Title: A Phase 1b/2 Study Assessing Safety and Anti-tumor Activity of AMG 820 in Combination With Pembrolizumab in Select Advanced Solid Tumors

Amgen Protocol Number (AMG 820) 20150195

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Investigator's Agreement

I have read the attached protocol entitled "A Phase 1b/2 Study Assessing Safety and Anti-tumor Activity of AMG 820 in Combination with Pembrolizumab in Select Solid Tumors," dated 15 June 2018, and agree to abide by all provisions set forth therein.

I agree to comply with the International Conference on Harmonisation (ICH) Tripartite Guideline on Good Clinical Practice (GCP) and applicable national or regional regulations/guidelines.

I agree to ensure that Financial Disclosure Statements will be completed by:

- me (including, if applicable, my spouse [or legal partner] and dependent children)
- my subinvestigators (including, if applicable, their spouses [or legal partners] and dependent children)

at the start of the study and for up to one year after the study is completed, if there are changes that affect my financial disclosure status.

I agree to ensure that the confidential information contained in this document will not be used for any purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of Amgen Inc.

Signature	
Name of Investigator	Date (DD Month YYYY)

Protocol Synopsis

Title: A Phase 1b/2 Study Assessing Safety and Anti-tumor Activity of AMG 820 in Combination with Pembrolizumab in Select Advanced Solid Tumors

Study Phase: 1b/2

Indication: Colorectal cancer (CRC), pancreatic cancer and non-small cell lung cancer (NSCLC), and other indications dependent on emerging data

Hypotheses:

- AMG 820 in combination with pembrolizumab is safe and well tolerated when administered in subjects with select advanced solid tumors
- AMG 820 can enhance the anti-tumor activity observed with pembrolizumab alone and/or overcome lack of response to pembrolizumab monotherapy in subjects with select advanced solid tumors

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Primary Objective:

- Evaluate the safety and tolerability of AMG 820 administered in combination with pembrolizumab in subjects with select advanced solid tumors
- Evaluate the objective response rate (ORR) of AMG 820 and pembrolizumab combination as per irRECIST in subjects with select advanced solid tumors

Secondary Objective(s):

- Evaluate the anti-tumor activity of AMG 820 and pembrolizumab combination in select advanced solid tumors by assessing
    - ORR per RECIST1.1
    - time to response (TTR), duration of response (DOR), and time to progression (TTP)
    - progression free survival (PFS) and overall survival (OS) at 6 and 12 months
- Characterize the pharmacokinetics (PK) of AMG 820 after intravenous (IV) infusion administration of AMG 820 in combination with pembrolizumab
- Evaluate the relationship between the immune infiltrate status in pre-study tumor biopsies vs. clinical response

Primary Endpoint:

- Dose limiting toxicities (DLT), treatment-emergent adverse events, treatment-related adverse events and clinically significant changes in vital signs, physical examinations, and clinical laboratory tests
- ORR as per irRECIST in subjects treated at the recommended combination dose

Secondary Endpoint(s):

- Objective response (OR) as per RECIST 1.1; TTR, DOR and TTP; OS and PFS at 6 and 12 months
- PK parameters for AMG 820 including, but not limited to, maximum observed concentration (C_{max}) and minimum observed concentration (C_{min}). In addition, area under the concentration-time curve (AUC) and, if feasible, half-life ($t_{1/2}$) for AMG 820.
- CD4, CD8 & CD68 cells numbers in fresh pre-treatment biopsies

Study Design: This is a multi-center Phase 1b/2 study testing the combination of AMG 820 and pembrolizumab in subjects with select advanced solid tumors. Phase 1b of the study (part 1) will have a 6+3 design aimed at assessing the safety of the selected starting dose of AMG 820 in combination with pembrolizumab. Phase 2 of the study (part 2) will further evaluate safety and test whether AMG 820 can enhance the anti-tumor activity observed historically with

pembrolizumab alone and/or overcome lack of response to pembrolizumab monotherapy in subjects with select solid tumors.

Part 1: Up to 3 cohorts will be evaluated for safety in Part 1. The initial cohort will treat subjects who have select advanced solid tumors with 1400 mg AMG 820 plus 200 mg pembrolizumab every three weeks (Q3W) using a 6+3 design.

- If 0 or 1 of the initial 6 evaluable subjects experience a dose-limiting toxicity (DLT) then the dose combination will be determined to be tolerable and Part 2 initiated. The study Part 1 DLT period is 21 days.
- If 2 of the initial 6 evaluable subjects experience a DLT then 3 additional evaluable subjects will be enrolled.
- If 3 or more of the evaluable subjects experience a DLT (eg, 33% or higher with 9 evaluable subjects) then the dose combination will be determined to be non-tolerable and a second Part 1 cohort will be enrolled to test a decreased dose of AMG 820 in combination with 200 mg pembrolizumab. Further degree of dose modification and/or schedule of administration will be decided based on analysis of emerging safety and PK data.

Part 2: The evaluation of safety and efficacy in this part will include 6-9 subjects from Part 1 who have been treated with the recommended combination dose, and will enroll additional subjects with select solid tumors up to 185 subjects overall. Part 2 will have 5 groups, which will be evaluated using a Simon two-stage design. Analysis of data in Part 2 will be done separately for each group (Group 1, 2, 3, 4a, 4b).

- Group 1 will enroll up to 43 advanced MMR-proficient CRC subjects who are naïve to anti-PD-1/PD-L1/CSF-1/CSF-1R therapies. Eighteen (18) subjects will be enrolled during the first stage and treated with the AMG 820 plus pembrolizumab combination. If only 2 or fewer subjects have an objective response per irRECIST then further enrollment may be discontinued; otherwise, enrollment up to 43 subjects will occur.
- Group 2 will enroll up to 29 advanced pancreatic cancer subjects who are naïve to anti-PD-1/PD-L1/CSF-1/CSF-1R therapies. Ten (10) subjects will be enrolled during the first stage and treated with the AMG 820 plus pembrolizumab combination. If no subjects have an objective response per irRECIST then further enrollment may be discontinued; otherwise, enrollment up to 29 subjects will occur.
- Group 3 will enroll up to 55 advanced NSCLC subjects with low (< 50%) tumor PD-L1- expression who are naïve to anti-PD-1/PD-L1/CSF-1/CSF-1R agents. Nineteen (19) subjects will be enrolled first during the first stage and treated with the AMG 820 plus pembrolizumab combination. If 3 or fewer subjects have an objective response per irRECIST then further enrollment may be discontinued; otherwise, enrollment up to 55 subjects will occur.
- Group 4 will enroll up to 58 NSCLC subjects who have not responded to or have relapsed during monotherapy with anti-PD-1/PD-L1 agents, and are anti-CSF-1/CSF-1R naïve. These subjects will be further distributed equally between two sub-groups (4a and 4b) depending on the PD-L1 expression in the tumor tissue: high (≥ 50%) and low (< 50%) expression. Ten (10) subjects per subgroup will be enrolled first, during the first stage. If no objective response per irRECIST is seen in either of the subgroups then further enrollment may be discontinued; otherwise, enrollment up to 58 subjects will occur.

Sample Size:

It is anticipated that 67 to 197 subjects will be enrolled overall in this study.

Part 1 will enroll 6 to 18 evaluable subjects. The sample size in Part 1 is based on practical consideration, and it is consistent with conventional oncology studies with the objective to evaluate the safety and tolerability of a treatment combination. With 6 subjects in a cohort, there is a 47-91% probability of observing at least one DLT if the true DLT rate is 10-33%.

Part 2 evaluation of efficacy will include at least 6 subjects from part 1 who have been treated with the recommended combination dose, and will enroll additional subjects with CRC, pancreatic cancer and NSCLC up to a maximum of 185 subjects overall. The sample size in each group evaluated in Part 2 is chosen to test whether AMG 820 can enhance the anti-tumor activity observed historically with pembrolizumab alone and/or overcome lack of response to pembrolizumab monotherapy. Other indications may be included dependent on emerging data.

Summary of Subject Eligibility Criteria:

Subjects ≥ 18 years of age with pathologically documented, definitively diagnosed, advanced select solid tumors that are refractory to standard treatment, or the subjects have been intolerant to or refuse the standard treatment (certain prior therapies are restricted as per the study design) with no anti-tumor therapy (chemotherapy, antibody therapy, molecular targeted therapy, investigational agent) within 28 days prior to start of treatment and no active autoimmune disease. Once consented to the study, subjects will undergo safety tests and provide a medical history to confirm they meet all requirements of the study.

For a full list of eligibility criteria, please refer to Section 4.1 through Section 4.2.

Investigational Product

Amgen Investigational Product Dosage and Administration:

AMG 820 will be manufactured and packaged by Amgen Inc. AMG 820 will be presented as a sterile, clear, colorless to slightly yellow frozen liquid in 20 mL glass vials. Each glass vial will contain 3.0 mL of AMG 820 with a concentration of 70 mg/mL.

The starting dose for AMG 820 will be 1400mg administered via IV infusion Q3W (±3 days). AMG 820 will be administered in combination with pembrolizumab. AMG 820 will be administered on the same schedule as pembrolizumab and will be administered first. Further adjustments of the AMG 820 dose level will be evaluated as per the part 1 design based on the emerging safety data.

Refer to Sections 6.2.1.1.

Non-Amgen Investigational Product Dosage and Administration:

Pembrolizumab will be manufactured by Merck. Pembrolizumab is supplied in 100 mg/4mL vials (25 mg/mL) solution for intravenous infusion. Pembrolizumab will be administered at a dose of 200 mg intravenously Q3W (±3 days). Pembrolizumab will be administered on the same schedule as AMG 820 and will follow administration of AMG 820. Pembrolizumab infusion is to begin 15 minutes following the end of the AMG 820 infusion.

Both investigational products will be administered at the study center by a qualified staff member. A physician must be available at the time of administration of investigational product.

Refer to Section 6.2.1.1.

Procedures:

After written informed consent has been obtained, all screening tests and procedures will be performed within 28 days prior to administration of the first dose of AMG 820 and/or pembrolizumab, unless otherwise noted. The following procedures will occur per the Schedule of Assessments: medical, surgical and medication history, physical examination and vital signs, body weight, height, ECOG performance status, 12-lead electrocardiogram (ECG), recording of concomitant medications, review of adverse events, disease related events and serious adverse events. Blood will be collected for local laboratory testing including: chemistry, hematology, prothrombin time (PT) or international normalization ratio (INR) and partial thromboplastin time (PTT) or activated PTT (aPTT), endocrine function test, hepatitis B surface antigen, hepatitis B core antibody, hepatitis C virus antibody and human immunodeficiency virus (HIV). Urine will be collected for urinalysis. In females of childbearing potential urine or serum pregnancy test will be performed locally. Additional on-treatment pregnancy testing may be performed at the investigator's discretion. Central laboratory tests include: blood for biomarker analysis, anti-pembrolizumab antibodies, anti-AMG 820 antibodies and AMG 820 and pembrolizumab pharmacokinetics (PK). Formalin-fixed paraffin-embedded tumor tissue and fresh biopsied tumor tissue from either the primary tumor or a metastatic lesion and the associated pathology reports

will be collected and submitted to the central laboratory. Radiographic (computed tomography [CT] or magnetic resonance imaging [MRI]) scans and tumor assessment will also be performed. AMG 820 and pembrolizumab will be administered at day 1 and Q3W (± 3 days) thereafter in combination.

For a full list of study procedures, including the timing of each procedure, please refer to Section 7 and the Schedule of Assessments (Table 5).

Statistical Considerations:

All subjects who are enrolled and receive at least one administration of AMG 820 will be included in the analysis, unless otherwise specified.

During Part 1, safety data will be reviewed on an ongoing basis. Amgen, in consultation with the site investigators, will review in Dose Level Review Meetings (DLRMs) all available accumulating data, by cohort, prior to making dosing decisions.

The analysis of efficacy endpoints for Part 2 will be done and presented by group and sub-group, as appropriate. Efficacy data from Part 1 subjects may be combined with data from Part 2, as appropriate. The proportion of subjects with objective response per irRECIST (irCR or irPR) and RECIST1.1 (CR or PR) criteria with corresponding 90% and 95% CI will be calculated and tabulated for subjects treated at the recommended dose combination. Additional efficacy related endpoints (TTR, DOR, TTP, PFS at 6 and 12 months, and OS at 12 months) will be listed per patient. Kaplan Meier estimates may also be further presented, if data allows.

Descriptive statistics will be provided for selected demographics, safety, PK, PD and biomarker data by dose, group, sub-group and time as appropriate. Descriptive statistics on continuous data will include means, medians, standard deviations and ranges, while categorical data will be summarized using frequency counts and percentages.

For a full description of statistical analysis methods, please refer to Section 10.

Sponsor:

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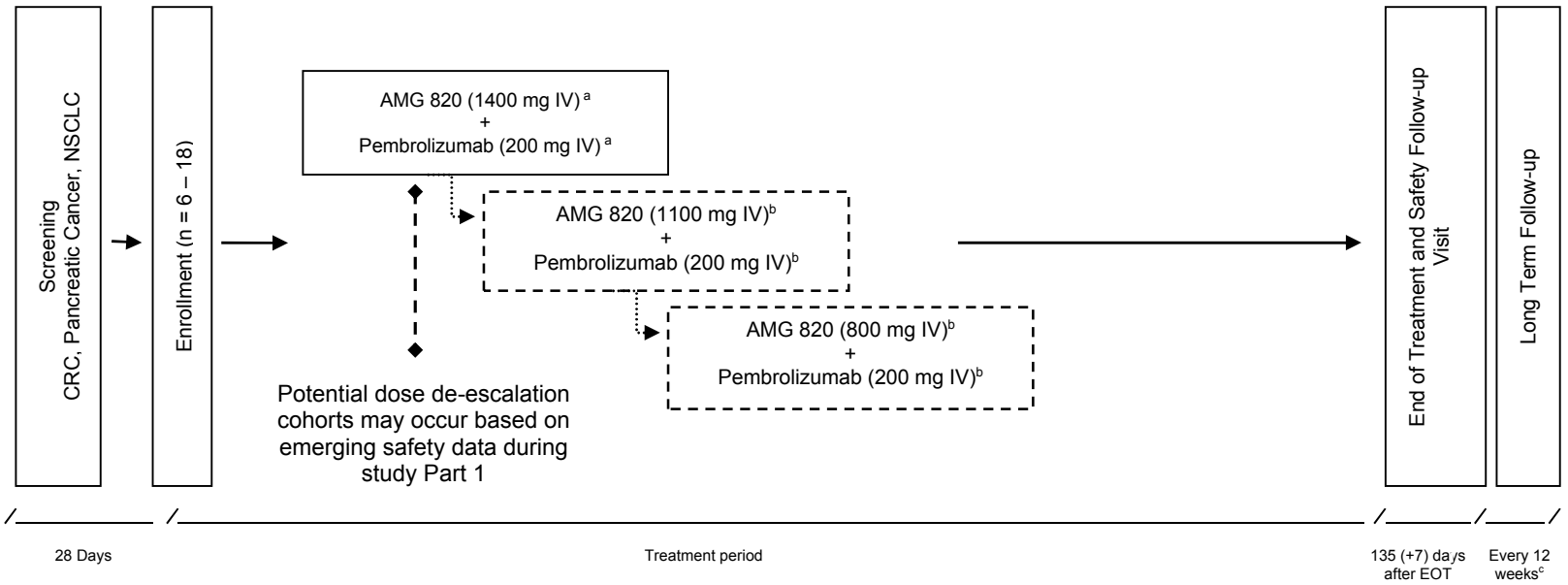
Study Design and Treatment Schema

PART 1



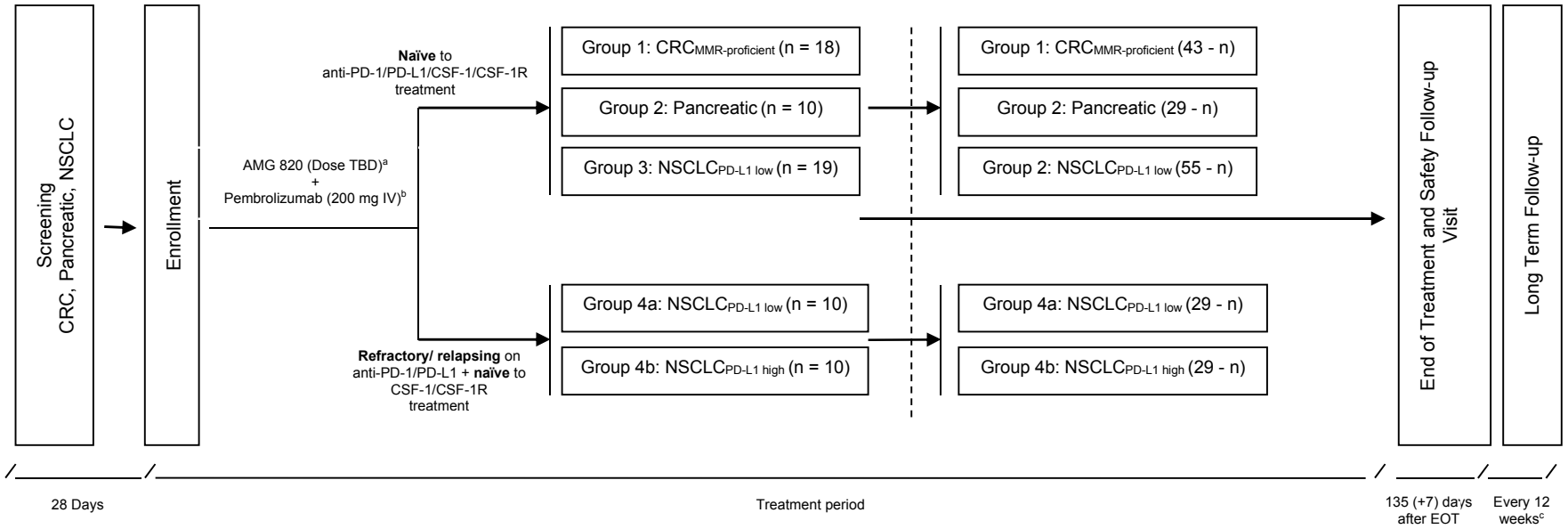
EOT = End of Treatment

[a] AMG 820 1400 mg will be administered intravenously in combination with pembrolizumab 200 mg every 3 weeks (± 3 days). AMG 820 will be dosed first. Pembrolizumab infusion will be started 15 min after completion of the AMG 820 infusion.

[b] Pre-specified de-escalation nominal dose levels shown above. Intermiediate dose levels may be used based on review of cohort DLT period safety data by the DLRT

[c] Long-term follow-up every 12 weeks (± 28 days) until approximately 12 months after subject enrolled.

PART 2 – DOSE EXPANSION



EOT = End of Treatment

[a] AMG 820 dose level for part 2 will be determined during study Part 1

[b] AMG 820 will be administered intravenously in combination with pembrolizumab 200 mg every 3 weeks (± 3 days). AMG 820 will be dosed first. Pembrolizumab infusion will be started 15 min after completion of the AMG 820 infusion.

[c] Long-term follow-up every 12 weeks (± 28 days) until approximately 12 months after subject enrolled.

Study Glossary

Abbreviation or Term	Definition/Explanation
ALT	alanine aminotransferase
ALP	alkaline phosphatase
ANC	absolute neutrophil count
AST	aspartate aminotransferase
CR	complete response
CRC	colorectal cancer
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CSF-1	Colony Stimulating Factor 1
CSF-1R	Colony Stimulating Factor 1 Receptor
DILI	drug-induced liver injury
DLRM	Dose Level Review Meeting
DLRT	Dose Level Review Team
DLT	dose limiting toxicity
dMMR	deficit in mismatch repair genes
DOR	duration of response
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EDC	electronic data capture
End of Study for Individual Subject	defined as the last day that protocol-specified procedures are conducted for an individual subject (ie, the date the subject withdraws full consent from the study, completes the safety follow-up visit or long-term follow-up [whichever is later] or death).
End of Study (primary completion)	defined as when the last subject is assessed or receives an intervention for the purposes of final collection of data for the primary endpoint(s).
End of Study (end of trial)	defined as when the last subject is assessed or receives an intervention for evaluation in the study; if the study includes multiple parts (eg, safety follow-up or survival assessment), the end of study would include these additional parts
End of Treatment	defined as the last assessment for the protocol-specified treatment phase of the study for an individual subject
Heart rate	number of cardiac cycles per unit of time
HIV	human immunodeficiency virus
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Conference on Harmonisation

Abbreviation or Term	Definition/Explanation
IL	interleukin
ILD	interstitial lung disease
INR	international normalization ratio
IPIM	Investigational Product Instruction Manual
IRB/IEC	institutional review board/independent ethics committee
irCR	Immune-related complete response
irPR	Immune-related partial response
irRECIST	Immune-related Response Evaluation Criteria in Solid Tumors (RECIST)
irSD	Immune-related stable disease
irPD	Immune-related progressive disease
IV	intravenous
LDH	lactate dehydrogenase
MRI	magnetic resonance imaging
NSCLC	non-small cell lung cancer
OR	objective response
ORR	objective response rate
OS	overall survival
PD	progressive disease
PD-1	programmed cell death-1
PD-L1	programmed death ligand 1
PET	positron emission tomography
PFS	progression free survival
PK	pharmacokinetics
PR	partial response
PR Interval	PR interval is measured from the beginning of the P wave to the beginning of the QRS complex in the heart's electrical cycle as measured by ECG
PT	prothrombin time
PTT/aPTT	partial thromboplastin time/activated partial thromboplastin time
QW	every week
Q2W	every two weeks
Q3W	every three weeks
QRS interval	QRS interval the interval between the Q wave and the S wave in the heart's electrical cycle as measured by ECG; represents the time it takes for the depolarization of the ventricles

Abbreviation or Term	Definition/Explanation
QT interval	QT interval is a measure of the time between the start of the Q wave and the end of the T wave in the heart's electrical cycle as measured by ECG
QTc interval	QT interval corrected for heart rate using accepted methodology
RECIST	Response Evaluation Criteria in Solid Tumor
SD	stable disease
Source Data	information from an original record or certified copy of the original record containing patient information for use in clinical research. The information may include, but is not limited to, clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents (original records or certified copies). (ICH Guideline (E6)). Examples of source data include Subject identification, Randomization identification, and Stratification Value.
Study Day 1	defined as the first day that protocol-specified investigational product(s)/protocol required therapies is/are administered to the subject
TAM	tumor associated macrophage
TIM	tumor infiltrating macrophage
TSH	thyroid stimulating hormone
TTP	time to progression
TTR	time to response
ULN	upper limit of normal

TABLE OF CONTENTS

List of Tables

List of Figures

List of Appendices

1. OBJECTIVES

1.1 Primary

- Evaluate the safety and tolerability of AMG 820 administered in combination with pembrolizumab in subjects with select advanced solid tumors
- Evaluate the objective response rate (ORR) of AMG 820 and pembrolizumab combination as per irRECIST in subjects with select advanced solid tumors

1.2 Secondary

- Evaluate the anti-tumor activity of AMG 820 and pembrolizumab combination in select advanced solid tumors by assessing
    - ORR per RECIST1.1
    - time to response (TTR), duration of response (DOR), and time to progression (TTP)
    - progression free survival (PFS) and overall survival (OS) at 6 and 12 months
- Characterize the pharmacokinetics (PK) of AMG 820 after intravenous (IV) infusion administration of AMG 820 in combination with pembrolizumab
- Evaluate the relationship between the immune infiltrate status in pre-study tumor biopsies vs. clinical response

1.3 Exploratory

- Evaluate the occurrence of anti-AMG 820 and anti-pembrolizumab antibody formation (immunogenicity)
- Investigate treatment-associated biomarker changes, and relationship of biomarkers baseline status vs. clinical outcome in tumor tissue and blood
- Evaluate pembrolizumab PK at end of pembrolizumab infusion administration. Blood samples collected for AMG 820 concentration measurement may also be used to measure the concentration profile of pembrolizumab, if deemed necessary

2. BACKGROUND AND RATIONALE

2.1 Disease and Background

2.1.1 c-fms PATHWAY, TUMOR ASSOCIATED MACROPHAGES (TAMs) and AMG 820

The c-fms receptor (also known as M-CSF receptor [M-CSFR] or CSF-1 receptor [CSF-1R]), belongs to the class III receptor tyrosine kinase family that includes PDGFR α and β, VEGFR1, R2 and R3, Flt3 and c-kit (van der Geer et al, 1994; Blume-Jensen et al, 2001). Expression of c-fms is primarily restricted to cells of the myelomonocytic lineage (including monocytes, tissue macrophages, microglial cells and osteoclasts), hematopoietic precursors and trophoblasts (Dai et al, 2002; Pixley et al, 2004). The colony stimulating factor-1 (CSF-1, also known as macrophage stimulating factor [M-CSF]) seems to be the main ligand for CSF-1R

(Van Wesenbeeck et al, 2005; Wiktor-Jedrzejczak et al,1990), while the relevance of IL-34, a second possible ligand (Lin et al, 2008), is yet to be fully elucidated. CSF-1 is expressed both as a membrane-bound and a soluble cytokine (Pixley et al, 2004). It influences the survival, proliferation, differentiation, chemotaxis and activation of macrophages and their precursors (Bourette et al, 2000; Cecchini et al, 1994, Hamilton, 1997).

All normal tissues are populated with macrophages, which are part of the innate immune system, recognizing, engulfing and destroying potential pathogens (Sasmono et al, 2004) through the release of reactive-oxygen species and reactive-nitrogen metabolites (Adams and Hamilton, 1984; Nathan et al, 1991). In addition, tissue macrophages contribute to both humoral and cell-mediated immune responses as antigen presenting cells. Conversion from a quiescent state to an immunologically active or microbicidal state can be induced by microbial products and pro-inflammatory cytokines including CSF-1, IL-1, TNFα, IL-4, IL-12, IL-13, GM-CSF, IFNγ (Bingle et al, 2002; Pollard, 2004). At the tumor level, macrophages can represent a prominent component of the inflammatory infiltrate: tumor associated macrophages (TAMs) or tumor infiltrating macrophages (TIMs) (Noy and Pollard, 2014; Chanmee et al, 2014, Pollard, 2004; Chen et al, 2005).

Over the past decades, the mechanisms supporting the tumor promoting functions of TAMs have become increasingly clear (Noy and Pollard, 2014; Colegio et al, 2014; Chanmee et al, 2014; Ribatti et al, 2007; Sica et al, 2006; Condeelis et al, 2006; Leek et al, 2002) through their production of various pro-angiogenic factors (Bingle et al, 2002; Mantovani et al, 1992) such as proteases that degrade the tumor extracellular matrix thus aiding invasion and metastasis and mitogenic factors directly stimulatory to tumors (Leek et al, 2002). In addition, CSF-1 derived macrophages have been shown to be immunosuppressive via production of factors such as prostaglandins, indolamine 2,3 dioxygenase, nitric oxide, IL-10, and TGF-β (Bronte et al, 2001; MacMicking et al, 1997). CSF-1 serum levels as well as TAMs number have been associated in different ways with prognosis in cancer depending on various factors including tumor type and TAM content in the primary tumor vs metastases (Noy and Pollard, 2014; Chanmee et al, 2014; Lewis et al, 2006; Funada et al, 2003; Ohno et al, 2003; Caruso et al, 1999). However, in all preclinical tumor models tested to date (using both human tumor xenograft and syngeneic models) decrease of TAM number and/or their function/survival through targeting CSF-1R axis (Colegio et al, 2014;

Nowicki et al, 1996; Lin et al, 2001; Aharinejad et al, 2004, Zeisberger et al, 2006; Luo et al, 2006) resulted always in inhibition of tumor growth, never tumor progression.

2.1.2 PD-1 AND PD-L1 inhibitors

Programmed cell death 1 (PD-1) is a negative costimulatory receptor expressed primarily on the surface of activated T cells. Binding of the ligands, PD-L1 and PD-L2, to the PD-1 receptor found on T cells, inhibits T cell proliferation and cytokine production. Upregulation of PD-1 ligands occurs in some tumors and signaling through this pathway can contribute to inhibition of active T cell immune surveillance of tumors (Philips and Atkins, 2015; Swaika et al, 2015).

To date, the two leading PD-1 inhibitors pembrolizumab and nivolumab, have been approved in advanced, previously treated melanoma and non-small cell lung cancer (NSCLC). Especially in the NSCLC setting, PD-L1 tumor expression seems to indicate an increase likelihood of responding to anti-PD-1 agents, and companion diagnostic kits for this biomarker have been developed (http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm466413.htm; Keytruda® USPI, 2015).

2.1.3 Metastatic Colorectal Cancer

Colorectal cancer (CRC) is among the most common forms of cancer worldwide. CRC has the third highest cancer incidence and rate of death in the USA for men and women, although the related numbers have been steadily declining in the past decades (Gill et al, 2014). Among patients already diagnosed with CRC, approximately one-fifth present with synchronous metastasis, and half of the remaining patients will develop subsequent metastases. In the treatment of metastatic CRC (mCRC) several cytotoxic agents have demonstrated efficacy, including 5-fluorouracil (5-FU), folinic acid, irinotecan, oxaliplatin and capecitabine. These drugs are commonly combined in various regimens, and can be further partnered with monoclonal antibodies targeting VEGF or EGFR signaling. Recently, two additional therapeutic options have gained approval. The clinical efficacy and safety of STIVARGA (regorafenib), a kinase inhibitor, were evaluated in an international, randomized (2:1), placebo-controlled trial in previously-treated 760 mCRC patients (Grothey et al, 2013). The major efficacy outcome measure was OS which showed significant, although modest, improvement (6.4 vs 5mo), and no effect on PFS nor ORR: 2mo vs 1.7mo, and 1% vs 4%, respectively (Stivarga USPI, 2012). LONSURF is a combination of trifluridine (a nucleoside metabolic inhibitor), and tipiracil (a thymidine phosphorylase inhibitor)

(LONSURF USPI, 2015). Its clinical efficacy and safety were evaluated in a similar setting (800 patients with previously treated mCRC). A statistically significant improvement in overall survival (7.1 vs 5.3mo) and progression-free survival were demonstrated. Evidently, for most patients with mCRC available treatment is palliative rather than curative, with an overall 5-year survival of approximately 10%. Subsequently, additional options are needed for patients who have disease progression despite available standard therapies, since many of them maintain good performance status and might be candidates for further treatments.

In the light of recent advances in the immunotherapeutics space, the potential significance of the immune system in tumor biology has been investigated for CRC as well (Kroemer et al, 2015; Markman and Shiao, 2015). The presence of tumor infiltrating lymphocytes—especially CD8 + lymphocytes—in the tumor microenvironment, as well as regional lymph nodes, has been linked to better prognosis. Also, increased infiltration of specific regions of the CRC tumors by cytotoxic memory T lymphocytes (CD8+CD45RO+T cells) was highly correlated with reduced risk of recurrence of CRC and better survival. The prognostic significance of T cells—unlike other inflammatory cells—argues that cancer immunotherapies modulating T cell responses could lead to improved survival. Nonetheless, there was an almost complete lack of response to anti-PD-1/PD-L1 agents in CRC patients, except when administered in combination with bevacizumab +/-FOLFOX (a ph1b study with MPDL3280A), or in CRC patients with a deficit in mismatch repair genes (dMMR). A dMMR system is present in 10–20% of patients with sporadic CRC and is associated with a favorable prognosis in early-stage disease. In contrast, dMMR occurs in only 3–6% of patients with advanced CRC (Llosa et al, 2015). Recent findings have suggested that checkpoint inhibitors may have increased activity in dMMR tumors, since dMMR have several times as many somatic mutations as proficient MMR tumors, and have prominent lymphocyte infiltrates, which are more likely to express PD-L1, a hypothesis which was tested in a Phase II trial (Le et al, 2015). This study showed that MMR status may be a predictive biomarker for clinical benefit from checkpoint inhibition. Although immunotherapy in dMMR tumors holds great promise, the complete absence of response in patients with proficient MMR CRC—who represent the vast majority—highlights the ongoing need to understand why patients with conventional CRC lack robust responses to immunotherapy.

2.1.4 Advanced Pancreatic Cancer

Pancreatic ductal adenocarcinoma (PDA), representing 95% of pancreatic cancers, remains one of the most lethal cancer types with an overall 5-year survival rate of less than 5 %, and a median survival of less than 6 months. It is estimated that near 40,000 people died of PDA in 2014, rendering it the fourth leading cause of cancer-related death in the USA (Cid-Aregui and Juarez, 2015). Early-stage PDA is asymptomatic, while patients with symptoms are often diagnosed as advanced and metastatic disease when less than 15 % are suitable for surgical resection. Hence, chemotherapy is the only option for most patients. For the last two decades, gemcitabine has been the standard first-line drug, however with only modest survival benefits. While different gemcitabine based combinations have been investigated in a number of randomized trials, only very few showed some beneficial effects, like for example gemcitabine plus erlotinib or gemcitabine plus S-1 (Cid-Aregui and Juarez, 2015). Recently, gemcitabine plus albumin bound-paclitaxel (nab-paclitaxel) as well as a regimen combining fluorouracil, irinotecan, oxaliplatin, and leucovorin (FOLFIRINOX) have shown clear therapeutic advantage in advanced PDAC in phase III trials, over single agent gemcitabine. With the pending issue of their higher toxicities, these regimens now set the reference for ongoing and future clinical studies in advanced PDAC. FOLFIRINOX showed significant improvement in median overall survival (11.1 months vs. 6.8 months with gemcitabine) in patients with Eastern Cooperative Oncology Group (ECOG) performance status 0-1. Progression-free survival was also improved, from 3.4 to 6.4 months. Definitive deterioration in the quality of life at 6 mo was observed in 31% of patients in the FOLFIRINOX and in 66% in the gemcitabine group. However, the toxicity associated with FOLFIRINOX is important, in particular grade 3 and 4 myelosuppression and fatigue. For nab-paclitaxel combined with gemcitabine the median overall survival improved to 8.5 mo from 6.7 mo with gemcitabine alone ($p < 0.001$). The 1-year survival rate was 35% and 22%, respectively, and the 2-year survival was 9% and 4%, respectively. ORR was 23% and 7%, respectively. Adverse events of grade 3 or higher, such as myelosuppression and peripheral neuropathy were however increased in the combined nab-paclitaxel plus gemcitabine arm (Cid-Aregui and Juarez, 2015). In addition to chemotherapies, a number of agents targeting signaling pathways in tumor or stroma cells are being investigated. Likewise, immunotherapies that target PDAC in various ways are the subject of a number of clinical trials (Cid-Aregui and Juarez, 2015).

A heavy infiltration of CD4 and CD8+ T cells expressing programmed cell death 1 (PD-1) and smaller numbers of myeloid cells and regulatory T cells seen in the PDA tissues provided rationale for the clinical evaluation of immune checkpoint inhibition as a pancreatic cancer therapeutic strategy (Komura et al, 2015; Brahmer et al, 2012). However, anti-PD-1 agents have been unsuccessful when tested in a small number of patients with advanced stage PDA, suggesting that it may be necessary to address the immunosuppressive effects of other PD-1 ligands or block additional co-inhibitory pathways (Brahmer et al, 2012). The PDA tissues appear also to be infiltrated by macrophages, especially M2 macrophages. In the recent years, line of evidence had tried to clarify how the monocytes were recruited and the mechanism by which they differentiate to macrophages. CSF/CSFR is a commonly accepted signaling pathway that associates with the process. Generally, the regional microenvironment, which is featured by dense stroma infiltration, plays a decisive role in recruiting monocytes and modulating macrophage phenotype. Since different areas of a solid tumor may exhibit distinct microenvironment, TAMs differ in phenotype as well as function from one region to another. Typically, TAMs in the hypoxia region polarize to M2, while those within the normoxic regions tend to be M1-like (Colegio et al, 2014). Recent reports suggested that the macrophage phenotype is also stage dependent. For example, the anti-inflammation M1-like macrophages, which usually locate in chronic pancreatitis where tumor occurs, gradually converted to M2-like during tumor initiation and progression, reflecting the plasticity as well as heterogeneity of TAMs. As a support, pathological data revealed that M2-like macrophages were more abundant in PDA samples than those diagnosed as chronic pancreatitis (Komura et al , 2015). Consistently, further analysis showed that the M2-like macrophages associated with lymphatic metastasis, distant metastasis, chemoresistance, and hence the survival of the PDA patients. Additional evidence of inflammatory features of PDA form findings of the significantly elevated levels of interleukin (IL)-6, IL-7, IL-15, monocyte chemotactic protein-1, and interferon-c-inducible protein-1 in the sera of PDAC patients. The gene expression profile of CD14+ monocytes and CD4+ T cells was discernible between PDAC patients and healthy volunteers, and the differentially expressed genes were related to active inflammation. Intriguingly, PD-1 was significantly upregulated in the peripheral blood CD4+ T cells of PDAC patients. Correspondingly, the frequency of CD4+PD-1+ T cells was increased in the peripheral blood cells of PDAC patients, and this increase correlated to chemotherapy resistance. In conclusion, inflammatory conditions in both PDAC tissue and peripheral blood cells in PDAC patients appear to be

prominent, highlighting monocytes/macrophages as well as CD4+ T cells with influence of the clinical prognosis (Komura et al, 2015).

2.1.5 Non-Small Lung Cancer (NSLC)

Metastatic lung cancer is the leading cause of cancer death worldwide with a 5-year survival for advanced disease of less than 5% despite of a comprehensive therapeutic approach. In few tumor types with distinct molecular alterations, unprecedented benefits can be delivered by very specific molecular targeted therapies. For most patients with advanced NSCLC, platinum-based chemotherapy with or without maintenance therapy, and subsequently followed by second-line cytotoxic chemotherapy, is the standard treatment (median survival of approximately 1 year). Second-line cytotoxic therapies (ie, docetaxel, pemetrexed and erlotinib) have only moderate efficacy and are associated with significant toxicities. For this reason, strategies such as immunotherapy, which may have efficacy irrespective of histology or mutational status, are particularly attractive (Minguet et al, 2015; Garon et al, 2015). Latest approvals (2015) of several immunotherapy agents reflect the scientific progress poised to shape further the patient outcomes in this indication (Garon et al, 2015; Romero, 2015). As such, anti–PD-1 and anti–PD-L1 antibodies have been shown to produce durable responses in clinical trials in approximately 20% of patients with advanced non–small-cell lung cancer, even without selecting for PD-L1 tumor expression. Pembrolizumab has been recently approved for the treatment of subjects with advanced (metastatic) NSCLC whose disease has progressed after other treatments and have tumors that express PD-L1. In a phase 1 study (KEYNOTE-001) 495 patients received pembrolizumab (at a dose of either 2 mg or 10 mg per kilogram of body weight every 3 weeks or 10 mg per kilogram every 2 weeks) (Garon et al 2015). Among all the patients, the objective response rate was 19.4%, and the median duration of response was 12.5 months. The median duration of progression-free survival was 3.7 months, and the median duration of overall survival was 12.0 months. Among all the patients with a PD-L1 tumor proportion score (TPS) of at least 50%, median progression-free survival was 6.3 months, and the median overall survival was not reached. In a subgroup of these patients (73/313 patients in the validation group with TPS of at least 50%), the response rate was 45.2%. Among the 1143 screened patients, 824 had samples that could be evaluated by the clinical-trial assay, with a prevalence of 23.2% of patients with a PD-L1 TPS of at least 50%, 37.6% with a score of 1 to 49%, and 39.2% with a score of less than 1% by the clinical-trial assay. The prevalence of a proportion score of at least 50% was 24.9% among previously untreated patients and 22.7% among previously treated patients. The ORR in

NSCLC patients with PD-L1 TPS between 1-49% and <1% was 16.5% and 10.7%, respectively (validation set). ORR values were similar in previously treated patients vs treatment naïve: 15.6% vs 19.2% (PD-L1 TPS between 1-49%), and 9.1% vs 16.7% (PD-L1 TPS <1%) (Garon et al, 2015).

A recent sensitivity analysis of nivolumab, and pembrolizumab activity according to the tumor expression of PD-L1 (Carbognin et al, 2015) suggests a significant differential effect in terms of activity according to PD-L1 expression on tumor cells status, which translated into a higher ORR for PD-L1 positive advanced tumors in comparison to PD-L1 negative tumors. With respect to disease setting, the analysis showed evidence of such effect for melanoma and NSCLC, and less for genitourinary cancers. Considering the PD-L1 expression cut-off, the difference in ORR between PD-L1 positive and negative patients was significantly higher in studies adopting the cut-off of 5%, with an absolute difference of 15.5% (95% CI 9.5–21.4). No significant difference was seen for trials where the cut-off was 1% (p=0.108) (Carbognin et al, 2015). In two randomized phIII studies in squamous NSCLC (CheckMate 017) (Brahmer et al, 2015) and non-squamous NSCLC (CheckMate 057) (Borghaei et al, 2015) OPDIVO was evaluated against docetaxel. Significant improvement was reported in both trials for OS (9.2 vs 6.2mo, and 12,2 vs 9.4mo, respectively). ORR in the CheckMate 057 study was 19% in the OPDIVO arm vs 12% in the docetaxel arm. In the CheckMate 063 study , a phII, single arm study of OPDIVO in squamous NSCLC patients who had progressed after platinum based therapy and second line systemic chemotherapy, ORR was 15%, with 59% patients having responses of 6 months or longer (Rizvi et al, 2015).

2.2 AMG 820 Background

AMG 820 is a fully human IgG2 c-fms (CSF-1R) antagonistic antibody. This antibody binds to the first and second IgG regions of the extracellular domain of c-fms and blocked CSF-1 induced proliferation of primary human bone marrow-derived monocytic cells *in vitro* with an IC_{50} of 15.8 pM. AMG 820 had no detectable agonistic activity in the in vitro proliferation assays. AMG 820 cross-reacts with cynomolgus monkey c-fms as measured by binding to cynomolgus c-fms expressed on 2936E cells with a K_d of 29.7 pM and inhibition of CSF-1-induced proliferation of primary bone marrow-derived monocytic cells from cynomolgus monkeys *in vitro* with an IC_{50} of 31.2 pM. A maximal plateau level of CSF-1 elevation (500-1000 ng/mL) was observed in serum after a single IV dosing of 20 mg/kg AMG 820 in normal cynomolgus monkeys. The increase of serum

CSF-1 is presumably due to the ability of AMG 820 to block CSF-1 binding to c-fms and subsequent internalization and degradation of the ligand (Bartocci et al,1987).

Refer to the specific section of the AMG 820 Investigator's Brochure (IB) for additional information related to the physical, chemical, and pharmaceutical properties and formulation(s).

2.2.1 AMG 820 Clinical Experience

In the first-in-human, open-label, dose-escalation study, 25 subjects with advanced solid tumors received AMG 820 at doses of 0.5 mg/kg every week (QW) and 1.5, 3, 6, 10, and 20 mg/kg every 2 weeks (Q2W). The study was terminated after the dose-escalation part; the maximum administered dose was 20 mg/kg Q2W AMG 820, and the MTD was not determined. Key adverse events reported in the study included DLT of grade 3 bilateral deafness in 1 subject, as well as commonly-reported adverse events of periorbital edema (without clinical sequelae) and AST increase (both noted in preclinical studies). Exposure to AMG 820 was increased with increasing AMG 820 dose, and no marked (> 2 fold) accumulation was observed after repeated-dose administrations. AMG 820 mediated pharmacodynamic effects included increase in CSF-1 levels, reduction of macrophages number in the skin, and decrease in TRAP5b levels. No subjects tested positive for anti-AMG 820 binding antibodies. Per central assessment, 8 subjects (32%) had a best response of stable disease. Median of maximum percentage change from baseline in tumor volume was 19.32% (range: -24.0% to 104.8%).

Refer to the AMG 820 IB for additional clinical experience information. For non-clinical toxicology information, refer to Section 5.3 of the AMG 820 IB.

2.2.2 AMG 820 Pharmacokinetics

AMG 820 PK analysis was conducted for all 25 evaluable adult subjects with advanced solid tumors from the first-in-human study (20060347). The initial study design was based on weekly IV infusions of AMG 820 at a starting dose of 0.5 mg/kg. In subsequent higher dose cohorts, the dosing regimen was revised to IV infusion over a 60-minute period Q2W. Escalation of AMG 820 dose was advanced through the 1.5, 3, 6, 10, and 20 mg/kg levels. After single intravenous infusion dosing, mean AMG 820 C_{max} exposures were increased by approximately 13-fold and AUC exposures were increased by approximately 24-fold over a 13.3-fold range (1.5 to 20 mg/kg) of dose levels. Over a narrower dose range from 3 to 20 mg/kg (6.7-fold), mean estimates of AUC increased by approximately 8-fold. At the 20 mg/kg Q2W dose level, mean

estimates of C_{max} and $AUC_{0\text{-}last}$ were 619 µg/mL and 89200 µg•hr/mL, respectively, after the first dose. AMG 820 accumulation in the systemic circulation was minimal (<2-fold) after repeated dose administration.

2.2.3 AMG 820 Pharmacodynamics

Serum CSF-1 levels were determined for several time points following each AMG 820 dose for subjects in the 0.5-mg/kg QW and 1.5-mg/kg to 20-mg/kg Q2W cohorts. At 0.5 mg/kg QW AMG 820, CSF-1 levels were observed to rise from baseline over 3 to 5 days following dosing before decreasing towards baseline. At higher doses of AMG 820 (1.5 mg/kg to 20 mg/kg Q2W AMG 820), CSF-1 levels were similarly increased after dosing and elevated CSF-1 levels were sustained for the remainder of the dosing interval. At 10 mg/kg Q2W AMG 820, CSF-1 levels appeared to reach a plateau after 3 weeks of exposure to AMG 820.

Changes in serum IL-34 levels over time were assessed in all cohorts. IL-34 levels did not demonstrate a dose-response relationship to AMG 820 administration.

2.2.4 AMG 820 Dose Rationale

In this study, AMG 820 will be administered at a fixed dose of 1400 mg in combination with 200 mg fixed dose of pembrolizumab as an intravenous infusion Q3W.

The AMG 820 dose of 1400 mg Q3W IV infusion is supported by AMG 820 PK and PD (serum CSF-1 concentration) observed in the first-in-human FIH study (20060347).

Maximum concentrations (C_{max}) are predicted to be within a range of observed C_{max} exposures at AMG 820 dose levels that were safe and tolerated in the FIH study. In addition, AMG 820 concentrations after IV infusion at 1400 mg are predicted to remain above concentrations associated with the observed maximum CSF-1 response in the FIH study.

In the FIH study, subjects received AMG 820 Q2W by IV infusion at doses that ranged from 1.5 to 20 mg/kg, with body weights ranging from 44.4 to 159 kg. Among all subjects, AMG 820 was determined to be safe and tolerated. A maximum tolerated dose level was not identified in the FIH study.

A transition from weight-based dosing (mg/kg) to fixed dosing (mg) is supported by AMG 820 PK in the FIH study. In terms of clinical experience, the 1400 mg AMG 820 dose is clearly bracketed by observed exposures in the FIH study. After accounting for body weights of subjects in the FIH study, the resulting increases in IV dose were from 102 mg to 2260 mg. Linear increases in the corresponding AMG 820 exposures

(C_{max} and C_{336h}) were observed for all subjects. Predictions of AMG 820 exposure at 1400 mg include:

- The range of C_{max} (at 1 hour, end of infusion) values observed in FIH subjects on day 1 were 44.9 to 744 µg/mL. At 1400 mg IV, a C_{max} of approximately 550 µg/mL was predicted from interpolation of C_{max} versus dose.
- The range of trough concentration (at 336 hours), C_{336h}, values observed in FIH subjects on day 1 were 1.23 to 231 µg/mL. At 1400 mg IV, a C_{336h} of approximately 150 µg/mL was predicted from interpolation of C_{336h} versus dose.

Importantly, a summary of C_{max} and AUC exposures from the FIH study, normalized by dose, did not reveal an apparent trend over the range of body weights of subjects, providing support for a flat-based dose approach.

In addition, a population PK model developed from the FIH study was used to predict trough concentrations anticipated at the end of the proposed 3 week dosing interval. Based on population PK predictions, following Q3W dosing of 1400 mg AMG 820, trough concentrations are predicted to remain above concentrations associated with maximum CSF-1 response observed in the FIH study.

2.3 Risk Assessment

There are no important identified risks for AMG 820.

Important potential risks for AMG 820 include increased extracellular matrix, infection, growth plate changes and immunogenicity. Refer to the AMG 820 IB for additional risk information.

No significant risks or drug-drug interactions with pembrolizumab are anticipated at the AMG 820 starting dose of 1400 mg in the proposed study. Explored AMG 820 dose levels ranging from 0.5 mg/kg QW and 1.5mg/kg to 20 mg/kg Q2W were generally well-tolerated in the FIH study. Approximately 25 subjects have received AMG 820. Treatment-related toxicities have been mild or moderate in most patients, and the most common toxicities are transient aspartate aminotransferase increase and periorbital edema. No subjects have developed treatment emergent neutralizing antibodies.

2.4 Non-Amgen Medicinal Product Background: Pembrolizumab

Pembrolizumab is a potent humanized immunoglobulin G4 (IgG4) monoclonal antibody (mAb) with high specificity of binding to the programmed cell death 1 (PD-1) receptor, thus inhibiting its interaction with programmed cell death ligand 1 (PD-L1) and programmed cell death ligand 2 (PD-L2). Based on preclinical in vitro data, pembrolizumab has high affinity and potent receptor blocking activity for PD-1.

Pembrolizumab has an acceptable preclinical safety profile and is in clinical development as an intravenous (IV) immunotherapy for advanced malignancies. Keytruda™ (pembrolizumab) is indicated for the treatment of patients across a number of indications. For more details on specific indications refer to the Pembrolizumab Investigator's Brochure.

2.5 Rationale

To date, anti-PD-1 antibodies have been approved for a number of indications However, the majority of patients do not show a response to monotherapy. A potential mechanism of resistance to anti-PD-1 therapy is the immunosuppressive activity of tumor infiltrating/associated macrophages, which may impair the T cells' ability to enter the tumor itself or hamper the intra-tumoral T cell activation. CSF-1R mediates proliferation, survival, and differentiation of tissue resident macrophages. Inhibition and depletion of TAMs through CSF-1R blockade may therefore relieve immunosuppressive pathways that restrict productive anti-tumor T cell responses and result in enhanced T cell responses against tumors. CSF-1R blockade as monotherapy was shown to reduce TAMs frequency in human tumors and pre-clinical murine tumor models, and had mild efficacy in syngeneic murine tumor models. CSF-1R blockade combined with chemo and/or T cell-targeted therapies, such as anti-PD-1, has led to increased T cell recruitment into tumors and enhanced efficacy. AMG 820 is a fully human IgG2 monoclonal antibody directed against human CSF-1R (c-fms) and represents a potential anti-tumor therapeutic approach by targeting macrophages in the tumor micro-environment. In a Phase 1 study, AMG 820 has shown a linear pharmacokinetic profile and promising pharmacodynamics effects (serum CSF-1 upregulation, depletion of macrophages in skin biopsies). AMG 820 dose options for Phase 2 were established without reaching a maximum-tolerated dose (MTD). Combination of a CSF-1R targeting antibody such as AMG 820, with an anti-PD-1 antibody like pembrolizumab may result in enhanced anti-tumor effect.

2.6 Clinical Hypotheses

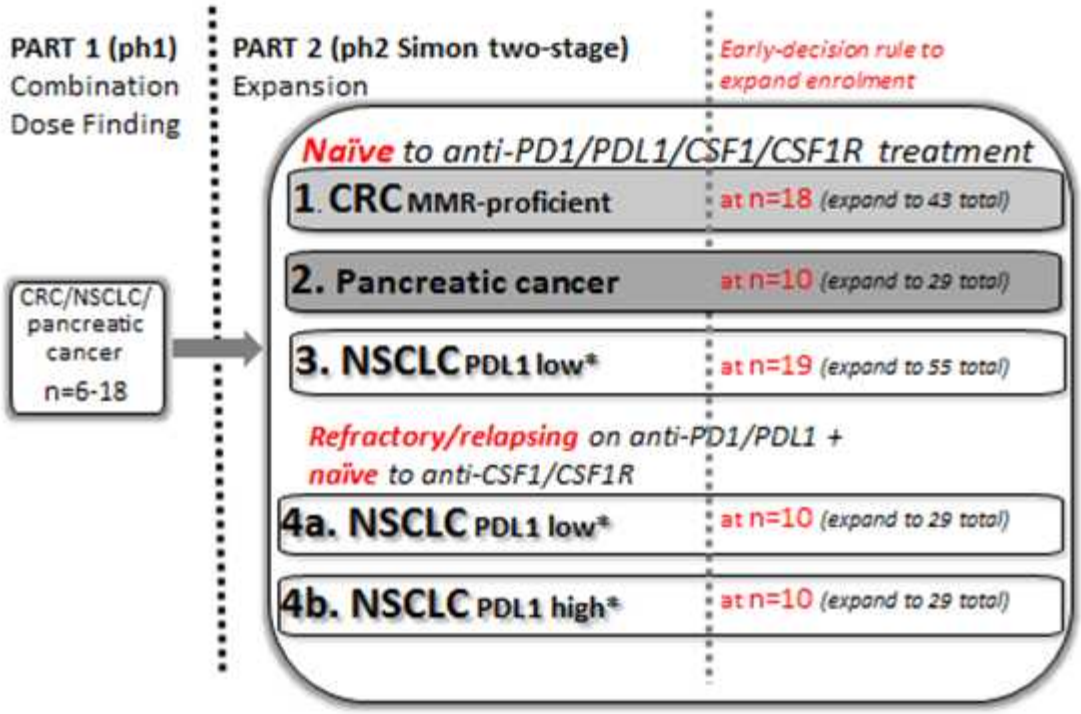
- AMG 820 in combination with pembrolizumab is safe and well tolerated when administered in subjects with select advanced solid tumors
- AMG 820 can enhance the anti-tumor activity observed with pembrolizumab alone and/or overcome lack of response to pembrolizumab monotherapy in subjects with select advanced solid tumors

3. EXPERIMENTAL PLAN

3.1 Study Design

This is a multi-center Phase 1b/2 study testing the combination of AMG 820 and pembrolizumab in subjects with select advanced solid tumors. Part 1 will evaluate safety of the selected starting dose for the combination. Part 2 will further evaluate safety and test whether AMG 820 in combination with pembrolizumab can enhance the anti-tumor activity observed historically with pembrolizumab alone and/or overcome lack of response to pembrolizumab monotherapy. Study part 2 will follow a Simon two-stage design to evaluate 4 groups as per the figure below:

Figure 1. Phase 1b/2 Simon Two-stage Study Design



**PD-L1 low expression defined as <50% staining, high expression ≥50%*

Eligible subjects enrolled in the study will receive AMG 820 1400 mg in combination with 200 mg pembrolizumab as an intravenous infusion Q3W. AMG 820 will initially be tested at a dose of 1400 mg Q3W based on the safety and tolerability demonstrated in the first-in-human study, which evaluated doses up to 20 mg/kg Q2W. In addition, maximal sustained serum concentrations of CSF-1 were observed at AMG 820 doses of 10 mg/kg Q2W and above. Pembrolizumab will be administered Q3W at a dose of 200 mg based on the dose currently being evaluated in pembrolizumab trials with registration intent in head and neck cancer.

If the starting dose is not well tolerated, the lower pre-specified nominal AMG 820 dose levels to be explored are 1100 mg and 800 mg Q3W. The de-escalated doses of AMG 820 at 1100 mg and 800 mg are anticipated to result in lower serum AMG 820 concentrations, based on inter-subject PK variability observed in the first-in-human study, while maintaining maximal sustained serum concentrations of CSF-1 observed at AMG 820 doses of 10 mg/kg Q2W and above. The pembrolizumab dose level will remain at 200 mg Q3W. While on study, subjects will undergo radiological MRI or CT assessment, and clinical measurement of their tumor lesions during week 10 ± 1 week, and at 10 ± 2 week intervals thereafter. In accordance with the irRECIST criteria, in absence of clinical deterioration the subjects may continue on AMG 820 and pembrolizumab until progressive disease is confirmed by a subsequent scan and/or clinical evaluation of tumor lesions 4 to 6 weeks after the first detection of tumor progression. Subjects will be treated with AMG 820 and pembrolizumab until confirmed disease progression per modified irRECIST (Appendix D), or intolerance of study treatment, or clinically significant deterioration of health status requiring discontinuation, whichever occurs first, or the subject withdrawal of consent. Due to the mechanism of action of immune-enhancing therapies, subjects may experience enhanced T cell expansion and infiltration into tumors, leading to an apparent enlargement of existing lesions or the appearance of new lesions prior to maximal clinical benefit being observed. A modified response criteria is necessary to allow the potential delayed clinical response to immune-enhancing therapies to be captured more accurately.

The overall study design is also described by a detailed study schema at the end of the protocol synopsis section.

The study endpoints are defined in Section 10.1.1.

3.1.1 Phase 1b Study Design (Part 1)

Part 1 of the study has a single-arm 6+3 design aimed at assessing the safety of the selected starting dose of AMG 820 in combination with pembrolizumab. It will be conducted in subjects with select advanced solid tumors (CRC, pancreatic cancer, NSCLC and potentially other tumor types as per eligibility criteria). If the selected starting dose is determined not tolerable following review of safety data, additional lower dose levels will be evaluated. Up to 3 cohorts will be evaluated for safety and will include at least 6 subjects per cohort, and up to 18 subjects in total. The initial cohort will treat subjects at the selected starting dose of 1400 mg AMG 820 plus 200 mg pembrolizumab Q3W. The period for evaluation of a DLT in cycle 1 is 21 days. A

subject is not DLT-evaluable if he/she drops out before completion of cycle 1 for reasons other than an adverse event related to study drug.

- If 0 or 1 of the initial 6 evaluable subjects experience a dose-limiting toxicity (DLT) then the dose combination will be determined to be tolerable and Part 2 initiated.
- If 2 of the initial 6 evaluable subjects experience a DLT then 3 additional evaluable subjects will be enrolled.
- If 3 or more of the evaluable subjects experience a DLT (eg, 33% or higher with 9 evaluable subjects) then the dose combination will be determined to be non-tolerable and a second Part 1 cohort will be enrolled to test a decreased dose of AMG 820 in combination with 200 mg pembrolizumab. Further degree of dose modification and/or schedule of administration will be decided based on analysis of emerging safety and PK data.

Prior to opening a subsequent cohort for enrollment, the Dose Level Review Team (DLRT) will evaluate data from subjects enrolled into prior cohorts (at least 21 days of safety follow-up) including events with a longer onset time or events following exposure to multiple doses. If late onset events occur during a cohort, the DLRT may adaptively re-consider the doses evaluated within a cohort for subsequent dosing and/or possibly trigger a de-escalation or withholding of additional doses in subsequent cohorts.

3.1.2 Phase 2 Study Design

The primary objective of study Part 2 is to further evaluate safety and efficacy of the combination dose in the 4 selected CRC, pancreatic cancer and NSCLC subject groups. Other tumor types may be explored based on emerging data. The dose or doses to be evaluated in Part 2 will be based on results from Part 1. Part 2 will begin after safety of the dose level(s) explored in Part 1 has been assessed and determined to be safe.

Part 2 will include 6-9 subjects from Part 1 who have been treated with the recommended combination dose, and will enroll additional CRC, pancreatic cancer and NSCLC subjects following a Simon two-stage design: stage 1 will enroll up to 67 subjects overall, stage 2 may add another 118 subjects as per the rules described below. The recommendations to enroll stage 2 are based on ORR (see rules described below); nonetheless, the DLRT (see Section 6.2.1.2.1) will make decisions after reviewing all available safety, efficacy, pharmacokinetic and pharmacodynamic data. Analysis of data in Part 2 will be done separately for each group (Group 1, 2, 3, 4a, 4b).

- Group 1 will enroll up to 43 advanced MMR-proficient CRC subjects who are naïve to anti-PD-1/PD-L1/CSF-1/CSF-1R therapies. Eighteen (18) subjects will be enrolled during the first stage and treated with the AMG 820 plus pembrolizumab combination. If 2 or fewer subjects have an objective response per irRECIST then,

depending on the review of all available data, further enrollment may be discontinued; otherwise, enrollment up to 43 subjects will occur.

- Group 2 will enroll up to 29 advanced pancreatic cancer subjects who are naïve to anti-PD-1/PD-L1/CSF-1/CSF-1R therapies. Ten (10) subjects will be enrolled during the first stage and treated with the AMG 820 plus pembrolizumab combination. If no subjects have an objective response per irRECIST then, depending on the review of all available data, further enrollment may be discontinued; otherwise, enrollment up to 29 subjects will occur.
- Group 3 will enroll up to 55 advanced NSCLC subjects with low (< 50%) tumor PD-L1- expression who are naïve to anti-PD-1/PD-L1/CSF-1/CSF-1R agents. Nineteen (19) subjects will be enrolled during the first stage and treated with the AMG 820 plus pembrolizumab combination. If 3 or fewer subjects have an objective response per irRECIST then, depending on the review of all available data, further enrollment may be discontinued; otherwise, enrollment up to 55 subjects will occur.
- Group 4 will enroll up to 58 NSCLC subjects who have not responded to or have relapsed during monotherapy with anti-PD-1/PD-L1 agents and are anti-CSF-1/CSF-1R naïve. These subjects will be further distributed equally between two sub-groups (4a and 4b) depending on the PD-L1 expression in the tumor tissue: high (≥ 50%) and low (< 50%) expression (up to 29 in each sub-group). For each sub-group, an initial set of 10 subjects will be enrolled during the first stage and treated with the AMG 820 plus pembrolizumab combination. If no subjects have an objective response per irRECIST for either subgroup then, depending on the review of all available data, further enrollment may be discontinued; otherwise, enrollment up to 58 subjects will occur.

The overall study design is described by a study schema at the end of the protocol synopsis section and Figure 1 above.

3.2 Number of Sites

The study will be conducted at approximately 15 sites in Australia, Canada, the United States, and Europe. Additional sites and countries may be added.

Sites that do not enroll subjects within 4 months of site initiation may be closed.

3.3 Number of Subjects

Participants in this clinical investigation shall be referred to as “subjects”.

Overall, this study may enroll between 67 and 197 subjects. Six (6) to eighteen (18) subjects will be enrolled in part 1. Once the safety of the recommended dose of the combination is established in Study Part 1, stage 1 of Study Part 2 will expand enrollment up to 67 subjects (including 6-9 subjects from Part 1 who have been treated with the recommended combination dose). The subsequent stage 2 of part 2 may add another 118 subjects as per the study design rules.

Refer to Section 10.2 for sample size considerations.

3.4 Replacement of Subjects

Subjects enrolled may be replaced if they are not evaluable for DLT (eg, a subject did not receive study treatment, or ended the study treatment before completion of DLT evaluation period for a reason other than experiencing a DLT).

3.5 Estimated Study Duration

3.5.1 Study Duration for Subjects

The duration of screening for each subject will be approximately 28 days. The duration of treatment will vary for each subject. Subjects enrolled in Part 1 and 2 of the study can be treated for up to 24 months if treatment is tolerable and clinical benefit is observed. All subjects will complete a safety follow-up visit approximately 135 (+7) days after the last dose of study treatment. After the safety follow-up visit, depending on the duration of their treatment on the study, some subjects will enter the long-term follow-up. The goal of the long-term follow-up is to obtain disease progression and survival information for a period of 12 months after the first combination dose. The actual duration of the study for an individual subject is dependent upon the time required to assess PFS and OS at 12 months.

For subjects who continue treatment past 12 months and up to 24 months (if tolerable and clinical benefit is observed), only Visit Date, IP Administration, and AE/SAE information will be collected in EDC. Remaining follow-up to be performed per institutional standard of care.

3.5.2 End of Study

Primary Completion: is anticipated to occur when all Study Part 1 and 2 subjects have been enrolled and treated for at least 12 months, been followed up for PFS and OS at 12 months or discontinued from the study.

End of Trial: is when the last subject is assessed or receives an intervention for evaluation in the study. This is anticipated to occur no sooner than when the last subject enrolled in the study has been followed for at least 12 months after the administration of the first combination dose of study treatment.

4. SUBJECT ELIGIBILITY

Investigators will be expected to maintain a screening log of all potential study candidates that includes limited information about the potential candidate (eg, date of screening).

Before any study-specific activities/procedure, the appropriate written informed consent must be obtained (see Section 11.1). All windows in Inclusion and Exclusion criteria below are relative to first day of study treatment.

4.1 Inclusion Criteria

101 Subject has provided informed consent prior to initiation of any study-specific activities/procedures

102 Male or female age ≥ 18 years at the time of informed consent

103 Pathologically documented, definitively diagnosed, advanced CRC, pancreatic cancer or NSCLC that is refractory to standard treatment, or the subjects have been intolerant to or refuse standard treatment. The select tumor types must also meet the following criteria:

- Part 1 and Group 1: advanced MMR-proficient CRC subjects naïve to anti-PD-1/PD-L1/CSF-1/CSF-1R therapies
- Part 1 and Group 2: advanced pancreatic cancer subjects with good performance status (defined as ECOG 0-1, good pain management and adequate nutritional intake) naïve to anti-PD-1/PD-L1/CSF-1/CSF-1R therapies
- Part 1 and Group 3: advanced NSCLC subjects with *low* (< 50%) tumor PD-L1- expression naïve to anti-PD-1/PD-L1/CSF-1/CSF-1R therapies
- Part 1 and Group 4a: NSCLC subjects with *low* (< 50%) tumor PD-L1-expression who are anti-CSF-1/CSF-1R naïve and have not responded to (disease progression or stable disease > 6 months) or have relapsed during monotherapy with anti-PD-1/PD-L1 therapies
- Part 1 and Group 4b: NSCLC subjects with *high* (≥ 50%) tumor PD-L1-expression who are anti-CSF-1/CSF-1R naïve and have not responded to (disease progression or stable disease > 6 months) or have relapsed during monotherapy with anti-PD-1/PD-L1 therapies

104 Subject must have radiographically and/or clinically measurable disease per RECIST 1.1 (Eisenhauer et al, 2009). Index lesions must not be chosen from a previously irradiated field unless there has been radiographic tumor progression in that lesion prior to enrollment. See Note: Appendix D for index lesion and non-index lesion criteria.

105 ECOG performance status of 0 - 1

106 Adequate organ function determined prior to enrollment, defined as follows:

- Hematological
  - ANC ≥ 1.5 x 10^9/L
  - platelet count ≥ 100 x 10^9/L
  - hemoglobin ≥ 9 g/dL (without need for hematopoietic growth factor or transfusion support)
- Renal
  - serum creatinine ≤ 1.5 x upper limit of normal (ULN), OR 24 hr creatinine clearance ≥ 60 mL/min for subject with creatinine levels > 1.5 x ULN.

(Note: Creatinine clearance need not be determined if the baseline serum creatinine is within normal limits. Creatinine clearance should be determined per institutional standard).

- Hepatic
  - serum bilirubin ≤ 1.5 x ULN OR direct bilirubin ≤ ULN for a subject with total bilirubin level > 1.5 x ULN
  - aspartate aminotransferase (AST) ≤ 2.5 x ULN OR ≤ 5 x ULN for subject with liver metastases
  - alanine aminotransferase (ALT) ≤ 2.5 x ULN OR ≤ 5 x ULN for subject with liver metastases
- Coagulation
  - international normalization ratio (INR) or prothrombin time (PT) ≤ 1.5 x ULN, unless the subject is receiving anticoagulant therapy, in which case PT and partial thromboplastin time (PTT)/activated PTT (aPTT) must be within therapeutic range of intended use of anticoagulants
  - PTT or aPTT ≤ 1.5 x ULN unless the subject is receiving anticoagulant therapy as long as PT and PTT/aPTT is within therapeutic range of intended use of anticoagulants

107 Subjects with NSCLC: Available information regarding recently (within 3 months prior to day 1 and no systemic therapy given since the biopsy) evaluated PD-L1 tumor expression status or willing to provide fresh tumor biopsy to determine eligibility. NSCLC subjects that failed to respond to or relapse during previous anti-PD-1/PD-L1 inhibitors immediately before considering enrolling into current study, may be accepted into the trial based on previously established PD-L1 tumor expression, if discussed and agreed by the Sponsor.

108 Subjects with CRC: Availability of a recent (within 3 months prior to day 1 and no systemic therapy given since the biopsy) and biomarker evaluable tumor tissue sample required at baseline.

109 Subjects with pancreatic cancer: Availability of a recent (within 3 months prior to day 1 and no systemic therapy given since the biopsy) and biomarker evaluable tumor tissue sample required at baseline, whenever feasible.

4.2 Exclusion Criteria

201 Has known active central nervous system (CNS) metastases and/or carcinomatous meningitis. Subjects with previously treated brain metastases may participate provided they are stable (without evidence of progression by imaging for at least four weeks prior to the first study dose and neurologic symptoms should have returned to baseline), have no evidence of new or progressing brain lesions, and are not using steroids > 10 mg prednisone equivalent for at least 7 days prior to trial treatment. This exception does not include carcinomatous meningitis which is excluded regardless of clinical stability.

202 History of other malignancy within the past 2 years with the following exceptions:

- malignancy treated with curative intent and with no known active disease present and has not received chemotherapy for ≤ 2 years before enrollment and felt to be at low risk for recurrence by the treating physician

- adequately treated non-melanoma skin cancer, cervical carcinoma *in situ*, superficial or *in situ* carcinoma of the bladder or breast ductal carcinoma *in situ*, without evidence of disease for any of these at the time of enrollment
- prostatic intraepithelial neoplasia without evidence of prostate cancer at the time of enrollment

203 Subject has history of interstitial lung disease, (non-infectious) pneumonitis that required steroids, or current pneumonitis.

204 History or evidence of other active autoimmune diseases that has required prolonged systemic treatment in past 2 years (ie, with use of disease modifying agents such as corticosteroids or immunosuppressive drugs).

Note: Replacement therapy (eg, thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency, etc.) is not considered a form of systemic treatment.

205 Evidence of clinically significant immunosuppression such as the following:

- organ transplant or prior stem cell transplantation
- any severe congenital or acquired cellular and/or humoral immune deficiency
- other signs or symptoms of clinical immune system suppression or diagnosis of immunodeficiency
- concurrent opportunistic infection

206 receiving systemic immunosuppressive therapy (> 2 weeks) within 7 days prior to the first dose of study treatment, including oral steroid doses > 10 mg/day of prednisone or equivalent except for management of adverse events during the course of the study. Subjects that require intermittent use of bronchodilators or local steroid injection will not be excluded from the study.

207 receiving systemic immunostimulatory agents within 6 weeks or five half-lives, whichever is shorter, prior to first dose of study treatment (except anti PD-1/PD-L1 treatment if recruited into Group 4a or 4b).

208 Evidence of active infection within 2 weeks prior to first dose of study treatment.

209 Prior chemotherapy, radiotherapy, biological cancer therapy or major surgery within 28 days prior to enrollment. Note: patients may have received anti PD-1/PD-L1 treatment if recruited into group 4a and 4b (refractory/relapsed on anti-PD-1/PD-L1 + naïve to CSF-1/CSF-1R treatment).

210 Currently participating or has participated in a study (treatment period only) of an investigational agent or used an investigational device within 28 days of enrollment.

211 Adverse event due to cancer therapy administered more than 28 days prior to enrollment that has not recovered to CTCAE grade 1 or better. Note: Subjects with ≤ grade 2 neuropathy and alopecia are an exception to this criterion and may qualify for the study.

212 Expected to require other cancer therapy while on study (eg, need of local palliative radiation treatment to the site of bone and other metastasis will be considered sign of clinical progression).

213 Other investigational procedures while participating in this study are excluded.

214 Positive for human immunodeficiency virus (HIV).

215 Hepatitis B and C based on the following results:

- Positive for hepatitis B surface antigen (HBsAg) (indicative of chronic hepatitis B or recent acute hepatitis B).
- Negative HBsAg and positive for hepatitis B core antibody: hepatitis B virus DNA by polymerase chain reaction (PCR) is necessary. Detectable hepatitis B virus DNA suggests occult hepatitis B.
- Positive Hepatitis C virus antibody (HCVAb): hepatitis C virus RNA by PCR is necessary. Detectable hepatitis C virus RNA suggests chronic hepatitis C

216 Received live vaccine within 28 days prior to enrollment.

217 Men of reproductive potential and women of childbearing potential who are unwilling to practice a highly effective method(s) of birth control while on study through 4 months after receiving the last dose of study drug. Highly effective methods of birth control are defined as those which result in a low failure rate (ie, less than 1% per year) when used consistently and correctly such as implants, injectables, combined oral contraceptives, intrauterine devices (IUDs), sexual abstinence or vasectomised partner.

Note: Men and women who do not meet the definitions below are considered to be of reproductive potential or childbearing potential respectively.

- Men of non-reproductive potential are defined as having azoospermia, whether due to having had a vasectomy or due to an underlying medical condition.
- Women not of childbearing potential are defined as: Any female who is postmenopausal defined as at least 12 months with no menses without an alternative medical cause; in women < 45 years of age, a high follicle stimulation hormone [FSH] level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy; in the absence of 12 months of amenorrhea, a single FSH measurement is sufficient OR have had a hysterectomy and/or bilateral oophorectomy, or bilateral salpingectomy at least 6 weeks prior to screening, OR has a congenical or acquired condition that prevents childbearing.

218 Women who are lactating /breastfeeding or who plan to breastfeed while on study through 4 months after receiving the last dose of study drug.

219 Women with a positive pregnancy test.

220 Women planning to become pregnant while on study through 4 months after receiving the last dose of study drug.

221 Subject has known sensitivity to any of the products or components to be administered during dosing.

222 Subject likely to not be available to complete all protocol-required study visits or procedures, and/or to comply with all required study procedures to the best of the subject and investigator's knowledge.

223 History or evidence of psychiatric, substance abuse, or any other clinically significant disorder, condition or disease (with the exception of those outlined above) that, in the opinion of the investigator or sponsor physician, if consulted, would pose a risk to subject safety or interfere with the study evaluation, procedures or completion.

5. SUBJECT ENROLLMENT

Before subjects begin participation in any study-specific activities/procedures, Amgen requires a copy of the site's written IRB/IEC approval of the protocol, informed consent form, and all other subject information and/or recruitment material, if applicable (see Section 11.2). All subjects must personally sign and date the IRB/IEC and Amgen approved informed consent form before commencement of study-specific activities/procedures.

A subject is considered enrolled when the investigator decides that the subject has met all eligibility criteria. The investigator is to document this decision and date, in the subject's medical record and in/on the enrollment case report form (CRF).

Each subject who enters into the screening period for the study (defined when the subject signs the informed consent) receives a unique subject identification number before any study-related activities/procedures are performed. The subject identification number will be assigned manually. This number will be used to identify the subject throughout the clinical study and must be used on all study documentation related to that subject. Subjects who do not meet all eligibility criteria may be rescreened at the discretion of the investigator. If a subject is being rescreened, he or she may need to reconsent to the study to ensure that the IRB/IEC approved main informed consent form is signed within 28 days of enrollment. Subjects who are determined not eligible after rescreen must be screen-failed and the reason for the screen-failure provided. Subjects may only be enrolled once into this study.

The subject identification number must remain constant throughout the entire clinical study; it must not be changed after initial assignment, including if a subject is rescreened.

5.1 Treatment Assignment

All subjects enrolled into the study will receive open-label AMG 820 in combination with pembrolizumab. The treatment assignment date is to be documented in the subject's medical record.

6. TREATMENT PROCEDURES

6.1 Classification of Product(s) and/or Medical Device(s)

The Amgen Investigational Product used in this study is AMG 820.

The Non-Amgen Investigational product(s) used in this study is pembrolizumab. The Investigational Product Instruction Manual (IPIM), a document external to this protocol, contains detailed information regarding the storage, preparation, destruction, and administration of AMG 820 and pembrolizumab.

6.2 Investigational Product

AMG 820 and pembrolizumab will be administered intravenously Q3W on the same day in sequence. The recommended starting dose of AMG 820, 1400 mg, is guided by the AMG 820 First in Human study. Pembrolizumab will be administered at 200 mg and will remain unchanged during the course of the study. If the treatment combination is not well tolerated during Study Part 1, AMG 820 will be de-escalated to pre-specified nominal dose levels, 1100 mg and 800 mg.

AMG 820 must be administered before pembrolizumab on the same treatment day. The pembrolizumab infusion is to begin 15 minutes following the end of the AMG 820 infusion.

6.2.1 Amgen Investigational Product: AMG 820

AMG 820 will be manufactured and packaged by Amgen Inc. and distributed using Amgen clinical study drug distribution procedures. AMG 820 will be presented as a sterile, clear, colorless to slightly yellow frozen liquid in 20 mL glass vials. Each glass vial will contain 3.0 mL of AMG 820 with a concentration of 70 mg/mL.

6.2.1.1 Dosage, Administration, and Schedule: AMG 820

AMG 820 must be prepared and administered by a qualified healthcare professional. Subjects should be assessed clinically for adverse events/toxicity prior to each dose using the CTCAE version 4 (Appendix A). Complete blood count with differential and chemistry panels including liver enzyme laboratory tests (ALT and AST) and total bilirubin should be obtained according to the Schedule of Assessments (Table 5) and the results should be checked within 2 days prior to each treatment.

Each cycle of AMG 820 will be 3 weeks. The initial cohort will treat subjects with 1400 mg AMG 820 plus 200 mg pembrolizumab Q3W. All subsequent doses will be administered Q3W (± 3) days. The treatment cycle interval may be increased due to toxicity as described in Section 6. AMG 820 must be administered before pembrolizumab on treatment days. Lower AMG 820 dose levels may be explored based on emerging safety data during study part 1. If a subject requires corticosteroid dosing of > 10 mg prednisone daily (or equivalent) as supportive care, AMG 820 and pembrolizumab dosing must be withheld until the corticosteroid dose has decreased to ≤ 10 mg prednisone daily (or equivalent).

AMG 820 will be diluted with the appropriate amount of 0.9% NaCl for a total volume of 100 mL. The final concentration of the AMG 820 will be 14 mg/mL (1400 mg total dose).

AMG 820 preparations will be administered via intravenous (IV) infusion, through a 0.22 µm, low protein binding filter, over a 60-minute period during the first dosing administration. If the first administration is well-tolerated, the investigator may adopt a 30-minute infusion period for subsequent infusions. A physician or medical staff involved in study evaluation must be available during the administration of the investigational product to assess and treat adverse events that may arise during dosing. Subjects will be monitored in the clinic for at least 2 hours or longer if necessary, following dosing of drug combination for the first 3 cycles and as needed thereafter.

The effects of overdose of this product are not known.

Subjects will be treated with AMG 820 plus pembrolizumab until subjects experience confirmed PD as per irRECIST, intolerance to study treatment, or until the end of study, whichever occurs first. The dose, start date, and lot number of AMG 820 are to be recorded on each subject's CRF.

6.2.1.2 Dose-cohort Study Exploration and Stopping Rules

6.2.1.2.1 Dose Level Review Meetings

A Dose Level Review Team (DLRT) will review the safety data to evaluate DLT. The DLRT will be composed of the Investigator(s), Amgen Medical Monitor / Early Development Leader, Amgen Global Safety Officer or designee, Amgen Clinical Research Study Manager (CRSM) and Biostatistics representative or designee. Additional members may be added as needed (eg, clinical pharmacologist). A quorum, defined as ≥ 50% of the participating investigators or their qualified designee (ie, sub-PI or research nurse or study coordinator possessing hard copy documentation [eg, e-mail]

of the PI's vote), must be in attendance for DLRM. The DLRM will be rescheduled if a quorum is not reached.

The DLRM members will recommend dosing decisions, which may include enrolling more subjects for DLT evaluation in part 1 of the study, de-escalation to a lower dose, delay or termination of dosing, or declare that the combination is tolerable based on DLT evaluation period data. All DLRT decisions will be communicated to team members via formal correspondence.

The Dose Level Review Team (DLRT) will evaluate data from all subjects enrolled into all cohorts including events with a longer onset time or events following exposure to multiple doses. If late onset events occur during a cohort, the DLRT may adaptively re-consider the doses evaluated within a cohort for subsequent dosing and/or possibly trigger a de-escalation or withholding of additional doses in subsequent cohorts. For Part 2 of the study, DLRT safety reviews will only be held during stage 1. A total of 3 DLRT safety reviews will occur: after the first 20 subjects (collectively from all 5 groups) have enrolled and completed 2 cycles of therapy, after an additional 20 subjects have enrolled and completed 2 cycles of therapy and after all subjects in stage 1 have enrolled completed 2 cycles of therapy.

The DLRT may request additional reviews or recommend modifying or suspending the study if safety concerns arise during the study. Refer to Section 10.3.2 for additional details regarding the DLRT.

All DLRM requirements are outlined in the protocol. A DLRM Charter will not be used.

6.2.1.2.2 Rules for DLT Evaluation in Part 1 of the study

The DLT evaluation period for a subject is 21 days from the initial administration of study treatment. To be evaluable for a DLT, subjects must have had the opportunity to be on treatment for at least 21 days from the initial dosing of study treatment and have received at least 1 dose of AMG 820 and 1 dose of pembrolizumab in combination, or have a DLT during the DLT evaluation period after at least 1 dose of AMG 820 and pembrolizumab. Subjects may be replaced if they are not evaluable for DLT to obtain at least 6 DLT-evaluable subjects in a cohort during Study Part 1 (eg, a subject did not receive study treatment, or ended the study treatment before completion of DLT evaluation period for a reason other than experiencing a DLT).

Safety will be evaluated considering the incidence of DLTs among all DLT-evaluable subjects enrolled in part 1, which will include up to 3 cohorts. The initial cohort will treat subjects with 1400 mg AMG 820 plus 200 mg pembrolizumab Q3W using a 6+3 design.

- If 0 or 1 of the initial 6 evaluable subjects experience a dose-limiting toxicity (DLT) then the dose combination will be determined to be tolerable and Study Part 2 will be initiated.
- If 2 of the initial 6 evaluable subjects experience a DLT then 3 additional evaluable subjects will be enrolled.
- If 33% or more of the evaluable subjects experience a DLT then the dose combination will be determined to be non-tolerable and a second Part 1 cohort will be enrolled to test a decreased dose of AMG 820 in combination with 200 mg pembrolizumab. Further degree of dose modification and/or schedule of administration will be decided based on analysis of emerging safety and PK data.

6.2.1.2.3 Dose-limiting Toxicity Definition

An adverse event will be considered related to study treatment (possibly, probably, or definitely related to the study treatment) if there is a suspected "reasonable causal relationship" to the study treatment (ICH E2A), and not only a lack of an alternative explanation for the toxicity. All toxicities will be graded using the CTCAE version 4.0 (Appendix A).

The occurrence of any of the following toxicities during DLT evaluation period (ie, 21 day period from the initial administration of AMG 820 and pembrolizumab in combination) will be considered a DLT, if judged by the investigator to be related to the administration of AMG 820 and/or pembrolizumab:

- Grade 4 non-hematologic toxicity
- Grade 3 or higher pneumonitis
- Grade 3 non-hematologic toxicity lasting > 7 days despite appropriate treatment
  - Grade 3 fatigue will not be classified as DLT, irrespective of duration
- Any grade 3 or higher non-hematologic laboratory value if:
  - medical intervention is required, or
  - the abnormality leads to hospitalization, or
  - the abnormality persists at grade 3 or higher for >1 week unless deemed not clinically important per both investigator and sponsor
- Grade 3 or grade 4 febrile neutropenia

- Grade 3 or higher thrombocytopenia with bleeding and Grade 4 or higher thrombocytopenia lasting > 48 hours or any thrombocytopenia requiring intervention
- Delay in cycle 2 treatment for > 2 weeks due to study drug-related toxicity (unless clearly attributable to pembrolizumab only and delay is caused due to tapering of steroids)
- Any other intolerable toxicity leading to permanent discontinuation of AMG 820 or pembrolizumab

Lymphopenia of any grade is not considered a DLT

Dose limiting toxicities do not include the following:

- A transient (resolving to grade ≤ 1 within 6 hours of onset) grade 3 infusion-related adverse event
- Any grade 3 endocrinopathy that is adequately controlled by hormonal replacement

Cumulative adverse events profile will be taken into consideration when making decisions on dose escalation or de-escalation.

If an AE is clearly attributable to pembrolizumab (based on its known safety profile) and does not exceed the expected severity, this specific AE may be considered exempt from being a DLT.

Disease related events should not be considered a DLT.

Any subject meeting the criteria for Hy's Law case (ie, severe drug-induced liver injury) will be considered a DLT. A Hy's Law case is defined as: AST or ALT values of ≥ 3 x ULN AND with serum total bilirubin level (TBL) of > 2 x ULN without signs of cholestasis and with no other clear alternative reason to explain the observed liver-related laboratory abnormalities (see Section 6.4 on hepatotoxicity management and Appendix A for further explanation of Hy's law case and Management of Hepatic Function).

If a subject experiences a DLT during the DLT evaluation period, study treatment should be discontinued for that subject. Additionally, any treatment related toxicity meeting the DLT definition after day 21 should result in discontinuation of therapy. In subjects with irPR, irCR or evidence of clinical benefit (as determined by the investigator), an option to continue at the same or at a reduced dose level can be considered once the toxicity returns to the subject's baseline value or CTCAE grade ≤ 1 if deemed appropriate by the investigator and sponsor.

6.2.1.2.4 Determination of Adverse Event Severity and Relatedness

Determination of the severity of adverse events will be consistent with CTCAE, version 4.0. The relationship of an adverse event to investigational product will be determined by the investigator. An adverse event will be considered related to study treatment (possibly, probably, or definitely related to the study treatment) if there is a suspected "reasonable causal relationship" to the study treatment (ICH E2A), and not only a lack of an alternative explanation for the toxicity *(NCI Guidelines for Investigators - Adverse Event Reporting Requirements , Sept, 2013)* (see Section 9 – Safety Data Collection, Recording, and Reporting).

6.2.1.2.5 Cohort Dose Level Determination

Study Part 1

A Dose Level Review Team (DLRT) will convene before a decision is made to open study Part 2. At the start of Part 1, enrollment of the first cohort of 6 to 9 evaluable patients will open for enrollment with a starting dose of AMG 820 1400 mg plus pembrolizumab 200 mg Q3W. Following subject completion of the DLT period, the DLRT will review all available safety data for the first cohort. If the data supports continued dosing at the selected starting dose, study Part 2 will be initiated at the same dose level. If it is determined that the starting dose is non-tolerable (if 33% or more of the evaluable subjects experience a DLT), dose de-escalation will occur and a second Part 1 cohort will be enrolled to test a decreased dose of AMG 820 in combination with 200 mg pembrolizumab Q3W. This will occur until identification of a well-tolerated dose for study Part 2. The AMG 820 (mg) pre-specified nominal cohort dose levels to be explored are 1100 mg and 800 mg Q3W. The pembrolizumab dose level will remain at 200 mg Q3W.

Part 2

Part 2 will have 4 groups, which will be evaluated using a Simon two-stage design:

Table 1. Study Part 2 Subject Groups

Naïve to anti-PD-1/PD-L1/CSF-1/CSF-1R treatment	
Group 1	$CRC_{MMR\text{-}proficient}$
Group 2	Pancreatic Cancer
Group 3	$NSCLC_{PD\text{-}L1\ low}$
Refractory/ relapsing on anti-PD-1/PD-L1 + naïve to CSF-1/CSF-1R treatment	
Group 4a	$NSCLC_{PD\text{-}L1\ low}$
Group 4b	$NSCLC_{PD\text{-}L1\ high}$

The dose or doses (proposed recommended phase 2 dose, RP2D) to be evaluated in part 2 of the study will be based on results from part 1. The DLRT may determine the RP2D, which is defined as a dose(s) that is/are safe and produces pharmacodynamic effects. Emerging safety data may be used to re-challenge the selected dose in Study Part 1. If the initially selected dose is re-challenged, additional subjects may be enrolled in the corresponding cohort. In addition, the study may be discontinued or modified at any time due to documented safety findings.

Enrollment into the second stage of the Simon two-stage design will be determined by results through Study Part 2 stage 1.

All dose level and enrollment decisions will be formally communicated to investigators via a memorandum.

The dosing schedule is described by a schema in the protocol synopsis.

6.2.1.3 Dosage Adjustments, Delays, Rules for Withholding or Restarting, Permanent Discontinuation: AMG 820

A subject experiencing a DLT (days 1-21) will not receive additional AMG 820 plus pembrolizumab treatment and will be followed until resolution of the event or toxicity. Subjects withdrawn from AMG 820 plus pembrolizumab therapy will be treated as deemed appropriate by the investigator. End of study procedures should be performed and the appropriate CRFs should be completed. Any treatment related toxicity meeting the DLT definition after day 21 may result in discontinuation of therapy. In subjects with irPR, irCR or evidence of clinical benefit (as determined by the investigator), an option to continue at the same dose level or a lower dose level can be considered. If deemed appropriate by the investigator and sponsor, AMG 820 can be re-initiated once the

toxicity returns to the subject's baseline value or CTCAE grade ≤ 1. For subjects with hepatotoxicity, refer to Section 6.4. For such subjects, there will be an increased frequency of monitoring at an interval deemed appropriate by the investigator and sponsor. Subjects requiring more than 6 weeks from the last dose to recover from AMG 820 and/or pembrolizumab related grade 3 or 4 toxicities that meet the definition of a DLT will be permanently discontinued (please also see Table 2 for additional details).

If a subject experiences ≥ grade 3 toxicities or SAEs that are unrelated to AMG 820 and/or pembrolizumab, then treatment will be postponed until the toxicity has resolved to grade 1 (as defined by the CTCAE, version 4) or returns to the subject's baseline value. If the treatment break is longer than 6 weeks from the last dose the subject may resume treatment only after discussing the case with the Sponsor. If resuming treatment, AMG 820 may be administered at the same dose level or a lower dose level as per the Principal Investigator and Sponsor.

In the event one of the combination drugs is delayed or permanently discontinued for related toxicity, the subjects will have the option to continue on the other drug as long as the toxicity is clearly not related to the combination partner and the investigator and Sponsor assessment is that the patient may derive benefit from continuation with monotherapy.

6.2.2 Non-Amgen Investigational Product: Pembrolizumab

Non-Amgen investigational product pembrolizumab will also be used in this study. Pembrolizumab will be manufactured by Merck. Pembrolizumab will be labeled, packaged, and distributed by Amgen (or designee) using Amgen (or designee) clinical study drug distribution procedures. Pembrolizumab is supplied as pembrolizumab 100 mg/4mL vials (25 mg/mL) solution for intravenous infusion.

Additional details regarding the pembrolizumab product are provided in the IPIM.

6.2.2.1 Dosage, Administration, and Schedule: Pembrolizumab

Pembrolizumab must be prepared and administered by a qualified healthcare professional. Subjects should be assessed clinically for adverse events/toxicity prior to each dose using the CTCAE version 4 (Appendix A). Complete blood count with differential and chemistry panels including liver enzyme laboratory tests (ALT and AST) and total bilirubin and thyroid function tests (triiodothyronine [T3] or free T3 [FT3] per local standard, free thyroxine [FT4], and thyroid stimulating hormone [TSH]) should be obtained according to the Schedule of Assessments (Table 5) and the results should be

checked within 2 days prior to each treatment. Dosing will occur only if these test values are acceptable per Section 6.2.2.2.

Pembrolizumab at a dose of 200 mg will be administered intravenously Q3W (± 3 days). AMG 820 and pembrolizumab should be administered on the same day, with AMG 820 administered first. The pembrolizumab infusion is to begin 15 minutes following the end of the AMG 820 infusion. Pembrolizumab dosing will continue as long as there is derived clinical benefit, until confirmed PD per irRECIST, intolerance to treatment, 24 months from the date of the first dose of pembrolizumab or end of study, whichever occurs first.

Pembrolizumab infusion will be administered as a 30-minute intravenous infusion. Investigators should make every effort to target infusion timing to be as close to 30 minutes as possible. However, given the variability of infusion pumps from site to site, a window of -5 and +10 minutes is permitted (ie, infusion time is 30 minutes:-5 minutes/+ 10 minutes). 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. A 0.2 or 0.22 µm in-line filter made of polyethersulfone must be used during administration to remove any adventitious particles. If the infusion set does not contain a 0.2 or 0.22 µm in-line filter, it is recommended to use an extension line containing the filter. Details on the dose calculation, preparation, and administration are provided in the IPIM.

The dose, start date, and lot number of pembrolizumab are to be recorded on each subject's CRF.

6.2.2.2 Dosage Adjustments, Delays, Rules for Withholding or Restarting, Permanent Discontinuation: Pembrolizumab

Pembrolizumab will be withheld for treatment-related adverse events as described in Table 2.

Table 2. Dose Modification Guidelines for Pembrolizumab Related Adverse Events

Toxicity	Hold Pembrolizumab Treatment For Grade	Timing for Restarting Treatment	Treatment Discontinuation
Diarrhea/Colitis	2-3	Toxicity resolves to grade 0-1.	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks.
	4	Permanently discontinue	Permanently discontinue
AST, ALT, or Increased Bilirubin[3]	2	Toxicity resolves to grade 0-1	Toxicity does not resolve within 12 weeks of last dose.
	3-4	Permanently discontinue (see exception below)[1]	Permanently discontinue
Type 1 diabetes mellitus (if new onset) or Hyperglycemia	Type 1 diabetes mellitus or 3-4	Hold pembrolizumab for new onset Type 1 diabetes mellitus or grade 3-4 hyperglycemia associated with evidence of beta cell failure.	Resume pembrolizumab when subjects are clinically and metabolically stable.
Hypophysitis	2-4	Toxicity resolves to grade 0-1. Therapy with pembrolizumab can be continued while endocrine replacement therapy is instituted	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks.
Hyperthyroidism	3	Toxicity resolves to grade 0-1	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks.
	4	Permanently discontinue	Permanently discontinue
Hypothyroidism		Therapy with pembrolizumab can be continued while thyroid replacement therapy is instituted	Therapy with pembrolizumab can be continued while thyroid replacement therapy is instituted.
Infusion Reaction	3-4	Permanently discontinue	Permanently discontinue
Pneumonitis	2	Toxicity resolves to grade 0-1	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks.
	3-4 or Recurrent 2	Permanently discontinue	Permanently discontinue

Note: Permanently discontinue for any severe or grade 3 drug-related adverse event that recurs or any life-threatening event.

AST = aspartate aminotransferase ALT = alanine aminotransferase

[1] For subjects with liver metastasis who begin treatment with grade 2 AST or ALT, if AST or ALT increases by greater than or equal to 50% relative to baseline and lasts for at least 1 week then subjects should be discontinued.

[2] Subjects with intolerable or persistent grade 2 drug-related adverse event may hold study medication at physician discretion. Permanently discontinue study drug for persistent grade 2 adverse reactions for which treatment with study drug has been held, that do not recover to grade 0-1 within 12 weeks of the last dose

[3] Subjects who have isolated elevated AST (with grade ≤ 1 ALT and normal bilirubin) attributed to AMG 820 and are clinically asymptomatic may potentially continue with treatment upon discussion and agreement with Medical Monitor.

Table 2. Dose Modification Guidelines for Pembrolizumab Related Adverse Events

Toxicity	Hold Pembrolizumab Treatment For Grade	Timing for Restarting Treatment	Treatment Discontinuation
Renal Failure or Nephritis	2	Toxicity resolves to grade 0-1	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks.
	3-4	Permanently discontinue	Permanently discontinue
All Other Drug-Related Toxicity[2]	3 or Severe	Toxicity resolves to grade 0-1	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks.
	4	Permanently discontinue	Permanently discontinue

Page 2 of 2

Note: Permanently discontinue for any severe or grade 3 drug-related adverse event that recurs or any life-threatening event.
AST = aspartate aminotransferase ALT = alanine aminotransferase
[1] For subjects with liver metastasis who begin treatment with grade 2 AST or ALT, if AST or ALT increases by greater than or equal to 50% relative to baseline and lasts for at least 1 week then subjects should be discontinued.
[2] Subjects with intolerable or persistent grade 2 drug-related adverse event may hold study medication at physician discretion. Permanently discontinue study drug for persistent grade 2 adverse reactions for which treatment with study drug has been held, that do not recover to grade 0-1 within 12 weeks of the last dose.

In case of related toxicity that does not resolve to grade 0 to 1 or baseline within 12 weeks after the last infusion of pembrolizumab, pembrolizumab treatment should be discontinued after consultation with the Sponsor medical monitor. With the investigator and Sponsor medical monitor agreement, subjects with laboratory adverse events still at grade 2 after 12 weeks may continue pembrolizumab treatment in the trial only if asymptomatic and controlled.

Subjects enrolled in phase 1b, who develop a DLT during the DLT evaluation period will permanently discontinue pembrolizumab. In subjects who develop a DLT clearly related to AMG 820 and have evidence of clinical benefit (as determined by the investigator), an option to continue at the same AMG 820 dose level or a lower dose level can be considered. If deemed appropriate by the investigator and sponsor, treatment can be re-initiated once the toxicity returns to the subject's baseline value or CTCAE grade ≤ 1. The reason for dose changes is to be recorded on each subject's CRF.

6.2.3 Management of AMG 820 Related Periorbital or Conjunctival Swelling

If a subject experiences grade 3 (severe) periorbital or conjunctival swelling, the study treatment should be withheld until the toxicity resolves or improves to grade 2 (moderate). If the event requires > 4 weeks to recover to grade 2 or lower (with or

without appropriate therapeutic intervention), the subject will be discontinued from the study and should be followed until the swelling resolves to grade 2. Appropriate therapeutic intervention (eg topical 1% hydrocortisone with 0.25% phenylephrine and/or diuretics) to resolve the swelling may be administered at the discretion of the Investigator to any subject experiencing periorbital edema or conjunctival swelling of any grade.

6.2.4 Rescue Medications and Supportive Care Guidelines for Pembrolizumab

Subjects should receive appropriate supportive care measures as deemed necessary by the treating investigator including, but not limited, to the items outlined below. If a subject requires corticosteroid dosing of > 10 mg prednisone daily (or equivalent) as supportive care, AMG 820 and pembrolizumab dosing must be withheld until the corticosteroid dose has decreased to ≤10 mg prednisone daily (or equivalent) as detailed in Section 6.2.2.2.

6.2.4.1 Pneumonitis and Interstitial Lung Disease (ILD)

Subjects with symptomatic pneumonitis, ILD, or acute interstitial pneumonitis (symptoms may include but are not limited to abnormal breath sounds, chest pain and/or tightness, dyspnea, dry cough, fatigue, fever, hemoptysis) should immediately stop receiving pembrolizumab and have an evaluation. The evaluation may include bronchoscopy and pulmonary function tests to rule out other causes such as infection. All attempts should be made to rule out other causes such as metastatic disease, bacterial or viral infection. It is important that subjects with a suspected diagnosis of pneumonitis be managed as per the guidance in Table 3. until treatment-related pneumonitis is excluded. Treatment of both a potential infectious etiology and pneumonitis in parallel may be warranted. Management of the treatment of suspected pneumonitis with steroid treatment should not be delayed for a therapeutic trial of antibiotics. If an alternative diagnosis is established, the subject does not require management as in Table 3; however, the adverse event should be reported regardless of etiology.

If the subject is determined to have pembrolizumab associated pneumonitis, ILD, or acute interstitial pneumonitis, the suggested treatment is as follows (detailed plan in Table 3).

- For grade 2 events, treat with systemic corticosteroids. When symptoms improve to grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.
- For grade 3-4 events, immediately treat with intravenous steroids. Administer additional anti-inflammatory measures, as needed.
- Add prophylactic antibiotics for opportunistic infections in the case of prolonged steroid administration.

Table 3. Recommended Approach to Handling Pneumonitis and ILD

Pembrolizumab Drug Associated Pneumonitis and ILD	Withhold/Discontinue Pembrolizumab?	Supportive Care
Grade 1 (asymptomatic)	No action	Intervention not indicated.
Grade 2	Withhold pembrolizumab, may return to treatment if improves to grade 1 or resolves within 12 weeks	Consider pulmonary consultation with bronchoscopy and biopsy/ bronchoalveolar lavage (BAL) and infectious disease consultation if appropriate. Conduct an in person evaluation approximately twice per week until the subject is improving. Consider frequent Chest X-ray as part of monitoring. Treat with systemic corticosteroids at a dose of 1 to 2 mg/kg/day prednisone or equivalent. When symptoms improve to grade 1 or less, steroid taper should be started and continued over no less than 4 weeks. Permanently discontinue for inability to reduce corticosteroid dose to 10 mg or less of prednisone or equivalent per day within 12 weeks. Discontinue pembrolizumab if upon re-challenge the subject develops a second episode of grade 2 or higher pneumonitis.
Recurrent Grade 2	Discontinue pembrolizumab	Supportive care per instructions for Grade 2 above.
Grade 3 and Grade 4	Discontinue pembrolizumab	Hospitalize the subject and consider bronchoscopy with biopsy and/or BAL. Immediately treat with intravenous steroids (methylprednisolone 125 mg IV). When symptoms improve to Grade 1 or less, a high dose oral steroid (prednisone 1 to 2 mg/kg once per day or dexamethasone 4 mg every 4 hours) taper should be started and continued over no less than 4 weeks. If IV steroids followed by high dose oral steroids does not reduce initial symptoms within 48 to 72 hours, treat with additional anti-inflammatory measures. Discontinue additional anti-inflammatory measures upon symptom relief and initiate a prolonged steroid taper over 45 to 60 days. If symptoms worsen during steroid reduction, initiate a re-tapering of steroids starting at a higher dose of 80 or 100 mg followed by a more prolonged taper and administer additional anti-inflammatory measures, as needed. In addition, prophylactic antibiotics for opportunistic infections should be considered.

IV = intravenous

6.2.4.2 Diarrhea

- Subjects should be carefully monitored for signs and symptoms of enterocolitis (such as diarrhea, abdominal pain, blood and mucus in stool, with or without fever) and of bowel perforation (such as peritoneal signs and ileus).
- All subjects who experience diarrhea/colitis should be advised to drink liberal quantities of clear fluids. If sufficient oral fluid intake is not feasible, fluid and electrolytes should be substituted via intravenous infusion. For grade 2 or higher diarrhea, consider gastrointestinal (GI) consultation and endoscopy to confirm or rule out colitis.
- For grade 2 diarrhea/colitis that persists greater than 3 days, administer oral corticosteroids.
- For grade 3 or 4 diarrhea/colitis that persists > 1 week, treat with intravenous steroids followed by high dose oral steroids.
- When symptoms improve to grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.

6.2.4.3 Type 1 Diabetes Mellitus (if new Onset, Including Diabetic Ketoacidosis) or ≥ Grade 3 Hyperglycemia, if Associated With Ketosis (Ketonuria) or Metabolic Acidosis (Diabetic ketoacidosis)

For type1 diabetes mellitus or grade 3-4 Hyperglycemia

- Insulin replacement therapy is recommended for Type 1 diabetes mellitus and for grade 3-4 hyperglycemia associated with metabolic acidosis or ketonuria.
- Evaluate subjects with serum glucose and a metabolic panel, urine ketones, glycosylated hemoglobin, and C-peptide.

6.2.4.4 Hypophysitis

- For grade 2 events, treat with corticosteroids. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks. Replacement of appropriate hormones may be required as the steroid dose is tapered.
- For grade 3-4 events, treat with an initial dose of IV corticosteroids followed by oral corticosteroids. When symptoms improve to grade 1 or less, steroid taper should be started and continued over no less than 4 weeks. Replacement of appropriate hormones may be required as the steroid dose is tapered.

6.2.4.5 Hyperthyroidism or Hypothyroidism

Thyroid disorders can occur at any time during treatment. Monitor subjects for changes in thyroid function (at the start of treatment, periodically during treatment, and as indicated based on clinical evaluation) and for clinical signs and symptoms of thyroid disorders.

- Grade 2 hyperthyroidism events (and grade 2-4 hypothyroidism)
  - In hyperthyroidism, non-selective beta-blockers (eg, propranolol) are suggested as initial therapy.
  - In hypothyroidism, thyroid hormone replacement therapy, with levothyroxine or liothyronine, is indicated per standard of care.
- Grade 3-4 hyperthyroidism
  - Treat with an initial dose of IV corticosteroid followed by oral corticosteroids. When symptoms improve to grade 1 or less, steroid taper should be started and continued over no less than 4 weeks. Replacement of appropriate hormones may be required as the steroid dose is tapered.

6.2.4.6 Hepatic Toxicity

- In case of hepatotoxicity, monitor liver function tests more frequently (see Section 6.4.2 and Appendix A) until returned to baseline values or stabilized and subject is asymptomatic.
- For grade 2 events, treat with IV or oral corticosteroids.
- For grade 3-4 events, treat with intravenous corticosteroids for 24 to 48 hours.
- Subjects who have isolated elevated AST (with grade ≤ 1 ALT and normal bilirubin) attributed to AMG 820 and are clinically asymptomatic may not require treatment with corticosteroids. These cases should be discussed with the medical monitor.
- When symptoms improve to grade 1 or less, a steroid taper should be started and continued over no less than 4 weeks.

6.2.4.7 Renal Failure or Nephritis

- For grade 2 events, treat with IV or oral corticosteroids.
- For grade 3-4 events, treat with IV corticosteroids.
- When symptoms improve to grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.

6.2.4.8 Infusion 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 adverse events. Signs and symptoms usually develop during or shortly after drug infusion and generally resolve completely within 24 hours of completion of infusion.

Table 4 below shows treatment guidelines for subjects who experience an infusion reaction associated with administration of pembrolizumab:

Table 4. Infusion Reaction Treatment Guidelines

NCI CTCAE Grade	Treatment	Premedication at subsequent dosing
Grade 1 Mild reaction; infusion interruption not indicated; intervention not indicated	Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator.	None
Grade 2 Requires infusion interruption but responds promptly to symptomatic treatment (eg, antihistamines, 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: 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 one hour of stopping drug infusion, the infusion may be restarted at 50% of the original infusion rate (eg, from 100 mL/hr to 50 mL/hr). Otherwise dosing 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 trial treatment administration.	Subject may be premedicated 1.5 hours (± 30 minutes) prior to infusion of pembrolizumab (MK-3475) with: Diphenhydramine 50 mg orally (or equivalent dose of antihistamine). Acetaminophen 500-1000 mg orally (or equivalent dose of antipyretic).
Grades 3 or 4	Stop Infusion.	No subsequent dosing
Grade 3: Prolonged (ie, not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae (eg, renal impairment, pulmonary infiltrates)	Additional appropriate medical therapy may include but is not limited to: IV fluids Antihistamines NSAIDS Acetaminophen Narcotics Oxygen Pressors Corticosteroids Epinephrine	
Grade 4: Life-threatening; pressor or ventilatory support indicated	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 trial treatment administration.	

6.2.4.9 Pembrolizumab Events of Clinical Interest

Events of Clinical Interest that occur after the first dose of pembrolizumab through 135 (+7) days after the last dose of pembrolizumab, or 135 (+7) days after initiation of a new anticancer therapy, whichever is earlier, must be reported to Amgen within 24 hours

of the investigator's knowledge of the event regardless of attribution to pembrolizumab. Information on how to identify and report Events of Clinical Interest can be referenced in Section 9.4.

6.2.4.10 Diet and Other Considerations While Taking AMG 820 and/or Pembrolizumab

6.2.4.10.1 Diet During Treatment With AMG 820 and/or Pembrolizumab

Subjects should maintain a normal diet unless modifications are required to manage adverse events such as diarrhea, nausea or vomiting.

6.2.4.10.2 Contraception Requirements for AMG 820 and/or Pembrolizumab

AMG 820 and/or Pembrolizumab may have adverse effects on a fetus *in utero*. Furthermore, it is not known if AMG 820 or pembrolizumab has transient adverse effects on the composition of sperm. Non-pregnant, non-breast-feeding women may be enrolled if they are willing to use acceptable method(s) of effective contraception or are considered of non-childbearing potential. Refer to Section 4.2, exclusion criteria 214, for contraception requirements and definition of women of non-childbearing potential for this study. Refer to the informed consent form for acceptable method(s) of effective contraception for subjects to use in this study. Additional country-specific contraception requirements may be defined in a country-specific protocol supplement at the end of the Appendix Section of protocol as required by local laws and regulations.

Subjects should be informed that taking AMG 820 and/or pembrolizumab may involve unknown risks to the fetus (unborn baby) if pregnancy were to occur during the treatment and for 4 months after end of pembrolizumab. In order to participate in the study they must adhere to the contraception requirements described above for the duration of the study treatment and during the follow-up period defined in Section 9.3 (Pregnancy and Lactation Reporting). If there are any concerns that a subject will not reliably comply with the requirements for contraception, that subject should not be enrolled into the study.

6.2.4.10.3 Use of AMG 820 and/or Pembrolizumab in Pregnancy

If a subject inadvertently becomes pregnant while on treatment with pembrolizumab, the subject will immediately be removed from the study treatment. The outcome of the pregnancy will be reported to the sponsor and followed as described in Section 9.3 (Pregnancy and Lactation Reporting). If a male subject impregnates his female partner, the investigator must be informed immediately and the pregnancy reported to the sponsor and followed as described in Section 9.3 (Pregnancy and Lactation Reporting).

6.2.4.10.4 Use of AMG 820 and/or Pembrolizumab in Nursing Women

It is unknown whether AMG 820 and/or pembrolizumab are excreted in human milk. Since many drugs are excreted in human milk, and because of the potential for serious adverse reactions in the nursing infant, female subjects who are breast-feeding are not eligible for enrollment in this study.

6.3 Other Protocol-required Therapies

Systemic steroids for management of pembrolizumab immune related adverse events, that are commercially available are not provided or reimbursed by Amgen (except if required by local regulation). The investigator will be responsible for obtaining supplies of these protocol-required therapies.

6.4 Hepatotoxicity Stopping and Rechallenge Rules

Subjects with abnormal hepatic laboratory values (ie, alkaline phosphatase [ALP], aspartate aminotransferase [AST], alanine aminotransferase [ALT], total bilirubin [TBL]) and/or international normalized ratio [INR] and/or signs/symptoms of hepatitis (as described below) may meet the criteria for withholding or permanent discontinuation of AMG 820 and/or pembrolizumab as specified in the protocol and the United States Food And Drug Administration Guidance for Industry Drug-Induced Liver Injury: Premarketing Clinical Evaluation, July 2009.

6.4.1 Criteria for Permanent Discontinuation of AMG 820 and Pembrolizumab Due to Potential Hepatotoxicity

AMG 820 and pembrolizumab should be discontinued permanently and the subject should be followed according to the recommendations in Appendix A (Additional Safety Assessment Information) for possible drug-induced liver injury (DILI), if ALL of the criteria below are met:

- TBL ≥ 2x upper limit of normal (ULN) following baseline total bilirubin < ULN or INR > 1.5
- AND increased AST or ALT from the relevant baseline value as specified below:

Baseline AST or ALT value	AST or ALT elevation
< ULN	≥ 3x ULN

- AND no other cause for the combination of the above laboratory abnormalities is immediately apparent; important alternative causes for elevated AST/ALT and/or TBL values include, but are not limited to:
  - Hepatobiliary tract disease
  - Viral hepatitis (eg, Hepatitis A/B/C/D/E, Epstein-Barr Virus, cytomegalovirus, Herpes Simplex Virus, Varicella, toxoplasmosis, and Parvovirus)

- Right sided heart failure, hypotension or any cause of hypoxia to the liver causing ischemia.
- Exposure to hepatotoxic agents/drugs or hepatotoxins, including herbal and dietary supplements, plants and mushrooms
- Heritable disorders causing impaired glucuronidation (eg, Gilbert's Syndrome, Crigler-Najjar syndrome) and drugs that inhibit bilirubin glucuronidation (eg, indinavir, atazanavir)
- Alpha-one antitrypsin deficiency
- Alcoholic hepatitis
- Autoimmune hepatitis
- Wilson's disease and hemochromatosis
- Nonalcoholic Fatty Liver Disease including Steatohepatitis (NASH)
- Non-hepatic causes (eg, rhabdomylosis, hemolysis)

If an alternative cause for hepatotoxicity is identified or less stringent conditions developed than what are noted above, determine (based on patient population and/or severity of the hepatotoxicity or event) if AMG 820 and/or pembrolizumab should be withheld or permanently discontinued, as deemed appropriate for the safety of the subject.

6.4.2 Criteria for Conditional Withholding of AMG 820 and/or Pembrolizumab due to Potential Hepatotoxicity

For subjects who do not meet the criteria for permanent discontinuation of AMG 820 and/or pembrolizumab outlined above and have no underlying liver disease, and eligibility criteria requiring normal transaminases and total bilirubin at baseline or subjects with underlying liver disease and baseline abnormal transaminases, the following rules are recommended for withholding of Amgen investigational product and other protocol-required therapies:

- Elevation of either AST or ALT according to the following schedule:

Baseline AST or ALT value	AST or ALT elevation
Any	> 8x ULN at any time
Any	> 5x ULN but < 8x ULN for ≥ 2 weeks
Any	> 5x ULN but < 8x ULN and unable to adhere to enhanced monitoring schedule
Any	> 3x ULN with clinical signs or symptoms that are consistent with hepatitis (such as right upper quadrant pain/tenderness, fever, nausea, vomiting, jaundice).

- OR: TBL > 3x ULN at any time
- OR: ALP > 8x ULN at any time

Amgen investigational product should be withheld pending investigation into alternative causes of DILI. If investigational product(s) is withheld, the subject is to be followed according to recommendations in Appendix A for possible DILI. Rechallenge may be considered if an alternative cause for impaired liver tests (ALT, AST, ALP) and/or elevated total bilirubin, is discovered and the laboratory abnormalities resolve to normal or baseline (Section 6.4.3).

6.4.3 Criteria for Rechallenge of Amgen Investigational Product and Other Protocol-required Therapies After Potential Hepatotoxicity

The decision to rechallenge the subject should be discussed and agreed upon unanimously by the subject, investigator, and Amgen.

If signs or symptoms recur with rechallenge, then Amgen investigational product and other protocol-required therapies, as appropriate should be permanently discontinued. Subjects who clearly meet the criteria for permanent discontinuation (as described in Section 6.4.1) should never be rechallenged.

6.5 Concomitant Therapy

Throughout the study, investigators may prescribe any concomitant medications or treatments deemed necessary to provide adequate supportive care except for those listed in Section 6.9.

Concomitant therapies are to be collected in the CRF from informed consent through 135 (+7) days after the last dose of AMG 820 or pembrolizumab, whichever is later. In addition, any concomitant medications associated with serious adverse events that occur through 135 (+7) days after the cessation of all study treatment will be reported to Amgen and recorded in the CRF.

For concomitant therapies collect therapy name, indication, dose, unit, frequency, route, start date, and stop date.

6.6 Other Treatment Procedures

If a subject demonstrates evidence of new or worsening CNS metastases, all study treatments should be withheld and the investigator or designee should notify the sponsor's medical monitor as soon as possible. Subjects may be allowed to remain on study after discussion between the sponsor's medical monitor and the investigator to determine the appropriateness of treatment resumption provided CNS lesions can be treated with stereotactic radiotherapy, Gamma Knife, or craniotomy. After approval is obtained from the sponsor's medical monitor, subjects may be allowed to reinitiate

AMG 820 and/or pembrolizumab treatment per Section 6.2.1.3 and 6.2.2.2, respectively, following stereotactic radiotherapy only when dosing of corticosteroid is ≤ 10 mg prednisone daily or equivalent. If higher doses of corticosteroid are used, AMG 820 and/or pembrolizumab must be held until that dose level is reached during the period of steroid tapering.

6.7 Medical Devices

Medical devices (eg, 0.2 or 0.22 µm in-line filter made of polyethersulfone, intravenous administration set, infusion pump syringes, sterile needles, alcohol prep pads) that are commercially available are not usually provided or reimbursed by the Sponsor (except, for example, if required by local regulation). The investigator will be responsible for obtaining supplies of these devices.

6.8 Product Complaints

A product complaint is any written, electronic or oral communication that alleges deficiencies related to the identity, quality, durability, reliability, safety, effectiveness, or performance of a drug(s) or device(s) after it is released for distribution to market or clinic by either Amgen or by distributors and partners for whom Amgen manufactures the material.

This includes any drug(s) or device(s) provisioned and/or repackaged /modified by Amgen. Drug(s) or device(s) includes investigational product.

Any product complaint(s) associated with an investigational product(s) or non-investigational product(s) or device(s) supplied by Amgen are to be reported according to the instructions provided in the IPIM.

6.9 Excluded Treatments, Medical Devices, and/or Procedures During Study Period

Subjects must not use any of the following therapies during screening or treatment period, unless indicated otherwise:

- other investigational agents or procedures
- concurrent experimental or approved antitumor therapies other than study drugs and radiation therapy required for palliation.
- immunosuppressive agents with the exception of treatment for adverse events and CNS metastases
    - If the subject requires corticosteroid dosing of > 10 mg prednisone daily (or equivalent) for related toxicities, AMG 820 and pembrolizumab dosing must be withheld until the corticosteroid dose has decreased to ≤ 10 mg prednisone daily (or equivalent)

- any live vaccine therapies used for the prevention of infectious disease within 28 days prior to enrollment and during treatment period. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, chicken pox, yellow fever, rabies, BCG, and typhoid (oral) vaccine. Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed. However, intranasal influenza vaccines (eg, Flu - Mist®) are live attenuated vaccines, and are not allowed
- any surgery or definitive radiotherapy (within 28 weeks prior to study day 1)

Subjects must not schedule any elective surgeries during the treatment period and for at least 30 days after the last administration of study drugs. If a subject undergoes any unexpected surgery during the course of the study, all study treatments must be withheld and the investigator or designee should notify the sponsor's medical monitor as soon as possible. A subject may be allowed to resume study drugs if both the investigator and sponsor's medical monitor agree to restart study therapy.

7. STUDY PROCEDURES

7.1 Schedule of Assessments

Table 5. Schedule of Assessments

Sample Schedule of Assessments																																		
Cycle		1									2									3				4				5						
Weeks		1					2	3			4					5	6	7			9	10			12	13	Q3W	Q6W	Q4C	Safety [b]	LTFU			
Days	Screen	1			2	5	8	15			22					23	26	29	36	43			57	64			78	85							
Hours (relative to EOI)		Pre [m]	0	EOI	1	6	24	96	168	336	Pre	0	EOI	2	4	24	96	168	336	Pre	0	EOI	336	Pre	0	EOI	336							
GENERAL & SAFETY ASSESSMENTS																																		
Informed consent [a]	X																																	
Medical History [a]	X																																	
Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Physical exam [c]	X	X					X		X	X	X							X	X	X			X	X			X	X	X			X		
12-lead ECG [d]	X																																X	
Vital signs	X	X		X	X	X	X	X	X	X	X		X		X	X	X	X	X	X		X	X	X		X	X	X	X			X		
Weight	X																																X	
Height	X																																	
Review of adverse events, disease related events and serious adverse events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Survival Assessment [e]																																		X
LABORATORY ASSESSMENTS																																		
Serum/Urine Pregnancy Test [f]	X	X									X									X				X				X	X		X	X		
PT or INR and PTT or aPTT	X	X					X	X	X	X	X					X	X	X	X	X			X	X			X	X	X			X		
Hematology	X	X					X	X	X	X	X					X	X	X	X	X			X	X			X	X	X			X		
Chemistry	X	X					X	X	X	X	X					X	X	X	X	X			X	X			X	X	X			X		
Urinalysis	X	X																		X								X		X		X		
Lipase and Amylase	X	X									X									X				X						X		X		
T3 (or FT3), FT4, TSH, Cortisol	X	X									X									X				X				X			X	X		
HBsAg, HBcAb, HCV Ab, HIV	X																																	
Tumor Specific Blood Test [n]	X																			X									X					

Footnotes defined on the last page of the table

Table 5. Schedule of Assessments

Sample Schedule of Assessments																																				
Cycle		1									2										3				4				5								
Weeks		1						2	3		4						5	6			7		9	10			12	13	Q3W	Q6W	Q4C	Safety (b)	LTFU			
Days	Screen	1					2	5	8	15	22					23	26	29	36		43			57	64			78	85								
Hours (relative to EOI)		Pre (m)	0	EOI	1	6	24	96	168	336	Pre	0	EOI	2	4	24	96	168	336	Pre	0	EOI	336	Pre	0	EOI	336									
Central Laboratory ASSESSMENTS																																				
New Tumor tissue for PD-L1 testing[i]	X																																			
RADIOLOGICAL ASSESSMENTS																																				
Radiographic (CT or MRI,) Scans & Tumor Assessment[a][j]	X																								X							X	X	X[o]		
Dosing																																				
AMG 820[g]			X									X									X				X				X	X					
Pembrolizumab[g]			X									X									X				X				X	X					
PK ASSESSMENTS																																				
AMG 820 PK collection[k]		X		X	X	X	X	X	X	X	X		X	X	X	X	X	X	X	X		X		X		X		X		X	X			X		

EOI = End of Infusion; LTFU = Long Term Follow-Up; Q3W = Every 3 Weeks; Q6W = Every 6 Weeks; Q4C = Every 4 Cycles

[a] Procedures to be performed ≤ 28 days prior to enrollment

[b] Safety follow-up will be performed 135 (+7) days after the last dose of AMG 820 or the last dose of pembrolizumab, whichever is later. Suggested frequency of visits to follow any continuing events are approximately: every week for SAEs, Q2W for grade 3 or higher AEs (excluding AST elevation without drug-associated hepatotoxicity), and Q3W for other abnormalities until resolved to grade 1 or baseline.

[c] Physical exam including ECOG.

[d] ECG performed at screening and safety follow-up visits and as clinically indicated during the study.

[e] Subjects will be followed for survival every 12 weeks (±28 days) from the date of the safety follow-up visit until up to approximately 12 months after date of enrollment. Subsequent cancer treatments and disease status will be collected as part of the long-term follow-up survival assessment.

[f] Female subject of childbearing potential to have serum pregnancy test at screening; urine pregnancy test at all other time points. If urine pregnancy test is positive or cannot be confirmed as negative, a serum pregnancy test will be required.

[g] AMG 820 in combination with pembrolizumab will be administered every 3 weeks.

[h] Anti-AMG 820 and anti-pembrolizumab antibodies samples will be collected pre-dose and at indicated time points throughout the study.

[i] Tumor biopsy tissue is required per section 7.6.

[j] Radiographic imaging (CT or MRI) of the chest, abdomen and pelvis, and MRI of the brain if a subject has signs and symptoms suggestive of CNS metastases, are required at screening. MRI of the brain is required for all NSCLC subjects at screening. Tumor assessments must also include all other sites of disease. The screening scans must be done within 28 days prior to enrollment. During treatment, radiographic imaging (CT or MRI) of the chest, abdomen and pelvis, along with tumor assessments of all other sites of disease, (MRI of the brain if a subject has symptoms or signs suggestive of CNS metastases), will be performed independent of treatment cycle at week 10 (±1 week), and then every 10 weeks (±2 weeks) or more frequently if clinically indicated until confirmed PD per irRECIST or start of new anticancer treatment. Imaging should not be adjusted for cycle initiation delays and performed according to the calendar. The imaging modality selected (eg, CT or MRI) should remain constant for any individual subject. Response or progression should be confirmed by repeated radiographic imaging ≥ 4 weeks after the first indication of response or progression. Radiographic imaging is required at the safety follow-up visit if the subject ended treatment prior to confirmed PD and has not had radiographic tumor imaging performed within 6 weeks (+1 week) of the visit. The radiographic images will be submitted to a central imaging lab.

[k] PK samples should be collected at the exact nominal time point as noted, where collection times are to be defined relative to the end of AMG 820 infusion. If unable to collect a PK sample at the specified nominal time point collect it as close as possible to the nominal time point and record the actual collection time. PK samples not collected at exact nominal time point will not be considered protocol deviations.

[m] Safety labs should be performed and reviewed within 2 days prior to each dose.

[n] CEA for CRC and CA 19-9 for pancreatic cancer every 6 weeks ± 2 weeks

[o] For subjects who discontinued treatment for any reason other than confirmed PD, every effort should be made to perform radiographic imaging (CT or MRI) of the chest, abdomen and pelvis, along with tumor assessments of all other sites of disease every 12 weeks until documentation of confirmed PD per irRECIST, clinical progression, start of new anticancer therapy, or up to 12 months after subject's enrollment for the study, whichever occurs first.

Refer to the applicable supplemental (eg, laboratory, imaging) manuals for detailed collection and handling procedures.

7.2 General Study Procedures

A signed and dated IRB/IEC-approved informed consent must be obtained before any study-specific procedures are performed.

Procedures that are part of routine care are not considered study-specific procedures and may be used at screening to determine eligibility. All subjects will be screened for eligibility before enrollment. Only eligible subjects will be enrolled into the study. During treatment, assessments and procedures can be performed within 3 days of the planned visit. It is recommended that dosing occur on the same day of the week (eg, if first dose is administered on Monday, all subsequent doses should be administered on a Monday), however a ± 3-day dosing and study procedure window is allowed.

The following laboratory analytes in Table 6 will be assessed at various times throughout the study.

Table 6. Laboratory Analytes

Chemistry	Coagulation	Endocrine Function	Hematology	Other Labs
Sodium	PT or INR	TSH	RBC	Urine or serum pregnancy test
Potassium	PTT or aPTT	T3 (or FT3 per local standard)	Hemoglobin	Urinalysis
Chloride		FT4	Hematocrit	*Specific gravity*
Bicarbonate or CO2		Cortisol	MCV	*pH*
Total protein			MCH	*Blood*
Albumin			MCHC	*Protein*
Calcium			RDW	*Glucose*
Magnesium			Reticulocytes	*Bilirubin*
Phosphorus			Platelets	*Microscopic exam (performed at the discretion of the Principal Investigator)*
Glucose			WBC	Hep B surface antigen and Hep B total core antibody
BUN or Urea			Differential	Hep C antibody
Creatinine			• Total Neutrophils or Bands/stabs and Segmented Neutrophils^	HIV
Uric acid			• Eosinophils^	CA 19-9 and CEA
Total bilirubin			• Basophils^	Tumor PD-L1 testing
Direct bilirubin			• Lymphocytes	Anti-AMG 820 antibody
Alkaline phosphatase			• Monocytes or Mid Cell Fraction	AMG 820 PK
AST (SGOT)			Nucleated RBC	Anti-pembrolizumab antibody
ALT (SGPT)				Pembrolizumab PK
Amylase				Biomarkers development and immunophenotyping blood
Lipase				Archived tumor tissue
				Fresh tumor biopsy tissue
				Serum IL34, IL10, VEGF, MCP-1, MMPs, CSF-1

^Local lab may report Granulocytes instead of Neutrophils, Eosinophils, and Basophils individually
AST = aspartate aminotransferase; ALT = alanine aminotransferase ; PT = prothrombin time; INR = international normalization ratio; PTT/aPTT = partial thromboplastin time/activated partial thromboplastin time; TSH = thyroid stimulating hormone; T3/FT3=free triiodothyronine ; FT4 = free thyroxine; PD-L1 = programmed cell death-1 ligand 1.

7.2.1 Screening Enrollment

The following procedures are to be completed during the screening period within 28 days of enrollment at time points designated in the Schedule of Assessments (Table 5):

- Confirmation that the Informed Consent Form has been signed.
- Demographic data including sex, age, race, and ethnicity will be collected in order to study their possible association with subject safety and treatment effectiveness. Additionally demographic data may be used to study the impact on biomarkers variability and pharmacokinetics of the protocol required therapies.
- Vital signs (systolic/diastolic blood pressure, heart rate, respiratory rate, temperature): Subject should be in a supine position in a rested and calm state for at least 5 minutes before blood pressure assessments are conducted. If the subject is unable to be in the supine position, the subject should be in most recumbent position as possible. The position selected and temperature location for a subject should be the same that is used throughout the study and documented on the vital sign CRF. Record all measurements on the vital signs CRF.
- Complete medical and surgical history will be collected. Medical history will include information on the subject's concurrent medical conditions. The current toxicity grade will be collected for each condition that has not resolved. Disease history must date back to the original diagnosis. Record all findings on the medical history CRF.
- Medication History: Therapy name, indication, dose, unit, frequency, and start and stop date will be collected for prior therapies taken for current or prior malignancies.
- Physical examination as per standard of care including ECOG performance status assessment. Physical examination findings should be recorded on the appropriate CRF (eg, medical history, event).
- Body weight in kilograms should be measured without shoes.
- Height in centimeters should be measured without shoes.
- Documentation of concomitant medications (per Section 6.5).
- A 12-lead electrocardiogram (ECG) per standard of care: The ECG must include the following measurements: heart rate, PR interval, QRS, QT and QTc intervals. Subject must be in supine position in a rested and calm state for at least 5 minutes before ECG assessment is conducted. If the subject is unable to be in the supine position, the subject should be in most recumbent position as possible. The investigator or designated site physician will review all ECGs. Once signed, the original ECG tracing will be retained with the subject's source documents. At the request of the sponsor, a copy of the original ECG will be made available to the Sponsor.
- Local Laboratory Assessments:
  - Within ≤ 28 days prior to enrollment:
    - hematology panel
    - chemistry panel
    - lipase and amylase
    - hepatitis B surface antigen and Hepatitis B core antibody

- hepatitis C virus antibody
- HIV
- coagulation: PT or INR and PTT or aPTT
- thyroid function tests: T3 (or FT3), FT4, TSH
- urinalysis
- Serum or urine pregnancy test for female subjects of childbearing potential

- Central Laboratory Assessment
  - Obtaining of tumor tissue for biomarker analyses is required as described below:
    - Submit a newly obtained or recent (tissue obtained within 3 months prior to day 1 and no systemic therapy given since the biopsy) formalin-fixed paraffin-embedded tumor biopsy tissue and associated pathology report from the primary or metastatic lesion for PD-L1 analysis and for biomarker analysis within 28 days prior to enrollment. Subjects with an inadequate or indeterminate samples may undergo re-biopsy, when feasible, as per the investigator assessment. PD-L1 testing will be performed at central laboratory. This tumor biopsy is required:
      - in all NSCLC subjects naïve to PD-1/PD-L1 inhibitors
      - whenever feasible in NSCLC subjects refractory/relapsing during treatment with PD-1/PD-L1 inhibitors, if enrolling immediately after into the current study and upon discussion with the Sponsor
      - in all CRC subjects
      - Whenever feasible in pancreatic cancer subjects
    - If available, submit also a formalin fixed paraffin embedded archival tumor tissue sample and associated pathology report.
- Radiographic tumor imaging assessment must include CT or MRI scans of the chest, abdomen and pelvis. MRI of the brain should be performed for all NSCLC subjects at screening, and in any subject if clinically indicated. See Section 7.4.
- Recording of serious adverse events that occur after subject signs informed consent
- Review of inclusion and exclusion criteria

Subjects may be rescreened. If a subject is being rescreened, he or she may need to reconsent to the study to ensure that the IRB/IEC approved main informed consent form is signed within 28 days of enrollment or randomization.

7.2.2 Treatment

Treatment begins when the first dose of protocol-required therapies is administered to a subject.

The following procedures will be completed during the treatment period at the times designated in the Schedule of Assessments (Table 5). Administration of

protocol-required therapies is to be performed after all other procedures are completed during each visit that it is required, unless otherwise stated.

- Physical examination as per standard of care including ECOG performance status assessment. Physical examination findings should be recorded on the appropriate CRF (eg, medical history, adverse event)
- Vital signs (systolic/diastolic blood pressure, heart rate, respiratory rate, temperature): Subject should be in a supine position in a rested and calm state for at least 5 minutes before blood pressure assessments are conducted. If the subject is unable to be in the supine position, the subject should be in most recumbent position possible. The blood pressure position selected and temperature location for a subject should be the same that is used throughout the study and be documented on the vital signs CRF.
- Local laboratory assessments: On treatment tests can be performed within 2 days of the planned visit. Results should be reviewed prior to the administration of study treatment:
  - hematology panel
  - chemistry panel
  - lipase and amylase
  - coagulation: PT or INR and PTT or a PTT
  - thyroid function tests: T3 (or FT3), FT4, TSH
  - urinalysis
  - Serum or urine pregnancy test for female subjects of childbearing potential: Additional, on-treatment pregnancy testing may be performed at the investigator's discretion.
- Central laboratory assessments (refer to Schedule of Assessments as not all tests will be required after Amendment 2):
  - whole blood for biomarker analyses (Immunophenotyping)
  - serum for biomarker analyses of baseline circulating markers (IL34, IL10, VEGF MCP-1, MMPs, CSF-1)
  - Blood for immunogenicity (anti-AMG 820 antibody and anti-pembrolizumab antibody). Note: All samples should be drawn within 24 hours before infusion of AMG 820 or pembrolizumab and at the same time as the pre-dose trough blood collection for the PK sample.
  - blood for PK of AMG 820 and pembrolizumab
  - biomarker development blood sample
  - tumor tissue biopsy for biomarker analyses is strongly encouraged in all subjects
    - Recommended collection of biopsies during the study at the time of the second CT scan at week 10 ± 2 weeks (formalin-fixed paraffin-embedded tumor biopsy tissue and associated pathology report, if available) or whenever feasible. Subjects with an inadequate or indeterminate samples may undergo re-biopsy, when feasible, as per the investigator assessment.

- Radiographic tumor imaging assessments must include CT scan or MRI scans of the chest, abdomen and pelvis. In addition, MRI of the brain will be performed if signs or symptoms suggestive of CNS metastasis are present. Imaging will be performed per the Schedule of Assessment (Table 5).
- AMG 820 administration. Note: AMG 820 must be administered before pembrolizumab
- Pembrolizumab administration
- Recording of adverse events, serious adverse events and disease related events
- Documentation of concomitant medications (see Section 6.5)

7.2.3 Safety Follow-up Visit(s)

All subjects will complete a safety follow-up visit approximately 135 (+7) days after the last dose of study treatment.

The following procedures will be performed:

- Physical examination as per standard of care including ECOG performance status assessment. Physical examination findings should be recorded on the appropriate CRF (eg, medical history, event)
- Body weight in kilograms should be measured without shoes.
- Vital signs (systolic/diastolic blood pressure, heart rate, respiratory rate, temperature): Subject should be in a supine position in a rested and calm state for at least 5 minutes before blood pressure assessments are conducted. If the subject is unable to be in the supine position, the subject should be in most recumbent position as possible. The position selected and temperature location for a subject should be the same that is used throughout the study and documented on the vital sign CRF. Record all measurements on the vital signs CRF
- A 12-lead ECG per standard of care: The ECG must include the following measurements: heart rate, PR, QRS, QT and QTc intervals . Subject must be in supine position in a rested and calm state for at least 5 minutes before ECG assessment is conducted. If the subject is unable to be in the supine position, the subject should be in most recumbent position as possible. The investigator or designated site physician will review all ECGs. Once signed, the original ECG tracing will be retained with the subject's source documents. At the request of the sponsor, a copy of the original ECG will be made available to the Sponsor.
- Local laboratory Assessments
  - hematology panel
  - chemistry panel
  - lipase and amylase
  - coagulation: PT or INR and PTT or a PTT
  - thyroid function tests: T3 (or FT3), FT4, TSH
  - urinalysis
  - serum or urine pregnancy test for female subjects of childbearing potential

- Central laboratory assessments (refer to Schedule of Assessments as not all tests will be required after Amendment 2):
  - All subjects
    - Blood for immunogenicity
- Radiographic tumor imaging and tumor response assessments are to be performed if the subject ended study treatment prior to confirmed PD per irRECIST and has not had assessments performed within 6 weeks of the visit.
  - Radiographic tumor imaging assessments must include CT scan or MRI scans of the chest, abdomen and pelvis. In addition MRI of the brain will be performed if signs or symptoms suggestive of CNS metastasis are present.
- Recording of adverse events
- Recording of serious adverse events. Note: Serious adverse events that occur through 135 (+7) days after the cessation of all study treatment are recorded in the subject's medical record and are submitted to Amgen.
- Recording of disease related events
- Documentation of concomitant medications (see Section 6.5)

7.2.4 Long-term Follow-up

After the safety follow-up visit all subjects will enter the long-term follow-up. Subjects will be contacted by clinic visit or telephone to assess survival, disease status and initiation of first subsequent anti-tumor therapy following end of AMG 820 and pembrolizumab treatment.

Contact for all subjects will be attempted every 12 weeks (± 28 days) following the safety follow-up visit, as applicable, until death, subject withdraws full consent, or up to 12 months after subject's enrollment for the study, whichever comes first.

For subjects who discontinued treatment for any reason other than confirmed PD, every effort should be made to perform radiographic imaging (CT or MRI) of the chest, abdomen and pelvis, along with tumor assessments of all other sites of disease every 12 weeks until documentation of confirmed PD per irRECIST, clinical progression, start of new anticancer therapy, or up to 12 months after subject's enrollment for the study, whichever occurs first.

7.3 Physical Examinations

A complete physical examination will be performed by the investigator or designee according to local practices and at screening and time points specified in the Schedule of Assessments (Section 7.1). At minimum, the examination should include assessments of the head and neck, skin, neurological system, lungs, cardiovascular system, abdomen (liver and spleen), thyroid, lymph nodes and extremities.

7.4 Radiological Imaging Assessment

Radiological imaging to assess the extent of disease will be assessed by standardized contrast-enhanced MRI / CT and evaluated according to Immune-related Response Criteria in Solid tumor irRECIST (ref, Appendix D). A contrast-enhanced MRI should be the preferred imaging method for tumor staging. A CT should be done when MRI is not possible, is relatively contraindicated (eg, allergy to contrast) or for the evaluation of body sites where MRI is not the recommended adequate staging method. In order to reduce radiation exposure for subjects, low dose CT techniques should be applied whenever possible. Organ-specific imaging protocols or existing diagnostic guidelines should be followed whenever possible to evaluate the full extent of the disease appropriately.

Radiographic imaging of the chest, abdomen and pelvis are required at screening. Tumor assessments must also include all other sites of disease. The screening scans must be performed within 28 days prior to enrollment and will be used as baseline. For NSCLC subjects, MRI of the brain is required at screening. During treatment, follow-up radiographic imaging of the abdomen, pelvis and chest, along with tumor assessments of all other sites of disease, will be performed independent of treatment cycle at week 10 (±1 week), and then every 10 weeks (±2 weeks) or more frequently if clinically indicated until confirmed PD per irRECIST or start of new anticancer treatment. Response (immune-related Complete Response [irCR], immune-related Partial Response [irPR]) and progression (immune-related Progressive Disease [irPD]) require confirmation by a repeat, consecutive assessment no less than 4 to 6 weeks from the date of the first documented assessment. For confirming response, the repeat scan may be performed any time after 4 weeks from the first suspected radiologic evidence of response and may be delayed, at the discretion of the managing physician, until the next scheduled scan to avoid unnecessary procedures. Upon discussion with the Sponsor, subjects may continue to receive treatment after radiographic confirmation of progressive disease as long as they continue to derive clinical benefit and until further increase in tumor burden. For analyses purpose, date of PD is the date of initial observed PD.

Radiographic assessment at the end of the study or during the EOT visit should be performed if the last imaging assessment was performed ≥ 6 weeks before the EOT and the subject has not had evidence of confirmed disease progression.

All radiological imaging scans will be done as indicated in the Imaging Manual provided by the core laboratory. All subsequent scans will be performed in the same manner as at screening, preferably on the same scanner (unless a subject develops hypersensitivity

to MRI contrast during the study, in which case a switch to CT is acceptable after consultation with Amgen and the imaging core laboratory).

Determination of disease response for clinical management of subjects will be assessed at the clinical sites per irRECIST. Scans will be submitted to the imaging core laboratory and may be used for response assessment including RECIST 1.1, irRECIST and exploratory analysis such as volumetric and viable tumor measurements. Detailed information regarding the submission of images to the core laboratory is found in the Imaging Manual.

7.4.1 Brain Magnetic Resonance Imaging Scans

Brain MRI scans will be conducted at screening for all NSCLC subjects. In subjects with known brain metastasis, brain MRI scans will be conducted at screening and at the same schedule as MRI/CT scans. Brain MRI scans may also be performed at any time, if in the judgment of the investigator, the subject displays signs or symptoms of central nervous system (CNS) disease progression.

7.4.2 Tumor Assessments

Tumor assessments will be performed at the sites based on modified irRECIST as outlined in Appendix D.

7.5 Antibody Testing Procedures

Blood sample(s) for Antibody testing are to be collected as indicated in the Schedule of Assessments, Table 5, for the potential measurement of anti-AMG 820 and anti-pembrolizumab binding antibodies. Samples testing positive for anti-AMG 820 or anti-pembrolizumab binding antibodies may also be tested for neutralizing antibodies and may be further characterized for quantity/titer, isotype, affinity and presence of immune complexes. Additional blood samples may be obtained to rule out anti-AMG 820 antibodies during the study.

Refer to the Schedule of Assessments (Table 5), as applicable, for specific time points and the laboratory manual for detailed collection and handling instructions.

7.6 Biomarker Development

Fresh Pre-and Post-dose Tumor Tissues (and archival, if available)

All subjects enrolled into the study will be asked to provide fresh tumor tissue, whenever feasible, and archival tumor tissue, if available:

Baseline:

- The most recent (within 3 months) tumor biopsy (primary or metastatic lesion) obtained between last anti-cancer systemic treatment and day 1 of the current study (formalin-fixed paraffin-embedded tumor biopsy tissue and associated pathology report, if available)
    - Required in all NSCLC subjects naïve to PD-1/PD-L1 inhibitors
    - Whenever feasible in NSCLC subjects refractory/relapsing during treatment with PD-1/PD-L1 inhibitors, if enrolling immediately after into the current study and upon discussion with the Sponsor
    - Required in all CRC subjects
    - Whenever feasible in pancreatic cancer subjects
- an archival formalin fixed paraffin embedded tumor tissue sample and the associated pathology report, if available.

During study treatment:

- Collection of at least one biopsy at the time of second CT scan (week 10 ± 2 weeks) and additional sequential tumor biopsies strongly encouraged, whenever possible, in all subjects. Note: this biopsy will no longer be encouraged per the data of Amendment 2.

In order to satisfy inclusion criteria and secondary objective assessments, fresh and/or archival pre-treatment biopsies will be analyzed to evaluate PD-L1 expression by IHC and immune infiltrate (CD4, CD8 and CD68 cells) status.

In addition, within the exploratory analyses planned for the study all tumor material available may be analyzed to evaluate immune cell subsets and activation status through additional relevant protein and RNA biomarkers, including, but not limited to CD3, CD4, CD8, CD68, CD163, Ki67, PD-L1, FoxP3, GITR as well as transcriptome analysis using the NanoString Cancer ImmunePanel. Further testing of biomarkers may be done dependent on emerging data.

Circulating Markers Blood Samples

Blood samples will be collected for evaluation of circulating markers that may include, and are not limited to CSF-1, IL-34, IL-10, VEGF, MCP-1, MMPs.

These samples will be used to help with understanding further subjects' disease and their response to treatment.

Refer to the laboratory manual for detailed collection and handling procedures for all biomarker samples.

Flow Cytometry Whole Blood Samples

Whole blood samples will be collected for immunophenotyping flow cytometry to identify changes in peripheral blood cell subsets and activation status.

Refer to the laboratory manual for detailed collection and handling procedures for all biomarker samples.

Refer to the Schedule of Assessments for specific time points and the laboratory manual for detailed collection and handling instructions. Note that not all samples will be required after Amendment 2.

7.7 Pharmacogenetic Studies

If the subject consents to the optional pharmacogenetic analysis of this study, DNA analyses may be performed. These optional pharmacogenetic analyses focus on inherited genetic variations to evaluate their possible correlation to the disease and/or responsiveness to the therapies used in this study. No additional samples are collected for this part of the study. For subjects who consent to this/these analysis/analyses, DNA may be extracted from the available blood samples collected during the study.

7.8 Sample Storage and Destruction

Any blood or tissue sample collected according to the Schedule of Assessments (Table 5) can be analyzed for any of the tests outlined in the protocol and for any tests necessary to minimize risks to study subjects. This includes testing to ensure analytical methods produce reliable and valid data throughout the course of the study. This can also include, but is not limited to, investigation of unexpected results, incurred sample reanalysis, and analyses for method transfer and comparability.

All samples and associated results will be coded prior to being shipped from the site for analysis or storage. Samples will be tracked using a unique identifier that is assigned to the samples for the study. Results are stored in a secure database to ensure confidentiality.

If informed consent is provided by the subject, Amgen can do additional testing on remaining samples (ie, residual and back-up) to investigate and better understand the disease, dose response and/or prediction of response to the combination of AMG 820 and pembrolizumab, characterize antibody response, and other drug aspects (eg, mechanism of action/target, metabolites). Results from these analyses are to be documented and maintained, but will not be necessarily reported as part of this study. Samples can be retained for up to 20 years.

Since the evaluations are not expected to benefit the subject directly or to alter the treatment course, the results of pharmacogenetic, biomarker development, or other exploratory studies are not placed in the subject's medical record and are not to be made available to the subject, members of the family, the personal physician, or other third parties, except as specified in the informed consent.

The subject retains the right to request that the sample material be destroyed by contacting the investigator. Following the request from the subject, the investigator is to provide the sponsor with the required study and subject number so that any remaining blood or tumor tissue samples and any other components from the cells can be located and destroyed. Samples will be destroyed once all protocol-defined procedures are completed. However, information collected from samples prior to the request for destruction, will be retained by Amgen.

The sponsor is the exclusive owner of any data, discoveries, or derivative materials from the sample materials and is responsible for the destruction of the sample(s) at the request of the subject through the investigator, at the end of the storage period, or as appropriate (eg, the scientific rationale for experimentation with a certain sample type no longer justifies keeping the sample). If a commercial product is developed from this research project, the sponsor owns the commercial product. The subject has no commercial rights to such product and has no commercial rights to the data, information, discoveries, or derivative materials gained or produced from the sample.

See Section 11.3 for subject confidentiality.

8. WITHDRAWAL FROM TREATMENT, PROCEDURES, AND STUDY

8.1 Subjects' Decision to Withdraw

Subjects have the right to withdraw from the study at any time and for any reason without prejudice to their future medical care by the physician or at the institution.

Subjects (or a legally acceptable representative) can decline to continue receiving investigational product and/or other protocol-required therapies or procedures at any time during the study but continue participation in the study (eg, safety / long-term follow-up). If this occurs, the investigator is to discuss with the subject the appropriate processes for discontinuation from investigational product or other protocol-required therapies and must discuss with the subject the options for continuation of the Schedule of Assessments (Table 5) and collection of data, including endpoints and adverse events. The investigator must document the change to the Schedule of Assessments

(Table 5) and the level of follow-up that is agreed to by the subject (eg, in person, by telephone/mail, through family/friends, in correspondence/communication with other physicians, from review of the medical records).

Withdrawal of consent for a study means that the subject does not wish to receive further protocol-required therapies or procedures, and the subject does not wish to or is unable to continue further study participation, including any long-term follow up. Subject data up to withdrawal of consent will be included in the analysis of the study, and where permitted, publically available data can be included after withdrawal of consent. The investigator is to discuss with the subject appropriate procedures for withdrawal from the study.

8.2 Investigator or Sponsor Decision to Withdraw or Terminate Subjects' Participation Prior to Study Completion

The investigator and/or sponsor can decide to withdraw a subject(s) from investigational product and/or other protocol-required therapies, protocol procedures, or the study as a whole at any time prior to study completion.

Subjects may be eligible for continued treatment with Amgen investigational product(s) and/or other protocol-required therapies by a separate protocol or as provided for by the local country's regulatory mechanism, based on parameters consistent with Section 12.1.

8.3 Reasons for Removal From Treatment, or Study

8.3.1 Reasons for Removal From Treatment

Reasons for removal from protocol-required investigational product(s) or procedural assessments include any of the following:

- subject request
- safety concern (eg, due to an adverse event, ineligibility determined, protocol deviation, non-compliance, requirement for alternative therapy)
- pregnancy
- potential hepatotoxicity (as per Section 6.4.1)
- other protocol-specified criteria (see Sections 6)
- death
- lost to follow-up
- decision by Sponsor (other than subject request, safety concern, lost to follow-up)
- disease progression

8.3.2 Reasons for Removal From Study

Reasons for removal of a subject from the study are:

- decision by sponsor
- withdrawal of consent from study
- death
- lost to follow-up

9. SAFETY DATA COLLECTION, RECORDING, AND REPORTING

9.1 Definition of Safety Events

9.1.1 Disease Related Events

Disease Related Events are events (serious or non-serious) anticipated to occur in the study population due to the underlying disease. These could include overall disease progression or pain or discomfort caused by growing tumors. Such events do not meet the definition of an Adverse Event unless assessed to be more severe than expected for the subject's condition.

Disease Related Events and/or Disease Related Outcomes that do not qualify as Serious Adverse Events:

- An event which is part of the normal course of disease under study (eg, disease progression in oncology or hospitalization due to disease progression) is to be reported as a Disease Related Event.
- Death due to the disease under study is to be recorded on the Event CRF.

If the outcome of the underlying disease is worse than that which would normally be expected for the subject, or if the investigator believes there is a causal relationship between the investigational product(s)/study treatment protocol required therapies and disease worsening, this must be reported as an Adverse Event or Serious Adverse Event.

9.1.2 Adverse Events

An adverse event is defined as any untoward medical occurrence in a clinical trial subject. The event does not necessarily have a causal relationship with study treatment. The investigator is responsible for ensuring that any adverse events observed by the investigator or reported by the subject are recorded in the subject's medical record.

The definition of adverse events includes worsening of a pre-existing medical condition. Worsening indicates that the pre-existing medical condition or underlying disease (eg, diabetes, migraine headaches, gout) has increased in severity, frequency, and/or duration more than would be expected, and/or has an association with a significantly

worse outcome than expected. A pre-existing condition that has not worsened more than anticipated (ie, more than usual fluctuation of disease) during the study or involves an intervention such as elective cosmetic surgery or a medical procedure while on study, is not considered an adverse event.

For situations when an adverse event or serious adverse event is due to the primary tumor type being studied, report all known signs and symptoms. Death due to disease progression in the absence of signs and symptoms should be reported as the primary tumor type (eg, metastatic pancreatic cancer).

Note: The term "disease progression" should not be used to describe the disease related event or adverse event.

The investigator's clinical judgment is used to determine whether a subject is to be removed from treatment due to an adverse event. In the event a subject, or subject's legally acceptable representative requests to withdraw from protocol-required therapies or the study due to an adverse event, refer to Section 8.1 for additional instructions on the procedures recommended for safe withdrawal from protocol-required therapies or the study.

9.1.3 Serious Adverse Events

A serious adverse event is defined as an adverse event that meets at least 1 of the following serious criteria (unless it meets the definition of a Disease Related Event as defined in Section 9.1.1):

- fatal
- life threatening (places the subject at immediate risk of death)
- requires in-patient hospitalization or prolongation of existing hospitalization
- results in persistent or significant disability/incapacity
- congenital anomaly/birth defect
- other medically important serious event

A disease related event (eg, disease progression or pain or discomfort caused by growing tumors) is to be reported as a serious adverse event if

- the subject's pre-existing condition becomes worse than what the investigator would consider typical for a patient with the same underlying condition, or
- if the investigator believes a causal relationship exists between the investigational medicinal product(s)/protocol-required therapies and the event,
- and the event meets at least 1 of the serious criteria above.

An adverse event would meet the criterion of “requires hospitalization”, if the event necessitated an admission to a health care facility (eg, overnight stay).

If an investigator considers an event to be clinically important, but it does not meet any of the serious criteria, the event could be classified as a serious adverse event under the criterion of “other medically important serious event”. Examples of such events could include allergic bronchospasm, convulsions, blood dyscrasias, DILI (see Appendix A for drug-induced liver injury reporting criteria), or events that necessitate an emergency room visit, outpatient surgery, or urgent intervention.

9.2 Safety Event Reporting Procedures

9.2.1 Reporting Procedures for Disease Related Events

The investigator is responsible for ensuring that all Disease Related Events observed by the investigator or reported by the subject that occur after the first dose of AMG 820 or pembrolizumab through the safety follow-up visit (ie, 135 [+7] days after the last dose of AMG 820 or pembrolizumab, whichever is later) are reported using the Event CRF. Additionally, the investigator is required to report a fatal Disease Related Event on the Event CRF.

Disease-Related Events assessed by the Investigator to be more severe than expected and/or related to the investigational medicinal product(s)/study treatment/protocol-required therapies, and determined to be serious, must be recorded on the Event CRF as Serious Adverse Events.

9.2.2 Adverse Events

9.2.2.1 Reporting Procedures for Adverse Events That do not Meet Serious Criteria

The investigator is responsible for ensuring that all adverse events observed by the investigator or reported by the subject that occur after first dose of AMG 820 or pembrolizumab through the safety follow-up visit (ie, 135 [+7] days after the last dose of AMG 820 or pembrolizumab, whichever is later) are reported using the Event CRF.

The investigator must assign the following adverse event attributes:

- Adverse event diagnosis or syndrome(s), if known (if not known, signs or symptoms),
- Dates of onset and resolution (if resolved or improved to a lower grade),
- Severity [and/or toxicity per protocol],
- Assessment of relatedness to AMG 820 and/or pembrolizumab and
- Action taken.

The adverse event grading scale used will be the CTCAE version 4.0. The grading scale used in this study is described in Appendix A. The investigator must assess whether the adverse event is possibly related to the AMG 820 and/or pembrolizumab. This relationship is indicated by a "yes" or "no" response to the question: Is there a reasonable possibility that the event may have been caused by the investigational product(s)?

The investigator must assess whether the adverse event is possibly related to any study-mandated activity (eg, administration of investigational product, protocol-required procedure (including any screening procedure(s)). This relationship is indicated by a "yes" or "no" response to the question: "Is there a reasonable possibility that the event may have been caused by a study activity (eg, administration of investigational product, protocol-required procedure"?

The investigator is responsible for reviewing laboratory test results and determining whether an abnormal value in an individual study subject represents a clinically significant change from the subject's baseline values. In general, abnormal laboratory findings without clinical significance (based on the investigator's judgment) are not to be recorded as adverse events. However, laboratory value changes that require treatment or adjustment in current therapy are considered adverse events. Where applicable, clinical sequelae (not the laboratory abnormality) are to be recorded as the adverse event.

If the severity of an adverse event changes from the date of onset to the date of resolution, record a single event for each level of severity on the Event CRF.

The Investigator is expected to follow reported adverse events until stabilization or reversibility.

9.2.2.2 Reporting Procedures for Serious Adverse Events

The investigator is responsible for ensuring that all serious adverse events observed by the investigator or reported by the subject that occur after signing of the consent through 135 (+7) days after the cessation of all study treatment are recorded in the subject's medical record and are submitted to Amgen. Additionally, treatment related serious adverse events that occur after the safety follow-up visit through the end of the long-term follow-up will be reported.

All serious adverse events must be submitted to Amgen within 24 hours following the investigator's knowledge of the event via the Event CRF.

If the electronic data capture (EDC) system is unavailable to the site staff to report the serious adverse event, the information is to be reported to Amgen via an electronic Serious Adverse Event Contingency Report Form within 24 hours of the investigator's knowledge of the event. See Appendix B for a sample of the Serious Adverse Event Worksheet /electronic Serious Adverse Event Contingency Report Form. For EDC studies where the first notification of a Serious Adverse Event is reported to Amgen via the electronic Serious Adverse Event Contingency Report Form, the data must be entered into the EDC system when the system is again available.

The investigator must assess whether the serious adverse event is possibly related to any study-mandated activity or procedure. This relationship is indicated by a "yes" or "no" response to the question: "Is there a reasonable possibility that the event may have been caused by a study activity/procedure"?

The investigator is expected to follow reported serious adverse events until stabilization or resolution.

All new information for serious adverse events must be sent to Amgen within 24 hours following knowledge of the new information. The investigator may be asked to provide additional follow-up information, which may include a discharge summary or extracts from the medical record. Information provided about the serious adverse event must be consistent with that recorded on the Event CRF.

If a subject is permanently withdrawn from protocol-required therapies because of a serious adverse event, this information must be submitted to Amgen.

Amgen will report serious adverse events and/or suspected unexpected serious adverse reactions as required to regulatory authorities, investigators/institutions, and IRBs/IECs in compliance with all reporting requirements according to local regulations and GCP.

The investigator is to notify the appropriate IRB/IEC of serious adverse events occurring at the site and other adverse event reports received from Amgen, in accordance with local procedures and statutes.

9.2.2.3 Reporting Serious Adverse Events After the Protocol-required Reporting Period

There is no requirement to monitor study subjects for new serious adverse events following the protocol-required reporting period after the end of study. However, these serious adverse events can be reported to Amgen. In some countries (eg, European Union [EU] member states), investigators are required to report serious adverse events

that they become aware of after the protocol-required reporting period after the end of study. If serious adverse events are reported, the investigator is to report them to Amgen within 24 hours following the investigator's knowledge of the event.

Serious adverse events reported outside of the protocol-required reporting period will be captured within the safety database as clinical trial cases for the purposes of expedited reporting.

9.3 Pregnancy and Lactation Reporting

If a pregnancy occurs in a female subject, or female partner of a male subject, while the subject is taking protocol-required therapies report the pregnancy to Amgen as specified below.

In addition to reporting any pregnancies occurring during the study, investigators should monitor for pregnancies that occur after the last dose of protocol-required therapies through 7 months after the last dose of AMG 820 or 4 months after the last dose of pembrolizumab.

The pregnancy should be reported to Amgen's Global Safety within 24 hours of the investigator's knowledge of the event of a pregnancy. Report a pregnancy on the Pregnancy Notification Worksheet (Appendix C). Amgen's Global Safety will seek to follow with the Investigator regarding additional information that may be requested.

If a female subject becomes pregnant during the study, the Investigator should attempt to obtain information regarding the birth outcome and health of the infant.

If the outcome of the pregnancy meets a criterion for immediate classification as a Serious Adverse Event (eg, female subject experiences a spontaneous abortion, stillbirth, or neonatal death or there is a fetal or neonatal congenital anomaly) the Investigator will report the event as a Serious Adverse Event.

If a female breastfeeds while taking protocol-required therapies report the lactation case to Amgen as specified below.

Any lactation case should be reported to Amgen's Global Safety within 24 hours of the investigator's knowledge of event. Report a lactation case on the Lactation Notification Worksheet (Appendix C). Amgen Global Patient Safety will follow-up with the Investigator regarding additional information that may be requested.

If a male subject's female partner becomes pregnant, the Investigator should discuss obtaining information regarding the birth outcome and health of the infant from the pregnant partner.

9.4 Pembrolizumab Events of Clinical Interest

Selected adverse events known as Pembrolizumab Events of Clinical Interest must be reported to Amgen within 24 hours of the investigator's knowledge of the event regardless of attribution to pembrolizumab.

For the time period beginning at time of first dose of pembrolizumab through 135 (+7) days following cessation of pembrolizumab treatment, or 135 (+7) days after initiation of a new anti-cancer therapy, any Pembrolizumab Events of Clinical Interest, or follow-up to a Pembrolizumab Events of Clinical Interest, whether or not related to the pembrolizumab, must be reported within 24 hours to Amgen.

Pembrolizumab Events of Clinical Interest for this trial include:

- an overdose of pembrolizumab, as defined in Section 9.5
- potential drug-induced liver injury (DILI) from pembrolizumab as defined in Section 9.6

Subjects should be assessed for possible Pembrolizumab Events of Clinical Interest prior to each dose.

9.5 Definition of an Overdose of Pembrolizumab for This Protocol and Reporting of Pembrolizumab Overdose

For the purpose of this trial, an overdose of pembrolizumab will be defined as any dose of pembrolizumab equal to or greater than 300 mg. No specific information is available on the treatment of overdose of pembrolizumab. In the event of overdose, pembrolizumab should be discontinued and the subject should be observed closely for signs of toxicity. Appropriate treatment should be provided if clinically indicated.

If an adverse event(s) or serious adverse event(s) is associated with ("result from") the overdose of pembrolizumab, the adverse event(s) or serious adverse event is to be reported to Amgen as described in Section 9.2.2. In addition, the adverse event(s) or serious adverse event(s) associated with ("result from") the overdose of pembrolizumab should be reported as Event of Clinical Interest as described in Section 9.4.

9.6 Definition and Reporting of Pembrolizumab Drug-induced Liver Injury

For the purpose of this trial, potential DILI associated with ("resulting from") pembrolizumab will be defined as:

- elevated AST or ALT ≥ 3 x ULN and elevated total bilirubin ≥ 2 x ULN
- AND ALP < than 2 x ULN, 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 will be provided in separate guidance document entitled, the pembrolizumab Event of Clinical Interest Guidance for Potential DILI in Clinical Trials.

To facilitate appropriate monitoring for signals of DILI associated with pembrolizumab, cases of concurrent DILI according to the criteria specified above require the following:

- The event is to be reported to Amgen as an adverse event of potential DILI within 24 hours of discovery or notification of the event (ie, before additional etiologic investigations have been concluded)
- The appropriate CRF (eg, Event CRF) that captures information necessary to facilitate the evaluation of treatment-emergent liver abnormalities is to be completed.
- Workup to confirm DILI should be immediately initiated as described in the pembrolizumab Event of Clinical Interest Guidance for Potential DILI in Clinical Trials document. Any confirmed event of DILI is to be reported as a serious adverse event within 24 hours after confirmation of the event.

Other events of hepatotoxicity and potential DILI are to be reported as serious adverse events if they meet the criteria for a serious adverse event defined in Section 9.1.3.

10. STATISTICAL CONSIDERATIONS

10.1 Study Endpoints, Analysis Sets, and Covariates

10.1.1 Study Endpoints

10.1.1.1 Primary Endpoints

- Dose limiting toxicities (DLT), treatment-emergent adverse events, treatment-related adverse events and clinically significant changes in vital signs, physical examinations, and clinical laboratory tests
- Objective response rate (ORR) per irRECIST in subjects treated at the recommended combination dose

10.1.1.2 Secondary Endpoints

- OR per RECIST 1.1; TTR, DOR and TTP; OS and PFS at 6 and 12 months
- PK parameters for AMG 820 including, but not limited to, maximum observed concentration (C_{max}) and minimum observed concentration (C_{min}). In addition, area under the concentration-time curve (AUC) and, if feasible, half-life ($t_{1/2}$) for AMG 820.
- CD4, CD8 & CD68 cells number in fresh pre-treatment biopsies

10.1.1.3 Exploratory Endpoints

- Anti-AMG 820 and anti-pembrolizumab antibodies levels
- Biomarker readouts at baseline and treatment related changes
- PK parameters for pembrolizumab include, but are not limited to, concentration at end of pembrolizumab infusion administration, maximum observed concentration (C_{max}) and minimum observed concentration (C_{min}).

10.1.2 Analysis Sets

The analysis of all endpoints, unless noted otherwise, will be conducted on the Safety Analysis Set defined as all subjects that are enrolled and receive at least 1 dose of AMG 820. The analysis of DLT will be restricted to DLT-evaluable subjects (see Section 6.2.1.2.2). The PK Analysis Set will contain all subjects who have received at least 1 dose of the investigational product and have at least 1 PK sample collected. These subjects will be evaluated for PK analysis unless the number of data points required for analysis is not enough, or significant protocol deviations have affected the data, or if key dosing or sampling information is missing.

10.1.3 Covariates and Subgroups

The relationship of covariates to efficacy endpoints will be explored if appropriate. Biomarker data (eg, PD-L1 expression) may be incorporated in additional exploratory subgroup or multivariate analyses. The exploratory analyses of biomarkers may be performed after collection of all samples during the conduct of the study and therefore may be reported after the primary analysis of the safety and efficacy endpoints.

10.2 Sample Size Considerations

It is anticipated that 67 to 197 subjects will be enrolled overall in this study.

Part 1 will enroll 6 to 18 evaluable subjects. The sample size in Part 1 is based on practical consideration, and it is consistent with conventional oncology studies with the objective to evaluate the safety and tolerability of a treatment combination. With 6 subjects in a cohort, there is a 47-91% probability of observing at least one DLT if the true DLT rate is 10-33%.

Part 2 evaluation of efficacy will include at least 6 subjects from part 1 who have been treated with the recommended combination dose, and will enroll additional CRC, pancreatic cancer and NSCLC subjects up to maximum 185 subjects overall. The sample size in each group evaluated in Part 2 is chosen to test whether AM820 can enhance the anti-tumor activity observed historically with pembrolizumab alone and/or overcome lack of response to pembrolizumab monotherapy. For each group and sub-group enrollment may stop early due to insufficient clinical activity. The pre-planned recommendation for early termination is based on ORR (evaluated when the subjects complete at least 6 months of treatment or earlier if already reaching the recommended number of responders), nonetheless the DLRT (see Section 6.2.1.2.1) will make the decision for early termination after reviewing all available safety, efficacy, pharmacokinetic and pharmacodynamic data.

Group 1 will consist of up to 43 subjects with MMR–proficient CRC (only 18 enrolled initially in the first stage) who are naïve to anti-PD-1/PD-L1/CSF-1/CSF-1R treatment. In 2015, Le et al reported a pembrolizumab objective response rate (ORR) per RECIST1.1 and irRC of 0% (0 of 18 patients) for MMR–proficient colorectal cancers. It is anticipated that the combination treatment of AMG 820 and pembrolizumab will have an ORR of 25% or higher in MMR–proficient CRC tumors; an ORR of 10% or less is considered to be insufficient anti-tumor activity to warrant future research. If 2 or fewer of the initial 18 subjects have an objective response then the recommendation is for enrollment to Group 1 be stopped for futility. If 8 or more of the 43 subjects have an objective response then the true ORR is determined to be >10%. This Simon Two-Stage design provides 80% power when the true ORR is 25% while maintaining a 1-sided, 5% alpha error when the true ORR is 10% or lower.

Group 2 will consist of up to 29 subjects with advanced pancreatic cancer (only 10 enrolled initially in the first stage) who have not received prior treatment with a PD-1/PD-L1/CSF-1/CSF-1R inhibitor. In 2012, Brahmer et al reported a pembrolizumab ORR of 0% (0 of 14 patients) for pancreatic cancer. It is anticipated that the combination treatment of AMG 820 and pembrolizumab will have an ORR of 20% or higher in pancreatic tumors; an ORR of 5% or less is considered to be insufficient anti-tumor activity to warrant future research. If none of the initial 10 subjects have an objective response then the recommendation is for enrollment to Group 2 be stopped for futility. If 4 or more of the 29 subjects have an objective response then the true ORR is determined to be >5%. This Simon Two-Stage design provides 80% power when the

true ORR is 20% while maintaining a 1-sided, 5% alpha error when the true ORR is 5% or lower.

Group 3 will consist of up to 55 subjects (only 19 enrolled initially in the first stage) with NSCLC who have not received prior treatment with a PD-1/PD-L1/CSF-1/CSF-1R inhibitor, and who have tumor PD-L1 expression <50%. Garon et al in 2015 reported a pembrolizumab ORR per RECIST1.1 of 13.1% (28 of 214 patients) for NSCLC patients with tumor PD-L1 expression <50%, and an ORR of 14.4% (21 or 146 patients) for those with tumor PD-L1 expression from 1% to 49%. It is anticipated that the combination treatment of AMG 820 and pembrolizumab will have an ORR of 30% or higher in low PD-L1 expressing subjects; an ORR of 15% or less is considered to be insufficient anti-tumor activity to warrant future research. If 3 or fewer of the initial 19 subjects have an objective response then enrollment to Group 3 will be stopped for futility. If 13 or more of the 55 subjects have an objective response then the true ORR is determined to be >15%. This Simon Two-Stage design provides 80% power when the true ORR is 30% while maintaining a 1-sided, 5% alpha error when the true ORR is 15% or lower.

Group 4 will consist of up to 58 NSCLC who received prior treatment with a PD-1/PD-L1 inhibitor, and failed to respond to or relapsed during therapy. These subjects must be also naive to anti-CSF-1/CSF-1R agents. There will be two sub-groups. Sub-group 4a will enroll up to 29 (only 10 enrolled initially in the first stage) subjects who have tumor PD-L1 expression <50% (see Garon et al., 2015) while sub-group 4b will enroll up to 29 subjects who have tumor PD-L1 expression ≥50% (only 10 enrolled initially in the first stage). It is anticipated that the combination treatment of AMG 820 and pembrolizumab will have an ORR of 20% or higher in these NSCLC subjects; an ORR of 5% or less is considered to be insufficient anti-tumor activity to warrant future research. If none of the initial 10 subjects in a sub-group have an objective response then the recommendation is for enrollment to the sub-group be stopped for futility. If 4 or more of the 29 subjects in the sub-group have an objective response then the true ORR is determined to be >5%. This Simon Two-Stage design provides 80% power when the true ORR is 20% while maintaining a 1-sided,5% alpha error when the true ORR is 5% or lower.

10.3 Planned Analyses

10.3.1 Interim Analyses

Safety and all clinical data will be monitored on an ongoing basis. All available cumulative data will be reviewed in Part 1 by cohort, prior to making dose escalation decisions, by the Dose Level Review Team (DLRT, see Section 6.2.1.2). In study Part 2

stage 1, similar assessments will be held after each set of 20 subjects have enrolled through the end of Part 2 stage 1 enrollment.

In Part 2, a Simon Two-Stage design is used for all groups (Group 1-3, 4a, 4b) with the first stage enrolling n=18, 10 19, 10 and 10 subjects, respectively (see design schema). Each group will enroll subjects to a first stage. The second stage for each group will be enrolled depending on clinical activity from stage 1, evaluated when the subjects have been treated for at least 6 months or earlier if the required number of responders have been reached (see Section 10.2 for details). The pre-planned recommendations for enrollment to stage 2 are based on ORR per local irRECIST, however the DLRT will make the decisions for stage 2 enrollment after reviewing all available safety, efficacy, pharmacokinetic and pharmacodynamic data.

10.3.2 Dose Level Review Team (DLRT)

Dose Level Review Meetings (DLRMs) will be held to review data, monitor safety, and make decisions on dose escalation / change decisions. The DLRT will be composed of the investigators or designees, and the following Amgen representatives: medical monitor, early development leader, global safety officer or designee, clinical study manager, biostatistician and clinical pharmacologist. Additional members may be added as needed. The following members are responsible for DLRT decisions: investigators, Amgen medical monitor, and global safety officer or designee. Study decisions by DLRM participants must be unanimous. All available study data, including data collected after the initial DLT window, and including demographics, IP administration, medical history, concomitant medications, adverse events, ECGs, vital signs, laboratory data, efficacy and PK/PD information will be reviewed. In addition to DLTs, all ≥ grade 3 toxicities not meeting DLT criteria will be reviewed and may be considered in DLRT decisions. The study may be discontinued or modified at any time due to documented safety findings.

All DLRM requirements are outlined in the protocol. A DLRM Charter will not be used.

10.3.3 Primary Analysis

The primary analysis (primary and secondary endpoints) may be done separately for each group (eg, if the pancreatic cancer group completes target enrollment months ahead of the other cancer groups, analysis for Group 2 would be executed):

1. At 6 months: once the target enrollment is complete and each subject has been treated for at least 6 months or responded or withdrawn from the study, the analysis of the primary endpoints will occur.
2. At 12 months: once the target enrollment is complete and each subject has been treated for at least 12 months or has been followed up for PFS and OS for 12 months or withdrawn from the study, the analysis of primary and secondary endpoints (safety endpoints, ORR, PFS and OS at 6 and 12 months) will occur

10.3.4 Final Analysis

A final analysis is planned after all subjects from Part 1 and Part 2 have ended the study.

10.4 Planned Methods of Analysis

10.4.1 General Considerations

Descriptive statistics will be provided for selected demographics, safety, PK, PD and biomarker data by dose, dose schedule, and time as appropriate. Descriptive statistics on continuous data will include means, medians, standard deviations and ranges, while categorical data will be summarized using frequency counts and percentages. Graphical summaries of the data may also be presented. Analysis of data in Part 2 will be done separately for each group (Group 1, 2, 3, 4a, 4b).

10.4.2 Primary Efficacy Endpoint

For subjects treated at the maximum tolerated combination (combining subjects from Part 1 and Part 2), the proportion of subjects with OR (a complete or partial response to treatment) per irRECIST with corresponding 90% and 95% CI will be calculated and tabulated.

10.4.3 Secondary Efficacy Endpoint(s)

The following analyses will be done using secondary efficacy endpoint data for all subjects treated at the maximum tolerated combination (combining subjects from Part 1 and Part 2). The proportion of subjects with OR per RECIST 1.1 and corresponding 90% and 95% CI will be calculated and tabulated. Using the Kaplan Meier estimate, the PFS at 6 and 12 months and the OS at 6 and 12 months with corresponding 90% CI will be tabulated. Listings will be produced for all subjects indicating the OS, PFS, TTR, DOR and TTP. Kaplan Meier curve will be presented for OS, PFS, TTR, DOR and TTP with estimates for rates and 80% CI at selected weeks.

10.4.4 Safety Endpoints

Unless otherwise specified, statistical analyses on safety endpoints will be done using subjects from the Safety Analysis Set, which includes subjects that are enrolled and received at least 1 dose of AMG 820**.**

10.4.4.1 Adverse Events

Subject incidence of all treatment-emergent adverse events will be tabulated by system organ class and preferred term. The number and percentage of subjects reporting adverse events will be evaluated overall and by AMG 820 dose level and will also be tabulated by relationship to AMG 820. Tables of dose limiting toxicities, fatal adverse events, serious adverse events, adverse events leading to withdrawal from investigational product or other protocol-required therapies, and significant treatment-emergent adverse events will also be provided.

10.4.4.2 Clinical Laboratory Tests

Clinical chemistry, hematology, and urinalysis data will be listed and reviewed for each subject. Values outside the normal laboratory reference ranges will be flagged as high or low on the listings. Depending on the size and scope of changes in laboratory data, summaries of laboratory data over time and/or changes from baseline over time may be provided. Tables of maximum shifts from baseline for selected laboratory values may also be provided.

10.4.4.3 Vital Signs

Vital signs data will be listed and reviewed for each subject. Depending on the size and scope of changes, summaries of vital signs data over time and/or changes from baseline over time may be provided.

10.4.4.4 Pharmacokinetic Endpoints

The analysis of pharmacokinetic endpoints will include data from all subjects who have received at least 1 dose of the investigational product and have at least 1 pharmacokinetic sample collected.

The PK parameters for AMG 820 and pembrolizumab will be estimated using standard non-compartmental PK methods and summarized by treatment groups using means, standard deviations, medians, minimums and maximums for intensive and peak/trough determinations. PK parameters for AMG 820 and pembrolizumab will include, but not be limited to, maximum observed concentration (C_{max}) and minimum observed concentration (C_{min}). In addition, area under the concentration-time curve (AUC) and, if

feasible, half-life ($t_{1/2}$) will be determined for AMG 820. Serum concentrations at each time point along with PK parameter values may be listed for each subject. Individual AMG 820 concentration/time profiles will be plotted by treatment group. Summary statistics will be computed for each sampling time and parameter as appropriate. Analyses to explore relationship between exposure and safety and exposure and efficacy may also be performed.

10.4.4.5 Relationship in Immune Infiltrate Status in Pre-treatment Biopsies vs. Clinical Response

Logistic regression will be used to model immune infiltrate status vs. clinical response. Immune infiltrate will be measured by CD4, CD8 and CD68 T cell numbers in fresh pre-treatment biopsies. Clinical response will be measured by OR per irRECIST and RECIST 1.1. The logistic regression models will be done separately for each tumor type and sub-type, as appropriate.

11. REGULATORY OBLIGATIONS

11.1 Informed Consent

An initial sample informed consent form is provided for the investigator to prepare the informed consent document to be used at his or her site. Updates to the template are to be communicated formally in writing from the Amgen Clinical Study Manager to the investigator. The written informed consent document is to be prepared in the language(s) of the potential patient population.

Before a subject's participation in the clinical study, the investigator is responsible for obtaining written informed consent from the subject after adequate explanation of the aims, methods, anticipated benefits, and potential hazards of the study and before any protocol-specific screening procedures or any investigational product(s) is/are administered.

The investigator is also responsible for asking the subject if the subject has a primary care physician and if the subject agrees to have his/her primary care physician informed of the subject's participation in the clinical study. If the subject agrees to such notification, the investigator is to inform the subject's primary care physician of the subject's participation in the clinical study. If the subject does not have a primary care physician and the investigator will be acting in that capacity, the investigator is to document such in the subject's medical record.

The acquisition of informed consent and the subject's agreement or refusal of his/her notification of the primary care physician is to be documented in the subject's medical

records, and the informed consent form is to be signed and personally dated by the subject and by the person who conducted the informed consent discussion. The original signed informed consent form is to be retained in accordance with institutional policy, and a copy of the signed consent form is to be provided to the subject.

If a potential subject is illiterate or visually impaired and does not have a legally acceptable representative, the investigator must provide an impartial witness to read the informed consent form to the subject and must allow for questions. Thereafter, both the subject and the witness must sign the informed consent form to attest that informed consent was freely given and understood.

11.2 Institutional Review Board/Independent Ethics Committee

A copy of the protocol, proposed informed consent form, other written subject information, and any proposed advertising material must be submitted to the IRB/IEC for written approval. A copy of the written approval of the protocol and informed consent form must be received by Amgen before recruitment of subjects into the study and shipment of Amgen investigational product.

The investigator must submit and, where necessary, obtain approval from the IRB/IEC for all subsequent protocol amendments and changes to the informed consent document. The investigator is to notify the IRB/IEC of deviations from the protocol or serious adverse events occurring at the site and other adverse event reports received from Amgen, in accordance with local procedures.

The investigator is responsible for obtaining annual IRB/IEC approval/renewal throughout the duration of the study. Copies of the investigator's reports and the IRB/IEC continuance of approval must be sent to Amgen.

11.3 Subject Confidentiality

The investigator must ensure that the subject's confidentiality is maintained for documents submitted to Amgen.

- Subjects are to be identified by a unique subject identification number.
- Where permitted, date of birth is to be documented and formatted in accordance with local laws and regulations.
- On the CRF demographics page, in addition to the unique subject identification number, include the age at time of enrollment.

- For Serious Adverse Events reported to Amgen, subjects are to be identified by their unique subject identification number, initials (for faxed reports, in accordance with local laws and regulations), and date of birth (in accordance with local laws and regulations).
- Documents that are not submitted to Amgen (eg, signed informed consent forms) are to be kept in confidence by the investigator, except as described below.

In compliance with Federal regulations/ICH GCP Guidelines, it is required that the investigator and institution permit authorized representatives of the company, of the regulatory agency(s), and the IRB/IEC direct access to review the subject's original medical records for verification of study-related procedures and data. Direct access includes examining, analyzing, verifying, and reproducing any records and reports that are important to the evaluation of the study. The investigator is obligated to inform and obtain the consent of the subject to permit such individuals to have access to his/her study-related records, including personal information.

11.4 Investigator Signatory Obligations

Each clinical study report is to be signed by the investigator or, in the case of multi-center studies, the coordinating investigator.

The coordinating investigator, identified by Amgen, will be any or all of the following:

- a recognized expert in the therapeutic area
- an Investigator who provided significant contributions to either the design or interpretation of the study
- an Investigator contributing a high number of eligible subjects

12. ADMINISTRATIVE AND LEGAL OBLIGATIONS

12.1 Protocol Amendments and Study Termination

The IRB/IEC must be informed of all amendments and give approval. The investigator **must** send a copy of the approval letter from the IRB/IEC to Amgen.

Amgen reserves the right to terminate the study at any time. Both Amgen and the Investigator reserve the right to terminate the Investigator's participation in the study according to the study contract. The investigator is to notify the IRB/IEC in writing of the study's completion or early termination and send a copy of the notification to Amgen.

Subjects may be eligible for continued treatment with Amgen investigational product(s) by an extension protocol or as provided for by the local country's regulatory mechanism. However, Amgen reserves the unilateral right, at its sole discretion, to determine

whether to supply Amgen investigational product(s) and by what mechanism, after termination of the study and before the product(s) is/are available commercially.

12.2 Study Documentation and Archive

The investigator is to maintain a list of appropriately qualified persons to whom he/she has delegated study duties. All persons authorized to make entries and/or corrections on CRFs will be included on the Amgen Delegation of Authority Form.

Source documents are original documents, data, and records from which the subject's CRF data are obtained. These include but are not limited to hospital records, clinical and office charts, laboratory and pharmacy records, diaries, microfiches, radiographs, and correspondence.

The Investigator and study staff are responsible for maintaining a comprehensive and centralized filing system of all study-related (essential) documentation, suitable for inspection at any time by representatives from Amgen and/or applicable regulatory authorities.

Elements to include:

- Subject files containing completed CRFs, informed consent forms, and subject identification list
- Study files containing the protocol with all amendments, Investigator's Brochure, copies of prestudy documentation, and all correspondence to and from the IRB/IEC and Amgen
- Investigational product-related correspondence including Proof of Receipts (POR), Investigational Product Accountability Record(s), Return of Investigational Product for Destruction Form(s), Final Investigational Product Reconciliation Statement, as applicable.
- Non-investigational product(s) and or medical device(s) documentation, as applicable.

In addition, all original source documents supporting entries in the CRFs must be maintained and be readily available.

Retention of study documents will be governed by the Clinical Trial Agreement.

12.3 Study Monitoring and Data Collection

The Amgen representative(s) and regulatory authority inspectors are responsible for contacting and visiting the investigator for the purpose of inspecting the facilities and, upon request, inspecting the various records of the clinical study (eg, CRFs and other pertinent data) provided that subject confidentiality is respected.

The Amgen Clinical Monitor is responsible for verifying the CRFs at regular intervals throughout the study to verify adherence to the protocol; completeness, accuracy, and consistency of the data; and adherence to local regulations on the conduct of clinical research. The Clinical Monitor is to have access to subject medical records and other study-related records needed to verify the entries on the CRFs.

The investigator agrees to cooperate with the clinical monitor to ensure that any problems detected in the course of these monitoring visits, including delays in completing CRFs, are resolved.

In accordance with ICH GCP and the sponsor's audit plans, this study may be selected for audit by representatives from Amgen's Global Compliance Auditing function (or designees). Inspection of site facilities (eg, pharmacy, protocol-required therapy storage areas, laboratories) and review of study-related records will occur to evaluate the study conduct and compliance with the protocol, ICH GCP, and applicable regulatory requirements.

Data capture for this study is planned to be electronic:

- All source documentation supporting entries into the CRFs must be maintained and readily available.
- Updates to CRFs will be automatically documented through the software's "audit trail".
- To ensure the quality of clinical data across all subjects and sites, a clinical data management review is performed on subject data received at Amgen. During this review, subject data are checked for consistency, omissions, and any apparent discrepancies. In addition, the data are reviewed for adherence to the protocol and GCP. To resolve any questions arising from the clinical data management review process, data queries are created in the EDC system database for site resolution and subsequently closed by the EDC system or by an Amgen reviewer.
- The investigator signs only the Investigator Verification Form for this electronic data capture study or the investigator applies an electronic signature in the EDC system if the study is set up to accept an electronic signature. This signature indicates that investigator inspected or reviewed the data on the CRF, the data queries, and agrees with the content.

Amgen (or designee) will perform self-evident corrections (SECs) to obvious data errors in the clinical trial database. SECs will be documented in the Standard Self Evident Corrections document and the eCRF Specific Instructions, both of these will be available through the EDC system. Examples of obvious data errors that may be corrected by Amgen (or designee) include deletion of obvious duplicate data (ie, the same results sent twice with the same date but different visits eg, week 4 and early termination) and

updating a specific response if the confirming datum is provided in the "other, specify" field (eg, for race, reason for ending study).

12.4 Investigator Responsibilities for Data Collection

The investigator is responsible for complying with the requirements for all assessments and data collection (including subjects not receiving protocol-required therapies) as stipulated in the protocol for each subject in the study. For subjects who withdraw prior to completion of all protocol-required visits and are unable or unwilling to continue the Schedule of Assessments (Table 5), the investigator can search publically available records [where permitted]) to ascertain survival status. This ensures that the data set(s) produced as an outcome of the study is/are as comprehensive as possible.

12.5 Language

All written information and other material to be used by subjects and investigative staff must use vocabulary and language that are clearly understood. CRFs must be completed in English. TRADENAMES® (if used) for concomitant medications may be entered in the local language.

12.6 Publication Policy

Authorship of any publications resulting from this study will be determined on the basis of the Uniform Requirement for Manuscripts Submitted to Biomedical Journals (International Committee of Medical Journal Editors), which states:

- Authorship credit should be based on (1) substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; (2) drafting the article or revising it critically for important intellectual content; (3) final approval of the version to be published (4) agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. Authors should meet conditions 1, 2, and 3.
- When a large, multicenter group has conducted the work, the group should identify the individuals who accept direct responsibility for the manuscript. These individuals should fully meet the criteria for authorship defined above.
- Acquisition of funding, collection of data, or general supervision of the research group, alone, does not justify authorship.
- All persons designated as authors should qualify for authorship, and all those who qualify should be listed.
- Each author should have participated sufficiently in the work to take public responsibility for appropriate portions of the content.

All publications (eg, manuscripts, abstracts, oral/slide presentations, book chapters) based on this study must be submitted to Amgen for review. The Clinical Trial

Agreement among the institution, investigator, and Amgen will detail the procedures for, and timing of, Amgen's review of publications.

12.7 Compensation

Any arrangements for compensation to subjects for injury or illness that arises in the study are described in the Compensation for Injury section of the Informed Consent that is available as a separate document.

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14. APPENDICES

Appendix A. Additional Safety Assessment Information

Adverse Event Grading Scale

The Common Terminology Criteria for Adverse Events (CTCAE) is available at the following location:

http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm

Drug-induced Liver Injury Reporting & Additional Assessments

Reporting

To facilitate appropriate monitoring for signals of DILI, cases of concurrent AST or ALT and TBL and/or INR elevation according to the criteria specified in Section 6.4 require the following:

- The event is to be reported to Amgen as a serious adverse event within 24 hours of discovery or notification of the event (ie, before additional etiologic investigations have been concluded)
- The appropriate CRF (eg, Adverse Event CRF) that captures information necessary to facilitate the evaluation of treatment-emergent liver abnormalities is to be completed and sent to the Amgen.

Other events of hepatotoxicity and potential DILI are to be reported as serious adverse events if they meet the criteria for a serious adverse event defined in Section 9.1.3.

Additional Clinical Assessments and Observation

All subjects in whom investigational product(s) or protocol-required therapies is/are withheld (either permanently or conditionally) due to potential DILI as specified in Sections 6.4.1 and 6.4.2 or who experience AST or ALT elevations ≥ 3 x ULN are to undergo a period of “close observation” until abnormalities return to normal or to the subject’s baseline levels. Assessments that are to be performed during this period include:

- Repeat AST, ALT, ALP, bilirubin (total and direct), and INR within 24 hours
- In cases of TBL ≥ 2x ULN or INR > 1.5, retesting of liver tests, BIL (total and direct), and INR is to be performed every 24 hours until laboratory abnormalities improve

Testing frequency of the above laboratory tests may decrease if the abnormalities stabilize or the investigational product(s) or protocol-required therapies has/have been discontinued AND the subject is asymptomatic.

- Initiate investigation of alternative causes for elevated AST or ALT and/or elevated TBL:
  - Obtain complete blood count (CBC) with differential to assess for eosinophilia
  - Obtain serum total immunoglobulin IgG, Anti-nuclear antibody (ANA), Anti Smooth Muscle Antibody, and Liver Kidney Microsomal antibody 1 (LKM1) to assess for autoimmune hepatitis
  - Obtain serum acetaminophen (paracetamol) levels
  - Obtain a more detailed history of:
    - Prior and/or concurrent diseases or illness
    - Exposure to environmental and/or industrial chemical agents
    - Symptoms (if applicable) including right upper quadrant pain, hypersensitivity-type reactions, fatigue, nausea, vomiting and fever
    - Prior and/or concurrent use of alcohol, recreational drugs and special diets
    - Concomitant use of medications (including non-prescription medicines and herbal and dietary supplements), plants, and mushrooms
  - Obtain viral serologies
  - Obtain CPK, haptoglobin, LDH, and peripheral blood smear
  - Perform appropriate liver imaging if clinically indicated
- Obtain appropriate blood sampling for pharmacokinetic analysis if this has not already been collected
- Obtain hepatology consult (liver biopsy may be considered in consultation with an hepatologist)
- Follow the subject and the laboratory tests (ALT, AST, TBL, INR) until all laboratory abnormalities return to baseline or normal. The “close observation period” is to continue for a minimum of 4 weeks after discontinuation of all investigational product(s) and protocol-required therapies.

The potential DILI event and additional information such as medical history, concomitant medications and laboratory results must be captured in corresponding CRFs.

Appendix B. Sample Serious Adverse Event Report Form

AMGEN Study # 20150195 AMG 820	Electronic Adverse Event Contingency Report Form For Restricted Use

Reason for reporting this event via fax

The Clinical Trial Database (eg. Rave):

☐ Is not available due to internet outage at my site
☐ Is not yet available for this study
☐ Has been closed for this study

<<For completion by Amgen prior to providing to sites: SELECT OR TYPE IN A FAX#>>

1. SITE INFORMATION

Site Number	Investigator	Country

Reporter	Phone Number	Fax Number
	( )	( )

2. SUBJECT INFORMATION

Subject ID Number	Age at event onset	Sex	Race	If applicable, provide End of Study date
		☐F ☐M		

If this is a follow-up to an event reported in the EDC system (eg, Rave), provide the adverse event term: _____
and start date: Day_____ Month_____ Year_____

3. ADVERSE EVENT

Provide the date the Investigator became aware of this information: Day____ Month____ Year_____

Adverse Event diagnosis or syndrome If diagnosis is unknown, enter signs / symptoms and provide diagnosis, when known, in a follow-up report *List one event per line. If event is fatal, enter the cause of eeath. Entry of "death" is not acceptable, as this is an outcome.*	Date Started Day Month Year	Date Ended Day Month Year	Check only if event occurred before first dose of IP/drug under study	Is event serious?	If serious enter Serious Criteria code *(see codes below)*	Relationship Is there a reasonable possibility that the Event may have been caused by IP/drug under study or an Amgen device used to administer the IP/drug under study? AMG 820 No✓ Yes✓ Pembrolizumab No✓ Yes✓	Outcome of Event -Resolved -Not resolved -Fatal -Unknown	Check only if event is related to study procedure eg, biopsy
				☐ Yes ☐ No				
				☐ Yes ☐ No				
				☐ Yes ☐ No				

Serious Criteria:
01 Fatal
02 Immediately life-threatening
03 Required/prolonged hospitalization
04 Persistent or significant disability /incapacity
05 Congenital anomaly / birth defect
06 Other medically important serious event

4. Was subject hospitalized or was a hospitalization prolonged due this event? ☐No ☐Yes If yes, please complete all of Section 4

Date Admitted Day Month Year	Date Discharged Day Month Year

AMGEN
Study # 20150195
AMG 820

Electronic Adverse Event Contingency Report Form

For Restricted Use

Site Number	Subject ID Number

5. Was IP/drug under study administered/taken prior to this event? ☐No ☐Yes If yes, please complete all of Section 5

IP/Drug/Amgen Device:		Date of Initial Dose (Day Month Year)	Prior to, or at time of Event: Date of Dose (Day Month Year)	Dose	Route	Frequency	Action Taken with Product 01 Still being Administered 02 Permanently discontinued 03 Withheld	Lot # and Serial #
AMG 820	☒ open label							Lot #_____ ☐ Unknown Serial # _____ ☐ Unavailable / Unknown
Pembrolizumab	☒ open label							Lot #_____ ☐ Unknown Serial # _____ ☐ Unavailable / Unknown

6. CONCOMITANT MEDICATIONS (eg, chemotherapy) Any Medications? ☐ No ☐ Yes If yes, please complete:

Medication Name(s)	Start Date (Day Month Year)	Stop Date (Day Month Year)	Co-suspect No✓	Co-suspect Yes✓	Continuing No✓	Continuing Yes✓	Dose	Route	Freq.	Treatment Med No✓	Treatment Med Yes✓

7. RELEVANT MEDICAL HISTORY ***(include dates, allergies and any relevant prior therapy)***

8. RELEVANT LABORATORY VALUES ***(include baseline values)*** Any Relevant Laboratory values? ☐ No ☐ Yes If yes, please complete:

Date (Day Month Year)	Test / Unit											

9. OTHER RELEVANT TESTS ***(diagnostics and procedures)*** Any Other Relevant tests? ☐ No ☐ Yes If yes, please complete:

Date (Day Month Year)	Additional Tests	Results	Units

AMGEN Study # 20150195 AMG 820	Electronic Adverse Event Contingency Report Form For Restricted Use

Site Number	Subject ID Number

10. CASE DESCRIPTION ***(Provide narrative details of events listed in section 3)*** Provide additional pages if necessary. For each event in section 3, where relationship=Yes, please provide rationale.

Signature of Investigator or Designee -	Title	Date
I confirm by signing this report that the information on this form, including seriousness and causality assessments, is being provided to Amgen by the investigator for this study, or by a Qualified Medical Person authorized by the investigator for this study.		

Appendix C. Pregnancy and Lactation Notification Worksheets

AMGEN® Pregnancy Notification Worksheet

Fax Completed Form to the Country-respective Safety Fax Line

SELECT OR TYPE IN A FAX#

1. Case Administrative Information

Protocol/Study Number:

Study Design: ☐ Interventional ☐ Observational (If Observational: ☐ Prospective ☐ Retrospective)

2. Contact Information

Investigator Name **Site #**

Phone ( ) **Fax** ( ) **Email**

Institution

Address

3. Subject Information

Subject ID # **Subject Gender:** ☐ Female ☐ Male **Subject DOB:** mm / dd / yyyy

4. Amgen Product Exposure

Amgen Product	Dose at time of conception	Frequency	Route	Start Date
				mm/dd/yyyy

Was the Amgen product (or study drug) discontinued? ☐ Yes ☐ No

If yes, provide product (or study drug) stop date: mm/dd/yyyy

Did the subject withdraw from the study? ☐ Yes ☐ No

5. Pregnancy Information

Pregnant female's LMP mm / dd / yyyy ☐ Unknown

Estimated date of delivery mm / dd / yyyy ☐ Unknown ☐ N/A

If N/A, date of termination (actual or planned) mm / dd / yyyy

Has the pregnant female already delivered? ☐ Yes ☐ No ☐ Unknown ☐ N/A

If yes, provide date of delivery: mm / dd / yyyy

Was the infant healthy? ☐ Yes ☐ No ☐ Unknown ☐ N/A

If any Adverse Event was experienced by the infant, provide brief details:

Form Completed by:

Print Name: **Title:**

Signature: **Date:**

Effective Date: March 27, 2011 Page 1 of 1

AMGEN Lactation Notification Worksheet

Fax Completed Form to the Country-respective Safety Fax Line
SELECT OR TYPE IN A FAX# enter fax number

1. Case Administrative Information

Protocol/Study Number: _____

Study Design: ☐ Interventional ☐ Observational (If Observational: ☐ Prospective ☐ Retrospective)

2. Contact Information

Investigator Name _____ **Site #** _____

Phone (____) _____ **Fax** (____) _____ **Email** _____

Institution _____

Address _____

3. Subject Information

Subject ID # _____ **Subject Date of Birth:** mm____ / dd____ / yyyy____

4. Amgen Product Exposure

Amgen Product	Dose at time of breast feeding	Frequency	Route	Start Date
				mm____/dd____/yyyy____

Was the Amgen product (or study drug) discontinued? ☐ Yes ☐ No

If yes, provide product (or study drug) stop date: mm____/dd____/yyyy____

Did the subject withdraw from the study? ☐ Yes ☐ No

5. Breast Feeding Information

Did the mother breastfeed or provide the infant with pumped breast milk while actively taking an Amgen product? ☐ Yes ☐ No

If No, provide stop date: mm_____/dd_____/yyyy_____

Infant date of birth: mm_____/dd_____/yyyy_____

Infant gender: ☐ Female ☐ Male

Is the infant healthy? ☐ Yes ☐ No ☐ Unknown ☐ N/A

If any Adverse Event was experienced by the mother or the infant, provide brief details: _____

Form Completed by:

Print Name: _____ **Title:** _____

Signature: _____ **Date:** _____

Effective Date: 03 April 2012, version 2.

Page 1 of 1

Appendix D. Modified Immune-Related Response Criteria in Solid Tumors (irRECIST)

The Immune-related Response Criteria (irRC) based on bidimensional measurements were derived from WHO/RECIST to serve as guidelines to systematically characterize additional patterns of response in patients with advanced melanoma receiving ipilimumab therapy and to allow the potential delayed clinical response to immune-enhancing therapies to be captured more accurately (Wolchok JD et al., 2009). Recent evaluation showed that irRC using unidimensional measurements provided highly concordant tumor response assessment and less measurement variability compared with bidimensional measurements (Nishino M et al., 2013). This study will utilize a modified criteria (irRECIST), adapting the immune-related response criteria to conventional RECIST 1.1 (Eisenhauer et al, 2009) as outlined below.

Antitumor response based on total measurable tumor burden

- For irRECIST, only index and measurable new lesions are taken into account (in contrast to conventional RECIST 1.1, which does not require the measurement of new lesions, nor do they include new lesion measurements in the characterization of evolving tumor burden).

Tumor burden assessment:

- All measurable and non-measurable lesions should be assessed at screening and at the defined tumor assessment time points.
    - At baseline tumor assessment: tumor burden is the sum of the longest diameters (SLD) of all index lesions (5 lesions per organ, up to 10 total lesions).
    - At each subsequent tumor assessment: tumor burden is the SLD of the index lesions and of new, measurable lesions ($\geq$ 10 mm in the longest diameter; up to 5 new lesions per organ and up to 10 total lesions) added together
        - Tumor burden = $SLD_{\text{index lesions}} + SLD_{\text{new, measurable lesions}}$

Time point response assessment using modified irRECIST

Percentage changes in tumor burden per assessment time point describe the size and growth kinetics of both conventional and new lesions as they appear. At each tumor assessment, the response in index and new measurable lesions is defined based on the change in tumor burden (after ruling out irPD). Decreases in tumor burden must be assessed relative to baseline measurements (ie, the SLD of all index lesions at screening).

Definitions:

- Methods of measurement:
  - The same imaging modality, method of assessment, and technique must be used throughout the study to characterize each identified and reported lesion.
  - MRI or CT scans should be performed with contiguous slice thickness of 5 mm or less according to the Imaging Manual. Subjects should be evaluated at screening for tolerance to MRI/CT IV contrast. Subjects intolerant of CT IV contrast ie, allergy or renal insufficiency should be imaged using non-contrast CT for the chest and MRI (with or without contrast) for the abdomen and pelvis to enable the best detection of disease throughout the study starting at baseline. If a subject develops a medical contradiction to the MRI/CT IV contrast while on study, preapproval of the sponsor is needed to switch from contrast enhanced MRI to non-contrast MRI or to CT (and vice versa).
  - If a combined PET/CT scan is performed at the discretion of the investigator at baseline and subsequent timepoints, the CT portion of that exam should not be substituted for the dedicated diagnostic CT exams required by this protocol unless the investigator or the site radiologist can document that the CT performed as part of a PET/CT is of identical diagnostic quality to the diagnostic CT as described in the Imaging Manual, then the CT portion of the PET/CT can be used for tumor measurements.
  - Pathological lymph nodes (short axis >10 mm) should be assessed by MRI/CT. Only nodes with short axis $\geq$ 15 mm are to be included as measurable lesions.
  - Patients with suspected brain metastases will also undergo MRI of the brain.
  - All baseline evaluations should be performed as closely as possible to the beginning of treatment, and not more than 28 days before the beginning of the treatment (cycle 1 day 1).
- Measurable disease: Subject must have radiographically measurable disease per RECIST 1.1 (Eisenhauer et al, 2009).
  - Measurable lesions:
    - Lesions with clear borders that can be measured accurately in one dimension (longest diameter $\geq$ 10 mm as measured by MRI/CT with scan slice thickness $\leq$ 5 mm).
    - Pathologic lymph nodes are measurable when the longest diameter perpendicular to the long axis (short axis) is $\geq$ 15 mm on MRI/CT.
    - Must exclude cystic lesions, pleural/pericardial effusions and ascites.
  - Non-Measurable lesions:
    - All other lesions, including small lesions (longest diameter < 10 mm or pathological lymph nodes with ≥ 10 mm but < 15 mm short axis) and other truly non-measurable lesions are considered non-measurable and characterized as non-index lesions.

- Only cancerous lesions should be selected as non-measurable lesions and not indeterminate lesions and lesions that could be cancer. Other examples of non-measurable lesions include some bone lesions*, leptomeningeal disease, inflammatory breast disease, lymphangitic involvement of the skin or (lymphangitis cutis/pulmonis), and groups of lesions that are small and numerous.
- Fluid collections
    - Ascites, pleural effusion, or pericardial effusion, should not be selected as non-measurable disease at baseline or, if new or increased, as evidence of progressive disease. These collections may occur with both benign and malignant conditions, and their etiology is often not clear. These collections may often be removed via interventional procedures, which can lead to a false interpretation of disease response. Thus, these fluid collections should not be used as a baseline non-index or as evidence of disease response.
- Bone Lesions
    - Bone scans, PET scans or plain films are not considered adequate imaging techniques to measures bone lesions. However, these techniques can be used to confirm the presence or absence of bone lesions.
    - Osteolytic (lytic) bone lesions or mixed lytic-blastic lesions, with identifiable soft tissue components, that can be evaluated by cross-sectional imaging technique such as CT or MRI can be considered as measurable lesions if the soft tissue component meets the definition of measurability described above. Only the soft tissue component of the bone lesion should be measured.
    - Many osteoblastic (blastic) bone abnormalities can be benign and should not be selected as baseline lesions. An isolated new small blastic lesion should not be selected as a new lesion unless there is demonstrated growth on subsequent scans. Multiple new blastic lesions that are clearly cancerous may be considered for new lesions.
- Cystic lesions:
    - Lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable or non-measurable) since they are, by definition, simple cysts.
    - Cystic lesions thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same subject, these are preferred for selection as index lesions. If a cystic lesion is clearly cancerous and has both cystic and solid components, then the complete lesion should be measured including both components without excluding the cystic portion of a cystic tumor lesion when measuring.

- Lesions with prior local treatment:
  - Tumor lesions situated in a previously irradiated area, or an area subject to other loco-regional therapy, should not be considered measurable unless there has been demonstrated progression in the lesion.

- Index lesions: all measurable lesions up to a maximum of 5 lesions per organ and 10 lesions in total, representative of all involved organs, are to be identified as Index lesions, recorded and measured. Index lesions are to be selected on the basis of their size and their suitability for accurate repeated measurements by imaging, and most representative of the subject's tumor burden and overall disease status.
- New lesions: New measureable lesions (ie, accurately and serially measureable in at least 1 dimension $\geq$ 10 mm for non-nodal lesions or the short axis is ≥ 15 mm for nodal lesions). The new measurable lesions should be selected on the basis of their size and suitability for accurate repeated measurements by CT or MRI. If there are more than 10 measureable new lesions detected at an imaging time point for a subject, lesions not selected for measurements would be considered non-Index lesions.
- Non-Index lesions: measurable lesions, other than index lesions, and all sites of non-measurable disease, will be identified as non-index lesions. Non-index lesions will be evaluated at the same assessment time points as the index lesions. In subsequent assessments, changes in non-index lesions will contribute only in the assessment of complete response.
  - Pathologic lymph nodes with short axis ≥ 10 mm but < 15 mm at baseline should be considered as non-index lesions
- Unable to evaluate (UE): Any lesion present at baseline which was not assessed or was unable to be evaluated leading to an inability to determine the status of that particular tumor for that time point
- Not Available (NA): Scan not available
- Not Done (ND): Radiographic imaging were not performed at this time point to evaluate the index lesions
- Merging lesions:
  - When two or more index lesions merge, the smaller lesion should have 0 mm recorded for the current and all future assessments, and the larger lesion should have the longest diameter of the merged lesion recorded for the current assessment and be followed for future assessments.
- Separating lesions:
  - When an index lesion splits into 2 or more lesions, the largest measurable part of the split lesion should be considered to be the previously recorded index lesion with measurements provided for the current assessment and followed for future assessments. The remaining lesions would be non-index lesions. Any new lesions that result from separating should be documented as non-index lesions that were generated by separating and not truly new lesions.

- Index lesion response
    - Immune-related Complete Response (irCR) – complete disappearance of all index lesions in two consecutive observations at least 4 weeks apart
        - Pathologic lymph nodes must have reduction in short axis to < 10 mm
    - Immune-related Partial Response (irPR) – decrease of 30% or greater in tumor burden compared with baseline in two consecutive observations at least 4 weeks apart
    - Immune-related Stable Disease (irSD) - not meeting the criteria for irCR or irPR, in the absence of immune-related progressive disease
    - Immune-related Progressive Disease (irPD) – at least a 20% increase in tumor burden compared with nadir (at any single time point) in two consecutive observations at least 4 weeks apart
    - When the size of the tumor lesion is considered 'too small to measure' (eg, less than 5 mm), a default value of 5 mm should be assigned for index lesions. If this is nadir, irPD will be judged from the tumor burden calculated using the default value.
- Non-Index Lesion Response
    - irCR – complete disappearance of all non-index lesions.
        - Pathologic lymph nodes must have reduction in short axis to < 10 mm
    - irPR and irSD – non-Index lesions are not considered in the definition of irPR or irSD. Measurements of non-index lesions are not required, but they are evaluated at each timepoint as 'present', 'absent' or 'unequivocal progression'. If a significant partial response is observed in a non-index lesion, it should be described as a comment.
    - irPD – increases in number or size of non-index lesion(s) does not constitute progressive disease. New lesions that are measurable up to 5 new lesions per organ and 10 total) are included in the calculation of tumor burden in response assessments
- Overall response
    - irCR – complete disappearance of all lesions (whether measurable or not, and no new lesions)
        - Confirmation by a repeat, consecutive assessment no less than 4 weeks from the date of the first documented response
    - irPR – decrease in tumor burden $\geq$ 30% relative to baseline.
        - Confirmation by a repeat, consecutive assessment no less than 4 weeks after the first documentation
    - irSD – not meeting criteria for irCR or irPR, in the absence of irPD
    - irPD – increase in tumor burden ≥ 20% relative to nadir (minimum recorded tumor burden) and at least 5 mm absolute increase compared to nadir.
        - Confirmation by a repeat, consecutive assessment no less than 4 weeks from the date of the first documented assessment.

Response confirmation:

- irCR and irPR:
    - the repeat confirmation scan may be performed any time after 4 weeks from the first suspected radiologic evidence of response and may be delayed until the next scheduled scan to avoid necessary procedures
- irPD:
    - In subjects who have initial evidence of radiological PD by irRECIST (irPD on one scan), it is at the discretion of the PI whether to continue a subject on study treatment until repeat imaging is obtained based on their assessment of clinical stability. Subjects may receive study treatment and tumor assessment should be repeated ≥ 4 weeks later in order to confirm irPD per site assessment.
    - In determining whether or not the tumor burden has increased or decreased per irRECIST, the local site investigator should consider all index as well as any incremental new measureable lesion(s).
    - irPD is confirmed at repeat imaging (irPD on two consecutive scans at least 4 weeks apart) if tumor burden remains ≥ 20% and at least 5 mm absolute increase compared to nadir
    - Subjects with a global deterioration of health status requiring discontinuation of treatment without radiographic confirmation of disease progression (confirmed irPD) at the time should have the reason for treatment discontinuation classified as ‘ clinical disease progression’. In this case, irPD cannot be assigned at the time as the overall objective tumor response. Every effort should be made to radiographically confirm irPD even after discontinuation of treatment.

Measurement and Tumor Response Assessment Based on modified irRECIST	
Measurable lesions	• ≥ 10 mm (unidirectional measure) • Pathologic lymph nodes: short axis ≥ 15 mm
Measurement of each lesion	The longest diameter (mm)
The sum of the measurements (SLD)	• The sum of the longest diameters (SLD) of all index lesions and new measurable lesions, if any • Up to 5 lesions per organ, up to 10 total
Response assessment	• irPD: ≥ 20% increase from nadir and at least 5 mm absolute increase compared to nadir (requires confirmation) • irSD: < 30% decrease from baseline and < 20% increase from nadir • irPR: ≥ 30% decrease from baseline (requires confirmation) • irCR: Disappearance of all lesions (requires confirmation)
New Lesions	The presence of new lesion(s) does not define progression. Measurable new lesions (≥10 mm): The measurements of the new lesions(s) are included in the SLD
Confirmation	Confirmation by 2 consecutive observations at least 4 weeks apart required for irCR, irPR and irPD.

Modified irRECIST Overall Response Assessment			
Measurable Response	Non-measurable Response		Overall Response
Index and new measurable lesions (tumor burden)[a], %	Non-Index lesions	New non-measurable lesions	Using irRECIST
↓ 100%	Absent	Absent	irCR[b]
↓ 100%	Stable/NA	Any	irPR[b]
↓ 100%	Unequivocal progression	Any	irPR[b]
↓ ≥30%	Absent/Stable/NA	Any	irPR[b]
↓ ≥30%	Unequivocal progression	Any	irPR[b]
↓ <30% to ↑ <20%	Absent/Stable/NA	Any	irSD
↓ <30% to ↑ <20%	Unequivocal progression	Any	irSD
↑ ≥20%	Any	Any	irPD[b]
UE	Any	Any	UE
ND	Any	Any	UE
NA	Any	Any	UE

NA = not available; ND = not done; UE = unable to evaluate
[a] Decrease assessed relative to baseline, including new measurable lesions (≥ 10 mm)
[b] Response (irCR, irPR) and progression (irPD) are confirmed by a second, consecutive assessment at least 4 weeks apart.

Appendix E. Eastern Cooperative Oncology Group (ECOG) Performance Status

Grade	ECOG Performance Status
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, eg, light house work, office work
2	Ambulatory and capable of all self-care but unable to carry out any work activities; up and about more than 50% of waking hours
3	Capable of only limited self-care; confined to a bed or chair more than 50% of waking hours
4	Completely disabled; cannot carry on any selfcare; totally confined to bed or chair
5	Dead

Amendment 2

Protocol Title: A Phase 1b/2 Study Assessing Safety and Anti-tumor Activity of AMG 820 in Combination With Pembrolizumab in Select Advanced Solid Tumors

Amgen Protocol Number: AMG 820 20150195

Eudra CT Number: 2016-001080-36

Amendment Date: 15 June 2018

Rationale:

The following updates were made to the protocol dated 03 October 2016 to incorporate requested changes from Merck as well as clarifying language and administrative updates:

- Updated language for Section 2.4 and Section 2.5 with Merck-provided language for pembrolizumab product background.
- Updated language in Section 3.4 to clarify that all subjects who are not DLT evaluable can be replaced.
- Updated language in Section 3.5.1 to clarify the data collected for subjects who continue past 12 months and up to 24 months on treatment.
- Updated language in Section 4 to clarify that all windows in Inclusion and Exclusion criteria are relative to first day of study treatment.
- Modified Exclusion Criterion to exclude subjects with history of or active pneumonitis.
- Updated relevant sections to require safety labs to be reviewed within 2 days prior to dosing.
- Updated Table 2 to indicate that pembrolizumab should be permanently discontinued for Recurrent Grade 2 pneumonitis.
- Updated Table 2 with footnote to indicate that treatment may possibly continue under certain circumstances of isolated elevated AST attributed to AMG 820 with agreement from Medical Monitor.
- Updated Table 3 to indicate that pembrolizumab should be permanently discontinued for Recurrent Grade 2 pneumonitis or ILD.
- Provided language for corticosteroid treatment of Hepatic Toxicity (Section 6.2.4.6) or Renal Failure or Nephritis (Section 6.2.4.7): Grade 2 events should be treated with IV or oral corticosteroids while grade 3-4 events should be treated with IV corticosteroids.
- Updated the reporting period of Pembrolizumab Events of Clinical Interest (Section 6.2.4.9) to be after the first dose of pembrolizumab through 135 (+7) days after the last dose of pembrolizumab, or 135 (+7) days after initiation of a new cancer therapy.

- Updated Section 6.2.4.10 through Section 6.2.4.10.4 to include AMG 820 as well as pembrolizumab in diet and other considerations while taking treatment.
- Removed anticoagulation therapy from Excluded Treatments (Section 6.9) as the statement conflicted with Inclusion/Exclusion criteria.
- Provided language in relevant sections of protocol for suggested follow up frequency of AEs after EOS (Q3W for SAEs, Q2W for grade 3 or higher AEs, Q3W for other abnormalities) until return to baseline.
- Per Merck, removed all pembrolizumab PK testing from Schedule of Assessments.
- As Amgen has decided to discontinue investigating the combination of AMG 820 and pembrolizumab, removed non-essential biomarker and tissue sample collection from Schedule of Assessments.
- Corrected Schedule of Assessments footnotes to align with text in body of protocol.
- Removed Myeloblasts, Promyelocytes, Myelocytes, Metamyelocytes, Atypical lymphocytes from required routine hematology laboratory analytes.
- Updated Section 9.3 with new template language for pregnancy and lactation reporting.
- Clarified guidance for use of PET/CT scans in Appendix D by removing vague language.
- Provided clarifying language in Section 9.2.1 for when disease-related events should be considered serious adverse events.
- Corrected typo in Section 3.5.1 updating the safety follow-up visit to occur 135 days after last dose of study treatment.
- Updated Sponsor Contact information.
- Updated protocol amendment date throughout document.
- Corrected grammar errors throughout document.
- Updated Page numbers in Table of Contents.

Description of Changes:

Section: Headers

Replace: 03 October 2016

With (changes are bolded): **15 June 2018**

Section: Title Page

Replace: [redacted] MD, [redacted]

With: [redacted] **MD MS,** [redacted]

Section: Title Page

Replace: [redacted]

With: [redacted]

Section: Title Page

Add: **Amendment 2 Date: 15 June 2018**

Section: Investigator's Agreement, Paragraph 1:

Replace: 03 October 2016

With: **15 June 2018**

Section: 2.4 Non-Amgen Medicinal Product Background: Pembrolizumab:

Replace entire section: In the United States, pembrolizumab is approved for patients with unresectable or metastatic melanoma and disease progression following ipilimumab and a BRAF inhibitor (if BRAF V600 mutation positive) and patients with metastatic NSCLC whose tumors express PD-L1 as determined by an FDA-approved test and who have disease progression on or after platinum-containing chemotherapy or FDA-approved therapy for EGFR or ALK genomic tumor aberrations (Keytruda® USPI, 2014).

Pembrolizumab is a humanized monoclonal antibody (IgG4 kappa immunoglobulin with an approximate molecular weight of 149 kDa) that blocks the interaction between PD-1 and its ligands, PD-L1 and PD-L2 (Keytruda® USPI, 2014). Consequently, the PD-1 pathway-mediated inhibition of the immune response is released, including the anti-tumor immune response, with resultant tumor recognition by the cytotoxic T cells.

(Hamid el al, 2013).

For additional information, refer to the Pembrolizumab Investigator's Brochure.

With:

Pembrolizumab is a potent humanized immunoglobulin G4 (IgG4) monoclonal antibody (mAb) with high specificity of binding to the programmed cell death 1 (PD-1) receptor, thus inhibiting its interaction with programmed cell death ligand 1 (PD-L1) and programmed cell death ligand 2 (PD-L2). Based on preclinical in vitro data, pembrolizumab has high affinity and potent receptor blocking activity for PD-1. Pembrolizumab has an acceptable preclinical safety profile and is in clinical development as an intravenous (IV) immunotherapy for advanced malignancies. Keytruda™ (pembrolizumab) is indicated for the treatment of patients across a number of indications. For more details on specific indications refer to the Pembrolizumab Investigator's Brochure.

Section: 2.5 Rationale, Paragraph 1:

Replace: To date, anti-PD-1 antibodies have been approved for melanoma (unresectable or metastatic that progressed following ipilimumab and, if BRAF V600 mutation positive, a BRAF inhibitor), and for squamous NSCLC (metastatic disease that progressed on or after platinum-based chemotherapy). They have also shown, and are further investigated, for promising single agent activity in other selected solid and hematological malignancies. Most patients still, however, do not show a response to the monotherapy.

With: **To date, anti-PD-1 antibodies have been approved for a number of indications. However, the majority of patients do not show a response to monotherapy.**

Section: 3.4 Replacement of Subjects:

Delete: Subjects enrolled ~~**in Study Part 1**~~ may be replaced if they are not evaluable for DLT (eg, a subject did not receive study treatment, or ended the study treatment before completion of DLT evaluation period for a reason other than experiencing a DLT).

~~**Subjects enrolled in phase 2 who withdraw or are removed form treatment or from the study will not be replaced.**~~

Section: 3.5.1 Study Duration for Subjects, Line 4:

Replace: 30

With: **135**

Section: 3.5.1 Study Duration for Subjects, End of Section:

Add**: For subjects who continue treatment past 12 months and up to 24 months (if tolerable and clinical benefit is observed), only Visit Date, IP Administration, and AE/SAE information will be collected in EDC. Remaining follow-up to be performed per institutional standard of care.**

Section: 4 Subject Eligibility, End of Sentence 2:

Add: **All windows in Inclusion and Exclusion criteria below are relative to first day of study treatment.**

Section: 4.2 Exclusion Criteria, Criterion 203:

Replace:

203 Evidence of active or radiological sequelae of non-infectious pneumonitis/ interstitial lung disease.

With:

203 **Subject has history** ~~**Evidence of active or radiological sequelae**~~ of **interstitial lung disease, (**non-infectious**)** pneumonitis **that required steroids, or current pneumonitis.** ~~**/interstitial lung disease.**~~

Section: 4.2 Exclusion Criteria, Criterion 204:

Add:

204 History or evidence of other active autoimmune diseases that has required prolonged systemic treatment in past 2 years (ie, with use of disease modifying agents~~**,**~~ **such as** corticosteroids or immunosuppressive drugs).

Section: 6.1 Classification of Product(s) and/or medical Devices(s), Line 1:

Delete: The Amgen Investigational Product ~~**(except if required by local regulation)**~~ use in this study is AMG 820.

Section: 6.2.1.1 Dosage, Administration, and Schedule: AMG 820, Line 6:

Replace: 48hrs

With: **2 days**

Section: 6.2.2.1 Dosage, Administration, and Schedule: Pembrolizumab, Paragraph 1, Lines 8:

Replace: 48hrs

With: **2 days**

Section: 6.2.2.2 Dosage Adjustments, Delays, Rules for Withholding or Restarting, Permanent Discontinuation: Pembrolizumab, Table 2, AST, ALT, or Increased Bilirubin Toxicity:

Add Footnote 3: **Subjects who have isolated elevated AST (with grade ≤ 1 ALT and normal bilirubin) attributed to AMG 820 and are clinically asymptomatic may potentially continue with treatment upon discussion and agreement with Medical Monitor.**

Section: 6.2.2.2 Dosage Adjustments, Delays, Rules for Withholding or Restarting, Permanent Discontinuation: Pembrolizumab, Table 2, Pneumonitis Toxicity, Grade 3-4:

Add: **or Recurrent 2**

Section: 6.2.4.1 Pneumonitis and Interstitial Lung Disease (ILD), Table 3:

Add: **Recurrent Grade 2, Discontinue pembrolizumab, Supportive care per instruction for Grade 2 above.**

Section: 6.2.4.1 Pneumonitis and Interstitial Lung Disease (ILD), After Table 3:

Delete: ~~**For grade 2 pneumonitis or ILD that improves to ≤ grade 1 within 12 weeks, the following rules should apply:**~~

- ~~Second episodes of pneumonitis ir ILD: Permanently discontinue pembrolizumab if upon rechallenge subjects develops pneumonitis ≥ grade 2~~

Section: 6.2.4.6 Hepatic, Section Title:

Add: Hepatic **Toxicity**

Section: 6.2.4.6 Hepatic, 1st Bullet:

Replace: For grade 2 events, monitor liver function tests more frequently until returned to baseline values (consider weekly).

With: **In case of hepatotoxicity ~~For grade 2 events~~**, monitor liver function tests more frequently **(see Section 6.4.2 and Appendix A)** until returned to baseline values **or stabilized and subject is asymptomatic ~~(consider weekly)~~**.

Section: 6.2.4.6 Hepatic, 2nd Bullet:

Add: **For grade 2 events, t~~T~~**reat with IV or oral corticosteroids**.**

Section: 6.2.4.6 Hepatic, 3rd Bullet:

Add: **Subjects who have isolated elevated AST (with grade ≤ 1 ALT and normal bilirubin) attributed to AMG 820 and are clinically asymptomatic may not require treatment with corticosteroids. These cases should be discussed with the medical monitor.**

Section: 6.2.4.7 Renal Failure or Nephritis, 1st Bullet:

Add: For grade 2 events, treat with **IV or oral** corticosteroids.

Section: 6.2.4.7 Renal Failure or Nephritis, 2nd Bullet:

Replace: For grade 3-4 events, treat with **IV ~~systemic~~** corticosteroids.

Section: 6.2.4.9 Pembrolizumab Events of Clinical Interest, Line 2-3:

Replace: …90 (+7) days after the last dose of pembrolizumab, or 30 (+7) days after initiation of a new anticancer therapy…

With: …**135 ~~90~~** (+7) days after the last dose of pembrolizumab, or **135 ~~30~~** (+7) days after initiation of a new anticancer therapy…

Section: 6.2.4.10 Diet and Other Considerations While Taking Pembrolizumab, Section Title:

Add: Diet and Other Considerations While Taking **AMG 820 and** Pembrolizumab

Section: 6.2.4.10.1 Diet During Treatment With Pembrolizumab, Section Title:

Add: Diet During Treatment With **AMG 820 and** Pembrolizumab

Section: 6.2.4.10.2 Contraception Requirements for Pembrolizumab, Section Title:

Add: Contraception Requirements for **AMG 820 and** Pembrolizumab

Section: 6.2.4.10.2 Contraception Requirements for Pembrolizumab, Paragraph 1, Lines 1-2:

Add: **AMG 820 and** Pembrolizumab may have adverse effects on a fetus *in utero*. Furthermore, it is not known if **AMG 820 or** pembrolizumab has transient adverse effects…

Section: 6.2.4.10.2 Contraception Requirements for Pembrolizumab, Paragraph 2, Lines 1:

Add: Subjects should be informed that taking **AMG 820 and** pembrolizumab may involve…

Section: 6.2.4.10.3 Use of Pembrolizumab in Pregnancy, Section Title:

Add: Use of **AMG 820 and** Pembrolizumab in Pregnancy

Section: 6.2.4.10.3 Use of Pembrolizumab in Pregnancy, Line 2:

Add: … subject will immediately be removed from the study **treatment**.

Section: 6.2.4.10.4 Use of Pembrolizumab in Nursing Women, Section Title:

Add: Use of **AMG 820 and** Pembrolizumab in Nursing Women

Section: 6.4.2 Criteria for Conditional Withholding of AMG 820 and/or Pembrolizumab due to Potential hepatotoxicity, Paragraph 1, 4th Bullet:

Delete: OR: ALP > 8x ULN at any time~~>>~~

Section: 6.9 excluded Treatments, Medical Devices, and/or Procedures During Study Period, 3rd Bullet, 1st Sub-Bullet:

Add:

- If the subject requires corticosteroid dosing of > 10 mg prednisone daily (or equivalent) for related toxicities, AMG 820 **and pembrolizumab** dosing must be withheld until the corticosteroid dose has decreased to ≤ 10 mg prednisone daily (or equivalent)

Section: 6.9 excluded Treatments, Medical Devices, and/or Procedures During Study Period, 5th Bullet:

Delete: ~~**anticoagulation therapy (low dose warfarin [<2 mg/day] or low molecular weight heparing for prophylaxis against central venous catheter thrombosis is allowed)**~~

Section: Table 5. Schedule of Assessments:

Delete:

- All Whole Blood for Biomarker Analyses (Immunophenotyping)
- All Serum for Biomarker Analyses of baseline circulating markers (IL34, IL10, VEGF, MCP-1, MMPs, CSF-1)
- All Archive tumor tissue
- All New Tumor tissue for biomarker analyses
- All Anti-AMG 820 antibody collection
- All Anti-pembrolizumab antibody collection
- All Biomarker Development Blood sample
- All pembrolizumab PK testing.

Section: Table 5. Schedule of Assessments, Footnote b:

Replace: Safety follow-up will be performed approximately 135 (+7) days after the last dose of AMG 820 or the last dose of pembrolizumab, whichever is later.

With: Safety follow-up will be performed ~~**approximately**~~ 135 (+7) days after the last dose of AMG 820 or the last dose of pembrolizumab, whichever is later. **Suggested frequency of visits to follow any continuing events are approximately: every week for SAEs, Q2W for grade 3 or higher AEs (excluding AST elevation without drug-associated hepatotoxicity), and Q3W for other abnormalities until resolved to grade 1 or baseline.**

Section: Table 5. Schedule of Assessments, Footnote i:

Delete: ~~**Obtaining of tumor biopsies during study (week 10 +/- 2 weeks) are strongly encouraged.**~~

Section: Table 5. Schedule of Assessments, Footnote j, Second to Last Sentence:

Replace: …prior to confirmed PD and has not had radiographic tumor imaging performed within 4 weeks (+1 week) of the visit.

With: …prior to confirmed PD and has not had radiographic tumor imaging performed within ~~**4**~~ **6** weeks (+1 week) of the visit.

Section: Table 5. Schedule of Assessments, Footnote m:

Replace: 48hrs

With: **2 days**

Section: Table 5. Schedule of Assessments, Footnote l:

Delete:

l ~~**PK samples indicated in table should be collected at the end of pembrolizumab infusion. AMG 820 pre-dose samples may also be assayed for pembrolizumab concentrations.**~~

Section: Table 6. Laboratory Analytes, Hematology:

Delete:

- ~~**Myeloblasts**~~
- ~~**Promyelocytes**~~
- ~~**Myelocytes**~~
- ~~**Metamyelocytes**~~
- ~~**Atypical lymphocytes**~~

Section: 7.2.2 Treatment, Central Laboratory Assessments:

Add: Central laboratory assessments **(refer to Schedule of Assessments as not all tests will be required after Amendment 2)**:

Section: 7.2.3 Safety Follow-up Visit(s), Central Laboratory Assessments:

Add: Central laboratory assessments **(refer to Schedule of Assessments as not all tests will be required after Amendment 2)**:

Section: 7.4 Radiological Imaging Assessment, Paragraph 1, Line 2:

Replace: …contrast-enhanced MRI or CT and evaluated according...

With: …contrast-enhanced MRI **/**~~**or**~~ CT and evaluated according...

Section: 7.4 Radiological Imaging Assessment, Paragraph 2, Line 16:

Add: … continue to receive treatment after **radiographic** confirmation of progressive disease…

Section: 7.6 Biomarker Development, During Study Treatment:

Add: Collection of at least one biopsy at the time of second CT scan (week 10 ± 2 weeks) and additional sequential tumor biopsies strongly encouraged, whenever possible, in all subjects**. Note: this biopsy will no longer be encouraged per the data of Amendment 2.**

Section: 7.6 Biomarker Development, Flow Cytometry Whole Blood Samples:

Add: Refer to the Schedule of Assessments for specific time points and the laboratory manual for detailed collection and handling instructions. **Note that not all samples will be required after Amendment 2.**

Section: 9.2.1 Reporting Procedures for Disease Related Events, Paragraph 2:

Delete: ~~**Events assessed by the investigator to be related to the investigational medicinal product(s)/study treatment/protocol-required therapies, and determined to be serious, require reporting of the event on the Event CRF**~~.

Section: 9.2.1 Reporting Procedures for Disease Related Events, Paragraph 2:

Add: **Disease-Related Events assessed by the Investigator to be more severe than expected and/or related to the investigational medicinal product(s)/study treatment/protocol-required therapies, and determined to be serious, must be recorded on the Event CRF as Serious Adverse Events.**

Section: 9.3 Pregnancy and Lactation Reporting, Paragraph 3:

Replace: Amgen's Global Safety will seek to follow the pregnant woman throughout her pregnancy and her baby up to 12 months after birth.

With: Amgen's Global Safety will seek to follow **with** the **Investigator regarding additional information that may be requested.** ~~**pregnant woman throughout her pregnancy and her baby up to 12 months after birth.**~~

If a female subject becomes pregnant during the study, the Investigator should attempt to obtain information regarding the birth outcome and health of the infant.

If the outcome of the pregnancy meets a criterion for immediate classification as a Serious Adverse Event (eg, female subject experiences a spontaneous abortion, stillbirth, or neonatal death or there is a fetal or neonatal congenital anomaly) the Investigator will report the event as a Serious Adverse Event.

Section: 9.3 Pregnancy and Lactation Reporting, Paragraph 4+5:

Replace: If a lactation case occurs while the female subject is taking protocol-required therapies report the lactation case to Amgen as specified below.

In addition to reporting a lactation case during the study, investigators should monitor for lactation cases that occur after the last dose of protocol-required therapies through

1 week after the last dose of AMG 820 or 4 months after the last dose of pembrolizumab.

With: If a **female breastfeeds while ~~lactation case occurs while the female subject is~~** taking protocol-required therapies report the lactation case to Amgen as specified below.

~~In addition to reporting a lactation case during the study, investigators should monitor for lactation cases that occur after the last dose of protocol-required therapies through 1 week after the last dose of AMG 820 or 4 months after the last dose of pembrolizumab.~~

Section: 9.3 Pregnancy and Lactation Reporting, End of Paragraph 6:

Add: **Amgen Global Patient Safety will follow-up with the Investigator regarding additional information that may be requested.**

If a male subject's female partner becomes pregnant, the Investigator should discuss obtaining information regarding the birth outcome and health of the infant from the pregnant partner.

Section: 9.4 Pembrolizumab Events of Clinical Interest, Paragraph 2, Lines 2-3:

Replace: …90 (+7) days following cessation of pembrolizumab treatment, or 30 (+7) days after initiation of a new anti-cancer therapy…

With: …**135 ~~90~~** (+7) days following cessation of pembrolizumab treatment, or **135 ~~30~~** (+7) days after initiation of a new anti-cancer therapy…

Section: 10.3.1 Interim Analyses, End of Section:

Delete: **~~The study may be discontinued or modified at any time due to documented safety findings.~~**

Section: 10.3.2 Dose Level Review Team (DLRT), End of Paragraph 1:

Add: **The study may be discontinued or modified at any time due to documented safety findings.**

Section: Appendix D. Modified Immune-Related Response Criteria in Solid Tumors (irRECIST), Time point response assessment using modified irRECIST, Definitions, 1st Bullet, Methods of Measurement, 3rd Sub-Bullet:

Replace: If a combined PET/CT scan is performed at the discretion of the investigator at baseline and subsequent timepoints. The CT portion of that exam should not be

substituted for the dedicated diagnostic CT exams required by this protocol. The PET portion of the CT may introduce additional data which may bias the investigator's assessment of response if it is not routinely or serially performed. However, if the investigator or the site radiologist…

With: If a combined PET/CT scan is performed at the discretion of the investigator at baseline and subsequent **timepoints, the** CT portion of that exam should not be substituted for the dedicated diagnostic CT exams required by this protocol **unless~~. The PET portion of the CT may introduce additional data which may bias the investigator's assessment of response if it is not routinely or serially performed. However, if the investigator~~ the Investigator** or the site radiologist…

Section: Appendix D. Modified Immune-Related Response Criteria in Solid Tumors (irRECIST), Time point response assessment using modified irRECIST, Definitions, 2nd Bullet, Mesureable disease, 4th Sub-Bullet:

Replace: New lesions: New measured lesions (ie, accurately and serially measureable in at least 1 dimension ≥ 10 mm for non-nodal lesions or the short axis is ≥ 15 mm for nodal lesions).

With: New lesions: New **measureable ~~measured~~** lesions (ie, accurately and serially measureable in at least 1 dimension ≥ 10 mm for non-nodal lesions or the short axis is ≥ 15 mm for nodal lesions).

Section: Appendix D. Modified Immune-Related Response Criteria in Solid Tumors (irRECIST), Time point response assessment using modified irRECIST, Response confirmation, 2nd Bullet, irPD, 2nd Sub-Bullet:

Replace: In determining whether or not the tumor burden has increased or decreased per irRECIST, the local site investigator should consider all index and non-index lesions as well as any incremental new lesion(s).

With: In determining whether or not the tumor burden has increased or decreased per irRECIST, the local site **Investigator ~~investigator~~** should consider all index **~~and non-index lesions~~** as well as any incremental new **measureable** lesion(s).

Section: Appendix D. Modified Immune-Related Response Criteria in Solid Tumors (irRECIST), Time point response assessment using modified irRECIST, Response confirmation, 2nd Bullet, irPD, 4th Sub-Bullet:

Replace: Subjects with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at the time should have the reason for treatment discontinuation classified as 'non-confirmed disease progression'. In this case, irPD cannot be assigned at the time as the overall objective tumor response. Every effort should be made to document the objective progression even after discontinuation of treatment.

With: Subjects with a global deterioration of health status requiring discontinuation of treatment without **radiographic confirmation** ~~**objective evidence**~~ of disease progression **(confirmed irPD)** at the time should have the reason for treatment discontinuation classified as '**clinical** ~~**non-confirmed**~~ disease progression'. In this case, irPD cannot be assigned at the time as the overall objective tumor response. Every effort should be made to **radiographically confirm irPD** ~~**document the objective progression**~~ even after discontinuation of treatment.

Amendment 1

Protocol Title: A Phase 1b/2 Study Assessing Safety and Anti-tumor Activity of AMG 820 in Combination With Pembrolizumab in Select Advanced Solid Tumors

Amgen Protocol Number: AMG 820 20150195
Eudra CT Number: 2016-001080-36

Amendment Date: 03 October 2016

Rationale:

The following updates were made to the protocol dated 11 December 2015 to incorporate requested changes from EU VHP review:

- Updated Safety Follow Up period from 30 days to 135 days after last study treatment throughout the protocol.
- Added a Dose Rationale section for AMG 820 (Section 2.2.4) and corresponding Table of Contents entry.
- Clarified important identified risks, important potential risks, and referred to most current IB for AMG 820 in Risk Assessment Section 2.3.
- Added new exclusion criterion to exclude subjects with active infection within 2 weeks prior to study enrollment.
- Added new exclusion criterion to exclude subjects who have received systemic immunostimulatory agents within 6 weeks or five half-lives, whichever is shorter, prior to first dose of study treatment (except anti PD-1/PD-L1 treatment if recruited into Group 4a or 4b).
- Modified existing exclusion criteria to also exclude subjects with prior stem cell transplantation.
- Modified existing exclusion criteria to also exclude subjects who have other signs or symptoms of clinical immune system suppression.
- Part of an existing exclusion criterion was updated to be a stand-alone criterion (previously part of Exclusion 205, the following is now Exclusion 206: receiving systemic immunosuppressive therapy (> 2 weeks) within 7 days prior to the first dose of study treatment, including oral steroid doses > 10 mg/day of prednisone or equivalent except for management of adverse events during the course of the study. Subjects that require intermittent use of bronchodilators or local steroid injection will not be excluded from the study).
- Updated exclusion criteria to include only highly effective methods of birth control which are in accordance with CTFG's recommendations (removed statements regarding barrier methods of contraception as being acceptable).
- Updated exclusion criteria to define women and men of reproductive potential or childbearing potential, respectively.

- Updated Dose Limiting Toxicity Definition for thrombocytopenia to indicate that any Grade 3 or higher thrombocytopenia with bleeding, and Grade 4 or higher thrombocytopenia lasting >48 hours or any thrombocytopenia requiring intervention is considered a DLT.
- Updated Schedule of Assessments to require urine pregnancy test prior to each infusion for women of childbearing potential.
- Updated Schedule of Assessments and relevant areas of protocol to require MRI of brain for subjects with NSCLC at screening.
- Updated Reasons for Removal from Treatment to include “pregnancy” and “potential hepatotoxicity” (in accordance with section 6.4.1).
- Removed reference not cited in protocol.
- Corrected spelling and grammatical errors throughout protocol.
- Table of Contents page numbers updated at page 26 and beyond to reflect addition of Section 2.2.4 AMG 820 Dose Rationale.