signed. These therapies may be continued IF treatment with an agent from one of these two classes was initiated PRIOR to signing informed consent.
- Subjects who, in the assessment by the investigator, require the use of any of the aforementioned treatments for clinical management should be removed from the trial.
- Subjects may receive other medications that the investigator deems to be medically necessary.
- Medications listed in the Exclusion Criteria are prohibited in this trial.
- There are no prohibited therapies during the Post-Treatment Follow-up Phase

5.5.3. Other Restrictions and Precautions

The following non-drug therapies must not be administered or performed during the study (and within 28 days before the start of trial treatment):

- Major surgery (excluding prior diagnostic biopsy).
- Herbal remedies with immunostimulating properties (e.g., mistletoe extract) or that are known to potentially interfere with major organ function (e.g., hypericin).
- Subjects should not abuse alcohol or other drugs during the study.

5.6. Management of Immune-related Adverse Events

Immuno-oncology agents such as AGEN2034 are associated with irAEs. Early recognition and management of irAEs may mitigate severe toxicity. Investigators should also monitor subjects closely for potential irAEs, which may manifest at the earliest after weeks of treatment. 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 immune related AEs 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 study drug. Particular attention should be paid to AEs that may be suggestive of potential irAEs as outlined below.

Immune-related AEs are considered are considered AESIs and should be reported to the Sponsor per Section 7.2.2.2.

5.6.1. Dermatological Immune-related Adverse Events

Rule out non-inflammatory causes, if non-inflammatory cause is identified, treat accordingly and continue therapy per protocol.

Table 4: Dermatological Immune-related Adverse Event Management Algorithm

Dermatological Immune-related Adverse Events		
Grade of Rash (NCI CTCAE v4.03)	**Management**	**Follow-Up**
Grade 1–2 Covering ≤30% body surface area.	• Symptomatic therapy (e.g., antihistamines, topical corticosteroids). • Continue AGEN2034 therapy per protocol.	• If persists >1 to 2 weeks or recurs: Consider skin biopsy. • Delay AGEN2034 therapy. • Consider 0.5–1 mg/kg/day methylprednisolone IV or oral equivalent. Once improving, taper corticosteroids over at least 1 month; consider prophylactic antibiotics for opportunistic infections; and resume AGEN2034 therapy per protocol. • **If worsens:** treat as Grade 3–4.
Grade 3–4 Covering >30% body surface area; life-threatening consequences.	• Delay or discontinue AGEN2034 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 at least 1 month; add prophylactic antibiotics for opportunistic infections. • Resume AGEN2034 therapy per protocol.

5.6.2. Gastrointestinal Immune-related Adverse Events

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 5: Gastrointestinal Immune-related Adverse Event Management Algorithm

Gastrointestinal Immune-related Adverse Events		
Severity of Diarrhea/Colitis (NCI CTCAE v4.03)	**Management**	**Follow-Up**
Grade 1 Diarrhea: <4 stools/day over baseline. Colitis: asymptomatic.	• Continue AGEN2034 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 AGEN2034 therapy per protocol. • Symptomatic treatment.	• **If improves to Grade 1:** resume AGEN2034 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 at least 1 month; consider prophylactic antibiotics for opportunistic infections; resume AGEN2034 therapy per protocol. • If worsens or persists >3 to 5 days with oral corticosteroids: treat as Grade 3–4.
Grade 3 to 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 AGEN2034 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 at least 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.

5.6.3. Pulmonary Immune-related Adverse Events

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 6: Pulmonary Immune-related Adverse Event Management Algorithm

Pulmonary Immune-related Adverse Events		
Grade of Pneumonitis (NCI CTCAE v4.03)	**Management**	**Follow-Up**
Grade 1 Radiographic changes only.	• Consider delay of AGEN2034 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 AGEN2034 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 at least 1 month, then resume AGEN2034 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 AGEN2034 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 at least 6 weeks. • **If not improving after 48 hours or worsening:** add additional immunosuppression (e.g., infliximab, cyclophosphamide, IV immunoglobulin, mycophenolate mofetil).

5.6.4. Hepatic Immune-related Adverse Events

Rule out non-inflammatory causes, if non-inflammatory cause is identified, treat accordingly and continue therapy per protocol. Consider imaging for obstruction.

Table 7: Hepatic Immune-related Adverse Event Management Algorithm

Hepatic Immune-related Adverse Events		
Grade of Liver Test Elevation (NCI CTCAE v4.03)	**Management**	**Follow-Up**
Grade 1 AST or ALT >ULN to 3 x ULN and/or total bilirubin >ULN to 1.5 x ULN.	• Continue AGEN2034 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.	• Delay AGEN2034 therapy per protocol. • Increase frequency of monitoring to every 3 days. • If subject has concurrent AST or ALT > 3 x ULN AND total bilirubin > 2 x ULN, Discontinue AGEN2034 therapy per protocol.	• **If returns to baseline:** resume routine monitoring; resume AGEN2034 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 at least 1 month, consider prophylactic antibiotics for opportunistic infections, and resume AGEN2034 therapy per protocol.
Grade 3–4 AST or ALT >5 x ULN and/or total bilirubin >3 x ULN.	• Discontinue AGEN2034 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 over at least 1 month. • **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.

*The recommended starting dose for Grade 4 hepatitis is 2 mg/kg/day methylprednisolone IV.

5.6.5. Endocrine Immune-related Adverse Events

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 8: Endocrine Immune-related Adverse Event Management Algorithm

Endocrine Immune-related Adverse Events		
Endocrine Disorder	**Management**	**Follow-Up**
Asymptomatic thyroid-stimulating hormone (TSH) abnormality	• Continue AGEN2034 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 (fT4) at subsequent cycles as clinically indicated; consider endocrinology consult.	
Symptomatic endocrinopathy	• Evaluate endocrine function. • Consider pituitary scan. • **Symptomatic with abnormal lab/pituitary scan:** delay AGEN2034 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 wk/MRI in 1 month.	• **If improves (with or without hormone replacement):** taper corticosteroids over at least month and consider prophylactic antibiotics for opportunistic infections. • Resume AGEN2034 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 AGEN2034 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.	

5.6.6. Renal Immune-related Adverse Events

Rule out non-inflammatory causes, if non-inflammatory cause is identified, treat accordingly and continue therapy per protocol.

Table 9: Renal Immune-related Adverse Event Management Algorithm

Renal Immune-related Adverse Events		
Grade of Creatinine Elevation (NCI CTCAE v4.03)	**Management**	**Follow-Up**
Grade 1 Creatinine > upper limit of normal (ULN) and > than baseline but ≤ 1.5x baseline.	• Continue AGEN2034 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 > 1.5x baseline to ≤ 6x ULN.	• Delay AGEN2034 therapy per protocol. • Monitor creatinine every 2-3 days • 0.5 to 1.0 mg/kg/day methylprednisolone IV or oral equivalent. • Consider renal biopsy	• **If returns to Grade 1:** taper corticosteroids over at least 1 month, consider prophylactic antibiotics for opportunistic infections, and resume AGEN2034 therapy and routine creatinine monitoring per protocol. • If elevations persist > 7 days or worsen: treat as Grade 4.
Grade 4 Creatinine > 6x ULN.	• Discontinue AGEN2034 therapy per protocol. • Monitor creatinine daily. • 1.0 to 2.0 mg/kg/day methylprednisolone IV or IV equivalent. • Consult nephrologist. • Consider renal biopsy	• **If returns to Grade 1:** taper corticosteroids over at least 1 month and add prophylactic antibiotics for opportunistic infections.

5.6.7. Neurological Immune-related Adverse Events

Rule out non-inflammatory causes, if non-inflammatory cause is identified, treat accordingly and continue therapy per protocol.

Table 10: Neurological Immune-related Adverse Event Management Algorithm

Neurological Immune-related Adverse Events		
Grade of Neurological Toxicity (NCI CTCAE v4.03)	**Management**	**Follow-Up**
Grade 1 Asymptomatic or mild symptoms; intervention not indicated.	• Continue AGEN2034 therapy per protocol.	• Continue to monitor subject. • **If worsens:** treat as Grade 2 or Grade 3–4.
Grade 2 Moderate symptoms; Limiting instrumental activities of daily life (ADL).	• Delay AGEN2034 therapy per protocol. • Treat symptoms per local guidelines. • Consider 0.5 to 1.0 mg/kg/day methylprednisolone IV or oral equivalent.	• **If returns to baseline:** resume AGEN2034 therapy per protocol. • **If worsens**: treat as Grade 3-4.
Grade 3-4 Severe symptoms; Limiting self-care activities of daily life; Life-threatening.	• Discontinue AGEN2034 therapy per protocol. • Obtain neurology consult. • Treat symptoms per local guidelines. • 1.0 to 2.0 mg/kg/day methylprednisolone IV or IV equivalent. • Add prophylactic antibiotics for opportunistic infections.	• **If improves to Grade 2:** taper corticosteroids over at least 1month. • **If worsens or atypical presentation:** consider IV immunoglobulin or other immunosuppressive therapies per local guidelines.

6. TRIAL ASSESSMENTS AND PROCEDURES

6.1. Phase 1 Schedules of Assessments and Procedures

The assessments and procedures to be performed in Phase 1 are shown in Table 11 for Part A1 and in Table 12 for PartA2.

Table 11: Phase 1 Part A1 — Schedule of Assessments and Procedures

	Screening	Treatment Phase (2-week cycles)								End of Treatment		Follow-up[1]		
		Cycle 1			Cycle 2			Every Subsequent Odd Cycle	Every Subsequent Even Cycle	Discontinuation Visit	Safety Visit	Visit 1	Visit 2	Visits 3 and 4
Visits Schedule (days)		1	2	8	1	2	8	1	1	At Discontinuation	4 w from last dose	3 m from last dose	6 m from last dose	3 m from last visit
Schedule Window (days) [2]		–3/+1			–3/+1			–3/+1	–3/+1	≤ 7	± 7	± 7	± 7	± 7
Administrative Procedures	<-42 days													
Informed consent	X													
Review of inclusion / exclusion criteria	X	X												
Issue Emergency Medical Support and Subject Card	X													
Review of medical history and demographics	X													
Review of baseline symptoms	X	X												
Review of prior and concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Cancer disease details and prior treatment	X													
Subsequent antineoplastic therapy status										X	X	X	X	X
Clinical Procedures / Assessments	<-7 days													
Review AEs[3]		X	X	X	X	X	X	X	X	X	X	X	X	X
Full Physical Examination	X									X				
Focused Physical Examination		X					X	X	X		X	X	X	X
Vital Signs and Weight	X	X					X	X	X	X	X	X	X	X
12-lead ECG[4]	X	X			X			X		X	X			
ECOG Performance Status	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Imaging Assessments[5]	<-21 days													
Tumor Imaging	X	Every 6 weeks (±3 days) from first dose until discontinuation of study drug.												
Brain Imaging	X													

Continued on next page

	Screening	Treatment Phase (2-week cycles)								End of Treatment		Follow-up[1]		
		Cycle 1			Cycle 2			Every Subsequent Odd Cycle	Every Subsequent Even Cycle	Discontinuation Visit	Safety Visit	Visit 1	Visit 2	Visits 3 and 4
Visits Schedule (days)		1	2	8	1	2	8	1	1	At Discontinuation	4 w from last dose	3 m from last dose	6 m from last dose	3 m from last visit
Schedule Window (days)[2]		–3/+1			–3/+1			–3/+1	–3/+1	≤ 7	± 7	± 7	± 7	± 7
Central Laboratory Procedures / Assessments[6]	<-7 days													
Serum for PK and/or ADA Assays		X[7]	X[8]	X	X[7]	X[8]	X	X[9]	X[9]	X	X	X	X	
Plasma for Cytokine Assay		X[10]	X[8]		X[10]	X[8]								
Blood for Biomarkers (whole blood, PBMC, serum, and/or plasma)	X	X	X[8]	X	X	X[8]	X	X		X	X	X		
Local Laboratory Procedures / Assessments[11]	<-7 days													
Core serum chemistry[12]					X		X	X	X					
Full serum chemistry[13]	X									X	X	X		
Hematology tests[14]	X			X	X		X	X	X	X	X	X		
Coagulation tests[15]	X				X		X	X		X	X	X		
Endocrine function tests[16]	X				X		X	X		X	X	X		
Autoimmunity tests[17]	X													
Urinalysis[18]	X				X		X	X		X	X	X		
Serum pregnancy test	X[19]													
Urine pregnancy test		X[19]						X		X	X	X		
Study drug administration[20]														
AGEN2034		X			X			X	X					

ADA: anti-drug antibody; AEs: adverse events; d: day; ECG: electrocardiogram; ECOG: Eastern Cooperative Oncology Group; HPV: human papilloma virus; m: month; PBMC: peripheral blood mononuclear cell; PK: pharmacokinetics; w: week.

Note: Where applicable, assessments performed prior to treatment unless otherwise indicated.

[1] All subjects who discontinue treatment will have at least one Follow-up Visit at 3 months (± 7 days) from last dose of study drug. Subjects who discontinue due to disease progression and/or start of a new line of therapy will then end participation in the trial. Subjects who received the maximum administrations of the combination of AGEN2034; who have achieved a complete response (CR) according to RECIST 1.1; or who have discontinued treatment due to reasons other than disease progression and/or start of a new line of therapy will be in Follow-up for up to approximately 12 months after last dose of study drug or until disease progression and/or start of a new line of therapy. Every effort should be made to collect subject information on the start of new antineoplastic therapy, disease progression, and death.

[2] Treatment administration and associated procedures for that visit may be delayed for treatment-related AEs beyond the window and subsequent schedule adjusted accordingly.

[3] Adverse events will be documented from time of consent until the End-of-Treatment Safety Follow-up Visit, after which only treatment-related AEs will be documented through the Follow-up Period of up to 12 months after the last dose of study drug or until disease progression and/or initiation of a new line of therapy. DLTs will be assessed during the first 3 weeks of trial treatment for the first 3 subjects at each dose level.

[4] 12-lead ECG on Cycle 1 Day 1, before and 2 hours (-10 / + 20 min) after AGEN2034 administration; on subsequent cycles as indicated 2 hours (-10 / + 20 min) after AGEN2034 infusion or as indicated.
[5] The initial tumor imaging will be performed within 21 days prior to first dose. Scans performed as part of routine clinical management are acceptable for use as screening scan if they are of diagnostic quality and < -21 days prior to first dose; and brain MRI if <-21 days prior to first dose. For subjects with no previous history of brain metastases, screening brain imaging will need to be obtained; except for subjects with cervical cancer, cutaneous squamous-cell carcinoma, gastric/gastroesophageal junction cancer, head and neck squamous-cell carcinoma, ovarian cancer, prostate cancer, mesothelioma, or urothelial carcinoma, for whom this scan is necessary only if clinically indicated. MRI is the preferred brain imaging modality; however, CT is acceptable if an MRI is clinically contraindicated. On-study imaging will be performed every 6 weeks (+/- 3 days), or more frequently if clinically indicated. Imaging assessments will continue until disease progression per the investigator or until a new line of therapy is initiated. The timing of imaging assessments should follow calendar days and should not be adjusted for delays in treatment administration or for visits. The same imaging technique should be used in a subject throughout the trial. Additional imaging at Discontinuation Visit and Safety Follow-up Visit is not required provided imaging assessments have been performed per schedule.
[6] Unless otherwise specified, samples should be collected before treatment administration. Refer to the Laboratory Manual for instructions and additional information.
[7] Before administration of AGEN2034, and 30 (± 15) min, 2 hours (± 15 min), and 4 hours (± 15 min) post-administration of AGEN2034.
[8] At 24 (± 2) hours post-infusion of AGEN2034.
[9] Before and 1 hour (± 15 min) post-administration of AGEN2034.
[10] Before and 4 hours (± 15 min) post-administration of AGEN2034.
[11] For screening, laboratory tests should be performed within 7 days prior to the first dose of trial treatment. Unless otherwise specified, for treatment phase visits, laboratory tests may be collected up to 48 hours before visits and results must be available before treatment.
[12] Core serum chemistry: alkaline phosphatase, alanine aminotransferase (ALT), aspartate aminotransferase (AST), blood urea nitrogen (BUN)/total urea, calcium, chloride, creatinine, glucose, magnesium, phosphorus/phosphates, potassium, sodium, total bilirubin. Results must be available prior to dosing.
[13] Full serum chemistry: core serum chemistry and albumin, amylase, cholesterol, creatine kinase, C-reactive protein (CRP), gamma glutamyl transferase (GGT), lactate dehydrogenase (LDH), lipase, total protein, triglycerides, uric acid. Results must be available prior to dosing.
[14] Hematology tests: absolute eosinophil count, absolute lymphocyte count, absolute neutrophil count (ANC), hematocrit, hemoglobin, mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), mean corpuscular volume (MCV), platelet count, red blood cell (RBC), white blood cell (WBC) and differential count. Results must be available prior to dosing.
[15] Coagulation tests: activated partial thromboplastin time (aPTT), prothrombin time - international normalized ratio (INR). Results must be available prior to dosing.
[16] Endocrine function tests: adrenocorticotropic hormone (ACTH), follicle-stimulating hormone (FSH) (if applicable), free thyroxine (T4), thyroid-stimulating hormone (TSH). Results must be available prior to dosing.
[17] Autoimmunity tests: anti-nuclear antibody, rheumatoid factor.
[18] Urinalysis including blood, glucose, protein, specific gravity, and microscopic exam if abnormal. Results must be available prior to dosing.
[19] Serum β-human chorionic gonadotropin (β-HCG) pregnancy test for women of child bearing potential at screening within 72 hours of first treatment dose (if performed earlier in screening period then a urine pregnancy test may be performed prior to first dose); urine pregnancy test at all other indicated visits (centers where urine pregnancy testing is not routine may substitute with serum β-HCG pregnancy test). Results must be available prior to dosing.
[20] AGEN2034 should be administered over 60 minutes (-10/+20 min). Subjects must be observed for 2 hours post-infusion for infusion-related reaction. If administration of AGEN2034 is delayed due to an AE, treatment visits may be delayed beyond the window of 3 days and schedules for subsequent visits should be adjusted accordingly.

Table 12: Phase 1 Part A2 — Schedule of Assessments and Procedures

	Screening	Treatment Phase (3-week cycles)										End of Treatment		Follow-up[1]		
		Cycle 1				Cycle 2				Every Subsequent Odd Cycle	Every Subsequent Even Cycle	Discontinuation Visit	Safety Visit	Visit 1	Visit 2	Visits 3 and 4
Visits Schedule (days)		1	2	8	15	1	2	8	15	1	1	At Discontinuation	4 w from last dose	3 m from last	6 m from last	3 m from
Schedule Window (days)[2]		–3/+1				–3/+1				–3/+1	–3/+1	± 3	± 3	± 7	± 7	± 7
Administrative Procedures	<-42 days															
Informed consent	X															
Review of inclusion / exclusion criteria	X	X														
Issue Emergency Medical Support and Subject Card	X															
Review of medical history and demographics	X															
Review of baseline symptoms	X	X														
Review of prior and concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Cancer disease details and prior treatment	X															
Subsequent antineoplastic therapy status												X	X	X	X	X
Clinical Procedures / Assessments	<-7 days															
Review AEs[3]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Full Physical Examination	X											X				
Focused Physical Examination		X				X				X	X		X	X	X	X
Vital Signs and Weight	X	X				X				X	X	X	X	X	X	X
12-lead ECG[4]	X	X				X				X		X	X			
ECOG Performance Status	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Imaging Assessments[5]	<-21 days															
Tumor Imaging	X	Every 6 weeks (±3 days) from first dose until discontinuation of study drug.														
Brain Imaging	X															
Central Laboratory Procedures / Assessments[6]	<-7 days															
Serum for PK and/or ADA Assays		X[7]	X[8]	X	X	X[7]	X[8]	X	X	X[9]	X[9]	X	X	X	X	
Plasma for Cytokine Assay		X[10]	X[8]			X[10]	X[8]									
Blood for Biomarkers (whole blood, PBMC, serum, and/or plasma)	X	X	X[8]	X	X	X	X[8]	X	X	X		X	X	X		

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	Screening	Treatment Phase (3-week cycles)										End of Treatment		Follow-up[1]		
		Cycle 1				Cycle 2				Every Subsequent Odd Cycle	Every Subsequent Even Cycle	Discontinuation Visit	Safety Visit	Visit 1	Visit 2	Visits 3 and 4
Visits Schedule (days)		1	2	8	15	1	2	8	15	1	1	At Discontinuation	4 w from last dose	3 m from last	6 m from last	3 m from
Schedule Window (days) [2]		–3/+1				–3/+1				–3/+1	–3/+1	± 3	± 3	± 7	± 7	± 7
Local Laboratory Procedures / Assessments[11]	<-7 days															
Core serum chemistry[12]					X	X				X	X					
Full serum chemistry[13]	X											X	X	X		
Hematology tests[14]	X			X	X	X				X	X	X	X	X		
Coagulation tests[15]	X					X				X		X	X	X		
Endocrine function tests[16]	X					X				X		X	X	X		
Autoimmunity tests[17]	X															
Urinalysis[18]	X					X				X		X	X	X		
Serum pregnancy test	X[19]															
Urine pregnancy test		X[19]				X				X	X	X	X	X		
Study drug administration[20]																
AGEN2034		X				X				X	X					

Abbreviations: ADA: anti-drug antibody; AEs: Adverse Events; d: day; ECG: electrocardiogram; ECOG: Eastern Cooperative Oncology Group; HPV: human papilloma virus; m: month; PBMC: peripheral blood mononuclear cell; PK: pharmacokinetics; w: week.

Note: Where applicable, assessments performed prior to treatment unless otherwise indicated.

[1] All subjects who discontinue treatment will have at least one Follow-up Visit at 3 months (± 7 days) after last dose of study drug. Subjects who discontinue due to disease progression and/or start of a new line of therapy will then end participation in the trial. Subjects who received the maximum administrations of the combination of AGEN2034; who have achieved a complete response (CR) according to RECIST 1.1; or who have discontinued treatment due to reasons other than disease progression and/or start of a new line of therapy will be in Follow-up for up to approximately 12 months after last dose of study drug or until disease progression and/or start of a new line of therapy. Every effort should be made to collect subject information on the start of new antineoplastic therapy, disease progression, and death.

[2] Treatment administration and associated procedures for that visit may be delayed for treatment-related AEs beyond the window and subsequent schedule adjusted accordingly.

[3] Adverse events will be documented from time of consent until the End-of-Treatment Safety Follow-up Visit, after which only treatment-related AEs will be documented through the Follow-up Period of up to 12 months after the last dose of study drug or until disease progression and/or initiation of a new line of therapy. DLTs will be assessed during the first 3 weeks of trial treatment for the first 3 subjects at each dose level.

[4] 12-lead ECG on Cycle 1 Day 1 and 15, before and 2 hours (-10 / + 20 min) after AGEN2034 administration; on subsequent cycles as indicated 2 hours (-10 / + 20 min) after AGEN2034 infusion or as indicated.

[5] The initial tumor imaging will be performed within 21 days prior to first dose. Scans performed as part of routine clinical management are acceptable for use as screening scan if they are of diagnostic quality and <-21 days prior to first dose; and brain MRI if <-28 days prior to first dose. For subjects with no previous history of brain metastases, screening brain imaging will need to be obtained; except for subjects with cervical cancer, cutaneous squamous-cell carcinoma, gastric/gastroesophageal junction cancer, head and neck squamous-cell carcinoma, ovarian cancer, prostate cancer, mesothelioma, or urothelial carcinoma, for whom this scan is necessary only if clinically indicated. MRI is the preferred brain imaging modality; however, CT is acceptable if an MRI is clinically contraindicated. On-study imaging will be performed every 6 weeks (+/- 3 days), or more frequently if clinically indicated. Imaging assessments will continue

until disease progression per the investigator or until a new line of therapy is initiated. The timing of imaging assessments should follow calendar days and should not be adjusted for delays in treatment administration or for visits. The same imaging technique should be used in a subject throughout the trial. Additional imaging at Discontinuation Visit and Safety Follow-up Visit is not required provided imaging assessments have been performed per schedule.

[6] Unless otherwise specified, samples should be collected before treatment administration. Refer to the Laboratory Manual for instructions and additional information.

[7] Before administration of AGEN2034, and 30 (± 15) minutes, 2 hours (± 15 min), and 4 hours (± 15 min) post-administration of AGEN2034.

[8] At 24 (± 2) hours post-infusion of AGEN2034.

[9] Before and 1 hour (± 15 min) post-administration of AGEN2034.

[10] Before and 4 hours (± 15 min) post-administration of AGEN2034.

[11] For screening, laboratory tests should be performed within 7 days prior to the first dose of trial treatment. Unless otherwise specified, for treatment phase visits, laboratory tests may be collected up to 48 hours before visits and results must be available before treatment.

[12] Core serum chemistry: alkaline phosphatase, alanine aminotransferase (ALT), aspartate aminotransferase (AST), blood urea nitrogen (BUN)/total urea, calcium, chloride, creatinine, glucose, magnesium, phosphorus/phosphates, potassium, sodium, total bilirubin. Results must be available prior to dosing.

[13] Full serum chemistry: core serum chemistry and albumin, amylase, cholesterol, creatine kinase, C-reactive protein (CRP), gamma glutamyl transferase (GGT), lactate dehydrogenase (LDH), lipase, total protein, triglycerides, uric acid. Results must be available prior to dosing.

[14] Hematology tests: absolute eosinophil count, absolute lymphocyte count, absolute neutrophil count (ANC), hematocrit, hemoglobin, mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), mean corpuscular volume (MCV), platelet count, red blood cell (RBC), white blood cell (WBC) and differential count. Results must be available prior to dosing.

[15] Coagulation tests: activated partial thromboplastin time (aPTT), prothrombin time - international normalized ratio (INR). Results must be available prior to dosing.

[16] Endocrine function tests: adrenocorticotropic hormone (ACTH), follicle-stimulating hormone (FSH) (if applicable), free thyroxine (T4), thyroid-stimulating hormone (TSH). Results must be available prior to dosing.

[17] Autoimmunity tests: anti-nuclear antibody, rheumatoid factor.

[18] Urinalysis including blood, glucose, protein, specific gravity, and microscopic exam if abnormal. Results must be available prior to dosing.

[19] Serum β-human chorionic gonadotropin (β-HCG) pregnancy test for women of child bearing potential at screening within 72 hours of first treatment dose (if performed earlier in screening period then a urine pregnancy test may be performed prior to first dose); urine pregnancy test at all other indicated visits (centers where urine pregnancy testing is not routine may substitute with serum β-HCG pregnancy test). Results must be available prior to dosing.

[20] AGEN2034 should be administered over 60 minutes (-10/+20 min). Subjects must be observed for 2 hours post-infusion for infusion-related reaction. If administration of AGEN2034 is delayed due to an AE, treatment visits may be delayed beyond the window of 3 days and schedules for subsequent visits should be adjusted accordingly.

6.2. Phase 2 Schedule of Assessments and Procedures

The assessments and procedures for Phase 2 are summarized in Table 13 for PK, ADA, biomarkers, and pharmacogenomics assessments are shown in Table 14.

Table 13: Phase 2 — Schedule of Assessments and Procedures

	Screening	Treatment Phase (2-week cycles)								End of Treatment		Follow Up[1]			Survival Follow
		Cycle 1			Cycle 2			Every Subsequent Odd Cycle	Every Subsequent Even Cycle	Discontinuation Visit	Safety Visit	Visit 1	Visit 2	Visits 3 and 4	Telephone
Visits Schedule (days)		1	2	8	1	2	8	1	1	At Discontinuation	4 w from last dose	3 m from last	6 m from last	3 m from last visit	Every 2 months
Schedule Window (days) [3]		–3/+1			–3/+1			–3/+1	–3/+1	≤ 7	± 7	± 7	± 7	± 7	
Administrative Procedures	< -42 days														
Informed consent	X														
Review of inclusion / exclusion criteria	X	X													
Issue Emergency Medical Support and Subject Card	X														
Review of medical history and demographics	X														
Review of baseline symptoms	X	X													
Review of prior and concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Cancer disease details and prior treatment	X														
Subsequent antineoplastic therapy status										X	X	X	X	X	X
Survival status															X
Clinical Procedures / Assessments	< -7 days														
Review AEs[5]		X	X	X	X	X	X	X	X	X	X	X	X	X	
Full Physical Examination	X									X					
Focused Physical Examination		X					X	X	X		X	X	X	X	
Vital Signs and Weight	X	X					X	X	X	X	X	X	X	X	
12-lead ECG[6]	X	X			X			X	X	X	X	X			
Expanded ECG Evaluation[6a]		X	X						See [6a]						
ECOG Performance Status	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Biopsy & Imaging Assessments	< -21days														
Tumor Biopsy [4]	X								See [4]						
Tumor Imaging[7]	X	Every 6 weeks (± 3 days) from first dose until discontinuation of study drug													
Brain Imaging[8]	X														
Blood Samples for PK, ADA, Biomarkers, and		See Table 14and Laboratory Manual													

Continued on next page

	Screening	Treatment Phase (2-week cycles)								End of Treatment		Follow Up[1]			Survival Follow
		Cycle 1			Cycle 2			Every Subsequent Odd Cycle	Every Subsequent Even Cycle	Discontinuation Visit	Safety Visit	Visit 1	Visit 2	Visits 3 and 4	Telephone
Visits Schedule (days)		1	2	8	1	2	8	1	1	At Discontinuation	4 w from last dose	3 m from last	6 m from last	3 m from last visit	Every 2 months
Schedule Window (days)[3]		–3/+1			–3/+1			–3/+1	–3/+1	≤ 7	± 7	± 7	± 7	± 7	
Local Laboratory Procedures / Assessments[14]	< -7 days														
Core serum chemistry[15]					X			X	X						
Full serum chemistry[16]	X									X	X	X			
Hematology tests[17]	X			X	X			X	X	X	X	X			
Coagulation tests[18]	X				X			X		X	X	X			
Endocrine function tests[19]	X				X			X		X	X	X			
Urinalysis[21]	X				X			X		X	X	X			
Serum pregnancy test	X[22]														
Urine pregnancy test		X[22]						X		X	X	X			
Study drug administration[23]															
AGEN2034		X			X			X	X						

Abbreviations: ADA: anti-drug antibody; AEs: Adverse Events; d: day; ECG: electrocardiogram; ECOG: Eastern Cooperative Oncology Group; IERC: Independent Endpoint Review Committee; m: month; PBMC: peripheral blood mononuclear cell; PGx: pharmacogenomics; PK: pharmacokinetics; w: week.

Note: Where applicable, assessments performed prior to treatment unless otherwise indicated.

[1] All subjects who discontinue treatment will have at least one Follow-up Visit at 3 months (± 7 days) after last dose of study drug. Subjects who discontinue due to disease progression and/or start of a new line of therapy will then end participation in the trial. Subjects who received the maximum administrations of the combination of AGEN2034; who have achieved a complete response (CR) according to RECIST 1.1; or who have discontinued treatment due to reasons other than disease progression and/or start of a new line of therapy will be in Follow-up for up to approximately 12 months after last dose of study drug or until disease progression and/or start of a new line of therapy. Every effort should be made to collect subject information on the start of new antineoplastic therapy, disease progression and death.

[2] After the first Follow-up Visit, subjects that present(ed) with progressive disease and/or start new line of therapy will move into Survival Follow-up and should be contacted by telephone every 2 months for up to 12 months after last dose of study drug to assess for survival status. Post-study treatments and the subject's response to them will also be collected.

[3] Treatment administration and associated procedures for that visit may be delayed for treatment related AEs beyond the window and subsequent schedule adjusted accordingly.

[4] Tumor tissue for biomarker analysis from a biopsy of a tumor lesion not previously irradiated must be available for PD-L1 expression and HPV evaluation. Only biopsies obtained at the time of or after the diagnosis of metastatic disease will be evaluated for PD-L1 expression. 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. FOR SUBSEQUENT EVEN CYCLES: An **optional biopsy** is desired at Cycle 4 ONLY and, if provided, should be collected on Day 1 ***before*** AGEN2034 administration.

[5] Adverse events will be documented from time of consent up until 90 days after the last dose of study drug or the start of a new anticancer treatment, whichever comes first. Following the End-of-Treatment Safety Follow-up Visit, only treatment-related AEs will be documented through the Treatment Follow-up Period of up to 12 months after the last dose of study drug or until disease progression and/or initiation of a new line of therapy.

[6] 12-lead ECG on Cycle 1 Day 1, before AGEN2034 infusion starts and 2 hours (-10/+ 20 min) after infusion ends; on subsequent cycles as indicated 1 hour (-10 / + 20 min) after infusion ends or at visits indicated.

[6a] (At selected sites only) Expanded ECG Evaluation (triplicate tracings; see Section 6.4.3.4): 12-lead ECGs will be taken for Cycles 1 and 4 on Day 1 within 15 min (± 10 min) before the Predose PK sample and within 15 min (± 10 min) before the 30-min-after-end-of-infusion PK sample, and on Day 2 within 15 min (± 10 min) before the 24-h-after-end-of-infusion PK sample. ECGs (12-lead, triplicate tracings) will also be taken for every subsequent 8th cycle for up to 1 year (approximately every 4 mo [in Cycles 12, 20, and 28]) on Day 1 within 15 min (± 10 min) before the Predose PK sample and within 15 min (± 10 min) before the 30-min-after-end-of-infusion PK sample.

[7] The initial tumor imaging will be performed within 21 days prior to first dose. Scans performed as part of routine clinical management are acceptable for use as screening scan if they are of diagnostic quality and < 21 days prior to first dose. On-study imaging will be performed every 6 weeks (± 3 days), or more frequently if clinically indicated, and submitted for central review. Tumor assessments should be performed every 6 weeks (± 3 days) from first treatment dose until RECIST 1.1-defined disease progression has been established by the blinded independent central radiology review. Furthermore, if study drug is discontinued as a result of unacceptable toxicity, tumor assessments should continue every 6 weeks (± 3 days) until RECIST1.1-defined disease progression has been established by the blinded independent central radiology review. Imaging is required every 6 weeks (± 3 days) for those subjects with PD who remain on AGEN2034 per protocol exemption (Section 5.4.5) until treatment is discontinued.

[8] Screening brain imaging is only necessary if clinically indicated. MRI is the preferred brain imaging modality; however, CT is acceptable if an MRI is clinically contraindicated.

[9-13] Removed.

[14] For screening, laboratory tests should be performed within 7 days prior to the first dose of trial treatment. Unless otherwise specified, for treatment phase visits, laboratory tests may be collected up to 48 hours before visits and results must be available before treatment.

[15] Core serum chemistry: alkaline phosphatase, alanine aminotransferase (ALT), aspartate aminotransferase (AST), blood urea nitrogen (BUN)/total urea, calcium, chloride, creatinine, glucose, magnesium, phosphorus/phosphates, potassium, sodium, total bilirubin. Results must be available prior to dosing.

[16] Full serum chemistry: core serum chemistry and albumin, amylase, cholesterol, creatine kinase, C-reactive protein (CRP), gamma glutamyl transferase (GGT), lactate dehydrogenase (LDH), lipase, total protein, triglycerides, uric acid. Results must be available prior to dosing.

[17] Hematology Tests: absolute eosinophil count, absolute lymphocyte count, absolute neutrophil count (ANC), hematocrit, hemoglobin, mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), mean corpuscular volume (MCV), platelet count, red blood cell (RBC), white blood cell (WBC) and differential count. Results must be available prior to dosing.

[18] Coagulation Tests: activated partial thromboplastin time (aPTT), prothrombin time - international normalized ratio (INR). Results must be available prior to dosing.

[19] Endocrine function tests: adrenocorticotropic hormone (ACTH), follicle-stimulating hormone (FSH) (for postmenopausal women if applicable), free thyroxine (T4), thyroid-stimulating hormone (TSH). Results must be available prior to dosing.

[20] Removed.

[21] Urinalysis including blood, glucose, protein, specific gravity, and microscopic exam if abnormal. Results must be available prior to dosing.

[22] Serum β-human chorionic gonadotropin (β-HCG) pregnancy test for women of child bearing potential at screening within 72 hours of first treatment dose (if performed earlier in screening period then a urine pregnancy test may be performed prior to first dose); urine pregnancy test at all other indicated visits. Results must be available prior to dosing.

[23] AGEN2034 should be administered over 60 min (-10/+20 min). For the first 2 cycles, subjects must be observed for 2 hours post-infusion for infusion-related reaction; for subsequent cycles subjects must be observed for at least 1 hour post-infusion for infusion-related reaction. If administration of AGEN2034 is delayed due to an AE, treatment visits may be delayed beyond the window of 3 days and schedules for subsequent visits should be adjusted accordingly.

Table 14: Phase 2 — Blood Sampling for Pharmacokinetic, Pharmacodynamic, Genetic, and Other Assessments

Visit or Cycle	Day	For PK (see NOTE)	Additional Time Points for Rich PK Subset	For ADA	For PBMC	For [redacted]	For PGx
Screening	—	—	—	—	—	—	X[1]
Cycle 1	1	Predose[2] 30 min (± 15 min)[3]	—	Predose[2]	Predose[2]	Predose[2]	—
	2	—	24 h (± 60 min)[4]	—	—	—	—
	8	—	168 h (± 4 h)[4]	—	—	—	—
Cycle 2	1	Predose[2]	—	Predose[2]	Predose[2]	Predose[2]	—
Cycle 3	1	Predose[2]	—	Predose[2]	Predose[2]	—	—
Cycle 4	1	Predose[2] 30 min (± 15 min)[3]	—	Predose[2]	Predose[2]	Predose[2]	—
	2	—	24 h (± 60 min)[4]	—	—	—	—
	8	—	168 h (± 4 h)[4]	—	—	—	—
Cycles 5, 6, 12, 18, 24	1	—	—	Predose[2]	—	—	—
Discontinuation	—	X	—	X	X	X	—
Safety Follow-up Visit	4 wk after last dose	X	—	X	—	—	—
Follow-up Visit	3 mo after last dose	X	—	X	—	—	—

Abbreviations: ADA: antidrug antibody; [redacted] DNA: deoxyribonucleic acid; h: hour(s); mo: month; min: minute(s); PBMC: peripheral blood mononuclear cell; PGx: pharmacogenomics(s); PK: pharmacokinetic(s); wk: week(s).

[1] Blood sample for PGx is collected only if an 'optional' PGx consent is signed.

[2] Predose samples will be collected within 30 minutes before starting the AGEN2034 infusion.

[3] Blood samples collected on Day 1 at 30 (± 15) minutes after the ***end*** of infusion

[4] As of Amendment 5 (27 September 2019), additional rich PK sampling will be collected in a subset of approximately 20 subjects in selected sites. Rich PK sampling will occur on Days 2 and 8 of Cycles 1 and 4 at 24 hours (± 60 min) and 168 (± 4) hours, respectively, after the ***start*** of the infusion.

NOTE: It is important to record all infusion start dates/times, infusion end dates/times, infusion interruption(s) start and end dates/times, infusion flush end dates/times, and blood sample dates/times completely and accurately (to the nearest minute). Blood for the 30-minute postdose PK samples should ***never*** be taken during the infusion and should be drawn at least 15 min after the end of infusion.

6.3. Visit Requirements

6.3.1. Screening

Visit requirements are outlined for Phase 1 in Section 6.1 and for Phase 2 in Section 6.2. Specific procedure-related details are provided in Section 6.4.

6.3.2. Treatment Phase

Visit requirements are outlined for Phase 1 in Section 6.1 and for Phase 2 in Section 6.2. Specific procedure-related details are provided in Section 6.4.

Subject should continue to receive all assessments as defined in the Treatment phase of the Schedule of Assessments while they are actively receiving treatment.

6.3.3. End-of-Treatment Visits

Visit requirements are outlined for Phase 1 in Section 6.1 and for Phase 2 in Section 6.2. Specific procedure-related details are provided in Section 6.4.

6.3.3.1. Discontinuation Visit

The Discontinuation Visit should occur at the time study drug is discontinued for any reason. If the Discontinuation Visit occurs 4 weeks from the last dose of study drug, at the time of the mandatory Safety Follow up Visit, procedures do not need to be repeated. Procedures at the time of discontinuation are detailed in Section 6.3.3.2, Safety Follow up Visit.

6.3.3.2. Safety Follow-up Visit

The mandatory Safety Follow-Up Visit should be conducted for all subjects approximately 4 weeks 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 adverse drug reaction (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.

6.3.4. Follow-up Phase

In Phase 1, subjects who discontinue treatment will be followed for up to 12 months after the last dose of study drug or until death, withdrawal of consent, or becoming lost to follow-up.

In Phase 2, subjects who discontinue treatment will be followed for up to 24 months after the last dose of study drug or until death, withdrawal of consent, or becoming lost to follow-up.

Follow-up visits and survival follow-up requirements are outlined in Section 6.1 and Section 6.2, respectively, for Phase 1 and Phase 2. Specific procedure-related details are provided in Section 6.4.

6.3.4.1. Follow-up Visits

All subjects who discontinue treatment will have at least one post-treatment visit at 3 months (± 7 days) after last dose of study drug.

For both study Phases, subjects who received the maximum administrations of AGEN2034, who have achieved a complete response (CR) according to RECIST 1.1, or who have discontinued treatment due to reasons other than disease progression and/or start of a new line of therapy should be have Follow-up Visits every 3 months for up to 12 months after last dose of study drug (see schedules in Section 6.1) or until disease progression and/or start of a new line of therapy.

For Phase 2 (see schedule in Section 6.2), subjects who present with progressive disease and/or start a new line of therapy will move into the Survival Follow-up Phase. Every effort should be made to collect subject information on the start of new antineoplastic therapy, disease progression and death.

6.3.4.2. Survival Follow-up (Phase 2 only)

There is no survival follow-up for Phase 1.

For subjects in Phase 2, after the first Treatment Follow-up Visit, subjects with progressive disease and/or who start new line of therapy will move into Survival Follow-up. Subjects should be contacted by telephone to assess for survival status every 2 months for up to 12 months after their last dose of study drug.

6.4. Trial Procedures

The schedules of events in Section 6.1 and Section 6.2 summarize the trial procedures to be performed at each visit in Phase 1 and 2, respectively. Individual trial procedures are described in detail below. It may be necessary to perform these procedures at unscheduled time points if deemed clinically necessary by the investigator.

Furthermore, additional evaluations/testing may be deemed necessary by the investigator and or the Sponsor for reasons related to subject safety. In these cases, such evaluations/testing will be performed in accordance with clinical judgement.

6.4.1. Administrative Procedures

6.4.1.1. Informed Consent

The investigator or qualified designee must obtain documented consent from each potential subject prior to participating in the clinical trial and for optional pharmacogenomics research.

6.4.1.2. General Informed Consent

Consent must be documented by the subject's dated signature along with the dated signature of the person conducting the consent discussion. A copy of the signed and dated consent form should be given to the subject before participation in the trial.

The investigator is responsible for ensuring that a careful and thorough informed consent procedure is implemented before a subject enters the study and at any time during the study should ICF changes be introduced. This includes, but is not limited to: (1) allowing ample time

for this review by the subject; (2) ensuring that qualified medical personnel are available to directly answer questions that a subject may have; (3) ensuring that each potential study subject understands that his or her medical treatment will not be otherwise affected based on the decision whether or not to participate in the study, that his or her participation is completely voluntary, and that he or she can opt to stop participation in the study at any time for any reason; and (4) ensuring a full copy of the signed ICF is given to the subject to take home for his or her medical records. The process for obtaining informed consent should also be noted in the subject's source documentation.

The initial informed consent form, any subsequent revised written informed consent form, and any written information provided to the subject must receive the IRB/ERC's approval/favorable opinion in advance of use. The subject should be informed in a timely manner if new information becomes available that may be relevant to the subject's willingness to continue participation in the trial. The communication of this information will be provided and documented via a revised consent form or addendum to the original consent form that captures the subject's dated signature or by the subject's legally acceptable representative's dated signature.

The informed consent will adhere to IRB/ERC requirements, applicable laws and regulations and Sponsor requirements.

6.4.1.3. Consent for Pharmacogenomics Assessment (optional)

Participation in the pharmacogenomics portion of the trial is optional and requires separate informed consent. 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.

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 subject, answer all of his/her questions, and obtain written informed consent before performing any procedure related to pharmacogenomics assessment. A copy of the informed consent will be given to the subject.

6.4.1.4. Review of Inclusion and Exclusion Criteria

All inclusion and exclusion criteria will be reviewed by the investigator or qualified designee to ensure that the subject qualifies for the trial.

6.4.1.5. Emergency Medical Support and Subject Card

All subjects will be given an Emergency Medical Support and Subject Card identifying them as participants in a research trial. The card will contain trial site contact information (including direct telephone numbers) to be utilized in the event of an emergency. The investigator or qualified designee will provide the subject with an Emergency Medical Support and Subject Card immediately after the subject provides written informed consent.

6.4.1.6. Medical History

A medical history will be obtained by the investigator or qualified designee. Medical history will include all active conditions; history of hepatitis B virus (HBV), hepatitis C virus (HCV), HIV and/or HPV; and any condition diagnosed within the prior 10 years that are considered to be clinically significant by the Investigator. Medical history will also include an assessment of smoking history.

History of the cancer under study will be recorded ***separately*** (see Section 6.4.1.9); all other cancer history should be captured in the medical history.

For subjects in Phase 2, in addition, record any prior cancer other than cervical cancer even if diagnosed greater than 10 years prior to Visit 1.

6.4.1.7. Review of Baseline Symptoms

Baseline symptoms associated with the disease under study will be assessed for each subject at screening. Baseline symptoms will be Graded and recorded according to NCI CTCAE Version 4.03. Baseline symptoms will be characterized in terms including seriousness, causality to previous treatment, toxicity grading, and action(s) taken if any.

6.4.1.8. Review of Prior and Concomitant Medications

6.4.1.8.1. Prior Medications

All medication — other than chemotherapy — taken by the subject within 30 days before starting the trial will be recorded. In addition, all treatments for a prior cancer other than current cancer will be recorded, even if taken greater than 30 days prior to Visit 1.

Prior treatments for the current cancer will be recorded ***separately*** (see Section 6.4.1.9) and not listed as a prior medication.

6.4.1.8.2. Concomitant Medications

Any medication taken by the subject during the trial, from the date of consent through the 30-day Safety Follow-up Visit, will be recorded. After the Safety Follow-up Visit, record all medications related to reportable SAEs and AESIs as defined in Section 7.2.2.2.

6.4.1.9. Cancer Disease Details and Prior Treatment

Obtain current cancer disease details and prior treatment for all subjects including:

- Detailed history of the tumor at diagnosis *and* study entry including histopathological diagnosis, grading, and staging in accordance with the AJCC-8 Tumor Node Metastasis (TNM) classification (Amin et al 2017).
- All therapy used for prior treatment of the disease under study (including but not limited to surgery, radiotherapy [including total radiation dose received and general treatment field], and any systemic treatment) – and for each therapy, complete dosing schedule and their corresponding best response.
- Any other conditions treated with radiation therapy or and any systemic treatment.

- Current cancer signs and symptoms, and side effects from current and/or previous anticancer treatments.
- Current cancer disease status.
- Relevant somatic or germline mutations detected.
- Chronic viral infection status, if available.
- Human epidermal growth factor receptor 2 (HER2) status, if available.
- Smoking history.
- Tumor markers, including but not limited to, molecular/genetic or immunohistochemistry markers (such as PSA, CA125, AFP, *BRCA*, PD-L1 status, etc.), if applicable and available.
- HPV status, if available.

6.4.1.9.1. Subsequent Antineoplastic Therapy

The investigator or qualified designee will review all new antineoplastic therapy initiated after the last dose of study drug. If a subject initiates a new antineoplastic therapy within 4 weeks after the last dose of study drug, the Safety Follow-up Visit must occur before the first dose of the new therapy.

Subjects in Phase 2 will move into survival follow-up once new antineoplastic therapy has been initiated.

6.4.1.9.2. Survival Follow-up (Phase 2 only)

Once a subject in Phase 2 moves into the survival follow-up period, they should be contacted by telephone every 2 months for up to 12 months after their last dose of study drug. (See also Section 6.3.4.2.)

6.4.1.10. Assignment of Subject Trial Number

After a subject signs an informed consent form, the subject will be assigned a unique, sequential subject number. Once a number is assigned, it cannot be reassigned if the original subject is found to be ineligible or withdraws consent.

6.4.1.11. Trial Compliance

Any delay from the protocol-specified AGEN2034 dosing frequency which is due to toxicity and which results in > 6 weeks between AGEN2034 doses requires consultation between the investigator and the Sponsor, and written documentation of the collaborative decision on subject management.

Administration of trial medication will be witnessed by the investigator and/or trial staff. The total volume of trial treatment infused will be compared to the total volume prepared to determine compliance with each dose administered.

Any reason for noncompliance should be documented. Noncompliance is defined as a subject missing >1 cycle of study treatment *for non-medical reasons*. If 1 cycle was missed and the

interval between the subsequent treatment cycle and the last administered treatment cycle is longer than 4 weeks for non-medical reasons, criteria for insufficient compliance are met.

6.4.2. Tissue Collection and Tumor Biomarker Assessment

For Phase 2, expression of PD-L1 and HPV status will be among the exploratory biomarkers assessed in tumor samples from archival tissues or biopsies.

6.4.2.1. Tissue Collection

Tumor tissue for biomarker analysis from a biopsy of a tumor lesion not previously irradiated must be available for biomarker assessments including but not limited to PD-L1 expression and HPV evaluation. Biomarker assessment will be performed on the most recent FFPE biopsy of a tumor lesion, collected either at the time of or after the diagnosis of metastatic disease has been made, and from a site not previously irradiated. An optional tumor biopsy will be collected at Cycle 4, Day 1 (-3/+1 day) if clinically feasible to assess pharmacodynamic effects of the drug on tumor microenvironment.

- Tissue from needle or excisional biopsy or from resection is required.
- An FFPE tumor tissue block that is less than 4 years old should be provided. If an archival tumor-containing FFPE tissue block is not available, freshly cut FFPE slides (within 10 days) are acceptable for submission to the sponsor. If an FFPE tumor tissue block or freshly cut slides are not available, fresh biopsy will be required, and an FFPE tumor tissue block should be provided. If a block or freshly cut FFPE slides are not available, discuss with the study Medical Monitor prior to patient enrollment.
- Fine needle aspirates, endobronchial ultrasound (EBUS), or cell blocks are not acceptable.

If limited tissue is available, preference will be given to PD-L1 assessment.

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 that is less than 4 years old
2. If an archival tumor-containing FFPE tissue block is not available, a fresh biopsy will be required, and an FFPE tumor tissue block should be provided.
3. Priority: 25 freshly cut tumor tissue FFPE slides (within 10 days) must be provided. Minimum 15 slides are required. The FFPE slides must be freshly cut and submitted to the sponsor within 10 days from the slide sectioning date. All submitted slides must be cut from a single tumor tissue sample specimen. The site must ensure that the newly obtained tissue sample collection data and slide cut date are documented in the

requisition forms. Slides submitted more than 10 days after cutting or cut from more than one tissue specimen block will be rejected, and a new specimen will be required.

Sample shipment: The tumor blocks should be sent with the next scheduled monthly shipment to the central lab at room temperature.

Sample storage: At the central laboratory, the FFPE tissue blocks shall be stored at room temperature in the dark and the FFPE tumor block 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.

6.4.2.2. PD-L1 Expression Assessment

Tumor expression of PD-L1 will be assessed using an FDA-approved test in all subjects in Phase 2.

6.4.2.3. HPV Assessment

For subjects with cervical cancer (Phase 2), tissue sample provided at screening will be used for HPV assessment. Should tissue only be sufficient for PD-L1 expression assessment, the subject may still be enrolled and HPV status will not be assessed.

6.4.3. Clinical Assessments and Procedures

6.4.3.1. Review of Adverse Events

The investigator or qualified designee will assess each subject to evaluate for potential new or worsening AEs as specified in the Schedule of Assessments and Procedures and more frequently if clinically indicated. Adverse experiences will be Graded and recorded throughout the study and during the follow-up period according to NCI CTCAE Version 4.03 (see Section 7). Toxicities will be characterized in terms including seriousness, causality, toxicity grading, and action taken with regard to trial treatment.

Comprehensive assessment of any AE experienced by the subject will be performed throughout the course of the trial, from time of the subject's consent. Trial site personnel will report any AE, whether observed by the investigator or reported by the subject (Section 7.2). Given the intended mechanism of action, particular attention should be given to AEs that may result from enhanced T-cell activation, such as dermatitis, colitis, hepatitis, uveitis, or other immune-related reactions. When clinically indicated, ophthalmologic examinations should be considered for signs or symptoms of uveitis.

An irAE may be defined as an AE 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 AE immune related. Immunological, serological and histological (biopsy) data should be used to support the diagnosis of an immune-related toxicity. Following the guidance described in Section 7.2.2.2, certain irAEs should also be reported to the Sponsor as AESIs.

The reporting period for AEs is described in Section 7.2.1.

6.4.3.2. Physical Examination

6.4.3.2.1. Full Physical Examination

The investigator or qualified designee will perform a complete physical exam during the screening period, as per Section 6.1 (Phase 1) or Section 6.2 (Phase 2). Clinically significant abnormal findings should be recorded as medical history. After consent, new clinically significant abnormal findings should be recorded as AEs.

6.4.3.2.2. Focused Physical Examination

For cycles that do not required a full physical exam per Section 6.1 (Phase 1) or Section 6.2 (Phase 2), the investigator or qualified designee will perform a directed physical exam as clinically indicated prior to trial treatment administration. New clinically significant abnormal findings should be recorded as AEs.

6.4.3.3. Vital Signs, Height and Weight

Vital signs, height, and weight will be measured and recorded as specified in Section 6.1 (Phase 1, Table 11 or Table 12) or Section 6.2 (Phase 2, Table 13). The investigator or qualified designee will take vital signs at the specified times including prior to the administration of each dose of trial treatment. Vital signs include temperature, pulse, respiratory rate, and blood pressure. Weight should be measured prior to dosing. Height will be measured at Visit 1 only.

6.4.3.4. 12-lead Electrocardiogram

A standard 12-lead ECG will be performed using local standard procedures at screening and as specified in Section 6.1 (Phase 1, Table 11 or Table 12) or Section 6.2 (Phase 2, Table 13). Clinically significant abnormal findings at Screening should be recorded as medical history.

6.4.3.5. Expanded Electrocardiogram Evaluation (in selected sites only)

In Phase 2, in addition to the standard 12-lead ECGs, expanded ECG evaluation will occur with 12-lead ECG tracings recorded in *triplicate* at selected sites only and on the following schedule (see also Table 13):

- Cycles 1 and 4:
  - On Day 1 (day of infusion), within 15 min (± 10 min) before the Predose PK sample and within 15 min (± 10 min) before the 30-min-after-end-of-infusion PK sample
  - On Day 2, within 15 min (± 10 min) before 24-h-after-end-of-infusion PK sample
- Every subsequent 8th cycle (that is, approximately every 4 months for up to 1 year, in Cycles 12, 20, and 28):
  - On Day 1 (day of infusion), within 15 min (± 10 min) before the Predose PK sample and within 15 min (± 10 min) before the 30-min-after-end-of-infusion PK sample

Every attempt should be made to use the same ECG machine for all measurements within a subject, and ECG values should be computer-generated.

6.4.3.6. Eastern Cooperative Oncology Group Performance

ECOG status will be assessed (see Appendix II) at screening, prior to the administration of each dose of trial treatment and during the Follow-up period as specified in Section 6.1 (Phase 1) or Section 6.2 (Phase 2).

6.4.4. Imaging Assessments

6.4.4.1. Tumor Imaging

In Phase 1, the initial tumor imaging will be performed within 21 days prior to first dose; however, scans performed as part of routine clinical management are acceptable for use as screening scan if they are of diagnostic quality and performed < 21 days prior to first dose. On-study imaging will be performed every 6 weeks (± 3 days) from first treatment dose (or more frequently if clinically indicated) until discontinuation of study drug.

In Phase 2, the initial tumor imaging will be performed within 21 days prior to first dose; however, scans performed as part of routine clinical management are acceptable for use as screening scan if they are of diagnostic quality and performed < 21 days prior to first dose. All subjects must have an independent central radiologic review to confirm measurable disease by RECIST 1.1 prior to first dose. Subjects without centrally confirmed measurable disease at baseline will not be eligible for this trial. On-study imaging will be performed every 6 weeks (± 3 days) from first dose (or more frequently if clinically indicated) until discontinuation of study drug. Imaging studies will be submitted for central review by the IERC.

The timing of on-study-treatment imaging should follow calendar days and should not be adjusted for delays in treatment administration or for visits. Additional imaging at the Discontinuation Visit and Safety Follow-up Visit is not required provided imaging assessments have been performed per schedule.

Throughout the trial, the same imaging technique should be used in a subject. In general, lesions detected at baseline should be followed using the same imaging methodology and preferably the same imaging equipment at subsequent tumor evaluation visits. The investigator may perform scans in addition to a scheduled trial scan for medical reasons or if progressive disease is suspected.

6.4.4.2. Brain Imaging

MRI is the preferred brain imaging modality; however, CT is acceptable if an MRI is clinically contraindicated.

In Phase 1, subjects with no previous history of brain metastases are required to have brain imaging at screening (within 21 days from prior to first treatment dose) unless adequate imaging is available for exams within 21 days prior to the first dose of trial treatment; except for subjects with cervical cancer, cutaneous squamous-cell carcinoma, gastric/gastroesophageal junction cancer, head and neck squamous-cell carcinoma, ovarian cancer, prostate cancer, mesothelioma, or urothelial carcinoma, for whom brain imaging is necessary only if clinically indicated.

In Phase 2, brain imaging should only be conducted if clinically indicated.

During the trial, brain CT/MRI (with contrast if not contraindicated) scans should be conducted if clinically indicated by development of new specific symptoms.

6.4.4.3. Response Assessment

Response assessment will be done according to RECIST 1.1 (Eisenhauer et al 2009) in Phase 1 and Phase 2. In Phase 1, response will be assessed by an investigator; in Phase 2 response will be assessed by an investigator and by an IERC.

For all subjects, tumor response assessment will be performed by CT or MRI of the chest/abdomen/pelvis (plus other regions as required for specific tumor types) and other established assessments of tumor burden if CT/MRI imaging is insufficient for the individual subject. All scans performed at baseline and other imaging performed as clinically required (other supportive imaging) will be repeated at subsequent visits. In general, lesions detected at baseline should be followed using the same imaging methodology and preferably the same imaging equipment at subsequent tumor evaluation visits.

For each subject, the investigator will designate 1 or more of the following measures of tumor status to follow for determining response: CT or MRI images of primary and/or metastatic tumor masses, physical examination findings, and results of other assessments. All available images collected during the trial period will be considered. The most appropriate measures to evaluate a subject's tumor status should be used. Measure(s) chosen for sequential evaluation during the trial must correspond to measures used to document progressive tumor status that qualifies the subject for enrollment.

In Phase 2, radiographic images used for local determination of disease progression will be read centrally and reviewed by a blinded IERC. The IERC will make a determination as to whether criteria for tumor response or progression according to RECIST 1.1 have been met.

Tumor responses to treatment will be assigned based on evaluation of response of target, non-target, and new lesions according to RECIST 1.1 (all measurements should be recorded in metric notation; see Eisenhauer et al 2009). Assessment of tumor response by the IERC will be defined in the IERC Charter.

- To assess objective response, tumor burden at baseline will be estimated and used for comparison with subsequent measurements. At baseline, tumor lesions will be categorized in target and non-target lesions as described by Eisenhauer et al (2009).

Results for these evaluations will be recorded with as much specificity as possible so that pre- and post-treatment results will provide the best opportunity for evaluating tumor response.

Any complete response (CR) or partial response (PR) should be confirmed as described by Eisenhauer et al (2009).

In the case of a PR or CR, a confirmatory CT or MRI scan must be conducted ≥ 28 days later.

The investigator may perform scans in addition to a scheduled trial scan for medical reasons or if progressive disease is suspected.

6.4.5. Pharmacokinetic, Pharmacodynamic, Genetic, and Other Assessments

Sample collection, labeling, storage and shipment instructions will be provided in the operations/laboratory manual.

A full chain of custody will be maintained for all samples throughout their lifecycle. Sponsor will keep oversight of the entire life cycle through internal procedures, monitoring of study sites, and auditing of external laboratory providers.

6.4.5.1. Pharmacokinetic Assessments

Blood samples will be collected in both study phases for plasma AGEN2034 concentration determinations (for pharmacokinetic evaluation).

In Phase 1, PK samples will be collected as shown in Table 11 or Table 12.

In Phase 2, PK samples will be collected as shown in Table 14.

It is important to record all infusion start dates/times, infusion end dates/times, infusion interruption(s) start and end dates/times, infusion flush end dates/times, and blood sample collection dates/times completely and accurately (and to the nearest minute).

6.4.5.2. Immunogenicity Assessment

Blood samples for assessment of the immunogenicity of AGEN2034 will be collected for all subjects at the time points described in Section 6.1 (Phase 1).

In Phase 2, ADA samples will be collected as shown in Table 14.

The immunogenicity assessment will be conducted to detect and measure ADA (antibody against AGEN2034).

6.4.5.3. Blood Biomarker Assessments

To complete all assessments on blood samples (whole blood and plasma), the Sponsor or designated contract research organization (CRO) will provide instructions and necessary supplies to the site, including shipping materials and prepaid mailers. Refer to the Laboratory Manual for detailed information.

All proposed biomarker analyses are exploratory objectives and are dependent on the quality and availability of sufficient materials. Collection and storage of samples will be detailed in the Laboratory Manual. The panel of biomarkers might be adjusted based on results from ongoing research related to anti–PD1/PD- L1 and anti-CTLA-4 therapies and/or safety.

6.4.5.3.1. In Phase 1

6.4.5.3.1.1. Receptor Occupancy

In Phase 1 only, PD-1 receptor occupancy on circulating T cells will be measured as an indication of target engagement.

6.4.5.3.1.2. IMMUNOPHENOTYPING

Leukocyte subpopulations and immune activation status will be assessed by flow cytometric analysis and/or transcriptional profiling by either RNAseq or other comparable technology using PBMCs. T cell lymphocytes, B lymphocytes, and natural killer cells (TBNK) profiling will be assessed by flow cytometric analysis using whole blood. All analyses will follow the schedule of events shown in Section 6.1. A complete differential blood count will be provided for each time point for calculations of absolute lymphocyte counts. As biomarker research is constantly evolving, selection of markers with the highest specificity and relevance to treatment effect may change.

6.4.5.3.1.3. CYTOKINE ASSESSMENT

In Phase 1 only, cytokine profiles will be evaluated at various time points from plasma samples collected according to Section 6.1.

6.4.5.3.2. In Phase 2

[redacted] The blood collection schedule for biomarker assessments in Phase 2 is detailed in in Table 14.

6.4.5.3.2.1. [redacted]

[redacted]

6.4.5.3.2.2. [redacted]

[redacted]

6.4.5.4. Pharmacogenomics Assessments (Optional)

The Sponsor may conduct research on DNA from blood or tumor tissue specimens collected during this trial. This research may include genetic analysis (DNA) and gene expression profiling (RNA).

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 pharmacogenomics assessments and a pharmacogenomics ICF (optional) is signed.

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

6.4.6. Local Laboratory Tests

It is essential that the Sponsor be provided with a list of laboratory normal ranges before shipment of study drug. Any change in laboratory normal ranges during the trial will additionally be forwarded to the CRO and the Sponsor.

Blood samples will be collected from non-fasted subjects. All routine laboratory analyses will be performed at a laboratory facility local to the investigational site.

The overall amount of blood to be drawn for safety laboratory testing, pregnancy testing, and exploratory biomarker investigation from a single subject with a body weight ≤ 70 kg (154 lb) must not exceed 120 mL/week.

Laboratory tests for screening should be performed within 7 days prior to the first dose of trial treatment. After Cycle 1, predose laboratory procedures can be conducted up to 48 hours prior to dosing.

Results must be reviewed by the investigator or qualified designee and found to be acceptable prior to each dose of trial treatment.

The report of the results must be retained as a part of the subject's medical record or source documents. Blood samples for study related tests will be collected at time points specified in per Section 6.1 (Phase 1) or Section 6.2 (Phase 2).

Laboratory tests are shown in Table 15.

Table 15: Required Local Laboratory Panel Tests

Full Chemistry
Albumin
Alkaline phosphatase[1]
ALT (SGPT) [1]
Amylase
AST (SGOT) [1]
BUN/total urea[1]
Calcium[1]
Chloride[1]
Cholesterol
Creatine kinase
Creatinine[1]
CRP
GGT
Glucose[1]
LDH
Lipase
Magnesium[1]
Phosphorus/phosphates[1]
Potassium[1]
Sodium[1]
Total bilirubin[1]
Total protein
Triglycerides
Uric acid

Pregnancy Tests
Serum pregnancy test
Urine pregnancy test

Hematology
Absolute lymphocyte count
Absolute neutrophil count
Hematocrit
Hemoglobin
MCH
MCHC
MCV
Platelet count
RBC
WBC and differential count

Coagulation Studies
aPTT
Prothrombin time (INR)

Endocrine Function Tests
ACTH
FSH (for postmenopausal women if applicable)
T4
TSH

Autoimmunity Tests
Anti-nuclear antibody (Phase 1 only)
Rheumatoid factor (Phase 1 only)

Abbreviations: ACTH: adrenocorticotropic hormone; ALT: alanine aminotransferase; aPTT: activated partial thromboplastin time; AST: aspartate aminotransferase; BUN: blood urea nitrogen; CRP: C-reactive protein; FSH: follicle-stimulating hormone; GGT: gamma glutamyl transferase; INR: international normalized ratio; LDH: lactate dehydrogenase; MCH: mean corpuscular hemoglobin; MCHC: mean corpuscular hemoglobin concentration; MCV: mean corpuscular volume; RBC: red blood cell; SGOT: serum glutamic oxaloacetic transaminase; SGPT: serum glutamic pyruvic transaminase; T4: free thyroxine; TSH: thyroid-stimulating hormone; WBC: white blood cell.
[1]Core serum chemistries.

7. ADVERSE EVENTS

7.1. Adverse Event Definitions

7.1.1. Adverse Event

An AE is any untoward medical occurrence in a subject or clinical investigation subject administered a pharmaceutical product, which 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), symptom, or disease temporally associated with use of a medicinal product, whether or not considered related to the medicinal product. In cases of surgical or diagnostic procedures, the condition/illness leading to such a procedure is considered as the AE rather than the procedure itself.

The investigator is required to Grade the severity/intensity of each AE. Investigators will reference NCI CTCAE v4.03, which is a descriptive terminology that can be used for AE reporting. A general grading (severity/intensity) scale is provided at the beginning of the referenced document, and specific event Grades are also provided. If a particular AE's severity/intensity is not specifically Graded by the guidance document, the investigator is to revert to the general definitions of Grade 1 through Grade 5 and use his/her best medical judgement.

The 5 general Grades of AE severity are:

Grade 1: Mild

Grade 2: Moderate

Grade 3: Severe

Grade 4: Life-threatening or disabling

Grade 5: Death related to AE

According to the Sponsor's convention, if a severity/intensity of Grade 4 or 5 is applied to an AE, the investigator must also report the event as an SAE as per Section 7.2.2. However, a laboratory abnormality with a severity/intensity of Grade 4, such as anemia or neutropenia, is considered serious only if the condition meets one of the serious criteria described below.

In the case of death, the primary cause of death or the event leading to death should be recorded and reported as an SAE. "Fatal" will be recorded as the outcome of this respective event; death will not be recorded as separate event. Only if no cause of death can be reported (e.g., sudden death, unexplained death), might the death per se be reported as an SAE.

Investigators must also systematically assess the causal relationship of AEs to AGEN2034 using the following definitions. Decisive factors for assessment of causal relationship of an AE to AGEN2034 include, but may not be limited to, temporal relationship between the AE and AGEN2034, known side effects of AGEN2034, medical history, concomitant medication, course of the underlying disease, and trial procedures.

Not related: Not suspected to be reasonably related to AGEN2034. AE could not medically (pharmacologically/clinically) be attributed to the AGEN2034 under study in this clinical trial protocol. A reasonable alternative explanation must be available.

Related: Suspected to be reasonably related to AGEN2034. AE could medically (pharmacologically/clinically) be attributed to the AGEN2034 under study in this clinical trial protocol.

7.1.2. Abnormal Laboratory Findings and Other Abnormal Investigational Findings

Abnormal laboratory findings and other abnormal investigational findings (e.g., on an ECG trace) should not be reported as AEs unless they are associated with clinical signs and symptoms, lead to treatment discontinuation, or are considered otherwise medically important by the investigator. If an abnormality fulfills these criteria, the identified medical condition (e.g., anemia, increased ALT) must be reported as the AE rather than the abnormal value itself.

7.1.3. Adverse Drug Reaction

An ADR is defined in this trial as any AEs suspected to be related to AGEN2034 by the investigator and/or Sponsor.

7.1.4. Serious Adverse Event

An SAE is any untoward medical occurrence that at any dose:

- Results in death.
- Is life-threatening.

  Note: The term "life-threatening" in this definition refers to an event in which the subject is at risk of death at the time of the event; it does not refer to an event that hypothetically might cause death if it were more severe.

- Requires in-patient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect
- An overdose of Sponsor's product, as defined in Section 7.5
- Is otherwise considered as medically important

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered as SAEs when, based on appropriate medical judgement, they may jeopardize the subject or may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in in subject hospitalization, or development of drug dependency or drug abuse.

For purposes of reporting, any suspected transmission of an infectious agent via a study drug is also considered a serious adverse reaction, and all such cases should be reported in an expedited manner as described in Section 7.2.2.

7.1.5. Events That Do Not Meet the Definition of an SAE

Elective hospitalizations to administer or to simplify trial treatment or trial procedures (e.g., overnight stay to facilitate chemotherapy and related hydration therapy application) are not

considered SAEs. However, all events leading to unplanned hospitalizations or unplanned prolongation of an elective hospitalization (e.g., undesirable effects of any administered treatment) must be documented and reported as SAEs.

7.1.6. Events not to be Considered as AEs/SAEs

Medical conditions present at the initial trial visit that do not worsen in severity or frequency during the trial are defined as baseline medical conditions, and are not to be considered AEs.

7.1.7. AE/SAEs Observed in Association with Disease Progression

Disease progression recorded in the course of efficacy assessments only, but without any adverse signs or symptoms, should not be reported as an AE. However, if adverse signs or symptoms occur in association with disease progression, these should be recorded as AEs and as SAEs if they meet any seriousness criteria.

7.1.8. Predefined Potential AEs of Special Interest for Safety Monitoring

Selected non-serious and SAEs defined below are considered AESIs and must be recorded as such on the Adverse Event case report forms/worksheets and reported within 24 hours to the Sponsor either by electronic media or paper. Sponsor Contact information can be found in the Investigator Trial File Binder (or equivalent).

Events of clinical interest for this trial include:

- Infusion-related reactions.
- An elevated AST or ALT lab value that is greater than or equal to 3X the upper limit of normal and an elevated total bilirubin lab value that is greater than or equal to 2X the upper limit of normal and, at the same time, an alkaline phosphatase lab value that is less than 2X the upper limit of normal, as determined by way of protocol-specified laboratory testing or unscheduled laboratory testing.

  Note: These criteria are based upon available regulatory guidance documents. The purpose of the criteria is to specify a threshold of abnormal hepatic tests that may require an additional evaluation for an underlying etiology. The trial site guidance for assessment and follow up of these criteria can be found in Section 5.6.4.
- Any AE that is reasonably suspected to be immune-mediated (ie, an irAE).

AESIs (both non-serious and serious AEs) identified in this guidance document from the date of first dose through 90 days following cessation of treatment, or 30 days after the initiation of a new anticancer therapy, whichever is earlier, need to be reported to the SPONSOR within 24 hours of the event, regardless of attribution to study treatment, consistent with standard SAE reporting guidelines and either by electronic media or paper.

Subjects should be assessed for possible AESIs prior to each dose. Lab results should be evaluated and subjects should be asked for signs and symptoms suggestive of an immune-related event. Subjects who develop an AE thought to be immune-related should have additional testing to rule out other etiologic causes. If lab results or symptoms indicate a possible irAE, then additional testing should be performed to rule out other etiologic causes. If no other cause is found, then it is assumed to be immune-related.

Any infusion reaction, regardless of Grade, must be reported in an expeditious manner and will be considered an AESI. The reporting of AESI is described in Section 7.2.2.

7.2. Methods of Recording and Assessing Adverse Events

At each trial visit, the subject will be queried on changes in his/her condition. During the reporting period of the trial, any unfavorable changes in the subject's condition will be recorded as AEs, whether reported by the subject or observed by the investigator.

Complete, accurate, and consistent data on all AEs experienced for the duration of the reporting period (defined below) will be reported on an ongoing basis in the appropriate section of the eCRF. Among these AEs, all SAEs and all non-serious AESIs must be additionally documented and reported using the appropriate report form as described in Section 7.2.2.

It is important that each AE report include a description of the event, its duration (onset and resolution dates and times to be completed when it is important to assess time of AE onset relative to recorded treatment administration time), its severity, causal relationship with trial treatment, any other potential causal factors, any treatment administered or other action taken (including dose modification or discontinuation of study drug), and outcome. In addition, serious cases should be identified and the appropriate seriousness criteria documented.

Specific guidance can be found in the eCRF Completion and Monitoring Conventions.

7.2.1. Definition of the Adverse Event Reporting Period

The AE reporting period for safety surveillance begins when the subject provides written consent and continues until either 90 days after the last dose of study drug or the start of new anticancer treatment, whichever comes first. Following the End-of-Treatment Safety Follow-up Visit, only treatment-related AEs will be documented through the Treatment Follow-up Period of up to 12 months after the last dose of study drug or until disease progression and/or initiation of a new line of therapy, whichever comes first.

Any SAE suspected to be related to trial treatment must be reported whenever it occurs, irrespective of time elapsed since last dose of study drug.

7.2.2. Procedure for Reporting SAEs / AESIs

All adverse reactions will be reported to the FDA according to 21 Code of Federal Regulations (CFR) 312.32 and according to applicable regulatory authorities and institutional ethics committees.

7.2.2.1. Serious Adverse Events

In the event of any new SAE (of any Grade) occurring during the reporting period, the investigator must immediately (i.e., ≤ 24 hours after becoming aware of the event) inform the Sponsor or designee by telephone, fax, or e-mail. For the following significant SAEs the reporting period to the Sponsor is ≤ 8 hours after becoming aware of the event:

- Drug-related death less than 30 days of dosing
- Drug-related life-threatening event.

When an event (or follow-up information) is reported by telephone, a written report must be sent immediately thereafter by fax or e-mail.

Reporting procedures and timelines are the same for any new information on a previously reported SAE (= follow-up).

For names, addresses, telephone, and fax numbers for SAE reporting, see information included on the SAE report form.

All written reports should be transmitted using the SAE report form, which must be completed by the investigator following specific completion instructions. The AE section of the eCRF must be completed. Relevant pages from the eCRF may be provided in parallel (e.g., medical history, concomitant drugs).

In all cases, information provided in the SAE report form must be consistent with data on the event that is recorded in the corresponding eCRF sections.

The investigator/reporter must respond to any request for follow-up information (e.g., additional information, outcome and final evaluation, specific records where needed) or to any question the Sponsor or designee may have regarding the AE within the same timelines as described for initial reports. This is necessary to permit a prompt assessment of the event by the Sponsor or designee and (as applicable) to allow the company to meet strict regulatory timelines associated with expedited safety reporting obligations.

Requests for follow-up will usually be made by the responsible monitor, although in exceptional circumstances the Sponsor's global drug safety department may contact the investigator directly to obtain clarification or to discuss a particularly critical event.

7.2.2.2. Adverse Events of Special Interest

In the event of a non-serious 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.

7.2.2.3. Safety Reporting to Health Authorities, Independent Ethics Committees/ Institutional Review Boards, and Investigators

The Sponsor will send appropriate safety notifications to health authorities in accordance with applicable laws and regulations.

The investigator must comply with any applicable site-specific requirements related to reporting of SAEs (and in particular deaths) involving his/her subjects to the IEC/IRB that approved the trial.

In accordance with International Conference on Harmonization Good Clinical Practice (GCP) guidelines, the Sponsor or designee will inform the investigator of "findings that could adversely affect the safety of subjects, impact the conduct of the trial, or alter the IEC's/IRB's approval/favorable opinion to continue the trial." In accordance with respective regulations, the Sponsor or designee will inform the investigator of AEs that are both serious and unexpected, and are considered to be related to the administered product (suspected unexpected serious adverse reactions [SUSARs]). The investigator should place copies of safety reports in the

investigator site file. National regulations with regard to safety report notifications to investigators will be taken into account.

When specifically required by regulations and guidelines, the Sponsor or designee will provide appropriate safety reports directly to the concerned health authority and lead IEC/IRB, and will maintain records of these notifications. When direct reporting by the Sponsor or designee is not clearly defined by national or site-specific regulations, the investigator will be responsible for promptly notifying the concerned IEC/IRB of any safety reports provided by the Sponsor or designee, and for filing copies of all related correspondence in the investigator site file.

7.3. Monitoring of Subjects with Adverse Events

Adverse events are recorded and assessed continuously throughout the trial starting at the time the subject receives his/her first treatment (Section 7.2.1) and are assessed for final outcome at the end-of-treatment visit.

After the End-of-Treatment Safety Follow-up Visit, only treatment-related AEs will be documented through the Treatment Follow-up Period of up to 12 months after the last dose of study drug or until disease progression and/or initiation of a new line of therapy.

All SAEs ongoing at the post-treatment safety follow-up visit must be monitored and followed by the investigator until stabilization or until the outcome is known, unless the subject is documented as “lost to follow-up.”

Reasonable attempts to obtain this information must be made and documented. It is also the responsibility of the investigator to ensure that any necessary additional therapeutic measures and follow-up procedures are performed.

7.4. Pregnancy and In Utero Drug Exposure

Only pregnancies considered by the investigator as related to trial treatment (e.g., resulting from a drug interaction with a contraceptive medication) are considered as AEs.

However, all pregnancies with an estimated conception date during the period defined in Section 7.2.1 must be recorded by convention in the AE page/section of the eCRF.

The same rule applies to pregnancies in female subjects and in female partners of male subjects. The investigator must notify the Sponsor or designee in an expedited manner of any pregnancy using the pregnancy report form, which must be transmitted according to the same process as described for SAE reporting in Section 7.2.2.

Investigators must actively follow up, document, and report the outcome of these pregnancies, even if subjects are withdrawn from the trial. A separate consent will be obtained for follow-up of these subjects.

The investigator must notify the Sponsor or designee of these outcomes using the pregnancy report form and, in case of abnormal outcome, the SAE report form if the subject sustains an event and the parent-child/fetus AE report form when the child/fetus sustains an event).

Any abnormal outcome must be reported in an expedited manner, as described in Section 7.2.2, whereas normal outcomes must be reported within 45 days from delivery.

In the event of a pregnancy in a subject occurring during the course of the trial, the subject must be discontinued from trial medication immediately. The Sponsor or designee must be notified without delay and the subject must be followed as described above.

7.5. AGEN2034 Overdose

An overdose is defined as any dose 5% greater than the highest daily dose included in the clinical trial protocol. Any overdose must be recorded in the trial medication section of the eCRF.

For monitoring purposes, any case of overdose, whether or not associated with an AE (serious or non-serious), must be reported to the Sponsor's or designated CRO's global drug safety department in an expedited manner using the SAE report form.

There is no data on AGEN2034 overdose to date. Data available with agents from the same class indicate that the correlation between dose and toxicity is relatively flat.

The investigator should use his or her clinical judgement when treating an overdose of AGEN2034.

8. 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 will be documented in the Clinical Study Report (CSR).

8.1. Sample Size

The study includes 2 phases: Phase 1: Dose Escalation Phase, and Phase 2: Expansion Phase. The total sample size for both phases is expected to be approximately 200 subjects.

8.1.1. Phase 1

It is expected that approximately 50 subjects will be enrolled in the Phase 1 part of the study. The sample size in the Phase 1 is not driven by statistical hypothesis testing, but driven by clinical considerations. Final sample size in this phase may vary depending on the total number of dose levels to be tested, and subject replacement for DLT evaluation, if applicable.

8.1.2. Phase 2

The aim in this phase is to detect preliminary evidence of clinical activity in subjects with metastatic cervical cancer. The primary endpoint is the ORR per IERC based on RECIST 1.1. ORR will be estimated as binomial proportion of best overall response (BOR) of confirmed PR

or CR and reported with 95% Wilson score confidence interval (CI); the CI will be interpreted as a plausible range for a true (unobserved) ORR.

Phase 2 is expected to enroll approximately 150 subjects. With 150 subjects in the final analysis, the power to exclude an ORR of 5% by the lower limit of the 95% Wilson score interval is 92.2% and 96.2%, assuming a true ORR of 12% and 13%, respectively. The sample size will provide ≥ 77% probability to observe an AE with and underlying rate of ≥ 1%. With 100 patients in the interim analysis, the power to exclude an ORR of 5% by the lower limit of the two-sided 95% Wilson score interval will be 77.4% and 85.2%, assuming a true ORR of 12% and 13%, respectively.

Historical published data may be used for the interpretation of the clinical significance of the study endpoints.

Interim analyses will be performed to assess the safety and efficacy (using the ORR and selected secondary efficacy endpoints) when (1) data are available for approximately 30 subjects treated for at least 3 months and (2) approximately 3 months after approximately 100 patients are dosed. No early stopping for efficacy will be performed, as a more complete safety assessment and evaluation of durability of responses is necessary for determination of risks and benefits. Consequently, interim analyses will not affect the overall type I error. A non-binding futility analysis may be performed using methods described in the statistical analysis plan. Additional interim analyses for safety and efficacy assessment may performed.

8.2. Analysis Sets

The following analysis sets will be defined and used separately for Phase 1 and Phase 2, as applicable:

- Phase 1 DLT analysis set: All subjects with data used for implementing the confirmation of the safety of the combination. These subjects should have received all study treatment administrations in the DLT evaluation period or should have stopped treatment because of DLTs in the DLT evaluation period.
- Safety analysis set: All subjects who have received ≥ 1 dose of trial treatment.
- Pharmacokinetics analysis set: All subjects who have completed ≥ 1 infusion of study drug, and who have provided sufficient concentration measurements.
- Evaluable efficacy analysis set: All subjects in Phase 2 who have received ≥ 1 dose of trial treatment and have measurable disease at baseline, according to the IERC assessment.

8.3. Description of Statistical Analyses

8.3.1. General Considerations

All data recorded during the study will be presented in individual data listings performed on the safety analysis set. All data will be evaluated as observed, and no imputation method for missing values will be used unless otherwise specified. All data will be presented in a descriptive manner. Statistical inference of the primary efficacy endpoint will be performed for the efficacy expansion cohort based on the pre-planned significance level.

Descriptive statistics will be used in general to summarize trial results, i.e., statistics for continuous variables may include means, standard deviations, medians, and ranges (min, max). Categorical variables will be summarized by counts and percentages. Unless otherwise specified, calculation of proportions will be based on the number of subjects in the analysis set of interest. Counts of missing observations will be included in the denominator and presented as a separate category if not otherwise specified in the SAP.

The DLT analysis set is the underlying dataset for determination of the safety. Safety analyses will be performed on the Safety analysis set. Analyses of PK variables will be performed on the PK analysis set. The primary analysis of the ORR and other efficacy variables will be based on the evaluable efficacy analysis set, defined as all subjects dosed with study drug who had measurable disease at baseline by IERC assessment. Details of the analysis will be described in the SAP.

Unless otherwise specified, endpoint analyses will be performed separately for Phase 1 and Phase 2.

8.3.2. Analysis of Primary Endpoints

8.3.2.1. In Phase 1: Dose-limiting Toxicity

For determination of safety of AGEN2034, individual subject data from the Phase 1 portion of the trial will be reported. In addition, for final statistical analysis, the following will be summarized:

- At each dose level, number and proportion of subjects in the DLT analysis set who experience a DLT during the DLT evaluation period.
- At each dose level, number and proportion of TEAEs experienced by subjects in the DLT analysis set during the DLT evaluation period.

8.3.2.2. In Phase 2: Objective Response Rate

- The primary endpoint for Phase 2 is the confirmed ORR according to RECIST 1.1, as determined by an IERC. ORR will be estimated as the binomial proportion of patients with BOR of PR or CR, taking into account the following requirement for confirmation: for PR or CR, confirmation of the response according to RECIST 1.1 will be required at no sooner than 4 weeks after initial documentation of CR or PR. ORR will be reported with two-sided, 95% Wilson score CI.

8.3.3. Analysis of Secondary Endpoints

The following secondary endpoints will be summarized.

8.3.3.1. Efficacy Parameters

Efficacy parameters, including confirmed ORR according to RECIST 1.1, as determined by investigator; disease control rate (DCR), defined as proportion of subjects with CR, PR, or SD for at least 12 weeks; duration of response (DOR) according to RECIST 1.1; time to response (TTR); and duration of stable disease, defined as time from treatment start until documented

progression, will be listed and summarized in Phase 2 using both IERC and investigator assessments.

DOR and TTR will be summarized in only a subset of patients with confirmed response using the Kaplan-Meier method and displayed graphically, where appropriate. The median event time and 95% CI for the median will be provided. Duration of stable disease will also be summarized by the Kaplan-Meier method.

In addition, PFS, and OS time will be presented in subject listings, analyzed using Kaplan-Meier method and displayed graphically where appropriate. The median event time and 95% CI for the median will be provided.

8.3.3.2. Pharmacokinetic Parameters

Both noncompartmental (NCA) and compartmental modeling (e.g., population PK [PopPK]) techniques will be used to analyze AGEN2034 PK.

The PK parameters to be estimated and reported may include, but may not be limited to: maximum drug concentration observed postdose at steady-state (C_{max-ss}); minimum observed concentration at steady-state (C_{min-ss}); area under the drug concentration-time curve (AUC) within a dosing interval within the time span t1 to t2 at steady-state ($AUC_{(t1-t2)-ss}$); AUC from time of dosing (0 h) to time t, the time of last observation (calculated by linear trapezoidal summation) (AUC_{0-t}); AUC from time of dosing (0 h) extrapolated to infinity (calculated by linear trapezoidal summation and extrapolated to infinity using C_{last}/λ_z) ($AUC_{0-\infty}$); time to maximum observed concentration (ie, time at which C_{max} occurs) (t_{max}); terminal disposition rate constant, determined from the slope of the regression line of log (concentration) vs. time (λ_z); terminal elimination half-life, determined as $0.693/\lambda_z$ ($t_{½}$ or HL); systemic clearance (CL); and volume of distribution (Vd).

8.3.3.3. Immunogenicity

Antidrug antibody concentrations in correlation with AGEN2034 PK exposure matrix will be summarized.

8.3.3.4. Exploratory Biomarkers

Summary statistics for biomarkers will be provided for all preplanned time points. Changes from baseline for continuous biomarkers may also be presented as applicable and categorical biomarkers will be tabulated.

Possible relationship of biomarker levels with efficacy may be investigated.

8.3.4. Safety Analyses

The extent of exposure to AGEN2034 will be characterized by duration (weeks), number of administrations, cumulative dose (mg/kg), dose intensity (mg/kg/week), relative dose intensity (actual dose given/planned dose), number of dose reductions, and number of dose delays.

Safety analyses will be performed on the safety analysis set. Safety endpoints will be summarized by dose cohort in each phase.

Safety assessments will be based on incidence of AEs, including AESIs, ADRs, immunogenicity, and changes in vital signs (including body weight), ECG, and laboratory values (hematology and serum chemistry).

The on-treatment period is defined as time from first dose of study treatment to last dose of study drug plus 30 days, or the earliest date of new anticancer therapy minus 1 day, whichever occurs first.

8.3.4.1. Adverse Events

Adverse events will be coded according to Medical Dictionary for Regulatory Activities (MedDRA) version 21.0. Severity of AEs will be graded using CTCAE (version 4.03) toxicity grading scale whenever possible.

Treatment-emergent AEs are AEs with onset dates during the on-treatment period, or the worsening of an event during the on-treatment period. Incidence of TEAEs, regardless of attribution, and AEs defined as related to AGEN2034 will be summarized by system organ class and preferred term, and described in terms of severity and relationship to AGEN2034.

Analysis of AES will be performed for events that are considered as treatment emergent. Adverse events leading to death or discontinuation of trial treatment, events with CTCAE Grade 3 or higher, study drug-related events, and SAEs will be summarized.

Indications of dose-related ADRs will also be examined.

8.3.4.2. Laboratory Variables

Laboratory results will be classified by grade according to NCI CTCAE. The worst on-trial grades after first trial treatment will be summarized. Shifts in toxicity grading from first treatment to highest grade will be tabulated. Results for variables that are not part of NCI CTCAE will be presented as below, within, or above normal limits. Only subjects with post-baseline laboratory values will be included in these analyses.

8.3.4.3. Physical Examination, Vital Signs, and Electrocardiogram

Physical examination data, vital signs (body temperature, respiratory rate, heart rate, and blood pressure), and 12-lead ECG data will be presented.

8.3.5. Interim and Final Analysis

Phase 2 is designed to have at least 2 interim analyses of the primary endpoint and selected secondary efficacy and safety endpoints. No early stopping for efficacy will be performed, as a more complete assessment of safety and durability of responses will be required for evaluation of risks and benefits. Consequently, the overall type I error will not be affected by the interim analyses. A non-binding futility analysis may be performed using methods described in the SAP.

The first interim analysis will be performed when data are available for approximately 30 subjects treated for at least 3 months. The primary analysis of efficacy and safety data will include all subjects dosed prior to a borderline date (specified as at least 3 months prior to the data cutoff). Another interim analysis will be performed 3 months after approximately 100 subjects have been dosed and will include, as the primary analysis of safety and efficacy, all subjects in the evaluable efficacy analysis set among the first approximately 100 subjects dosed. Sensitivity safety analyses

will be performed on all subjects in the safety analysis set dosed as of the data cutoff. Details of the interim analyses will be provided in a separate SAP.

Additional interim analyses for safety and efficacy assessment may be performed.

The final analysis will be performed after study completion.

The primary analysis set for efficacy assessment will be the evaluable efficacy analysis set. The primary analysis set for safety assessment will be the safety analysis set.

The interim analyses may include PD-1 expression data if available. Details will be provided in a separate SAP. After the interim analyses, subsequent enrollment of subjects may be based on biomarker enrichment (including but not limited to PD-L1 expression). In such cases, tumor tissue must be positive for the selected entry biomarker prior to subject enrollment.

9. TRIAL GOVERNANCE AND OVERSIGHT

9.1. Safety Monitoring Committee

A Safety Monitoring Committee (SMC) will regularly review safety data to ensure subjects' safety throughout the study.

The SMC will consist of permanent members from the Sponsor and/or CRO:

- Sponsor: head of development/chief medical officer, pharmacovigilance physician, study physician, and Principal Investigator(s).
- CRO: lead statistician and study physician.

During the Phase 1 portion of the trial, the SMC assess safety; decide on dose-escalation and opening of backfill enrollment; define the recommended Phase 2 dose (RP2D); and determine opening of the Phase 2 cohorts. The SMC recognizes that with the limited prior human experience with AGEN2034, a conservative approach will be adopted in ascribing the relationship of the treatment-related toxicity to the drug.

At each SMC review, all safety information of the participating subjects will be reviewed and the SMC will decide by consensus on continuation, modification, or suspension of the trial.

The SMC may modify the frequency of meetings as deemed appropriate during the course of the trial. The specific working procedures will be described in a separate SMC charter.

9.2. Independent Endpoint Review Committee

For the Phase 2 portion of the study, a central facility will read and interpret all radiographic scans for subjects enrolled in the study. Data for all images will be transferred from trial sites to the central reading center for evaluation. Scans will be evaluated at the central facility in accordance with RECIST 1.1. Imaging data will be transferred to the designee at regular intervals. A manual from the vendor will be provided to each trial site.

For all subjects in Phase 2, the IERC will perform a blinded determination as to whether RECIST 1.1 criteria for tumor response or progression have been met. The IERC will be composed of a minimum of 3 properly qualified members.

The role of the IERC will be to review radiographic image findings for determination of the time point for overall response and date of disease progression (per RECIST 1.1) for each subject. The full membership, mandate, and processes of the IERC will be detailed in a separate IERC charter.

9.3. Independent Data Monitoring Committee (IDMC)

For the Phase 2 portion of the study, an IDMC will be established supplement the routine trial monitoring outlined in this protocol. The voting members of the committee are external to and independent of the Sponsor. The members of the IDMC must not be involved with the trial in any other way (e.g., they cannot be trial investigators) and must have no competing interests that could affect their roles with respect to the trial. The IDMC will include 4 oncologists (a minimum of 1 of which is experienced in cervical cancer) and 1 external statistician.

The IDMC will make recommendations to the Sponsor regarding steps to ensure both subject safety and the continued ethical integrity of the trial. Also, the IDMC will review interim trial results, consider the overall risk and benefit to trial participants (see Section 8.3.5) and recommend to the Sponsor if the trial should continue in accordance with the protocol.

Specific details regarding responsibilities and governance, including the roles and responsibilities of the various members and the Sponsor protocol team; meeting facilitation; the trial governance structure; and requirements for and proper documentation of IDMC reports, minutes, and recommendations will be described in a separate charter that is reviewed and approved by the IDMC. The IDMC will monitor the trial at an appropriate frequency, as described in the detailed IDMC charter. The IDMC will also make recommendations to the Sponsor protocol team regarding steps to ensure both subject safety and the continued ethical integrity of the trial.

10. ETHICAL AND REGULATORY ASPECTS

10.1. Ethics Review

The study protocol, subject information and consent form, Investigator's Brochures and bridging Investigator's Brochure, any written instructions to be given to the subject, available safety information, subject recruitment procedures (e.g., study website), information about payments and compensation available to the subjects and documentation evidencing the investigator's qualifications will be approved by the IRB/EC per local regulations prior to study start. The written approval should identify all documents reviewed by name and version.

Changes in the conduct of the study or planned analysis will be documented in a protocol amendment. The investigator must submit and, where necessary, obtain IRB and/or Sponsor approval for all subsequent protocol amendments and changes to the ICF or changes of the investigational site, facilities, or personnel. The investigator should notify the IRB of protocol deviations or SAEs occurring at the site and other AE reports received from the Sponsor in accordance with local procedures.

Safety updates for AGEN2034 will be prepared by the Sponsor or its representative as required, for submission to the relevant IRB.

10.2. Responsibilities of the Investigator

The investigator is responsible for conduct of the trial at his/her site. He/she will ensure that the trial is performed in accordance with the clinical trial protocol and the approved protocol amendments; the current version of the Declaration of Helsinki (Ethical Principles for Medical Research Involving Human Subjects), ICH Good Clinical Practice (ICH E6 guideline) as adopted by the respective health authorities; and applicable Health Authority requirements and national and state laws. In particular, the investigator must ensure that only subjects who have given their written informed consent are included into the trial.

10.3. Subject Information and Informed Consent

An unconditional prerequisite for a subject's participation in the trial is his/her written informed consent. The subject's written informed consent to participate in the trial must be given before any trial-related activities are carried out. Subjects may also sign a separate, optional section of the ICF, related to pharmacogenomics, 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 AGEN2034.

Adequate information must therefore be given to the subject by the investigator before informed consent is obtained. In addition to providing this written information to a potential subject, the investigator will inform the subject verbally of all pertinent aspects of the trial. The language used in doing so must be chosen so that the information can be fully and readily understood by lay persons.

Informed consent will be obtained for participation in the trial and for optional participation in pharmacogenomics assessments. Additionally, should a female subject become pregnant in during the study, a separate informed consent for follow-up of the pregnancy will be obtained.

The ICF must be signed and personally dated by the subject and investigator. The signed and dated declaration of informed consent will remain at the investigator's site, and must be safely archived by the investigator so that the forms can be retrieved at any time for monitoring, auditing, and inspection purposes. A copy of the signed and dated information and ICF should be provided to the subject before participation.

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.

10.4. Subject Identification and Privacy

In compliance with ICH GCP guidelines, it is a requirement that the investigator and institution permit authorized representatives of the Sponsor, regulatory authorities, and IRB direct access to review the subject's original medical records at the site for verification of trial-related procedures and data.

Measures to protect confidentiality include: only the study number, subject number, subject initials, and date of birth will identify the subject on the electronic case report form (eCRF) or other documents submitted to the Sponsor. This information will be used in the database for subject identification. Subject names or addresses will not be entered on the eCRF or in the database. No material bearing a subject's name will be kept on file by the Sponsor. Subjects will be informed of their rights within the ICF.

In studies conducted in the United States, confidentiality of subject's personal data will be protected in accordance with the Health Insurance Portability and Accountability Act (HIPAA) of 1996 and national data protection laws, as applicable. HIPAA regulations require that in order to participate in the trial, a subject must sign an authorization from the trial that he or she has been informed of following:

- What Protected Health Information (PHI) will be collected from subjects in this trial;
- Who will have access to that information and why;
- Who will use or disclose that information;
- That health information may be further disclosed by the recipients of the information, and that if the information is disclosed the information may no longer be protected by federal or state privacy laws;
- The information collected about the research trial will be kept separate from the subject's medical records, but the subject will be able to obtain the research records after the conclusion of the trial;
- Whether the authorization contains an expiration date; and
- The rights of a research subject to revoke his or her authorization.

In the event that a subject revokes authorization to collect or use his or her PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of subject authorization. For subjects that have revoked authorization to collect or use PHI, attempts should be made to obtain permission to collect at least vital status (i.e., that the subject is alive) at the end of their scheduled trial period.

10.5. Emergency Medical Support and Subject Card

Subjects enrolled in this clinical trial will be provided with emergency medical support cards during their trial participation, which will be furnished by the Sponsor or designee. The emergency medical support card is based on the need to provide clinical trial subjects with a way of identifying themselves as participating in a clinical trial, and subsequently give health care providers access to information about this participation that may be needed to determine the course of the subject's medical treatment.

This service is designed to provide information to health care providers who are not part of the clinical trial. Clinical trial investigators, who are already aware of the clinical trial protocol and treatment, have other means of accessing the necessary medical information for management of emergencies occurring in their subjects.

The first point of contact for all emergencies will be the clinical trial investigator caring for the affected subject. The investigator agrees to provide his or her emergency contact information on the card for this purpose. If the investigator is available when an event occurs, he/she will answer any questions. Any subsequent action will follow the standard processes established for the investigators.

In cases in which the investigator is not available, the site will provide the appropriate means to contact a physician. This includes provision of a 24-hour contact number at the facility, whereby the health care providers will be given access to an appropriate physician to assist with the medical emergency.

10.6. Clinical Trial Insurance and Compensation to Subjects

Insurance coverage shall be provided for each country participating to the trial. Insurance conditions shall meet good local standards, as applicable.

10.7. Health Authorities

The clinical trial protocol and any applicable documentation (e.g., investigational medicinal product dossier, subject information, and ICF) will be submitted or notified to health authorities by the Sponsor or designated CRO in accordance with regulations of the countries involved in the trial.

11. TRIAL MANAGEMENT

11.1. Sponsor and Trial Administrative Structure

The Sponsor of this study is Agenus Inc.

In countries where a local sponsor is required a qualified local legal Sponsor will be designated by Agenus, and will act as the legal Sponsor for the study, and will fulfil the obligations that this role entails. In these cases, the local legal Sponsor shall, to the extent required by the applicable laws and regulations, interact with regulatory and health authorities on behalf of the Sponsor in connection with this study.

Details of logistical and administrative structures and associated procedures will be defined in a separate manual of operations, which will be prepared by the Sponsor or designated CRO.

11.2. Investigational Sites

The trial will be global, with approximately 10 to 15 enrolling centers participating in Phase 1 and approximately 60 centers in Phase 2.

11.3. Trial Coordination/Monitoring

The Sponsor will coordinate the trial and may delegate certain trial activities to CROs, including certain laboratory assessments, safety reporting, biostatistics, etc. The Sponsor’s clinical operations department will oversee activities performed by CROs.

11.4. Data Collection

The eCRF is the primary data collection instrument for the trial. The clinical site will keep eCRFs current to enable the monitor to review the subjects' status throughout the course of the trial. To maintain confidentiality, only the study number, subject number, subject initials, and date of birth will identify the subject on the eCRF. All data requested on the eCRF must be supported by and be consistent with the subject's source documentation.

Source documents are the original documents, data, records and certified copies of original records of clinical findings, observations and activities from which the subject's eCRF data are obtained. These can include, but are not limited to, hospital records, clinical and office charts, laboratory, medico-technical department and pharmacy records, diaries, microfiches, ECG traces, copies or transcriptions certified after verification as being accurate and complete, photographic negatives, microfilm or magnetic media, X-rays, and correspondence.

All missing data must be explained. When a required laboratory test, assessment, or evaluation has not been done or an "Unknown" box is not an option on the eCRF, a note should be created verifying that the field was "Not Done" or "Unknown". For any entry errors made, the error(s) must be corrected, and a note explaining the reason for change should be provided.

The investigator will sign and date the subject eCRF casebook indicating that the data on the eCRF have been assessed. Each completed eCRF will be electronically signed and dated by the PI, once all data for that subject is final.

11.5. Investigator Site File and Archiving

The investigator will be provided with an investigator site file upon initiation of the trial. This file will contain all documents necessary for the conduct of the trial and will be updated by the site throughout the trial. It must be available for review by the monitor; be ready for Sponsor audit as well as for inspection by health authorities during and after the trial; and safely archived for ≥ 15 years (or per local requirements or as otherwise notified by the Sponsor) after the end of the trial. Documents to be thus archived include the subject identification list and signed subject ICFs. If archiving of the investigator site file is no longer possible at the site, the investigator must notify the Sponsor.

All original subject files (medical records) must be stored at the site (hospital, research institute, or practice) for the longest possible time permitted by applicable regulations, and/or as per ICH GCP guidelines, whichever is longer. In any case, the investigator should ensure that no destruction of medical records is performed without the Sponsor's written approval.

11.6. Monitoring, Quality Assurance and Inspection by Health Authorities

This trial will be monitored in accordance with the current version of the ICH Good Clinical Practice guideline (ICH E6). The site monitor will visit the trial site at regular intervals.

Representatives of the Sponsor's quality assurance unit or a designated organization, as well as health authorities, must be permitted to inspect all trial-related documents and other materials at the site, including investigator site file, completed eCRFs, ICFs, and the subjects' original medical records/files.

The clinical trial protocol, data capture procedures, and data handling, including final clinical trial report, will be subject to independent quality assurance activities. Audits may be conducted at any time during or after the trial to ensure the validity and integrity of trial data.

11.7. Publication Policy

11.7.1. Clinical Trial Report

After completion of the trial, a clinical trial report according to ICH E3 guideline will be written by the Sponsor or designated CRO in consultation with the Principal Investigator.

11.7.2. Publications

All information provided regarding the trial, as well as all information collected/documented during the course of the trial, will be regarded as confidential. The Sponsor reserves the right to release literature publications based on the results of the trial. Results from the trial will be published/presented as per the Sponsor's publication strategy.

Inclusion of the Investigator in the authorship of any multi-center publication will be based upon substantial contribution to the design, analysis, interpretation of data, drafting and/or critically revising any manuscript(s) derived from the trial. The investigator acknowledges that the trial is part of a multi-center trial and agrees that any publication by the investigator of the results of the trial conducted at his/her research site shall not be made before the first multi-center publication. In the event, there is no multi-center publication within 15 months after the trial has been completed or terminated at all trial sites, and all data has been received, the investigator shall have the right to publish its results from the trial, subject to the notice requirements described herein and subject to acknowledgement of the Sponsor as appropriate. The investigator shall provide the Sponsor 30 days to review a manuscript or any poster presentation, abstract or other written or oral material that describes the results of the trial for the purpose only of determining if any confidential or patentable information is disclosed thereby. If the Sponsor requests in writing, the investigator shall withhold any publication or presentation an additional 60 days solely to permit the Sponsor to seek patent protection.

12. REFERENCES

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APPENDIX 1. EASTERN COOPERATIVE ONCOLOGY GROUP PERFORMANCE SCALE

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

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

APPENDIX 2. SIGNATURE PAGES AND RESPONSIBLE PERSONS FOR THE TRIAL

Signature Page – Protocol Lead

Title	A Phase 1/2, Open-Label, Multiple Ascending Dose Trial to Investigate the Safety, Tolerability, Pharmacokinetics, Biological, and Clinical Activity of AGEN2034 in Subjects with Metastatic or Locally Advanced Solid Tumors, with Expansion to Second Line Cervical Cancer
Clinical Trial Version / Date	Version 6.0, 27 September 2019
Previous Version	Version 5.0, 24 January 2019

I approve the design of the clinical trial.

[redacted] [redacted]

Signature Date of Signature

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

Signature Page – Principal Investigator

Title	A Phase 1 / 2, Open-Label, Multiple Ascending Dose Trial to Investigate the Safety, Tolerability, Pharmacokinetics, Biological, and Clinical Activity of AGEN2034 in Subjects with Metastatic or Locally Advanced Solid Tumors, with Expansion to Second Line Cervical Cancer
Clinical Trial Version / Date	Version 6.0, 27 September 2019
Center Number	_____
Principal Investigator	_____

I, the undersigned, am responsible for the conduct of the trial at this site and affirm that:

- I understand and will conduct the trial according to the clinical trial protocol, and the approved protocol amendments; the current version of the Declaration of Helsinki Ethical Principles for Medical Research Involving Human Subjects), ICH Good Clinical Practice (ICH E6 guideline) as adopted by the applicable Health Authority requirements and national and state laws.
- I will not deviate from the clinical trial protocol without prior written permission from the Sponsor, and prior review and written approval from the Institutional Review Board or Independent Ethics Committee, except where necessary to prevent immediate danger to the subject.

I understand that some regulatory health authorities require the Sponsors of clinical trials to obtain and supply, when required, details about the investigators' ownership interests in the Sponsor or investigational medicinal product and information regarding any financial ties with the Sponsor. The Sponsor will use any such information that is collected solely for the purpose of complying with the regulatory requirements. I therefore agree to supply the Sponsor with any necessary information regarding ownership interest and financial ties (including those of my spouse and dependent children), and to provide updates as necessary.

_____ _____
Signature Date of Signature

Name, academic degree _____

Position (job title) _____

Institution _____

Address _____

Telephone number _____

E-mail address _____