STATISTICAL ANALYSIS PLAN

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

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TABLE OF CONTENTS

List of Figures

List of Appendices

Table of Abbreviations

Abbreviation/Acronym	Definition
AE	Adverse event
ALP	alkaline phosphatase
ALT	alanine transaminase
AST	aspartate aminotransferase
$AUC_{0\text{-last}}$	Area under the concentration-time curve from time 0 to the time of the last quantifiable concentration
BMI	Body Mass Index
CI	confidence interval
C_{max}	maximum observed concentration
C_{min}	minimum observed concentration
CPMS	Clinical Pharmacology Modeling and Simulation
CRC	colorectal cancer
CRF	case report form
CSF-1	Colony Stimulating Factor 1
CSF-1R	Colony Stimulating Factor 1 Receptor
CTCAE	Common terminology for adverse events
DLRM	Dose level review meeting
DLRT	Dose level review team
DLT	Dose limiting toxicity
DMP	Data management plan
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EOS	End of study
EOT	End of treatment
GBS	Global biostatistical science
IP	Investigational product
IPD	Important protocol deviation
IV	Intravenous
MedDRA	Medical dictionary for regulatory activities
MRI	magnetic resonance imaging
NSCLC	non-small cell lung cancer
OR	objective response
ORR	objective response rate
OS	overall survival

Abbreviation/Acronym	Definition
PD	pharmacodynamics
PD-1	programmed cell death-1
PD-L1	programmed death ligand 1
PFS	progression free survival
PK	Pharmacokinetic(s)
PK-PD	Pharmacokinetic and pharmacodynamics
QW	every week
Q2W	every two weeks
Q3W	every three weeks
QT	QT interval is a measure of the time between the start of the Q wave
SAP	Statistical Analysis Plan
TBL	Total Bilirubin
TFL	Tables, Figures, and Listings
TTP	time to progression
TTR	time to response

1. Introduction

The purpose of this statistical analysis plan (SAP) is to provide details of the statistical analyses that have been outlined within the protocol amendment **#2** for AMG 820, Study 20150195, **dated 15 Oct 2018**. The scope of this plan includes the final analysis that will be executed by the Global Biostatistical Science (GBS) department unless otherwise specified (eg, standard pharmacokinetic (PK) tables will be provided by Clinical Pharmacology Modeling and Simulation [CPMS]).

2. Objectives

2.1 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 Immune-related Response Evaluation Criteria in Solid Tumors (irRECIST) in subjects with select advanced solid tumors

2.2 Secondary

- Evaluate the anti-tumor activity of AMG 820 and pembrolizumab combination **as per Immune-related Response Evaluation Criteria in Solid Tumors (irRECIST) in subject with** advanced solid tumors by assessing
    - 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

2.3 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

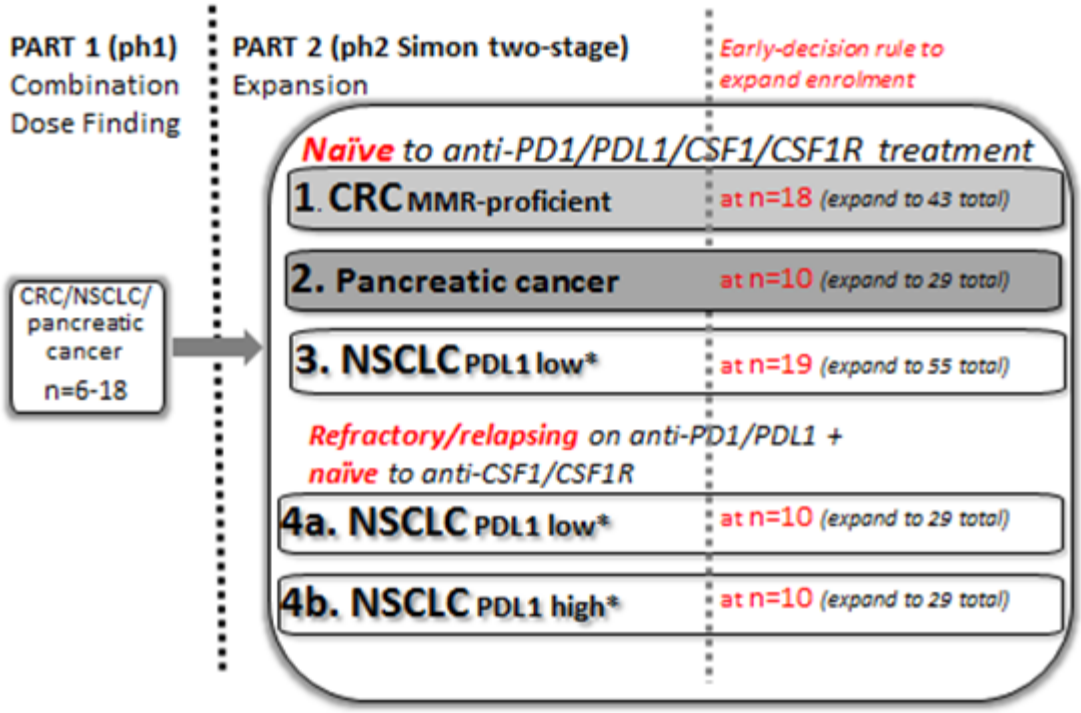
3. Study Overview

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 in the Protocol), 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.

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 (colorectal cancer [CRC], pancreatic cancer, non-small cell lung 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 of protocol) 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.

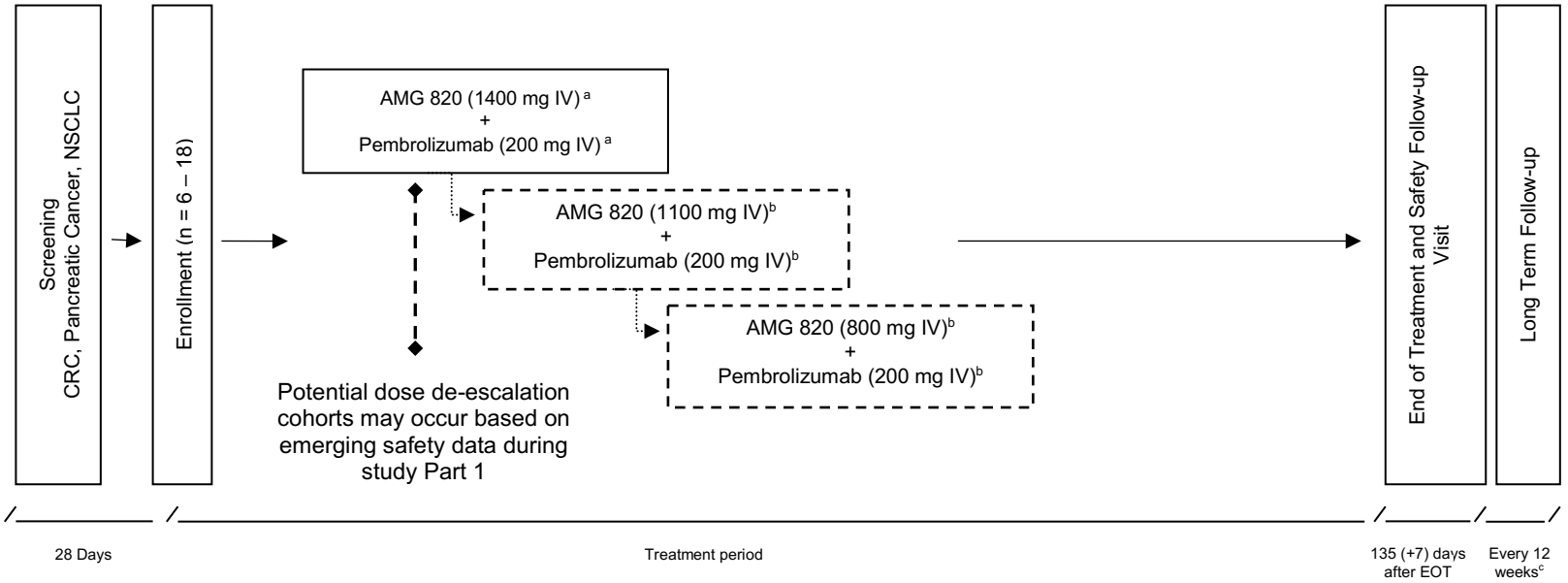
- Group 3 will enroll up to 55 advanced NSCLC subjects with low (<50%) tumor PD-L1- expression who are naïve to anti-PD-1/PD-L1/CSF-1/CSF-1R agents. Nineteen (19) subjects will be enrolled during the first stage and treated with the AMG 820 plus pembrolizumab combination. If 3 or fewer subjects have 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.

3.1.3 Study Schema

The overall study design is described in the study schema below:

Figure 2. Study Design and Treatment Scheme

PART 1



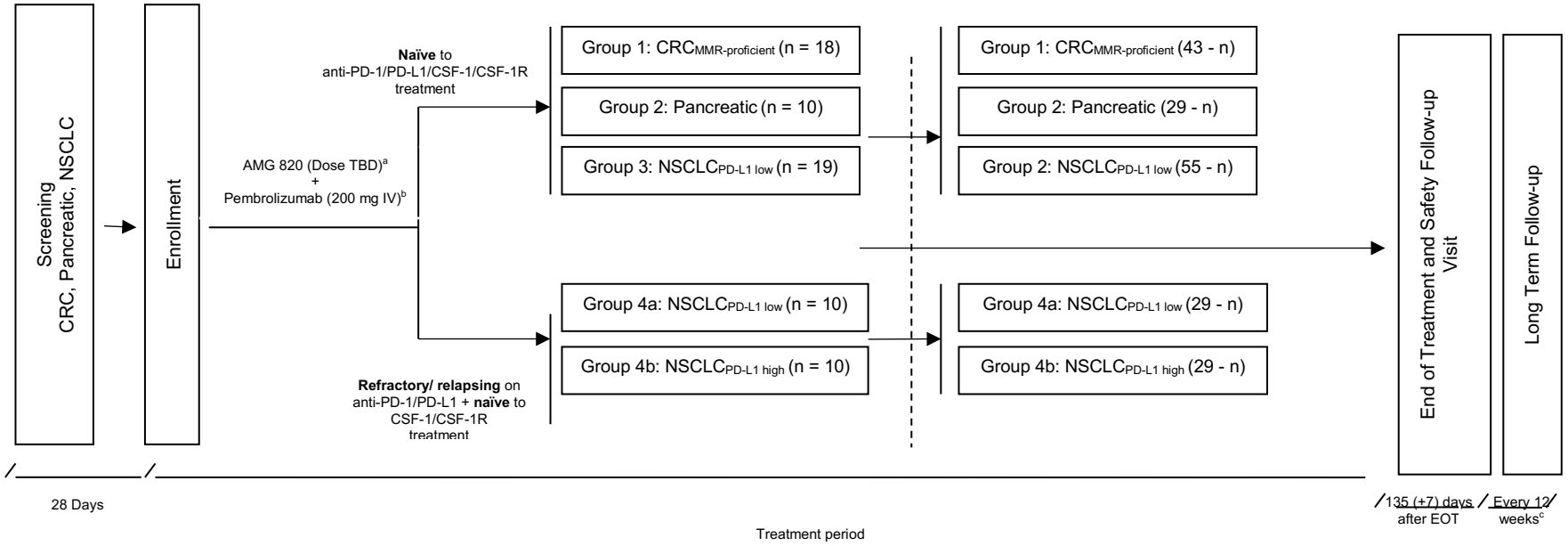
EOT = End of Treatment

[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. Intermediate 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.

3.2 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 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 AMG 820 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 Le et al, 2015 reported a pembrolizumab objective response rate (ORR) per RECIST1.1 and Immune-related Response Criteria (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 Brahmer et al, 2012 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, 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 of 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.

4. Study Endpoints and Covariates

4.1 Study Endpoints

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

Secondary Endpoint(s):

- TTR, DOR and TTP per irRECIST; OS and PFS per irRECIST 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

Exploratory Endpoint(s):

- 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}).

4.2 Planned 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.

5. Hypotheses and/or Estimations

- 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

6. Definitions

$AUC_{0\text{-last}}$

Area under the concentration-time curve from time 0 to the time of the last quantifiable concentration.

Baseline

For any variable, unless otherwise specified the baseline is the last assessment taken prior to the first administration of AMG 820. For parameters/assessments not scheduled to be performed (or scheduled but not performed) on the same day as the first administration of AMG 820, the baseline value is the value from the screening period measured closest to the day of first administration of AMG 820.

Change From Baseline

Change from Baseline is the arithmetic difference between a post-Baseline value and Baseline value:

Change (absolute) from Baseline = (Post-baseline Value – Baseline Value)

Change (percent) from Baseline = [(Post-baseline Value – Baseline Value) / Baseline Value] x 100

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.

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.

Dose Limiting Toxicity

A DLT will be defined as any grade ≥ 3 adverse event occurring during a DLT window (21 day period from the initial administration of AMG 820 and pembrolizumab in

combination), and if judged by the investigator to be related to the administration of AMG 820 and/or pembrolizumab.

For details see the Section 6.2.1.2.3 of the protocol.

Duration of Response

Duration of response is defined as the number of days between the date of the first tumor assessment indicating an objective response through to the subsequent date of progression as classified by irRECIST or death, or where applicable date of censoring [date of first progressive disease assessment or death or date of censoring – date of the first objective response result +1]. Subjects who respond and have not progressed while on study or died will be censored at the date of the last evaluable radiological assessment. Subjects who do not achieve an objective response will be excluded from the analysis of duration of response.

End-of-Study

The EOS is the last planned clinical visit for each subject enrolled in this study.

Primary Completion:

Defined as 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:

Defined as the time 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.

Enrollment

A subject will be considered enrolled when the investigator decides that the subject has met all eligibility criteria. Enrollment Date is defined as the date collected on the CRF.

Investigational Product

The term ‘investigational product’ is used in to reference to AMG 820 in combination with pembrolizumab.

Last Investigational Product Dose Date

The last AMG 820 dose date for each subject is defined as the latest date AMG 820 is administered.

Objective Response as per irRECIST (irOR)

Objective response is defined as a complete response or partial response, as defined by the irRECIST. Confirmation is done by a repeat, consecutive assessment no less than 4 weeks from the date of first documented assessment.

Objective Response Rate as per irRECIST (irORR)

Immune-related ORR (irORR) is defined as the percentage of subjects with irOR.

Overall Survival Time

Overall survival time is calculated as the number of days from the first administration of AMG 820 to death or if applicable censoring [(date of death or censoring – date of first dose of AMG 820 + 1]. Subjects who withdraw from treatment without withdrawing consent will be followed for survival status up to 12 months.

Subjects who are alive (no record of death) and are lost to follow-up will be censored at the date of last contact.

Progression-Free Survival Time per irRECIST (PFS)

Progression-free survival time is calculated as the number of days from the first administration of AMG 820 to the first assessment of disease progression as per irRECIST or death due to any cause, or if applicable date of censoring (date of progressive disease or death or censoring – first administration of AMG 820 +1).

The following censoring strategies will be used for the progression free survival analysis:

If a subject's disease has not progressed and the subject is alive, progression-free survival time will be censored at the last date they are known to be progression-free (ie, the last evaluable radiological assessment date).

If a subject has no tumor evaluation in the study, progression-free survival time will be censored at the date of the first administration of AMG 820.

Subjects who withdraw consent to participate in the study prior to disease progression will be censored at their last evaluable radiological assessment date.

Study Day

Post study day 1: study day= (date - date of Study Day 1) + 1

Pre study day 1: study day= (date – date of Study Day 1)

Study Day 1

Study day 1 is defined as the first day of administration of AMG 820 after enrollment. The day prior to Study Day 1 is considered Day -1.

Time to Response per irRECIST (TTR)

Time to response is defined as the time from first dose of AMG 820 until first documented complete or partial response per irRECIST. The following censoring strategies will be used:

If a subject has not responded during the study, TTR will be censored at the last evaluable radiological assessment date.

If a subject has no tumor evaluation in the study, TTR will be censored at the date of the first administration of AMG 820.

Time to progression per irRECIST (TTP)

Time to progression is calculated as the number of days from the first administration of AMG 820 to the first objective assessment of disease progression as per irRECIST, clinical progression, or if applicable date of censoring (date of progressive disease or censoring – date of first administration of AMG 820 +1). The following censoring strategies will be used:

If a subject's disease has not progressed, time to progression will be censored at the last date they are known to be progression-free (ie, the last evaluable radiological assessment date).

If a subject has no tumor evaluation in the study, time to progression will be censored at the date of the first administration of AMG 820.

Treatment-Emergent Adverse Event(TEAE)

A treatment-emergent adverse event is any adverse event starting on or after the first dose of AMG 820 **or pembrolizumab**, as determined by the flag indicating if the adverse event started prior to the first dose on the Adverse Events Summary CRF, and up to and including **135 [+7]** days after **the last dose of** AMG 820 or **pembrolizumab, whichever is later.**

Treatment-Related Adverse Event

Treatment-related AEs are adverse events deemed by the investigator to be possibly or probably related to AMG 820 or pembrolizumab. 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." 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.

7. Analysis Subsets

The analysis of all endpoints, unless noted otherwise, will be conducted on the Safety Analysis Set.

7.1 Safety Analysis Set

The Safety Analysis Set will consist of all subjects that are enrolled and receive at least 1 dose of AMG 820.

7.2 Dose Limiting Toxicity Analysis Set

The Dose Limiting Toxicity Analysis Set will contain DLT-evaluable subjects (see protocol section 6.2.1.2.2 for definition of DLT-evaluable).

7.3 Pharmacokinetic (PK) Analysis Set

The PK concentration analysis set will contain all subjects who have received at least 1 dose of AMG 820 and have at least one PK sample collected.

8. Interim Analysis and Early Stopping Guidelines

8.1 Interim Analysis

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). 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, 2, 3, 4a, 4b) with the first stage enrolling n=18, 10, 19, 10 and 10 subjects, respectively (see Figure 1 of Study 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. 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.

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

8.2 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.

A DLRM Charter will not be used.

9. Data Screening and Acceptance

9.1 General Principles

The objective of the data screening is to assess the quantity, quality and statistical characteristics of the data relative to the requirements of the planned analyses.

9.2 Data Handling and Electronic Transfer of Data

Amgen's Clinical Data Management department will provide all data to be used in the planned analyses. The database will be subject to edit checks outlined in the Clinical Data Management Plan (DMP). See details of this section in the DMP.

9.3 Handling of Missing and Incomplete Data

Imputation Rules for Partial or Missing Start Dates

	Missing	Imputation	Exception
Start date (AE, concomitant medication)	Day	01	Default to Study Day 1 if an adverse event starts the same year and month as Study Day 1 and the flag indicates that the adverse event started on or after the first dose on the Adverse Events eCRF
	Day/Month	01JAN	Default to Study Day 1 if an event started the same year as Study Day 1 and the flag indicates that the adverse event started on or after the first dose on the Adverse Events eCRF
	Day/Month/Year	No imputation	

Imputation Rules for Partial or Missing Stop Dates

If the month and year are present, impute the last day of the month. If only the year is present, impute December 31 of that year. If the stop date is entirely missing, assume the event or medication is ongoing. If a partial or complete stop date is present and the 'ongoing' or 'continuing' box is checked, then it will be assumed that the AE or conmed stopped and the stop date will be imputed, if partial. Ensure the imputed stop date is on or after the complete or imputed start date.

9.4 Detection of Bias

Lack of protocol compliance and the potential for biased statistical analyses will be examined by assessing the incidence of important protocol deviations (IPD). The clinical study team will identify and document the criteria for IPD.

9.5 Outliers

Outlier data will not be excluded unless scientifically justified.

PK serum concentration data will be evaluated for outliers by visual inspection and decisions to re-assay individual samples will be made in accordance with standard pharmacokinetic evaluation practices.

9.6 Distributional Characteristics

Where appropriate, the assumptions underlying the proposed statistical methodologies will be assessed. If required data transformations or alternative non-parametric methods of analyses will be utilized.

9.7 Validation of Statistical Analyses

Programs will be developed and maintained, and output will be verified in accordance with current risk-based quality control procedures. Tables, figures and listings will be produced with validated standard macro programs where standard macros can produce the specified outputs.

The production environment for statistical analyses consists of Amgen-supported versions of statistical analysis software, for example the SAS System version 9.4 or later.

Additional statistical software may be used to perform exploratory/ad-hoc analyses.

10. Statistical Methods of Analysis

10.1 General Principles

Descriptive statistics will be provided for selected demographic, 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 standard errors for post-baseline data), quartiles, 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).

When data are summarized by time, the values recorded against the scheduled time points listed in the protocol will be used. When assessing minimum/maximum increases or decreases over the study, all assessments, including unscheduled assessments will be used. Data listings will include all available data from all enrolled subjects unless specified otherwise.

10.2 Subject Accountability

The number and percent of subjects who were enrolled, received investigational product, completed investigational product, discontinued from investigational product (including reasons for discontinuing), completed study, and discontinued the study (including reasons for discontinuing) will be summarized by dose group, by cohort.

Key study dates for the first subject enrolled, last subject enrolled, and last subject's end of study will be presented.

A list of subjects who withdraw early will be reviewed. It will include the reason and timing of the withdrawal. Similarly, the reason any subject is excluded from an analysis set will also be reviewed.

10.3 Important Protocol Deviations

IPD categories are defined by the study team before the first patient visit and updated during the IPD reviews throughout the study prior to database lock. These definitions of IPD categories, sub-category codes and descriptions will be used during the course of the study.

The final IPD list is used to produce the Summary of IPDs table and the list of Subjects with IPDs. In addition, a separate listing of all inclusion and exclusion deviations will be provided.

10.4 Demographic and Baseline Characteristics

Demographic (ie, age, sex, race, ethnicity, and baseline characteristics (height, weight, ECOG status, disease stage criteria, and BMI) will be summarized by dose using descriptive statistics. If multiple races have been reported for a subject, the subject will be categorized as multiple race as well as by the combination of races.

A listing of the demographic and baseline characteristics will be provided. In addition listings of medical history, surgical history, prior anti-cancer usage and prior radiotherapy usage will be provided.

10.5 Safety Analyses

10.5.1 Adverse Events

The Medical Dictionary for Regulatory Activities (MedDRA) version 20.1 or later will be used to code all adverse events to a system organ class and a preferred term. The subject incidence of adverse events will be summarized for all treatment-emergent, serious treatment emergent, treatment-related to AMG 820 or pembrolizumab, those leading to withdrawal of IP, fatal and of special interest. **Immune-mediated events associated with oncologic immunotherapies AMQ can be considered as event of interest and list of EOI's will be provided programming note of TFL shell document.** The severity of each adverse event will be graded using CTCAE version 4.0 criteria.

Subject incidence of all treatment-emergent, serious treatment-emergent, treatment-related to AMG 820 or pembrolizumab, those leading to withdrawal of IP, and fatal AE will be tabulated by system organ class and preferred term, where treatment refers to IP. Where appropriate the tables will also be presented by worst grade. The above adverse event tables will not be created if two or fewer subjects experience the adverse event.

Details of each adverse event from will be listed. Listings and/or narratives of any on-study deaths, serious and significant treatment-emergent adverse events, including early withdrawals due to adverse events, also will be provided should they occur.

10.5.1.1 Dose Limiting Toxicities

Summary of the subject incidence of dose limiting toxicities (DLT) will be provided should they occur.

10.5.2 Laboratory Test Results

10.5.2.1 Chemistry, Hematology and Coagulation

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. The worst value for each subject within the time interval of interest will be used for subjects with multiple measurements within the interval. Subjects with missing data for a defined time interval will not contribute to the tabulations for that time interval.

Corrected calcium will also be included in above mentioned analysis, which will be calculated as below

Corrected Calcium = [0.8 * (normal albumin – subject albumin(g/dl))] + serum calcium(mg/dl)

Where Normal Albumin level will be considered as 4 g/dl.

Subject incidence of liver function test results (including AST, ALT, Total Bilirubin (TBL), and Alkaline Phosphatase (ALP)) will also be summarized by dose group. In addition, subject incidence of suspected Hy's Law cases will also be presented by dose group.

10.5.3 Vital Signs

Vital signs will be 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 will be provided.

10.5.4 Electrocardiogram (ECG)

The ECG measurements from this clinical study were performed as per standard of care for routine safety monitoring, rather than for purposes of assessment of potential QTc effect. Since these evaluations may not necessarily be performed under the rigorous conditions expected to lead to meaningful evaluation of QTc data; summaries and statistical analyses of ECG measurements are not planned, and these data would not be expected to be useful for meta-analysis with data from other trials.

10.5.5 Physical Measurements

Physical examination results will be reviewed for each subject. Depending on the size and scope of change in weight and BMI, summaries may be provided.

10.5.6 Exposure to Investigational Product

Descriptive statistics will be produced to describe the exposure to investigational product by dosing schedule.

A listing of the unique manufacturing lot numbers, and a listing of the subjects administered each manufacturing lot number will be provided.

10.5.7 Exposure to Concomitant Medication

All medication will be coded using the WHO drug dictionary. A subject listing of all prior and concomitant medications will be presented.

10.6 Efficacy Analyses

10.6.1 Primary Analysis

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. For SAS code, see Appendix A.

Analysis will be done using local lab data ie, investigator reported.

10.6.2 Secondary Analysis

The following analyses will be done using secondary efficacy endpoint data **collected using irRECIST** for all subjects treated at the maximum tolerated combination (combining subjects from Part 1 and Part 2).

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 curves will be presented for OS, PFS, TTR, DOR and TTP with estimates for rates and 80% CI at selected weeks. TTR will also be analyzed excluding subjects that do not achieve an objective response.

Analysis will be done using local lab data ie, investigator reported.

10.7 Analyses of Exploratory Endpoints

10.7.1 Antibody Formation

The incidence and percentage of subjects who develop anti-AMG 820 antibodies (binding and if positive, neutralizing) at any time will be tabulated by dose group, if tested and if data available.

10.8 Pharmacokinetic or Pharmacokinetic/Pharmacodynamic 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 dose 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 dose 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. Analyses will be conducted by Amgen Clinical Pharmacology Modeling and Simulation (CPMS).

10.9 Biomarker Endpoints

The exploratory biomarker analysis will be carried out by computation biology group and is beyond the scope of this document.

10.10 Changes from Protocol-Specified Analyses

Due to business reason data is not collected for RECIST 1.1 hence analysis of RECIST 1.1 is excluded during SAP amendment 1 dated 16 January 2019.

11. List of Planned Tables, Figures and Listings [TFLs]

The definitive list of TFLs to be produced for this study is documented in the PRISM.

12. Literature Citations / References

Brahmer, Julie R., et al. "Safety and activity of anti–PD-L1 antibody in patients with advanced cancer." *N Engl J Med*. 366.26 (2012): 2455-2465.

Garon, Edward B., Naiyer A. Rizvi, Rina Hui, Natasha Leighl, Ani S. Balmanoukian, Joseph Paul Eder, Amita Patnaik et al. Pembrolizumab for the Treatment of Non-Small-Cell Lung Cancer. *New England Journal of Medicine*. 2015.

Le, Dung T., Jennifer N. Uram, Hao Wang, Bjarne R. Bartlett, Holly Kemberling, Aleksandra D. Eyring, Andrew D. Skora et al. PD-1 Blockade in Tumors with Mismatch-Repair Deficiency. *New England Journal of Medicine.* 372, no. 26 (2015): 2509-2520.

13. Data Not Covered by This Plan

Exploratory data not included in this plan may be analyzed at a later date or may be analyzed by a different Amgen Department.

14. Appendices

Appendix A. Code Fragments

Provisional Code Fragments for calculating a confidence interval using the Clopper Pearson Method. The following example SAS code will be utilized for the response rate analysis providing the proportion of subjects responding to treatment with corresponding 95% confidence intervals.

```
data propci (keep = ns p low_ci upp_ci);
n=xx; * total n within the treatment group;
ns= xx; *number of responders;
p=ns/n; * response rate;
q=1-p;
lowF=FINV(0.025, 2*ns, 2*(n-ns+1)); /* use for 2-sided 95% CI */
UppF=FINV(1-0.025, 2*(ns+1), 2*(n-ns)); /* use for 2-sided 95% CI */
low_ci = 1 / (1+(n-ns+1) / (ns*lowf)); * lower CI for response rate;
upp_ci = 1 / (1+(n-ns) / ((ns+1)*uppf)); *upper CI for response rate;
if p=1 then upp_ci=1;
if p=0 then low_ci =0;
output;
end;run;
```

For 90% confidence intervals.

```
data propci (keep = ns p low_ci upp_ci);
n=xx; * total n within the treatment group;
ns= xx; *number of responders;
p=ns/n; * response rate;
q=1-p;
lowF=FINV(0.05, 2*ns, 2*(n-ns+1)); /* use for 2-sided 90% CI */
UppF=FINV(1-0.05, 2*(ns+1), 2*(n-ns)); /* use for 2-sided 90% CI */
low_ci = 1 / (1+(n-ns+1) / (ns*lowf)); * lower CI for response rate;
upp_ci = 1 / (1+(n-ns) / ((ns+1)*uppf)); *upper CI for response rate;
if p=1 then upp_ci=1;
if p=0 then low_ci =0;
output;
end;run;
```