Title Page

Protocol Title:		A Phase 3 Multicenter, Randomized, Open Label, Active-controlled, Study of AMG 510 Versus Docetaxel for the Treatment of Previously Treated Locally Advanced and Unresectable or Metastatic NSCLC Subjects With Mutated KRAS p.G12C
Short Protocol Title:		A Phase 3 Study to Compare AMG 510 With Docetaxel in NSCLC Subjects With *KRAS p.G12C* Mutation (CodeBreak 200)
Protocol Number:		20190009
Investigational Product:		AMG 510
Trade Name:		Not available
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Data Elements Standards Version:		6.2

This protocol was developed, reviewed, and approved in accordance with Amgen's standard operating procedures. This format and content of this protocol is aligned with Good Clinical Practice: Consolidated Guidance (ICH E6).

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Investigator's Agreement:

I have read the attached protocol entitled A Phase 3 Multicenter, Randomized, Open Label, Active-controlled, Study of AMG 510 Versus Docetaxel for the Treatment of Previously Treated Locally Advanced and Unresectable or Metastatic NSCLC Subjects With Mutated KRAS p.G12C, dated **06 January 2022**, and agree to abide by all provisions set forth therein.

I agree to comply with the International Council for Harmonisation (ICH) Tripartite Guideline on Good Clinical Practice (GCP), Declaration of Helsinki, 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) and my subinvestigators (including, if applicable, their spouses [or legal partners] and dependent children) at the start of the study and for up to 1 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)

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1. Protocol Summary

1.1 Synopsis

Protocol Title: A Phase 3 Multicenter, Randomized, Open Label, Active-controlled, Study of AMG 510 Versus Docetaxel for the Treatment of Previously Treated Locally Advanced and Unresectable or Metastatic NSCLC Subjects With Mutated KRAS p.G12C
Short Protocol Title: A Phase 3 Study to Compare AMG 510 With Docetaxel in NSCLC Subjects With *KRAS p.G12C* Mutation (CodeBreak 200)

Study Phase: 3

Indication: Previously treated locally advanced and unresectable or metastatic non-small cell lung cancer (NSCLC) with *KRAS p.G12C* mutation

Rationale

Lung cancer is the most common type of cancer occurring in both males and females worldwide (WHO statistics, 2018), and the 5-year survival rate for advanced NSCLC is low (between 6% and 33%, depending on the stage (American Cancer Society, 2019). The rat sarcoma (RAS) proto-oncogene has been identified as an oncogenic driver of tumorigenesis in several cancers, including NSCLC. The RAS proteins can be mutationally activated at codons 12, 13, or 61, leading to human cancers. Different tumor types are associated with mutations in certain isoforms of RAS, with Kirsten rat sarcoma viral oncogene homolog (KRAS) being the most frequently mutated isoform in most cancers (Prior et al, 2012). While the role of *KRAS* mutations in human cancers has been known for decades, no anti-cancer therapies specifically targeting *KRAS* mutations have been successfully developed, largely because the protein has been intractable for inhibition by small molecules (McCormick, 2016). AMG 510 is a small molecule that specifically and irreversibly inhibits the KRAS G12C mutated protein. Nonclinical studies of AMG 510 have demonstrated inhibition of growth and regression of cells and tumors harboring *KRAS p.G12C*, and in clinical Study 20170543, AMG 510 demonstrated antitumor activity in *KRAS p.G12C* mutated NSCLC. These data suggest that inhibition of KRAS G12C may have therapeutic benefit for subjects with *KRAS p.G12C* driven cancers. Therefore, the aim of Study 20190009 is to evaluate the efficacy, safety, and tolerability of AMG 510 compared to docetaxel in subjects with previously treated, locally advanced, and unresectable or metastatic NSCLC with *KRAS p.G12C* mutation.

Objective(s)/Endpoint(s)

Objectives	Endpoints
Primary	
• To compare the efficacy of AMG 510 versus docetaxel as assessed by progression-free survival (PFS) in previously treated subjects with *KRAS p.G12C* mutated non-small cell lung cancer (NSCLC)	• PFS - defined as time from randomization until disease progression or death from any cause, whichever occurs first for all subjects. Progression will be based on blinded independent central review (BICR) of disease response per Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST v1.1).
Attributes	**Primary Estimand**
• Target Population	• Subjects with previously treated locally advanced and unresectable or metastatic NSCLC with *KRAS p.G12C* mutation
• Primary Endpoint	• PFS
• Summary Measures	• Hazard Ratio (HR)
• Intercurrent Events and Strategies	• Start of new anti-cancer therapy prior to PFS event • PFS is censored at the date of last evaluable assessment before or on start of new anti-cancer therapy.
Primary Estimand Description	
HR of PFS between AMG 510 and docetaxel, for subjects with previously treated locally advanced and unresectable or metastatic NSCLC with KRAS p.G12C mutation, before or on start of new anti-cancer therapy	
Key Secondary	

• To compare the efficacy of AMG 510 versus docetaxel as assessed by:
  • Overall Survival (OS)
  • Objective response rate (ORR)
	• Overall survival - defined as time from randomization until death from any cause.
	• Objective response (complete response [CR] + partial response [PR]), assessed per RECIST v1.1. Response will be assessed by BICR. Complete response and PR require confirmatory repeat radiologic assessment at no less than 4 weeks after the original response. The normal subsequent assessment is acceptable to confirm response.

• To compare patient-reported outcomes (PRO) as assessed by: European Organization for Research and Treatment of Cancer Quality-of-life Questionnaire Core 13 (EORTC QLQ-LC13) and European Organization for Research and Treatment of Cancer Quality-of-life	• Change from baseline (cycle 1 day 1) over time to week 12 in disease related symptoms of:
	  ○ Dyspnea as measured by a 4-item dyspnea domain from QLQ-C30 and QLQ-LC13
	  • Cough as measured by QLQ-LC13
	  • Chest Pain as measured by QLQ-LC13
	• Change from baseline over time to week 12 in
	  • Physical functioning as measured by QLQ-C30

Questionnaire Core 30 (EORTC QLQ-C30)	• Global health status as measured by QLQ-C30
Attributes	**Secondary Estimand - OS**
• Target Population	• Subjects with previously treated locally advanced and unresectable or metastatic NSCLC with KRAS p.G12C mutation
• Key Secondary Endpoint	• OS
• Summary Measures	• Hazard Ratio (HR)

• Intercurrent Events and Strategies	• Start of new anti-cancer therapy
	  • OS will be estimated regardless of subsequent anti-cancer therapy.
	• Crossover from control group to treatment group
	  • OS will be estimated regardless of crossover.

Secondary Estimand Description - OS	
HR of OS between AMG 510 and docetaxel, for subjects with previously treated locally advanced and unresectable or metastatic NSCLC with KRAS p.G12C mutation, regardless of subsequent anti-cancer therapy and/or crossover.	
Attributes	**Secondary Estimand – Objective Response**
• Target Population	• Subjects with previously treated locally advanced and unresectable or metastatic NSCLC with KRAS p.G12C mutation
• Key Secondary Endpoint	• Objective Response
• Summary Measures	• Odds Ratio
• Intercurrent Events and Strategies	• Discontinuation of treatment prior to achieving an objective response (PR or CR) • Subjects will be considered as non-responders.
Secondary Estimand Description – Objective Response	
Odds ratio of objective response between AMG 510 and docetaxel, for subjects with previously treated locally advanced and unresectable or metastatic NSCLC with KRAS p.G12C mutation. Subjects who discontinued treatment prior to achieving an objective response are considered as non-responders.	
Attributes	**Secondary Estimand - PRO**
• Target Population	• Subjects with previously treated locally advanced and unresectable or metastatic NSCLC with KRAS p.G12C mutation
• Key Secondary Endpoint	• PRO
• Summary Measures	• Change from baseline to Week 12

• Intercurrent Events and Strategies	• Start of new anti-cancer therapy including crossover before Week 12 • PRO measurements before or on start of new anti-cancer therapy including crossover will be used to estimate treatment effect.
Secondary Estimand Description - PRO	
Change from baseline to Week 12 in PRO endpoints between AMG 510 and docetaxel, for subjects with previously treated locally advanced and unresectable or metastatic NSCLC with KRAS p.G12C mutation. PRO measurements before or on start of new anti-cancer therapy including crossover will be used to estimate treatment effect.	
Secondary	
• To compare efficacy of AMG 510 versus docetaxel as assessed by: duration of response (DOR), time to response (TTR), and disease control rate (DCR)	• Duration of response - defined as time from first evidence of PR or CR to disease progression or death due to any cause, whichever occurs first. Progression will be based on an BICR assessment of disease response per RECIST v1.1. • Time to response - defined as time from randomization to first evidence of PR or CR. • Disease control rate - defined as rate of confirmed objective response (CR or PR) + stable disease per RECIST v1.1 of at least 6 weeks measured
• To compare the safety and tolerability of AMG 510 versus docetaxel	• Subject incidence of treatment-emergent adverse events, treatment-related adverse events, changes in vital signs, and clinical laboratory tests.
• To compare the effect of treatment with AMG 510 on other treatment and disease related symptoms, and health related quality of life relative to docetaxel	• Change from baseline over time to week 12 for the remaining subscales for QLQ-LC13 and QLQ-C30 • Time to deterioration for the subscales for QLQ-LC13 and QLQ-C30 • Summary scores at each assessment and changes from baseline of visual analogue scale (VAS) scores as measured by EuroQol-5 Dimension (EQ5D5L)
• To characterize the pharmacokinetics (PK) of AMG 510 and its major metabolites	• Pharmacokinetic (PK) parameters of AMG 510 including, but not limited to, maximum plasma concentration (C_{max}), area under the plasma concentration-time curve (AUC) on Days 1 and 8, and pre-dose (trough) concentrations through cycle 4

Overall Design

This is a phase 3, multicenter, randomized, open label, active-controlled, study to evaluate the efficacy, safety, and tolerability of AMG 510 versus docetaxel in subjects with previously treated locally advanced and unresectable or metastatic NSCLC with *KRAS p.G12C* mutation. The study will be conducted at approximately 290 sites globally. The study will consist of a screening period, a treatment period, a safety follow-up (SFU) period, and long-term follow-up period. See Section 8.1.6 and Section 8.1.7 for AMG 510 and docetaxel treatment beyond radiologic progression. See Section 8.1.8 for crossover. Approximately 330 previously treated subjects with locally

advanced and unresectable or metastatic NSCLC with centrally confirmed *KRAS p.G12C* mutation will be enrolled and randomized 1:1 to receive either AMG 510 or docetaxel.

Subjects will be stratified by number of prior lines of therapy in advanced disease (1 versus 2 versus > 2), race (Asian versus non-Asian), and history of central nervous system (CNS) involvement (present or absent).

Cycle 1 day 1 will be defined as the first day subject receives study medication. A cycle is 21 days in length ± 3 days, unless a delay is medically necessary. A ± 3-day window is allowed for protocol required assessments, unless otherwise specified. Tumor assessment will be conducted (by magnetic resonance imaging [MRI] and/or contrast enhanced computerized tomography [CT]) during screening (within 28 days of day 1); every 6 weeks from cycle 1 day 1; (± 7 days) (at weeks 7, 13, 19, 25, 31, 37, 43, and 49), and then at 9 week intervals (± 7 days) thereafter until independent central confirmation of progression, start of another anti-cancer therapy, withdrawal of consent, lost to follow up, or death, whichever occurs earliest. Subjects' scans will undergo independent central confirmation of progression (COP) at the time of first progressive disease (PD). Subjects that undergo treatment beyond progression or crossover, from docetaxel to AMG 510, will continue to receive scans after confirmation of first PD. Further details with regards to imaging assessments post treatment period are listed in Section 8.1.4.

Once subjects on the docetaxel arm are determined to have radiological progression according to RECIST v1.1 by the investigator and progressive disease undergoes independent central confirmation, they will be given the opportunity to crossover and receive AMG 510. Alternatively, should an early efficacy of the study be noted by the DMC, crossover will be considered for all subjects who randomized into the docetaxel arm (so that they will be able to immediately receive AMG 510). All subjects remaining on study will be followed for survival, as specified in the Schedule of Activities (Section 1.3), until the pre-specified OS events are reached, regardless of the OS analysis result at the PFS primary analysis.

Tumor assessment and response will be confirmed by BICR who will evaluate disease progressions and responses without the knowledge of randomization assignments, in accordance with the RECIST v1.1.

Subjects will continue treatment until independent central confirmation of progression, intolerance of treatment leading to treatment discontinuation, initiation of another anticancer therapy or withdrawal of consent. Subjects that consent to treatment beyond progression or consent to crossover, from docetaxel to AMG 510, will continue to receive investigational product after independent central confirmation of progression at the time of first progressive disease (PD).

In select cases, subjects may continue on treatment following radiologic progression if they are continuing to demonstrate clinical benefit (see Section 8.1.6 and 8.1.7).

In all subjects, after end of investigational product, information regarding date of progression, the type and duration of subsequent therapies, response to subsequent therapy, date of progression on subsequent therapy, and survival data will be collected. Subjects who discontinue treatment prior to RECIST v1.1 disease progression (eg, due to unacceptable toxicity) will also continue to be followed with tumor assessments until independent central confirmation of disease progression, withdrawal of consent, or start of another anti-cancer therapy, then followed for subsequent anti-cancer therapy and survival.

The assessments to be conducted in this study are described below and will be carried out at the timepoints designated in the Schedule of Activities (SOA) (Table 1-1 and Table 1-2).

- Central confirmation of *KRAS p.G12C* mutation status for all enrolling subjects.
- Disease progression will be assessed using RECIST v1.1.
- Primary efficacy objective will be assessed by BICR.
- Expedited independent confirmation of progression (COP), at time of first progressive disease (PD), will be performed by a single radiologist separate from the central radiologist group reading the images for (as described in Section 8.2.2.1.2) prior to moving forward with treatment beyond progression or crossover.
- Safety will be monitored by assessing serious and non-serious adverse events, safety laboratory tests, vital signs and electrocardiograms (ECGs). Adverse events will be graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, Version 5.0 (NCI CTCAE v5.0).
- Laboratory safety tests will include hematology, blood chemistry, cholesterol, coagulation, urinalysis, and thyroid function test. Vital sign assessments will include oxygen saturation, respiratory rate, blood pressure, heart rate, and body temperature; additional vital signs will be collected only if clinically warranted. The urine studies may be performed at a local laboratory and/or by the central laboratory, depending on the availability of the testing facility.
- PK characterization will be conducted using sparse sampling and population PK modeling approach.

- PRO/quality of life (QOL) assessments will be assessed using the PRO instruments EORTC QLQ-C30, EORTC QLQ-LC13, EQ-5D-5L, and PRO-CTCAE plus a single item about symptom bother (GP5 of the Functional Assessment of Cancer Therapy Tool General form [FACT-G]). Patient pain and patient impression of change and severity will be assessed using the brief pain inventory (BPI), patient global impression of change (PGIC) and patient global impression of severity (PGIS) questionnaires. Patient-reported outcomes scores will be determined for all **subject**s at baseline (cycle 1 day 1) and at timepoints designated in the SOA and will be compared across treatment groups.

[redacted]

- Further tissue assessments at the time of independent central confirmation of progression
  - If a subject is not continuing AMG 510 upon radiologic progression, they will be encouraged to enroll in an optional sub-study assessing exploratory biomarkers via an optional tumor biopsy (excisional, core needle, or fine needle aspirates) only if biomarker research is allowed according to local regulations and agreed by local EC/IRB
  - If a subject plans to continue on AMG 510 treatment beyond radiologic progression, the subject must be willing to undergo biopsy, if clinically feasible or advisable, (excisional, core needle, or fine needle aspirates) of one of the new or progressing lesions (see Section 8.1.6 for additional criteria) only if biomarker research is allowed according to local regulations and agreed by local EC/IRB

An independent (external to Amgen) data monitoring committee (DMC) will review safety and efficacy data as per DMC charter. Interim safety analysis will be conducted after approximately 50, 100, and 200 subjects have been enrolled and have had the opportunity to complete at least 6 weeks of study treatment, and then at approximately 6-month intervals until the primary analysis (PA) of PFS. Interim analysis (IA) data will be reviewed by an independent (external to Amgen) DMC. There will be 2 planned PFS efficacy analyses. The PA of PFS will occur when approximately 230 PFS events have been observed. The PFS PA may be delayed to ensure that the enrollment is finished and the delayed PA will be triggered when the last randomized subject has had the opportunity to have at least 6 weeks of follow up. An IA of PFS for superiority is planned when approximately 70% (160 events) of the total PFS events have been observed from both arms, or when the enrollment is finished and the last randomized subject have had the opportunity to have 6 weeks of follow up, whichever occurs later.

Early efficacy at the proposed PFS interim analysis will be claimed if the observed PFS difference meets the pre-specified statistical significance as well as being considered clinically meaningful. More details will be included in the DMC charter.

If PFS achieves statistical significance at the interim analysis, an administrative interim summary for OS will be performed. Otherwise, the OS will be assessed for superiority of AMG 510 over docetaxel at either the time of PFS primary analysis or after 175 OS events have been observed, whichever is later. The OS primary analysis will occur when at least 198 OS events (~60% maturity) have been observed, which is expected to be at approximately 3 months after PFS primary analysis. The analysis of ORR will be done at the time when PFS is claimed statistically significant and the last randomized subject has had the opportunity to have at least 12 weeks of follow up. The final analysis will be performed after the last subject completes long-term follow-up (LTFU).

Number of Subjects

Approximately 330 subjects with locally advanced unresectable or metastatic NSCLC with centrally confirmed *KRAS p.G12C* mutation will be enrolled in the study, with approximately 165 subjects in each of the 2 treatment groups.

Summary of Subject Eligibility Criteria

Eligible subjects will have histologically or pathologically documented, locally-advanced and unresectable or metastatic NSCLC with *KRAS p.G12C* mutation (and no other known oncogenic driver mutation for which there is an approved targeted therapy (according to local standard of care or guidelines), and will have failed at least 1 prior systemic therapy. For a full list of eligibility criteria, please refer to Section 5.1 to Section 5.2.

Treatments

Treatment begins on day 1 of cycle 1 when the first dose of investigational product is administered to a subject. AMG 510 will be dispensed at 960 mg once daily (QD) orally (PO) administered to subjects at the beginning of each cycle. Subjects are required to bring bottle(s) of AMG 510 as per guidance in the Investigational Product Instruction Manual, and return the remaining pills when they come off treatment. For the first 2 cycles, subjects will be instructed to take their AMG 510 dose in the clinic after all pre-dose assessments have been performed during clinic visit days. For non-clinic days, subjects will be instructed to take their AMG 510 dose at home. Docetaxel at 75 mg/m^2 will be administered intravenously over 1 hour (additional administration time allowed as per local guidelines) every 3 weeks
(Taxotere® Summary of Product Characteristics [SmPC]; Taxotere® United States Prescribing Information [USPI]).

Procedures

Tumor evaluation is to be performed by contrast-enhanced CT of the chest and one of the following: contrast-enhanced CT abdomen with cuts through to the pubic symphysis, contrast-enhanced CT abdomen and pelvis, contrast-enhanced MRI abdomen and pelvis, or contrast-enhanced MRI abdomen with cuts through to the pubic symphysis. Contrast-enhanced images are strongly preferred. If contrast enhanced CT imaging is contraindicated (allergy, medical contraindication, etc), radiological imaging to be performed as indicated by site imaging manual will be performed during screening (within 28 days of day 1); every 6 weeks after cycle 1 day 1 (± 7 days) at week 7, 13, 19, 25, 31, 37, 43, and 49 ± 7 days, and then at 9 week intervals thereafter (± 7 days) until end of investigational product. Investigational product is either AMG 510, or docetaxel, depending on the treatment group to which the subject is randomized. If investigational product was ended before radiologically documented and independently confirmed progressive disease, radiologic imaging and tumor assessment will continue to be performed until independently confirmed disease progression, start of new anticancer treatment, death, withdrawal of consent or until end of study, whichever occurs first. Baseline brain imaging by contrast enhanced MRI will be obtained for all subjects at screening. For subjects with known brain metastases, brain MRI should also be obtained at every subsequent imaging assessment. Computerized tomography scan with contrast of the brain may be used in lieu of MRI for those subjects who cannot undergo an MRI. Non-contrast only CT of the brain is not acceptable. Patient-reported outcomes questionnaires including the EQ-5D-5L, QLQ-C30, the disease specific module QLQ-LC13, and PRO-CTCAE, plus a single item about symptom bother (GP5 of the FACT-G) will be administered to all subjects, and collected as indicated in the Schedule of Activities (Section 1.3 and Table 1-2). For a full list of study procedures, including safety assessments and the timing of each procedure, please refer to the study assessments and procedures in Section 8.2 and the Schedule of Activities in Section 1.3 and Table 1-2.

Statistical Considerations

The efficacy analyses of primary endpoint and key secondary endpoints to compare AMG 510 vs docetaxel will be conducted on the full analysis set (intention-to-treat [ITT] population). The PA of PFS and key secondary endpoint of ORR will be based on BICR assessed outcomes.

The hypotheses of the primary efficacy endpoint and key secondary efficacy endpoints will be tested using the graphical multiple testing procedure (Maurer and Bretz, 2013) to control the study-level overall type I error rate (α) below 1-sided 0.025 levels. A hypothesis can be re-tested repeatedly with a different nominal level that is propagated from rejecting other hypothesis test(s).

Starting with PFS, if the hypothesis of PFS is rejected, ORR will be tested using 1-sided α/5 (0.005) level. With the rejection of ORR hypothesis, OS will be tested using 1-sided full α (0.025) level. If ORR hypothesis is failed to be rejected, OS will be tested using 1-sided 0.001 level if at PFS IA, otherwise using 4 α/5 (0.02) level. With the rejection of OS hypothesis, ORR can be retested using 1-sided full α (0.025) level.

If all 3 hypotheses of PFS, OS, ORR are rejected, the next 3 endpoints of change from baseline over time to week 12 in 3 lung cancer symptoms will be tested using Holm's procedure, including change from baseline over time to week 12 for the symptom of dyspnea as measured by a 4 item dyspnea domain from QLQ-C30 and QLQ-LC13 (dyspnea), change from baseline over time to week 12 for the symptom of cough as measured by QLQ-LC13 (cough), and change in baseline over time to week 12 for the symptom of chest pain as measured by QLQ-LC13 (pain). Hypotheses are rejected sequentially based on the smallest p-value. If all 6 hypotheses listed above are rejected, the next two PRO endpoints will be tested using the Holm's procedure, including change from baseline over time to week 12 in physical functioning as measured by QLQ-C30 (physical), change from baseline over time to week 12 in global health status as measured by QLQ-C30 (global health status). Hypotheses are rejected sequentially based on the smallest p-value.

As designed, the trial will not be terminated at PFS analyses and subjects will continue to be followed for OS data until the targeted number of events are reached, regardless of the OS analysis result at the PFS primary analysis, to enable OS analyses and a robust description of the totality of the data.

Sample size: The planned enrollment is approximately 330 subjects with locally advanced unresectable or metastatic NSCLC with centrally confirmed *KRAS p.G12C* mutation. A total of 230 PFS events are required to provide at least 90% power to demonstrate superiority at an alternative Hazard Ratio (HR) of 0.65 for the AMG 510 arm versus control arm with 1-sided overall type I error of 0.025, in a group sequential design setting with 1 potential IA for superiority and 1 PA. The PA of PFS will occur when approximately 230 PFS events have been observed. With 230 PFS events, the

study will have ~90% power to show a statistically significant PFS at the 2.5% 1-sided significance level if the true treatment effect hazard ratio (HR) is assumed 0.65 for the AMG 510 arm versus the control arm. The sample size is chosen to have 70% maturity realizing PFS events, which is approximately 330 subjects with 1:1 randomization ratio into the AMG 510 arm and the docetaxel arm. The PFS PA may be delayed to ensure that the enrollment is finished and the delayed PA will be triggered when the last randomized subject has had the opportunity to have at least 6 weeks of follow up.

An IA is planned when approximately 70% (160) of the target PFS events have been observed from both arms, or when the enrollment is finished and the last randomized subject has had the opportunity to have 6 weeks of follow up, whichever occurs later. The monitoring boundary for early stopping for efficacy will be based on an O'Brien-Fleming type alpha spending function for multiplicity adjustment. The actual information fraction will be calculated based on the number of observed events at the time of the analysis. Under exponential distribution, the minimum detectable difference for success in this design is an HR of 0.68 between AMG 510 arm and the docetaxel arm with 160 PFS events, 70% of the target PFS events, and an HR of 0.769 at the PA with 230 PFS events. Assuming an enrollment rate of 40 subjects per month after a 3-month ramp-up period, with a total sample size of 330, it is estimated that approximately 19 months will be required to reach 230 PFS events, and 13 months will be required to reach 70% (160) of the target PFS events. This estimation is based on a median PFS of 5 months for the control arm (Charpidou et al, 2019) and 7.7 months for the AMG 510 arm, and a 10% dropout rate.

If PFS achieves statistical significance at the interim analysis, an administrative interim summary for OS will be performed with approximately 107 OS events (~32% maturity) observed. A nominal alpha of 0.01% (negligible impact on overall type I error rate) will be spent on this OS interim summary. Otherwise, the OS will be assessed for superiority of AMG 510 over docetaxel at either the time of PFS primary analysis or after 175 OS events (~53% maturity) have been observed, whichever is later. Assuming the actual crossover rate of approximately 30% at the time of PFS primary analysis for subjects on the control arm who have disease progression, then with 175 OS events, the study has ~96% probability to observe a HR < 1 when the true OS HR is 0.75.

The OS primary analysis will occur when at least 198 OS events (~60% maturity) have been observed, which is expected to be at approximately 3 months after PFS primary analysis, with the same enrollment assumptions. The estimation is based on a median

OS of 9 months for the control arm and 12 months for the AMG 510 arm (OS HR = 0.75). The multiplicity will be adjusted as necessary based on O'Brien-Fleming type alpha spending function.

Analysis Method: The distribution of PFS and OS will be estimated using the Kaplan-Meier method. The HR and its 95% CI will be estimated using a Cox proportional hazards model stratified by the randomization stratification factors. The inferential comparison will be made using a stratified log rank test. Objective response rate will be calculated and the associated 95% CI will be estimated using the Clopper-Pearson method. The inferential comparison for ORR will be made using the Cochran-Mantel-Haenszel chi-square test controlling for the randomization stratification factors. The inferential comparison for the endpoints of change from baseline over time to week 12 in symptoms of dyspnea as measured by a 4 item dyspnea domain from QLQ-C30 and QLQ-LC13, change from baseline over time to week 12 in physical functioning, global health status as measured by QLQ-C30 will be made through a mixed model for repeated measurement (MMRM). The inferential comparison for the endpoints of change from baseline over time to week 12 in symptoms of cough and chest pain as measured by a single question from QLQ-LC13 will be made through generalized estimating equations (GEE) method for cumulative logits model (Lipsitz et al, 1994). Multiple imputation approach with non-ignorable missing pattern will be explored as the sensitivity analysis for all the key secondary PRO endpoints.

Subgroup Analyses: In addition to the stratification factors for randomization, number of prior lines of therapy in advanced disease (1 versus 2 versus > 2), race (Asian versus non-Asian), history of CNS involvement (yes versus no), primary and selected secondary endpoints will be examined in the following subgroups to investigate the consistency of treatment effects:

- region (North America and Europe vs rest of world)
- best response on prior therapy primary refractory (progression on first scan), suboptimal response (stable disease), recurrent (initial response with subsequent growth)
- age (< 65 vs ≥ 65)
- sex (male **vs** female)
- race (white, black, Asian, other)
- Eastern Cooperative Oncology Group (ECOG) status (0 vs 1)
- liver metastasis at baseline (yes **vs** no)
- stage (locally advanced and unresectable versus metastatic)

- smoking history (yes **vs** no)
- histology (squamous **vs** non-squamous)
- presence of specific co-mutation at baseline (yes **vs** no). Specific co-mutations to be specified in SAP.
- brain metastasis at baseline (yes vs no)
- bone metastasis at baseline (yes vs no)
- PD-L1 protein expression (< 1% **vs** ≥ 1%, and < 50% **vs** ≥ 50%)
- STK11 mutation
- KEAP1 mutation

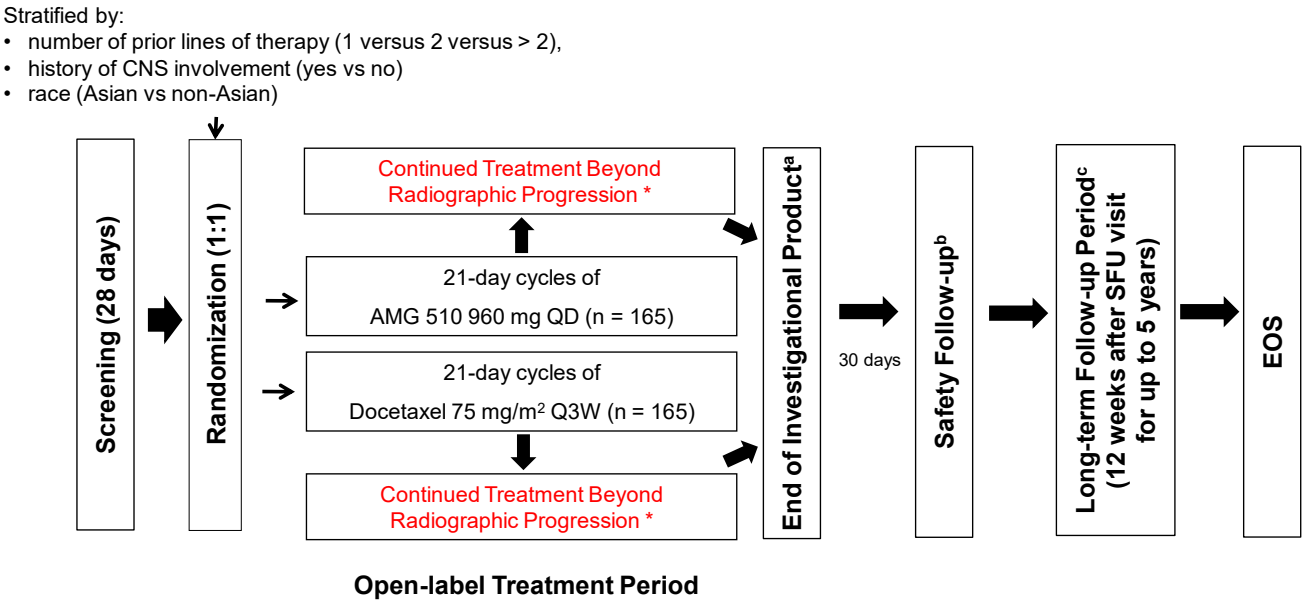
In the event that there are insufficient number of subjects in the subgroup (ie, less than 10% of the whole population), relevant subgroups may be combined. For a full description of statistical analysis methods, please refer to Section 9.

Statistical Hypotheses

The hypotheses of the primary efficacy endpoint and key secondary efficacy endpoints will be tested using the following graphical multiple testing procedure (Maurer and Bretz, 2013) to control the study-level overall type I error rate below 1-sided 0.025 levels, as discussed above.

Sponsor Name: Amgen Inc.

1.2 Study Schema



Open-label Treatment Period

BID = twice daily; CNS = central nervous system; EOS = End of Study; LTFU = long term follow up; PI = Principal Investigator; QD = once a day; Q3W = every 3 weeks; RECIST = Response Evaluation Criteria in Solid Tumors; SFU = safety follow up

[a] Treatment with investigational product continues until independent central confirmation of progression, intolerance of treatment, initiation of another anticancer therapy, withdrawal of consent, or death. Subjects that consent to treatment beyond progression or consent to crossover, from docetaxel to AMG 510, will continue to receive investigational product after independent central confirmation of progression at the time of first progressive disease (PD).

[b] Upon permanent discontinuation from the study treatment for any reason, a safety follow-up visit will be performed 30 days (± 7 days) after the end of the last dosing interval of investigational product.

[c] Details with regards to imaging assessments post treatment period are listed in Section 8.1.4.

[*] See Section 8.1.6 and 8.1.7 (respectively) for details on AMG 510 and docetaxel treatment beyond radiograph progression.

Note: See Section 8.1.8 for details on crossover from docetaxel to AMG 510.

1.3 Schedule of Activities

Table 1-1. Schedule of Activities: AMG 510

	Screening	Treatment Cycle																		
Cycle (1 Cycle is 21 Days ± 3 days)		1													2 to 4		5+			
Day	-28 to 1	1[a]						5	8						1	5	1			
Hours (Relative to Dosing)		Pre	0	0.5	1	2	4	NA	Pre	0	0.5	1	2	4	Pre	NA	Pre	SFU[b]	LTFU[c]	Notes
GENERAL & SAFETY																				
Informed consent	X																			
Eligibility criteria	X																			
Demographics	X																			
Medical history	X																			
Other anticancer therapies	X																	X	X	
Physical exam	X	X													X		X	X		
Physical measurements	X	X													X		X	X		Height collected at screening only. Weight collected every clinic visit.
Substance abuse history	X																			
ECOG	X	X													X		X	X		
Vital signs including oxygen saturation	X	X													X		X	X		
ECG	X	X			X										(X)			X		See Section 8.2.3.2. ECGs must be performed at screening, C1D1 (predose and 1-hour post dose), C2D1 predose, and at safety follow-up. Screening ECG: standardized method in triplicate. All other ECGs: standardized method – single copy

	Screening	Treatment Cycle																		
Cycle (1 Cycle is 21 Days ± 3 days)		1													2 to 4		5+			
Day	-28 to 1	1[a]						5	8						1	5	1			
Hours (Relative to Dosing)		Pre	0	0.5	1	2	4	NA	Pre	0	0.5	1	2	4	Pre	NA	Pre	SFU[b]	LTFU[c]	Notes
Vital Assessments																			X	In addition to survival, LTFU period will collect data on the subjects' health condition, disease status, and subsequent anticancer treatment.
Concomitant medications	X	←==========→																		Concomitant therapy data to be collected should include supplemental oxygen volume usage per day.
Adverse events		←==========→																		
Serious adverse events[d]	←==========→																			
LABORATORY																				
Chemistry	X	X													X		X	X		Laboratory Assessments may be performed within ± 3 days before day 1 of each cycle. The urine studies may be performed at a local laboratory and/or by the central laboratory, depending on the availability of the testing facility.
Hematology	X	X													X		X	X		
Coagulation	X																	X		
Urinalysis	X	X													X		X	X		
Serum or urine pregnancy test	X	X													X		X	X		Only for females of childbearing potential. Pregnancy test must be within 3 days before day 1 of each cycle.
Hepatitis B and Hepatitis C testing	X																			
Thyroid function tests	X														X		X	X		Thyroid function testing at screening, pre-dose on day 1 of each cycle (except cycle 1), at the end of treatment, and at safety follow-up. They should also be obtained if the subject displays clinical signs or symptoms concerning for thyroid dysfunction.

	Screening	Treatment Cycle																	
Cycle (1 Cycle is 21 Days ± 3 days)		1												2 to 4		5+			
Day	-28 to 1	1[a]						5	8					1	5	1			
Hours (Relative to Dosing)		Pre	0	0.5	1	2	4	NA	Pre	0	0.5	1	2	4	Pre	NA	Pre	SFU[b]	LTFU[c]	Notes
Cholesterol and Triglycerides		X													(X)		(X)	X		Cholesterol and triglyceride levels on pre-dose on day 1 of every other cycle (ie, cycle 1, 3, 5, 7, etc).
DOSING																				
AMG 510[e]			←==========→																	AMG 510 is to be administered during the clinic visit on Day 1 and Day 8 of the first cycle, Day 1 of the second cycle, and outside of the clinic on the other days of the cycle and during subsequent cycles. Every effort should be made to administer IP at the same dosing time; in the event not possible, AMG 510 should not be taken 2 hours before the dosing time. AMG 510 dose should not be taken 6 hours after the dosing time **(based on the previous day's dose)**. **Do not take 2 doses at the same time to make up for the missed dose.** AMG 510 will be administered daily on a repeated basis with no planned off treatment days until independent central confirmation of progression, intolerance to treatment necessitating treatment discontinuation, need for other anti-cancer therapy, withdrawal of consent, or death. **Please refer to footnote "e" for further dosing details.

	Screening	Treatment Cycle																	
Cycle (1 Cycle is 21 Days ± 3 days)		1							2 to 4								5+		
Day	-28 to 1	1[a]						5	8						1	5	1		
Hours (Relative to Dosing)		Pre	0	0.5	1	2	4	NA	Pre	0	0.5	1	2	4	Pre	NA	Pre	SFU[b]	LTFU[c]	Notes
Dosing diary			←==========																	A dosing diary will be provided for subjects to record their adherence to the oral medication
TUMOR ASSESSMENTS																				
CT/MRI[f]	X	• Imaging every 6 weeks from cycle 1 day 1 (± 7 days) (at weeks 7, 13, 19, 25, 31, 37, 43, and 49), and then at 9-week intervals (± 7 days) thereafter																		Contrast enhanced CT scan or MRI of the brain is required for <u>all</u> subjects at screening For subjects with brain metastases or history of brain metastases, contrast enhanced brain MRI (contrast enhanced CT scan if unable to have MRI) at screening and at each tumor evaluation is required. **Please refer to footnote "f" for further tumor assessment details.
PK ASSESSMENT																				
AMG 510 PK		X		X	X	X	X		X		X	X	X	X	X					PK blood samples should be collected within a 10% window of the nominal time point (see hour post dose column ie, 0.5 hour ± 3 min, 1 hour ± 6 min, 2 hours ± 12 min, 4 hours ± 24 min). Day 8 PK is to be collected ± 1 day
[redacted]																				

	Screening	Treatment Cycle																	
Cycle (1 Cycle is 21 Days ± 3 days)		1												2 to 4		5+			
Day	-28 to 1	1[a]						5	8						1	5	1		
Hours (Relative to Dosing)		Pre	0	0.5	1	2	4	NA	Pre	0	0.5	1	2	4	Pre	NA	Pre	SFU[b]	LTFU[c]	Notes
[redacted]																				

	Screening	Treatment Cycle																		
Cycle (1 Cycle is 21 Days ± 3 days)		1													2 to 4		5+			
Day	-28 to 1	1[a]						5	8						1	5	1			
Hours (Relative to Dosing)		Pre	0	0.5	1	2	4	NA	Pre	0	0.5	1	2	4	Pre	NA	Pre	SFU[b]	LTFU[c]	Notes
TREATMENT AND DISEASE RELATED SYMPTOMS AND HRQOL																				
PRO/QOL assessments: FACT-G GP5, and PRO-CTCAE		X													X		X	X		
Pain assessment (BPI)	X	X													X		X	X		Pain will be assessed at screening, on day 1 of every cycle and at the SFU by using the brief pain inventory (BPI) scale.
PRO/QOL assessments: QLQ-C30	X	X													X		X	X		
PRO/QOL assessments: QLQ-LC13,	X	X													X		X	X		
PRO/QOL assessments: PGIC															(X)		(X)			PGIC will be collected in the clinic on day 1 of cycles 3 and cycle 5 (no collection needed at screening or cycle 1 for PGIC).
PRO/QOL assessments: PGIS	X	X													(X)		(X)			PGIS will be collected in the clinic at screening and day 1 of cycles 1, 3, and 5.
PRO/QOL assessments: EQ-5D-5L	X	X						X							X	(X)	X	X	X	The EQ-5D-5L questionnaire will be completed at screening, in the clinic on clinic visit days, including SFU, and at home (data collected by phone) for the scheduled non-clinic visit days (day 5 of cycles 1, 2 and 3). EQ-5D-5L will also be collected during LTFU.

CxDx = cycle x day x; CT = computerized tomography; CTCAE = Common Terminology Criteria for Adverse Events; ctDNA = circulating tumor DNA; EC = Ethics Committee; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; EQ-5D-5L = EuroQol-5 Dimension; FACT-G = Functional Assessment of Cancer Therapy Tool General form; FFPE = formalin fixed, paraffin embedded; HRQOL = health-related quality of life; IRB = Institutional Review Board; KRAS = Kirsten rat sarcoma viral oncogene homolog; LTFU = long-term follow-up; MRI = magnetic resonance imaging; NA = not applicable; PD = progressive disease; PGIC = patient global impression of change; PGIS = patient global impression of severity; PI = Principal Investigator; PK = pharmacokinetic; PRO = patient-reported outcome; QLQ-LC13 = Quality-of-life Questionnaire Core 13; QLQ-C30 = Quality-of-life Questionnaire Core 30; QOL = quality of life; RECIST = Response Evaluation Criteria in Solid Tumors; SFU = safety follow-up; (X) = parentheses indicate that the particular test is situational at that time point, as specified in the respective notes

[a] Randomisation can take place up to 48 hours before first dose/C1D1.

[b] SFU will be performed 30 days (± 7 days) after the last dose of investigational product. Subjects who reach PD have a LTFU visit 12 weeks after SFU.

[c] LTFU will be 5 years after last subject enrolled, or until withdrawal of consent, loss to follow-up, or subject death, whichever occurs first. Vital status and subsequent treatment for NSCLC will be recorded after the SFU period during the LTFU.

[d] Serious adverse events observed by the investigator or reported by the subject that occur after the safety follow-up visit through the end of the long-term follow up period should be reported if there is a reasonable possibility that the event may have been caused by investigational product.

[e] Below is applicable to AMG 510 dosing:

- Subjects that consent to treatment beyond progression or consent to crossover, from docetaxel to AMG 510, will continue to receive investigational product after independent central confirmation of progression at the time of first progressive disease (PD).
- Progressive disease must undergo independent central confirmation prior to crossover
- See Section 8.1.6 for treatment beyond radiologic progression.
- See Section 8.1.8 for docetaxel to AMG 510 crossover details, once the subject crosses over in the AMG 510 arm, the AMG 510 Schedule of Activities (Table 1-1) will be utilized.
- Once the subject starts treatment beyond radiologic progression, they will adhere to the same schedule of events as long as they are receiving drug.
- Once subject begins crossover, AMG 510 Schedule of Activities (Table 1-1) is to be followed. See Section 8.1.8 for details on crossover.

[f] Below is applicable to Tumor Assessments:

- Tumor evaluation is to be performed by contrast-enhanced CT of the chest and one of the following: contrast-enhanced CT abdomen with cuts through the pubic symphysis, contrast-enhanced CT abdomen and pelvis, contrast-enhanced MRI abdomen and pelvis, or contrast-enhanced MRI abdomen with cuts through to the pubic symphysis. Contrast-enhanced images are strongly preferred. If contrast enhanced CT imaging is contraindicated (allergy, medical, etc), radiological imaging to be performed as indicated by site imaging manual.
- Imaging assessments are indicated until independent central confirmation of progression, start of another anti-cancer therapy, withdrawal of consent, lost to follow up, or death, whichever occurs earliest. Subjects' scans will undergo independent central confirmation of progression (COP) at the time of first progressive disease (PD).
- Subjects that undergo treatment beyond progression or crossover, from docetaxel to AMG 510, will continue to receive scans after confirmation of first PD.
- Safety follow up CT/MRI should be performed only for subjects that discontinue treatment for a reason other than disease progression per RECIST v1.1. Imaging should continue in LTFU until RECIST radiologic progression is documented.
- Further details with regards to imaging assessments post treatment period are listed in Section 8.1.4.
- Further details with regards to the process of independent central confirmation of progression are detailed in Section 8.2.2.1.2.

[redacted]

Table 1-2. Schedule of Activities: Docetaxel

	Screening	Treatment Cycle							Follow-up Visit		
Cycle (1 Cycle is 21 Days ± 3 days)		**1[a]**		**2**		**3**		**4+**	**SFU[b]**	**LTFU[c]**	**Notes**
Day	**-28 to 1**	**1**	**5**	**1**	**5**	**1**	**5**	**1**			
GENERAL AND SAFETY											
Informed consent	X										
Eligibility criteria	X										
Demographics	X										
Medical history	X										
Other anticancer therapies	X								X	X	
Physical exam	X	X		X		X		X	X		
Physical measurements	X	X		X		X		X	X		Height collected at screening only. Weight collected every cycle.
Substance abuse history	X										
ECOG	X	X		X		X		X	X		
Vital signs including oxygen saturation	X	X		X		X		X	X		
ECG	X										See Section 8.2.3.2. Screening ECG: standardized method in triplicate.
Vital Assessments										X	In addition to survival, LTFU period will collect data on the subjects' health condition, disease status, and subsequent anticancer treatment.
Concomitant medications	X	←==========						==========→			Concomitant therapy data to be collected should include supplemental oxygen volume usage per day.
Adverse events		←==========						==========→			
Serious adverse events[d]	←==========							==========→			
LABORATORY											
Chemistry	X	X		X		X		X	X		Laboratory Assessments may be performed within ± 3 days before day 1 of each cycle. The urine studies may be performed at a local laboratory and/or by the central laboratory, depending on the availability of the testing facility.
Hematology	X	X		X		X		X	X		
Coagulation	X								X		
Urinalysis	X	X		X		X		X	X		
Serum or urine pregnancy test	X	X		X		X		X	X		Only for females of childbearing potential. Pregnancy test must be within 3 days before day 1 of each cycle.
Hepatitis B and Hepatitis C testing	X										

	Screening	Treatment Cycle							Follow-up Visit		
Cycle (1 Cycle is 21 Days ± 3 days)		**1[a]**		**2**		**3**		**4+**	**SFU[b]**	**LTFU[c]**	
Day	**-28 to 1**	**1**	**5**	**1**	**5**	**1**	**5**	**1**			**Notes**
Thyroid function tests	X			X		X		X	X		Thyroid function testing at screening, pre-dose on day 1 of each cycle (except cycle 1), at the end of treatment, and at safety follow-up. They should also be obtained if the subject displays clinical signs or symptoms concerning for thyroid dysfunction
Cholesterol and Triglyceride		X				X		(X)	X		Cholesterol and triglyceride levels on pre-dose on day 1 of every other cycle (ie, cycle 1, 3, 5, 7, etc).
DOSING											
Docetaxel[e]		X		X		X		X			Docetaxel will be administered every 3 weeks ± 3 days until independent central confirmation of progression, intolerance to treatment necessitating treatment discontinuation, need for other anti-cancer therapy, withdrawal of consent, or death. **Please refer to footnote “e” for further dosing details.
TUMOR ASSESSMENTS											
CT/MRI[f]	X	Imaging every 6 weeks from cycle 1 day 1 (± 7 days) (at weeks 7, 13, 19, 25, 31, 37, 43, and 49), and then at 9-week intervals (± 7 days) thereafter									Contrast enhanced CT scan or MRI of the brain is required for all subjects at screening, and if positive for metastasis, must be performed at every subsequent tumor assessment. For subjects with brain metastases or history of brain metastases, contrast enhanced brain MRI (contrast enhanced CT scan if unable to have MRI) at screening and at each tumor evaluation is required. **Please refer to footnote “f” for further tumor assessment details.
[redacted]											

	Screening	Treatment Cycle							Follow-up Visit		
Cycle (1 Cycle is 21 Days ± 3 days)		**1[a]**		**2**		**3**		**4+**	**SFU[b]**	**LTFU[c]**	
Day	**-28 to 1**	**1**	**5**	**1**	**5**	**1**	**5**	**1**			**Notes**
[redacted]											
TREATMENT AND DISEASE RELATED SYMPTOMS AND HRQOL											
PRO/QOL assessments: FACT-G GP5 and PRO-CTCAE		X		X		X		X	X		
Pain assessment (BPI)	X	X		X		X		X	X		Pain will be assessed at screening and on day 1 of every cycle and at the SFU by using the brief pain inventory (BPI) scale
PRO/QOL assessments: QLQ-C30	X	X		X		X		X	X		
PRO/QOL assessments: QLQ-LC13	X	X		X		X		X	X		
PRO/QOL assessments: PGIC						X		(X)			PGIC will be collected in the clinic on day 1 of cycle 3 and cycle 5 (no collection needed at screening or cycle 1 for PGIC).
PRO/QOL assessments: PGIS	X	X				X		(X)			PGIS will be collected in the clinic at screening and day 1 of cycles 1, 3, and cycle 5.
PRO/QOL assessments: EQ-5D-5L	X	X	X	X	X	X	X	X	X	X	The EQ-5D-5L questionnaire will be completed at screening, in the clinic on clinic visit days, including SFU, and at home (data collected by phone) for the scheduled non-clinic visit days (day 5 of cycles 1, 2 and 3). EQ-5D-5L will also be collected during LTFU.

CxDx = cycle x day x; CT = computerized tomography; CTCAE = Common Terminology Criteria for Adverse Events; ctDNA = circulating tumor DNA; EC = Ethics Committee; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; EQ-5D-5L = EuroQol-5 Dimension; FACT-G = Functional Assessment of Cancer Therapy Tool General form; FFPE = formalin fixed, paraffin embedded; HRQOL = health-related quality of life; IRB = Institutional Review Board; KRAS = Kirsten rat sarcoma viral oncogene homolog; LTFU = long-term follow-up; MRI = magnetic resonance imaging; PGIC = patient global impression of change; PGIS = patient global impression of severity; PI = Principal Investigator; PRO = patient-reported outcome; QLQ-LC13 = Quality-of-life Questionnaire Core 13; QLQ-C30 = Quality-of-life Questionnaire Core 30; QOL = quality of life; RECIST = Response Evaluation Criteria in Solid Tumors; SFU = safety follow-up; (X) = parentheses indicate that the particular test is situational at that time point, as specified in the respective notes

[a] Randomisation can take place up to 48 hours before first dose/C1D1.

[b] SFU will be performed 30 days (± 7 days) after the last dose of investigational product

[c] LTFU will be 5 years after last subject enrolled, or until withdrawal of consent, loss to follow-up, or subject death, whichever occurs first. Vital status and subsequent treatment for NSCLC will be recorded after the SFU period during the LTFU.

[d] Serious adverse events observed by the investigator or reported by the subject that occur after the safety follow-up visit through the end of the long-term follow up period should be reported if there is a reasonable possibility that the event may have been caused by investigational product.

[e] Below is applicable to docetaxel dosing:

- Subjects that consent to treatment beyond progression or consent to crossover, from docetaxel to AMG 510, will continue to receive investigational product after independent central confirmation of progression at the time of first progressive disease (PD).
- Progressive disease must undergo independent central confirmation prior to crossover
- See Section 8.1.7 for treatment beyond radiologic progression.
- See Section 8.1.8 for crossover details, once the subject crosses over in the AMG 510 arm, the AMG 510 Schedule of Activities (Table 1-1) will be utilized.
- Once the subject starts treatment beyond radiologic progression, they will adhere to the same schedule of events as long as they are receiving drug.
- Once subject begins crossover, AMG 510 Schedule of Activities (Table 1-1) is to be followed. See Section 8.1.8 for details on crossover.

[f] Below is applicable to Tumor Assessments:

- Tumor evaluation is to be performed by contrast-enhanced CT of the chest and one of the following: contrast-enhanced CT abdomen with cuts through the pubic symphysis, contrast-enhanced CT abdomen and pelvis, contrast-enhanced MRI abdomen and pelvis, or contrast-enhanced MRI abdomen with cuts through to the pubic symphysis. Contrast-enhanced images are strongly preferred. If contrast enhanced CT imaging is contraindicated (allergy, medical, etc), radiological imaging to be performed as indicated by site imaging manual.
- Imaging assessments are indicated until independent central confirmation of progression, start of another anti-cancer therapy, withdrawal of consent, lost to follow up, or death, whichever occurs earliest. Subjects' scans will undergo independent central confirmation of progression (COP) at the time of first progressive disease (PD).
- Subjects that undergo treatment beyond progression or crossover will continue to receive scans after confirmation of first PD.
- Safety follow up CT/MRI should be performed only for subjects that discontinue treatment for a reason other than disease progression per RECIST v1.1. Imaging should continue in LTFU until RECIST radiologic progression is documented.
- Further details with regards to imaging assessments post treatment period are listed in Section 8.1.4.
- Further details with regards to the process of independent central confirmation of progression are detailed in Section 8.2.2.1.2.

[redacted]

2. Introduction

2.1 Study Rationale

Lung cancer is the most common type of cancer occurring in both males and females worldwide (WHO statistics, 2018), and the 5-year survival rate for advanced non-small cell lung cancer (NSCLC) is low (between 6% and 33%, depending on the stage [American Cancer Society, 2019]).

The rat sarcoma (RAS) proto-oncogene has been identified as an oncogenic driver of tumorigenesis in several cancers, including NSCLC. The RAS proteins can be mutationally activated at codons 12, 13, or 61, leading to human cancers. Different tumor types are associated with mutations in certain isoforms of *RAS*, with Kirsten rat sarcoma viral oncogene homolog (*KRAS*) being the most frequently mutated isoform in most cancers (Prior et al, 2012). While the role of KRAS mutations in human cancers has been known for decades, no anti-cancer therapies specifically targeting *KRAS* mutations have been successfully developed, largely because the protein had been intractable for inhibition by small molecules (McCormick, 2016). AMG 510 is a small molecule that specifically and irreversibly inhibits the KRASG12C mutated protein. Nonclinical studies of AMG 510 have demonstrated inhibition of growth and regression of cells and tumors harboring *KRAS p.G12C*. These data suggest that inhibition of KRAS G12C may have therapeutic benefit for subjects with *KRAS p.G12C* driven cancers. Accordingly, the ongoing phase 1/2 study, Study 20170543, is evaluating the safety, tolerability, pharmacokinetics (PK), pharmacodynamics, and efficacy of AMG 510 in subjects with *KRAS p.G12C*-mutated advanced NSCLC, colorectal cancer (CRC), and other solid tumors.

Study 20170543 was the first clinical test of this hypothesis in subjects with *KRAS p.G12C* mutated solid tumors, including 27 subjects with NSCLC (as of the 12 June 2019 data cutoff date). In Study 20170543, AMG 510 demonstrated antitumor activity in *KRAS p.G12C* mutated NSCLC, with 7 of 17 evaluable subjects having a partial response (PR) (5 confirmed) and 8 subjects having stable disease (2 subjects had progression), as of the 12 June 2019 data cutoff date. AMG 510 was well tolerated at the 180 mg once daily (QD) to 960 mg QD dose levels tested. AMG 510 dose of 960 mg QD orally administered (PO) was selected to be the dose for the phase 2 part of Study 20170543 and Study 20190009. The types and frequency of adverse events at the 960 mg dose were consistent with those observed at lower doses.

The aim of Study 20190009 is to evaluate the efficacy, safety, and tolerability of AMG 510 compared with docetaxel in subjects with previously treated, locally advanced, and unresectable or metastatic NSCLC with *KRAS p.G12C* mutation. The target population is subjects with pathologically documented, locally advanced unresectable or metastatic lung malignancy with *KRAS p.G12C* mutation identified through molecular testing and no other previously identified driver mutation (eg, epidermal growth factor receptor (EGFR) mutation or anaplastic lymphoma kinase (ALK) fusion). Subjects must have received at least 1 prior systemic therapy for advanced disease. Prior treatment should include a platinum-based doublet chemotherapy and a checkpoint inhibitor, either in one line or separate lines of therapy, unless there is a contraindication to those therapies. This target population represents previously treated, locally advanced, and unresectable or metastatic NSCLC patients with unmet medical need and is consistent with the NSCLC subjects who demonstrated clinical responses to AMG 510 in Study 20170543.

2.1.1 Choice of Docetaxel as Comparator

Docetaxel is indicated (Taxotere® Summary of Product Characteristics [SmPC] 2019; Taxotere® United States Prescribing Information [USPI] 2019) for the treatment of patients with locally advanced or metastatic NSCLC after failure of prior chemotherapy or platinum-based chemotherapy. In clinical practice, patients with NSCLC are usually treated in first line with platinum-based doublet therapy and/or checkpoint inhibitors either alone or in combination. Patients whose tumors have been screened and identified to have “actionable” mutations (eg, EGFR, ALK, ROS, BRAF) will receive targeted therapies directed at these specific oncogenic drivers in first- or later-lines (NCCN, 2019). Since the *KRAS p.G12C* mutation rarely occurs concomitantly with these other targetable mutations (Scheffler et al, 2018; Gainor et al, 2013), patients with *KRAS p.G12C* rarely have this option. The European Society for Medical Oncology (ESMO) treatment guidelines list the checkpoint inhibitors and platinum-based chemotherapy, either alone or in combination, as the recommended first-line treatment in patients with NSCLC who test negative for mutations other than *KRAS p.G12C.* For patients who did not receive both a checkpoint inhibitor and platinum-based chemotherapy concurrently in first-line treatment, the alternate treatment (ie, a checkpoint inhibitor for those patients who received platinum-based therapy in first line and vice versa) is the recommended second-line treatment. For patients whose cancer progressed after treatment with both a checkpoint inhibitor and platinum-based chemotherapy, the taxanes, such as docetaxel, are the recommended treatment. In

Study 20190009, docetaxel has been chosen as the active control treatment; since subjects must have already failed or their tumors progressed on both checkpoint inhibitor therapy and platinum-containing doublet therapy, additional treatment with a programmed cell death-1 (PD-1) or programmed cell death ligand 1 (PD-L1) agent or another platinum-containing doublet agent would not be indicated.

Although the REVEL study indicated an added benefit of docetaxel in combination with ramucirumab for second-line treatment of NSCLC (Garon et al, 2014), this additional benefit was small (survival gain of 1.4 months) and appeared primarily in younger patients (Ramalingam et al, 2018). Some adverse events in the docetaxel plus ramucirumab group were notably worse than those of docetaxel alone, with greater incidences of grade 4 neutropenia, hospitalization for neutropenia, anemia, and bleeding events in the combination treatment group. With the small increase in survival and the more severe toxicity profile, this combination is not widely used and may be best limited to younger patients with better Eastern Cooperative Oncology Group (ECOG) performance status (Uprety, 2019). Patients who are not eligible for treatment with docetaxel (eg, patients with ECOG status ≥ 2) would most likely receive only palliative care, with outcomes significantly worse than those patients who are eligible for docetaxel treatment. AMG 510 offers an alternative treatment option, with a favorable benefit-risk profile, for patients with *KRAS pG12C* mutations.

Docetaxel combined with nintedanib has also shown an added benefit over docetaxel alone for the treatment of advanced NSCLC (Gottfried et al, 2017). Nintedanib, however, is not available in all countries selected for this phase 3 study, and thus docetaxel alone was selected as the comparator.

Individuals with other oncogenic driver mutations will be excluded from the Study 20190009 study population, and thus therapies targeting those mutations would not be indicated as second- or third-line therapy. However, since other oncogenic driver mutations rarely occur concomitantly with the *KRAS p.G12C* mutation (Scheffler et al, 2018; Gainor et al, 2013), this exclusion is not expected to have a significant effect on study enrollment.

A docetaxel dose of 75 mg/m^2 every 3 weeks was chosen for the study as the recommended dose for treatment of NSCLC following failure of prior platinum-based therapy. However, docetaxel dose reductions will be allowed as needed. All subjects assigned to receive docetaxel will start at 75 mg/m^2, with dose reductions allowed as

described in Section 6.2.2.2, as the standard dosing regimen in Japan is 60 mg/m^2 based on the occurrence of myelosuppression at higher doses (Taguchi et al, 1994).

In summary, Amgen considers that docetaxel is the appropriate comparator for this study because:

- Docetaxel is indicated for the treatment of NSCLC in patients who have progressed after checkpoint inhibitor and platinum-based doublet therapy and is regionally widely available.
- Alternative choices are not widely available or would be appropriately used in only a narrower population of younger, healthier patients.
- Compared with the overall population of patients with NSCLC, the subjects enrolled in this study must have better performance status (ECOG status ≤ 1). Docetaxel mortality in clinical studies was increased in subjects with ECOG status of 2. In addition, because AMG 510 is expected to have better tolerability than docetaxel, enrolling subjects with better performance status is expected to maximize the tolerability of the docetaxel control group compared with AMG 510.

2.1.2 Primary Endpoints

The primary endpoint of Study 20190009 is progression-free Survival (PFS). Progression-free survival is defined as time from randomization until disease progression or death from any cause, whichever occurs first for all subjects. Subjects who do not progress or die will be censored at their last evaluable disease assessment date. Progression will be based on an independent radiologic assessment of disease response per Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST v1.1). Often used as an endpoint in diseases with very low survival rates, PFS is considered an acceptable surrogate endpoint for overall survival (OS) (Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics Guidance for Industry, FDA 2018; Clinical Trial Endpoints for the Approval of Non-Small Cell Lung Cancer Drugs and Biologics, FDA 2015; Guideline on the evaluation of anticancer medicinal products in man, EMA/CHMP 2017). Given the poor prognosis of refractory NSCLC, PFS is an appropriate early endpoint to evaluate efficacy in this setting. The endpoint of PFS will be included in the planned early interim efficacy analyses for this study. Estimand framework will be utilized to align the clinical trial design and analysis with the endpoints of interest while accounting for any intercurrent events. See Section 3 and Section 9.4.2.2 for details of the estimand framework.

2.1.3 Key Secondary Endpoints

The key secondary endpoints are OS, objective response rate (ORR), patient-reported outcomes (PRO), including change from baseline (cycle 1 day 1) over time to week 12 in

disease related symptoms (dyspnea, cough, and chest pain), physical functioning, and health related quality of life (QOL).

Overall survival, defined as time from randomization until death from any cause (subjects who do not die will be censored at the date of last contact through the analysis trigger date), is considered the gold standard for demonstrating clinical benefit for cancer drugs. This endpoint is precise and easy to measure, documented by the date of death and bias is not a factor in endpoint measurement (Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics Guidance for Industry, FDA 2018; Guideline on the evaluation of anticancer medicinal products in man, EMA/CHMP 2017).

Objective response rate is defined as complete response (CR) + PR, as assessed by RECIST v1.1. When defined in this manner, ORR is a direct measure of antitumor activity; therefore, this data will reflect any direct therapeutic effect of AMG 510. Given the poor prognosis of refractory NSCLC, ORR is an appropriate early endpoint to evaluate efficacy in this setting.

The effect of treatment with AMG 510 on treatment and disease related symptoms and health related QOL relative to docetaxel will be assessed. The 5-year survival rate for advanced NSCLC cancer is between 6% and 33% depending on the stage (American Cancer Society, 2019). Due to this poor prognosis, the effect of treatment on QOL is especially important. The QOL in lung cancer patients is lower than both healthy people, and patients suffering from other malignancies. It is affected by the severity and the number of symptoms such as fatigue, loss of appetite, dyspnea, cough, pain, and blood in sputum, which are specific for lung tumors (Polanski et al, 2016). Assessing change from baseline over time to week 12 in dyspnea, cough, and chest pain in NSCLC subjects receiving AMG 510 compared to docetaxel is predicted to give a meaningful assessment of whether AMG 510 improves these disease related symptoms. Change from baseline over time to week 12 in physical functioning and global health status will also be compared in subjects receiving AMG 510 compared to docetaxel, to allow assessment of possible impact on health related QOL.

2.2 Background

2.2.1 Disease

Worldwide, lung cancer (small cell and non-small cell) is the most common type of cancer occurring in both males and females (WHO statistics, 2018). It was estimated that in 2019 there would be approximately 228 150 new cases of lung cancer in the United States (US) alone (American Cancer Society, 2019). The 5-year survival rate

for advanced NSCLC cancer is between 6% and 33% depending on the stage (American Cancer Society, 2019).

2.2.1.1 Oncogenic RAS Driven Tumorigenesis

The *RAS* proto-oncogene has been identified as an oncogenic driver of tumorigenesis in NSCLC (Johnson et al, 2001; Der et al, 1982). The RAS family consists of 3 closely related genes that express guanosine triphosphatases (GTPases) responsible for regulating cellular proliferation and survival (Simanshu et al, 2017; Barbacid et al, 1987). The RAS proteins, KRAS, Harvey rat sarcoma viral oncogene homolog (HRAS), and neuroblastoma RAS viral oncogene homolog (NRAS) (Hall et al, 1983; Taparowsky et al, 1983; Chang et al, 1982; Kirsten and Mayer, 1967; Harvey, 1964), can be mutationally activated at codons 12, 13, or 61, leading to human cancers. Different tumor types are associated with mutations in certain isoforms of *RAS*, with *KRAS* being the most frequently mutated isoform in most cancers (Prior et al, 2012). While the role of *KRAS* mutations in human cancers has been known for decades, no anti-cancer therapies specifically targeting *KRAS* mutations have been successfully developed, largely because the protein had been intractable for inhibition by small molecules (McCormick, 2016).

2.2.1.2 *KRAS p.G12C* Mutation and AMG 510

Of the *KRAS* mutations, it is estimated that approximately 80% occur at codon 12 (Prior et al, 2012). The *KRAS p.G12C* mutation is estimated to occur in approximately 13% of lung adenocarcinoma (including NSCLC), 3% of CRC, and 1% to 2% of numerous other solid tumors (including pancreatic, endometrial, bladder, ovarian, and small cell lung tumors) (The AACR Project GENIE Consortium, 2017; Biernacka et al, 2016; Neumann et al, 2009). This specific mutation has been identified as a putative oncogenic driver in several types of solid tumors including NSCLC (Fernández-Medarde and Santos, 2011) and CRC (Jones et al, 2017) and other solid tumors such as pancreatic, endometrial, bladder, ovarian, and small cell lung tumors (The AACR Project GENIE Consortium, 2017; Zhou et al, 2016).

The *KRAS p.G12C* mutation is a single guanine to thymine substitution that results in a glycine to cysteine substitution at amino acid position 12. This structural change in the protein results in a defect in the association of GAPs, thereby reducing the hydrolysis of guanosine triphosphate (GTP) by KRAS. The resulting accumulation of active, GTP-bound KRAS leads to enhanced proliferative and survival signaling in tumor cells (Jones et al, 2017).

AMG 510 is a small molecule that specifically and irreversibly inhibits the KRAS G12C mutated protein. AMG 510 binds to the P2 pocket of KRAS adjacent to the mutated cysteine at position 12 and the nucleotide-binding pocket. The inhibitor contains a thiol-reactive portion which covalently modifies the cysteine residue and locks KRAS G12C in an inactive, guanosine diphosphate (GDP)-bound conformation. This blocks the interaction of KRAS with effectors such as Rapidly Accelerated Fibrosarcome (RAF) proto oncogene serine/threonine-protein kinase (RAF), thereby preventing downstream signaling, including the phosphorylation of extracellular signal-regulated kinase (ERK) (Simanshu et al, 2017; Ostrem et al, 2013; Cully and Downward, 2008). Inactivation of KRAS by RNA interference (RNAi) or small-molecule inhibition has previously demonstrated an inhibition of cell growth and induction of apoptosis in tumor cell lines and xenografts harboring *KRAS* mutations (including the *KRAS p.G12C* mutation) (Janes et al, 2018; McDonald et al, 2017; Xie et al, 2017; Ostrem and Shokat, 2016; Patricelli et al, 2016). Studies with AMG 510 have confirmed these in vitro findings and have likewise demonstrated inhibition of growth and regression of cells and tumors harboring *KRAS p.G12C* mutations. These data suggest that inhibition of *KRAS p.G12C* may have therapeutic benefit for subjects with *KRAS p.G12C*-driven cancers. Accordingly, the first-in-human (FIH) and phase 2 Study 20170543, were designed to evaluate the safety, tolerability, PK/PD, and efficacy of AMG 510 in subjects with *KRAS p.G12C* mutated advanced NSCLC, CRC, and other solid tumors.

2.2.1.3 Current Therapy for Cancers Harboring the *KRAS p.G12C* Mutation

While the incidence of the G12C KRAS mutation in these tumor types is relatively low (approximately 13%) the overall incidence of NSCLC and the poor prognosis of subjects with advanced/metastatic disease makes this mutation an important molecular target. There is currently no anticancer therapy specifically targeting tumors that harbor the *KRAS p.G12C* mutation. Subjects with metastatic or unresectable NSCLC, CRC and other solid tumors (including pancreatic, endometrial, bladder, ovarian, appendiceal, ampullary, and small intestine) with the *KRAS p.G12C* mutation are generally being treated with combinations of chemotherapy, immunotherapy or antiangiogenic agents.

Although somatic mutations in *EGFR, BRAF,* and human epidermal growth factor receptor 2 (*HER*2), and rearrangements in *ALK, ROS,* Neurotrophic Tyrosine Receptor Kinase *(NTRK),* and Rearranged During Transfection (*RET)* have been validated as powerful predictive biomarkers, and have expanded treatment options for these molecularly defined subsets of subjects, since the KRAS mutation rarely occurs

concomitantly with these other molecular abnormalities, subjects with KRAS mutations are not usually candidates for these therapies (Scheffler et al, 2018; Gainor et al, 2013). Efforts to target KRAS mutated NSCLC by inhibiting downstream signaling mechanisms such as with Mitogen Activated Protein Kinase Kinases (MEK1/2) or Cyclin Dependent Kinase 4/6 (CDK4/6) inhibitors have been unsuccessful to date (Roman et al, 2018). More recently, NSCLC subjects with the *KRAS p.G12C* mutation are, like subjects without other molecularly defined targets, receiving anti-PD-1 inhibitors with or without chemotherapy in first and/or second line therapy, followed by therapy with a taxane with or without a Vascular Endothelial Growth Factor (VEGF) inhibitor.

Preliminary literature review performed by Amgen on *KRAS p.G12C* mutated subjects (from 15 publications with NSCLC G12C specific data over the past 10 years) suggests that in general, in NSCLC subjects, the *KRAS p.G12C* mutation appeared to be associated with poorer progression-free and disease-free survival. However, the magnitude of these differences was modest and there were a few studies that reported no difference or slightly better outcomes of subjects with *KRAS p.G12C* mutations. Based on the preliminary literature review described above, it is assumed that subjects with the *KRAS p.G12C* mutation respond similarly to chemotherapy, immunotherapy, and anti-angiogenic agents as subjects who do not harbor a *KRAS p.G12C* mutation.

For advanced/metastatic NSCLC subjects, multiple large phase 3 trials have demonstrated ORR in ≥ second line (following first line platinum-containing chemotherapy doublets, such as cisplatin/pemetrexed) of 5.5 to 13 % with chemotherapy (typically a taxane) and 9.7 to 22.5 % with chemotherapy plus a Vascular Endothelial Growth Factor Receptor (VEGFR) inhibitor (Gridell et al, 2018; Rittmeyer et al, 2017; Herbst et al, 2016; Borghaei et al, 2015; Herbst et al, 2007). These trials have also demonstrated PFS of 2.8 to 4.2 months and 4.8 to 5.4 months and OS of 6 to 11.4 months and 9.9 to 12.6 months for chemotherapy and chemotherapy plus a VEGFR inhibitor, respectively. Recent studies of ≥ second line NSCLC subjects receiving anti-PD1 therapy (post-chemo doublet therapy in first line) have yielded more substantial ORR and OS (Vokes et al, 2018; Herbst et al, 2016; Borghaei et al, 2015); however, due to recent approvals of anti-PD1 therapy for first line NSCLC the sequence of immunotherapy in NSCLC is in flux and the standard of care (and outcomes) for subjects who progress or recur after first line anti-PD1 therapy remains unclear.

2.2.2 Amgen Investigational Product Background: AMG 510

AMG 510 is a small molecule that specifically and irreversibly inhibits the KRAS G12C mutated protein. AMG 510 binds to the P2 pocket of KRAS adjacent to the mutated cysteine at position 12 and the nucleotide-binding pocket. The inhibitor contains a thiol-reactive portion which covalently modifies the cysteine residue and locks KRAS G12C in the inactive GDP-bound conformation. This blocks the interaction of KRAS with effectors like RAF, thus preventing downstream signaling, including the phosphorylation of ERK (Ostrem et al, 2013; Simanshu et al, 2017). Inactivation of KRAS through a small molecule inhibitor has previously demonstrated an inhibition of cell growth and induction of apoptosis in tumor cell lines and xenografts with the *KRAS p.G12C* mutation (Janes et al, 2018; Ostrem and Shokat, 2016; Patricelli et al, 2016). Likewise, studies of AMG 510 have demonstrated inhibition of growth and regression of cells and tumors harboring *KRAS p.G12C* (Section 2.2.1.3). These data suggest that inhibition of KRAS G12C may have therapeutic benefit for subjects with *KRAS p.G12C*-driven cancers. Accordingly, the FIH and phase 2 Study 20170543, was designed to evaluate the safety and efficacy of AMG 510 in subjects with *KRAS p.G12C* mutated advanced NSCLC, CRC, and other solid tumors.

AMG 510 Preclinical Experience

In vitro AMG 510 inhibited nucleotide exchange of recombinant mutated KRAS G12C/C118A (half maximal inhibitory concentration (IC_{50}) = 0.09 µM), but had minimal effect on KRAS C118A, which is wildtype at G12. In cells, AMG 510 covalently modified KRAS G12C and inhibited KRAS signaling as measured by phosphorylation of ERK1/2 in all *KRAS p.G12C*-mutated cell lines tested (IC_{50} values from 0.01 to 0.12 µM), but did not inhibit phospho-ERK1/2 in cell lines with various other *KRAS* mutations. AMG 510 also impaired viability in all but one *p.G12C*-mutated cell lines (IC_{50} values from 0.004 to 0.032 µM), but did not affect the viability of cell lines that did not harbor the *KRAS p.G12C* mutation. The cellular maximum potential rate (k_{inact}) and inhibitor concentration (K_i) values for AMG 510 were also experimentally determined in the human pancreatic cell line MIA PaCa-2 to be 0.00133 sec^{-1} and 6.97×10^{-7} M, respectively, with k_{inact}/K_i ratio of 1.9×10^{3} M^{-1} sec^{-1}.

In vivo AMG 510 covalently modified KRAS G12C and significantly inhibited phosphor-ERK1/2 in human *KRAS p.G12C* MIA PaCa-2 T2 pancreatic and *KRAS p.G12C* NCI-H358 NSCLC tumor xenografts in mice in a dose-dependent manner at doses as low as 1 mg/kg in the MIA PaCa-2 T2 model. After a single, 10 mg/kg dose

in mice bearing MIA PaCa-2 T2 tumors, exposure of AMG 510 peaked at 0.5 hours, followed closely by maximal inhibition of phospho-ERK1/2 by 1 hour to 2 hours.

Covalent modification of KRAS G12C by AMG 510 tracked with inhibition and maximal modification occurred after 2 hours. Significant inhibition and modification of KRAS G12C persisted for 48 hours after a single, 10 mg/kg dose. In tumor xenograft studies AMG 510 significantly inhibited the growth of MIA PaCa-2 T2 and NCI-H358 tumors at doses as low as 3 mg/kg and achieved 62% and 49% regression, respectively, at 100 mg/kg. Notably AMG 510 had no effect on SW480-1AC (*KRAS p.G12V*) tumor xenografts at 100 mg/kg and did not impact body weight in any study.

AMG 510 Clinical Experience in NSCLC and Other Tumor Types

The FIH study (which later was amended to phase 1/2), Study 20170543, was initiated in August 2018 to evaluate the safety and tolerability of AMG 510 as an oral therapeutic in subjects with advanced or metastatic *KRAS p.G12C* mutated NSCLC, CRC, or other solid tumors.

The phase 1 monotherapy dose exploration part of Study 20170543 has yielded early evidence of activity (even in this heavily pretreated population), as demonstrated by preliminary data. As of the 12 June 2019 data cutoff date, Study 20170543 had enrolled 62 subjects, 27 with NSCLC, 31 with CRC, and 4 with other solid tumors. Thirty-nine of the 62 enrolled subjects were evaluable for efficacy as of the 12 June 2019 data cutoff date. Preliminary results demonstrated antitumor activity in *KRAS p.G12C* mutated NSCLC, with 7 of 17 evaluable subjects having a PR (5 confirmed) and 8 subjects having stable disease (2 subjects had progression).

AMG 510 was well tolerated at the 180 mg QD to 960 mg QD dose levels tested. As of the data cut-off date of 28 August 2019, preliminary safety data were available for 95 subjects who had received AMG 510 doses between 180 and 960 mg QD. In the preliminary safety data, none of these 95 subjects had dose-limiting toxicities (DLTs). Eighty-one subjects (85.3%) had at least 1 treatment-emergent adverse event during the study. The most frequently reported adverse events (reported in ≥ 10% subjects in all the cohorts combined) were diarrhea (25 subjects [26.3%]), nausea (20 subjects [21.1%]), fatigue (18 subjects [18.9%]), vomiting (12 subjects [12.6%]), abdominal pain, decreased appetite (11 subjects [11.6%] each), and headache (10 subjects [10.5%]). Most adverse events were grade 1 or 2 in severity. Thirty-five subjects (36.8%) had adverse events that were grade ≥ 3 in severity; anemia (5 subjects [5.3%]), diarrhea

(4 subjects [4.2%]), metastatic CRC, increased alanine aminotransferase (ALT) (3 subjects [3.2%] each), and dyspnea, metastatic lung cancer, adult failure to thrive, respiratory failure, and vomiting (2 subjects [2.1%] each) were reported in > 1 subject; the remaining adverse events were all reported in 1 subject (1.1%) each.

Treatment-related (as reported by the investigator) treatment-emergent adverse events were reported for 43 subjects (45.3%). The most frequently reported treatment-related adverse events were diarrhea (16 subjects, 16.8%), nausea (8 subjects, 8.4%), increased ALT (6 subjects [6.3%] each), vomiting (5 subjects [5.3%]), increased blood alkaline phosphatase (ALP), fatigue (4 subjects [4.2%] each), abdominal pain, dry mouth, anemia (3 subjects [3.2%] each), increased blood creatine phosphokinase, decreased white blood cell count, decreased appetite, peripheral neuropathy, and pruritus (2 subjects [2.1%] each). Most treatment-related adverse events were grade 1 or 2 in severity; grade 3 treatment-related adverse events that were reported in > 1 subject were diarrhea (4 subjects [4.2%]), increased ALT, and anemia (3 subjects [3.2%] each). No grade 4 related adverse events were reported.

Twenty-seven subjects (28.4%) had serious adverse events. Two subjects (2.1%) had treatment-related serious adverse events: lung infection (1 subject) and increased ALT (1 subject); both these events were grade 3 in severity. Eight subjects (8.4%) had fatal adverse events; all were considered unrelated to AMG 510 treatment by the investigator.

Phase 2 portion, which further evaluate efficacy of AMG 510 monotherapy in previously treated NSCLC, CRC, and other tumor types, is ongoing.

2.2.3 Non-Amgen Investigational Product Background: Docetaxel

Docetaxel is a semisynthetic taxane, a class of anticancer agents that bind to β tubulin, thereby stabilizing microtubules and inducing cell-cycle arrest and apoptosis.

Docetaxel Clinical Experience as Second Line Treatment in NSCLC

Two trials have shown the benefit of docetaxel as a second-line agent in **subject**s with non-small-cell lung cancer who had platinum-resistant tumors. The first trial (TAX 317) assigned patients with stage IIIB or IV disease that was refractory to platinum-based regimens to either docetaxel or best supportive care. **Subject**s in the docetaxel group were assigned 100 mg/m^2 as a 1-h intravenous infusion once every 21 days, but because of an unexpectedly high incidence of febrile neutropenia and deaths from sepsis, the dose was lowered to 75 mg/m^2. Median time to progression favored docetaxel over supportive care. In an intention-to-treat (ITT) analysis of all **subject**s

allocated docetaxel, median OS was significantly extended compared with controls (7·0 months vs 4·6 months, p = 0·047). One-year OS was also enhanced in the docetaxel group compared with controls (29% vs 19%). Febrile neutropenia was less frequent with 75 mg/m^2 docetaxel (2%) than at the higher dose (22%), with no deaths from sepsis.

TAX 320 assigned 373 **subject**s with stage IIIB or IV non-small-cell lung cancer who had disease progression during or after one or more platinum-based chemotherapy regimens to 1 of 3 treatments: 100 mg/m^2 docetaxel every 3 weeks; 75 mg/m^2 docetaxel every 3 weeks; or to either 30 mg/m^2 weekly vinorelbine or 2 g/m^2 ifosfamide for 3 days every 3 weeks. About 90% of **subject**s had stage IV disease at the time of enrol**l**ment. Overall response was 11% with 100 mg/m^2 docetaxel and 7% with 75 mg/m^2 docetaxel, both of which were significantly greater than the 1% response noted for those assigned vinorelbine or ifosfamide. Intention-to-treat analysis showed a modest but significant improvement in time to progression and 26-week PFS in favor of docetaxel. Groups did not differ in median OS. However, 1 year OS favored 75 mg/m^2 docetaxel compared with vinorelbine or ifosfamide. Moreover, a third of **subject**s in each group received subsequent chemotherapy on removal from the trial (including taxane treatment in 21% of **subject**s in the control group) and thus an ITT survival curve, in which survival observations were censored when **subject**s received subsequent chemotherapy, was generated. In this analysis, 1-year survival significantly favored docetaxel over vinorelbine or ifosfamide. Quality-of-life analysis, which was assessed prospectively, suggested that docetaxel was more effective than control treatment. Grade 4 neutropenia and febrile neutropenia were more frequent in both groups assigned docetaxel compared with the control group. However, documented infection and grade 4 thrombocytopenia were much the same for all 3 groups (reviewed in Montero et al, 2005).

Indication

Docetaxel 75 mg/m^2 administered intravenously over 1 hour every 3 weeks as a monotherapy is approved by the Food and Drug Administration (FDA) and the European Medicines Agency (EMA) for the treatment of patients with locally advanced or metastatic NSCLC after failure of prior platinum-based chemotherapy. It is also approved by the FDA and the EMA in combination with cisplatin for the treatment of chemotherapy naïve unresectable, locally advanced, or metastatic NSCLC. Refer to the

regional manufacturer package insert for additional information (for example; Taxotere® SmPC; Taxotere® United States Prescribing Information [USPI]).

2.3 Benefit/Risk Assessment

Based on preclinical data, nonclinical toxicity studies, and the clinical experience with AMG 510, the overall benefit/risk profile favors clinical development of AMG 510 for NSCLC subjects with *KRAS p.G12C* mutation.

Preliminary efficacy data from Study 20170543 demonstrated anti-tumor activity of AMG 510 monotherapy in NSCLC subjects with $KRAS^{G12C}$. As of the 12 June 2019 data cutoff date, Study 20170543 had enrolled 62 subjects, 27 with NSCLC, 31 with CRC, and 4 with other solid tumors. Thirty-nine of the 62 enrolled subjects were evaluable for efficacy as of the 12 June 2019 data cutoff date. Preliminary results demonstrated antitumor activity in *KRAS p.G12C* mutated NSCLC, with 7 of 17 evaluable subjects having a PR (5 confirmed) and 8 subjects having stable disease (2 subjects had progression).

In addition, no cumulative toxicities were noted with extended treatment, suggesting that AMG 510 may provide a safe and novel therapeutic option for subjects with advanced cancer.

Based on nonclinical toxicity studies of AMG 510, the key safety information to be monitored in clinical studies of AMG 510 includes renal toxicity, anemia, leukocytosis, and splenomegaly. **Based on the clinical study data of AMG 510, the key risks to be monitored include increases to aspartate aminotransferase (AST) and alanine aminotransferase (ALT) and interstitial lung disease (ILD)/pneumonitis. Clinical signs and symptoms along with safety laboratories, such as liver enzymes, will be monitored during the study to ensure the subjects' safety. More detailed information about the safety profile and risks of AMG 510, including the most recent information on adverse drug reactions based on the ongoing clinical program, may be found in the AMG 510 Investigator's Brochure and the regional Prescribing Information (if applicable).**

The above benefit risk assessment supports the conduct of this clinical trial. Refer to the AMG 510 Investigator's Brochure for further data on AMG 510.

3. Objectives and Endpoints

Objectives	Endpoints
Primary	
• To compare the efficacy of AMG 510 versus docetaxel as assessed by progression-free survival (PFS) in previously treated subjects with *KRAS p.G12C* mutated non-small cell lung cancer (NSCLC)	• PFS - defined as time from randomization until disease progression or death from any cause, whichever occurs first for all subjects. Progression will be based on blinded independent central review (BICR) of disease response per Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST v1.1).
Attributes	**Primary Estimand**
• Target Population	• Subjects with previously treated locally advanced and unresectable or metastatic NSCLC with *KRAS p.G12C* mutation
• Primary Endpoint	• PFS
• Summary Measures	• Hazard Ratio (HR)
• Intercurrent Events and Strategies	• Start of new anti-cancer therapy prior to PFS event • PFS is censored at the date of last evaluable assessment before or on start of new anti-cancer therapy.
Primary Estimand Description	
HR of PFS between AMG 510 and docetaxel, for subjects with previously treated locally advanced and unresectable or metastatic NSCLC with KRAS p.G12C mutation, before or on start of new anti-cancer therapy	
Key Secondary	

• To compare the efficacy of AMG 510 versus docetaxel as assessed by:
  • Overall Survival (OS)
  • Objective response rate (ORR)
	• Overall survival - defined as time from randomization until death from any cause.
	• Objective response (complete response [CR] + partial response [PR]), assessed per RECIST v1.1. Response will be assessed by BICR. Complete response and PR require confirmatory repeat radiologic assessment at no less than 4 weeks after the original response. The normal subsequent assessment is acceptable to confirm response.

• To compare patient-reported outcomes (PRO) as assessed by: European Organization for Research and Treatment of Cancer Quality-of-life Questionnaire Core 13 (EORTC QLQ-LC13) and European Organization for Research and Treatment of Cancer Quality-of-life	• Change from baseline (cycle 1 day 1) over time to week 12 in disease related symptoms of:
	  ○ Dyspnea as measured by a 4-item dyspnea domain from QLQ-C30 and QLQ-LC13
	  • Cough as measured by QLQ-LC13
	  • Chest Pain as measured by QLQ-LC13
	• Change from baseline over time to week 12 in
	  • Physical functioning as measured by QLQ-C30

Questionnaire Core 30 (EORTC QLQ-C30)	• Global health status as measured by QLQ-C30
Attributes	**Secondary Estimand - OS**
• Target Population	• Subjects with previously treated locally advanced and unresectable or metastatic NSCLC with KRAS p.G12C mutation
• Key Secondary Endpoint	• OS
• Summary Measures	• Hazard Ratio (HR)

• Intercurrent Events and Strategies	• Start of new anti-cancer therapy
	  • OS will be estimated regardless of subsequent anti-cancer therapy.
	• Crossover from control group to treatment group
	  • OS will be estimated regardless of crossover.

Secondary Estimand Description - OS	
HR of OS between AMG 510 and docetaxel, for subjects with previously treated locally advanced and unresectable or metastatic NSCLC with KRAS p.G12C mutation, regardless of subsequent anti-cancer therapy and/or crossover.	
Attributes	**Secondary Estimand – Objective Response**
• Target Population	• Subjects with previously treated locally advanced and unresectable or metastatic NSCLC with KRAS p.G12C mutation
• Key Secondary Endpoint	• Objective Response
• Summary Measures	• Odds Ratio
• Intercurrent Events and Strategies	• Discontinuation of treatment prior to achieving an objective response (PR or CR) • Subjects will be considered as non-responders.
Secondary Estimand Description – Objective Response	
Odds ratio of objective response between AMG 510 and docetaxel, for subjects with previously treated locally advanced and unresectable or metastatic NSCLC with KRAS p.G12C mutation. Subjects who discontinued treatment prior to achieving an objective response are considered as non-responders.	
Attributes	**Secondary Estimand - PRO**
• Target Population	• Subjects with previously treated locally advanced and unresectable or metastatic NSCLC with KRAS p.G12C mutation
• Key Secondary Endpoint	• PRO
• Summary Measures	• Change from baseline to Week 12

• Intercurrent Events and Strategies	• Start of new anti-cancer therapy including crossover before Week 12 • PRO measurements before or on start of new anti-cancer therapy including crossover will be used to estimate treatment effect.
Secondary Estimand Description - PRO	
Change from baseline to Week 12 in PRO endpoints between AMG 510 and docetaxel, for subjects with previously treated locally advanced and unresectable or metastatic NSCLC with KRAS p.G12C mutation. PRO measurements before or on start of new anti-cancer therapy including crossover will be used to estimate treatment effect.	
Secondary	
• To compare efficacy of AMG 510 versus docetaxel as assessed by: duration of response (DOR), time to response (TTR), and disease control rate (DCR)	• Duration of response - defined as time from first evidence of PR or CR to disease progression or death due to any cause, whichever occurs first. Progression will be based on an BICR assessment of disease response per RECIST v1.1. • Time to response - defined as time from randomization to first evidence of PR or CR. • Disease control rate - defined as rate of confirmed objective response (CR or PR) + stable disease per RECIST v1.1 of at least 6 weeks measured
• To compare the safety and tolerability of AMG 510 versus docetaxel	• Subject incidence of treatment-emergent adverse events, treatment-related adverse events, changes in vital signs, and clinical laboratory tests.
• To compare the effect of treatment with AMG 510 on other treatment and disease related symptoms, and health related quality of life relative to docetaxel	• Change from baseline over time to week 12 for the remaining subscales for QLQ-LC13 and QLQ-C30 • Time to deterioration for the subscales for QLQ-LC13 and QLQ-C30 • Summary scores at each assessment and changes from baseline of visual analogue scale (VAS) scores as measured by EuroQol-5 Dimension (EQ5D5L)
• To characterize the pharmacokinetics (PK) of AMG 510 and its major metabolites	• Pharmacokinetic (PK) parameters of AMG 510 including, but not limited to, maximum plasma concentration (C_{max}), area under the plasma concentration-time curve (AUC) on Days 1 and 8, and pre-dose (trough) concentrations through cycle 4
Exploratory	
[redacted]	

4. Study Design

4.1 Overall Design

This is a phase 3, multicenter, randomized, open label, active-controlled, study to evaluate the efficacy, safety, and tolerability of AMG 510 versus docetaxel in subjects with previously treated locally advanced and unresectable or metastatic NSCLC with *KRAS p.G12C* mutation. The study will be conducted at approximately 290 sites globally. The study will consist of a screening period, a treatment period, a safety follow-up (SFU) period, and long term follow up period. See Section 8.1.6 and Section 8.1.7 for AMG 510 and docetaxel treatment beyond radiologic progression. See Section 8.1.8 for crossover. Approximately 330 previously treated subjects with locally advanced and unresectable or metastatic NSCLC with centrally confirmed KRAS p.*G12C* mutation will be enrolled.

Subjects must have documentation of *KRAS p.G12C* mutation identified by central laboratory testing with the Qiagen KRAS *therascreen*® KRAS Rotor-Gene Q (RGQ) PCR Kit through Amgen Study 20190294 or through this protocol.

Subjects will be randomized 1:1 to receive either AMG 510 or docetaxel and stratified by number of prior lines of therapy in advanced disease (1 versus 2 versus > 2), race (Asian versus non-Asian), and history of CNS involvement (present or absent). Prior lines of therapy will be assessed using the criteria below:

- Chemoradiation for locally advanced and unresectable disease is a line of therapy for advanced disease if progression occurs within 6 months of end of treatment.
- Chemoradiation followed by planned systemic therapy (including checkpoint inhibitor) or vice versa without documented intervening progression is considered one line of therapy if progression occurs within 6 months of end of treatment
- Adjuvant therapy is a line of therapy for advanced disease if progression occurs within 6 months of end of treatment.
- Each new systemic anti-cancer regimen for progressive locally advanced and unresectable or metastatic disease is a line of therapy.
- Maintenance therapy is not considered a new line of therapy.
- Chemotherapy regimen adjustments for intolerability is not a new line of therapy.

Cycle 1 day 1 will be defined as the first day subject receives study medication. A cycle is 21 days in length ± 3 days, unless a delay is medically necessary. A ± 3-day window is allowed for protocol required assessments, unless otherwise specified. Tumor assessment will be conducted (by magnetic resonance imaging [MRI] and/or contrast enhanced computerized tomography [CT]) during screening (within 28 days of day 1); every 6 weeks from cycle 1 day 1; (± 7 days) (at weeks 7, 13, 19, 25, 31, 37, 43, and 49), and then at 9 week intervals (± 7 days) thereafter until independent central confirmation of progression, start of another anti-cancer therapy, withdrawal of consent, lost to follow up, or death, whichever occurs earliest. Subjects' scans will undergo independent central confirmation of progression (COP) at the time of first progressive disease (PD). Subjects that undergo treatment beyond progression or crossover, from docetaxel to AMG 510, will continue to receive scans after confirmation of first PD. Further details with regards to imaging assessments post treatment period are listed in Section 8.1.4.

Once subjects on the docetaxel arm are determined to have radiological progression according to RECIST v1.1 by the investigator and progressive disease is confirmed by independent central imaging review, they will be given the opportunity to crossover and

receive AMG 510. Alternatively, should an early efficacy of the study be noted by the DMC, crossover will be considered for all subjects who randomized into the docetaxel arm (so that they will be able to immediately receive AMG 510). All subjects remaining on study will be followed for survival, as specified in the Schedule of Activities (Section 1.3), until the pre-specified OS events are reached, regardless of the OS analysis result at the PFS primary analysis.

Tumor assessment and response will be confirmed by BICR who will evaluate disease progressions and responses without the knowledge of randomization assignments, in accordance with the RECIST v1.1. This assessment will be used for the primary analysis (PA) of endpoints.

In all subjects, after the end of IP, information regarding the date of progression, type and duration of subsequent therapies following disease progression, response to subsequent therapy, date of progression on subsequent therapy, and survival data will be collected. Subjects who discontinue treatment prior to RECIST v1.1 disease progression (eg, due to unacceptable toxicity) will also continue to be followed with tumor assessments until independent central confirmation of progression, withdrawal of consent, or start of another anti-cancer therapy then followed for subsequent anti-cancer therapy and survival. **Subjects** that consent to treatment beyond progression or consent to crossover, from docetaxel to AMG 510, will continue to receive investigational product after independent central confirmation of progression at the time of first progressive disease (PD). In select cases, subjects may continue on treatment following radiologic progression if they are continuing to demonstrate clinical benefit (see Section 8.1.6 and 8.1.7).

The assessments to be conducted in this study are described below and will be carried out at the timepoints designated in the Schedule of Activities (Table 1-1 and Table 1-2):

- Central confirmation of *KRAS p.G12C* mutation status for all enrolling subjects.
- Disease progression will be assessed using RECIST v1.1. The primary efficacy objective will be assessed by BICR.
- Expedited independent confirmation of progression (COP), at time of first progressive disease (PD), will be performed by a single radiologist separate from the central radiologist group reading the images for (as described in Section 8.2.2.1.2) prior to moving forward with treatment beyond progression or crossover.
- Safety will be monitored by assessing serious and non-serious adverse events, safety laboratory tests, vital signs and electrocardiograms (ECGs). Adverse events will be graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, Version 5.0 (NCI CTCAE v5.0).

- Laboratory safety tests will include hematology, blood chemistry, cholesterol, coagulation, urinalysis, and thyroid function test. Vital sign assessments will include blood pressure, heart rate, oxygen saturation, respiratory rate, and body temperature; additional vital signs will be collected only if clinically warranted. The urine studies may be performed at a local laboratory and/or by the central laboratory, depending on the availability of the testing facility.
- PK characterization will be conducted using sparse sampling and population PK modeling approach.
- PRO/QOL assessments will be assessed using the PRO instruments QLQ-C30, QLQ-LC13, EQ-5D-5L, and PRO-CTCAE, plus a single item about symptom bother (GP5 of the FACT-G). Patient pain and patient impression of change and severity will be assessed using the brief pain inventory (BPI), patient global impression of change (PGIC) and patient global impression of severity (PGIS) questionnaires. Patient-reported outcomes scores will be determined for all subjects at baseline (cycle 1 day 1) and at timepoints designated in the SOA and will be compared across treatment groups.

[redacted]

- Further tissue assessments at the time of independent central confirmation of progression:
  - If a subject is not continuing AMG 510 upon radiologic progression, they will be encouraged to enroll in an optional sub-study assessing exploratory biomarkers via an optional tumor biopsy (excisional, core needle, or fine needle aspirates) only if biomarker research is allowed according to local regulations and agreed by local EC/IRB.
  - If a subject plans to continue on AMG 510 treatment beyond radiologic progression, the subject must be willing to undergo biopsy, if clinically feasible or advisable, (excisional, core needle, or fine needle aspirates) of one of the new or progressing lesions (see Section 8.1.6 for additional criteria) only if biomarker research is allowed according to local regulations and agreed by local EC/IRB.

An independent data monitoring committee (DMC) will be convened for this study and will act in an advisory capacity to the sponsor with respect to safeguarding the interests of study subjects, assessing interim safety and efficacy data, monitoring the overall conduct of the study, and providing recommendations relating to continuing, modifying, or stopping the study based on these findings (International Council for Harmonisation Good Clinical Practice [ICH GCP 5.5.2]). Details of the DMC will be described in the DMC Charter.

Data monitoring committee will review safety and efficacy data as per DMC charter. Data monitoring committee will meet to review safety after 50, 100, and 200 subjects are enrolled and have had the opportunity to be treated for at least 6 weeks and thereafter at

approximately 6-month intervals, until the PA of PFS. The DMC will also review the IA data for PFS and OS, whenever these are triggered.

There will be 2 planned PFS efficacy analyses. The PA of PFS will occur when approximately 230 PFS events have been observed. The PFS PA may be delayed to ensure that the enrollment is finished and the delayed PA will be triggered when the last randomized subject have had the opportunity to have at least 6 weeks of follow up. An IA of PFS for superiority is planned when approximately 70% (160 events) of the total PFS events have been observed from both arms, or when the enrollment is finished and the last randomized subject have had the opportunity to have 6 weeks of follow up, whichever occurs later.

Early efficacy at the proposed PFS interim analysis will be claimed if the observed PFS difference meets the pre-specified statistical significance as well as being considered clinically meaningful. More details will be included in the DMC charter.

If PFS achieves statistical significance at the interim analysis, an administrative interim summary for OS will be performed. Otherwise, the OS will be assessed for superiority of AMG 510 over docetaxel at either the time of PFS primary analysis or after 175 OS events have been observed, whichever is later. The OS primary analysis will occur when at least 198 OS events (~60% maturity) have been observed, which is expected to be at approximately 3 months after PFS primary analysis. The analysis of ORR will be done at the time when PFS is claimed statistically significant and the last randomized subject has had the opportunity to have at least 12 weeks of follow up. The final analysis will be performed when the last subject has completed long-term follow-up (LTFU).

As designed, the trial will not be terminated at PFS analyses and subjects will continue to be followed for OS data until the targeted number of events are reached, regardless of the OS analysis result at the PFS primary analysis, to enable OS analyses and a robust description of the totality of the data.

The overall study design is described by a study schema in Section 1.2. The endpoints are defined in Section 3.

4.2 Number of Subjects

Approximately 330 subjects with locally advanced unresectable or metastatic centrally confirmed *KRAS p.G12C* mutation will be enrolled in the study (approximately 165 subjects in each of the 2 treatment groups). Subjects will be randomized 1:1 to

receive either monotherapy AMG 510 or docetaxel. Once subjects on the docetaxel arm are determined to have radiological progression according to RECIST v1.1 by the investigator and progressive disease is confirmed by independent central imaging review, they will be given the opportunity to crossover and receive AMG 510. Alternatively, should an early efficacy of the study be noted by the DMC, crossover will be considered for all subjects who randomized into the docetaxel arm (so that they will be able to immediately receive AMG 510). All subjects remaining on study will be followed for survival, as specified in the Schedule of Activities (Section 1.3), until the pre-specified OS events are reached, regardless of the OS analysis result at the PFS primary analysis.

Subjects in this clinical investigation shall be referred to as "subjects". For the sample size justification, see Section 9.2.

4.2.1 Replacement of Subjects

Subjects who are withdrawn or removed from treatment or the study will not be replaced.

4.2.2 Number of Sites

Approximately 290 investigative sites globally will be included in the study. Sites that do not enroll subjects within 6 months of site initiation may be closed.

4.3 Justification for Investigational Product Dose

4.3.1 Amgen Investigational Product Dose

The nonclinical profile of AMG 510 suggests that a high initial exposure (C_{max}), with enough residual exposure to inhibit a resynthesized pool of $KRAS^{G12C}$ could be ideal for inhibition of mutated KRAS in humans, while limiting exposure to non-target tissues.

Study 20170543 is the first clinical test of this hypothesis in subjects with *KRAS p.G12C* mutated solid tumors. Study 20170543 is a phase 1/2, multicenter, nonrandomized, open-label study of PO AMG 510 in subjects with *KRAS p.G12C* mutated advanced or metastatic NSCLC, CRC, or other solid tumors. The phase 1 portion of the study was conducted in 2 parts: part 1 - dose exploration and part 2 - dose expansion. Phase 1 part 1 was aimed at evaluating the safety, tolerability, PK, and pharmacodynamics of AMG 510 and determining the maximum tolerated dose (MTD) and/or a biologically active dose (eg, recommended phase 2 dose [RP2D]) of repeat QD dosing schedule in subjects with advanced *KRAS p.G12C* mutated solid tumors using a Bayesian Logistics Regression Model (BLRM) design. The evaluation period for DLTs was the first

treatment cycle (ie, 21 days after the first dose) of the dose exploration part of the study (part 1).

The phase 1 monotherapy dose exploration part of Study 20170543 has yielded early evidence of activity (even in this heavily pretreated population), as demonstrated by preliminary data. As of the 12 June 2019 data cutoff date, Study 20170543 had enrolled 62 subjects, 27 with NSCLC, 31 with CRC, and 4 with other solid tumors. Thirty-nine of the 62 enrolled subjects were evaluable for efficacy as of the 12 June 2019 data cutoff date. Preliminary results demonstrated antitumor activity in *KRAS p.G12C* mutated NSCLC, with 7 of 17 evaluable subjects having a PR (5 confirmed) and 8 subjects having stable disease (2 subjects had progression).

AMG 510 was well tolerated at the 180 mg QD to 960 mg QD dose levels tested (Section 2.2.2).

In conclusion, 960 mg QD PO AMG 510 was recommended as the dose to be administered for the phase 2 portion of the study. From a PK perspective, correlations were observed between AUC, C_{max}, and concentration at 24 hours ($C_{24\text{-hour}}$) (on both day 1 and day 8) and the percent change in sum of tumor lesion from screening to cycle 3, day 1. The types and frequency of adverse events at the 960 mg dose were consistent with those observed at lower doses, suggesting that the overall benefit-risk profile at 960 mg QD PO will be favorable.

4.3.2 Non-Amgen Investigational Product Dose

Docetaxel at a dose of 75 mg/m^2 was tolerable and yielded a favorable outcome in patients previously treated with platinum-based chemotherapy. Docetaxel at a dose of 100 mg/m^2, however, was associated with unacceptable hematologic toxicity, infections, and treatment-related mortality and this dose should not be used (eg, Taxotere® SmPC; Taxotere® United States Prescribing Information [USPI]). The dose of docetaxel in Study 20190009 is 75 mg/m^2 administered intravenously over 1 hour every 3 weeks, in accordance with the terms of the Taxotere® product information documentation.

4.4 End of Study

4.4.1 End of Study Definition

Primary Completion: The primary completion date is defined as the date when the last subject is assessed or receives an intervention for the final collection of data for the primary and key secondary endpoint(s).

If the study concludes prior to the primary completion date originally planned in the protocol (ie, early termination of the study), then the primary completion will be the date when the last subject is assessed or receives an intervention for evaluation in the study (ie, last subject last visit).

End of Study: The end of study date is defined as the date when the last subject across all sites is assessed or receives an intervention for evaluation in the study (ie, last subject last visit), following any additional parts in the study (eg, LTFU, additional antibody testing), as applicable.

4.4.2 Study Duration for Subjects

The total study duration is estimated to be up to 6.5 years. This includes a screening period of up to 28 days, duration of treatment for an individual subject of approximately 8 months followed by a**n** SFU visit that occurs 30 days (± 7 days) after the last dose of all study drug. After the SFU visit, subjects enter LTFU for up to 5 years.

4.5 Patient Input on Study Design

Feedback on general concepts around study design (eg, screening requirements, hospitalization, length of study), procedures, and the informed consent form (ICF) were considered based on a patient panel conducted by Amgen in patients with NSCLC.

5. Study Population

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).

Eligibility criteria will be evaluated during the screening period.

Before any study-specific activities/procedures, the appropriate written informed consent must be obtained (see Section 11.3).

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, will not be provided.

5.1 Inclusion Criteria

Subjects are eligible to be included in the study only if all of the following criteria apply:

101. Subject or subject's legally acceptable representative has provided informed consent prior to initiation of any study specific activities/procedures.
102. Age ≥ 18 years of age
103. Histologically or pathologically documented, locally-advanced and unresectable or metastatic NSCLC.

104. Have documentation of *KRAS p.G12C* mutation confirmed by central testing through the current protocol or have documentation of *KRAS p.G12C* mutation through Amgen Study 20190294 prior to enrollment.

105. Subjects will have received and progressed or experienced disease recurrence on or after receiving at least 1 prior systemic therapy for locally advanced and unresectable or metastatic disease. Prior treatment must include a platinum-based doublet chemotherapy and checkpoint inhibitor for advanced or metastatic disease, either given as one line of therapy or as individual lines of therapy unless the subject has a medical contraindication to one of the required therapies. If the subject has a medical contraindication to a required therapy, the subject may be enrolled only after the investigator discusses and obtains approval from the Amgen medical monitor.

    a) Adjuvant therapy will count as a line of therapy if the subject progressed on or within 6 months of adjuvant therapy administration.
    b) In locally advanced and unresectable NSCLC, disease progression on or within 6 months of end of prior curatively intended multimodal therapy will count as a line of therapy. If chemoradiation is followed by planned systemic therapy without documented progression between chemoradiation and systemic therapy, the entire treatment course counts as one line of therapy.
    c) Maintenance therapy following platinum doublet-based chemotherapy is not considered as a separate line of therapy.

106. Subjects must have archived tumor tissue samples (formalin fixed, paraffin embedded [FFPE] sample [FFPE of excisional, core needle, or fine needle aspirate] collected within 5 years) or be willing to undergo pre-treatment tumor biopsy (excisional, core needle, or fine needle aspirate) for tissue prior to enrollment.

107. Measurable disease per RECIST v1.1 criteria. Lesions previously radiated are not considered measurable unless they have progressed after radiation.

108. ECOG Performance Status of ≤ 1

109. Adequate hematologic laboratory assessments, defined as the following within 10 days prior to start of study therapy:

    a) Absolute neutrophil count (ANC) $\geq$ 1500 cells/μl (without granulocyte colony-stimulating factor support within 10 days of laboratory test used to determine eligibility)
    b) Hemoglobin $\geq$ 9.0 g/dL (without transfusion within 2 weeks of laboratory test used to determine eligibility)
    c) Platelet count $\geq$ 100 000/μl (without transfusion within 2 weeks of laboratory test used to determine eligibility)

110. Life expectancy of > 3 months, in the opinion of the investigator

111. Adequate liver function, defined as the following:

    a) Aspartate aminotransferase (AST) and, alanine aminotransferase (ALT) $\leq$ 2.5 times the upper limit of normal (ULN), except if alkaline phosphatase > 2.5 times the ULN, then AST and/or ALT must be $\leq$ 1.5 times the ULN
    b) Serum bilirubin $\leq$ 1.0 x ULN

112. International normalized ratio (INR) and activated partial thromboplastin time ≤ 1.5 x ULN

113. Serum creatinine ≤ 1.5 x ULN OR creatinine clearance ≥ 60 mL/min. Cockcroft-Gault formula will be used for creatinine clearance calculation. Twenty-four hour urine collection is not required but is allowed.

114. QTc ≤ 470 msec in females and ≤ 450 msec in males (based on average of screening triplicates)

115. Ability to take oral medications and willing to record daily adherence to investigational product

5.2 Exclusion Criteria

Subjects are excluded from the study if any of the following criteria apply:

Disease Related

201. Subjects have received prior docetaxel in unresectable or metastatic setting (including subjects who received prior docetaxel in first line for metastatic disease, but not including subjects who received prior docetaxel neoadjuvantly or adjuvantly and did not progress within 6 months of end of therapy).

202. Mixed small-cell lung cancer or mixed NSCLC histology

203. Previously identified driver mutation (according to local standard of care or guidelines) other than *KRAS p.G12C* for which an approved therapy is available (including EGFR, ALK, etc).

204. Active brain metastases. Subjects who have had brain metastases resected or have received whole brain radiation therapy ending at least 4 weeks (or stereotactic radiosurgery ending at least 2 weeks) prior to study day 1 are eligible if they meet all of the following criteria: a) residual neurological symptoms grade ≤ 2; b) on stable doses of dexamethasone or equivalent for at least 2 weeks, if applicable; and c) follow-up MRI performed within 30 days prior to enrollment shows no progression or new lesions appearing.

    Active brain metastases are defined as: Untreated brain lesions (new or progressing) and/or symptomatic brain lesions (symptoms as determined by the investigator), present at the time of study entry.

205. Leptomeningeal disease.

206. Uncontrolled pleural effusion, pericardial effusion, or ascites requiring recurrent drainage procedures at a frequency greater than monthly. Subjects with PleurX catheters in place may be considered for the study with Medical Monitor approval.

Other Medical Conditions

207. Known history of Human Immunodeficiency Virus (HIV) infection

208. Exclusion of hepatitis infection based on the following results and/or criteria:

    a) Positive hepatitis B surface antigen (HepBsAg) (indicative of chronic Hepatitis B or recent acute hepatitis B)

    b) Negative HepBsAg with a positive for hepatitis B core antibody (Hepatitis B core antibody testing is not required for screening, however if this is done and is positive, then hepatitis B surface antibody [Anti-HBs] testing is necessary.

Undetectable anti-HBs in this setting would suggest unclear and possible infection, and needs exclusion).

c) Positive Hepatitis C virus antibody: Hepatitis C virus RNA by polymerase chain reaction is necessary. Detectable Hepatitis C virus RNA renders the subject ineligible.

If above antibody/antigen testing is not able to be obtained, positive hepatitis B or C viral load

209. Malignancy other than NSCLC within 3 years prior to randomization, with the exception of those with a negligible risk of metastases or death and treated with expected curative outcome (such as adequately treated carcinoma in situ of the cervix, basal cell carcinoma, cutaneous squamous cell carcinoma, localized prostate cancer treated with curative intent, or ductal carcinoma in situ treated surgically with curative intent).

210. Major surgery within 28 days of study day 1

211. Significant gastrointestinal disorder that results in significant malabsorption, requirement for intravenous alimentation, or inability to take oral medication.

212. Significant cardiovascular disease, such as New York Heart Association cardiac disease (Class II or greater), myocardial infarction within 6 months prior to study day 1, unstable arrhythmias or unstable angina.

213. Severe infections within 4 weeks prior to randomization including, but not limited to hospitalization for complications of infection, bacteremia or severe pneumonia.

214. Therapeutic oral or intravenous antibiotics within 2 weeks prior to randomization. Prophylactic antibiotics are allowed with Amgen medical monitor approval.

215. Current CTCAE version 5.0 grade $\geq$ 2 peripheral neuropathy

Prior/Concomitant Therapy

216. Unresolved toxicities from prior anti-tumor therapy, defined as not having resolved to CTCAE version 5.0 grade 0 or 1, or to levels dictated in the eligibility criteria with the exception of alopecia (any grade allowed) or toxicities from prior anti-tumor therapy that are considered irreversible (defined as having been present and stable for > 6 months), endocrine adverse events that are stably maintained on appropriate replacement therapy.

217. Anti-tumor therapy (chemotherapy, antibody therapy, molecular targeted therapy, retinoid therapy, hormonal therapy [except for subjects with history of completely resected breast cancer with no active disease for over 3 years on long term adjuvant endocrine therapy], or investigational agent) within 4 weeks of study day 1; Please note that bisphosphonates or anti-Receptor Activator of Nuclear Factor Kappa Beta Ligand (anti-RANKL) antibody therapy is allowed if needed for management of hypercalcemia or for prevention of skeletal events.

218. Therapeutic or palliative radiation therapy within 2 weeks of study day 1. Subjects must have recovered from all radiotherapy related toxicity to CTCAE version 5.0 grade 1 or less with the exception of alopecia (any grade of alopecia allowed).

219. Other investigational procedures are excluded

220. Previous treatment with AMG 510 or other KRAS G12C inhibitor

221. History of severe hypersensitivity to docetaxel or to other drugs formulated with polysorbate 80, or known sensitivity to any of the products or components to be administered during dosing.

222. Use of known cytochrome P450 (CYP) 3A4 or P-gp sensitive substrates (with a narrow therapeutic window), within 14 days or 5 half-lives of the drug or its major active metabolite, whichever is longer, prior to study day 1 that was not reviewed and approved by the principal investigator and the Amgen medical monitor.

223. Use of strong inducers of CYP3A4 (including herbal supplements such as St. John's wort) within 14 days or 5 half-lives (whichever is longer) prior to study day 1 that was not reviewed and approved by the principal investigator and the Amgen medical monitor.

224. Use of warfarin. Other anticoagulation may be allowed with Amgen medical monitor approval

Prior/Concurrent Clinical Study Experience

225. Currently enrolled in another investigational device or drug study, or less than 4 weeks since ending another investigational device or drug(s), or receiving other investigational agent(s)

Other Exclusions

226. Female subject is pregnant or breastfeeding or planning to become pregnant or breastfeed during treatment and for an additional 7 days after the last dose of AMG 510 or during treatment with docetaxel and 6 months after last dose of docetaxel if planning to become pregnant.

227. Female subjects of childbearing potential unwilling to use 1 highly effective method of contraception during treatment and for an additional 7 days after the last dose of AMG 510 and 6 months after the last dose of docetaxel.

228. Female subjects of childbearing potential with a positive pregnancy test assessed at Screening or day 1 by a serum pregnancy test and/or urine pregnancy test.

229. Male subjects with a female partner of childbearing potential who are unwilling to practice sexual abstinence (refrain from heterosexual intercourse) or use contraception during treatment and for an additional 7 days (AMG 510) or 6 months (docetaxel) after the last dose of investigational product.

230. Male subjects with a pregnant partner who are unwilling to practice abstinence or use a condom during treatment and for an additional 7 days (AMG 510) or 6 months (docetaxel) after the last dose of investigational product.

231. Male subjects unwilling to abstain from donating sperm during treatment and for an additional 7 days (AMG 510) or 6 months (docetaxel) after the last dose of investigational product. Refer to Section 11.5 for additional contraceptive information.

232. Subject likely to not be available to complete all protocol-required study visits or procedures, and/or to comply with all required study procedures (eg, Clinical Outcome Assessments) to the best of the subject and investigator's knowledge.

233. History or evidence of any other clinically significant disorder, condition or disease (with the exception of those outlined above) that, in the opinion of the investigator or Amgen physician, if consulted, would pose a risk to subject safety

or interfere with the study evaluation, procedures or completion, or interpretation of results.

5.3 Subject Enrollment

Before subjects begin participation in any study-specific activities/procedures, Amgen requires a copy of the site's written IRB/independent ethics committee (IEC) approval of the protocol, ICF, (and all other subject information and/or recruitment material, if applicable [see Section 11.3]).

The subject or the subject's legally acceptable representative must personally sign and date the IRB/IEC and Amgen approved informed consent before commencement of study-specific 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 on the enrollment case report form (CRF).

Each subject who enters into the screening period for the study (defined as 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 by Interactive Response Technology (IRT). 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.

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. This number will not necessarily be the same as the randomization number assigned for the study.

5.4 Screen Failures

Screen failures are defined as subjects who consent to participate in the clinical study but are not subsequently enrolled in the study. A minimal set of screen failure information will be collected that includes demography, screen failure details, eligibility criteria, medical history, prior therapies, and any serious adverse events.

Individuals who do not meet the criteria for participation in this study (screen failure) due to reasons other than *KRAS p.G12C* mutation status may be rescreened once (total number of possible screenings ≤ 2). Refer to Section 8.1.1.

Subjects who experience a technical failure of laboratory samples at screening (for example sample is lost or damaged in transit, or otherwise cannot be analyzed) will not

be considered a screen failure. Lab samples may be retested during screening in such cases, provided the screening window will not be exceeded.

Central confirmation of *KRAS p.G12C* status (if applicable), and the following assessments do not have to be repeated during rescreening, if they were performed as standard of care or during the initial screening attempt within the time frames specified below:

- Infectious hepatitis serology assessments and/or viral load does not need to be repeated if it was performed within 6 weeks prior to enrollment with AMG 510 or docetaxel.
- Imaging assessments do not need to be repeated if they were performed within 28 days prior to cycle 1 day 1 with AMG 510 or docetaxel.

Any other assessments do not need to be repeated if they were performed within the specified time frame prior to enrollment with AMG 510 or docetaxel;

6. Treatments

Study treatment is defined as any investigational product(s), non-investigational product(s), placebo, or medical device(s) intended to be administered to a study subject according to the study protocol.

Note that in several countries, investigational product and non-investigational product are referred to as investigational medicinal product and non-investigational medicinal product, respectively.

The Investigational Product Instruction Manual (IPIM), a document external to this protocol, contains detailed information regarding the storage, preparation, destruction, and administration of each treatment.

6.1 Treatment(s) Administered

6.1.1 Investigational Products

AMG 510 and docetaxel are the investigational products used in this study. The details of these drug treatments are shown in Table 6-1 below.

Table 6-1. Study Treatments

Study Treatment Name	Amgen Investigational Product:[a] AMG 510	Non-Amgen Investigational Product: Docetaxel
Dosage Formulation	Solid dosage form in strengths of 120 mg. The 120 mg coated tablet is presented as film-coated yellow, oblong, debossed tablet. Excipients used in the tablets include lactose monohydrate, microcrystalline cellulose, croscarmellose sodium, magnesium stearate and Opadry® II Yellow.	20 mg/1 mL single dose vial: 20 mg docetaxel in 1 mL in 50/50 (v/v) ratio polysorbate 80/dehydrated alcohol 80 mg/4 mL single-dose vial: 80 mg docetaxel in 4 mL 50/50 (v/v) ratio polysorbate 80/dehydrated alcohol
Unit Dose Strength(s)/ Dosage Level(s) and Dosage Frequency	960 mg/QD	75 mg/m^2 every 3 weeks
Route of Administration	Oral	IV
Accountability	The amount dispensed, amount returned, date dispensed, start and stop date, date returned, and lot number of investigational product are to be recorded on each subject's CRF	The planned dose, quantity administered, start date/time, stop date/time, lot number are to be recorded on each subject's CRF
Dosing Instructions	AMG 510 will be dispensed at the clinic by a qualified staff member. For the first 2 cycles, subjects will be instructed to take their AMG 510 dose in the clinic after all pre-dose assessments have been performed during clinic visit days. Subjects will take AMG 510 at home on non-clinic visit days. Subject should take the AMG 510 dose (all tablets at the same time) with or without food at approximately the same time every day (see Section 6.7.2 for concomitant administration of AMG 510 with proton-pump inhibitors [PPIs]). The AMG 510 dose should also not be taken more than 2 hours earlier than the scheduled time. The AMG 510 dose should not be taken more than 6 hours after the dosing time **(based on the previous day's dose)**. **Do not take 2 doses at the same time to make up for the missed dose.** A dose of AMG 510 can be replaced in the event of vomiting if the vomiting occurs within 15 minutes of the dosing, all tablets administered have been accounted for (eg, 4 tablets must be collected if 4 tablets were administered) and are intact by visual inspection (not broken, partially dissolved, chewed, or crushed). A dosing diary will be provided for subjects to record their adherence to the oral medication. Additional information relating to pH-elevating agents may be collected for subjects randomized to AMG-510, if needed.	Docetaxel will be infused at the clinic by a qualified staff member over a time frame of 1 hour (additional administration time allowed as per local guidelines).

CRF = case report form; IV = intravenous; QD = once daily; PPIs = proton-pump inhibitor**(s)**
[a] AMG 510 will be manufactured and packaged by Amgen and distributed using Amgen clinical study drug distribution procedures.

6.1.2 Non-investigational Products

There will be no non-investigational products in Study 20190009.

6.1.3 Medical Devices

No investigational medical devices will be used in the conduct of this study.

Other non-investigational medical devices may be used in the conduct of this study as part of standard care.

Non-Amgen non-investigational medical devices (eg, syringes, sterile needles), that are commercially available are not usually provided or reimbursed by Amgen (except, for example, if required by local regulation). The investigator will be responsible for obtaining supplies of these devices.

6.1.4 Other Protocol-required Therapies

All other protocol-required therapies including, pre- and post-infusion medications for docetaxel, that are commercially available will not be provided or reimbursed by Amgen (except if required by local regulation). The investigator will be responsible for obtaining supplies of these protocol-required therapies.

6.1.4.1 Pre- and Post-infusion Medications for Docetaxel

Subjects receiving docetaxel should be premedicated with oral corticosteroids, such as dexamethasone 8 mg twice daily for 3 days starting 1 day prior to docetaxel administration (or as per local guidance) to reduce the incidence and severity of fluid retention and severity of hypersensitivity reactions. Antiemetic medication may be administered on the day of docetaxel infusion as per institutional guidelines.

6.1.5 Other Treatment Procedures

6.1.5.1 Biopsies

Tumor Biopsy for Enrollment: When archival tumor tissue is not available, collection of new tumor tissue is required, as described in Section 8.2.7.3.

Optional Tumor Biopsy for Biomarkers: Additional tissue biopsy samples will be collected at disease progression for exploratory biomarkers related to mechanisms of primary and secondary resistance.

Biomarker assessment can be done only if the biomarker research is allowed according to local regulations and agreed by the local EC/IRB.

Mandatory Tumor Biopsy for Continued Treatment with AMG 510 Beyond Radiologic Progression: In order to continue to receive AMG 510 beyond radiologic

progression, the subject must be willing to undergo biopsy of one of the new or progressing lesions as well as meet criteria listed in Section 8.1.6. If tumor biopsy is not clinically feasible or advisable, the subject may continue on treatment with AMG 510 beyond radiologic progression only upon agreement with investigator and the Amgen Medical Monitor.

Biomarker assessment can be done only if the biomarker research is allowed according to local regulations and agreed by the local EC/IRB.

6.1.6 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, or device after it is released for distribution to market or clinic by either **(1)** Amgen or **(2)** distributors **or** partners for whom Amgen manufactures the material. **This includes all components distributed with the drug, such as packaging drug containers, delivery systems, labeling, and inserts.**

This includes any investigational/non-investigational products provisioned and/or repackaged/modified by Amgen. AMG 510 and docetaxel are the investigational products in this study for which Amgen wants to collect complaints.

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

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

The following medications and supplements to be avoided for times stated prior to study day 1, and during the study period unless reviewed and approved by the principal investigator and the Amgen medical monitor:

- Known strong inducers of CYP 3A4 including herbal supplements, such as St. John's wort within 14 days or 5 half-lives (whichever is longer) prior to study day 1
- Known CYP 3A4 or P-gp sensitive substrates with a narrow therapeutic window within 14 days or 5 half-lives of the drug or its major active metabolite, whichever is longer, prior to study day 1

If a subject needs palliative radiotherapy for pain control during the course of the study, **the sponsor should be notified prior to initiation of therapy (**as soon as possible**) and** all study drugs should be withheld **during radiation therapy and for 7 days after completion of radiation therapy**. A subject may be allowed to resume study drug after

discussion between the Amgen medical monitor and the investigator to determine the appropriateness of treatment resumption.

Subjects must not schedule any major elective surgeries within 28 days of study day 1, during the treatment period, and for at least 28 days after the last administration of AMG 510. Minor elective surgery may be allowed after discussion with the Amgen medical monitor. If a subject undergoes any unexpected surgery during the course of the study, all study drugs must be withheld, and the investigator or designee should notify the sponsor as soon as possible. A subject may be allowed to resume investigational product only if both the investigator and Amgen medical monitor agree to restart study therapy.

See Section 6.7.2 for more details about concomitant medications.

A complete list of excluded treatments are listed in the exclusion criteria (Section 5.2).

6.2 Dose Modification

6.2.1 Dose-cohort Study Escalation/De-escalation and Stopping Rules

There are no dose-cohort study escalation/de-escalation and/or stopping rules in Study 20190009.

6.2.2 Dosage Adjustments, Delays, Rules for Withholding or Restarting, Permanent

6.2.2.1 Amgen Investigational Product: AMG 510

The reason for dose change of AMG 510 is to be recorded on each subject's CRF. All subjects randomized to the AMG 510 group will receive AMG 510 at a starting dose of 960 mg QD. Dose reduction levels of AMG 510 for toxicity management of individual subjects are provided in Table 6-2. AMG 510 will be discontinued, temporarily delayed or dosage temporarily reduced, in the event of a toxicity that, in the opinion of the investigator, warrants the discontinuation, or dose reduction as indicated in Table 6-3. Up to two dose reductions are allowed. Dose reductions below 240 mg are not allowed. Subjects who experience an adverse event requiring dose reductions below 240 mg should be permanently discontinued from AMG 510 treatment.

If day 1 of a cycle is delayed, day 1 of subsequent cycles should be adjusted accordingly to maintain the 21-day cycle duration. However, if a within-cycle dose is held the missed dose will not be made up and day 1 of subsequent cycles should not be adjusted.

Table 6-2. Dose Reductions for AMG 510

AMG 510 Doses		
Starting Dose	Dose -1	Dose -2
960 mg QD	480 mg QD	240 mg QD

QD = once daily.

Table 6-3. AMG 510 Dose Modification Guidelines for Hematologic and Non-hematologic Toxicities

Toxicity	Recommended Action [a]	
	Hold Until:	Restart Dose:
Hematologic toxicities		
Grade ≥ 3 thrombocytopenia	Recovery to grade 1 or less or to baseline grade (without platelet transfusion in last 7 days)	• resume dosing at 1 dose decrement
Grade ≥ 3 febrile neutropenia, or grade ≥ 3 neutropenia lasting longer than 7 days	Recovery to grade 1 or less or to baseline grade	• resume dosing at 1 dose decrement
Grade 4 hemoglobin decrease	Recovery to grade 1 or less or to baseline grade	• resume dosing at 1 dose decrement
Nonhematologic toxicities		
Grade ≥ 3 nausea, vomiting, or diarrhea lasting longer than 3 days despite optimal medical support	Recovery to grade 1 or less or to baseline grade	• resume dosing at 1 dose decrement
Suspected interstitial lung disease (ILD)/pneumonitis of any grade	**ILD/pneumonitis confirmed or excluded**	• **if confirmed, permanently discontinue AMG 510** • **if excluded, restart at same dose if no other AMG 510 dose modification guidelines are applicable.**
Any other drug-related nonhematologic toxicity ≥ grade 3[c]	Recovery to grade 1 or less or to baseline grade ≤ 4 weeks from toxicity event	• resume dosing at 1 dose decrement
	Recovery to grade 1 or less or to baseline grade > 4 weeks from toxicity event	• resume dosing at 2 dose decrement [b]

[a] If these toxicity events occur after the first dose reduction, then a second dose reduction is permitted. If toxicities continue after 2 dose decrements, then the subject should be discontinued from the study and enter the follow-up phase.
[b] If 2 dose decrements are not possible (for example if the subject has already had 2 dose reductions), subject should be discontinued from the study and enter the follow-up phase.
[c] For suspected hepatotoxicity, refer to Section 6.2.3 and Section 11.7.
Note: Subjects may be resumed at a lower dose with the recommended restarting dose after discussion with the medical monitor.

Note: If renal dysfunction has a clear etiology unrelated to AMG 510 and in the opinion of the investigator, is not expected to recur, no dose reduction may be needed after recovery, but this requires investigator discussion with Amgen medical monitor for approval.

6.2.2.2 Non-Amgen Investigational Product(s): Docetaxel

The reason for dose change of docetaxel is to be recorded on each subject's CRF. Dose reduction levels of docetaxel for toxicity management of individual subjects are provided in Table 6-4. Docetaxel will be discontinued or dosage reduced, in the event of a toxicity that, in the opinion of the investigator, warrants the discontinuation, or dose reduction as indicated in Table 6-5.

If docetaxel treatment was held or delayed by > 21 days, that dose will be deemed to have been missed and the subject will proceed to the next scheduled treatment visit. If docetaxel administration is held or delayed ≤ 21 days, day 1 of subsequent cycles should be adjusted accordingly to maintain the 21-day cycle duration.

Table 6-4. Dose Decrements for Docetaxel

Docetaxel Doses (mg/m^2)			
Starting Dose	Dose -1	Dose -2	Dose -3
75	55	37.5	Discontinue

Table 6-5. Docetaxel Dose Modification Guidelines for Hematologic and Non-hematologic Toxicities

	Recommended Action[a]	
Toxicity[c]	**Hold Until[b]:**	**Restart Dose:**
Hematologic toxicities		
≥ grade 3 drug related thrombocytopenia associated with bleeding	No restart permitted	• permanently discontinue treatment
Febrile neutropenia	Recovery to grade 1 neutropenia or less or to baseline grade	• resume dosing at 1 dose decrement
Neutrophils < 500 cells/mm^3 for more than 1 week	Recovery to grade 1 or less or to baseline grade	• resume dosing at 1 dose decrement
Grade 4 anemia (low hemoglobin)	Recovery to grade 1 or less or to baseline grade (without blood transfusion in last 7 days)	• resume dosing at 1 dose decrement
ANC < 1500 cells/mm^3	Recovery to a level > 1500 cells/mm^3	• resume dosing at 1 dose decrement
Nonhematologic toxicities		
Severe or cumulative cutaneous reactions	Recovery to grade 1 or less or to baseline grade	• resume dosing at 1 dose decrement
Other grade 3 or 4 non-hematological toxicities	Recovery to grade 1 or less or to baseline grade	• resume dosing at 1 dose decrement
≥ grade 3 peripheral neuropathy	No restart permitted	• permanently discontinue treatment
Bilirubin > ULN or if AST and/or ALT > 1.5 x ULN concomitant with alkaline phosphatase > 2.5 x ULN.	Recovery to normal liver function	• resume dosing at 1 dose decrement
≥ grade 3 AST or ALT elevation related to drug for > 2 weeks	No restart permitted	• permanently discontinue treatment
Concurrent AST or ALT > 3 x ULN and total bilirubin > 2 x ULN if related to drug	No restart permitted	• permanently discontinue treatment
Severe hypersensitivity reactions	No restart permitted	• permanently discontinue treatment

ALT = alanine aminotransferase; ANC = absolute neutrophil count; AST = aspartate aminotransferase; ULN = upper limit of normal.

[a] If these toxicity events occur after the first dose reduction, then a second dose reduction is permitted. A third dose reduction is not permitted, and if toxicities continue after 2 dose decrements, then the subject should be discontinued from the study and enter the follow-up phase

[b] Subjects requiring more than 4 weeks to recover from docetaxel related grade ≥ 3 toxicities should be discontinued from study

[c] Subjects with impaired vision should undergo prompt and comprehensive ophthalmologic examination. If cystoid macular edema is diagnosed, docetaxel should be discontinued and appropriate treatment initiated

6.2.3 Hepatotoxicity Stopping and Re-Challenge Rules

Unless specified otherwise in Section 6.2.2.2, refer to Section 11.7 for details regarding drug-induced liver injury guidelines, as specified in the *Guidance for Industry Drug-Induced Liver Injury: Premarketing Clinical Evaluation, July 2009*.

Guidelines for management and monitoring of subjects with increased AST, ALT, or ALP are presented in Table 6-6.

Table 6-6. AMG 510 Hepatoxicity Guidelines

If the conditions for permanent discontinuation are met (below): Participant to be permanently discontinued

AST or ALT >3x ULN and INR > 1.5x ULN (for subjects not on anticoagulation therapy) in the presence of no important alternative causes for elevated AST/ALT values

OR

AST or ALT > 3x ULN and TBL > 2x ULN in the presence of no important alternative causes for elevated AST/ALT and/or TBL values

If conditions are not met: Exclude other causes[a]
Upon failure to identify any other causes and AMG 510 relation to increase in LFTs cannot be excluded, proceed with guidelines below:

CTCAE Grade	AMG 510 Action	Medical Management	Monitoring and Follow-up
Grade 2 AST or ALT and ALP ≤ 8 x ULN with no clinical symptoms consistent with hepatitis (right upper quadrant pain/tenderness, fever, nausea, vomiting, and jaundice)	Continue	Consider steroids[b]	Closely monitor liver function tests
Grade 2 AST or ALT with symptoms Or Grade 3 or 4 AST or ALT Or > 8 x ULN ALP[d]	**First Occurrence**	Initiate steroids[b]	Closely monitor liver function tests Await resolution to baseline or grade 1 and resolution or improvement of hepatitis symptoms Restart at 1 dose level reduction[c, e]
	Withhold		
	Second Occurrence	Initiate steroids[b]	Closely monitor liver function tests Await resolution to baseline or grade 1 and resolution or improvement of hepatitis symptoms Resume at an additional 1 dose level reduction only with MEDICAL MONITOR approval[c, e]
	Withhold		
	Third Occurrence	**NOT APPLICABLE**	
	Permanently discontinue AMG 510		

ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; CTCAE = Common Terminology Criteria for Adverse Events; INR = international normalized ratio; LFT = liver function test; TBL = total bilirubin; ULN = upper limit of normal

[a] If increase in AST/ALT is likely related to alternative agent, discontinue causative agent and await resolution to baseline or grade 1 prior to resuming AMG 510.

[b] Example: prednisone 1.0 **to 2.0** mg/kg/day**, dexamethasone equivalent, or methylprednisolone** equivalent, followed by a taper. **The taper may occur after restarting AMG 510.**

[c] Close monitoring at restart (eg, daily LFTs x 2, then weekly x 4).

[d] AMG 510 dose may be increased after discussion with medical monitor.

[e.] There is no limit to the number of AMG 510 re-challenges for isolated alkaline phosphatase elevations that resolve to baseline or grade 1.

[f.] Dose decrements below 240 mg are not allowable.

6.3 Preparation/Handling/Storage/Accountability

Guidance and information on preparation, handling, storage, accountability, destruction, or return of the investigational product during the study are provided in the IPIM.

6.4 Measures to Minimize Bias: Randomization and Blinding

6.4.1 Method of Treatment Assignment

Subjects will be randomized in a 1:1 allocation ratio, to either AMG 510 or docetaxel, in an open-label manner after meeting all enrollment requirements.

The randomization will be performed by IRT and the randomization number will be provided to the site by the IRT system.

The randomization will be stratified by number of prior lines of therapy in advanced disease (1 versus 2 versus > 2), race (Asian versus non-Asian), and history of CNS involvement (present or absent).

The randomization date is to be documented in the subject's medical record and on the enrollment CRF.

6.4.2 Blinding

This is an open-label study; blinding procedures are not applicable.
Amgen pre-defined authorized roles with a business need for access and handling of data should follow standard operational procedures for restricted data in open-label randomized trials (SOP-428127, effective 08 Jan 2018). Aggregated safety and efficacy data should only be disclosed to the study team at protocol prespecified analyses. Authorized roles with access to ongoing clinical trial data should emphasize precautions to maintain aggregated-level data confidentiality in study team interactions and not let it influence their input into any changes to the study design or conduct.

6.5 Treatment Compliance

Treatment compliance on AMG 510 will be documented in the medical records and will be collected in the CRF and through subject input into an electronic diary. Subjects are required to bring bottle(s) of AMG 510 as per guidance in the Investigational Product Instruction Manual and return the remaining pills when they come off treatment. Pill counts will be collected by the study staff, and at treatment discontinuation, or SFU. eDiary must be completed daily with the response yes (if IP taken) or no (in the event of dose interruption due to adverse event, etc).

6.6 Treatment of Overdose

6.6.1 AMG 510 Overdose

The effects of overdose of AMG 510 are not known. There are no AMG 510 specific antidotes. Consultation with the Amgen medical monitor is required for prompt reporting of clinically apparent or laboratory adverse events possibly related to overdosage. Consultation with the Amgen medical monitor is also required even if there are no adverse events, in order to discuss further management of the subject. If the overdose results in clinically apparent or symptomatic adverse events, the subject should be followed carefully until all signs of toxicity are resolved or returned to baseline and the adverse event(s) should be recorded/reported per Section 11.4.

6.6.2 Docetaxel Overdose

There is no known antidote for docetaxel overdosage. In case of overdosage, the subject should be kept in a specialized unit where vital functions can be closely monitored. Anticipated complications of overdosage include: bone marrow suppression, peripheral neurotoxicity, and mucositis. Subjects should receive therapeutic Granulocyte-colony stimulating factor (G-CSF) as soon as possible after discovery of overdose. Other appropriate symptomatic measures should be taken, as needed (see regional labeling for Taxotere®).

6.7 Prior and Concomitant Treatment

6.7.1 Prior Treatment

Prior anticancer therapies must date back to the original diagnosis and will be collected through enrollment on the appropriate eCRF. For prior anticancer therapies collect the regimen/agent, type of therapy, setting, start date, stop date, reason for stopping therapy, dose, unit, route, frequency, best response, date of best response, and date of progression documented. For prior radiotherapy for current malignancy, collect body site, sub site, setting, type, start date, stop date, total dose, unit, best response, was chemotherapy part of concurrent therapy, did documented progression occur in this area, date progression documented. For prior surgeries for current malignancies collect date of surgery, surgery, reason for surgery, body site, subsite, intent of surgery, residual disease.

All other prior therapies that were being taken 28 days before enrollment through enrollment should be collected on each subject's eCRF(s). Collect therapy name, indication, dose, unit, frequency, route, start date and stop date.

6.7.2 Concomitant Treatment

Avoid coadministration with proton pump inhibitors (PPIs) and H2 receptor antagonists. If an acid-reducing agent cannot be avoided, administer AMG 510 4 hours before or 10 hours after a local antacid. **Breast cancer resistance protein (BCRP) substrates should be used with caution when co-administered with AMG 510, which may increase the circulating concentrations of BCRP substrates.**

Throughout the study, investigators may prescribe any concomitant medications or treatments deemed necessary to provide adequate supportive care except for those listed in Section 6.1.7.

Concomitant therapies are to be collected from enrollment through the end of SFU period (30 days after the last dose of all study drugs). Subsequent treatment for NSCLC will be recorded after the SFU period during the LTFU. For all concomitant therapies, collect therapy name, indication, dose, unit, frequency, route, start date and stop date and record on Concomitant Medications eCRF. Supplemental oxygen use should be captured in the concomitant medication eCRF.

7. Discontinuation Criteria

Subjects have the right to withdraw from investigational product and/or other protocol-required therapies, protocol procedures, or the study as a whole at any time and for any reason without prejudice to their future medical care by the physician or at the institution.

The investigator and/or sponsor can decide to withdraw a subject(s) from investigational product, device, and/or other protocol-required therapies, protocol procedures, or the study as a whole at any time prior to study completion for the reasons listed in Sections 7.1, 7.2.1, and 7.2.2.

7.1 Discontinuation of Study Treatment

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. 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 possibilities for continuation of the Schedule of Activities (Table 1-1 and Table 1-2) including different options of follow-up (eg, in person, by phone/mail, through family/friends, in correspondence/communication with other treating physicians, from the

review of medical records) and collection of data, including endpoints, adverse events, and must document this decision in the subject's medical records. Subjects who have discontinued investigational product and/or other protocol-required therapies or procedures should not be automatically removed from the study. Whenever safe and feasible, it is imperative that subjects remain on-study to ensure safety surveillance and/or collection of outcome data.

Subjects may be eligible for continued treatment with Amgen investigational product(s) and/or other protocol-required therapies in a separate protocol or as provided for by the local country's regulatory mechanism, based on parameters consistent with Section 11.3.

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

- Decision by Sponsor
- Lost to follow-up
- Death
- Adverse event
- Subject request
- Ineligibility determined
- Protocol deviation
- Non-compliance
- Disease progression
- Requirement for alternative therapy
- Pregnancy

7.2 Discontinuation From the Study

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 long-term follow up. Subject data up to withdrawal of consent will be included in the analysis of the study, and where permitted, publicly available data can be included after withdrawal of consent. The investigator is to discuss with the subject appropriate procedures for withdrawal from the study, and must document the subject's decision to withdraw in the subject's medical records.

If a subject withdraws from the study, he/she may request destruction of any samples taken and not tested, and the investigator must notify Amgen accordingly (see Section 11.6 for further details). Refer to the Schedule of Activities (Table 1-1 and

Table 1-2) for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed.

7.2.1 Reasons for Removal From Washout Period, Run-in Period, or Invasive Procedures

Not Applicable.

7.2.2 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

7.3 Lost to Follow-up

A subject will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a subject fails to return to the clinic for a required study visit:

- The site must attempt to contact the subject and reschedule the missed visit as soon as possible and counsel the subject on the importance of maintaining the assigned visit schedule and ascertain whether or not the subject wishes to and/or is able to continue in the study.
- In cases in which the subject is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the subject (where possible, 3 telephone calls and, if necessary, a certified letter to the subject's last known mailing address or local equivalent methods). These contact attempts are to be documented in the subject's medical record.
- If the subject continues to be unreachable, he/she will be considered to have withdrawn from the study with a primary reason of lost to follow-up.
- For subjects who are lost to follow-up, the investigator can search publicly 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.

8. Study Assessments and Procedures

Study procedures and their time points are summarized in the Schedule of Activities (see Table 1-1 and Table 1-2).

As protocol waivers or exemptions are not allowed if an enrolled subject is subsequently determined to be ineligible for the study, this must be discussed with the sponsor immediately upon occurrence or awareness to determine if the subject is to continue or discontinue study treatment.

Adherence to the study design requirements, including those specified in the Schedule of Activities, is essential and required for study conduct.

Ongoing subjects who are unable or unwilling to attend protocol-specified trial visits and procedures, due to COVID-19, should generally remain on study even if AMG 510 is interrupted, as continued collection of even limited clinical information is valuable for safety and efficacy assessments. In cases where the subject is unable to visit the site, Amgen has explored alternative methods for safety assessments and continuation of study medication (eg, phone contact, virtual visit, alternative location for assessment including local labs or radiological assessment, direct to subject shipment of Investigational Product where possible). Each case should be discussed with the medical monitor before temporary adjustments are made to the subject's schedule of activities.

8.1 General Study Periods

8.1.1 Screening, Enrollment and/or Randomization

Informed consent must be obtained before completing any screening procedure or discontinuation of standard therapy for any disallowed therapy. After the subject has signed the ICF, the site will register the subject in the IRT and screen the subject in order to assess eligibility for participation. Imaging scans obtained as part of standard of care prior to signing consent may be used for screening provided they meet the time windows specified in the study. The screening window is up to 28 days from C1D1.

All screening evaluations must be completed and reviewed to confirm that potential subjects meet all eligibility criteria, including confirmation of positive *KRAS p.G12C* mutation status. Central confirmation of *KRAS p.G12C* mutation status is required before randomization. The investigator will maintain a screening log to record details of all subjects screened and to confirm eligibility or record reasons for screening failure, (see Section 5.4) as applicable.

If a subject has not met all eligibility criteria at the end of the screening period, the subject will be registered as a screen fail. Screen fail subjects may be eligible for re-screening 1 additional time, unless the failure was due to *KRAS p.G12C* mutation status, in which case the subject cannot rescreen.

Rescreen subjects must first be registered as screen failures in IRT and subsequently registered as rescreens. Once the subject is registered as rescreened, a new 28-day screening window will begin. Subjects will retain the same subject identification number

assigned at the original screening. If the rescreening period begins more than 28 days after the original signing of the ICF, all screening procedures, including informed consent, must be repeated if they are out of window.

8.1.2 Treatment Period

Visits will occur per the Schedule of Activities (Table 1-1 and Table 1-2). On-study visits may be completed within 3 days of the scheduled visit. The date of the first dose of investigational product is defined as day 1. All subsequent doses and study visits will be scheduled based on the day 1 date. For subjects randomized to AMG 510, administration of AMG 510 is to be administered during the clinic visit on day 1 and day 8 of the first cycle, day 1 of the second cycle, and outside of the clinic on other days of the cycle, and during subsequent cycles.

Images are to undergo independent central confirmation of progression as described in Section 8.2.2.1.2.

8.1.3 Safety Follow-up

Upon permanent discontinuation from the study treatment for any reason, a SFU visit will be performed 30 days (± 7 days) after the end of the last dosing interval of investigational product.

Safety follow-up is to be performed upon completion of any and all of the following: initial study treatment, crossover treatment, and treatment beyond progression treatment.

8.1.4 Long-term Follow-up

Following the SFU visit (30 days ± 7 days after the end of the last dosing interval of investigational product), there will be an LTFU period, during which data will be collected on the subjects' health condition, disease status, and subsequent anticancer treatment. Safety follow-up must be completed prior to moving into LTFU.

For subjects who discontinued study treatment without independent central confirmation of progression or without start of subsequent anticancer treatment (excluding the administration of single agent docetaxel), tumor assessments will continue at the same frequency during LTFU, but with a larger window in which assessments can be completed (every 6 weeks from cycle 1 day 1; [at weeks 7, 13, 19, 25, 31, 37, 43, and 49], and then at 9 week intervals thereafter [± 4 weeks]) from SFU until independent central confirmation of progression per RECIST v1.1, start of subsequent anticancer treatment, death, withdrawal of consent, loss to follow-up, or end of study.

Subjects who have had independent central confirmation of progression or started subsequent anticancer treatment (other than single agent docetaxel), will be followed via telephone or visit (clinic or virtual [eg, Tele-Health]) every 12 weeks (± 4 weeks) (or ad hoc to support analysis) for assessment of survival and documentation of anticancer treatment. Subjects will be followed for 5 years after last subject enrolled, or until withdrawal of consent, loss to follow-up, or subject death, whichever occurs first. When the last subject has completed LTFU, the final analysis will occur.

8.1.5 End of Study

The end of study visit for an individual subject is defined as the date of the final study contact (eg, LFTU visit) when assessments or procedures are done.

8.1.6 Continuation on AMG 510 Treatment After Independent Central Confirmation of Progression at the time of First PD

This section details the conditions necessary to allow continued treatment with AMG 510 post disease progression. If, in the investigator's opinion, it is believed that the subject will continue to have clinical benefits from AMG 510, the subject may continue on AMG 510 after radiographic progression provided all of the following criteria below are met. The decision to continue on treatment beyond progression is at the discretion of the PI.

- Documentation of progressive disease per RECIST v1.1
- PD imaging must undergo independent central confirmation. If a subject has been deemed to have objective disease progression according to investigator tumor assessment by RECIST v1.1, but is imaging does not undergo independent central confirmation, subject is not eligible to continue AMG 510 beyond progression
- Signed separate informed consent for AMG 510 treatment beyond radiologic progression.
- Absence of threat to vital organs or critical anatomical sites (eg, CNS metastasis, respiratory failure due to tumor compression, spinal cord compression) requiring urgent alternative medical intervention.
- No other treatment discontinuation criteria are met (Table 6-6 and Table 11-2).
- No significant, unacceptable, or irreversible toxicities related to any dose of the study treatment or treatment-related adverse events of CTCAE grade 4 at the current dose at the time of progression.
- No current signs or symptoms of clinical disease progression that have decreased the ECOG performance status to ≥ 2.
- Disease progression is in one of the following settings: small or oligometastasis candidate for stereotactic body radiation therapy (SBRT), palliative radiation, or surgery
- The subject is willing to undergo biopsy of one of the new or progressing lesions (only if biomarker research is allowed according to local regulations and agreed by

local EC/IRB). If tumor biopsy is not clinically feasible or advisable, the subject may continue only upon agreement with investigator and the Amgen Medical Monitor.

- Approval for continuation from the Amgen Medical Monitor
- Palliative radiation and/or surgery for new, progressive, or symptomatic lesions is permitted prior to crossover, but AMG 510 must be held until after completion of these treatments and until 7 days after completion of radiation.
- If the time between the subject's initial progression scan and the restart of AMG 510 is > 28 days, the scan must be repeated to serve as the new baseline.
- All protocol-mandated procedures must be performed as noted in the protocol (imaging, labs, and clinic visits may be obtained earlier per clinical judgment and if clinically indicated).
- Continued growth of tumor(s) on a subsequent scan should result in permanent discontinuation of the study drug.

For subjects who continue treatment beyond radiologic progression, the date of first progression, will be used for PFS analysis and subject's response post first progression will not be used for the primary analyses to evaluate objective response endpoints including PFS, ORR, DOR, T**T**R, and DCR.

Biomarker assessment can be done only if the biomarker research is allowed according to local regulations and agreed by the local EC/IRB.

8.1.7 Continuation on Docetaxel Treatment After Independent Central Confirmation of Progression at the Time of First PD

This section details the conditions necessary to allow continued treatment with docetaxel post disease progression. If, in the investigator's opinion, it is believed that the subject will continue to have clinical benefits from docetaxel, the subject may continue on docetaxel after radiographic progression provided all of the following criteria below are met. The decision to continue on treatment beyond progression is at the discretion of the PI.

- Documentation of progressive disease per RECIST v1.1
- PD imaging must undergo independent central confirmation. If a subject has been deemed to have objective disease progression according to investigator tumor assessment by RECIST v1.1, but is imaging does not undergo independent central confirmation, subject is not eligible to continue docetaxel beyond progression
- Signed separate informed consent for docetaxel treatment beyond radiologic progression.
- Absence of threat to vital organs or critical anatomical sites (eg, CNS metastasis, respiratory failure due to tumor compression, spinal cord compression) requiring urgent alternative medical intervention.
- No other treatment discontinuation criteria are met (Table 6-6 and Table 11-2).

- No significant, unacceptable, or irreversible toxicities related to any dose of the study treatment or treatment-related adverse events of CTCAE grade 4 at the current dose at the time of progression.
- No current signs or symptoms of clinical disease progression that have decreased the ECOG performance status to ≥ 2.
- Disease progression is in one of the following settings: small or oligometastasis candidate for stereotactic body radiation therapy (SBRT), palliative radiation, or surgery
- Approval for continuation from the Amgen Medical Monitor.
- Palliative radiation and/or surgery for new, progressive, or symptomatic lesions is permitted, but docetaxel must be held until after completion of these treatments and until 7 days after completion of radiation
- If the time between the subject's initial progression scan and the restart of docetaxel is > 28 days, the scan must be repeated to serve as the new baseline.
- All protocol-mandated procedures must be performed as noted in the protocol (imaging, labs, and clinic visits may be obtained earlier per clinical judgment and if clinically indicated).
- Continued growth of tumor(s) on a subsequent scan should result in permanent discontinuation of the study drug.

For subjects who continue treatment beyond radiologic progression, the first date of progression will be used for PFS analysis and subject's response post first progression will not be used for the primary analyses to evaluate objective response endpoints including PFS, ORR, DOR, TTR, and DCR.

8.1.8 Crossover

This section details the conditions necessary to allow crossover for subjects in the docetaxel arm to the AMG 510 arm. The decision to crossover, from docetaxel to AMG 510, is at the discretion of the PI. Subjects that crossover may not initiate treatment with AMG 510 any earlier than 14 days after their last dose of docetaxel (regardless of the time of progression, if applicable). Safety follow up visit may occur on the same day as the first dose of AMG 510 in the crossover phase **(see Section 8.1.3)**. Subjects who are in LTFU at the time of crossover assessment cannot crossover, from docetaxel to AMG 510, if they have received any other systemic anti-cancer therapeutic administered other than docetaxel. All procedures and assessments completed at the time of withdrawal from the main study may be used, as appropriate, for the start of the crossover phase of the study, unless otherwise stated. Subjects who permanently discontinue the crossover phase will follow the same SFU and LTFU assessments outlined in the AMG 510 Schedule of Activities (Section 1.3).

For subjects who crossover from docetaxel to AMG 510, the subject's response post first progression or post crossover will not be used for the primary analyses to evaluate objective response endpoints including PFS, ORR, DOR, TTR, and DCR.

Once a subject crossover, the subject will begin a new cycle. For example: If a subject progress on cycle 2, day 15, once disease progression undergoes independent central confirmation, the PI will obtain approval from the medical monitor. Once approval is obtained, the subject will initiate cycle 3 for AMG 510 administration and follow the AMG 510 Schedule of Activities (Section 1.3). All assessments listed in the prior cycle (eg, cycle 2) must be completed prior to crossover and initiation of cycle 3.

Crossover Condition 1: Subjects who permanently discontinue chemotherapy due to an adverse event, or for any reason other than progressive disease, will not be eligible for crossover **until they have had radiographic progression and have undergone independent central confirmation of progression at the time of first PD as per Section 8.2.2.1.2**. Crossover from docetaxel to AMG 510 after Progressive Disease can be considered if the following conditions below are met.

1. Documentation of progressive disease per RECIST v1.1
2. PD imaging must undergo independent central confirmation. If a subject has been deemed to have objective disease progression according to investigator tumor assessment by RECIST v1.1, but is imaging does not undergo independent central confirmation, subject is not eligible to crossover.
3. Disease progression limited to CNS only must be treated prior to crossover
4. Subjects with symptomatic brain metastasis will not be permitted to crossover
5. Signed separate informed consent for AMG 510 crossover
6. Absence of threat to vital organs or critical anatomical sites (eg, CNS metastasis, respiratory failure due to tumor compression, spinal cord compression) requiring urgent alternative medical intervention. Subject may re-evaluate appropriateness for crossover after therapeutic intervention.
7. Brain imaging (CT/MRI with contrast) must be obtained prior to initiating therapy with AMG 510 in crossover (if brain scan has been performed > 28 days from the date of first crossover dose of AMG 510, brain scan must be repeated)
8. Subject must meet inclusion criteria requirements: 109, 110, 111, 112, and 113 (Section 5.1) on AMG 510 administration day 1 of crossover (labs to be obtained on crossover day 1 (± 3 days).
9. No AMG 510 treatment discontinuation criteria are met (Table 6-6 and Table 11-2).
10. No significant, unacceptable, or irreversible toxicities related to any dose of docetaxel or treatment-related adverse events of CTCAE (grade 1) at the current dose at the time of progression **(with the exception of alopecia and nail discoloration). Additional non-significant toxicities may be allowed but will need to be discussed with and approved by the medical monitor prior to crossover**.

11. No current signs or symptoms of clinical disease progression that have decreased the ECOG performance status to ≥ 2.
12. Palliative radiation and/or surgery for new, progressive, or symptomatic lesions is permitted prior to crossover, but AMG 510 must be held until after completion of these treatments and until 7 days after completion of radiation
13. If the time between the subject's initial progression scans and the start of AMG 510 is > 28 days, the imaging scans must be repeated to serve as the new baseline.
14. All protocol-mandated procedures must be performed as noted in the protocol (imaging, labs, and clinic visits may be obtained earlier per clinical judgment and if clinically indicated) as dictated by the AMG 510 Schedule of Activities (Table 1-1)
15. No other systemic anti-cancer directed therapeutic agents are to be administered during crossover
16. Subject has not received any other systemic anti-cancer therapies other than docetaxel administered during the treatment phase.
17. Approval for crossover from the Amgen Medical Monitor

Crossover Condition 2: Should an early efficacy of the study be noted by the DMC, crossover will be considered for all subjects who randomized into the docetaxel arm (so that they will be able to immediately receive AMG 510).

8.2 Description of General Study Assessments and Procedures

The sections below provide a description of the individual study procedures for required time points.

8.2.1 General Assessments

8.2.1.1 Informed Consent

All subjects or their legally authorized representative must sign and personally date the IRB/IEC and Amgen approved informed consent before any study-specific procedures are performed.

8.2.1.2 Demographics

Demographic data collection 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 will be used to study the impact on biomarkers variability and PK of the protocol-required therapies

8.2.1.3 Medical History

The Investigator or designee will collect a complete medical history from 28 days prior to enrollment through enrollment. Medical history will include information on the subject's concurrent medical conditions. Record all findings on the medical history CRF. The current toxicity grade will be collected for each condition that has not resolved. Cancer history will be collected dating back to the original diagnosis.

8.2.1.4 Physical Examination

Physical examination will be performed as per standard of care. Physical examination findings should be recorded on the appropriate CRF page (eg, Medical history, Adverse event).

8.2.1.5 Physical Measurements

Height in centimeters should be measured without shoes. Weight in kilograms should be measured without shoes. Height should only be recorded at screening, and weight should be recorded at every clinic visit (Schedule of Activities; Table 1-1 and Table 1-2).

8.2.1.6 Substance Abuse History

Obtain a detailed history of prior and/or concurrent use of tobacco. Tobacco usage must include current and any prior smoking history (number of pack years).

8.2.1.7 Performance Status

The subject's performance status will be assessed using the ECOG Performance Status.

8.2.2 Efficacy Assessments

8.2.2.1 Disease Assessments

8.2.2.1.1 Radiological Imaging Assessment

The extent of disease will be evaluated by contrast-enhanced MRI/CT according to RECIST v1.1 (Section 11.8). All radiological imaging will be performed as indicated in the Site Imaging Manual provided by the central imaging core laboratory. In order to reduce radiation exposure for subjects, low dose CT should be utilized whenever possible.

Contrast-enhanced CT of the chest, and one of the following: contrast-enhanced CT abdomen with cuts through to the pubic symphysis, contrast-enhanced CT abdomen and pelvis, contrast-enhanced MRI abdomen and pelvis, or contrast-enhanced MRI abdomen with cuts through to the pubic symphysis, and brain MRI with contrast (or brain CT scan with contrast) will be obtained at screening. The screening scans must be performed within 28 days prior to cycle 1 day 1 and will be used as baseline. Scans obtained as part of standard of care prior to signing informed consent may be used if they are within the window specified prior to cycle 1 day 1. All subsequent scans will be performed in the same manner as at screening, with the same contrast, preferably on the same scanner. Tumor evaluation is to be performed by contrast-enhanced CT of the chest and one of the following: contrast-enhanced CT abdomen with cuts through to the pubic symphysis, contrast-enhanced CT abdomen and pelvis, contrast-enhanced MRI

abdomen and pelvis, or contrast-enhanced MRI abdomen with cuts through to the pubic symphysis. Contrast-enhanced images are strongly preferred. If contrast enhanced CT imaging is contraindicated (allergy, medical contraindication, etc), radiological imaging to be performed as indicated by site imaging manual. Magnetic resonance imaging of the brain should be performed if subject has history of brain metastases, or if signs or symptoms suggestive of CNS metastases are present. All subjects with brain metastasis must have MRI of the brain performed within 28 days prior to cycle 1 day 1 of AMG 510 or docetaxel.

The same MRI field strength used at screening should be used for all subsequent assessments. Liver specific MRI contrast agents should not be used. To reduce potential safety concerns, macrocyclic gadolinium contrast agents are recommended per United States National Institute of Health guidelines, or follow local standards if more rigorous. All brain scans on protocol are required to be MRI unless MRI is contraindicated, and then CT with contrast is acceptable. Non-contrast only CT of the brain is not acceptable.

Imaging may also be performed more frequently if clinically necessitated at the discretion of the managing physician. Radiographic response (CR, PR) requires confirmation by a repeat, consecutive scan at a minimum of 4 weeks after the first documentation of response and may be delayed until the next scheduled scan to avoid unnecessary procedures.

Determination of disease response for clinical management of subjects will be assessed at the clinical sites per RECIST v1.1. Scans will be submitted to a central imaging core laboratory for archival, response assessment including RECIST v1.1, and/or exploratory analysis eg, volumetric and viable tumor measurements. Detailed information regarding submission of images to the central imaging core laboratory is found in the Site Imaging Manual.

In the event of crossover or treatment beyond progression imaging schedule is per Schedule of Activities (Table 1-1).

8.2.2.1.2 Independent Central Confirmation of Progression (COP) at Time of First Progressive Disease (PD)

All scheduled images for all study participants from the sites will be submitted to the central imaging vendor. In addition, images (including via other modalities) that are obtained at an unscheduled time point to determine disease progression, as well as

imaging obtained for other reasons, but captures radiologic progression based on investigator assessment should also be submitted to the central imaging vendor.

The purpose of the independent confirmation of progression is to provide the site PI with a second independent opinion regarding whether the participant has reached progressive disease according to RECIST v1.1. The expedited independent confirmation of progression (COP) will be performed by a single radiologist from a pool of highly qualified central radiologists that is entirely separate from the central radiologist group reading the images for efficacy. The results of the single radiologist COP review will not be discussed with the central efficacy reviewers and thus, will not influence the determination of response or progression by the efficacy reviewers. The COP will only be utilized to provide a second opinion on the presence or absence of progression at the current time point to the site PI, no clinical subject data is to be discussed.

When the investigator identifies radiographic progression per RECIST v1.1, the current imaging plus all images to date must be immediately sent to the central imaging vendor who, once any critical queries (as defined in the imaging manual) are resolved, will perform an expedited confirmation of radiologic disease progression and communicate the results to study site and Sponsor within 3 business days after receiving the images.

If the evaluation of radiologic disease progression, via central imaging vendor, does not confirm progression of disease at this timepoint, a web conference may be organized, by the central imaging vendor, to be held between the single radiologist and the site radiologist to review the participants' images for determination of confirmation of radiological disease progression. The site PI will make final treatment and subject management decisions. The results of the web conference will be documented and provided to the study team within 1 business day.

Progression of radiologic disease should be verified centrally prior to cessation of investigational product, local intervention, or initiation of new anti-cancer therapy, treatment beyond progression, or crossover. If there are no safety concerns and the study participant is clinically stable, the participant is to remain on investigational product while central confirmation of progression is ongoing and until confirmation of radiologic disease progression is complete.

8.2.2.1.3 Clinical Outcome Assessments

Patient-reported outcomes questionnaires include the, EORTC QLQ-C30 General Cancer Instrument, the disease specific module QLQ-LC13, a single item about

symptom bother (GP5 of the FACT-G), and the EQ-5D-5L. The patient Global Impression of Severity (PGIS), Patient Global Impression of Change (PGIC), and Brief pain Inventory (BPI), will provide additional context to interpret patient reported on the prespecified lung cancer symptoms of dyspnea, cough and chest pain. PRO-CTCAE will be administered to all subjects, and collected as indicated in the Schedule of Activities (Table 1-1 and Table 1-2). The PRO questionnaires completed in the clinic should be completed by the subject prior to any other clinical assessments and before receiving any study medications.

8.2.2.1.3.1 QLQ-C30

Physical function and the impact of treatment on disease-related symptoms and health-related quality of life (HRQOL) will be evaluated in all subjects using EORTC QLQ-C30. EORTC QLQ-C30 (Section 11.9): The EORTC QLQ-C30 was developed to assess the QOL in cancer subjects across tumor types. The QLQ-C30 has been tested and validated with multiple myeloma subjects (Leleu et al, 2013; Wisløff et al, 1996) and has also been used in NSCLC (Aaronson et al, 1993; Niezgoda and Pater, 1993). It is a self-reporting 30-item generic instrument which assesses 5 functional domains (physical, role, emotional, cognitive, social), 9 symptom scales (fatigue, nausea and vomiting, pain, dyspnea, insomnia, appetite loss, constipation, diarrhea, financial difficulties), and a global health status/QOL scale (Aaronson et al, 1993). The recall period is the past week. Subjects will complete the QLQ-C30 at clinic visits only.

8.2.2.1.3.2 EQ-5D-5L

Health-related QOL will also be assessed in all subjects using the EQ-5D-5L (Section 11.10). EuroQol-5 Dimension will be collected at timepoints listed in the SOAs (Table 1-1 and Table 1-2). The EQ-5D-5L questionnaire is a 2-page, standardized instrument for use as a measure of health outcome developed by the EuroQol group (Rabin and de Charro, 2001). It is comprised of a 5-dimension health status measure and a visual analogue scale (VAS), as applicable. The 5-dimension health status measure evaluates: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression based on a 5-level scale: no problems, slight problems, moderate problems, severe problems, and extreme problems. The VAS records the subject's self-rated health on a vertical, visual analogue scale where the endpoints are labelled 'The best health you can imagine' and 'The worst health you can imagine'. The EQ-5D-5L questionnaire will be completed in the clinic on clinic visit days, including

SFU, and at home (data collected by phone) for the scheduled non-clinic assessment days (day 5 of cycles 1, 2, and 3), and during LTFU.

8.2.2.1.3.3 QLQ-LC13

The supplementary disease specific module, QLQ-LC13, is a validated questionnaire to assess the impact of treatment on lung cancer-associated symptoms (cough, hemoptysis, dyspnea and site-specific pain) and treatment-related side effects (sore mouth, dysphagia, peripheral neuropathy and alopecia) and pain medication ([Koller et al, 2015; Bergman et al, 1994]; Section 11.11). It contains 13 questions. QLQ-LC13 includes: 1 multi-item scale and 9 single items that assess the specific symptoms (dyspnea, cough, hemoptysis, and site-specific pain), side effects (sore mouth, dysphagia, neuropathy, and alopecia), and pain medication use of patients with lung cancer receiving chemotherapy. Subjects will complete the QLQ-LC13 questionnaire at clinic visits only.

8.2.2.1.3.4 PGIS and PGIC

PGIS (Section 11.12) will be collected in the clinic at screening and on day 1 of cycles 1, 3, and 5 to assess patients' global impression of symptom severity of cough, dyspnea, and chest pain. PGIC (Section 11.13) will be collected in the clinic on day 1 of cycles 3 and cycle 5 to provide context for interpretation of change in key lung cancer symptoms as measured by the EORTC QLQ-C30 and QLQ-LC13

8.2.2.1.3.5 PRO-CTCAE

Treatment-related symptoms and impact on the subject will be assessed in all subjects (regardless of tumor types) using selected questions from the PRO version of the CTCAE (PRO-CTCAE) library (Section 11.14). PRO-CTCAE is a subject-reported outcome measure developed to evaluate symptomatic toxicity in subjects on cancer clinical trials. The questionnaire was designed to be used as a companion to the CTCAE, the standard lexicon for adverse event reporting in cancer trials. PRO-CTCAE item library version 1.0 is comprised of 124 individual questions developed to elicit 78 symptomatic AEs from subjects using between 1 to 3 attribute questions (ie, frequency, severity, and/or interference of the adverse event), (Basch et al, 2014). The recall period for PRO-CTCAE is the past 7 days. The PRO-CTCAE has been tested and validated in terms of construct validity, test-retest reliability, and item responsiveness (Dueck et al, 2015). Amgen has selected questions from the PRO-CTCAE for inclusion in the trial which represent symptoms of adverse events which are not addressed directly by questions in the EORTC QLQ-C30 or the

EORTC QLQ-LC13. The specific questions were selected based on a review of the symptoms most commonly observed with AMG 510 as of the June 12 2019 (AMG 510 Investigator's Brochure June 12 2019) and a review of the USPI for docetaxel for symptoms among patients treated with docetaxel and prior exposure to a platinum based chemotherapy. The specific questions to be asked in this study are composed of the general mouth sores, muscle aches, itchy skin, numbness and pain components from the library. Subjects will complete the PRO-CTCAE questionnaire at clinic visits only (with the exception of screening visit).

8.2.2.1.3.6 GP5 of the FACT-G

The GP5 of the FACT-G is a single item "I am bothered by side effects of treatment" rated on a 5-point Likert scale from "not at all" to "very much" is an item included in the Physical Well-Being subscale of the PRO assessment instrument FACT-G (Section 11.15). It has been evaluated and validated as a useful summary index of side effect impact or burden to the individual subject (Pearman et al, 2018). Subjects will complete the GP5 of the FACT-G on day 1 (administered by tablet in the clinic) of each cycle, and at the SFU.

8.2.2.1.3.7 Brief pain Inventory (BPI)

Pain will be assessed on day 1 of every cycle and at the SFU by using the BPI, which assesses the severity of pain and its impact on functioning (Section 11.16). The BPI will be administered in the clinic to provide context for interpretation of change in patient reported symptoms of chest pain.

8.2.3 Safety Assessments

Planned time points for all safety assessments are listed in the Schedule of Activities see (Table 1-1 and Table 1-2).

8.2.3.1 Vital Signs

The following measurements must be performed: systolic/diastolic blood pressure, heart rate, respiratory rate, oxygen saturation, and body temperature. Subject must 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 for a subject should be the same that is used throughout the study and documented on the vital sign CRF. The temperature location selected for a subject should be the same that is used throughout the study and documented on the vital signs CRF. All measurements will be recorded on the vital signs CRF.

8.2.3.2 Electrocardiograms

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 ECG must include the following measurements: Heart Rate, QRS, QT, QTc, and PR intervals. The Principal Investigator (PI) or delegate assigned via the Delegation of Authority log 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 Amgen.

8.2.3.3 Vital Status

Vital status must be obtained for all subjects within the limits of local law. This includes subjects who may have discontinued study visits with or without withdrawing consent and should include interrogation of public databases, if necessary. If deceased, the date and reported cause of death should be obtained.

8.2.3.4 Other Safety

Patient recorded outcome questionnaires are described in Section 8.2.2.1.3.

8.2.4 Adverse Events and Serious Adverse Events

8.2.4.1 Time Period and Frequency for Collecting and Reporting Safety Event Information

8.2.4.1.1 Adverse Events

The adverse event grading scale to be used for this study will be the CTCAE version 5.0 and is described in Section 11.4.

The investigator is responsible for ensuring that all adverse events observed by the investigator or reported by the subject that occur after enrollment through the SFU visit are reported using the Events CRF.

8.2.4.1.2 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 informed consent through the **safety follow-up visit or 30 days after the last day of dosing interval of investigational product(s)/protocol-required therapies, whichever occurs later** are reported using the Events CRF.

All serious adverse events will be collected, recorded and reported to the sponsor or designee within 24 hours of the investigator’s awareness of the event, as indicated in

Section 11.4. The investigator will submit any updated serious adverse event data to the sponsor within 24 hours of it being available.

The criteria for grade 4 in the CTCAE grading scale differs from the regulatory criteria for serious adverse events. It is left to the investigator's judgment to report these grade 4 abnormalities as serious adverse events.

8.2.4.1.3 Serious Adverse Events After the Protocol-required Reporting Period

After End of Study, there is no requirement to **actively** monitor study subjects **after the study has ended with regards to study subjects treated by the investigator. However, if the investigator becomes aware of** serious adverse events **suspected to be related to investigational products after** the protocol-required reporting period (as defined in Section 8.2.4.1.2)**, then** these serious adverse events **will** be reported to Amgen **within 24 hours following the investigator's awareness of the event.**

Since overall survival is a study endpoint, the investigator will also need to collect/report fatal serious adverse events (regardless of causality) to Amgen within 24 hours following the investigator's awareness 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 and handled accordingly based on relationship to investigational product.

If further safety-related data is needed to fulfill any regulatory reporting requirements for a reportable event, then additional information may need to be collected from the subject's medical records - even after the subject has ended the study (as long as the subject did not withdraw consent).

The method of recording, evaluating, and assessing causality of adverse events, and serious adverse events and the procedures for completing and transmitting serious adverse event reports are provided in Section 11.4.

8.2.4.2 Reporting a Safety Endpoint as a Study Endpoint

Safety endpoints (eg, mortality) that are study endpoints are reported on the Event**s** CRF. All endpoints that also meet the criteria of serious adverse event must also be transmitted to safety within 24 hours of the investigator's awareness of the event (refer to Section 11.4).

8.2.4.3 Method of Detecting Adverse Events and Serious Adverse Events

Care will be taken not to introduce bias when detecting adverse events and/or serious adverse events. Open-ended and non-leading verbal questioning of the subject is the preferred method to inquire about adverse event occurrence.

8.2.4.4 Follow-up of Adverse Events and Serious Adverse Events

After the initial adverse event/serious adverse event report, the investigator is required to proactively follow each subject at subsequent visits/contacts. All adverse events and serious adverse events will be followed until resolution, stabilization, until the event is otherwise explained, or the subject is lost to follow-up (as defined in Section 7.3). Further information on follow-up procedures is given in Section 11.4.

All new information for previously reported serious adverse events must be sent to Amgen within 24 hours following awareness of the new information. If specifically requested, the investigator may need to provide additional follow-up information, such as discharge summaries, medical records, or extracts from the medical records. Information provided about the serious adverse event must be consistent with that recorded on the Event**s** CRF.

8.2.4.5 Regulatory Reporting Requirements for Serious Adverse Events

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

Prompt notification by the investigator to the sponsor of serious adverse events is essential so that legal obligations and ethical responsibilities towards the safety of subjects and the safety of a study treatment under clinical investigation are met.

The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study treatment under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRBs/IECs, and investigators.

Individual safety reports must be prepared for suspected unexpected serious adverse reactions according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.

An investigator who receives an individual safety report describing a serious adverse event or other specific safety information (eg, summary or listing of serious adverse events) from the sponsor will file it along with the Investigator's Brochure and will notify the IRB/IEC, if appropriate according to local requirements.

8.2.4.6 Safety Monitoring Plan

Subject safety will be routinely monitored as defined in Amgen's safety surveillance and signal management processes.

8.2.4.7 Pregnancy and Lactation

Details of all pregnancies and/or lactation in female subjects and female partners of male subjects will be collected after the start of study treatment and until 7 days (AMG 510) or 6 months (docetaxel) post dose for female subjects and 7 days (AMG 510) or 6 months (docetaxel) post dose for female partners of male subjects. Female subjects who become pregnant while on study or within 7 days after receiving the last dose of AMG 510 will not receive subsequent scheduled doses and will be followed for safety until end of study visit.

If a pregnancy is reported, the investigator is to inform Amgen within 24 hours of learning of the pregnancy and/or lactation and is to follow the procedures outlined in Section 11.5. Amgen Global Patient Safety will follow-up with the investigator regarding additional information that may be requested.

Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered serious adverse events.

Further details regarding pregnancy and lactation are provided in Section 11.5.

8.2.5 Clinical Laboratory Assessments

Refer to Section 11.2 for the list of clinical laboratory tests to be performed and to the Schedule of Activities (Table 1-1 and Table 1-2) for the timing and frequency.

The investigator is responsible for reviewing laboratory test results and recording any clinically relevant changes occurring during the study on the Adverse Event CRF. The investigator must determine 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.

8.2.6 Pregnancy Testing

A highly sensitive (urine or serum) pregnancy test should be completed at screening and within 3 days before initiation of investigational product for females of childbearing potential.

Note: Females who have undergone a bilateral tubal ligation/occlusion should have pregnancy testing per protocol requirements. (If a female subject, or the partner of a male subject, becomes pregnant it must be reported on the Pregnancy Notification Form, see Figure 11-2). Refer to Section 11.5 for contraceptive requirements.

Additional pregnancy testing should be performed as outlined in the Schedule of Activities (Table 1-1 and Table 1-2).

Additional on-treatment pregnancy testing may be performed at the investigator's discretion or as required per local laws and regulations.

8.2.7 Pharmacokinetic Assessments

All subjects randomized to AMG 510 will have PK samples assessed. Whole blood samples will be collected for measurement of plasma concentrations of AMG 510, metabolites, and for exploratory exposure-response analyses as specified in the Schedule of Activities (Table 1-1 and Table 1-2). Instructions for the collection and handling of biological samples will be provided by the sponsor. The actual date and time (24-hour clock time) of each sample will be recorded.

8.2.7.1 Biomarker Assessment to Determine Eligibility (KRAS G12C): Tumor Tissue

Biomarkers are objectively measured and evaluated indicators of normal biologic processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention. In oncology, there is particular interest in the molecular changes underlying the oncogenic processes that may identify cancer subtypes, stage of disease, assess the amount of tumor growth, or predict disease progression, metastasis, and responses to investigational product(s) or protocol required therapies. In this study, a specific genomic biomarker (*KRAS p.G12C*) needs to be identified as part of the screening process.

A subject must have confirmation of *KRAS p.G12C* mutation by central laboratory testing prior to enrollment. Positivity for KRAS G12C will be determined at the central testing lab with an in vitro diagnostic device (Qiagen KRAS therascreen® KRAS RGQ PCR Kit).

This central laboratory testing can occur through the current protocol or Amgen Study 20190294.

The method used to confirm or detect KRAS G12C mutation by central testing should depend on whether the subject has KRAS G12C mutation results from a local test and whether they have sufficient archival tissue available or need to undergo a biopsy. (Table 8-1).

Table 8-1. Accepted Methods for Central Confirmation or Detection of KRAS G12C Mutation for Enrollment

Subject Presentation	Method
Local KRAS G12C results available (tissue or liquid)	Archived tissue through the Study 20190009 protocol
Local KRAS G12C results available, but no available tissue to confirm	Tumor biopsy through the Study 20190009 protocol
No local KRAS G12C result available	Receive confirmation of KRAS G12C mutation through screening protocol (Amgen Study 20190294)
No local KRAS G12C result available, and no available tissue to confirm	Tumor biopsy through the Study 20190009 protocol

If confirmation of KRAS G12C mutation is not available through participation in Amgen Study 20190294, tumor tissue will be required to identify *KRAS p.G12C* status prior to enrollment. Tumor tissue samples (FFPE of excisional, core needle, or fine needle aspirates) may be collected after informed consent is obtained. Tumor sample must be submitted to the central laboratory either as FFPE blocks or unstained slides (see study laboratory manual for details) for confirmation of mutation status. Tissue sample should be submitted along with the corresponding pathology report.

If archived tumor samples are not available, subjects will have the option to undergo a tumor biopsy to identify *KRAS p.G12C* status which must be sent as an FFPE block or unstained slides.

The FFPE tumor block or unstained slides of tissue (excisional, core needle, or fine needle aspirates) is to be carefully selected by a pathologist or a skilled experienced histology associate to include generous tumor tissue using the Pathology Report as a guide. In lieu of a block, unstained sections on superfrost or positively charged slides from the same block can be submitted according to the procedures defined in the study lab manual.

Subjects will submit tumor tissue samples (formalin fixed, paraffin embedded [FFPE] sample [FFPE of excisional, core needle, or fine needle aspirate] collected within 5 years) or be willing to undergo pre-treatment tumor biopsy (excisional, core needle, or fine needle aspirate) for tissue prior to enrollment. Tissue samples will be used for biomarker testing (If biomarker assessments are allowable under local regulations and if allowable by local IRB/EC) and Qiagen KRAS *therascreen*® testing for KRAS G12C.

8.2.7.2 Central KRAS p.G12C Laboratory Methods Summary

The *therascreen*® KRAS PCR Kit from QIAGEN is a real-time qualitative PCR assay performed on the RGQ MDx instrument for the detection of 7 somatic mutations in the human KRAS oncogene using DNA extracted from FFPE tissue. The mutations detected are: G12A, G12D, G12R, G12C, G12S, G12V, G13D. The *therascreen*® KRAS RGQ PCR Kit is an in vitro diagnostic device that will be used to confirm that the subjects, who are to be enrolled in the study**,** have tumors that are KRAS G12C positive.

[redacted]

[redacted]

8.2.8 Medical Resource Utilization and Health Economics

- Medical resource utilization and health economics data, associated with medical encounters, will be collected in the CRF by the investigator and study-site personnel for all subjects throughout the study. Protocol-mandated procedures, tests, and encounters are excluded.

[redacted]

9. Statistical Considerations

9.1 Statistical Hypotheses

The following 2-sided hypotheses will be tested in this trial.

Primary endpoint:

H_{01}: PFS survival distribution of AMG 510 arm is the same as for docetaxel arm versus

H_{11}: the 2 PFS survival distributions are different.

Key secondary endpoints:

H_{02}: odds ratio of ORR between AMG 510 arm and docetaxel arm = 1 versus H_{12}: odds ratio of ORR between AMG 510 arm and docetaxel arm ≠ 1

H_{03}: OS survival distribution of AMG 510 arm is the same as for docetaxel arm versus

H_{13}: the 2 OS survival distributions are different.

H_{04}: difference in mean change from baseline over time to week 12 in symptom of dyspnea as measured by a 4-item dyspnea domain from QLQ-C30 and QLQ-LC13 = 0 versus H_{14}: difference in mean change from baseline over time to week 12 in symptom

of dyspnea as measured by a 4-item dyspnea domain from QLQ-C30 and QLQ-LC13 ≠ 0

H_{05}: difference in mean change from baseline over time to week 12 in symptom of cough as measured by QLQ-LC13 = 0 versus H_{15}: difference in mean change from baseline over time to week 12 in symptom of cough as measured by QLQ-LC13 ≠ 0

H_{06}: difference in mean change from baseline over time to week 12 in symptom of chest pain as measured by QLQ-LC13 = 0 versus H_{16}: difference in mean change from baseline over time to week 12 in symptom of chest pain as measured by QLQ-LC13 ≠ 0

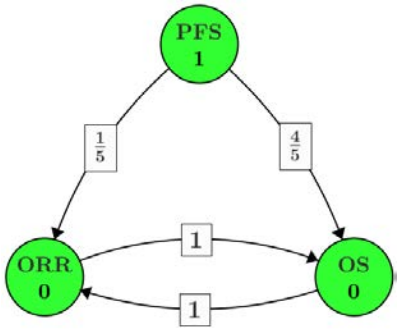
H_{07}: difference in mean change from baseline over time to week 12 in physical functioning as measured by QLQ-C30 = 0 versus H_{17}: difference in mean change from baseline over time to week 12 in physical functioning as measured by QLQ-C30 ≠ 0

H_{08}: difference in mean change from baseline over time to week 12 in global health status as measured by QLQ-C30 = 0 versus H_{18}: difference in mean change from baseline over time to week 12 in global health status as measured by QLQ-C30 ≠ 0

The hypotheses of the primary efficacy endpoint and key secondary efficacy endpoints will be tested using the following graphical multiple testing procedure (Maurer and Bretz, 2013) to control the study-level overall type I error rate below 1-sided 0.025 levels. A hypothesis can be re-tested repeatedly with a different nominal level that is propagated from rejecting other hypothesis test(s).

Figure 9-1 illustrates the Maurer-Bretz multiple testing procedure among PFS, OS and ORR. The fractions on the directed arrows indicate the proportion of α propagated from one hypothesis to the other when its hypothesis is rejected. Starting with PFS, if the hypothesis of PFS is rejected, ORR will be tested using 1-sided α/5 (0.005) level. With the rejection of ORR hypothesis, OS will be tested using 1-sided full α (0.025) level. If ORR hypothesis is failed to be rejected, OS will be tested using 1-sided 0.001 level if at PFS IA, otherwise using 4α/5 (0.02) level. With the rejection of OS hypothesis, ORR can be retested using 1-sided full α (0.025) level.

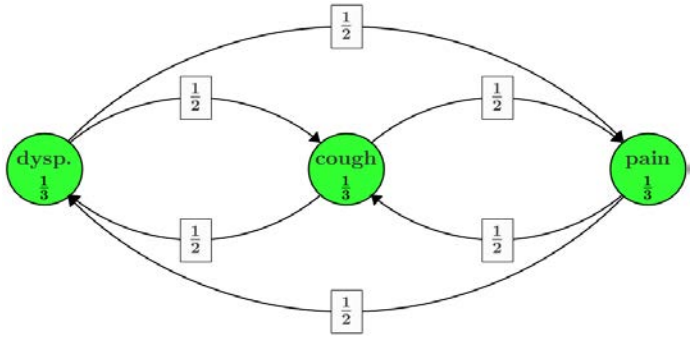
Figure 9-1. Initial Graph of Maurer-Bretz Multiple Testing Procedure for PFS, OS, and ORR.



ORR = objective response rate; OS = overall survival; PFS = progression-free survival

If all 3 hypotheses of PFS, OS, ORR are rejected, the next 3 endpoints of change from baseline over time to week 12 in 3 lung cancer symptoms will be tested using Holm's procedure, illustrated in Figure 9-2, including change from baseline over time to week 12 for the symptom of dyspnea as measured by a 4 item dyspnea domain from QLQ-C30 and QLQ-LC13 (dyspnea), change from baseline over time to week 12 for the symptom of cough as measured by QLQ-LC13 (cough), and change from baseline over time to week 12 for the symptom of chest pain as measured by QLQ-LC13 (pain). Hypotheses are rejected sequentially based on the smallest p-value.

Figure 9-2. Holm's Procedure for Change From Baseline Over Time to Week 12 in 3 Lung Cancer Symptoms

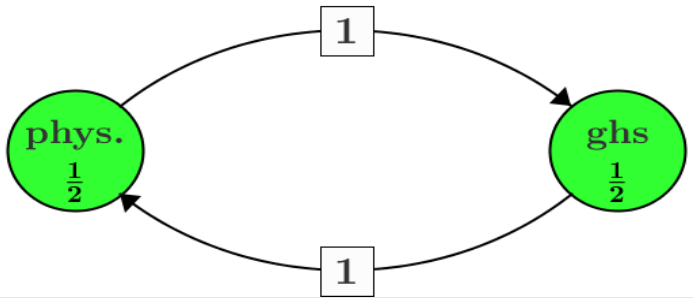


Dysp = dyspnea

If all 6 hypotheses listed above are rejected, the next 2 PRO endpoints will be tested using the Holm's procedure, illustrated in Figure 9-3, including change from baseline over time to week 12 in physical functioning as measured by QLQ-C30 (phys.), change

from baseline over time to week 12 in global health status as measured by QLQ-C30 (ghs). Hypotheses are rejected sequentially based on the smallest p-value.

Figure 9-3. Holm's Procedure for Change From Baseline Over Time to Week 12 on Physical Functioning and Global Health Status



phys = physical; ghs = global health status

9.2 Sample Size Determination

The PA of PFS will occur when approximately 230 PFS events have been observed. With 230 PFS events, the study will have ~90% power to show a statistically significant PFS at the 2.5% 1-sided significance level if the true treatment effect hazard ratio (HR) is assumed 0.65 for the AMG 510 arm versus the control arm. The sample size is chosen to have 70% maturity realizing PFS events, which is approximately 330 subjects with 1:1 randomization ratio into the AMG 510 arm and the docetaxel arm. The PFS PA may be delayed to ensure that the enrollment is finished and the delayed PA will be triggered when the last randomized subject have had the opportunity to have at least 6 weeks of follow up.

An IA is planned when approximately 70% (160) of the target PFS events have been observed from both arms, or when the enrollment is finished and the last randomized subject have had the opportunity to have 6 weeks of follow up, whichever occurs later. The monitoring boundary for early stopping for efficacy will be based on an O'Brien-Fleming type alpha spending function for multiplicity adjustment. The actual information fraction will be calculated based on the number of observed events at the time of the analysis. Under exponential distribution, the minimum detectable difference for success in this design is an HR of 0.68 between AMG 510 arm and the docetaxel arm with 160 PFS events, 70% of the target PFS events, and an HR of 0.769 at the PA with 230 PFS events. Assuming an enrollment rate of 40 subjects per month after a 3-month ramp-up period, with a total sample size of 330, it is estimated that approximately 19 months will be required to reach 230 PFS events, and 13 months will be required to reach 70% (160) of the target PFS events. This estimation is based on a

median PFS of 5 months for the control arm (Charpidou et al, 2019) and 7.7 months for the AMG 510 arm, and a 10% dropout rate.

If PFS achieves statistical significance at the interim analysis, an administrative interim summary for OS will be performed with approximately 107 OS events (~32% maturity) observed. A nominal alpha of 0.01% (negligible impact on overall type I error rate) will be spent on this OS interim summary. Otherwise, the OS will be assessed for superiority of AMG 510 over docetaxel at either the time of PFS primary analysis or after 175 OS events (~53% maturity) have been observed, whichever is later. Assuming the actual crossover rate of approximately 30% at the time of PFS primary analysis for subjects on the control arm who have disease progression, then with 175 OS events, the study has ~96% probability to observe a HR < 1 when the true OS HR is 0.75.

The OS primary analysis will occur when at least 198 OS events (~60% maturity) have been observed, which is expected to be at approximately 3 months after PFS primary analysis, with the same enrollment assumptions. The estimation is based on a median OS of 9 months for the control arm and 12 months for the AMG 510 arm (OS HR=0.75). The multiplicity will be adjusted as necessary based on O'Brien-Fleming type alpha spending function.

As designed, the trial will not be terminated at PFS analyses and subjects will continue to be followed for OS data until the targeted number of events are reached, regardless of the OS analysis result at the PFS primary analysis, to enable OS analyses and a robust description of the totality of the data.

9.3 Analysis Sets, Subgroups, and Covariates

9.3.1 Analysis Sets

9.3.1.1 Full Analysis Set

The full analysis set (ITT population) will include all randomized subjects. All subjects will be analyzed according to treatment to which they are randomized. Full analysis set will be used for the primary and key secondary efficacy endpoints.

9.3.1.2 Safety Analysis Set

The safety analysis set will include subjects in the full analysis set who received at least 1 dose of investigational product. Subjects in the analyses based on safety analysis set will be analyzed according to actual treatment received.

9.3.1.3 Per Protocol Analysis Set

The per protocol analysis set is a subset of the full analysis set which includes subjects who do not have important protocol deviations. The list of important protocol deviations is maintained by the sponsor on an ongoing basis and will be finalized before the PA of the study.

9.3.2 Covariates

Covariates may be incorporated in selected models of efficacy endpoints. In addition to the stratification factors for randomization, number of prior lines of therapy in advanced disease (1 versus 2 versus > 2), race (Asian versus non-Asian), history of CNS involvement (yes versus no), the following additional covariates may be included:

- region
- best response on prior therapy
- age
- sex
- race
- ECOG status
- Liver metastasis at baseline
- Disease stage
- smoking history
- histology
- brain metastasis at baseline
- bone metastasis at baseline
- presence of specific co-mutations at baseline (specific co-mutations to be specified in statistical analysis plan [SAP])
- PD-L1 protein expression (< 1%, ≥ 1%, and < 50%; ≥ 50%)
- STK11 mutation
- KEAP1 mutation

Detailed description of covariates to incorporate for each appropriate model will be pre-specified in the SAP.

9.3.3 Subgroups

In addition to the stratification factors for randomization, number of prior lines of therapy in advanced disease (1 versus 2 versus > 2), race (Asian versus non-Asian), history of

CNS involvement (yes versus no), primary and selected secondary endpoints will be examined in the following subgroups to investigate the consistency of treatment effects:

- region (North America and Europe vs rest of world)
- best response on prior therapy primary refractory (progression on first scan), suboptimal response (stable disease), recurrent (initial response with subsequent growth)
- age (< 65 vs ≥ 65)
- sex (male **vs** female)
- race (white, black, Asian, other)
- ECOG status (0 vs 1)
- Liver metastasis at baseline (yes **vs** no)
- stage (locally advanced and unresectable versus metastatic)
- smoking history (yes **vs** no)
- histology (squamous **vs** non-squamous)
- presence of specific co-mutation at baseline (yes **vs** no). Specific co-mutations to be specified in SAP.
- brain metastasis at baseline (yes **vs** no)
- bone metastasis at baseline (yes **vs** no)
- PD-L1 protein expression (< 1% **vs** ≥ 1%, and < 50% **vs** ≥ 50%)
- STK11 mutation
- KEAP1 mutation

In the event that there are insufficient number of subjects in the subgroup (ie, less than 10% of the whole population), relevant subgroups may be combined.

9.3.4 Handling of Missing and Incomplete Data

Incomplete adverse event start dates, concomitant medications start or stop dates, and death date will be imputed and the detailed rules will be specified in SAP. No imputation will be done for the PA of the primary and key secondary endpoints. The frequency of missing disease assessments and deviation of the actual disease assessment times from the scheduled assessment times will be summarized by treatment arms. Sensitivity analyses will be performed to assess the impact on the analysis of PFS due to any missing data/assessment, and any lost to follow-up or discontinuation of assessment of

PFS not due to an event. Similar analysis will be performed for Clinical Outcome Assessments (COA) endpoints.

Details of missing data analysis and imputation rules will be described in the SAP.

9.4 Statistical Analyses

The SAP will be developed and finalized before database lock. Below is a summary of the timing and methods for the planned statistical analyses. To preserve study integrity, the final analysis will be conducted and reported following the end of study, as defined in Section 4.4.

9.4.1 Planned Analyses

9.4.1.1 Interim Analysis and Early Stopping Guidelines

An IA of PFS for superiority is planned when approximately 70% (160 events) of the total PFS events have been observed, or when the enrollment is finished and the last randomized subject have had the opportunity to have 6 weeks of follow up, whichever occurs later. Early efficacy at the proposed PFS interim analysis will be claimed if the observed PFS difference meets the pre-specified statistical significance as well as being considered clinically meaningful.

If PFS achieves statistical significance at the interim analysis, an administrative interim summary for OS will be performed. Otherwise, the OS will be assessed for superiority of AMG 510 over docetaxel at either the time of PFS primary analysis or after 175 OS events (~53% maturity) have been observed, whichever is later.

Table 9-1: Potential Interim and Primary Analysis of PFS and OS

Analysis	PFS Information Fraction	Expected Timing from FSE	Analysis Trigger
PFS IA	70%	13 months	160 PFS events or LSE + 6 weeks, whichever occurs later
PFS PA	100%	19 months	230 PFS events or LSE + 6 weeks, whichever occurs later
OS at PFS PA	N.A.	19 months	175 OS events
OS PA	N.A.	22 months	198 OS events

IA = interim analysis; OS = overall survival; PA = primary analysis; PFS = progression-free survival.

9.4.1.2 Primary Analysis

The timing for the PA of PFS will be event driven and will happen when approximately 230 PFS events are reached cumulatively in 2 treatment groups. If PFS early success is achieved in the IA, the IA will serve the purpose of PA of PFS. The PFS PA may be delayed to ensure that the enrollment is finished and the delayed PA will be triggered when the last randomized subject have had the opportunity to have at least 6 weeks of follow up. The PA for OS will be event driven and will occur when approximately 198 OS events have been reached. There will be only one analysis for ORR (no interim analysis for ORR is planned). The primary analysis of ORR will be done when PFS is claimed statistically significant and the last randomized subject has had the opportunity to have at least 12 weeks of follow up.

9.4.1.3 Final Analysis

The final analysis of the study will be done when the last subject completes LTFU.

9.4.2 Methods of Analyses

9.4.2.1 General Considerations

The efficacy analyses of PFS and key secondary endpoints will be conducted on the full analysis set. In principle, summary statistics including mean, standard deviation, median, first and third quartiles, will be provided for continuous variables. Frequency and percentage will be summarized by treatment arm for binary and categorical variables. The distribution of PFS and OS will be estimated using the Kaplan-Meier method. The HR and its 95% CI will be estimated using a Cox proportional hazards model stratified by the randomization stratification factors. The inferential comparison

will be made using a stratified log rank test. Objective response rate will be calculated and the associated 95% CI will be estimated using the Clopper-Pearson method. The inferential comparison for ORR will be made using the Cochran-Mantel-Haenszel chi-square test controlling for the randomization stratification factors. For subjects who continue treatment post-progression or subjects who crossover from docetaxel to AMG 510, the first date of progression will be used for PFS analysis and subject's response post first progression or post crossover will not be used the primary analyses to evaluate objective response endpoints including PFS, ORR, DOR, T**T**R, and DCR. The inferential comparison for the endpoints of change from baseline over time to week 12 in symptoms of dyspnea as measured by a 4 item dyspnea domain from QLQ-C30 and QLQ-LC13, change from baseline over time to week 12 in physical functioning, global health status as measured by QLQ-C30 will be made through a mixed model for repeated measurement (MMRM). The inferential comparison for the endpoints of change from baseline over time to week 12 in symptoms of cough and chest pain as measured by a single question from QLQ-LC13 will be made through generalized estimating equations (GEE) method for cumulative logits model (Lipsitz et al, 1994). Multiple imputation approach with non-ignorable missing pattern will be explored as the sensitivity analysis for all the key secondary PRO endpoints.

Further details of secondary endpoint testing will be described in the SAP.

9.4.2.2 Efficacy Analyses

Estimand	Primary Analysis	Sensitivity Analysis
HR of PFS between AMG 510 and docetaxel, for subjects with previously treated locally advanced and unresectable or metastatic NSCLC with KRAS p.G12C mutation, before or on start of new anti-cancer therapy	The PA of PFS will be conducted on the full analysis set. The primary comparison for PFS between treatment and control will use the log rank test stratified by randomization factors per IRT. The HR and its 95% CI will be estimated using a Cox proportional hazards model stratified by the randomization stratification factors per IRT. Kaplan Meier curve will also be provided by treatment arm. The PA of PFS will be based on BICR centrally assessed outcomes. The analysis based on investigator-assessed local	To evaluate the robustness of the PFS endpoint for the intercurrent event of start of new anti-cancer therapy prior to PFS event, a sensitivity analysis based on a different set of censoring rules will be performed (see Table 9-2).

Estimand	Primary Analysis	Sensitivity Analysis
	outcome will serve as supportive analyses.	
HR of OS between AMG 510 and docetaxel, for subjects with previously treated locally advanced and unresectable or metastatic NSCLC with KRAS p.G12C mutation, regardless of subsequent anti-cancer therapy and/or crossover.	The analysis of OS will be conducted on the full analysis set. Overall survival will be analyzed using the same method as described for the PFS endpoints.	To address the intercurrent event of crossover from control group to treatment group, the primary comparison of OS between treatment and control will use one or more methods such as Rank preserving structural failure time (RPSFT) model to adjust for crossover effect. It will provide the randomization-based estimate of estimate of treatment effect (RBEE) corrected for the bias induced by crossover and the 95% CI of the OS HR adjusted for crossover effect. Additional methods will be explored to check the robustness of the model assumptions.
Odds ratio of objective response between AMG 510 and docetaxel, for subjects with previously treated locally advanced and unresectable or metastatic NSCLC with *KRAS p.G12C* mutation. Subjects who discontinued treatment prior to achieving an objective response are considered as non-responders.	The inferential comparison between treatment and control for ORR will be made using the Cochran-Mantel-Haenszel chi-square test controlling for the stratification factors per IRT. An estimate of the common odds ratio (95% CI) will be provided as a measure of the relative treatment effect.	
Change from baseline to Week 12 in PRO endpoints between AMG 510 and docetaxel, for subjects with previously treated locally advanced and unresectable or metastatic NSCLC with KRAS p.G12C mutation. PRO measurements before or on start of new anti-cancer therapy including crossover will be used to estimate treatment effect.	Change from baseline over time to week 12 in symptoms of dyspnea as measured by a 4 item dyspnea domain from QLQ-C30 and QLQ-LC13, change from baseline over time to week 12 in physical functioning, global health status as measured by QLQ-C30 will be compared between treatment arms using MMRM (Mallinckrodt et al, 2008). The dependent variable of this model will be the change from baseline score over time to week 12. The model will include intercept, time, baseline score, treatment, treatment by time interaction, and randomization stratification factors as fixed effects and	Multiple imputation approach with non-ignorable missing pattern will be explored as the sensitivity analysis for all the key secondary PRO endpoints.

Estimand	Primary Analysis	Sensitivity Analysis
	subject random intercept and subject random slope of time on score as random effect. Change from baseline over time to week 12 in symptoms of cough and chest pain as measured by a single question from QLQ-LC13 will be compared between treatment arms using GEE method for cumulative logits model. The model will include intercept, time, baseline score, treatment, treatment by time interaction and randomization stratification factors. Subgroup analysis for key secondary endpoints will be performed in subgroups defined in Section 9.3.3.	

Table 9-2. Censoring Rules for PFS Analyses per BICR

Situation (before data cutoff)	Primary Analysis		Sensitivity Analysis	
	Date of Event or Censor	Out come	Date of Event or Censor	Out come
Radiological disease progression per BICR prior to death	Date of first observation of radiological disease progression per BICR	Event		
No radiological disease progression per BICR, but death record	Date of death	Event		
No evaluable post-baseline tumor assessments per BICR, no death recorded	Date of randomization date	Censor		
No radiological disease progression per BICR, no death, but start of new anti-cancer therapy recorded	Date of last evaluable assessment per BICR before start of new anti-cancer therapy	Censor	If on study therapy, date of last evaluable assessment per BICR	Censor
			if not on study therapy, date of treatment discontinuation	Event

Situation (before data cutoff)	Primary Analysis		Sensitivity Analysis	
	Date of Event or Censor	Out come	Date of Event or Censor	Out come
No radiological disease progression per BICR, no death recorded, no start of new anti-cancer therapy	Date of last evaluable assessment per BICR	Censor	Date of start of new anti-cancer therapy	Event
Death or radiological disease progression per BICR immediately after more than one missed tumor assessment	Date of last evaluable assessment per BICR with documented non-progression prior to missing assessment(s)	Censor		

Endpoint	**Statistical Analysis Methods**
Primary	The PA of PFS will be conducted on the full analysis set. The primary comparison for PFS between treatment and control will use the log-rank test stratified by randomization factors per IRT. The HR and its 95% CI will be estimated using a Cox proportional hazards model stratified by the randomization stratification factors per IRT. Kaplan-Meier curve will also be provided by treatment arm. The PA of PFS will be based on BICR centrally assessed outcomes. The analysis based on investigator-assessed local outcome will serve as supportive analyses. As stated in Section 9.2, the PA of PFS will occur when approximately 230 events have been reached. The PFS PA may be delayed to ensure that the enrollment is finished and the delayed PA will be triggered when the last randomized subject have had the opportunity to have at least 6 weeks of follow up. An IA is planned when approximately 70% (160) of the target PFS events have been observed from both arms or when the enrollment is finished and the last randomized subject have had the opportunity to have 6 weeks of follow up, whichever occurs later. The monitoring boundary for early stopping for efficacy will be based on an O'Brien-Fleming type alpha spending function for multiplicity adjustment; the early stopping information fraction will be based on the actual PFS events observed and monitoring boundaries will be adjusted accordingly. Deviation from the scheduled IA will not affect the overall Type I error. The primary endpoint will be analyzed within each of the subgroups listed in Section 9.3.3. The estimate of the hazard ratios (95% CI) will be provided using Cox proportional hazard model.

Endpoint	Statistical Analysis Methods
Key Secondary	Objective response is defined as a complete response or partial response, as defined by RECIST v1.1. Confirmation is done by a repeat, consecutive assessment no less than 4 weeks from the date of first documented assessment. Response will be assessed by blinded independent central review (BIRC). ORR is therefore defined as the proportion of **subject**s with a best overall response of confirmed CR or confirmed PR. The analysis of ORR will be done at the time when PFS reaches statistical significance and the last randomized subject has had the opportunity to have at least 12 weeks of follow up, whichever is later. The inferential comparison between treatment and control for ORR will be made using the Cochran-Mantel-Haenszel chi-square test controlling for the stratification factors per IRT. An estimate of the common odds ratio (95% CI) will be provided as a measure of the relative treatment effect. The PA of ORR will be based on BICR centrally assessed outcomes. The analysis based on investigator-assessed local outcome will serve as supportive analyses. Overall survival is defined as the time from the date of randomization until event of death due to any cause. Subjects still alive will be censored at the date last known to be alive. If the date last known to be alive is after the date that triggers the analysis (ie, the data cutoff date), the subject will be censored at the date of last contact through the analysis trigger date. Overall survival will be analyzed using the same method as described for the PFS endpoints. The PA of OS will be performed when approximately 198 OS events have been reached. In addition, OS will also be tested at the PFS IA and/or PFS PA when PFS is claimed statistically significant. The monitoring boundary for early stopping for efficacy will be based on an O'Brien-Fleming type alpha spending function for multiplicity adjustment. The early stopping information fraction will be based on the actual OS events observed and monitoring boundaries will be adjusted accordingly. Deviation from the scheduled IA will not affect the overall type I error.
	Change from baseline over time to week 12 in symptoms of dyspnea as measured by a 4 item dyspnea domain from QLQ-C30 and QLQ-LC13, change from baseline over time to week 12 in physical functioning, global health status as measured by QLQ-C30 will be compared between treatment arms using MMRM (Mallinckrodt et al, 2008). The dependent variable of this model will be the change from baseline score over time to week 12. The model will include intercept, time, baseline score, treatment, treatment by time interaction and randomization stratification factors as fixed effects and subject random intercept and subject random slope of time on score as random effect. Change from baseline over time to week 12 in symptoms of cough and chest pain as measured by a single question from QLQ-LC13 will be compared between treatment arms using GEE method for cumulative logits model. The model will include intercept, time, baseline score, treatment, treatment by time interaction and randomization stratification factors. Multiple imputation approach with non-ignorable missing pattern will be explored as the sensitivity analysis for all the key secondary PRO endpoints. Subgroup analysis for key secondary endpoints will be performed in subgroups defined in Section 9.3.3.
Secondary and Exploratory	Will be described in the SAP finalized before database lock

9.4.2.3 Safety Analyses

9.4.2.3.1 Analyses of Primary Safety Endpoint(s)

There is no primary safety endpoint in Study 20190009. The safety and tolerability of AMG 510 compared to docetaxel will be assessed as a secondary endpoint. Unless otherwise specified, analyses of safety endpoints will be done in safety analysis set.

9.4.2.3.2 Adverse Events

Subject incidence of all treatment-emergent adverse events will be tabulated by system organ class and preferred term. Tables of fatal adverse events, serious adverse events, adverse events leading to discontinuation from investigational product or other protocol-required therapies, and significant treatment emergent adverse events will also be provided.

9.4.2.3.3 Laboratory Test Results

The analyses of safety laboratory endpoints will include summary statistics over time by treatment. Shifts in grades of safety laboratory values between baseline and the worst on-study value will be tabulated by treatment group.

9.4.2.3.4 Vital Signs

The analyses of vital signs will include summary statistics over time by treatment group. Shifts in vital sign values between baseline and the worst on-study value will be tabulated by treatment group.

9.4.2.3.5 Physical Measurements

The analyses of physical measurements will include summary statistics over time by treatment group.

9.4.2.3.6 Electrocardiogram

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.

9.4.2.3.7 Exposure to Investigational Product

The number of days on investigational product, the daily dose, and the total dose of investigational product will be summarized using descriptive statistics. Subject-level data may be provided instead of the summary if the subject incidence is low.

9.4.2.3.8 Exposure to Concomitant Medication

Number and proportion of subjects receiving therapies of interest will be summarized by preferred term for each treatment group as coded by the World Health Organization Drug dictionary. The subject incidence and time to first use of subsequent anti-cancer therapies will be summarized.

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11. Appendices

11.1 Appendix 1. List of Abbreviations and Definitions of Terms

Abbreviation or Term	Definition/Explanation
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANC	absolute neutrophil count
AST	aspartate aminotransferase
AUC	area under the plasma concentration-time curve
BCRP	**breast cancer resistance protein**
BCT	blood collection tubes
BICR	blinded independent central review committee
BLRM	Bayesian Logistics Regression Model
cfDNA	cell-free DNA
CFR	U.S. Code of Federal Regulations
C_{max}	maximum plasma concentration
CNA	copy number amplifications
CNS	central nervous system
COA	Clinical outcome assessment
COP	confirmation of progression
CR	complete response
CRC	colorectal cancer
CRF	case report form
CT	computerized tomography
ctDNA	circulating tumor DNA
CTCAE	Common Terminology Criteria for Adverse Events
ctDNA	circulating tumor DNA
CYP	cytochrome P450
DCR	disease control rate
DILI	drug induced liver injury
DLT	dose-limiting toxicity
DMC	data monitoring committee
DOR	duration of response
EC	Ethics Committee
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EDC	electronic data capture
EMA	European Medicines Agency
EMR	**electronic medical record**

Abbreviation or Term	Definition/Explanation
EORTC QLQ-C30	European Organization for Research and Treatment of Cancer Quality-of-life Questionnaire Core 30
EORTC QLQ-LC13	European Organization for Research and Treatment of Cancer Quality-of-life Questionnaire Core 13
EQ-5D-5L	EuroQol-5 Dimension
End of Study (primary completion)	defined as the date when the last subject is assessed or receives an intervention for the final collection of data for the primary and key secondary endpoint(s), for the purposes of conducting the primary analysis, whether the study concluded as planned in the protocol or was terminated early
End of Study (end of trial)	defined as the date when the last subject across all sites is assessed or receives an intervention for evaluation in the study (ie, last subject last visit), following any additional parts in the study (eg, long-term follow-up), as applicable
End of Treatment	defined as the last assessment for the protocol-specified treatment phase of the study for an individual subject
ERK	extracellular signal-regulated kinase
ESMO	European Society for Medical Oncology
FACT-G	Functional Assessment of Cancer Therapy Tool General form
FDA	Food and Drug Administration
FFPE	formalin fixed, paraffin embedded
FIH	first-in-human
FSH	follicle stimulating hormone
GCP	Good Clinical Practice
GDP	guanosine diphosphate
GTP	guanosine triphosphate
GTPase	guanosine triphosphatase
HepBsAg	Hepatitis B Surface Antigen
HIV	Human immunodeficiency virus
HR	Hazard ratio
HRQOL	health-related quality of life
HRAS	Harvey rat sarcoma viral oncogene homolog
HRQOL	health-related quality of life
HRT	hormone replacement therapy
IA	interim analysis
IBG	Independent Biostatistics Group
ICF	informed consent form
ICH	International Council for Harmonisation
IEC	independent ethics committee
ILD	**interstitial lung disease**

Abbreviation or Term	Definition/Explanation
INR	international normalized ratio
IPIM	Investigational Product Instruction Manual
IRB	institutional review board
IRT	interactive response technology that is linked to a central computer in real time as an interface to collect and process information
ITT	intention-to-treat
IUD	intrauterine device
IUS	intrauterine hormonal-releasing system
IV	intravenous
KRAS	Kirsten rat sarcoma viral oncogene homolog
LTFU	long-term follow-up
MMRM	mixed model for repeated measurement
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
NCI	National Cancer Institute
NCT	National Clinical Trials
NRAS	neuroblastoma RAS viral oncogene homolog
NSCLC	non-small cell lung cancer
ORR	objective response rate
OS	overall survival
PA	primary analysis
PCR	polymerase chain reaction
PD	progressive disease
PD-1	programmed cell death-1
PFS	progression-free survival
PGIC	Patient global impression of change
PGIS	Patient global impression of severity
PI	Principal Investigator
PK	pharmacokinetic
PO	orally-administered
PPI	proton-pump inhibitor
PR	partial response
PRO	patient-reported outcomes
QD	once daily
QOL	quality of life
RAS	rat sarcoma

Abbreviation or Term	Definition/Explanation
RECIST	Response Evaluation Criteria in Solid Tumors
RGQ	Rotor-Gene Q
RNAi	RNA interference
RP2D	recommended phase 2 dose
rSDR/V	**Source Data Review and Verification**
SAP	statistical analysis plan
SD	stable disease
SFU	safety follow up
SmPC	Summary of Product Characteristics
SOA	Schedule of Activities
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
TBL	total bilirubin
TMF	trial master folder
TTR	time to response
VAS	visual analogue scale
VEGF	Vascular Endothelial Growth Factor
ULN	upper limit of normal
US	United States
USPI	United States Prescribing Information

11.2 Appendix 2. Clinical Laboratory Tests

The tests detailed in Table 11-1 will be performed by the local laboratory and/or by the central laboratory.

Sites without local capabilities to perform protocol-required urine studies may send samples to the central laboratory for testing. Results will be provided to investigative sites.

Protocol-specific requirements for inclusion or exclusion of subjects are detailed in Sections 5.1 to 5.2 of the protocol.

Additional tests, including pregnancy tests, may be performed at any time during the study as determined necessary by the investigator or required by local regulations.

Table 11-1. Analyte Listing

Local Laboratory/Local/Central[f] Laboratory Urinalysis			Central Laboratory
Chemistry	**Hematology**	**Coagulation**	**PK and Biomarker (If allowable under local regulations and if allowable by local IRB/EC)**
Sodium	Hemoglobin	PT and INR	PK sampling
Potassium	Hematocrit	aPTT	Plasma ctDNA
Chloride	Mean corpuscular volume		Plasma cell pellet
Bicarbonate[e]	Platelets		Serum
Total CO_2[e]	RBC		PB Paxgene RNA
Triglycerides	WBC		Tumor biopsy[d]
Cholesterol	ANC		
Total protein	White blood cell Differential		
Albumin	• Total neutrophils		
Calcium	• Eosinophils		
Magnesium	• Basophils		
Phosphorous	• Lymphocytes		
Glucose	• Monocytes		
Blood urea nitrogen			
Urea[a]			
Creatinine			
Creatinine clearance			
Total creatine kinase			
Total bilirubin			
Direct bilirubin			
Alkaline phosphatase	**Serology[c]**	**Urinalysis[f]**	
Alanine aminotransferase	HepBsAg	Specific gravity	
Aspartate aminotransferase	HepCAb	pH	
	(if above cannot be obtained hepatitis viral load can be utilized)	Blood	
		protein	
Other Labs		glucose	
Serum or Urine Pregnancy[b]	Thyroid Function Tests	bilirubin	
	• TSH	ketones	
	• Total T3 (or Free T3 per local standard)	leukocyte (esterase)	
	• Free T4	nitrite	

ANC = absolute neutrophil count; aPTT = activated partial thromboplastin time; BUN = blood urea nitrogen; ctDNA = circulating tumor DNA; FT4 = free thyroxine; HepBsAg = hepatitis B surface antigen; HepCAb = hepatitis C antibody; INR = international normalized ratio; PB = peripheral blood; PCR = polymerase chain reaction; PK = pharmacokinetic; PT = prothrombin time; RBC = red blood cell; T3 = triiodothyronine; TCO2 = total carbon dioxide; TSH = thyroid stimulating hormone; WBC = white blood cell

[a] Urea collection is acceptable in absence of BUN.

[b] these data are collected separately from the chemistry form.

[c] Hepatitis B surface antigen, hepatitis C antibody, PCR for Hepatitis C RNA (if Hepatitis C antibody is positive).

[d] Archived tumor tissue is acceptable for screening for KRAS G12C mutation status.
[e] Bicarbonate/TCO_2 can also be obtained via capillary testing
[f] Investigative sites without local capability to perform urine studies may submit samples to central laboratory.

11.3 Appendix 3. Study Governance Considerations

Data Monitoring Committee

The data monitoring committee (DMC) will be comprised of 2 clinical oncologists, and 1 independent biostatistician. The DMC will act in an advisory capacity to the sponsor with respect to safeguarding the interests of study subjects, assessing interim safety and efficacy data, monitoring the overall conduct of the study, and providing with recommendations relating to continuing, modifying, or stopping the study based on these findings (International Council for Harmonisation Good Clinical Practice [ICH GCP 5.5.2]). Details of the DMC will be described in the DMC Charter. Data monitoring committee will review safety and efficacy data as per DMC charter. Data monitoring committee will meet to review safety after 50, 100, and 200 subjects are enrolled and have had the opportunity to be treated for at least 6 weeks and thereafter at approximately 6 month intervals, until the primary analysis of progression-free survival (PFS). The DMC will also review the IA data for PFS and overall survival (OS), whenever these are triggered. An Independent Biostatistics Group (IBG) will perform the IA and provide the interim report to an independent DMC. The IBG and DMC will have access to subjects' individual treatment assignments. To minimize the potential introduction of bias to the conduct of the study, members of the DMC will not have any direct contact with study site personnel or subjects. The DMC will communicate major concerns and recommendations regarding study modification or termination to Amgen in accordance with the DMC charter.

Records of all meetings will be maintained by the DMC for the duration of the study. Records of all meetings will be transferred and stored in the trial master folder (TMF) at the conclusion of the study. Further details are provided in the DMC charter.

Blinded Independent Central Review Committee (BICR)

A BICR committee will perform independent assessment of individual **subject** efficacy outcomes in accordance with the Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST v1.1). The committee will centrally review the disease related tests and assessments (Section 8.2.2.1.1) to evaluate disease progressions and responses without the knowledge of randomization assignments. This assessment will be used for

the primary analysis of endpoints. The membership criteria and operational details of the BICR will be described in the BICR Charter.

Regulatory and Ethical Considerations

This study will be conducted in accordance with the protocol and with:

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences International Ethical Guidelines
- Applicable ICH GCP Guidelines
- Applicable ICH laws and regulations

The protocol, protocol amendments, informed consent form (ICF), Investigator's Brochure, and other relevant documents (eg, subject recruitment advertisements) must be submitted to an institutional review board (IRB)/independent ethics committee (IEC) by the investigator and reviewed and approved by the IRB/IEC and Amgen. A copy of the written approval of the protocol and ICF must be received by Amgen before recruitment of subjects into the study and shipment of Amgen investigational product.

Amgen may amend the protocol at any time. 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 must send a copy of the approval letter from the IRB/IEC and amended protocol Investigator's Signature page to Amgen prior to implementation of the protocol amendment at their site.

The investigator will be responsible for the following:

- Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC
- 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
- Notifying the IRB/IEC of serious adverse events occurring at the site, deviations from the protocol or other adverse event reports received from Amgen, in accordance with local procedures
- Overall conduct of the study at the site and adherence to requirements of Title 21 of the U.S. Code of Federal Regulations (CFR), ICH guidelines, the IRB/IEC, and all other applicable local regulations

Recruitment Procedures

Site staff will identify potential subjects from their existing patient population or may seek referral patients through existing professional networks or other community sources such

as patient advocacy groups. All patient-facing materials must be reviewed/approved by the sponsor and the local IRB/IEC.

Informed Consent Process

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

The investigator or his/her delegated representative will explain to the subject, or his/her legally authorized representative, the aims, methods, anticipated benefits, and potential hazards of the study before any protocol-specific screening procedures or any investigational product(s) is/are administered, and answer all questions regarding the study.

Subjects must be informed that their participation is voluntary. Subjects or their legally authorized representative [defined as an individual or other body authorized under applicable law to consent, on behalf of a prospective subject, to the subject's participation in the clinical study] will then be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act requirements, where applicable, and the IRB/IEC or study site.

The medical record must include a statement that written informed consent was obtained before the subject was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.

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 unless it is a local requirement. The investigator shall then inform the primary care physician. 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 ICF is to be signed and personally dated by the subject or a legally

acceptable representative and by the person who conducted the informed consent discussion. Subject withdrawal of consent or discontinuation from study treatment and/or procedures must also be documented in the subject's medical records; refer to Section 7.

Subjects must be re-consented to the most current version of the ICF(s) during their participation in the study.

The original signed ICF is to be retained in accordance with institutional policy, and a copy of the ICF(s) must be provided to the subject or the subject's legally authorized representative.

A subject who is rescreened is not required to sign another ICF if the rescreening occurs within 28 days from the previous ICF signature date.

The ICF will contain a separate section that addresses the use of remaining mandatory samples for optional future research. The investigator or authorized designee will explain to each subject the objectives of the future research. Subjects will be told that they are free to refuse to participate and may withdraw their specimens at any time and for any reason during the storage period. A separate signature will be required to document a subject's agreement to allow any remaining specimens to be used for future research. Subjects who decline to participate will not provide this separate signature.

Data Protection/Subject Confidentiality

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

Subject will be assigned a unique identifier by the sponsor. Any subject records or datasets that are transferred to the sponsor will contain the identifier only; subject names or any information which would make the subject identifiable will not be transferred.

On the case report form (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 age (in accordance with local laws and regulations).

Documents that are not submitted to Amgen (eg, signed ICFs) are to be kept in confidence by the investigator, except as described below.

In compliance with governmental 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.

Publication Policy

To coordinate dissemination of data from this study, Amgen may facilitate the formation of a publication committee consisting of several investigators and appropriate Amgen staff, the governance and responsibilities of which are set forth in a Publication Charter. The committee is expected to solicit input and assistance from other investigators and to collaborate with authors and Amgen staff, as appropriate, as defined in the Publication Charter. Membership on the committee (both for investigators and Amgen staff) does not guarantee authorship. The criteria described below are to be met for every publication.

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 Recommendations for the Conduct of Reporting, Editing, and Publications of Scholarly Work in Medical Journals, which states: Authorship credit is to 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; and (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 need to meet conditions 1, 2, 3, and 4.

When a large, multicenter group has conducted the work, the group is to identify the individuals who accept direct responsibility for the manuscript. These individuals must 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 must qualify for authorship, and all those who qualify are

to be listed. Each author must 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.

Investigator Signatory Obligations

Each clinical study report is to be signed by the investigator or, in the case of multicenter 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

Data Quality Assurance

All subject data relating to the study will be recorded on printed or electronic CRF unless transmitted to the sponsor or designee electronically (eg, laboratory data, centrally or adjudicated data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.

The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.

The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.

The sponsor or designee is responsible for the data management of this study including quality checking of the data.

Clinical monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of subjects are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements per the sponsor's monitoring plan.

If permitted by national and/or local regulations, remote Source Data Review and Verification (rSDR/V) can be implemented. The clinical monitor should be provided with a secure, read-only access to the Electronic Medical Record (EMR) system, including all modules relevant for review. This access should be restricted to the records of only those subjects who participate in the trial and who did not object to remote access to their medical records. A list of the monitors to whom remote access has been granted should be maintained. In order to prevent unauthorized access, access rights should be revoked once rSDR/V tasks have been completed for the trial. If EMR is to be utilized, the site should attempt to ensure that the EMR system has an audit trail and is be able to log information on who accessed data and when. In addition, the site should attempt to ensure that remote access to the EMR should only be possible using a two-factor authentication.

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.

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.

In accordance with ICH GCP and the sponsor's audit plans, this study may be selected for audit by representatives from Amgen's Global Research and Development Compliance and Audit 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.

Retention of study documents will be governed by the Clinical Trial Agreement. Case report forms must be completed in English. TRADENAMES® (if used) for concomitant medications may be entered in the local language. Consult the country-specific language requirements.

All written information and other material to be used by subjects and investigative staff must use vocabulary and language that are clearly understood.

Source Documents

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 provide evidence for the existence of the subject and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.

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. Source documents may also include data captured in the Interactive Response Technology (IRT) system (if used, such as subject identifier (ID) and randomization number) and CRF entries if the CRF is the site of the original recording (ie, there is no other written or electronic record of data, such as paper questionnaires for a clinical outcome assessment).

Data reported on the CRF or entered in the electronic CRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

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, ICFs, 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, 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) or combination product(s) documentation, as applicable
- Retention of study documents will be governed by the Clinical Trial Agreement.

Remote Source Data Review and Verification

If permitted by national and/or local regulations, remote Source Data Review and Verification (rSDR/V) can be implemented. The clinical monitor should be provided with a secure, read-only access to the Electronic Medical Record (EMR) system, including all modules relevant for review. This access should be restricted to the records of only those subjects who participate in the trial and who did not object to remote access to their medical records. A list of the monitors to whom remote access has been granted should be maintained. In order to prevent unauthorized access, access rights should be revoked once rSDR/V tasks have been completed for the trial. The EMR system should have an audit trail and be able to log information on who accessed data and when. Remote access to the EMR should only be possible using a two-factor authentication.

Study and Site Closure

Amgen or its designee may stop the study or study site participation in the study for medical, safety, regulatory, administrative, or other reasons consistent with applicable laws, regulations, and GCP.

Both Amgen and the Investigator reserve the right to terminate the Investigator's participation in the study according to the Clinical Trial Agreement. 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.

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.

11.4 Appendix 4. Safety Events: Definitions and Procedures for Recording, Evaluating, Follow-up and Reporting

Definition of Adverse Event

Adverse Event Definition
• An adverse event is any untoward medical occurrence in a clinical study subject irrespective of a causal relationship with the study treatment. • Note: An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a treatment, combination product, medical device or procedure. • Note: Treatment-emergent adverse events will be defined in the statistical analysis plan (SAP).

Events Meeting the Adverse Event Definition
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital signs measurements), including those that worsen from baseline, that are considered clinically significant in the medical and scientific judgment of the investigator (ie, not related to progression of underlying disease). • Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition. • New conditions detected or diagnosed after study treatment administration even though it may have been present before the start of the study. • Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction. • Signs, symptoms, or the clinical sequelae of a suspected overdose of either study treatment or a concomitant medication. Overdose per se will not be reported as an adverse event/serious adverse event unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses are to be reported regardless of sequelae. • For situations when an adverse event or serious adverse event is due to non-small cell lung cancer (NSCLC), 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 adverse event. • “Lack of efficacy” or “failure of expected pharmacological action” per se will not be reported as an adverse event or serious adverse event. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as adverse event or serious adverse event if they fulfill the definition of an adverse event or serious adverse event.

Events NOT Meeting the Adverse Event Definition
• Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the adverse event. • Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital). • Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

Definition of Serious Adverse Event

A Serious Adverse Event is defined as any untoward medical occurrence that, meets at least 1 of the following serious criteria:
Results in death (fatal)
Immediately life-threatening The term "life-threatening" in the definition of "serious" refers to an event in which the subject was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.
Requires in-patient hospitalization or prolongation of existing hospitalization In general, hospitalization signifies that the subject has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are an adverse event. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the adverse event is to be considered serious. Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an adverse event.
Results in persistent or significant disability/incapacity The term disability means a substantial disruption of a person's ability to conduct normal life functions. This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

Is a congenital anomaly/birth defect
Other medically important serious event Medical or scientific judgment is to be exercised in deciding whether serious adverse event reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require medical or surgical intervention to prevent 1 of the other outcomes listed in the above definition. These events are typically to be considered serious. Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

Recording Adverse Events and Serious Adverse Events

Adverse Event and Serious Adverse Event Recording

- When an adverse event or serious adverse event occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory, and diagnostics reports) related to the event.
- The investigator will then record all relevant adverse event/serious adverse event information in the Event**s** case report form (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);
  - Did the event start prior to first dose of investigational product, other protocol-required therapies;
  - Assessment of seriousness;
  - Severity (or toxicity defined below);
  - Assessment of relatedness to investigational product (AMG 510, docetaxel), or other protocol-related therapies**, and/or study-mandated activity and/or procedures**;
  - Action taken; and
  - Outcome of 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**s** CRF
- It is not acceptable for the investigator to send photocopies of the subject's medical records to Amgen in lieu of completion of the Event**s** CRF page.
- If specifically requested, the investigator may need to provide additional follow-up information, such as discharge summaries, medical records, or extracts from the medical records. In this case, all subject identifiers, with the exception of the subject number, will be blinded on the copies of the medical records before submission to Amgen.

- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. In such cases, the diagnosis (not the individual signs/symptoms) will be documented as the adverse event/serious adverse event.

Evaluating Adverse Events and Serious Adverse Events

Assessment of Severity

The investigator will make an assessment of severity for each adverse event and serious adverse event reported during the study. The assessment of severity will be based on:
The **Common Terminology Criteria for Adverse Events**, version 5.0 which is available at the following location:
http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

Assessment of Causality

- The investigator is obligated to assess the relationship between investigational product (AMG 510, docetaxel), protocol-related therapies, and/or study mandated **activity and/or** procedure**s** and each occurrence of each adverse event/serious adverse event.
- Relatedness means that there are facts or reasons to support a relationship between investigational product and the event.
- The investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study treatment administration will be considered and investigated.
- The investigator will also consult the Investigator's Brochure and/or Product Information, for marketed products, in his/her assessment.
- For each adverse event/serious adverse event, the investigator must document in the medical notes that he/she has reviewed the adverse event/serious adverse event and has provided an assessment of causality.
- There may be situations in which a serious adverse event has occurred and the investigator has minimal information to include in the initial report. However, it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the serious adverse event data.
- The investigator may change his/her opinion of causality in light of follow-up information and send a serious adverse event follow-up report with the updated causality assessment.
- The causality assessment is 1 of the criteria used when determining regulatory reporting requirements.

Follow-up of Adverse Event and Serious Adverse Event
• The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by Amgen to elucidate the nature and/or causality of the adverse event or serious adverse event as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals. • If a subject is permanently withdrawn from protocol-required therapies because of a serious adverse event, this information must be submitted to Amgen. • If a subject dies during participation in the study or during a recognized follow-up period, the investigator should provide Amgen with a copy of any post-mortem findings including histopathology, if available. • New or updated information will be recorded in the originally completed Event CRF. • The investigator will submit any updated serious adverse event data to Amgen within 24 hours of receipt of the information.

Reporting of Serious Adverse Event

Serious Adverse Event Reporting via Electronic Data Collection Tool
• The primary mechanism for reporting serious adverse event will be the electronic data capture (EDC) system. • If the EDC system is unavailable for more than 24 hours, then the site will report the information to Amgen using a **paper-based** Serious Adverse **Event** Contingency Report Form (**also referred to as the electronic Serious Adverse Event [eSAE] Contingency Report Form;** see Figure 11-1) within 24 hours of the investigator's awareness of the event. • The site will enter the serious adverse event data into the electronic system as soon as it becomes available. • After the study is completed at a given site, the EDC system will be taken off-line to prevent the entry of new data or changes to existing data. • If a site receives a report of a new serious adverse event from a study subject or receives updated data on a previously reported serious adverse event after the EDC has been taken off-line, then the site can report this information on a paper**-based** Serious Adverse Event **Contingency** Report Form **(see Figure 11-1)**. • Once the study has ended, serious adverse event(s) **suspected to be related to investigational products** should be reported to Amgen (regardless of causality) if the investigator becomes aware of a serious adverse event. The investigator should use the paper-based Serious Adverse Event Contingency Report Form to report the event.

Figure 11-1. Sample Electronic Serious Adverse Event Contingency Report Form

General Instructions

The protocol will provide instruction on what types of events to report for the study. This form is to be used ONLY to report events that must be captured in the Amgen safety database. *Indicates a mandatory field.

Types of Events to be reported on this form

- **Serious Adverse Events (regardless of causal relationship to investigational product [IP])**

1. **Site Information**

   Site Number* – Enter your assigned site number for this study

   Investigator*, Country*, Reporter*, Phone No., and Fax No. – Enter information requested

2. **Subject Information**

   Subject ID Number* – Enter the entire number assigned to the subject

   Age at event onset, Sex, and Race – Enter the subject's demographic information

   End of Study date – If the subject has already completed the study or terminated the study early, enter the End of Study date

If you are submitting follow-up information to a previous report, provide the serious adverse event term for the previous report as well as the start date for the initial event.

3. **Serious Adverse Event**

   Provide the date the Investigator became aware of this Information

   Serious Adverse Event Diagnosis or Syndrome* –
   - If the diagnosis is known, it should be entered. Do not list all signs/symptoms if they are included in the diagnosis.
   - If a diagnosis is not known, the relevant signs/symptoms should be entered.
   - If the event is fatal, the cause of death should be entered and autopsy results should be submitted, when available.

   Date Started* – Enter date the adverse event first started (not the date on which the event met serious criteria) rather than the date of diagnosis or hospitalization. **This is a mandatory field.**

   Date Ended – Enter date the adverse event ended and not the date when the event no longer met serious criteria. If the event has not ended at the time of the initial report, a follow-up report should be completed when the end date is known. If the event is fatal, enter the date of death as the end date.

   If event occurred before the first dose of Investigational Product /drug under study, add a check mark in the corresponding box.

   Is event serious?* – Indicate Yes or No. This is a mandatory field.

   Serious Criteria Code* – This is a mandatory field for serious events. Enter all reasons why the reported event has met serious criteria:
   - Immediately life-threatening – Use only if the subject was at immediate risk of death from the event as it occurred. Emergency treatment is often required to sustain life in this situation.
   - If the investigator decides an event should be reported in an expedited manner, but it does not meet other serious criteria, "Other Medically Important Serious Event" may be the appropriate serious criterion.

   Relationship to Investigational Product – The Investigator must determine and enter the relationship of the event to the investigational product at the time the event is initially reported. **This is a mandatory field.**

   Relationship to Amgen device* – The Investigator must determine and enter the relationship of the event to the Amgen device (eg, prefilled syringe, auto-injector) at the time the event is initially reported. **If the study involves an Amgen device, this is a mandatory field. This question does not apply to non-Amgen devices used in the study (eg, heating pads, infusion pumps)**

   Outcome of Event* – Enter the code for the outcome of the event at the time the form is completed. **This is a mandatory field.**
   - Resolved – End date is known
   - Not resolved / Unknown – End date is unknown
   - Fatal – Event led to death

   If event is related to a study procedure, such as a biopsy, radiotherapy or withdrawal of a current drug treatment during a wash-out period, add a check mark to the corresponding box. This does not include relationship to investigational product or concomitant medication – only diagnostic tests or activities mandated by the protocol.

4. **Hospitalization**

   If the subject was hospitalized, enter admission and discharge dates. Hospitalization is any in-patient hospital admission for medical reasons, including an overnight stay in a healthcare facility, regardless of duration. A pre-existing condition that did

   not worsen while on study which involved a hospitalization for an elective treatment, is not considered an adverse event. Protocol specified hospitalizations are exempt.

At the top of Page 2, provide your Site Number and the Subject ID Number in the designated section.

5. **Investigational Product Administration including Lot # and Serial # when known / available.**

   Blinded or open-label – If applicable, indicate whether the investigational product is blinded or open-label

   Initial Start Date – Enter date the product was first administered, regardless of dose.

   Date of Dose Prior to or at the time of the Event – Enter date the product was last administered prior to, or at the time of, the onset of the event.

   Dose, Route, and Frequency at or prior to the event – Enter the appropriate information for the dose, route and frequency at, or prior to, the onset of the event.

   Action Taken with Product – Enter the status of the product administration.

6. **Concomitant Medications**

   Indicate if there are any medications.

   Medication Name, Start Date, Stop Date, Dose, Route, and Frequency – Enter information for any other medications the subject is taking. Include any study drugs not included in Section 5 (Product Administration) such as chemotherapy, which may be considered co-suspect.

   Co-suspect – Indicate if the medication is co-suspect in the event

   Continuing – Indicate if the subject is still taking the medication

   Event Treatment – Indicate if the medication was used to treat the event

7. **Relevant Medical History**

   Enter medical history that is relevant to the reported event, not the event description. This may include pre-existing conditions that contributed to the event allergies and any relevant prior therapy, such as radiation. Include dates if available.

8. **Relevant Laboratory Tests**

   Indicate if there are any relevant laboratory values.

   For each test type, enter the test name, units, date the test was run and the results.

9. **Other Relevant Tests**

   Indicate if there are any tests, including any diagnostics or procedures.

   For each test type, enter the date, name, results and units (if applicable).

At the top of Page 3, provide your Site Number and the Subject ID Number in the designated section.

10. **Case Description**

    Describe Event – Enter summary of the event. Provide narrative details of the events listed in Section 3. Include any therapy administered, such as radiotherapy; (excluding medications, which will be captured in Section 6). If necessary, provide additional pages to Amgen.

Complete the signature section at the bottom of page 3 and fax the form to Amgen. *If the reporter is not the investigator, designee must be identified on the Delegation of Authority form.*

A Study # 20190009 AMG 510	**Electronic Serious 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

USTO fax #: 1-888-814-8653 (for within US); Non-US fax #: +44 20 7136 1046 (non-US countries)

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. SERIOUS ADVERSE EVENT

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

Serious 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 death. 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	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 or an Amgen device used to administer the IP? AMG 510: No ✓ Yes ✓ Docetaxel: No ✓ Yes ✓ <Device>: No ✓ Yes ✓ <Device>: 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

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

IP/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 510	☐ blinded ☒ open label							Lot # _____ ☐ Unknown Serial # _____ ☐ Unavailable / Unknown
Docetaxel	☐ blinded ☒ open label							Lot # _____ ☐ Unknown Serial # _____ ☐ Unavailable / Unknown

A Study # 20190009 AMG 510	Electronic Serious Adverse Event Contingency Report Form For Restricted Use

Site Number	Subject ID Number

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

A Study # 20190009 AMG 510	Electronic Serious 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 - *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.*	Title	Date

11.5 Appendix 5. Contraceptive Guidance and Collection of Pregnancy and Lactation Information

Study-specific contraception requirements for male and female of childbearing potential are outlined in Section 5.2.

Male and female subjects of childbearing potential must receive pregnancy prevention counseling and be advised of the risk to the fetus if they become pregnant or father a child during treatment and for 7 days after the last dose of AMG 510 for female subjects and 7 days after the last dose of AMG 510 for male subjects, and during treatment with docetaxel and 6 months after the last dose of docetaxel for male and female subjects.

Additional medications given during the study may alter the contraceptive requirements. These additional medications may require female subjects to use highly effective methods of contraception and/or for an increased length of time. In addition, male subjects may also be required to use contraception. The investigator must discuss these contraceptive changes with the subject.

Definition of Females of Childbearing Potential

A female is considered fertile following menarche and until becoming post-menopausal unless permanently sterile. Permanent sterilization methods include hysterectomy, bilateral salpingectomy, and bilateral oophorectomy.

Females in the following categories are not considered female of childbearing potential:

- Premenopausal female with 1 of the following:
  - Documented hysterectomy;
  - Documented bilateral salpingectomy; or
  - Documented bilateral oophorectomy.

  Note: Site personnel documentation from the following sources is acceptable: 1) review of subject's medical records; 2) subject's medical examination; or 3) subject's medical history interview.
- Premenarchal female
- Postmenopausal female
  - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle stimulating 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 (HRT). However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.

- Females on HRT and whose menopausal status is in doubt will be required to use 1 of the non-hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment

Contraception Methods for Female Subjects

Highly Effective Contraceptive Methods

Note: Failure rate of < 1% per year when used consistently and correctly.

- Intrauterine device (IUD)
- Bilateral tubal ligation/occlusion
- Vasectomized partner (provided that partner is the sole sexual partner of the female subject of childbearing potential and that the vasectomized partner has received medical assessment of the surgical success)
- Sexual abstinence (defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments; the reliability of sexual abstinence must be evaluated in relation to the duration of the trial and the preferred and usual lifestyle of the subject)

Contraception Methods for Male Subjects

- Sexual abstinence (defined as refraining from heterosexual intercourse during the entire period of risk associated with protocol-required therapies; the reliability of sexual abstinence must be evaluated in relation to the duration of the trial and the preferred and usual lifestyle of the subject)
- Use a condom during treatment and for an additional 7 days (AMG 510) or 6 months (docetaxel) after the last dose of protocol-required therapies

The female partner should consider using an acceptable method of effective contraception such as: hormonal IUD, intrauterine hormonal-releasing system (IUS), female barrier method (diaphragm, cap, sponge [a female condom is not an option because there is a risk of tearing when both partners use a condom]).

Note: If the male's sole female partner is of non-childbearing potential or has had a bilateral tubal ligation/occlusion, he is not required to use additional forms of contraception during the study.

Unacceptable Methods of Birth Control for Male and Female Subjects

Birth control methods that are considered unacceptable in clinical trials include:

- Periodic abstinence (calendar, symptothermal, post-ovulation methods)
- Withdrawal (coitus interruptus)
- Spermicides only
- Lactational amenorrhea method

Collection of Pregnancy Information

Female Subjects Who Become Pregnant

- Investigator will collect pregnancy information on any female subject who becomes pregnant while taking protocol-required therapies through 7 days after last dose of AMG 510 and 6 months after the last dose of docetaxel.
- Information will be recorded on the Pregnancy Notification Form (see Figure 11-2). The form must be submitted to Amgen Global Patient Safety within 24 hours of learning of a subject's pregnancy. (Note: Sites are not required to provide any information on the Pregnancy Notification Form that violates the country or regions local privacy laws).
- After obtaining the female subject's signed authorization for release of pregnancy and infant health information, the investigator will collect pregnancy and infant health information and complete the pregnancy questionnaire for any female subject who becomes pregnant while taking protocol-required therapies through 7 days after the last dose of AMG 510 and 6 months after the last dose of docetaxel. This information will be forwarded to Amgen Global Patient Safety. Generally, infant follow-up will be conducted up to 12 months after the birth of the child (if applicable).
- Any termination of pregnancy will be reported to Amgen Global Patient Safety, regardless of fetal status (presence or absence of anomalies) or indication for procedure.
- While pregnancy itself is not considered to be an adverse event or serious adverse event, any pregnancy complication or report of a congenital anomaly or developmental delay, fetal death, or suspected adverse reactions in the neonate will be reported as an adverse event or serious adverse event. Note that an elective termination with no information on a fetal congenital malformation or maternal complication is generally not considered an adverse event, but still must be reported to Amgen as a pregnancy exposure case.
- 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.
- Any serious adverse event occurring as a result of a post-study pregnancy which is considered reasonably related to the study treatment by the investigator, will be reported to Amgen Global Patient Safety as described in Section 11.4. While the investigator is not obligated to actively seek this information in former study subjects, he or she may learn of a serious adverse event through spontaneous reporting.
- Any female subject who becomes pregnant while participating will discontinue study treatment (see Section 7.1 for details).

Male Subjects With Partners Who Become Pregnant

- In the event a male subject fathers a child during treatment, and for an additional 7 days (AMG 510) or 6 months (docetaxel) after discontinuing protocol-required therapies, the information will be recorded on the Pregnancy Notification Form. The form (see Figure 11-2) must be submitted to Amgen Global Patient Safety within 24 hours of the site's awareness of the pregnancy. (Note: Sites are not required to provide any information on the Pregnancy Notification Form that violates the country or regions local privacy laws).
- The investigator will attempt to obtain a signed authorization for release of pregnancy and infant health information directly from the pregnant female partner to obtain additional pregnancy information.
- After obtaining the female partner's signed authorization for release of pregnancy and infant health information, the investigator will collect pregnancy outcome and infant health information on the pregnant partner and her baby and complete the pregnancy questionnaires. This information will be forwarded to Amgen Global Patient Safety.
- Generally, infant follow-up will be conducted up to 12 months after the birth of the child (if applicable).
- Any termination of the pregnancy will be reported to Amgen Global Patient Safety regardless of fetal status (presence or absence of anomalies) or indication for procedure.

Collection of Lactation Information

- Investigator will collect lactation information on any female subject who breastfeeds while taking protocol-required therapies through 7 days post final dose.
- Information will be recorded on the Lactation Notification Form (see below) and submitted to Amgen Global Patient Safety within 24 hours of the investigator's knowledge of event.
- Study treatment will be discontinued if female subject breastfeeds during the study as described in exclusion criterion 226.
- With the female subjects signed authorization for release of mother and infant health information, the investigator will collect mother and infant health information and complete the lactation questionnaire on any female subject who breastfeeds while taking protocol-required therapies through 7 days after discontinuing protocol-required therapies.

Figure 11-2. Pregnancy and Lactation Notification Forms

AMGEN® Pregnancy Notification Form

Report to Amgen at: USTO fax: +1-888-814-8653, Non-US fax: +44 (0)207-136-1046 or email (worldwide): svc-ags-in-us@amgen.com

1. Case Administrative Information

Protocol/Study Number: 20190009

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 age (at onset):**____(in years)

4. Amgen Product Exposure

Amgen Product	Dose at time of conception	Frequency	Route	Start Date
AMG 510				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 last menstrual period (LMP) mm_____/ dd_____/ yyyy_____ ☐Unknown ☐N/A

Estimated date of delivery mm_____/ dd_____/ yyyy_____

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:** _____

FORM-115199 Version 1.0 Effective Date: 24-Sept-2018

AMGEN® Lactation Notification Form

Report to Amgen at: USTO fax: +1-888-814-8653, Non-US fax: +44 (0)207-136-1046 or email (worldwide): svc-ags-in-us@amgen.com

1. Case Administrative Information

Protocol/Study Number: 20190009

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 age (at onset):** ____ (in years)

4. Amgen Product Exposure

Amgen Product	Dose at time of breast feeding	Frequency	Route	Start Date
AMG 510				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:** _____

FORM-115201 Version 1.0 Effective Date: 24-Sept-2018

11.6 Appendix 6. Sample Storage and Destruction

Any blood, biopsy, biomarker, or pharmacokinetic (PK) sample collected according to the Schedule of Activities (Table 1-1 and Table 1-2) 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.

Biomarker assessment can be done only if the biomarker research is allowed according to local regulations and agreed by the local Ethics Committee (EC)/Institutional Review Board (IRB).

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 or legally acceptable representative, Amgen can do additional testing on remaining samples (ie, residual and back-up) to investigate and better understand the oncology, the dose response and/or prediction of response to AMG 510 and characterize aspects of the molecule (eg, mechanism of action/target, metabolites). Results from this analysis are to be documented and maintained, but are not 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 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.

11.7 Appendix 7. Hepatotoxicity Stopping Rules: Suggested Actions and Follow-up Assessments and Study Treatment Rechallenge Guidelines

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 Amgen investigational product or other protocol-required therapies, as specified in the *Guidance for Industry Drug-Induced Liver Injury: Premarketing Clinical Evaluation, July 2009*.

Criteria for Withholding and/or Permanent Discontinuation of Amgen Investigational Product and Other Protocol-required Therapies Due to Potential Hepatotoxicity

The following stopping and/or withholding rules apply to subjects for whom another cause of their changes in liver biomarkers (TBL, INR, and transaminases) has not been identified.

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
- Non-hepatic causes (eg, rhabdomyolysis, hemolysis)

If investigational product(s) is/are withheld, the subject is to be followed for possible drug induced liver injury (DILI) according to recommendations in the last section of this appendix.

Re-challenge may be considered if an alternative cause for impaired liver tests (ALT, AST, ALP) and/or elevated TBL, is discovered and/or the laboratory abnormalities resolve to normal or baseline (see next section in this appendix).

Table 11-2. Conditions for Withholding and/or Permanent Discontinuation of Amgen Investigational Product and Other Protocol-required Therapies Due to Potential Hepatotoxicity

Analyte	Temporary Withholding	Permanent Discontinuation
TBL	> 3 x ULN at any time	> 2 x ULN
		OR
INR	--	> 1.5 x (for subjects not on anticoagulation therapy)
	OR	AND
AST/ALT	> 5 x ULN at any time > 3 x ULN with clinical signs or symptoms that are consistent with hepatitis (such as right upper quadrant pain/tenderness, fever, nausea, vomiting, and jaundice)	In the presence of no important alternative causes for elevated AST/ALT and/or TBL values > 3 x ULN (when baseline was < ULN)
	OR	
ALP	> 8 x ULN at any time	--

ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; INR = international normalized ratio; TBL = total bilirubin; ULN = upper limit of normal.

Criteria for Re-challenge of Amgen Investigational Product and Other Protocol-required Therapies After Potential Hepatotoxicity

The decision to re-challenge the subject is to be discussed and agreed upon unanimously by the subject, investigator, and Amgen.

Subjects who clearly meet the criteria for permanent discontinuation (as described in Table 11-2.) are never to be re-challenged.

Drug-induced Liver Injury Reporting and 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 the above, 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 case report form (CRF) (eg, Event CRF) that captures information necessary to facilitate the evaluation of treatment-emergent liver abnormalities is to be completed and sent to 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 11.4.

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 Table 11-2. or who experience AST or ALT elevations > 3 x upper limit of normal (ULN) or 2-fold increases above baseline values for subjects with elevated values before drug 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 (BIL) (total and direct), and INR within 24 hours
- In cases of TBL > 2 x 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. The following are to be considered depending on the clinical situation:

- Complete blood count with differential to assess for eosinophilia
- Serum total immunoglobulin (Ig)G, anti-nuclear antibody, anti-smooth muscle antibody, and liver kidney microsomal antibody-1 to assess for autoimmune hepatitis
- Serum acetaminophen (paracetamol) levels
- 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
- Viral serologies
- Creatine phosphokinase, haptoglobin, lactate dehydrogenase, and peripheral blood smear
- Appropriate liver imaging if clinically indicated
- Appropriate blood sampling for pharmacokinetic analysis if this has not already been collected

Hepatology consult (liver biopsy may be considered in consultation with a hepatologist)

Follow the subject and the laboratory tests (ALT, AST, TBL, INR) until all laboratory abnormalities return to baseline or normal or considered stable by the investigator. 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 the corresponding CRFs.

11.8 Appendix 8. Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST v1.1)

MEASUREMENT OF EFFECT

Please provide response criteria. If the criteria for solid tumors below are not applicable, the investigator(s) should provide disease-appropriate criteria (eg, for specific hematologic malignancies) with references, and all solid tumor criteria should be deleted.

Antitumor Effect – Solid Tumor

For the purposes of this study, **subject**s should be re-evaluated for response every 6 weeks for the first 48 weeks and then every 9 weeks thereafter until progressive disease. In addition to a baseline scan, confirmatory scans should also be obtained at least 4 weeks following initial documentation of objective response.

Response and progression will be evaluated in this study using the new international criteria proposed by the revised Response Evaluation Criteria in Solid Tumors (RECIST) guideline (version 1.1) (RECIST **v**1.1 2009). Changes in the largest diameter (unidimensional measurement) of the tumor lesions and the shortest diameter in the case of malignant lymph nodes are used in the RECIST criteria.

Definitions

Evaluable for toxicity. All **subject**s will be evaluable for toxicity from the time of their first treatment with AMG 510 or docetaxel

Evaluable for objective response. Only those **subject**s who have measurable disease present at baseline, have received at least 1 cycle of therapy, and have had their disease re-evaluated will be considered evaluable for response. These **subject**s will have their response classified according to the definitions stated below.
(Note: **subject**s who exhibit objective disease progression prior to the end of cycle 1 will also be considered evaluable).

Evaluable Non-Target Disease Response. **Subject**s who have lesions present at baseline that are evaluable but do not meet the definitions of measurable disease, have received at least 1 cycle of therapy, and have had their disease re-evaluated will be considered evaluable for non-target disease. The response assessment is based on the presence, absence, or unequivocal progression of the lesions.

Disease Parameters

Measurable disease. Measurable lesions are defined as those that can be accurately measured in at least 1 dimension (longest diameter to be recorded) as ≥ 20 mm by chest x-ray, as ≥ 10 mm with computerized tomography (CT) scan, or ≥ 10 mm with calipers by clinical exam. All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters).

Note: Tumor lesions that are situated in a previously irradiated area might or might not be considered measurable.

Malignant lymph nodes. To be considered pathologically enlarged and measurable, a lymph node must be ≥ 15 mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed.

Non-measurable disease. All other lesions (or sites of disease), including small lesions (longest diameter < 10 mm or pathological lymph nodes with ≥ 10 to < 15 mm short axis), are considered non-measurable disease. Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonitis, inflammatory breast disease, and abdominal masses (not followed by CT or magnetic resonance imaging [MRI]), are considered as non-measurable.

Note: Cystic lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts.

'Cystic lesions' thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same **subject**, these are preferred for selection as target lesions.

Target lesions. All measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, representative of all involved organs, should be identified as target lesions and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion which can be measured reproducibly should be selected. A sum of the diameters

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

Non-target lesions. All other lesions (or sites of disease) including any measurable lesions over and above the 5 target lesions should be identified as non-target lesions and should also be recorded at baseline. Measurements of these lesions are not required, but the presence, absence, or in rare cases unequivocal progression of each should be noted throughout follow-up.

Methods for Evaluation of Measurable Disease

All measurements should be taken and recorded in metric notation using a ruler or calipers. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 4 weeks before the beginning of the treatment.

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging-based evaluation is preferred to evaluation by clinical examination unless the lesion(s) being followed cannot be imaged but are assessable by clinical exam.

Clinical lesions: Clinical lesions will only be considered measurable when they are superficial (eg, skin nodules and palpable lymph nodes) and ≥ 10 mm diameter as assessed using calipers (eg, skin nodules). In the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.

Chest x-ray: Lesions on chest x-ray are acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung. However, CT chest is preferred and as specified in the Imaging manual, CT chest **is** to be utilized for scheduled imaging assessment.

Conventional CT and MRI: This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. If CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. Magnetic resonance imaging is also acceptable in certain situations (eg, for body scans).

Use of MRI remains a complex issue. Magnetic resonance imaging has excellent contrast, spatial, and temporal resolution; however, there are many image acquisition variables involved in MRI, which greatly impact image quality, lesion conspicuity, and measurement. Furthermore, the availability of MRI is variable globally. As with CT, if an MRI is performed, the technical specifications of the scanning sequences used should be optimized for the evaluation of the type and site of disease. It is beyond the scope of the RECIST guidelines to prescribe specific MRI pulse sequence parameters for all scanners, body parts, and diseases. Ideally, the same type of scanner should be used and the image acquisition protocol should be followed as closely as possible to prior scans. Body scans should be performed with breath-hold scanning techniques, if possible.

Positron Emission Tomography-Computer Tomography (PET-CT): At present, the low dose or attenuation correction CT portion of a combined PET-CT is not always of optimal diagnostic CT quality for use with RECIST measurements. However, if the site can document that the CT performed as part of a PET-CT is of identical diagnostic quality to a diagnostic CT (with Intravenous (IV) and oral contrast), then the CT portion of the PET-CT can be used for RECIST measurements and can be used interchangeably with conventional CT in accurately measuring cancer lesions over time. Note, however, that the PET portion of the CT introduces additional data which may bias an investigator if it is not routinely or serially performed.

Ultrasound: Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement. Ultrasound examinations cannot be reproduced in their entirety for independent review at a later date and, because they are operator dependent, it cannot be guaranteed that the same technique and measurements will be taken from one assessment to the next. If new lesions are identified by ultrasound in the course of the study, confirmation by CT or MRI is advised. If there is concern about radiation exposure at CT, MRI may be used instead of CT in selected instances.

Endoscopy, Laparoscopy: The utilization of these techniques for objective tumor evaluation is not advised. However, such techniques may be useful to confirm complete pathological response when biopsies are obtained or to determine relapse in trials where recurrence following complete response (CR) or surgical resection is an endpoint.

Tumor markers: Tumor markers alone cannot be used to assess response. If markers are initially above the upper normal limit, they must normalize for a **subject** to be considered in complete clinical response. Specific guidelines for both CA-125 response

(in recurrent ovarian cancer) and Prostate Specific Antigen (PSA) response (in recurrent prostate cancer) have been published [*JNCI* 96:487-488, 2004; *J Clin Oncol* 17, 3461-3467, 1999; *J Clin Oncol* 26:1148-1159, 2008]. In addition, the Gynecologic Cancer Intergroup has developed CA-125 progression criteria which are to be integrated with objective tumor assessment for use in first-line trials in ovarian cancer [*JNCI* 92:1534-1535, 2000].

Cytology, Histology: These techniques can be used to differentiate between partial responses (PRs) and CRs in rare cases (eg, residual lesions in tumor types, such as germ cell tumors, where known residual benign tumors can remain).

Response Criteria
Evaluation of Target Lesions

Complete Response: Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to < 10 mm.

Partial Response: At least a 30% decrease in the sum of the diameters of target lesions, taking as reference the baseline sum diameters.

Progressive Disease (PD): At least a 20% increase in the sum of the diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progressions).

Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.

Evaluation of Non-target Lesions

Complete Response: Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (< 10 mm short axis).

Note: If tumor markers are initially above the upper normal limit, they must normalize for a **subject** to be considered in complete clinical response.

Non-CR/Non-PD: Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits.

Progressive Disease: Appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions. Unequivocal progression should not normally trump target lesion status. It must be representative of overall disease status change, not a single lesion increase.

Although a clear progression of "non-target" lesions only is exceptional, the opinion of the treating physician should prevail in such circumstances, and the progression status should be confirmed at a later time by the review panel (or Principal Investigator).

Evaluation of Best Overall Response

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for PD the smallest measurements recorded since the treatment started). The **subject**'s best response assignment will depend on the achievement of both measurement and confirmation criteria.

For Subjects With Measurable Disease (ie, Target Disease)

Target Lesions	Non-target Lesions	New Lesions	Overall Response	Best Overall Response when Confirmation is Required*
CR	CR	No	CR	≥ 4 wks Confirmation**
CR	Non-CR/Non-PD	No	PR	≥ 4 wks Confirmation**
CR	Not evaluated	No	PR	
PR	Non-PD/Not **a**ll evaluated	No	PR	
SD	Non-PD/Not **a**ll evaluated	No	SD	Documented at least once ≥ 4 wks from baseline**
PD	Any	Yes or No	PD	No prior SD, PR, or CR
Any	PD***	Yes or No	PD	
Any	Any	Yes	PD	

CR = complete response; PD = progressive disease; PR = partial response; RECIST = Response Evaluation Criteria in Solid Tumors; SD = stable disease.
* See RECIST v1.1 manuscript for further details on what is evidence of a new lesion.
** Only for non-randomized trials with response as primary endpoint.
*** In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression.
Note: **Subject**s with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as "*symptomatic deterioration."* Every effort should be made to document the objective progression even after discontinuation of treatment.

For Subjects With Non-measurable Disease (ie, Non-target Disease)

Non-target Lesions	New Lesions	Overall Response
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD*
Not all evaluated	No	Not evaluated
Unequivocal PD	Yes or No	PD
Any	Yes	PD

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

Duration of Response

Duration of overall response: The duration of overall response is measured from the time measurement criteria are met for CR or PR (whichever is first recorded) until the first date that recurrent or PD is objectively documented, or death, whichever is earlier (taking as reference for PD the smallest measurements recorded since the treatment started).

The duration of overall CR is measured from the time measurement criteria are first met for CR until the first date that PD is objectively documented or death, whichever is earlier.

Duration of SD: Stable disease is measured from the start of the treatment until the criteria for progression are met, or death, whichever is earlier, taking as reference the smallest measurements recorded since the treatment started, including the baseline measurements.

Progression-Free Survival

PFS is defined as the duration of time from start of treatment to time of progression or death, whichever occurs first.

Response Review

A blinded independent central review committee (BICR) will perform independent assessment of individual **subject** efficacy outcomes in accordance with the RECIST v1.1. The committee will centrally review the disease related tests and assessments (Section 8.2.2.1.1) to evaluate disease progressions and responses without the knowledge of randomization assignments. This assessment will be used for the primary analysis of endpoints. The membership criteria and operational details of the BICR will be described in the BICR Charter.

Any locoregional therapy not allowed per protocol

Any subject receiving locoregional therapy not allowed in the protocol while on study that directly affects one or more of the target lesions selected at baseline will be considered to be non-evaluable at all disease assessments that occur on or after the date of locoregional therapy with the exception of disease progression. However, if a lesion was completely resected where pathology was benign the subject will still be evaluable for response with 0 dimension reported.

If locoregional therapy was performed on a non-target lesion, that lesion will always be assessed as present unless pathology was benign.

11.9 Appendix 9. QLQ-C30

ENGLISH

EORTC QLQ-C30 (version 3)

We are interested in some things about you and your health. Please answer all of the questions yourself by circling the number that best applies to you. There are no "right" or "wrong" answers. The information that you provide will remain strictly confidential.

Please fill in your initials: ____
Your birthdate (Day, Month, Year): ____
Today's date (Day, Month, Year): 31 ____

	Not at All	A Little	Quite a Bit	Very Much
1. Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?	1	2	3	4
2. Do you have any trouble taking a long walk?	1	2	3	4
3. Do you have any trouble taking a short walk outside of the house?	1	2	3	4
4. Do you need to stay in bed or a chair during the day?	1	2	3	4
5. Do you need help with eating, dressing, washing yourself or using the toilet?	1	2	3	4

During the past week:	Not at All	A Little	Quite a Bit	Very Much
6. Were you limited in doing either your work or other daily activities?	1	2	3	4
7. Were you limited in pursuing your hobbies or other leisure time activities?	1	2	3	4
8. Were you short of breath?	1	2	3	4
9. Have you had pain?	1	2	3	4
10. Did you need to rest?	1	2	3	4
11. Have you had trouble sleeping?	1	2	3	4
12. Have you felt weak?	1	2	3	4
13. Have you lacked appetite?	1	2	3	4
14. Have you felt nauseated?	1	2	3	4
15. Have you vomited?	1	2	3	4
16. Have you been constipated?	1	2	3	4

Please go on to the next page

ENGLISH

During the past week:	Not at All	A Little	Quite a Bit	Very Much
17. Have you had diarrhea?	1	2	3	4
18. Were you tired?	1	2	3	4
19. Did pain interfere with your daily activities?	1	2	3	4
20. Have you had difficulty in concentrating on things, like reading a newspaper or watching television?	1	2	3	4
21. Did you feel tense?	1	2	3	4
22. Did you worry?	1	2	3	4
23. Did you feel irritable?	1	2	3	4
24. Did you feel depressed?	1	2	3	4
25. Have you had difficulty remembering things?	1	2	3	4
26. Has your physical condition or medical treatment interfered with your family life?	1	2	3	4
27. Has your physical condition or medical treatment interfered with your social activities?	1	2	3	4
28. Has your physical condition or medical treatment caused you financial difficulties?	1	2	3	4

For the following questions please circle the number between 1 and 7 that best applies to you

29. How would you rate your overall health during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

30. How would you rate your overall quality of life during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

11.10 Appendix 10. EQ-5D-5L

Under each heading, please tick the ONE box that best describes your health TODAY.

MOBILITY

I have no problems in walking about ❑
I have slight problems in walking about ❑
I have moderate problems in walking about ❑
I have severe problems in walking about ❑
I am unable to walk about ❑

SELF-CARE

I have no problems washing or dressing myself ❑
I have slight problems washing or dressing myself ❑
I have moderate problems washing or dressing myself ❑
I have severe problems washing or dressing myself ❑
I am unable to wash or dress myself ❑

USUAL ACTIVITIES *(e.g. work, study, housework, family or leisure activities)*

I have no problems doing my usual activities ❑
I have slight problems doing my usual activities ❑
I have moderate problems doing my usual activities ❑
I have severe problems doing my usual activities ❑
I am unable to do my usual activities ❑

PAIN / DISCOMFORT

I have no pain or discomfort ❑
I have slight pain or discomfort ❑
I have moderate pain or discomfort ❑
I have severe pain or discomfort ❑
I have extreme pain or discomfort ❑

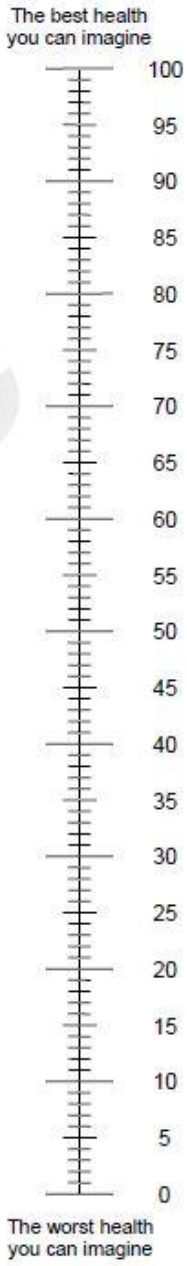
ANXIETY / DEPRESSION

I am not anxious or depressed ❑
I am slightly anxious or depressed ❑
I am moderately anxious or depressed ❑
I am severely anxious or depressed ❑
I am extremely anxious or depressed ❑

2

- We would like to know how good or bad your health is TODAY.
- This scale is numbered from 0 to 100.
- 100 means the best health you can imagine.
  0 means the worst health you can imagine.
- Mark an X on the scale to indicate how your health is TODAY.
- Now, please write the number you marked on the scale in the box below.

YOUR HEALTH TODAY = ☐



11.11 Appendix 11. QLQ-LC13

ENGLISH

EORTC QLQ - LC13

Patients sometimes report that they have the following symptoms or problems. Please indicate the extent to which you have experienced these symptoms or problems during the past week. Please answer by circling the number that best applies to you.

During the past week:		Not at All	A Little	Quite a Bit	Very Much
31.	How much did you cough?	1	2	3	4
32.	Did you cough up blood?	1	2	3	4
33.	Were you short of breath when you rested?	1	2	3	4
34.	Were you short of breath when you walked?	1	2	3	4
35.	Were you short of breath when you climbed stairs?	1	2	3	4
36.	Have you had a sore mouth or tongue?	1	2	3	4
37.	Have you had trouble swallowing?	1	2	3	4
38.	Have you had tingling hands or feet?	1	2	3	4
39.	Have you had hair loss?	1	2	3	4
40.	Have you had pain in your chest?	1	2	3	4
41.	Have you had pain in your arm or shoulder?	1	2	3	4
42.	Have you had pain in other parts of your body?	1	2	3	4
	If yes, where _____				
43.	Did you take any medicine for pain?				
	1 No 2 Yes				
	If yes, how much did it help?	1	2	3	4

11.12 Appendix 12. PGIS

Patient Global Impression of Severity

Please choose one answer for each of the following questions.

1. **How would you rate any cough you experienced in the past week?**
   - ☐ None
   - ☐ Mild
   - ☐ Moderate
   - ☐ Severe

2. **How would you rate any chest pain you experienced in the past week?**
   - ☐ None
   - ☐ Mild
   - ☐ Moderate
   - ☐ Severe

3. **How would you rate any shortness of breath you experienced in the past week?**
   - ☐ None
   - ☐ Mild
   - ☐ Moderate
   - ☐ Severe

11.13 Appendix 13. PGIC

Patient Global Impression of Change (PGIC)

1. **Compared to the beginning of this study, how would you rate your cough now?**
   - ☐ Much better
   - ☐ A little better
   - ☐ About the same
   - ☐ A little worse
   - ☐ Much worse

2. **Compared to the beginning of this study, how would you rate your chest pain now?**
   - ☐ Much better
   - ☐ A little better
   - ☐ About the same
   - ☐ A little worse
   - ☐ Much worse

3. **Compared to the beginning of this study, how would you rate your shortness of breath now?**
   - ☐ Much better
   - ☐ A little better
   - ☐ About the same
   - ☐ A little worse
   - ☐ Much worse

11.14 Appendix 14. PRO-CTCAE

NCI PRO-CTCAE™ ITEMS

Item Library Version 1.0
English
Form created on 24 August 2019

As individuals go through treatment for their cancer they sometimes experience different symptoms and side effects. For each question, please check or mark an ☒ in the one box that best describes your experiences over the past 7 days...

1.	In the last 7 days, what was the SEVERITY of your MOUTH OR THROAT SORES at their WORST?				
	○ None	○ Mild	○ Moderate	○ Severe	○ Very severe
	In the last 7 days, how much did MOUTH OR THROAT SORES INTERFERE with your usual or daily activities?				
	○ Not at all	○ A little bit	○ Somewhat	○ Quite a bit	○ Very much

2.	In the last 7 days, what was the SEVERITY of SKIN CRACKING AT THE CORNERS OF YOUR MOUTH at its WORST?				
	○ None	○ Mild	○ Moderate	○ Severe	○ Very severe

3.	In the last 7 days, what was the SEVERITY of your ITCHY SKIN at its WORST?				
	○ None	○ Mild	○ Moderate	○ Severe	○ Very severe

4.	In the last 7 days, did you LOSE ANY FINGERNAILS OR TOENAILS?	
	○ Yes	○ No

5.	In the last 7 days, did you have any RIDGES OR BUMPS ON YOUR FINGERNAILS OR TOENAILS?	
	○ Yes	○ No

6.	In the last 7 days, did you have any CHANGE IN THE COLOR OF YOUR FINGERNAILS OR TOENAILS?	
	○ Yes	○ No

7.	In the last 7 days, what was the SEVERITY of your NUMBNESS OR TINGLING IN YOUR HANDS OR FEET at its WORST?				
	○ None	○ Mild	○ Moderate	○ Severe	○ Very severe
	In the last 7 days, how much did NUMBNESS OR TINGLING IN YOUR HANDS OR FEET INTERFERE with your usual or daily activities?				
	○ Not at all	○ A little bit	○ Somewhat	○ Quite a bit	○ Very much

NCI PRO-CTCAE™ ITEMS

Item Library Version 1.0
English
Form created on 24 August 2019

8.	In the last 7 days, how OFTEN did you have PAIN?				
	○ Never	○ Rarely	○ Occasionally	○ Frequently	○ Almost constantly
	In the last 7 days, what was the SEVERITY of your PAIN at its WORST?				
	○ None	○ Mild	○ Moderate	○ Severe	○ Very severe
	In the last 7 days, how much did PAIN INTERFERE with your usual or daily activities?				
	○ Not at all	○ A little bit	○ Somewhat	○ Quite a bit	○ Very much

9.	In the last 7 days, how OFTEN did you have ACHING MUSCLES?				
	○ Never	○ Rarely	○ Occasionally	○ Frequently	○ Almost constantly
	In the last 7 days, what was the SEVERITY of your ACHING MUSCLES at their WORST?				
	○ None	○ Mild	○ Moderate	○ Severe	○ Very severe
	In the last 7 days, how much did ACHING MUSCLES INTERFERE with your usual or daily activities?				
	○ Not at all	○ A little bit	○ Somewhat	○ Quite a bit	○ Very much

10.	In the last 7 days, how OFTEN did you have ACHING JOINTS (SUCH AS ELBOWS, KNEES, SHOULDERS)?				
	○ Never	○ Rarely	○ Occasionally	○ Frequently	○ Almost constantly
	In the last 7 days, what was the SEVERITY of your ACHING JOINTS (SUCH AS ELBOWS, KNEES, SHOULDERS) at their WORST?				
	○ None	○ Mild	○ Moderate	○ Severe	○ Very severe
	In the last 7 days, how much did ACHING JOINTS (SUCH AS ELBOWS, KNEES, SHOULDERS) INTERFERE with your usual or daily activities?				
	○ Not at all	○ A little bit	○ Somewhat	○ Quite a bit	○ Very much

NCI PRO-CTCAE™ ITEMS

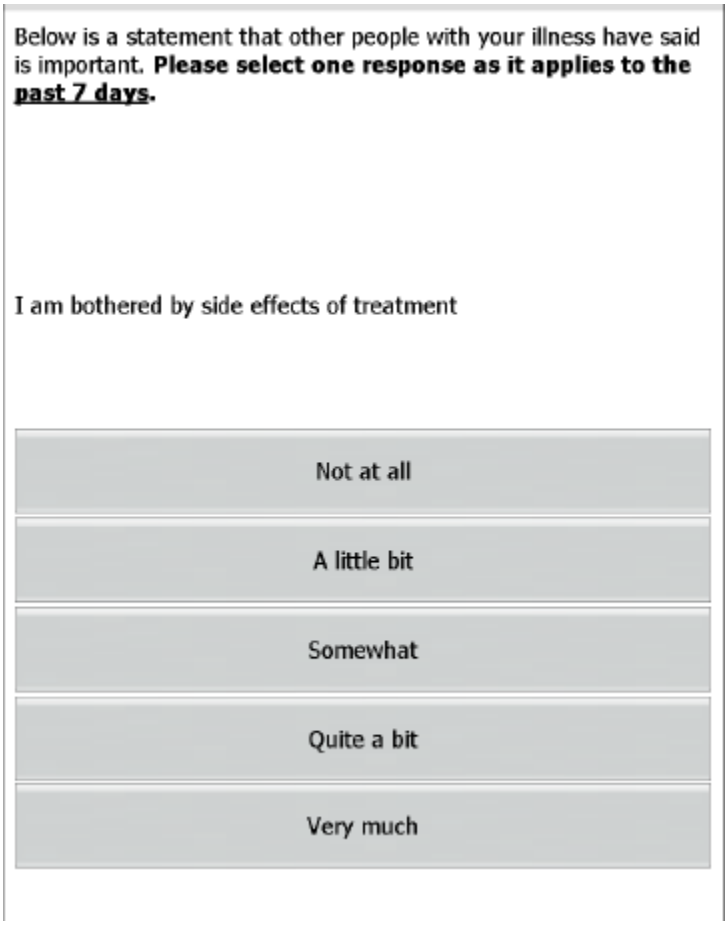
Item Library Version 1.0
English
Form created on 24 August 2019

Do you have any other symptoms that you wish to report?	
○ Yes	○ No

Please list any other symptoms:

1.	In the last 7 days, what was the SEVERITY of this symptom at its WORST?				
	○ None	○ Mild	○ Moderate	○ Severe	○ Very severe
2.	In the last 7 days, what was the SEVERITY of this symptom at its WORST?				
	○ None	○ Mild	○ Moderate	○ Severe	○ Very severe
3.	In the last 7 days, what was the SEVERITY of this symptom at its WORST?				
	○ None	○ Mild	○ Moderate	○ Severe	○ Very severe
4.	In the last 7 days, what was the SEVERITY of this symptom at its WORST?				
	○ None	○ Mild	○ Moderate	○ Severe	○ Very severe
5.	In the last 7 days, what was the SEVERITY of this symptom at its WORST?				
	○ None	○ Mild	○ Moderate	○ Severe	○ Very severe

11.15 Appendix 15. GP5 of the FACT-G



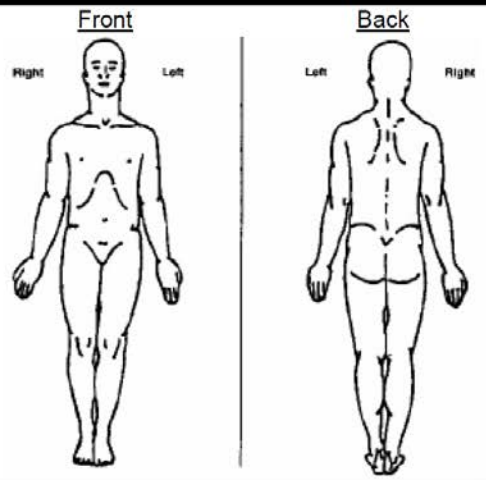
11.16 Appendix 16. Pain (BPI short form)

Brief Pain Inventory (Short Form)

1. Throughout our lives, most of us have had pain from time to time (such as minor headaches, sprains, and toothaches). Have you had pain other than these everyday kinds of pain today?

☐ Yes ☐ No

2. On the diagram, shade in the areas where you feel pain. Put an X on the area that hurts the most.



3. Please rate your pain by marking the box beside the number that best describes your pain at its worst in the last 24 hours.

☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10
No Pain — Pain As Bad As You Can Imagine

4. Please rate your pain by marking the box beside the number that best describes your pain at its least in the last 24 hours.

☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10
No Pain — Pain As Bad As You Can Imagine

5. Please rate your pain by marking the box beside the number that best describes your pain on the average.

☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10
No Pain — Pain As Bad As You Can Imagine

6. Please rate your pain by marking the box beside the number that tells how much pain you have right now.

☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10
No Pain — Pain As Bad As You Can Imagine

Page 1 of 2

7. What treatments or medications are you receiving for your pain?

8. In the last 24 hours, how much relief have pain treatments or medications provided? Please mark the box below the percentage that most shows how much relief you have received.

0%	10%	20%	30%	40%	50%	60%	70%	80%	90%	100%
☐ No Relief	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐ Complete Relief

9. Mark the box beside the number that describes how, during the past 24 hours, pain has interfered with your:

A. General Activity

☐ 0 Does Not Interfere ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 Completely Interferes

B. Mood

☐ 0 Does Not Interfere ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 Completely Interferes

C. Walking ability

☐ 0 Does Not Interfere ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 Completely Interferes

D. Normal Work (includes both work outside the home and housework)

☐ 0 Does Not Interfere ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 Completely Interferes

E. Relations with other people

☐ 0 Does Not Interfere ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 Completely Interferes

F. Sleep

☐ 0 Does Not Interfere ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 Completely Interferes

G. Enjoyment of life

☐ 0 Does Not Interfere ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 Completely Interferes

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Amendment 4

Protocol Title: A Phase 3 Multicenter, Randomized, Open Label, Active-controlled, Study of AMG 510 Versus Docetaxel for the Treatment of Previously Treated Locally Advanced and Unresectable or Metastatic NSCLC Subjects With Mutated KRAS p.G12C

Amgen Protocol Number AMG 510 (20190009)

EudraCT Number: 2019-003582-18

NCT Number: NCT04303780

Amendment Date: 06 January 2022

Rationale:

This protocol is being amended to include program wide pneumonitis safety language, to clarify the definition of an "Amgen product", to include language inadvertently left out of protocol amendment 3 with regards to hepatotoxicity, and to relax the crossover criteria for subjects in competitor arm. Key changes are summarized below:

Added Language:

- Language added to provide details on drug administration with regards to timing. (Table 1-1 and Table 6-1). Language has been added to be consistent with other study protocols within the AMG 510 program.
- Language added to Section 2.3 regarding the known risk/adverse drug reaction of increased aspartate aminotransferase and increased alanine aminotransferase. Text is listed in IB and was inadvertently left out of previous protocol version.
- Language added to Section 2.3 to inform investigators on new risk/adverse drug reaction of pneumonitis, as determined through Amgen safety governance.
- Language added to formally define, what is considered an Amgen product in Section 6.1.6. This update provides sites and investigators with additional guidance in the event of a product complaint.
- Section 6.2.2.1 (Table 6-3). Language added as ILD/pneumonitis was determined to be a risk/adverse drug reaction with sotorasib through Amgen

safety governance. This update provides investigators with dose modification guidance in the event pneumonitis is suspected or confirmed.

- Language added to Section 6.7.2 regarding breast cancer resistance protein (BCRP) to be consistent to other study protocols within the program. During the review of the NSCLC marketing application, Amgen received a postmarket requirement to conduct a clinical drug interaction study to assess the effect of concomitant AMG 510 administration on the systemic exposure of BCRP transporter substrates. This study is ongoing.
- Language added to align with the existing language in the Schedule of Activities and clarify SAE reporting requirements after end of study in Sections 8.2.4.1.3 and Appendix 4.

Relocated and Clarified Language:

- Language located in previous protocol versions but moved to Section 6.7.2, Section 8.1.3, and Section 8.1.8 to ensure clarity for sites and investigators as well as for protocol cohesion.
- Language added for clarification with regards to type of steroid(s) that can be utilized in the event of increased LFTs in Section 6.2.3 (Table 6-6, footnotes). In addition to provide guidance on timing of steroid administration with regards to resuming AMG 510. This clarification will ensure adequate treatment of increased LFTs and reduce early termination of study drug.
- Language added for further clarification in Section 8 and Appendix 3. This language will accommodate any restrictions with regards subject visits/data monitoring due to COVID-19.
- Language clarified in Section 8.1.8 (Crossover Condition 1) to accommodate crossover in subjects who have non-significant adverse events (alopecia and nail discoloration) related to docetaxel. This will allow more subjects the opportunity to access to crossover and not limiting subjects from crossing over if there are non-significant adverse events noted.

Amendment 3

Protocol Title: A Phase 3 Multicenter, Randomized, Open Label, Active-controlled, Study of AMG 510 Versus Docetaxel for the Treatment of Previously Treated Locally Advanced and Unresectable or Metastatic NSCLC Subjects With Mutated KRAS p.G12C

Amgen Protocol Number Sotorasib (AMG 510) 20190009

Amendment Date: 15 February 2021

Rationale:

This protocol is being amended to:

- Reduction of sample size, from n = 650 to n = 330
- Incorporation of progression-free survival (PFS) interim analysis planned at ~70% information fraction when approximately 160 PFS events observed from both arms.
- Allow subjects enrolled into docetaxel arm to crossover to AMG 510 upon disease progression confirmed by blinded independent central review (BICR) or should early efficacy of the study be noted by the Data Monitoring Committee (DMC) at the PFS interim analysis
- Removal of urine microscopy and urine electrolytes from lab assessments schedule of activities (SOA) and analyte table
- Update to “AMG 510 Dose Modification Guidelines for Hematologic and Non-hematologic Toxicities Table 6-3”, Section “Renal Dysfunction” updated to “Non-hematologic Toxicities”
- Addition of P-gp sensitive substrates (with a narrow therapeutic index) to exclusion criterion 222
- Addition of language detailing independent central confirmation of progression (COP) at the time of first progressive disease (PD) prior to discontinuation of investigational product (Section 8.2.2.1.2)
- Addition of Estimands Framework
- General administrative (typographical, editorial) fixes

Superseding Amendment 2

Protocol Title: A Phase 3 Multicenter, Randomized, Open Label, Active-controlled. Study of AMG 510 Versus Docetaxel for the Treatment of Previously Treated Locally Advanced and Unresectable or Metastatic NSCLC Subjects With Mutated KRAS p G12C

Amgen Protocol Number AMG 510 20190009

EudraCT Number: 2019-003582-18

Amendment Date:	03 June 2020
Superseding Amendment Date:	29 June 2020

Rationale:

The following changes were made to the protocol dated 03 June 2020:

- Schedule of assessments was updated to include identification and quantification of biomarker expression at protein, RNA, and DNA levels.
- In the case the subject chooses to continue on treatment beyond radiologic progression, the subject must meet certain criteria and the subject must undergo biopsy of the progressing lesions
- Schedule of assessments was updated to notate that collection of pharmacokinetic (PK) samples are to be within a 10% window of the nominal time points.
- Objectives and Endpoints, Exploratory: [redacted]
- Exclusion criteria updated to include clarification of previously identified driver mutation language to include identified driver mutations that are identified as per local standard of care guidelines
- Deleted the exclusion criteria for use of strong inhibitors of CYP3A4 or P-glycoproteins
- Revised the contraceptive guidance and collection of pregnancy and lactation information to exclude females who are pregnant planning to become pregnant within 6 months after last dose of docetaxel based on docetaxel guidelines
- List of analytes table updated to collect urine potassium and urine fraction (24 hour) or fractional excretion urine/potassium.
- Eligibility criteria notated to specify that If hepatitis B and C cannot be obtained hepatitis viral load to be utilized
- Subgroup analysis revised to include brain and bone metastasis at baseline and PD-L1 protein expression

- Additional changes to the protocol include:
  - For selected cases, subjects may continue in the study post radiologic progression if they are continuing to demonstrate clinical benefit
  - A clarification for a ± 3 day window for lab assessments is allowed, unless otherwise specified.
  - For select PRO assessments, evaluation at screening has been added Infectious hepatitis serology and assessments and/or viral load need not be repeated 6 weeks prior to enrollment.
  - Tumor evaluation should be performed by contrast-enhanced imaging and in the case contrast administration is contraindicated radiological imaging is as per guidance in the imaging manual is to be followed.
  - Updated the collection of biopsy information with addition of mandatory biopsy collection for continuation of treatment beyond radiologic progression.
  - Text with regards to concomitant administration of proton pump inhibitors is included in the protocol.
  - AMG 510 dose modification allowances have been modified biomarker assessments to determine eligibility of subjects via tumor biopsy should be sent as an FFPE block or unstained slides.

Amendment 2

Protocol Title: A Phase 3 Multicenter, Randomized, Open Label, Active-controlled. Study of Sotorasib Versus Docetaxel for the Treatment of Previously Treated Locally Advanced and Unresectable or Metastatic NSCLC Subjects With Mutated KRAS p G12C

Amgen Protocol Number Sotorasib 20190009

EudraCT Number: 2019-003582-18

Amendment Date: 03 June 2020

Rationale:

The following changes were made to the protocol dated 03 June 2020:

- Schedule of Assessments was updated to include identification and quantification of biomarker expression at protein, RNA, and DNA levels. Also, in case of progression of disease, if subject is not continuing sotorasib shall be encouraged to enroll in an optional sub-study and in case if the subject continues on treatment beyond radiologic progression, the subject must undergo biopsy of the progressing lesions
- Schedule of Assessments was updated to collect pharmacokinetic (PK) samples within a 10% window of the nominal time points.
- Objectives and Endpoints, Exploratory: [redacted]
- Exclusion criteria updated to include clarification for previously identified driver mutation as per local standard of care guidelines
- Statistical analysis plan updated with inferential comparison for the endpoints of change from baseline over to week 12 in symptoms of chest pain and cough as measured by QLQ LC13.
- Deleted the exclusion criteria for use of strong inhibitors of CYP3A4 or P-glycoproteins
- Revised the Contraceptive Guidance and Collection of Pregnancy and Lactation Information to exclude females who are pregnant or breastfeeding or planning to become pregnant within 6 months after last dose of docetaxel
- List of analytes updated to collect urine potassium and urine fraction (24 hour) or fractional excretion urine.
- If hepatitis B and C cannot be obtained hepatitis viral load to be utilized
- Subgroup analysis revised to include brain and bone metastasis at baseline and PD-L1 protein expression
- Additional changes to the protocol include:
    - For selected cases, subjects may continue in the study post radiologic progression if they are continuing to demonstrate clinical benefit

- A clarification for a ± 3 day window is allowed, unless otherwise specified.
- For baseline visits cycle 1 day 1 is added
- Infectious hepatitis serology and assessments and/or viral load need not be repeated 6 weeks prior to enrollment.
- Tumor evaluation should be performed by contrast-enhanced imaging and in case if it is contraindicated radiological imaging to be performed.
- Additional plasma and blood samples will not be collected for exploratory biomarkers (optional).
- Updated the collection of biopsy information with additional mandatory biopsy collection for continuation of treatment beyond radiologic progression.
- From the available study results it is known that the concomitant administration of proton-pump inhibitors decreased sotorasib concentrations which can affect efficacy. Text included in the protocol to avoid use of PPIs with sotorasib.
- Sotorasib doses modified as dose -2 at 240 mg, dose -1 at 480 mg, and starting dose at 960 mg.
- For biomarker assessment to determine eligibility subjects can undergo tumor biopsy which should be sent as an FFPE block or unstained slides.
- Potential interim and primary analysis of overall survival guideline included.

Amendment 1

Protocol Title: A Phase 3 Multicenter, Randomized, Open Label, Active-controlled, Study of AMG 510 Versus Docetaxel for the Treatment of Previously Treated Locally Advanced and Unresectable or Metastatic NSCLC Subjects With Mutated KRAS p.G12C

Amgen Protocol Number AMG 510 20190009

Amendment Date: 21 January 2020

Rationale:

This protocol is being amended to address the following regulatory agency feedback:

- Section 1.3, Schedule of Activities, Table 1-1 and Table 1-2 was updated to include Thyroid Function Test Assessments: Thyroid function tests assesements added to schedule of activities at screening, pre-dose on day 1 of each cycle, at the end of treatment, and safety follow up. They should also be obtained if the subject displays clinical signs or symptoms concerning for thyroid dysfucntion
- Additon of AMG 510 Hepatotoxicity Guidelines for management and monitoring of subjects with increased AST, ALT, or ALP while on trial
- Clarify the sample size determination section to note the trial will not be terminated at PFS analyses and subjects will continue to be followed for OS data until the targeted number of events are reached to enable OS analyses and a robust description of the totality of the data
- Section 1.3, Schedule of Activities, Table 1-2 was updated to include Cholesterol and Triglyceride Levels Assessments: Cholesterol and triglyceride levels on pre-dose on day 1 of every other cycle (ie, cycle 1, 3, 5, 7, etc).
- Section 3, Objectives and Endpoints, Exploratory: [redacted]
- Stratification Factors for randomization, number of prior lines of therapy revised to 1 versus 2 versus > 2

Additional changes to the protocol include:

- Food restriction around the time of AMG 510 administration was removed as the studies evaluating the effect of food (high fat meal) on pharmacokinetic characteristics of AMG 510 demonstrated that high-fat meal does not appear to result in clinically meaningful alteration of AMG 510 exposure
- Revised the Contraceptive Guidance and Collection of Pregnancy and Lactation Information based on data from recently completed nonclinical studies (absence of genotoxic risk for AMG 510 based on recently completed GLP-compliant in vitro bacterial mutagenicity Ames assay and in vivo genotoxicity study including the erythrocyte micronucleus test and the alkaline comet assay).

- Data from the most recent datacut from the Phase 1/2 Study 20170543 presented
- Dose modification section is updated to outline the dose reduction steps allowable on the study
- Guidelines for management and monitoring of subjects with increased AST, ALT or ALP are added
- Editiorial changes for clarification
    - Indication statement
    - Additional tumor evaluation technigues that are acceptable
    - Introduction under the rationale for choice of docetaxel as comparator, to clarify and reduce redundancy
    - Inclusion criteria 105, clarify that the subjects will have reiceved at least 1 prior systemic therapy