Title Page

Protocol Title:		A Phase 1b Study Evaluating the Safety, Tolerability, Pharmacokinetics, and Efficacy of Bemarituzumab Monotherapy and Combination with other Anti-Cancer Therapy in Subjects with Squamous-Cell Non-Small-Cell Lung Cancer (FORTITUDE-201)
Short Protocol Title:		A phase 1b study of bemarituzumab monotherapy and combination with other anti-cancer therapy in SqNSCLC with FGFR2b overexpression (FORTITUDE-201)
Protocol Number:		20210102
Investigational Product:		Bemarituzumab (AMG 552)
Trade Name:		Not applicable
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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 (International Council for Harmonisation [ICH] E6).

Confidentiality Notice

Investigator's Agreement:

I have read the attached protocol entitled A Phase 1b Study Evaluating the Safety, Tolerability, Pharmacokinetics, and Efficacy of Bemarituzumab Monotherapy and Combination with other Anti-Cancer Therapy in Subjects with Squamous-Cell Non-Small-Cell Lung Cancer (FORTITUDE-201), dated **27 April 2023**, 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 sub investigators (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)

_____

Title and Role of Investigator

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Table of Contents

List of Tables

List of Figures

1. Protocol Summary

1.1 Synopsis

Protocol Title: A Phase 1b Study Evaluating the Safety, Tolerability, Pharmacokinetics, and Efficacy of Bemarituzumab Monotherapy and Combination with other Anti-Cancer Therapy in Subjects with Squamous-Cell Non-Small-Cell Lung Cancer (FORTITUDE-201)

Short Protocol Title: A phase 1b study of bemarituzumab monotherapy and combination with other anti-cancer therapy in SqNSCLC with FGFR2b overexpression (FORTITUDE-201)

Study Phase: Phase 1b

Indication: FGFR2b-positive squamous non-small-cell lung cancer

Study Rationale

Bemarituzumab is a humanized monoclonal antibody that targets the fibroblast growth factor (FGF) receptor isoform 2b (FGFR2b) with a dual mechanism of FGF binding inhibition and antibody-dependent cellular cytotoxicity. Bemarituzumab monotherapy has been investigated in a phase 1 dose-finding study (FPA144-001) and in combination with mFOLFOX6 chemotherapy in FGFR2b-positive gastric cancer in the FIGHT study. Bemarituzumab efficacy correlated with the degree of FGFR2b overexpression by immunohistochemistry (IHC) in gastric cancer and has demonstrated a manageable safety profile in combination with mFOLFOX6. Genomic and IHC data suggest that other carcinomas including squamous-cell non-small-cell lung cancer (SqNSCLC) may also have a significant rate of FGFR2b overexpression. This study will evaluate the safety, tolerability, and efficacy of bemarituzumab monotherapy as well as the combination with other anti-cancer therapy, across different lines of therapy in the locally advanced/metastatic setting. Once a recommended dose of bemarituzumab in combination with docetaxel is determined, this study will explore the efficacy of the docetaxel combination in FGFR2b+ selected SqNSCLC, as well as the safety and efficacy of the bemarituzumab combination with other anti-cancer therapies in the first-line metastatic treatment setting.

Objective(s) and Endpoint(s)/Estimand(s)

Objectives	Endpoints
Primary	
• To evaluate the safety and tolerability of bemarituzumab monotherapy and combination with other anti-cancer therapies • To determine the recommended phase 3 dose of bemarituzumab in combination with other anti-cancer therapies	• Dose limiting toxicities (DLTs), treatment-emergent adverse events, and clinically significant changes in vital signs, physical examinations, clinical laboratory tests, and visual acuity
Secondary	
• To characterize the pharmacokinetics (PK) of bemarituzumab monotherapy and in combination with other anti-cancer therapies	• PK parameters for bemarituzumab including, but not limited to, area under the concentration time curve (AUC), maximum observed concentration (C_{max}), and observed concentration at the end of a dose interval (C_{trough})
• To evaluate preliminary anti-tumor activity of bemarituzumab monotherapy and in combination with other anti-cancer therapies	• Objective response [defined as complete response (CR) + partial response (PR)] (as determined by investigator per Response Evaluation Criteria in Solid Tumors [RECIST v1.1]) • Duration of response defined as the time from first response to disease progression (as determined by investigator per RECIST v1.1) or death from any cause, whichever comes first • Disease control defined as CR + PR + stable disease (SD) • Progression free survival (PFS), defined as time from first dose of investigational product until disease progression or death from any cause. Subjects alive without progression will be censored at their last evaluable disease assessment. Progression will be based on assessment by investigator per RECIST v1.1 • Overall survival (OS), defined as time from first dose of investigational product until death from any cause. Subjects still alive will be censored at the date last known to be alive

Primary Estimand(s)/Coprimary Estimand(s)

Not applicable.

Secondary Estimand(s)

Not applicable.

Overall Design

This is a phase 1b, open-label, multicenter study to evaluate the safety, tolerability, pharmacokinetics (PK), and efficacy of bemarituzumab monotherapy and combination across different lines of therapy in locally advanced/metastatic SqNSCLC. This study will explore the addition of bemarituzumab to the established standard of care immuno-chemotherapy in the first-line treatment setting and the addition to chemotherapy in the second line or later setting.

The study consists of a pre-screening period to collect tissue for FGFR2b testing (Parts 2, 3, and 4 only), a 28-day screening period, a treatment period, a safety follow-up (SFU) visit, and a long-term follow-up (LTFU) period. Subjects who discontinue bemarituzumab will undergo SFU approximately 28 (+ 3) days after the last dose of study treatment. In addition, subjects will undergo LTFU for survival approximately every 3 months (± 1 month) for up to 2 years from the first dose of bemarituzumab. Subjects will receive study treatment with bemarituzumab until disease progression (see Part 4 below for a possible exception), unacceptable toxicity, subject request, or death (whichever occurs first).

Radiographic assessments will be performed by the investigator according to Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 and will be performed every 6 weeks (Q6W) (± 7 days) until week 54 and then every 12 weeks (± 14 days). After discontinuation of study treatment for reasons other than radiographic disease progression or withdrawal of consent, tumor assessments will continue until radiographic progression or initiation of additional anticancer therapy.

The study consists of 4 Parts:

- Part 1: Combination dose exploration with docetaxel
- Part 2: Combination dose expansion with docetaxel
- Part 3: Monotherapy

- Part 4: Combination with carboplatin, paclitaxel or nab-paclitaxel, and pembrolizumab

Tumor samples from subjects will be required to demonstrate FGFR2b overexpression status prior to subjects entering Parts 2, 3, and 4 (and not Part 1) of this study. This study may be amended at a later date to include additional subjects for further efficacy evaluation.

Part 1

Part 1 of the study will explore the dosing of bemarituzumab in combination with docetaxel. During dose exploration, subjects will be enrolled in groups of 3 to 6 dose limiting toxicity (DLT) evaluable subjects per cohort, and escalation will be guided primarily by safety responses to different doses.

The starting dose of bemarituzumab is based on review of the available safety, PK, and efficacy data from bemarituzumab monotherapy and bemarituzumab plus mFOLFOX6 combination studies (FPA144-001, FPA144-004). The recommended phase 2 dose of bemarituzumab in combination with mFOLFOX6 (evaluated in study FPA144-004) was determined to be 15 mg/kg intravenous (IV) every 2 weeks (Q2W) with a single 7.5 mg/kg dose on day 8 of the first cycle.

The dosing interval will increase from Q2W to every 3 weeks (Q3W) to align with the other anti-cancer therapy Q3W dosing schedule. At Dose Level 1 the same dose of 15 mg/kg as in FPA144-004 will be tested, but at Q3W instead of Q2W and replacing the additional dose of 7.5 mg/kg day 8 with a 1 time loading dose of 22 mg/kg IV on the first dosing day. Dose Level 2 will proportionally increase the bemarituzumab dose, including the loading dose, from the Q2W dose studied in FPA144-004 to account for the increased Q3W dosing interval. One cycle of treatment will consist of 21 days. For Part 1, prospective tumor evaluation for FGFR2b overexpression status will not be required for enrollment and will enroll up to approximately 18 subjects.

The planned dose levels are:

- Dose Level 1: bemarituzumab 22 mg/kg IV cycle 1 day 1 followed by 15 mg/kg IV day 22 and Q3W thereafter
- Dose Level 2: bemarituzumab 30 mg/kg IV cycle 1 day 1 followed by 22 mg/kg IV day 22 and Q3W thereafter

An additional Dose Level 1a of bemarituzumab 15 mg/kg IV Q3W plus 1 additional 7.5 mg/kg dose on cycle 1 day 8 only may be explored if dose de-escalation is required

from Dose Level 1. Any other dose levels besides dose levels 1, 2, or 1a, will require a protocol amendment prior to enrollment.

At each dose level, and on each planned dosing day, docetaxel will be administered at 75 mg/m^2 IV Q3W (or 60 mg/m^2 IV Q3W for subjects from sites in Japan).

Part 1 will begin with Dose Level 1. The study DLT period is 21 days following the first dose. Once 3 to 6 subjects enrolled at a certain dose level are followed for safety for 21 days, a Dose Level Review Team (DLRT) meeting will be convened.

The DLRT will evaluate all available safety, laboratory, and PK data as well as rules generated from a modified toxicity probability interval design (mTPI-2) (Guo et al, 2017) to guide their dose finding recommendations. The team may recommend escalation to the next planned dose, continuation at the current dose level, de-escalation to a lower dose, termination of the study, or initiation of enrollment to Part 2 of the study with the evaluated dose level. The mTPI-2 escalation/de-escalation guideline for each dose cohort is derived with a target toxicity probability of 0.30, acceptable toxicity probability interval of (0.25, 0.33). A dose level will be considered unsafe, with no additional subjects enrolled at that dose level, if it has an estimated 95% or more probability of exceeding the target DLT (ie, the elimination boundary).

Dose exploration will continue until:

- a maximum of 18 subjects in Part 1 is reached; or
- 9 subjects have been treated at a specific dose level; or
- the lowest dose level exceeds the elimination boundary

Part 2

Once a dose level has been declared safe by the DLRT for Part 1, a dose level can enter Part 2 of the study. Part 2 enrollment will be limited to subjects with prospectively identified FGFR2b overexpression status. A minimum of 10 subjects and a maximum of 30 subjects will be treated per dose level in Part 2 to better understand the safety profile and preliminary efficacy of the combination, and to enable selection of the recommended phase 3 dose (RP3D). Up to 2 dose levels consisting of 10 to 30 subjects each can be expanded in Part 2 of the study. For Part 2, subjects can receive 1 dose of docetaxel during pre-screening or screening if initiation of treatment is deemed urgent by the investigator. This bridging dose is not a requirement of the study and is not considered part of the clinical study.

Part 3

Part 3 of the study will explore bemarituzumab monotherapy at the dose evaluated in study FPA144-004 of 15 mg/kg IV Q2W plus 1 additional 7.5 mg/kg dose on cycle 1 day 8. One cycle of treatment will consist of 14 days. Part 3 enrollment will be limited to subjects with prospectively identified tumor FGFR2b overexpression status. A minimum of 10 subjects and a maximum of 30 subjects will be treated in Part 3 to better understand the safety profile, PK, and preliminary efficacy of monotherapy bemarituzumab in FGFR2b+ SqNSCLC. Part 3 may enroll subjects concurrently with Parts 1, 2, and 4.

Part 4

Once a dose level has been declared safe by the DLRT for Part 1, a dose level can enter the Part 4 safety run-in. During the safety run-in, 6 subjects will be evaluated with a 21-day DLT period and once the dose has been declared safe in the first-line setting with immuno-chemotherapy combination, then Part 4 enrollment can proceed with dose expansion. Dose de-escalation may occur in Part 4, independently of the recommendation in Part 1. Part 4 enrollment will be limited to subjects with prospectively identified FGFR2b overexpression status. A minimum of 10 subjects and a maximum of 30 subjects, including the 6 subjects in the safety run-in, will be treated in Part 4 to better understand the safety profile and preliminary efficacy of the combination and to enable the selection of the RP3D. Up to 2 dose levels consisting of 10 to 30 subjects each can be expanded in Part 4 of the study. Subjects will receive up to 4 cycles of bemarituzumab, pembrolizumab, and chemotherapy followed by bemarituzumab and pembrolizumab maintenance. In addition to bemarituzumab administered on day 1 of every 21-day treatment cycle, subjects will be administered pembrolizumab 200 mg day 1 for up to 35 cycles and, for the first four cycles only, the combination of carboplatin 6 mg/mL/min and either paclitaxel 200 mg/m^2 on day 1 or nab-paclitaxel 100 mg/m^2 on days 1, 8, and 15. For Part 4 expansion (and not in safety run-in), subjects can receive 1 dose of carboplatin and paclitaxel or nab-paclitaxel with or without pembrolizumab during pre-screening or screening if initiation of treatment is deemed urgent by the investigator. This bridging dose is not a requirement of the study and is not considered part of the clinical study.

For Part 4 only, subjects may continue treatment beyond initial RECIST v1.1 progressive disease (PD), as assessed by the investigator, as long as they meet the following criteria:

- Investigator assessed clinical benefit
- Tolerance of study drug
- Stable Eastern Cooperative Oncology Group (ECOG) performance status
- Treatment beyond progression will not delay an imminent intervention to prevent serious complications of disease progression (ie, central nervous system [CNS] metastases)

Number of Subjects

It is anticipated that up to 180 subjects will be enrolled in this study, consisting of a maximum of 18 subjects in Part 1 and a maximum of 150 subjects in Parts 2, 3, and 4 combined. The 150 subjects includes the possibility of 2 cohorts at 2 dose levels of bemarituzumab, consisting of 10 to 30 subjects in each of Parts 2 and 4. Three to 6 Japanese subjects per dose level will be enrolled in Part 1, Part 2, and/or Part 4, either as part of the initial dose level evaluation, or as backfill once the RP3D has been determined. The planned regions for this study will include North America, Asia, Europe, and Australia.

Summary of Subject Eligibility Criteria

Subjects ≥ 18 years of age (or legal adult within country, whichever is older) at the time of informed consent with histologically documented SqNSCLC either previously untreated in the locally advanced/unresectable or metastatic setting (Part 4), or experienced disease recurrence on or after receiving at least 1 prior systemic therapy (Parts 1 and 2), or at least 2 prior systemic therapies (Part 3). For Parts 1 and 2 subjects must be candidates for docetaxel. For Part 4, subjects must be candidates for pembrolizumab, carboplatin, and either nab-paclitaxel or paclitaxel. Parts 2, 3, and 4 subjects must have FGFR2b overexpression as determined by centrally performed IHC testing. All subjects must have measurable disease per RECIST v1.1.

For a full list of eligibility criteria, please refer to Section 5.1 to Section 5.2.

Treatments

For Parts 1 and 2, bemarituzumab will be administered IV every 21 days on day (D1) of each cycle with docetaxel 75 mg/m^2 (or 60 mg/m^2 for subjects at sites in Japan). Bemarituzumab, at doses indicated in the dose exploration, will be administered as an approximately 30 minute (± 10 minutes) IV infusion via peripheral vein or central venous catheter. Docetaxel at a dose of 75 mg/m^2 (or 60 mg/m^2 for subjects at sites in Japan) only will be administered over 60 minutes via peripheral vein or central venous catheter. One treatment cycle is 21 days.

For Part 3, bemarituzumab will be administered IV every 14 days on day (D1) of each cycle. Bemarituzumab, at the dose of 15 mg/kg IV Q2W with a single 7.5 mg/kg dose on day 8 of the first cycle, will be administered as an approximately 30 minute (± 10 minutes) IV infusion via peripheral vein or central venous catheter. One treatment cycle is 14 days.

For Part 4, bemarituzumab, at the recommended dose, will be administered as an approximately 30-minute (± 10 minutes) IV infusion via peripheral vein or central venous catheter. Pembrolizumab at the dose of 200 mg will be administered by IV infusion on day 1 Q3W. For the first 4 cycles, bemarituzumab and pembrolizumab will be co-administered with carboplatin (day 1, at a dose calculated to provide an area under the concentration-time curve of 6 mg/mL/min) and either paclitaxel (day 1, 200 mg/m^2 of body-surface area) or nab-paclitaxel (days 1, 8, and 15, 100 mg/m^2 of body-surface area).

Statistical Considerations

Sample Size Considerations

With 3, 6, or 9 subjects in a dose level cohort in Part 1, there is approximately 58%, 82%, and 93% probability, respectively, of observing at least 1 DLT if the true DLT rate is 25%.

With a minimum of 10 subjects each in Parts 2, 3, and 4, there is an approximate 95% probability of observing at least 1 DLT if the true DLT rate is 25%, the lower end of the acceptable toxicity interval. Up to 30 subjects may be enrolled to gain further safety and preliminary efficacy data.

Planned Analyses:

Interim DLRT reviews:

In Part 1 and Part 4 safety run-in, the DLRT will convene to review all available safety, tolerability, laboratory, PK and efficacy data during dose exploration (when every 3-6 subjects [Part 1] or safety run-in 6 subjects [Part 4] are enrolled at a given dose level) and after dose exploration is completed. The DLRT will only convene when the last of those subjects has reached 21 days on study or treatment.

In Parts 2, 3, and Part 4 dose expansion, the DLRT will convene to review all available safety, tolerability, laboratory, PK, and efficacy data once 10 subjects have had the opportunity to be followed for at least 12 weeks and again once enrollment is complete, and at the primary and final analysis time point.

Part 3 may enroll simultaneously with Parts 1, 2, and 4, therefore the timing of DLRT meetings may be adjusted so data from multiple study parts can be reviewed at a single meeting.

Primary analysis:

The primary analysis will occur 12 months after the last subject has been enrolled in the study.

Final analysis

A final analysis is planned after all subjects have ended the study.

Analytic Methods:

Descriptive statistics will be provided for selected demographics, safety, PK, efficacy and biomarker data. Descriptive statistics on continuous data will include means, medians, standard deviations, and ranges, while categorical data will be summarized using frequency counts and percentages. Response rates will be presented with 95% exact CIs. Time-to-event endpoints will be summarized using the Kaplan-Meier (KM) method.

For a full description of statistical analysis methods, please refer to Section 9.

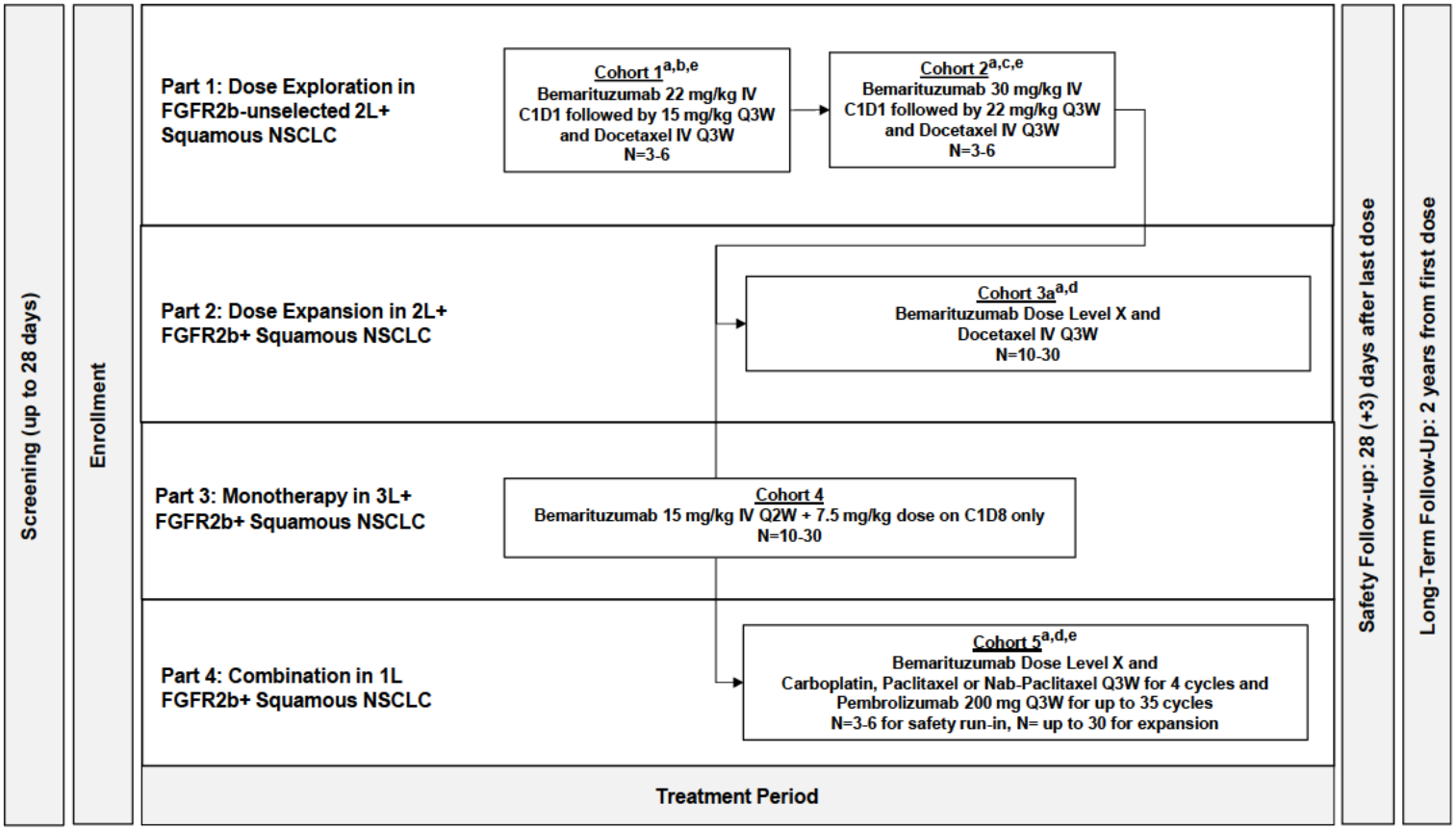
Statistical Hypotheses

No statistical hypothesis will be tested in this study.

Sponsor Name: Amgen Inc.

1.2 Study Schema

Figure 1-1. Study Schema



C1D1 = cycle 1 day 1; C1D8 = cycle 1 day 8; FGFR2b = fibroblast growth factor receptor 2; IV = intravenous; NSCLC = non-cell lung cancer; Q2W = every 2 weeks; Q3W = every 3 weeks

[a] Three to 6 Japanese subjects per dose level may be enrolled in Part 1, Part 2, and/or Part 4.

[b] For Dose level 1: 15 mg/kg IV Q3W is to be administered on day 22 and onward following a loading dose of 22 mg/kg IV on C1D1. An additional Dose Level 1a of bemarituzumab 15 mg/kg IV Q3W plus 1 additional 7.5 mg/kg dose on cycle 1 day 8 only may be explored if dose de-escalation is required from Dose Level 1.

[c] For Dose level 2: 22 mg/kg IV Q3W is to be administered on day 22 and onward following a loading dose of 30 mg/kg IV on C1D1.

[d] An additional 10-30 subject cohort at a different dose level of bemarituzumab declared safe in Part 1 may be expanded in each of Parts 2 and 4.

[e] Dose level review meeting will be convened in accordance with Section 6.2.1.

1.3 Schedule of Activities (SoA)

Table 1-1. Schedule of Activities (Parts 1 and 2 only)

Procedure[a]	Pre-SCR	SCR	Study Treatment (21-day cycles)							SFU[c]	LTFU[d]	Notes
			Cycles 1 and 2		Cycle 3 and Subsequent Cycles							
DAY		-28 to 0	C1 D1	C2 D1	Q1C D1	Q2C (odd subsequent cycles) D1	Q6W after C1D1	As clinically indicated	Bema EoT[b]			
SCREENING ARCHIVAL TUMOR TISSUE/BIOPSY PART 1 ONLY												
Informed consent		X										Part 1 only: Informed consent for Part 1 should be obtained prior to provision of tumor sample.
Archival tissue/fresh biopsy		X										Part 1 only: Subjects must consent at screening to provision of archival tissue (or fresh biopsy if not available). Tumor evaluation for FGFR2b overexpression status will be retrospectively assessed and is not required to be confirmed for enrollment. The age of archived samples must be within 5 years prior to screening informed consent or a fresh biopsy during screening. Refer to Section 8.1.1.
PD-L1 Testing		X										Utilizes leftover screening tissue, if available. PD-L1 will only be tested if FGFR2b overexpression is confirmed.
PRE-SCREENING ARCHIVAL TUMOR TISSUE/BIOPSY PART 2 ONLY												
Pre-screening informed consent (Part 2 only)	X											Pre-screening informed consent must be obtained prior to provision of tumor sample.
Archival tissue/fresh biopsy for IHC FGFR2b (Part 2 only)	X											For Part 2 only, Positive FGFR2b overexpression status by central IHC testing is required for enrollment. Provision of archival tissue within last 5 years (or fresh biopsy if archival tissue is not available) for assessment of FGFR2b overexpression status by IHC is required.

Table 1-1. Schedule of Activities (Parts 1 and 2 only)

Procedure[a]	Pre-SCR	SCR	Study Treatment (21-day cycles)							SFU[c]	LTFU[d]	Notes
			Cycles 1 and 2		Cycle 3 and Subsequent Cycles							
DAY		-28 to 0	C1 D1	C2 D1	Q1C D1	Q2C (odd subsequent cycles) D1	Q6W after C1D1	As clinically indicated	Bema EoT[b]			
PD-L1 testing	X											Utilizes leftover pre-screening tissue, if available. PD-L1 will only be tested if FGFR2b overexpression is confirmed.
GENERAL AND SAFETY ASSESSMENTS												
Informed consent (Part 2 only)		X										Part 2 only: Signed after FGFR2b overexpression status is confirmed
Eligibility criteria		X										
Medical history		X										Includes medical/surgical and cancer history (including local tumor biomarker testing results, such as PD-L1, if completed), ophthalmologic history, and medication history
Substance use		X										
Demographics	[X]	(X)										[X] For Part 2 only collect demographics at pre-screening (X) For Part 1 only collect demographics at screening
Physical exam		X	X	X	(X)					X		Prior to study drug administration in all cycles (X): Must include weight and body surface area (BSA) on day 1 of every cycle.
Height		X										
Weight		X	X	X	X							
ECOG PS		X				(X)				X		(X): Day 1 of every odd cycle

Table 1-1. Schedule of Activities (Parts 1 and 2 only)

Procedure[a]	Pre-SCR	SCR	Study Treatment (21-day cycles)							SFU[c]	LTFU[d]	Notes
			Cycles 1 and 2		Cycle 3 and Subsequent Cycles							
DAY		-28 to 0	C1 D1	C2 D1	Q1C D1	Q2C (odd subsequent cycles) D1	Q6W after C1D1	As clinically indicated	Bema EoT[b]			
Vital assessments											X	Survival status collected every 3 months (±1 month) after SFU visit
Concomitant medications		X	----------X----------								(X)	(X): Collect information on ophthalmologic medication only
Subsequent anticancer therapy											X	Record subsequent therapies for lung cancer
Vital signs and oxygen saturation		X	X	X	X					X		Prior to study drug administration in all cycles
12-lead ECG		X						X				12-lead ECG performed after subject rests for 5 minutes prior to recording
Ophthalmology exam		X					(X)	X		X	[X]	Includes assessment of distance corrected visual acuity, ocular surface staining, slit lamp examination of anterior segment, tonometry, and dilated retinal examination or 3 field retinal photographs. Examination may occur up to 5 days before dosing. (X): As above except dilated retinal examination or 3 field photographs are to be performed at every other ophthalmology exam. All examinations are to be performed Q6W (- 5 days) for the first 24 weeks, and then every 8 weeks (- 5 days) thereafter. [X]: Refer to the 'notes' for Adverse Events of Special Interest during LTFU within this table.

Table 1-1. Schedule of Activities (Parts 1 and 2 only)

Procedure[a]	Pre-SCR	SCR	Study Treatment (21-day cycles)							SFU[c]	LTFU[d]	Notes
			Cycles 1 and 2		Cycle 3 and Subsequent Cycles							
DAY		-28 to 0	C1 D1	C2 D1	Q1C D1	Q2C (odd subsequent cycles) D1	Q6W after C1D1	As clinically indicated	Bema EoT[b]			
Adverse events	(X)		----------X----------									(X): Adverse events of any grade occurring up to 14 days after the pre-screening procedure (Part 2 only) of tumor biopsy acquisition for the FGFR2b assay should be reported as adverse event if they are deemed related to the pre-screening procedure by the investigator. Refer to Section 8.4.6.1.1.
Serious adverse events	(X)	----------X----------									[X]	(X): Serious adverse events of any grade occurring up to 14 days after the pre-screening procedure (Part 2 only) of tumor biopsy acquisition for the FGFR2b assay should be reported as serious adverse events if they are deemed related to the pre-screening procedure for FGFR2b assay by the investigator. Refer to Section 8.4.6.1.2. [X]: During LTFU, only serious adverse events suspected to be related to investigational product or any fatal adverse event (regardless of causality) will be reported to Amgen immediately and no later than 24 hours following the investigator's awareness of the event.
Adverse events of special interest			X	----------X----------							X	Ophthalmological events of any grade up to 100 days after the last dose of bemarituzumab should be reported to the Sponsor.

Table 1-1. Schedule of Activities (Parts 1 and 2 only)

Procedure[a]	Pre-SCR	SCR	Study Treatment (21-day cycles)							SFU[c]	LTFU[d]	Notes
			Cycles 1 and 2		Cycle 3 and Subsequent Cycles							
DAY		-28 to 0	C1 D1	C2 D1	Q1C D1	Q2C (odd subsequent cycles) D1	Q6W after C1D1	As clinically indicated	Bema EoT[b]			
IMAGING ASSESSMENTS												
CT/MRI[e]		X					(X)			[X]	([X])	(X): Every 6 (± 1) weeks from cycle 1 day 1 until week 54, then every 12 (± 2) weeks. Confirmation of response is required after 4 weeks. [X]: Can be omitted if last scan was performed < 6 weeks (-3 days) prior to SFU visit or if tumor progression was previously determined. ([X]): Imaging assessments will continue for subjects who discontinue study treatment without disease progression.
LOCAL LABORATORY ASSESSMENTS												
Hematology		X	X	X	X			X		X		Local test results must be obtained up to 72 hours prior to dose on dosing days for both bemarituzumab and docetaxel. Lab results must be reviewed prior to study drug administration.
Chemistry panel		X	X	X	X			X		X		
Total cholesterol levels		X										
Coagulation		X	X	X				(X)				(X): As clinically indicated at any time (eg, subjects on anticoagulant therapy requiring close monitoring).
Urinalysis		X	X	X				X				May be collected within 72 hours of day 1 in each cycle.

Table 1-1. Schedule of Activities (Parts 1 and 2 only)

Procedure[a]	Pre-SCR	SCR	Study Treatment (21-day cycles)							SFU[c]	LTFU[d]	Notes
			Cycles 1 and 2		Cycle 3 and Subsequent Cycles							
DAY		-28 to 0	C1 D1	C2 D1	Q1C D1	Q2C (odd subsequent cycles) D1	Q6W after C1D1	As clinically indicated	Bema EoT[b]			
Pregnancy test (FCBP only)		X	X	X	X			X		(X)	(X)	Highly sensitive serum β-hCG results are required within 72 hours of cycle 1 day 1. Repeat pregnancy tests (urine is acceptable) are required day 1 of every cycle. (X): Repeat pregnancy tests (urine is acceptable) are required 28 (+3) days after discontinuing protocol-required therapies, and monthly (28 [± 3] days) pregnancy testing up to and inclusive of 75 (+3) days from the last bemarituzumab dose. During the LTFU period, local laboratory test results performed in walk-in clinics or health centers are acceptable if the subject does not have a scheduled clinic visit.
Amylase/lipase		X						X				
CENTRAL LABORATORY ASSESSMENTS												
Immunogenicity sampling			X	X		(X)			X			Anti-bemarituzumab blood samples will be collected ≤ 4 hours prior to dosing of bemarituzumab. (X): To be collected for cycles 5 and 9. See Section 8.7.

Table 1-1. Schedule of Activities (Parts 1 and 2 only)

Procedure[a]	Pre-SCR	SCR	Study Treatment (21-day cycles)							SFU[c]	LTFU[d]	Notes
			Cycles 1 and 2		Cycle 3 and Subsequent Cycles							
DAY		-28 to 0	C1 D1	C2 D1	Q1C D1	Q2C (odd subsequent cycles) D1	Q6W after C1D1	As clinically indicated	Bema EoT[b]			
PK samples			X	X		(X)			X			For Part 1 and 2 combination therapy, pharmacokinetic samples will be collected ≤ 4 hours prior to dosing of bemarituzumab (pre-dose) and at the following times after end of the infusion: 15 (+10) min, 3 hours (± 30 min), 6 hours (± 1 hour), 24 hours (day 2, ± 1 hour), 72 hours (day 4, ± 6 hours), 168 hours (day 8 ± 24 hours), 336 hours (day 15, ± 24 hours), 504 hours (day 22, ± 24 hours) for cycles 1 and 2. (X) Additional PK samples will be collected ≤ 4 hours prior to dosing of bemarituzumab (pre-dose) and 15 (+ 10) min after end of infusion for cycles 3 (504 hours collection for cycle 2 is the same as pre-dose cycle 3), 5, and 9.
Plasma ctDNA biomarker			(X)	(X)	(X)				X			(X) Pre-dose C1D1, C2D1, and C3D1 only. The buffy coat will also be collected at each timepoint.

Table 1-1. Schedule of Activities (Parts 1 and 2 only)

Procedure[a]	Pre-SCR	SCR	Study Treatment (21-day cycles)							SFU[c]	LTFU[d]	Notes
			Cycles 1 and 2		Cycle 3 and Subsequent Cycles							
DAY		-28 to 0	C1 D1	C2 D1	Q1C D1	Q2C (odd subsequent cycles) D1	Q6W after C1D1	As clinically indicated	Bema EoT[b]			
STUDY TREATMENT												
Optional tumor biopsy or archived tissue (FFPE)		(X)		[X]					[X]			(X): Remaining tissue from the pre-screening/screening IHC assays may be used. If pre-screening/screening sample not available, the subjects may provide archived FFPE (collected within 5 years) or undergo optional tumor biopsy. [X]: Optional tumor biopsy for exploratory biomarker testing will be performed for subjects who consent to this assessment. It will be performed, if feasible, on cycle 2 day 1 (± 7 days) and at the EoT (± 7 days) or at time of progression, prior to start of another anti-cancer therapy.
Bemarituzumab administration			X	X	X							Bemarituzumab is to be administered prior to all other study treatments. After cycle 1, bemarituzumab dose should be recalculated only if the weight changes > 10%. If the dose is recalculated, the weight used for the recalculated dose should function as the new baseline. For cycles 1 through 3, day 1 dose should be administered every 21 (± 3) days, regardless of delays in other anticancer treatment. Starting at cycle 4, may be delayed up to 7 days to be synchronized with other anti-cancer treatment. Doses should not be administered fewer than 14 days apart.
Docetaxel administration			X	X	X							Administered after bemarituzumab

NOTE: Unless otherwise indicated, all assessments during the treatment period are performed prior to study drug administration.

Bema = bemarituzumab; β-hCG = β-human chorionic gonadotropin; C = cycle; CT = computed tomography; ctDNA = circulating tumor DNA; D = day; ECG = electrocardiogram; ECOG PS = Eastern Cooperative Oncology Group performance status; EoT = end of treatment; FCBP = female subjects of childbearing potential; FFPE = formalin fixed paraffin embedded; FGFR2b = fibroblast growth factor receptor isoform 2b; IHC = immunohistochemistry; LTFU = Long-Term Follow-up; MRI = magnetic resonance imaging; PD-L1 = programmed death-ligand 1; PK = pharmacokinetic; Q6W = every 6 weeks; SCR = screening; SFU = safety follow-up; Q1C = every cycle; Q1C D1 = day 1 of every cycle; Q2C = every 2 cycles.

[a] Procedures are to be completed at scheduled time points, unless otherwise specified (eg, laboratory and safety assessments may be completed up to 72 hours prior to scheduled study treatment administration).

[b] Final samples will be collected 28 (+ 3) days after last dose of bemarituzumab (may be collected at SFU if all treatment is discontinued at same time).

[c] Safety follow-up assessments should be performed 28 (+ 3) days following the last study treatment administration.

[d] Subjects will complete LTFU for survival approximately every 3 months ± 1 month after the SFU visit up to 2 years from the first dose of bemarituzumab.

[e] Contrast enhanced CT scan is required for all 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. 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 MRI abdomen or 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.

Table 1-2. Schedule of Activities (Part 3 only)

Procedure[a]	Pre-SCR	SCR	Study Treatment (14-day cycles)									SFU[c]	LTFU[d]	Notes
			Cycles 1 and 2				Cycle 3 and Subsequent Cycles							
DAY		-28 to 0	C1 D1	C1 D8	C2 D1	C2 D8	Q1C D1	Q2C (odd subsequent cycles) D1	Q6W after C1D1	As clinically indicated	Bema EoT[b]			
PRE-SCREENING ARCHIVAL TUMOR TISSUE/BIOPSY														
Pre-screening informed consent	X													Pre-screening informed consent must be obtained prior to provision of tumor sample.
Archival tissue/fresh biopsy for IHC FGFR2b	X													Provision of archival tissue within last 5 years (or fresh biopsy if archival tissue is not available) for assessment of FGFR2b overexpression status by IHC is required. Positive FGFR2b overexpression status by central IHC testing is required for enrollment.
PD-L1 testing	X													Utilizes leftover pre-screening tissue, if available. PD-L1 will only be tested if FGFR2b overexpression is confirmed.
GENERAL AND SAFETY ASSESSMENTS														
Informed consent		X												Signed after FGFR2b overexpression status is confirmed
Eligibility criteria		X												
Medical history		X												Includes medical/surgical and cancer history (including local tumor biomarker testing results, such as PD-L1, if completed), ophthalmologic history, and medication history
Substance use		X												
Demographics	X													
Physical exam		X	X	X	X		(X)					X		Prior to study drug administration in all cycles (X): Must include weight and body surface area (BSA) on day 1 of every cycle.
Height		X												

Table 1-2. Schedule of Activities (Part 3 only)

Procedure[a]	Pre-SCR	SCR	Study Treatment (14-day cycles)									SFU[c]	LTFU[d]	Notes
			Cycles 1 and 2				Cycle 3 and Subsequent Cycles							
DAY		-28 to 0	C1 D1	C1 D8	C2 D1	C2 D8	Q1C D1	Q2C (odd subsequent cycles) D1	Q6W after C1D1	As clinically indicated	Bema EoT[b]			
Weight		X	X	X	X		X							
ECOG PS		X						(X)				X		(X): Day 1 of every odd cycle
Vital assessments													X	Survival status collected every 3 months (±1 month) after SFU visit
Concomitant medications		X	----------X----------										(X)	(X): Collect information on ophthalmologic medication only
Subsequent anticancer therapy													X	Record subsequent therapies taken for lung cancer
Vital signs and oxygen saturation		X	X	X	X		X					X		Prior to study drug administration in all cycles
Electrocardiogram (triplicate, central read)		X	(X)	(X)	(X)	(X)				X	[X]			(X) C1D1 and C2D1: Pre-dose, 15 (± 10) min and 3 hours (± 30 min) post end of infusion but before taking corresponding PK samples, and on C1D8 pre-dose and 15 (± 10) mins post end of infusion and C2D8 (± 24 hours) before taking corresponding PK samples [X] Collect 28 (+ 3) days after last dose of bemarituzumab before taking corresponding PK samples

Table 1-2. Schedule of Activities (Part 3 only)

Procedure[a]	Pre-SCR	SCR	Study Treatment (14-day cycles)									SFU[c]	LTFU[d]	Notes
			Cycles 1 and 2				Cycle 3 and Subsequent Cycles							
DAY		-28 to 0	C1 D1	C1 D8	C2 D1	C2 D8	Q1C D1	Q2C (odd subsequent cycles) D1	Q6W after C1D1	As clinically indicated	Bema EoT[b]			
Ophthalmology exam		X							(X)	X		X	[X]	Includes assessment of distance corrected visual acuity, slit lamp, examination of anterior segment, tonometry, and dilated retinal examination or 3 field retinal photographs. Examinations may occur up to 5 days before dosing. (X): As above except dilated retinal examination or 3 field photographs are to be performed at every other ophthalmology exam. All examinations are to be performed every 6 weeks (-5 days) for the first 24 weeks, and then every 8 weeks (-5 days) thereafter. [X]: Refer to the 'notes' for Adverse Events of Special Interest during LTFU within this table.
Adverse events	(X)		----------X----------											(X): Adverse events of any grade occurring up to 14 days after the pre-screening procedure of tumor biopsy acquisition for the FGFR2b assay should be reported as adverse event if they are deemed related to the pre-screening procedure by the investigator. Refer to Section 8.4.6.1.1.

Table 1-2. Schedule of Activities (Part 3 only)

Procedure[a]	Pre-SCR	SCR	Study Treatment (14-day cycles)									SFU[c]	LTFU[d]	Notes
			Cycles 1 and 2				Cycle 3 and Subsequent Cycles							
DAY		-28 to 0	C1 D1	C1 D8	C2 D1	C2 D8	Q1C D1	Q2C (odd subsequent cycles) D1	Q6W after C1D1	As clinically indicated	Bema EoT[b]			
Serious adverse events	(X)	----------X----------											[X]	(X): Serious adverse events of any grade occurring up to 14 days after the pre-screening procedure of tumor biopsy acquisition for the FGFR2b assay should be reported as serious adverse events if they are deemed related to the pre-screening procedure for FGFR2b assay by the investigator. Refer to Section 8.4.6.1.2. [X]: During LTFU, only serious adverse events suspected to be related to investigational product or any fatal adverse event (regardless of causality) will be reported to Amgen immediately and no later than 24 hours following the investigator's awareness of the event.
Adverse events of special interest			X	----------X----------									X	Ophthalmological events of any grade occurring up to 100 days after the last dose of bemarituzumab should be reported to the Sponsor.

Table 1-2. Schedule of Activities (Part 3 only)

Procedure[a]	Pre-SCR	SCR	Study Treatment (14-day cycles)									SFU[c]	LTFU[d]	Notes
			Cycles 1 and 2				Cycle 3 and Subsequent Cycles							
DAY		-28 to 0	C1 D1	C1 D8	C2 D1	C2 D8	Q1C D1	Q2C (odd subsequent cycles) D1	Q6W after C1D1	As clinically indicated	Bema EoT[b]			
IMAGING ASSESSMENTS														
CT/MRI[e]		X							(X)			[X]	([X])	(X): Every 6 (± 1) week from cycle 1 day 1 until week 54, then every 12 (± 2) weeks. Confirmation of response is required after 4 weeks. [X]: Can be omitted if last scan was performed < 6 weeks (- 3 days) prior to SFU visit or if tumor progression was previously determined. ([X]): Imaging assessments will continue for subjects who discontinue study treatment without disease progression.
LOCAL LABORATORY ASSESSMENTS														
Hematology		X	X	X	X		X			X		X		Local test results must be obtained up to 72 hours prior to dose on dosing days. Lab results must be reviewed prior to study drug administration.
Chemistry panel		X	X	X	X		X			X		X		
Total cholesterol levels		X												
Coagulation		X	X	X	X					(X)				(X): As clinically indicated at any time (eg, subjects on anticoagulant therapy requiring close monitoring).
Urinalysis		X	X	X	X					X				May be collected within 72 hours of day 1 in each cycle.

Table 1-2. Schedule of Activities (Part 3 only)

Procedure[a]	Pre-SCR	SCR	Study Treatment (14-day cycles)									SFU[c]	LTFU[d]	Notes
			Cycles 1 and 2				Cycle 3 and Subsequent Cycles							
DAY		-28 to 0	C1 D1	C1 D8	C2 D1	C2 D8	Q1C D1	Q2C (odd subsequent cycles) D1	Q6W after C1D1	As clinically indicated	Bema EoT[b]			
CENTRAL LABORATORY ASSESSMENTS														
Pregnancy test (FCBP only)		X	X					X		X		(X)	(X)	Highly sensitive serum β-hCG results are required within 72 hours of cycle 1 day 1. Repeat pregnancy tests (urine is acceptable) are required day 1 of every cycle. (X): Repeat pregnancy tests (urine is acceptable) are required 28 (+3) days after discontinuing protocol-required therapies, and monthly (28 [±3] days) pregnancy testing up to and inclusive of 75 (+3) days from the last bemarituzumab dose. During the LTFU period, local laboratory test results performed in walk-in clinics or health centers are acceptable if the subject does not have a scheduled clinic visit.
Amylase/lipase		X								X				
Immunogenicity sampling			X		X			(X)			X			Anti-bemarituzumab blood samples will be collected ≤ 4 hours prior to dosing of bemarituzumab. (X): To be collected for cycles 5 and 9. See Section 8.7.

Table 1-2. Schedule of Activities (Part 3 only)

Procedure[a]	Pre-SCR	SCR	Study Treatment (14-day cycles)									SFU[c]	LTFU[d]	Notes
			Cycles 1 and 2				Cycle 3 and Subsequent Cycles							
DAY		-28 to 0	C1 D1	C1 D8	C2 D1	C2 D8	Q1C D1	Q2C (odd subsequent cycles) D1	Q6W after C1D1	As clinically indicated	Bema EoT[b]			
PK samples			X	X	X	X		(X)			X			Pharmacokinetic samples will be collected ≤ 4 hours prior to dosing of bemarituzumab (pre-dose) and at the following times after end of the infusion: 15 (+10) min, 3 hours (± 30 min), 6 hours (± 1 hour), 24 hours (day 2, ± 1 hour), 72 hours (day 4, ± 6 hours), 168 hours (cycle 1 day 8 pre-dose, cycle 2 day 8 ± 24 hours), and 336 hours (day 15, ± 24 hours) for cycles 1 and 2. An additional sample is collected on day 8, 15 min after end of infusion for cycle 1. (X) Additional PK samples will be collected ≤ 4 hours prior to dosing of bemarituzumab (pre-dose) and 15 (+10) min after end of infusion for cycles 3 (336 hours collection for cycle 2 is the same as pre-dose cycle 3), 5, and 9. All PK samples should be collected after any corresponding ECG timepoints.
Plasma ctDNA biomarker			(X)		(X)		(X)				X			(X) Pre-dose C1D1, C2D1, and C3D1 only. The buffy coat will also be collected at each timepoint.

Table 1-2. Schedule of Activities (Part 3 only)

Procedure[a]	Pre-SCR	SCR	Study Treatment (14-day cycles)									SFU[c]	LTFU[d]	Notes
			Cycles 1 and 2				Cycle 3 and Subsequent Cycles							
DAY		-28 to 0	C1 D1	C1 D8	C2 D1	C2 D8	Q1C D1	Q2C (odd subsequent cycles) D1	Q6W after C1D1	As clinically indicated	Bema EoT[b]			
Optional tumor biopsy or archived tissue (FFPE)		(X)			[X]						[X]			(X): Remaining tissue from the pre-screening IHC assays may be used. If pre-screening sample not available, the subjects may provide archived FFPE samples (collected within 5 years) or undergo optional tumor biopsy. [X]: Optional tumor biopsy for exploratory biomarker testing will be performed for subjects who consent to this assessment. It will be performed, if feasible, on cycle 2 day 1 (± 7 days) and at the EoT (± 7 days) or at time of progression, prior to start of another anti-cancer therapy.
Bemarituzumab administration			X	X	X		X							After cycle 1, bemarituzumab dose should be recalculated only if the weight changes >10. If the dose is recalculated, the weight used for the recalculated dose should function as the new baseline. Bemarituzumab dosing should occur every 14 days (± 3 days) of the scheduled visit date for cycles 1 through 3. Starting at cycle 4, if needed, doses may be delayed up to 7 days. Doses should not be administered fewer than 7 days apart.

NOTE: Unless otherwise indicated, all assessments during the treatment period are performed prior to study drug administration.

Bema = bemarituzumab; β-hCG = β-human chorionic gonadotropin; C = cycle; CT = computed tomography; ctDNA = circulating tumor DNA; D = day; ECG = electrocardiogram; ECOG PS = Eastern Cooperative Oncology Group performance status; EoT = end of treatment; FCBP = female subjects of childbearing potential; FFPE = formalin fixed paraffin embedded; FGFR2b = fibroblast growth factor receptor isoform 2b; IHC = immunohistochemistry; LTFU = Long-Term Follow-up; MRI = magnetic resonance imaging; PD-L1 = programmed death-ligand 1; PK = pharmacokinetic; Q6W = every 6 weeks; SCR = screening; SFU = safety follow-up; Q1C = every cycle; Q1C D1 = day 1 of every cycle; Q2C = every 2 cycles

[a] Procedures are to be completed at scheduled time points, unless otherwise specified (eg, laboratory and safety assessments may be completed up to 72 hours prior to scheduled study treatment administration).

[b] Final samples will be collected 28 (+ 3) days after last dose of bemarituzumab (may be collected at SFU if all treatment is discontinued at same time).

[c] Safety follow-up assessments should be performed 28 (+ 3) days following the last study treatment administration.

[d] Subjects will complete LTFU for survival approximately every 3 months ± 1 month after the SFU visit up to 2 years from the first dose of bemarituzumab.

[e] Contrast enhanced CT scan is required for all 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. 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 MRI abdomen or 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.

Table 1-3. Schedule for Activities (Part 4 only)

Procedure[a]	Pre-SCR	SCR	Study Treatment (21-day cycles)							SFU[c]	LTFU[d]	Notes
			Cycles 1 and 2		Cycle 3 and Subsequent Cycles							
DAY		-28 to 0	C1 D1	C2 D1	Q1C D1	Q2C (odd subsequent cycles) D1	Q6W after C1D1	As clinically indicated	Bema EoT[b]			
PRE-SCREENING (ARCHIVAL TUMOR TISSUE/BIOPSY)												
Pre-screening informed consent	X											Pre-screening informed consent must be obtained prior to provision of tumor sample.
Archival tissue/fresh biopsy for IHC FGFR2b	X											Positive FGFR2b overexpression status by central IHC testing is required for enrollment. Provision of archival tissue within last 5 years (or fresh biopsy if archival tissue is not available) for assessment of FGFR2b overexpression status by IHC is required.
PD-L1 testing	X											Utilizes leftover pre-screening tissue, if available. PD-L1 will only be tested if FGFR2b overexpression is confirmed.
Demographics	X											
GENERAL AND SAFETY ASSESSMENTS												
Informed consent		X										Signed after FGFR2b overexpression status is confirmed
Eligibility criteria		X										
Medical history		X										Includes medical/surgical and cancer history (including local tumor biomarker testing results, such as PD-L1, if completed), ophthalmologic history, and medication history
Substance use		X										
Physical exam		X	X	X	(X)					X		(X): Day 1 of every cycle

Table 1-3. Schedule for Activities (Part 4 only)

Procedure[a]	Pre-SCR	SCR	Study Treatment (21-day cycles)							SFU[c]	LTFU[d]	Notes
			Cycles 1 and 2		Cycle 3 and Subsequent Cycles							
DAY		-28 to 0	C1 D1	C2 D1	Q1C D1	Q2C (odd subsequent cycles) D1	Q6W after C1D1	As clinically indicated	Bema EoT[b]			
Height		X										
Weight		X	X	X	(X)							(X): Must include weight and body surface area (BSA) on day 1 of every cycle.
ECOG PS		X				(X)				X		(X): Day 1 of every odd cycle
Vital assessments											X	Survival status collected every 3 months (±1 month) after SFU visit
Concomitant medications		X	----------X----------								(X)	(X): Collect information on ophthalmologic medication only
Subsequent anticancer therapy											X	Record subsequent therapies for lung cancer
Vital signs and oxygen saturation		X	X	X	X					X		Prior to study drug administration in all cycles (including nab-paclitaxel, if applicable)
12-lead ECG		X						X				12-lead ECG performed after subject rests for 5 minutes prior to recording

Table 1-3. Schedule for Activities (Part 4 only)

Procedure[a]	Pre-SCR	SCR	Study Treatment (21-day cycles)							SFU[c]	LTFU[d]	Notes
			Cycles 1 and 2		Cycle 3 and Subsequent Cycles							
DAY		-28 to 0	C1 D1	C2 D1	Q1C D1	Q2C (odd subsequent cycles) D1	Q6W after C1D1	As clinically indicated	Bema EoT[b]			
Ophthalmology exam		X					(X)	X		X	[X]	Includes assessment of distance corrected visual acuity, ocular surface staining, slit lamp examination of anterior segment, tonometry, and dilated retinal examination or 3 field retinal photographs. Examination may occur up to 5 days before dosing. (X): As above except dilated retinal examination or 3 field photographs are to be performed at every other ophthalmology exam. All examinations are to be performed every 6 weeks (- 5 days) for the first 24 weeks, and then every 8 weeks (- 5 days) thereafter. [X]: Refer to the 'notes' for Adverse Events of Special Interest during LTFU within this table.
Adverse events	(X)		----------X----------									(X): Adverse events of any grade occurring up to 14 days after the pre-screening procedure of tumor biopsy acquisition for the FGFR2b assay should be reported as adverse event if they are deemed related to the pre-screening procedure by the investigator. Refer to Section 8.4.6.1.1.

Table 1-3. Schedule for Activities (Part 4 only)

Procedure[a]	Pre-SCR	SCR	Study Treatment (21-day cycles)							SFU[c]	LTFU[d]	Notes
			Cycles 1 and 2		Cycle 3 and Subsequent Cycles							
DAY		-28 to 0	C1 D1	C2 D1	Q1C D1	Q2C (odd subsequent cycles) D1	Q6W after C1D1	As clinically indicated	Bema EoT[b]			
Serious adverse events	(X)	----------X----------									[X]	(X): Serious adverse events of any grade occurring up to 14 days after the pre-screening procedure of tumor biopsy acquisition for the FGFR2b assay should be reported as serious adverse events if they are deemed related to the pre-screening procedure for FGFR2b assay by the investigator. Refer to Section 8.4.6.1.2. [X]: During LTFU, only serious adverse events suspected to be related to investigational product or any fatal adverse event (regardless of causality) will be reported to Amgen immediately and no later than 24 hours following the investigator's awareness of the event.
Adverse events of special interest			X	----------X----------							X	Ophthalmological events of any grade up to 100 days after the last dose of bemarituzumab should be reported to the Sponsor.

Table 1-3. Schedule for Activities (Part 4 only)

Procedure[a]	Pre-SCR	SCR	Study Treatment (21-day cycles)							SFU[c]	LTFU[d]	Notes
			Cycles 1 and 2		Cycle 3 and Subsequent Cycles							
DAY		-28 to 0	C1 D1	C2 D1	Q1C D1	Q2C (odd subsequent cycles) D1	Q6W after C1D1	As clinically indicated	Bema EoT[b]			
IMAGING ASSESSMENTS												
CT/MRI[e]		X					(X)			[X]	([X])	(X): Every 6 (± 1) weeks from cycle 1 day 1 until week 54, then every 12 (± 2) weeks. Confirmation of response is required after 4 weeks. [X]: Can be omitted if last scan was performed < 6 weeks (-3 days) prior to SFU visit or if tumor progression was previously determined. ([X]): Imaging assessments will continue for subjects who discontinue study treatment without disease progression.
LOCAL LABORATORY ASSESSMENTS												
Hematology		X	X	X	X			X		X		Local test results must be reviewed and obtained up to 72 hours prior to dose on dosing days for bemarituzumab. Additional testing should occur at D8 and D15 prior to nab-paclitaxel dosing (if applicable).
Chemistry panel		X	X	X	X			X		X		
Total cholesterol levels		X										
Thyroid function testing		X					X	X				Collection of TSH is required. Free T4 is optional and should be collected as clinically indicated.
Coagulation		X	X	X				(X)				(X): As clinically indicated at any time (eg, subjects on anticoagulant therapy requiring close monitoring).
Urinalysis		X	X	X				X				May be collected within 72 hours of day 1 in each cycle.

Table 1-3. Schedule for Activities (Part 4 only)

Procedure[a]	Pre-SCR	SCR	Study Treatment (21-day cycles)							SFU[c]	LTFU[d]	Notes
			Cycles 1 and 2		Cycle 3 and Subsequent Cycles							
DAY		-28 to 0	C1 D1	C2 D1	Q1C D1	Q2C (odd subsequent cycles) D1	Q6W after C1D1	As clinically indicated	Bema EoT[b]			
Pregnancy test (FCBP only)		X	X	X	X			X		(X)	(X)	Highly sensitive serum β-hCG results are required within 72 hours of cycle 1 day 1. Repeat pregnancy tests (urine is acceptable) are required day 1 of every cycle. (X): Repeat pregnancy tests (urine is acceptable) are required 28 (+3) days after discontinuing protocol-required therapies, and monthly (28 [± 3] days) pregnancy testing up to and inclusive of 75 (+3) days from the last bemarituzumab dose. If the patient continues chemotherapy upon bemarituzumab discontinuation, a one-time pregnancy test will be performed upon the patient's discontinuation of chemotherapy during the SFU period. During the LTFU period, local laboratory test results performed in walk-in clinics or health centers are acceptable if the subject does not have a scheduled clinic visit.

Table 1-3. Schedule for Activities (Part 4 only)

Procedure[a]	Pre-SCR	SCR	Study Treatment (21-day cycles)							SFU[c]	LTFU[d]	Notes
			Cycles 1 and 2		Cycle 3 and Subsequent Cycles							
DAY		-28 to 0	C1 D1	C2 D1	Q1C D1	Q2C (odd subsequent cycles) D1	Q6W after C1D1	As clinically indicated	Bema EoT[b]			
Amylase/lipase		X						X				
CENTRAL LABORATORY ASSESSMENTS												
Immunogenicity sampling			X	X		(X)			X			Anti-bemarituzumab blood samples will be collected ≤ 4 hours prior to dosing of bemarituzumab. (X): To be collected for cycles 5 and 9. See Section 8.7.
PK samples			X	X		(X)			X			For Part 4 combination therapy, pharmacokinetic samples will be collected ≤ 4 hours prior to dosing of bemarituzumab (pre-dose) and at the following times after end of the infusion: 15 (+10) min, 3 hours (± 30 min), 6 hours (± 1 hour), 24 hours (day 2, ± 1 hour), 72 hours (day 4, ± 6 hours), 168 hours (day 8,± 24 hours), 336 hours (day 15, ± 24 hours), 504 hours (day 22, ± 24 hours) for cycles 1 and 2. (X) Additional PK samples will be collected ≤ 4 hours prior to dosing of bemarituzumab (pre-dose) and 15 (+ 10) min after end of infusion for cycles 3 (504 hours collection for cycle 2 is the same as pre-dose cycle 3), 5, and 9.
Plasma ctDNA biomarker			(X)	(X)	(X)				X			(X) Pre-dose C1D1, C2D1, and C3D1 only. The buffy coat will also be collected at each timepoint.

Table 1-3: Schedule for Activities (Part 4 only)

Procedure[a]	Pre-SCR	SCR	Study Treatment (21-day cycles)							SFU[c]	LTFU[d]	Notes
			Cycles 1 and 2		Cycle 3 and Subsequent Cycles							
DAY		-28 to 0	C1 D1	C2 D1	Q1C D1	Q2C (odd subsequent cycles) D1	Q6W after C1D1	As clinically indicated	Bema EoT[b]			
Optional tumor biopsy or archived tissue (FFPE)		(X)		[X]					[X]			(X): Remaining tissue from the pre-screening/screening IHC assays may be used. If pre-screening/screening sample not available, the subjects may provide archived FFPE (collected within 5 years), or undergo optional tumor biopsy. [X]: Optional tumor biopsy for exploratory biomarker testing will be performed for subjects who consent to this assessment. It will be performed, if feasible, on cycle 2 day 1 (± 7 days) and at the EoT (± 7 days) or at time of progression, prior to start of another anti-cancer therapy.
STUDY TREATMENT												
Bemarituzumab administration			X	X	X							Bemarituzumab is to be administered Q3W, prior to all other study treatments. After cycle 1, bemarituzumab dose should be recalculated only if the weight changes > 10%. If the dose is recalculated, the weight used for the recalculated dose should function as the new baseline. For cycles 1 through 3, day 1 dose should be administered every 21 (± 3) days, regardless of delays in other anti-cancer treatment. Starting at cycle 4, may be delayed up to 7 days to be synchronized with other anti-cancer treatment. Doses should not be administered fewer than 14 days apart.

Table 1-3: Schedule for Activities (Part 4 only)

Procedure[a]	Pre-SCR	SCR	Study Treatment (21-day cycles)							SFU[c]	LTFU[d]	Notes
			Cycles 1 and 2		Cycle 3 and Subsequent Cycles							
DAY		-28 to 0	C1 D1	C2 D1	Q1C D1	Q2C (odd subsequent cycles) D1	Q6W after C1D1	As clinically indicated	Bema EoT[b]			
Pembrolizumab administration			X	X	X							Administered Q3W after bemarituzumab and before chemotherapy for the first 4 cycles and administered after bemarituzumab as maintenance therapy for up to 35 cycles.
Paclitaxel administration			X	X	X							Choice of paclitaxel or nab-paclitaxel based on local availability and/or investigator's choice. Dosing for paclitaxel is Day 1 of each Q3W for up to 4 cycles. Dosing for nab-paclitaxel is on Day 1, Day 8, and Day 15 of each Q3W for up to 4 cycles.
Nab-Paclitaxel administration			X	X	X							
Carboplatin administration			X	X	X							Day 1 of each Q3W for up to 4 cycles.

NOTE: Unless otherwise indicated, all assessments during the treatment period are performed prior to study drug administration.

Bema = bemarituzumab; β-hCG = β-human chorionic gonadotropin; C = cycle; CT = computed tomography; ctDNA = circulating tumor DNA; D = day; ECG = electrocardiogram; ECOG PS = Eastern Cooperative Oncology Group performance status; EoT = end of treatment; FCBP = female subjects of childbearing potential; FFPE = formalin fixed paraffin embedded; FGFR2b = fibroblast growth factor receptor isoform 2b; IHC = immunohistochemistry; LTFU = Long-Term Follow-up; MRI = magnetic resonance imaging; PD-L1 = programmed death-ligand 1; PK = pharmacokinetic; SCR = screening; SFU = safety follow-up; Q1C = every cycle; Q1C D1 = day 1 of every cycle; Q2C = every 2 cycles; Q3W = every 3 **weeks**; Q6W = every 6 weeks; TSH = thyroid stimulating hormone; T4 = thyroxine

[a] Procedures are to be completed at scheduled time points, unless otherwise specified (eg, laboratory and safety assessments may be completed up to 72 hours prior to scheduled study treatment administration).

[b] Final samples will be collected 28 (+ 3) days after last dose of bemarituzumab (may be collected at SFU if all treatment is discontinued at same time).

[c] Safety follow-up assessments should be performed 28 (+ 3) days following the last study treatment administration.

[d] Subjects will complete LTFU for survival approximately every 3 months ± 1 month after the SFU visit up to 2 years from the first dose of bemarituzumab.

[e] Contrast enhanced CT scan is required for all 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. Tumor evaluation is to be performed by contrast-enhanced CT of the chest and 1 of the following: contrast-enhanced CT abdomen with cuts through the pubic symphysis, contrast-enhanced MRI abdomen or 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.

2. Introduction

2.1 Study Rationale

Bemarituzumab is a humanized monoclonal antibody that targets the fibroblast growth factor (FGF) receptor isoform 2b (FGFR2b) with a dual mechanism of FGF binding inhibition and antibody-dependent cellular cytotoxicity. Bemarituzumab monotherapy has been investigated in a phase 1 dose-finding study (FPA144-001) and in combination with mFOLFOX6 chemotherapy in FGFR2b-positive gastric cancer in the FIGHT study. Bemarituzumab efficacy correlated with the degree of FGFR2b overexpression by immunohistochemistry (IHC) in gastric cancer and has demonstrated a manageable safety profile in combination with mFOLFOX6. Genomic and IHC data suggest that other carcinomas including squamous-cell non-small-cell lung cancer (SqNSCLC) may also have a significant rate of FGFR2b overexpression. This study will evaluate the safety, tolerability, and efficacy of bemarituzumab monotherapy as well as the combination with other anti-cancer therapy, across different lines of therapy in the locally advanced/metastatic setting. Once a recommended dose of bemarituzumab in combination with docetaxel is determined, this study will explore the efficacy of the docetaxel combination in FGFR2b+ selected SqNSCLC, as well as the safety and efficacy of the bemarituzumab combination with other anti-cancer therapies in the first-line metastatic treatment setting.

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 2021 there would be approximately 235 760 new cases of lung cancer in the US alone (American Cancer Society, 2021). The 5-year survival rate for Non-small-Cell Lung Cancer (NSCLC) is 25% (American Cancer Society, 2021). Squamous-cell NSCLC accounts for 20% to 30% of all NSCLC, and while adenocarcinomas, the most common histologic subtype of NSCLC, harbor druggable genetic changes, the squamous-cell histologic subtype either has extremely low or no druggable genetic changes (Rekhtman et al, 2012; Drilon et al, 2012). So, while in the first-line advanced disease setting, SqNSCLC, like adenocarcinoma, is treated with platinum-based chemotherapy in combination with checkpoint inhibitor, in the second-line setting and later, there are currently no targeted therapy options for SqNSCLC as there are for most adenocarcinomas.

From studies of tumor DNA, the fibroblast growth factor receptor (FGFR) family is the most commonly altered tyrosine kinase family members in SqNSCLC. Alterations (mutations, amplifications, and translocations) in FGFRs 1 through 3 were observed in 12% of SqNSCLC specimens by exome sequencing and FGFR1 amplifications were observed in 22% of SqNSCLC specimens by fluorescence in situ hybridization (FISH) (Hammerman et al, 2012; Weiss et al, 2010). Tumors with FGFR1 amplification or FGFR2/3 mutations (some of which lead to dimerization/constitutive activation) have few other dominant oncogenic mutations, suggesting that over-activation of FGFRs could be genomic drivers of SqNSCLC (Liao et al, 2013; Heist et al, 2012). Recent data on FGFR2b overexpression by IHC (any 2+/3+ cut-point) suggests the target of bemarituzumab is expressed in approximately 21% (95% CI: 16% to 26%) of procured SqNSCLC tissues (Amgen, data on file).

This study will investigate a novel inhibitor of FGFR2b (described in Section 2.2) in combination with other anti-cancer therapies. The combination of pembrolizumab, carboplatin, and either nab-paclitaxel or paclitaxel is indicated for the first-line treatment of patients with locally advanced or metastatic squamous NSCLC (Paz-Ares et al, 2018; Keytruda® Summary of Product Characteristics [SPC] 2015; Keytruda® United States Prescribing Information [USPI], 2014) and is recommended according to the US National Comprehensive Cancer Network (NCCN) and European Society for Medical Oncology (ESMO) treatment guidelines (NCCN-Guidelines, 2022; Planchard et al, 2018). Docetaxel is indicated as a single agent for the treatment of patients with locally advanced or metastatic NSCLC after failure of platinum-based chemotherapy (Taxotere® SPC 2019; Taxotere® USPI 2019) and recommended according to the NCCN and ESMO treatment guidelines (NCCN-Guidelines, 2022; Planchard et al, 2018).

2.2.2 Amgen Investigational Product Background: Bemarituzumab

Bemarituzumab, also called AMG 552, is a humanized monoclonal antibody (immunoglobulin G1 [IgG1] isotype) specific to the human FGFR2b receptor that blocks FGF ligand binding to the receptor. Bemarituzumab is directed against the third Ig region of the FGFR2b receptor isoform, the region that is alternatively spliced and regulates ligand specificity. This antibody is glycosylated but is produced in a Chinese hamster ovary cell line that lacks the FUT8 gene (α1,6 Fucosyltransferase) and therefore lacks a core fucose in the polysaccharide portion of the antibody. The absence of the core fucose results in higher affinity for the Fc receptor FcγRIIIa compared to the fucosylated molecule and potentially enhances immune cell-mediated

tumor cell killing (Shinkawa et al, 2003). The antibody has thus been glycoengineered for enhanced antibody dependent cell-mediated cytotoxicity (ADCC) (Gemo et al, 2014). Bemarituzumab inhibits FGF ligand-stimulated FGFR2b phosphorylation and cell proliferation in cell culture in FGFR2b overexpressing gastric, breast cancer, and NSCLC cancer lines. Bemarituzumab also inhibits tumor growth in FGFR2b overexpressing gastric and breast xenograft models. The 3 potential mechanisms of action of bemarituzumab thus include blocking ligand binding and downstream signaling, decreasing expression of the FGFR2b driver protein, and enhancing ADCC.

Additionally, since bemarituzumab is specific for the FGFR2b receptor, it does not interfere with signaling of the other FGFs/FGFRs, including FGFR2c. In contrast to the FGFR tyrosine kinase inhibitors (TKIs), bemarituzumab does not inhibit FGF23 signaling. FGF23 is a ligand involved in calcium/phosphate metabolism and therefore, treatment with bemarituzumab is not associated with the hyperphosphatemia associated with the FGFR TKIs (Catenacci et al, 2020; Dienstmann et al, 2014; Sequist et al, 2014; Andre et al, 2013; Brown et al, 2005).

A detailed description of the chemistry, pharmacology, efficacy, and safety of bemarituzumab is provided in the Investigator's Brochure.

2.2.2.1 Nonclinical Studies with Bemarituzumab

Bemarituzumab blocks FGFR2b phosphorylation, downregulates the receptor, and inhibits downstream signaling. The effect on downstream signaling was measured by examining phosphorylation of a protein that is directly phosphorylated by the FGFR2 protein, FGFR substrate-2 (FRS2). Each of these mechanisms has been explored in vitro and in vivo and appears to contribute to the anti-tumor activity of bemarituzumab. In FGFR2b-overexpressing human tumor xenograft models, bemarituzumab shows dose-related anti-tumor activity with regression and complete responses at well-tolerated doses.

Bemarituzumab demonstrated consistent pharmacokinetic (PK) behavior following intravenous (IV) administration in rats and cynomolgus monkeys, and the PK characteristics observed were consistent across all studies. The half-life was dose-dependent, ranging from 0.8 days at the lowest doses (1 to 1.5 mg/kg) to at least 8 days at the highest doses (100 to 150 mg/kg) tested in cynomolgus monkeys. Bemarituzumab demonstrated dose-dependent, nonlinear PK that was marked by a faster clearance at the terminal phase of the plasma concentration time profile and a greater than dose proportional increase in exposure (area under the concentration time

curve [AUC]) with increasing dose. Target-mediated clearance was saturable, marked by dose-proportional increases in exposure at doses exceeding this level when dosed at weekly intervals. The PK studies supporting the toxicokinetic studies showed dose-dependent increases in exposure (AUCs) supporting the reliability of these studies to assess toxicity.

Significant reproductive and developmental toxicities were observed at all dose levels (5 to 100 mg/kg/doses) in the embryo-fetal development with prenatal and postnatal development study.

2.2.2.2 Clinical Studies with Bemarituzumab

Clinical safety data are available from 5 studies with bemarituzumab: FPA144-001 (phase 1), FPA144-002 (phase 1), FPA144-004 (phase 1/2), 20201098 (phase 1b safety run-in), and the current study from dose level review meeting (DLRM)1 and DLRM2 interim review.

A phase 1 first-in-human (FIH) dose escalation study (Study FPA144-001) found single-agent bemarituzumab to have a tolerable safety profile and a 17.9% (95% CI: 6.1, 36.9) confirmed response rate in late-line FGFR2b overexpressing gastric cancer (GC) (Catenacci et al, 2020). This phase 1 study was an open-label, multicenter trial consisting of a dose escalation in subjects with recurrent solid tumors and a dose expansion in subjects with advanced-stage GC that overexpressed FGFR2b at various levels. Bemarituzumab doses ranged from 0.3 to 15 mg/kg. Seventy-nine subjects were enrolled, and the recommended dose was identified as 15 mg/kg every 2 weeks (Q2W) based on safety, tolerability, PK parameters, and clinical activity. As a single agent in this late-line setting, the most frequent treatment-related adverse events in the 79 subjects were fatigue (17.7%), nausea (11.4%), and dry eye (10.1%). Grade 3 treatment-related adverse events included nausea (2 subjects) and anemia, neutropenia, increased aspartate aminotransferase (AST), increased alkaline phosphatase, vomiting, and an infusion reaction (1 subject each). Three of 28 subjects (10.7%) who received a dose of at least 10 mg/kg Q2W for at least 70 days reported reversible grade 2 corneal treatment-related adverse events. No treatment-related adverse events of grade 4 or higher were reported (Catenacci et al, 2020).

Study FPA144-002 was a phase 1, dose escalation study of bemarituzumab in Japanese subjects with advanced GC that evaluated 2 dose levels (10 mg/kg and 15 mg/kg). This single arm study explored the safety, tolerability, and PK of bemarituzumab in Japanese subjects with GC with or without FGFR2b overexpression.

No dose limiting toxicities (DLTs) were identified in subjects enrolled in the dose escalation cohorts with FPA144 monotherapy in FPA144-002. Five of 6 subjects (83%) enrolled in FPA144-002 experienced an adverse event. The reported events included worsening anemia (2 subjects), constipation, subconjunctival hemorrhage, upper respiratory infection, diarrhea, skin rash, nail change, fever, epistaxis, fatigue, myalgia, sore throat, arthralgia, pain, infusion related reaction, dry eyes, malaise, and nausea (1 subject). No serious adverse events were reported in this study. Pharmacokinetic data from all 6 subjects were analyzed and showed that bemarituzumab PK profiles from Japanese subjects in this study were similar to subjects in Study FPA144-001.

Study FPA144-004 is a phase 1/2, multicenter, international, double-blind, randomized, controlled study designed to evaluate the safety, tolerability, efficacy, and PK of bemarituzumab in combination with mFOLFOX6, compared with placebo in combination with mFOLFOX6, in selected subjects with unresectable, locally advanced, or metastatic GC including cancer of the gastroesophageal junction (GEJ). The phase 1 portion of the study identified that 15 mg/kg with 1 additional dose of 7.5 mg/kg on cycle 1 day 8 in combination with a fixed dose of mFOLFOX6 achieved target trough steady state plasma concentration ($C_{trough,ss}$) of 60 µg/mL on day 15.

In the phase 2 Part of FPA144-004, 910 subjects were prescreened for the trial, and 275 (30.2%) had tumors which overexpressed FGFR2b; 155 subjects were randomized, and 76 subjects were treated in the bemarituzumab + mFOLFOX6 group and 77 subjects were treated in the placebo+mFOLFOX6 group. Treatment-emergent adverse events of any grade reported at ≥ 10% higher frequency in the bemarituzumab + mFOLFOX6 group compared with the placebo + mFOLFOX6 group included AST increased (30.3% versus 19.5%), stomatitis (31.6% versus 13.0%), alanine aminotransferase (ALT) increased (28.9% versus 14.3%), dry eye (26.3% versus 6.5%), epistaxis (22.4% versus 3.9%), vision blurred (15.8% versus 1.3%), keratitis (14.5% versus 1.3%), and punctate keratitis (13.2% versus 2.6%). Grade 3 and higher treatment-emergent adverse events were reported in 82.9% of subjects in the bemarituzumab + mFOLFOX6 group compared with 74.0% of subjects in the placebo + mFOLFOX6 group. Grade 3 and higher treatment-emergent adverse events reported at ≥ 5% higher frequency in the bemarituzumab + mFOLFOX6 group compared with the placebo + mFOLFOX6 group were stomatitis (9.2% versus 1.3%) and limbal stem cell deficiency (6.6% versus 0%). Serious adverse events were reported in

31.6% of subjects on the bemarituzumab arm and 36.4% of subjects on the placebo arm and were qualitatively similar in both arms.

Ocular-related adverse events associated with the cornea or retina (defined as events with Preferred Terms using the Corneal Disorders Standard Medical Dictionary for Regulatory Activities [MedDRA] Queries [SMQ] broad search and Retinal Disorders SMQ broad search, MedDRA Version 20.1) are considered adverse events of interest with bemarituzumab. Ocular-related adverse events were considered treatment-emergent if they began on or after the study drug start date up to 100 days after the last dose of any study drug. Corneal toxicity is expected based on preclinical toxicology results in the rat and cynomolgus monkey and on results from the phase 1 study FPA144-001 with monotherapy bemarituzumab. Corneal toxicity is hypothesized to be related to the mechanism of action of bemarituzumab due to the expression of FGFR2b on corneal epithelial cells. Retinal pigmented epithelial detachment, which has been associated with small molecule pan-FGFR TKIs (Pemazyre® [pemigatinib] USPI, 2021; Balversa® [erdafitinib] UPSI, 2020), was not reported on the bemarituzumab arm in this study.

In the safety population, an increase in ocular-related adverse events was reported in the bemarituzumab+mFOLFOX6 arm compared with the placebo+mFOLFOX6 arm (71.1% versus 16.9%). No serious ocular adverse events were reported. The most frequent (> 10% of subjects) ocular-related adverse events in the bemarituzumab + mFOLFOX6 arm were dry eye (26.3%), keratitis (15.8%), vision blurred (15.8%), punctate keratitis (14.5%), and corneal epithelium defect (10.5%). Grade 3 ocular-related adverse events were reported in 23.7% of subjects in the bemarituzumab arm compared to no subjects in the placebo arm. No grade 4 ocular-related adverse events were reported.

Evidence of efficacy of adding bemarituzumab to chemotherapy in subjects with FGFR2b overexpressing gastric cancer is supported by results of the FPA144-004 phase 2 study. Compared with placebo+mFOLFOX6 treatment, the addition of bemarituzumab to mFOLFOX6 led to improvements in Progression Free Survival (PFS) (hazards ratio [HR] = 0.72, 95% CI: 0.494, 1.08), overall survival (OS) (HR = 0.77, 95% CI: 0.52, 1.14; p = 0.0268), and objective response rate (ORR) (difference of 14.4%, 95% CI: -1.5%, 30.3%). Efficacy was more pronounced with higher levels of FGFR2b overexpression (≥ 10% vs intent-to-treat [ITT]) across all three efficacy endpoints: PFS, OS, and ORR.

Data on the safety of bemarituzumab in combination with programmed death-ligand 1 (PD-L1) inhibitor in addition to mFOLFOX6 chemotherapy in gastric cancer is available from the Phase 1b portion of Study 20210098. On 14 July 2022 a DLRM was conducted to evaluate the safety of the combination of bemarituzumab, mFOLFOX6, and nivolumab. The bemarituzumab dose of 15 mg/kg IV Q2W with a single 7.5 mg/kg dose on day 8 of the first cycle was selected based on the results of the bemarituzumab and mFOLFOX6 combination. Eight subjects were enrolled in phase 1b and evaluated for DLTs. Six subjects were men, and 2 subjects were women. Four subjects were Asian, enrolled in Japan, and 4 subjects were White enrolled in the United States. Ages ranged from 50 to 71 years.

All 8 subjects had metastatic disease; 4 subjects had a diagnosis of gastric adenocarcinoma and 4 subjects had gastroesophageal junction adenocarcinoma. The duration from initial diagnosis to enrollment ranged from $<$ 1 to 99 months.

No DLTs were reported among the 8 subjects who completed the DLT observation window of 28 days.

Based on the absence of DLTs and consistent safety and PK profiles with the FIGHT study (FPA144-004), suggesting no interactions with nivolumab, the dose level review team (DLRT) unanimously agreed to initiate the phase 3 part of the study.

Data on the safety of bemarituzumab at 2 dose levels in combination with docetaxel in SqNSCLC is available from the current study. On 9 June 2022, a DLRM was conducted to evaluate the safety of bemarituzumab with docetaxel. The bemarituzumab dose level 1 was 15 mg/kg IV every 3 weeks (Q3W) with a single loading dose of 22 mg/kg on cycle 1 day 1 (C1D1). Four subjects were enrolled in cohort 1 and evaluated for DLTs. Four subjects were men. Two subjects were Asian, enrolled in Japan, and 2 subjects were White enrolled in Europe. Ages ranged from 60 to 71 years.

No DLTs were reported among the 4 subjects who completed the DLT observation window of 21 days.

Based on the absence of DLTs and consistent safety and pharmacokinetic profiles with the FIGHT study (FPA144-004), suggesting no interactions with docetaxel, the DLRT unanimously agreed to initiate cohort 2, escalating bemarituzumab to dose level 2 (22 mg/kg IV Q3W with a single loading dose of 30 mg/kg of C1D1) in combination with docetaxel.

On 31 August 2022, a second DLRM was conducted to evaluate the safety of bemarituzumab in combination with docetaxel in part 1, cohort 2. The bemarituzumab dose was 22 mg/kg IV Q3W with a single loading dose of 30 mg/kg on C1D1. Four subjects were enrolled in cohort 2 and evaluated for DLTs. There were three male subjects and one female subject. One Asian subject was enrolled in Japan, and 3 White subjects were enrolled in Europe. The ages ranged from 53 to 77 years.

One DLT was reported among the 4 evaluable subjects who completed the DLT observation window of 21 days. The DLT reported was a grade 3 stomatitis that began 9 days after C1D1 of bemarituzumab plus docetaxel, and resolved with supportive therapy to a grade 1 stomatitis within 4 days on onset.

Based on the data review by the DLRM voting members and the consistent safety and pharmacokinetic profiles with the FIGHT study (FPA144-004), suggesting no interactions with docetaxel, the DLRM unanimously agreed to expand cohort 2, to enroll 5 more patients at the dose level 2 (bemarituzumab 22 mg/kg IV Q3W with a single loading dose of 30 mg/kg of C1D1) in combination with docetaxel.

2.3 Benefit/Risk Assessment

NSCLC is a highly lethal disease and the SqNSCLC histologic subtype especially has limited treatment options especially after first-line treatment. The median Progression Free Survival (mPFS) and median overall survival (mOS) of SqNSCLC treated with immuno-chemotherapy in the first-line is 6.4 months and 15.9 months, respectively (Paz-Ares et al, 2018). The mPFS and mOS of SqNSCLC treated with docetaxel in the second-line is 2.7 to 2.8 months and 6.0 to 8.2 months, respectively, in recent phase 3 studies (Paz-Ares et al, 2017; Brahmer et al, 2015).

Genomic profiling of SqNSCLC and preclinical and clinical data from other FGFR TKIs suggest vulnerability to FGFR inhibition (Hashemi-Sadrai and Hanna, 2017; Brahmer et al, 2015). Data from bemarituzumab in gastric cancer (see Section 2.2.2.2) supports a tolerable safety profile and evidence of efficacy as monotherapy and in combination with chemotherapy. Recent data on procured SqNSCLC tissues suggests 21% (95% CI 16% - 26%) demonstrate FGFR2b overexpression by IHC (any 2+/3+ cut-point), which is comparable to the prevalence in gastric cancer. In addition, the preliminary safety data supporting combination of bemarituzumab with docetaxel from this study, therefore provides the basis for further exploring bemarituzumab in this combination and with doublet platinum-based chemotherapy and PD-L1 inhibition in first line. A summary of the safety profile of bemarituzumab, risk mitigation for ocular toxicity, risks associated

with non-investigational medicinal products, and hypothetical overlapping toxicities are discussed below.

Safety profile of bemarituzumab

To date, bemarituzumab has demonstrated an acceptable safety profile. Identified risks when used in combination with mFOLFOX6 include corneal toxicity, infusion related reactions, gastrointestinal toxicity (stomatitis and mucosal inflammation), palmar-plantar erythrodysesthesia syndrome, nail toxicity and increase in AST and ALT. (See Section 2.2.2.2 for details).

Corneal events are very common with bemarituzumab with the most common adverse event being dry eye (Section 2.2.2.2). Although nearly all of the events have been non-serious, grade 3 events such ulcerative keratitis and punctate keratitis which can lead to decreases in visual acuity have been observed. Corneal events were a common cause of treatment discontinuation. The majority of the corneal events typically resolve with treatment interruption or discontinuation and standard of care interventions for the corneal events.

Risk mitigation for corneal toxicity

The following criteria and measures have been adopted to mitigate the risk of corneal toxicity in this study:

- Eligibility is restricted to subjects without active eye disorders, subjects who do not require treatment for ongoing eye diseases, and subjects who agree to stop wearing contact lenses during treatment and for at least 100 days after the end of treatment.
- Eligibility is restricted from subjects who may be at risk for corneal complications including those with ongoing or recent corneal defects, corneal ulcerations, keratitis, or keratoconus, history of corneal transplant or recent corneal surgery or ophthalmic laser treatment.
- Ophthalmology examinations, including assessment of distance corrected visual acuity, ocular surface staining (eg, fluorescein), slit lamp exam of the anterior segment, tonometry, and retinal examination (either dilated retinal examination or 3 field retinal photographs).
- Prophylactic use of ocular lubricants and eyelid hygiene is recommended.
- Treatment interruption and/or discontinuation for higher grade corneal events (refer to Table 6-5 for details).

The potential risks of bemarituzumab include retinal toxicity, cataract, hypersensitivity, sucrose-related renal toxicity, embryo-fetal toxicity and mammary gland changes; the risks mitigation measures have been implemented for these potential risks.

In the FPA144-004 study which compared mFOLFOX6 with and without bemarituzumab in gastric cancer, there was no notable increase in myelosuppression or nausea or vomiting. Stomatitis was greater in the bemarituzumab arm (31.6% versus 13.0%) and grade 3 stomatitis events were greater (9.2% versus 1.3%) with 1 subject discontinuing treatment due to stomatitis in the bemarituzumab arm. Diarrhea was greater in the bemarituzumab arm 40.8% versus 31.2%, however it appears to be due to a difference in grade 1 (31.6% versus 20.8%), whereas grade ≥ 2 was similar across arms. Similarly, epistaxis was more frequently reported in the bemarituzumab + mFOLFOX6 arm (22.4% versus 3.9%) which was almost all due to a difference in grade 1 epistaxis (19.7% versus 3.9%). Onycholysis of any grade was higher in the bemarituzumab arm (6.6% versus 1.3%) and grade 3 onycholysis events were greater (1.3% versus 0%) in the bemarituzumab arm; no grade 3 events were reported in the placebo arm. AST and ALT elevations were frequently reported in the bemarituzumab + mFOLFOX6 arm however majority increases were grade 1 and 2 in severity and none led to treatment discontinuation.

Risks associated with non-investigational medicinal products

The combination regimen of pembrolizumab, carboplatin, and paclitaxel/nab-paclitaxel is associated with neutropenia (most frequently grade 3 to 4) reported in 38% of patients, anemia reported in 53% of patients, diarrhea reported in 30% of patients, and nausea reported in 36% of patients (Paz-Ares et al, 2018). Other adverse reactions for the combination of pembrolizumab, carboplatin, and paclitaxel/nab paclitaxel are alopecia, thrombocytopenia, anorexia, constipation, fatigue, asthenia, arthralgia, peripheral neuropathy, vomiting, cough, dyspnea, hypothyroidism, hyperthyroidism, pneumonitis, infusion reaction, colitis, hepatitis, severe skin reaction, hypophysitis, thyroiditis, and nephritis.

Docetaxel chemotherapy is associated with neutropenia (most frequently grade 3 to 4) reported in 33% of patients, anemia reported in 22% of patients, diarrhea reported in 20% of patients, nausea reported in 23% of patients and mucosal inflammation reported in 9% of patients (Brahmer et al, 2015). Other adverse reactions for docetaxel are infections, febrile neutropenia, hypersensitivity, thrombocytopenia, neuropathy, dysgeusia, dyspnea, constipation, anorexia, nail disorders, fluid retention, asthenia, pain, nausea, vomiting, alopecia, skin reactions, and myalgia.

The individual non-investigational anti-cancer therapies in this study are associated with other risks, in addition to the more common toxicities summarized herein. Refer to local prescribing information for complete details.

Hypothetical overlapping toxicities of bemarituzumab and non-investigational products to be used in combination

Stomatitis, ocular toxicity, infusion-related reaction, nail disorder, diarrhea, immune-mediated adverse reactions, and liver enzymes elevation and embryo-fetal toxicity represents possible overlapping toxicities when in combination with pembrolizumab and the other chemotherapies in this study. Significant hepatotoxicity is associated with docetaxel, thus also representing possible overlapping toxicity. These risks will be mitigated through dose adjustment and treatment interruption/discontinuation according to Table 6-5 and Section 6.2.2.2.

Summary of study population

As of July 2021, no drug has been approved specifically for the subset of patients with FGFR2b-positive cancer. Based on the FPA144-004 phase 2 trial data, bemarituzumab provides a meaningful clinical benefit with an acceptable tolerability profile in newly diagnosed patients with advanced stage GC whose tumors overexpress FGFR2b. This study will explore whether the safety profile of bemarituzumab monotherapy or combination with chemotherapy and checkpoint inhibitor is acceptable in SqNSCLC. At this early stage in the investigation of bemarituzumab in SqNSCLC, the level of expression of FGFR2b needed for efficacy and the prevalence of subjects with FGFR2b overexpression status is unknown. Therefore, the dose exploration part exploring the dose of bemarituzumab in combination with docetaxel will not select subjects for FGFR2b overexpression status. Based on the limited data in FPA144-001, in which responses were limited to subjects expressing FGFR2b, it is possible that FGFR2b-negative subjects in dose exploration may not derive additional benefit from the addition of bemarituzumab, however, subjects will still be receiving docetaxel as a standard of care after first-line therapy. FGFR2b-negative subjects may be exposed to the additional identified safety risk of corneal toxicity, however that risk is likely considerably lower than in FPA144-04 in the setting of absence of benefit from bemarituzumab because of the shorter expected duration of treatment. The mPFS of SqNSCLC treated with docetaxel in the second-line is 2.7 to 2.8 months, which is considerably shorter than the median onset of grade 2 or 3 ocular events in FPA144-04 of 5.0 months. Parts 2, 3, and 4 will select subjects for FGFR2b overexpression. Additionally, in Part 3 where

bemarituzumab monotherapy will be explored, subjects must have failed second line therapy to be eligible, and therefore have exhausted available therapies.

2.3.1 COVID-19

Amgen closely monitors the coronavirus disease 2019 (COVID-19) pandemic around the world. As part of this effort, Amgen performs a rigorous assessment, considering the study design, patient safety, public health risk, benefit-risk assessment, as well as the burden on country healthcare systems. Decisions are made on a study-by-study and country-by-country basis to minimize risk to patients and avoid undue burden on healthcare facilities.

Subjects enrolled in this study are permitted to receive vaccinations for COVID-19, however, vaccination should not be administered within 2 days before or after bemarituzumab infusion.

Amgen considers that it is important to continue the proposed development of bemarituzumab in this study in order to advance potential therapy options for patients as rapidly as possible, while balancing this with appropriate measures to monitor and mitigate the potential impact of COVID-19.

Based on the medical need in the SqNSCLC population and overall evaluation of risks, preliminary activity, and potential efficacy associated with bemarituzumab in gastric cancer, the Sponsor believes that bemarituzumab has a favorable benefit-risk profile for ongoing clinical evaluation. The above benefit risk assessment supports the conduct of this clinical trial. Reference should be made to the Investigator's Brochure for bemarituzumab and Regional Prescribing Information for other anti-cancer therapies for further data.

3. Objectives and Endpoints

Objectives	Endpoints
Primary	
• To evaluate the safety and tolerability of bemarituzumab monotherapy and combination with other anti-cancer therapies • To determine the recommended phase 3 dose of bemarituzumab in combination with other anti-cancer therapies	• Dose limiting toxicities (DLTs), treatment-emergent adverse events, and clinically significant changes in vital signs, physical examinations, clinical laboratory tests, and visual acuity

Secondary	
• To characterize the pharmacokinetics (PK) of bemarituzumab monotherapy and in combination with other anti-cancer therapies	• PK parameters for bemarituzumab including, but not limited to, area under the concentration time curve (AUC), maximum observed concentration (C_{max}), and observed concentration at the end of a dose interval (C_{trough})
• To evaluate preliminary anti-tumor activity of bemarituzumab monotherapy and in combination with other anti-cancer therapies	• Objective response [defined as complete response (CR) + partial response (PR)] (as determined by investigator per Response Evaluation Criteria in Solid Tumors [RECIST v1.1]) • Duration of response defined as the time from first response to disease progression (as determined by investigator per RECIST v1.1) or death from any cause, whichever comes first • Disease control defined as CR + PR + stable disease (SD) • Progression free survival (PFS), defined as time from first dose of investigational product until disease progression or death from any cause. Subjects alive without progression will be censored at their last evaluable disease assessment. Progression will be based on assessment by investigator per RECIST v1.1 • Overall survival (OS), defined as time from first dose of investigational product until death from any cause. Subjects still alive will be censored at the date last known to be alive

Estimand(s) for Primary Endpoint(s)

Not applicable.

Estimand(s) for Secondary Endpoint(s)

Not applicable.

Exploratory	
• To characterize the immunogenicity of bemarituzumab	• Anti-bemarituzumab antibody formation

• To evaluate the expression of biomarkers in tumor samples	• Expression of biomarkers, including, but not limited to FGFR2b and programmed death-ligand 1 (PD-L1)
• To evaluate the relationship between exploratory biomarkers and efficacy	• Correlation of biomarkers, including PD-L1 and FGFR2b overexpression status with efficacy endpoints
• To explore protein and nucleic acid biomarkers in blood and tissue	• Changes in protein and nucleic acid biomarkers in blood and in tumor biopsies pre-treatment, on-treatment, and at progression

4. Study Design

4.1 Overall Design

This is a phase 1b, open-label, multicenter study to evaluate the safety, tolerability, PK, and efficacy of bemarituzumab monotherapy and combination across different lines of therapy in locally advanced/metastatic SqNSCLC. This study will explore the addition of bemarituzumab to the established standard of care immuno-chemotherapy in the first-line treatment setting and the addition to chemotherapy in the second line or later setting.

The study consists of a pre-screening period to collect tissue for FGFR2b testing (Parts 2, 3, and 4 only), a 28-day screening period, a treatment period, a safety follow-up (SFU) visit, and a long-term follow-up (LTFU) period. Subjects who discontinue bemarituzumab will undergo SFU approximately 28 (+3) days after the last dose of study treatment. In addition, subjects will undergo LTFU for survival approximately every 3 months (±1 month) for up to 2 years from the first dose of bemarituzumab. Subjects will receive study treatment with bemarituzumab until disease progression (see Part 4 below for a possible exception), unacceptable toxicity, subject request, or death (whichever occurs first).

Radiographic assessments will be performed by the investigator according to Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 and will be performed every 6 weeks (Q6W) (± 7 days) until week 54 and then every 12 weeks (± 14 days). After discontinuation of study treatment for reasons other than radiographic disease progression or withdrawal of consent, tumor assessments will continue until radiographic progression or initiation of additional anticancer therapy.

The study consists of 4 Parts:

- Part 1: Combination dose exploration with docetaxel
- Part 2: Combination dose expansion with docetaxel
- Part 3: Monotherapy
- Part 4: Combination with carboplatin, paclitaxel or nab-paclitaxel, and pembrolizumab

Tumor samples from subjects will be required to demonstrate FGFR2b overexpression status prior to subjects entering Parts 2, 3, and 4 (and not Part 1) of this study. This study may be amended at a later date to include additional subjects for further efficacy evaluation.

Part 1

Part 1 of the study will explore the dosing of bemarituzumab in combination with docetaxel. During dose exploration, subjects will be enrolled in groups of 3 to 6 dose limiting toxicity (DLT) evaluable subjects per cohort, and escalation will be guided primarily by safety responses to different doses. See Section 6.2.1 for additional details on DLTs.

The starting dose of bemarituzumab is based on review of the available safety, PK and efficacy data from bemarituzumab monotherapy and bemarituzumab plus mFOLFOX6 combination studies (FPA144-001, FPA144-004). The recommended phase 2 dose of bemarituzumab in combination with mFOLFOX6 (evaluated in Study FPA144-004) was determined to be 15 mg/kg IV Q2W with a single 7.5 mg/kg dose on day 8 of the first cycle.

The dosing interval will increase from Q2W to Q3W to align with the other anti-cancer therapy Q3W dosing schedule. At Dose Level 1 the same dose of 15 mg/kg as in FPA144-004 will be tested, but at Q3W instead of Q2W and replacing the additional dose of 7.5 mg/kg day 8 with a one-time loading dose of 22 mg/kg IV on the first dosing day. Dose Level 2 will proportionally increase the bemarituzumab dose, including the loading dose, from the Q2W dose studied in FPA144-004 to account for the increased Q3W dosing interval. One cycle of treatment will consist of 21 days. For Part 1, prospective tumor evaluation for FGFR2b overexpression status will not be required for enrollment and will enroll up to approximately 18 subjects.

The planned dose levels are:

- Dose Level 1: bemarituzumab 22 mg/kg IV cycle 1 day 1 followed by 15 mg/kg IV day 22 and Q3W thereafter
- Dose Level 2: bemarituzumab 30 mg/kg IV cycle 1 day 1 followed by 22 mg/kg IV day 22 and Q3W thereafter

An additional Dose Level 1a of bemarituzumab 15 mg/kg IV Q3W plus one additional 7.5 mg/kg dose on cycle 1 day 8 only may be explored if dose de-escalation is required from Dose Level 1. Any other dose levels besides dose levels 1, 2, or 1a, will require a protocol amendment prior to enrollment.

At each dose level, and on each planned dosing day, docetaxel will be administered at 75 mg/m^2 IV Q3W (or 60 mg/m^2 IV Q3W for subjects from sites in Japan).

Part 1 will begin with Dose Level 1. The study DLT period is 21 days following the first dose. Once 3 to 6 subjects enrolled at a certain dose level are followed for safety for 21 days, a DLRT meeting will be convened. Refer to Section 6.2.1 for additional details on the DLRT and dose escalation/de-escalation.

Dose exploration will continue until:

- a maximum of 18 subjects in Part 1 is reached; or
- 9 subjects have been treated at a specific dose level; or
- the lowest dose level exceeds the elimination boundary

Part 2

Once a dose level has been declared safe by the DLRT for Part 1, a dose level can enter Part 2 of the study. Part 2 enrollment will be limited to subjects with prospectively identified FGFR2b overexpression status. A minimum of 10 subjects and a maximum of 30 subjects will be treated per dose level in Part 2 to better understand the safety profile and preliminary efficacy of the combination, and to enable selection of recommended phase 3 dose (RP3D). Up to 2 dose levels consisting of 10-30 subjects each can be expanded in Part 2 of the study. For Part 2, subjects can receive 1 dose of docetaxel during pre-screening or screening if initiation of treatment is deemed urgent by the investigator. This bridging dose is not a requirement of the study and is not considered part of the clinical study.

Part 3

Part 3 of the study will explore bemarituzumab monotherapy at the dose evaluated in study FPA144-004 of 15 mg/kg IV Q2W plus one additional 7.5 mg/kg dose on cycle 1 day 8. One cycle of treatment will consist of 14 days. Part 3 enrollment will be limited to subjects with prospectively identified tumor FGFR2b overexpression status. A minimum of 10 subjects and a maximum of 30 subjects will be treated in Part 3 to better understand the safety profile, PK, and preliminary efficacy of monotherapy

bemarituzumab in FGFR2b+ SqNSCLC. Part 3 may enroll subjects concurrently with Parts 1, 2, and 4.

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

Part 4

Once a dose level has been declared safe by the DLRT for Part 1, a dose level can enter the Part 4 safety run-in. During the safety run-in, 6 subjects will be evaluated with a 21-day DLT period and once the dose has been declared safe in the first-line setting with immuno-chemotherapy combination, then Part 4 enrollment can proceed with dose expansion. Dose de-escalation may occur in Part 4, independently of the recommendation in Part 1. Part 4 enrollment will be limited to subjects with prospectively identified FGFR2b overexpression status. A minimum of 10 subjects and a maximum of 30 subjects, including the 6 subjects in the safety run-in, will be treated in Part 4 to better understand the safety profile and preliminary efficacy of the combination and to enable the selection of the RP3D. Up to 2 dose levels consisting of 10 to 30 subjects each can be expanded in Part 4 of the study. Subjects will receive up to 4 cycles of bemarituzumab, pembrolizumab, and chemotherapy followed by bemarituzumab and pembrolizumab maintenance. In addition to bemarituzumab administered on day 1 of every 21-day treatment cycle, subjects will be administered pembrolizumab 200 mg day 1 for up to 35 cycles and, for the first four cycles only, the combination of carboplatin 6 mg/mL/min and either paclitaxel 200 mg/m^2 on day 1 or nab-paclitaxel 100 mg/m^2 on days 1, 8, and 15. For Part 4 expansion (and not in safety run-in), subjects can receive 1 dose of carboplatin and paclitaxel or nab-paclitaxel with or without pembrolizumab during pre-screening or screening if initiation of treatment is deemed urgent by the investigator. This bridging dose is not a requirement of the study and is not considered part of the clinical study.

For Part 4 only, subjects may continue treatment beyond initial RECIST v1.1 progressive disease (PD), as assessed by the investigator, as long as they meet the following criteria:

- Investigator assessed clinical benefit
- Tolerance of study drug
- Stable Eastern Cooperative Oncology Group (ECOG) performance status

- Treatment beyond progression will not delay an imminent intervention to prevent serious complications of disease progression (ie, central nervous system [CNS] metastases)

4.2 Patient Input into the Study Design

Patient input was not obtained for this study.

4.3 Justification for Dose

4.3.1 Justification for Amgen Investigational Product Dose:

Study FPA144-004 had clinically meaningful and statistically significant improvement in PFS, OS, and ORR in subjects with FGFR2b-positive, non-human epidermal growth factor receptor 2 (HER2) positive frontline advanced GC and GEJ with manageable safety using 15 mg/kg IV Q2W with 1 additional dose of 7.5 mg/kg on cycle 1 day 8. Therefore, the same dose and regimen will be tested in this trial for the monotherapy Part 3 arm. This dose of 15 mg/kg given Q3W instead of Q2W is the proposed dose level 1 of bemarituzumab in combination with docetaxel, to align with the docetaxel schedule of Q3W dosing. Dose level 1 will also explore removing the extra dose on cycle 1 day 8 and adding a loading dose of 22 mg/kg given once on the cycle 1 day 1.

Dose Level 2 will increase the bemarituzumab dose, including the loading dose, proportionally from the Q2W dose studied in FPA144-004 to account for the increased Q3W dosing interval. Dose level 2 is projected to match the observed concentration at the end of a dose interval at steady state ($C_{trough,ss}$) and area under the serum concentration versus time curve during the dosing interval at steady state divided by the dosing interval ($C_{avg,ss}$) of the target Q2W dose (FPA144-004). Early PK data from 20210102 Part 1 supports this dose-exposure relationship. The loading dose is recommended because advanced stage NSCLC is an aggressive disease with standard chemotherapy only providing a median of approximately 7 months of disease control. Shortening the time to achieve target C_{trough} levels may help to maximize the potential benefit from bemarituzumab.

A dose of bemarituzumab selected in Part 1 in combination with docetaxel will enter Part 4 safety run-in in combination with pembrolizumab, carboplatin, and nab-paclitaxel/paclitaxel. The same dose of bemarituzumab will be utilized because both backbone regimens use a Q3W dosing schedule and while the combination of individual agents with bemarituzumab is novel, prior studies have evaluated (or will have evaluated) the combination of bemarituzumab with other representative agents from these same drug classes:

1. Taxane (paclitaxel/nab-paclitaxel): Part 1 of this study will test combination with docetaxel
2. Platinum chemotherapy (carboplatin): Safety data with oxaliplatin as part of mFOLFOX6 chemotherapy in gastric cancer in Study FPA144-004 and the safety run-in of Study 20210098
3. PD-1 inhibitor (pembrolizumab): Safety run-in of study 20210098 evaluating bemarituzumab in combination with mFOLFOX6 and nivolumab in gastric cancer.

Refer to Section 2.2.2.2 for a summary of the prior clinical studies with bemarituzumab.

Bemarituzumab at 15 mg/kg Q2W with 1 additional dose of 7.5 mg/kg on cycle 1 day 8 was selected for study FPA144-004 based on the following data.

In the phase 1 FPA144-001 monotherapy dose escalation study, bemarituzumab demonstrated linear clearance from 1 mg/kg to 15 mg/kg in subjects with solid tumors including gastric cancers. In the linear dose range, maximum observed serum concentration (C_{max}) and AUC increased dose proportionally. The estimated half-life by noncompartmental analysis ranged from 6.01 to 11.7 days across 1 mg/kg to 15 mg/kg, which supports Q2W or less frequent dosing.

The target C_{trough} for bemarituzumab of ≥ 60 µg/mL was derived from nonclinical studies including binding affinity for human FGFR2b-Fc and human FcγRIIIa (V158), receptor occupancy in vitro, and an efficacy study in vivo.

Supporting the hypothesis that ≥ 60 µg/mL should be the target minimum C_{trough}, all subjects who demonstrated a partial response (PR) in the FIH FPA144-001 trial with FGFR2b overexpression achieved the target $C_{trough,ss}$ of ≥ 60 µg/mL, regardless of dose level. Among all subjects treated with 15 mg/kg Q2W dosing in Study FPA144-001, 23 of 51 subjects achieved target C_{trough} concentration on day 15. At the same dose by the eighth week (steady state), 14 of 16 subjects achieved target C_{trough} of ≥ 60 µg/mL.

The observed PK data from phase 1 portion of Study FPA144-004 indicated that all subjects with PK data treated at 15 mg/kg Q2W with 1 additional dose of 7.5 mg/kg on cycle 1 day 8 achieved target C_{trough} concentration on day 15 and C_{max} was within the range observed in Study FPA144-001. Therefore, the addition of a single dose of 7.5 mg/kg on cycle 1 day 8 minimized the time to reach target C_{trough} without increasing C_{max}.

Post FPA144-004 trial, PK modeling and simulation demonstrated that a higher loading dose on C1D1 can replace the need for the additional dose on day 8, while still maintaining target C_{trough} and dosing interval at C_{avg} exposures in the defined dosing interval.

4.3.2 Justification for Non-investigational Product Dose

Parts 1 and 2

The dosing of docetaxel for subjects in the US and European Union (EU) is 75 mg/m^2 administered intravenously over 1 hour every 3 weeks, in accordance with the docetaxel US and EU prescribing information (EU Summary of Product Characteristics [SPC], USPI). The dose of docetaxel for subjects in Japan is 60 mg/m^2 administered intravenously over 1 hour every 3 weeks, in accordance with the terms of the docetaxel regional prescribing information and approved docetaxel dose in Japan (Abe et al, 2015; Kudoh et al, 2006). Refer to Section 6.2.2.2 and regional prescribing information for further guidance on docetaxel dose adjustment in the setting of concomitant medications and toxicities.

Part 4

The dosing of the combination of pembrolizumab, paclitaxel, and nab-paclitaxel is according to the regimen studied as part of the KEYNOTE-407 study (Paz-Ares et al, 2018) and recommended according the NCCN and ESMO treatment guidelines (NCCN-Guidelines, 2022; Planchard et al, 2018). The order of administration should have bemarituzumab administered first followed by pembrolizumab, then taxane (paclitaxel or nab-paclitaxel) and finally carboplatin. Otherwise, local standards for administration can be followed. Either paclitaxel or nab-paclitaxel may be used, according to local availability, and if both are available, then according to investigator's preference. For all the non-investigational products listed here, refer to Section 6.2.2.2 and latest version of the local prescribing information for further guidance on dose adjustment in the setting of concomitant medications and toxicities. Subjects should be pre-medicated according to local standards to prevent hypersensitivity reactions.

Pembrolizumab

The dosing of pembrolizumab is 200 mg Q3W according to regional prescribing information (Keytruda® SPC 2015; Keytruda® USPI, 2014). Pembrolizumab should be administered for up to 35 cycles.

Paclitaxel

The dosing of paclitaxel is 200 mg/m^2 on day 1 of every 21-day treatment cycle for up to 4 cycles.

Nab-Paclitaxel

The dosing of nab-paclitaxel is 100 mg/m^2 on days 1, 8, and 15 of every 21-day treatment cycle for up to 4 cycles.

Carboplatin

The dosing of carboplatin is at a dose calculated using the Calvert Formula to produce an AUC-time curve of 6 mg/mL/min on day 1 of every 21-day treatment cycle for up to 4 cycles.

The carboplatin dose should not exceed 900 mg.

Calvert Formula

Total Dose (mg) = (target AUC) x (creatinine clearance [CrCl] + 25)

The estimated glomerular filtration rate (GFR) used in the Calvert formula should not exceed 125 mL/min.

4.4 End of Study

An individual subject is considered to have completed the study if they have completed the last visit shown in the Schedule of Activities (Section 1.3).

The end of study date for the entire study 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), including any additional parts in the study (eg, LTFU, antibody testing), as applicable.

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). This log may be completed and updated via an Interactive Response Technology (IRT).

Eligibility criteria will be evaluated during screening.

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 has provided informed consent/assent prior to initiation of any study specific activities/procedures

102 Age ≥ 18 years old (or legal adult within country, whichever is older) at the time that the Informed Consent Form (ICF) is signed

103 Pathologically confirmed squamous cell lung carcinoma. Patients with mixed histology (eg, adenosquamous) are allowed if there is a squamous component in the specimen.

104 Disease that is unresectable, locally advanced or metastatic (not amenable to curative therapy)

105 Part 2, 3, and 4 only: FGFR2b overexpression as determined by centrally performed IHC testing

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

107 Subject may or may not have received prior therapy for locally advanced and unresectable or metastatic disease depending on the study Part.

- For Parts 1 and 2, subjects may have progressed on, or recurred after at least 1 prior systemic therapy.
- For Part 3 subjects must have progressed on, or recurred after at least 2 prior systemic therapies.
- For Part 4, subjects may not have received prior systemic therapy for their locally advanced and unresectable or metastatic disease. For Part 4, subjects who received peri-operative systemic therapy are eligible if that adjuvant/neoadjuvant therapy was completed at least 12 months prior to diagnosis of locally advanced and unresectable or metastatic disease.

For Parts 1, 2, and 3, 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 (which must be documented in the eCRF). Additionally, if the subject's tumor was previously identified as having a driver mutation (according to local standard of care or guidelines, eg, KRAS G12C, NTRK), which has an approved therapy for which the subject is eligible and available, the subject must have received the approved therapy in a prior line of treatment.

If the subject has a medical contraindication to a required prior therapy, that medical contraindication must be documented in the eCRF and the subject may be enrolled only after the investigator discusses and obtains approval from the Amgen medical monitor. For Part 1 and 3 subjects may have received prior

docetaxel therapy in the unresectable or metastatic setting, provided none of the prior therapy exclusion criteria are met.

For Parts 1, 2, and 3:

- Adjuvant therapy will count as a line of therapy if the subject progressed on or within 6 months of adjuvant therapy administration
- If locally advanced and unresectable NSCLC, disease progression on or within 6 months of the end of prior curatively intended multimodal therapy will count as a prior line of therapy.
- Maintenance therapy following platinum-based doublet chemotherapy is not considered as a separate line of therapy.

108 Measurable disease per RECIST v1.1 criteria.

109 Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1.

110 Adequate organ function as follows:

- Absolute neutrophil count ≥ 1.5 x 10^9/L
- Platelet count ≥ 100 x 10^9/L
- Hemoglobin ≥ 9 g/dL
- Creatinine clearance ≥ 50 mL/min. Cockcroft-Gault formula will be used for creatinine clearance calculation. Twenty-four hour urine collection is not required but is allowed.
- International Normalized Ratio (INR) or prothrombin time (PT) < 1.5 × upper limit of normal (ULN) except for subjects receiving anticoagulation, who must be on a stable dose of anticoagulant therapy for 6 weeks prior to enrollment.

Part 1 and 2 only:

- AST and ALT ≤ 2.5 times ULN, except if alkaline phosphatase > 2.5 times the ULN, then AST and/or ALT must be ≤ 1.5 times the ULN
- Total bilirubin ≤ 1.0 x ULN

Part 3 only:

- AST and ALT < 3 x ULN (or < 5 x ULN if liver involvement).
- Total bilirubin <1.5 x ULN (or < 2 x ULN in case of liver involvement OR Gilbert's disease)

Part 4 only:

- AST and ALT < 2.5 x ULN (or < 5 x ULN if liver involvement).
- Total bilirubin < 1.5 x ULN (or < 2 x ULN in case of liver involvement OR Gilbert's disease)

111 Part 1 and 2 only: Subject must be a candidate to receive docetaxel.

112 Part 4 only: Subject must be a candidate to receive pembrolizumab, carboplatin, and paclitaxel or nab-paclitaxel.

5.2 Exclusion Criteria

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

Disease Related

201 Mixed small-cell lung cancer

202 Untreated or symptomatic central nervous system (CNS) metastases or leptomeningeal disease

- Subjects with asymptomatic CNS metastases are eligible if clinically stable for at least 4 weeks and do not require intervention (including use of corticosteroids)
- Subjects with treated brain metastases are eligible provided the following criteria are met:
  - Definite therapy was completed at least 2 weeks prior to the first planned dose of study treatment (stereotactic radiosurgery at least 7 days prior to first planned dose of study treatment)
  - At least 7 days prior to first dose of study treatment: any CNS disease is clinically stable, subject is off steroids for CNS disease (unless steroids are indicated for a reason unrelated to CNS disease), and subject is off or on stable doses of anti-epileptic drugs

203 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

204 Impaired cardiac function or clinically significant cardiac disease including: unstable angina within 6 months prior to first dose of study treatment, acute myocardial infarction < 6 months prior to first dose of study treatment, New York Heart Association (NYHA) class II-IV congestive heart failure, uncontrolled hypertension (defined as an average systolic blood pressure > 160 mmHg or diastolic >100 mm Hg despite optimal treatment, uncontrolled cardiac arrhythmias requiring anti-arrhythmic therapy other than beta blockers or digoxin, active coronary artery disease, Fridericia's correction formula (QTc) ≥ 470.

205 Peripheral sensory neuropathy grade 2 or higher

206 Active infection requiring systemic treatment or any uncontrolled infection within 14 days prior to first dose of study treatment

207 Known human immunodeficiency virus (HIV) infection with CD4+ T-cell (CD4+) counts < 350 cells/μL, hepatitis C infection (subjects with hepatitis C that achieve a sustained virologic response following antiviral therapy are allowed), or hepatitis B infection (subjects with hepatitis B surface antigen or core antibody that achieve sustained virologic response with antiviral therapy directed at hepatitis B are allowed).

230 For Part 4 only: History of solid organ transplantation

231 For Part 4 only: Active autoimmune disease that has required systemic treatment (except replacement therapy) within the past 2 years or any other diseases requiring immunosuppressive therapy while on the study

208 History of interstitial lung disease

233 For Part 4 only: Subjects who experienced severe, life-threatening or recurrent (grade 2 or higher) immune-mediated adverse events or infusion-related reactions including those that lead to permanent discontinuation while on treatment with immuno-oncology agents

209 History or evidence of systemic disease or ophthalmological disorders requiring chronic use of ophthalmic corticosteroids

210 Evidence of any ongoing ophthalmologic abnormalities or symptoms that are acute (within 4 weeks) or actively progressing

211 Unwillingness to avoid use of contact lenses during study treatment and for at least 100 days after the end of treatment

212 Recent (within 6 months) corneal surgery or ophthalmic laser treatment or recent (within 6 months) history of, or evidence of, corneal defects, corneal ulcerations, keratitis, or keratoconus, or other known abnormalities of the cornea that may pose an increased risk of developing a corneal ulcer.

Prior/Concomitant Therapy

213 Part 1 and Part 2: Subjects that experienced toxicity or hypersensitivity requiring discontinuation of prior docetaxel treatment.

214 Part 1 only: Subjects that had disease progression on prior therapy with docetaxel.

215 Part 2 only: 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) except for a maximum of 1 dose of docetaxel

216 Prior treatment with any selective inhibitor of the FGF-FGFR pathway.

217 Any anticancer therapy or immunotherapy within 4 weeks prior to enrollment;

- Palliative radiotherapy is allowed, provided it has been completed more than 14 days prior to the first dose of study treatment
- All treatment-related toxicity needs to be resolved to grade ≤ 1 prior the first dose of study treatment, with exception of alopecia or toxicities considered irreversible (defined as having been present and stable > 21 days) which are not otherwise described in the exclusion criteria
- Exception for Part 2 and 4 expansion only: subjects can receive 1 dose of each non-investigational anticancer therap(ies) in the respective study part, if initiation of treatment is deemed urgent by the investigator

232 Part 4 only: Immunosuppressive doses of systemic medications of > 10 mg/day of prednisone or equivalent must be discontinued at least 2 weeks before the first dose of study drug. Short courses of high dose corticosteroids and/or continuous low dose of prednisone (< 10 mg/day) are allowed. In addition, inhaled, intranasal, intraocular, and/or joint injections of corticosteroids are allowed

Prior/Concurrent Clinical Study Experience

218 Currently receiving treatment in another investigational device or drug study, or less than 28 days since ending treatment on another investigational device or

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

Other Exclusions

219 Major surgical procedure within 28 days prior to first dose of study treatment

220 History of other malignancy within the past 2 years, except:

- curatively treated non-melanoma skin malignancy
- cervical cancer in situ
- curatively treated uterine cancer stage I
- curatively treated ductal or lobular breast carcinoma in situ and not currently receiving any systemic therapy
- localized prostate cancer that has been treated surgically with curative intent and presumed cured

221 Female subjects of childbearing potential unwilling to use protocol specified method of contraception (see Section 11.5) during treatment and for an additional 6 months after the last dose of protocol-mandated therapy.

222 Female subjects who are breastfeeding or plan to breastfeed while on study through 4 months after the last dose of protocol-mandated therapy.

223 Female subjects planning to become pregnant while on study through 6 months after the last dose of protocol-mandated therapy.

224 Female subjects of childbearing potential with a positive pregnancy test assessed at screening by a serum pregnancy test.

225 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 6 months after the last dose of protocol-mandated therapy. Refer to Section 11.5.

226 Male subjects unwilling to abstain from donating sperm during treatment and for an additional 6 months after the last dose of protocol-mandated therapy.

227 Known allergy, hypersensitivity, or contraindication to docetaxel (Part 1 and 2 only), pembrolizumab, paclitaxel, nab-paclitaxel, and carboplatin (Part 4 only) or to components of the drug formulations formulation including polysorbate.

228 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.

229 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.

5.3 Subject Enrollment

Before subjects begin participation in any study-specific activities/procedures, Amgen requires a copy of the site's written institutional review board/independent ethics

committee (IRB/IEC) approval of the protocol, informed consent form, and all other subject information and/or recruitment material, if applicable (see Section 11.3).

The subject or the subject's legally authorized representative must personally sign and date the IRB/IEC and Amgen approved informed consent before commencement of study-specific procedures.

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 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.

Unless directed by Amgen 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.

A subject is considered enrolled when the investigator decides that the subject has met all eligibility criteria. The investigator is to document this decision and date, in the subject's medical record and in/on the Subject Enrollment Case Report Form (CRF).

Sites that do not enroll subjects within 6 months of site initiation may be closed.

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, and any serious adverse events. Both adverse events and serious adverse events occurring up to 14 days after the pre-screening procedure of tumor biopsy collection that the investigator deems to be related to the procedure will be collected.

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened. Refer to Section 8.1.1.

6. Study Intervention

Study intervention is defined as any investigational product(s), non-investigational product(s), or combination product(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.

A summary of the dosing and administration of each treatment is shown in Table 6-1 below.

6.1 Study Interventions Administered

6.1.1 Investigational Products

Table 6-1. Investigational Products

	Amgen Investigational Product:[a] Bemarituzumab
Dosage Formulation	Bemarituzumab is supplied as a sterile, aqueous, colorless to slightly yellowish, pyrogen-free solution supplied in single-use glass vials. The composition of the drug product contains 20 mg/mL active ingredient (supplied as 20 mL vial (in 400 mg/vial configuration [20 mL per vial]), L-histidine, sucrose, and polysorbate 20 at pH 6.0. The final investigational product will be provided as a solution which should be stored refrigerated (2°C to 8°C), protected from light; and will be refrigerated liquid protected from light which is diluted for administration according to instructions provided to the site in a separate Pharmacy Manual.
Unit Dose Strength(s)/Dosage Level(s)	Part 1: Dose level 1: 22 mg/kg IV cycle 1 day 1 followed by 15 mg/kg IV day 22 and Q3W thereafter Dose level 2: 30 mg/kg IV cycle 1 day 1 followed by 22 mg/kg IV day 22 and Q3W thereafter Part 2: At dose level identified in Part 1 Part 3: 15 mg/kg Q2W IV on day 1 of each cycle with an additional dose of 7.5 mg/kg on cycle 1 day 8 Part 4: At dose level identified in Part 1
Route of Administration	IV infusion
Accountability	The planned dose, quantity administered, start date/time, stop date/time, lot number of investigational product, reason total quantity changed or administration withheld, reason for administration delay, and reason for infusion interruption are to be recorded on each subject's eCRF(s).
Dosing Instructions	Bemarituzumab will be administered under medical supervision over approximately 30-minute (± 10 minutes) IV infusion via a peripheral vein or central venous catheter. The IV administration set for bemarituzumab infusion must contain a 0.22 µm in-line filter. Bemarituzumab dosing should occur ± 3 days of scheduled visit date for cycles 1 through 3, and may be delayed up to + 7 days for every cycle thereafter.

eCRF = electronic case report form; IV = intravenous; Q2W = every 2 weeks; Q3W = every 3 weeks
[a] Amgen investigational product will be manufactured and packaged by Amgen and distributed using Amgen clinical study drug distribution procedures.

Table 6-2. Study Groups

Group Title	Group Type	Group Description
Part 1	Combination Dose Exploration	Dose Level 1: Participants will receive bemarituzumab 22 mg/kg IV cycle 1 day 1 followed by 15 mg/kg IV day 22 and Q3W thereafter in addition to docetaxel. Dose Level 2: Participants will receive bemarituzumab 30 mg/kg IV cycle 1 day 1 followed by 22 mg/kg IV day 22 and Q3W thereafter in addition to docetaxel.
Part 2	Combination Dose Expansion	Bemarituzumab and docetaxel at the dose and schedule determined in Part 1.
Part 3	Monotherapy	Bemarituzumab 15 mg/kg IV Q2W with single 7.5 mg/kg dose on cycle 1 day 8.
Part 4	Combination immuno-chemotherapy	Bemarituzumab at the dose determined in Part 1 combined with pembrolizumab, carboplatin, and either paclitaxel or nab-paclitaxel.

IV = intravenous; Q2W = every 2 weeks; Q3W = every 3 weeks

6.1.2 Non-investigational Products

Table 6-3. Non-Investigational Products

Study Treatment Name	Non-Investigational Product: Docetaxel
Dosage Formulation	Sponsor designee will provide docetaxel where required from a commercial supply that is clinically labelled in accordance with relevant local guidelines. For further details, refer to the manufacturer's prescribing information for the respective chemotherapies and the study Pharmacy Manual (if applicable).
Unit Dose Strength(s)/Dosage Level(s)	75 mg/m^2 every 3 weeks for subjects in all countries except Japan; 60 mg/m^2 for subjects in Japan.
Route of Administration	IV infusion
Accountability	The planned dose, total volume of preparation, lot number (unless unable to be recorded due to local prescribing procedure in countries where standard of care is deemed non-investigational) concentration of preparation, quantity administered, start date/time, stop date/time, reason total quantity changed, or administration withheld, reason for administration delay, and reason for infusion interruption are to be recorded on each subject's eCRF(s).
Dosing Instructions	Docetaxel will be infused at the clinic by a qualified staff member over a time frame of 1 hour (additional administration time is allowed as per local guidelines).

Study Treatment Name	Non-Investigational Product: Carboplatin
Dosage Formulation	Sponsor designee will provide carboplatin where required from a commercial supply that is clinically labelled in accordance with relevant local guidelines. For further details, refer to the manufacturer's prescribing information for the respective chemotherapies and the study Pharmacy Manual (if applicable).
Unit Dose Strength(s)/Dosage Level(s)	The dosing of carboplatin is at a dose calculated using the Calvert Formula to produce an AUC-time curve of 6 mg/mL/min on day 1 of every 21-day treatment cycle for up to 4 cycles.
Route of Administration	IV infusion

Study Treatment Name	Non-Investigational Product: Carboplatin
Accountability	The planned dose, total volume of preparation, lot number (unless unable to be recorded due to local prescribing procedure in countries where standard of care is deemed non-investigational) concentration of preparation, quantity administered, start date/time, stop date/time, reason total quantity changed, or administration withheld, reason for administration delay, and reason for infusion interruption are to be recorded on each subject's eCRF(s).
Dosing Instructions	Carboplatin will be infused at the clinic by a qualified staff member over a time frame of 15-60 minutes (additional administration time is allowed as per local guidelines).

Study Treatment Name	Non-Investigational Product: Nab-paclitaxel
Dosage Formulation	Sponsor designee will provide nab-paclitaxel where required from a commercial supply that is clinically labelled in accordance with relevant local guidelines. For further details, refer to the manufacturer's prescribing information for the respective chemotherapies and the study Pharmacy Manual (if applicable).
Unit Dose Strength(s)/Dosage Level(s)	100 mg/m^2 on days 1, 8, and 15 of each 3 week cycle for up to 4 cycles.
Route of Administration	IV infusion
Accountability	The planned dose, total volume of preparation, lot number (unless unable to be recorded due to local prescribing procedure in countries where standard of care is deemed non-investigational) concentration of preparation, quantity administered, start date/time, stop date/time, reason total quantity changed, or administration withheld, reason for administration delay, and reason for infusion interruption are to be recorded on each subject's eCRF(s).
Dosing Instructions	Nab-paclitaxel will be infused at the clinic by a qualified staff member over a time frame of 30 minutes (additional administration time is allowed as per local guidelines).

Study Treatment Name	Non-Investigational Product: Paclitaxel
Dosage Formulation	Sponsor designee will provide paclitaxel where required from a commercial supply that is clinically labelled in accordance with relevant local guidelines. For further details, refer to the manufacturer's prescribing information for the respective chemotherapies and the study Pharmacy Manual (if applicable).
Unit Dose Strength(s)/Dosage Level(s)	200 mg/m^2 every 3 weeks for up to 4 cycles.
Route of Administration	IV infusion
Accountability	The planned dose, total volume of preparation, lot number (unless unable to be recorded due to local prescribing procedure in countries where standard of care is deemed non-investigational) concentration of preparation, quantity administered, start date/time, stop date/time, reason total quantity changed, or administration withheld, reason for administration delay, and reason for infusion interruption are to be recorded on each subject's eCRF(s).
Dosing Instructions	Paclitaxel will be infused at the clinic by a qualified staff member over a time frame of 3 hours (additional administration time is allowed as per local guidelines).

Study Treatment Name	Non-Investigational Product: Pembrolizumab
Dosage Formulation	Sponsor designee will provide pembrolizumab where required from a commercial supply that is clinically labelled in accordance with relevant local guidelines. For further details, refer to the manufacturer's prescribing information for the respective chemotherapies and the study Pharmacy Manual (if applicable).
Unit Dose Strength(s)/Dosage Level(s)	200 mg every 3 weeks
Route of Administration	IV infusion
Accountability	The planned dose, total volume of preparation, lot number (unless unable to be recorded due to local prescribing procedure in countries where standard of care is deemed non-investigational) concentration of preparation, quantity administered, start date/time, stop date/time, reason total quantity changed, or administration withheld, reason for administration delay, and reason for infusion interruption are to be recorded on each subject's eCRF(s).

Study Treatment Name	Non-Investigational Product: Pembrolizumab
Dosing Instructions	Pembrolizumab will be infused at the clinic by a qualified staff member over a time frame of 30 minutes (additional administration time is allowed as per local guidelines).

AUC = area under the concentration time curve; eCRF = electronic case report form; IV = intravenous

If local guidelines for non-investigational product dosage differs from study dosage guidance, then treatment according to local guidelines may be permissible if approved by Amgen Medical Monitor.

6.1.3 Other Protocol-required Therapies

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

6.1.3.1 Pre- and Post-infusion Medications for Chemotherapies

Subjects should receive Pre- and Post-infusion medications for chemotherapies including antiemetic medication according to regional prescribing information and institutional guidelines.

Subjects receiving docetaxel should be premedicated with oral corticosteroids prior to docetaxel administration according to regional prescribing information and local standards to reduce the incidence and severity of fluid retention and severity of hypersensitivity reactions.

Subjects receiving paclitaxel should be pre-medicated with oral or IV corticosteroids, and both H1 and H2 receptor antagonist according to regional prescribing information and local standards to reduce incidence and severity of hypersensitivity reactions.

6.1.3.2 Biopsies

Tumor Biopsy for Enrollment: When archival tumor tissue within 5 years is not available, collection of new tumor tissue is required, as described in Section 8.8.

Optional Tumor Biopsy for Biomarkers: Additional tissue biopsy samples will be collected at cycle 2 day 1 (± 7 days) at the end of treatment (EoT) (± 7 days) or at time of progression, prior to start of another anti-cancer therapy 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 Ethics Committees (EC)/Institutional Review Board (IRB).

6.1.4 Medical Devices

6.1.4.1 Investigational In Vitro Diagnostic Devices

An investigational in vitro diagnostic device, VENTANA FGFR2b (FPR2-D) Robust Prototype Assay, developed and manufactured by Ventana Medical Systems, Inc. (Roche Tissue Diagnostics 1910 E. Innovation Park Drive, Tucson, Arizona, 85755, USA) will be used to measure FGFR2b protein to prospectively identify subjects eligible for enrollment, as further described in Section 8.8.1. The device is intended for the qualitative detection fibroblast growth factor receptor type 2b (FGFR2b) protein in FFPE neoplastic tissue stained with the OptiView 3,3′-Diaminobenzidine (DAB) IHC Detection Kit on the automated BenchMark ULTRA instrument. The results should be interpreted by a qualified pathologist in conjunction with histological examination, relevant clinical information, and proper controls.

6.1.4.1.1 IVD Compliance

The investigational in vitro diagnostic (IVD) device will comply with requirements of local and other applicable national health authority regulations.

6.1.4.2 Other Non-Investigational Medical Devices

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).

6.1.5 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, combination product, 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 products provisioned and/or repackaged/modified by Amgen.

Any product complaint(s) associated with investigational products/non-investigational products supplied by Amgen are to be reported.

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

The following treatments and/or procedures are excluded during the treatment period of the study:

- Anticancer therapies other than those specified in the protocol are prohibited while on study treatment. Radiation therapy for symptom control (eg, bone metastasis) or brain may be allowed after discussion with the medical monitor. Radiation therapy may not be given concurrently with bemarituzumab with or without chemotherapy. If radiation therapy is administered, then the next dose of bemarituzumab, and chemotherapy, if applicable, must be delayed until at least 7 days after radiation therapy is completed.
- Methylcellulose-based ocular lubricants
- Vaccination with a live or live-attenuated vaccines will not be allowed during therapy. Subjects enrolled in this study are permitted to receive vaccinations for COVID-19, however, all side effects of the vaccine must be resolved prior to enrollment and vaccination should not be administered within 2 days before or after bemarituzumab infusion.
- Concomitant use of docetaxel, paclitaxel or nab-paclitaxel and drugs that inhibit CYP3A4 may increase exposure to docetaxel, paclitaxel or nab-paclitaxel and should be avoided. In subjects receiving treatment with docetaxel (Parts 1 and 2) and paclitaxel or nab-paclitaxel (Part 4), close monitoring for toxicity and dose reduction should be considered if systemic administration of a potent CYP3A4 inhibitor (such as ketoconazole, itraconazole, clarithromycin, indinavir, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin, and voriconazole) cannot be avoided. Refer to the regional prescribing information for additional information.
- Subjects must not wear contact lenses during bemarituzumab treatment. It is recommended to avoid contact lenses for 100 days after the end of bemarituzumab.

6.2 Dose Modification

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

Dose Level Determination

In Part 1, a recommendation to escalate to a higher dose cohort will only occur when the previous dose regimen(s) have been found to be reasonably tolerated based on available study data through the 21-day DLT period for 3 to 6 subjects and upon unanimous agreement of the DLRT members. Available data from previous subject groups will also be considered. Dose level recommendations will be made on a treatment cohort basis (not on an individual basis). After receiving the DLRT recommendation, Amgen will render a final decision and will issue a written notification

of the dose change decision to investigators. Further information on DLRM is provided in Appendix 3 (Section 11.3).

Part 1 will begin with Dose Level 1. The study DLT period is 21 days following the first dose. Once 3 to 6 subjects enrolled at a certain dose level are followed for safety for 21 days, a DLRT meeting will be convened.

The DLRT will evaluate all available safety, laboratory, and PK data as well as rules generated from a modified toxicity probability interval method (mTPI-2) (Guo et al, 2017) to guide their dose finding recommendations. The team may recommend escalation to the next planned dose, continuation at the current dose level, de-escalation to a lower dose, termination of the study, or initiation of enrollment in Part 2 of the study with the evaluated dose level. The mTPI-2 escalation/de-escalation guideline for each dose cohort is derived with a target toxicity probability of 0.30, acceptable toxicity probability interval of (0.25, 0.33). A dose level will be considered unsafe, with no additional subjects enrolled at that dose level, if it has an estimated 95% or more probability of exceeding the target DLT (ie, the elimination boundary).

In Part 1, the DLRT will use guidelines based on an mTPI-2 design as described below:

1. Subjects in the first cohort are treated at dose level 1.
2. To assign a dose to the next cohort of subjects, the guidelines in Table 6-4 will be used. In Table 6-4, note the following:
   - "Eliminate" means that the current and higher doses are eliminated from the trial to prevent treating any future subjects at these doses because they are overly toxic
   - When a dose is eliminated, de-escalation to the next lower dose level occurs. When the lowest dose is eliminated, the trial is stopped for safety.
   - If none of the actions (ie, escalation, de-escalation, or elimination) is triggered, new subjects are treated at the current dose.
   - If the current dose is the lowest dose and the rule indicates dose de-escalation, new subjects are treated at the lowest dose unless the number of DLTs reaches the elimination boundary, at which point the trial is stopped for safety.
3. Step 2 is repeated until the maximum sample size of 18 is reached or the number of subjects treated at the current dose reaches 9, and the decision according to Table 6-4 is to stay at the current dose.

Table 6-4. Dose Escalation/De-escalation Rules for the mTPI-2 Design

Subjects treated at the current dose	1	2	3	4	5	6	7	8	9
Escalate if # of DLT ≤	0	0	0	0	1	1	1	1	2
De-escalate if # of DLT ≥	1	1	1	2	2	2	3	3	3
Eliminate if # of DLT ≥	NA	NA	3	3	4	4	5	5	5

DLT = dose limiting toxicity; NA = not applicable; mTPI = modified toxicity probability interval
# of DLT is the number of subjects with at least 1 DLT.
When none of the actions (ie, escalate, de-escalate or eliminate) is triggered, stay at the current dose for treating the next cohort of subjects. “NA” means that a dose cannot be eliminated before treating 3 subjects.

Part 4 will begin with a safety run-in using the highest dose determined to be safe from Part 1. The study DLT period is 21 days. Once a minimum of 6 subjects are dosed and followed for 21 days, a DLRT meeting will be convened. Depending on the observed safety data, the following may occur: (1) expansion of Part 4 with up to 30 subjects at the current dose (including the subjects in safety run-in); (2) additional enrollment of approximately 6 subjects at the current dose level for DLRT evaluation; or (3) dose de-escalation.

A minimum of 6 subjects must be treated at a dose level with less than 30% incidence of DLTs to trigger expansion to up 30 subjects. A dose level can be expanded with up to 12 subjects to better understand the safety profile of the combination. Dose de-escalation will occur when a DLT incidence of 30% or higher is observed, or as advised by the DLRT. Information on DLRM is provided in Appendix 3 (Section 11.3).

The DLRT will meet in Parts 2, 3, and 4 (For Part 4, in addition to the safety run-in) when 10 subjects have had the opportunity to be followed for at least 12 weeks of response data and again once enrollment is complete, and at the primary and final analysis time points. At any point during the study, basing on evolving PK, safety, and/or efficacy data, the DLRT may recommend to de-escalate to bemarituzumab dose level 1 in Parts 2 and 4.

Enrollment Stopping Rules

At any point during the study, throughout Parts 1, 2, 3, and 4, enrollment will be paused at the occurrence of 2 or more grade 4 or one or more grade 5 adverse events unless the events are clearly attributed to causes other than bemarituzumab. If limited information is available at the time the investigator reports the event to the sponsor,

enrollment may continue while the sponsor collects additional information about the grade 4 or 5 event to determine the underlying cause. The DLRT will be reconvened to review the safety data and determine appropriate next steps that may include, but not be limited to, informing investigators and IRBs/IECs, implementing safety/toxicity management, informing health authorities, voluntarily putting the clinical trial on hold, or proceeding with enrollment.

Dose Limiting Toxicities

Dose limiting toxicities are defined as any of the following adverse events considered by the investigator related to study drug excluding toxicities clearly related to disease progression or intercurrent illness. Sites are requested to make sure that toxicities are at least possibly related to Bemarituzumab, and not considered to be related to the concomitant chemotherapy while evaluating DLTs.

- Grade 4 neutropenia of any duration
- Grade ≥ 3 Febrile neutropenia (absolute neutrophil count [ANC] < 1000/mm^3 with a single temperature of > 38.3°C [101°F] or a sustained temperature of ≥ 38°C [100.4°F] for more than 1 hour).
- Grade 4 thrombocytopenia
- Grade 3 thrombocytopenia with grade > 2 bleeding or lasting > 7 days
- Grade 4 anemia
- Grade 5 toxicity (eg, death not due to disease progression)
- Any grade 3 ophthalmologic adverse event that does not resolve within 7 days
- Any grade 4 ophthalmologic adverse event
- Any grade 4 laboratory value
- Any grade 4 vomiting or diarrhea
- Grade 3 vomiting or grade 3 diarrhea lasting more than 3 days despite optimal medical support
- Grade ≥ 3 nausea lasting 3 days or more despite optimal medical support
- Grade 3 fatigue lasting 1 week or longer
- Any subject meeting the criteria for Hy's Law case (ie, severe drug-induced liver injury [DILI]) will be considered a DLT. A Hy's Law case is defined as: AST or ALT values of ≥ 3 x ULN AND with serum TBIL level of > 2 x ULN or international normalized ratio (INR) > 1.5 without signs of cholestasis and with no other clear alternative reason to explain the observed liver related laboratory abnormalities (see Section 11.7 for further explanation of Hy's law case and Management of Hepatic Function).
- Any other grade ≥ 3 adverse event with the following exceptions:
  - DLT Exemption: Asymptomatic grade 3 amylase and/or lipase lasting < 72 hours, and without radiological signs of pancreatitis

- DLT Exemption: Asymptomatic grade 3 electrolyte abnormalities that last < 72 hours, are not clinically complicated, and resolve spontaneously or respond to medical interventions
- DLT Exemption: Other select lab abnormalities that do not appear to be clinically relevant or harmful to the subject (eg, grade 3 lymphopenia, grade 3 hypoalbuminemia), and/or can be corrected with replacement or modifications
- DLT Exemption: A transient (resolving to grade ≤ 1 within 6 hours of onset) grade 3 infusion-related adverse event
- DLT Exemption (Part 4 only): Any grade 3 endocrinopathy that is adequately controlled by hormonal replacement
- If an adverse event is clearly attributable to non-investigational anti-cancer therapy and does not exceed the expected severity, this specific adverse event may be considered exempt from being a DLT.

Subjects enrolled in dose exploration may be replaced if they are not evaluable for a DLT (ie, a subject did not receive planned study treatment [100% of planned doses of bemarituzumab] or ended the study treatment before completion of DLT evaluation period for a reason other than experiencing a DLT). The replaced subject may continue on study at the Investigator's discretion and after discussion with the Medical Monitor.

Dosing for an individual will be stopped for any occurrence of a DLT or if criteria are met as outlined in Section 6.2.2.

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

A toxicity may be due to one or more components (ie, bemarituzumab, docetaxel, pembrolizumab, carboplatin, paclitaxel, nab-paclitaxel) of the study treatment, depending on the study Part. Each study drug considered to be contributing to the toxicity, in the opinion of the investigator, should be delayed or modified in accordance with the guidelines below. The other components of the study treatment may be administered on schedule if there is no contraindication. If clinically appropriate, the treating investigator can delay any of the treatment components up to a maximum of 7 days to allow synchronized administration of all agents. Dosing intervals of subsequent doses may be adjusted as clinically feasible in order to gradually synchronize the entire study treatment. Intervals between 2 consecutive IV doses cannot be less than 14 days for Parts 1, 2, and 4 or less than 7 days for Part 3. Exception: If any component of anti-cancer regimen is delayed or held in the first 3 cycles, bemarituzumab should be administered ± 3 days of scheduled visit date for cycles 1 through 3. For Part 3 only, there is no window for cycle 1 day 8 dose, ie, the visit must occur 7 days after C1D1.

Delay of any component of the anti-cancer regimen longer than 21 days should be discussed with the medical monitor prior to re-initiation. If one component is permanently discontinued, the rest of the components of the study treatment may continue.

6.2.2.1 Amgen Investigational Product: Bemarituzumab

Bemarituzumab doses may be held for bemarituzumab-related adverse events following the guidelines outlined in Table 6-5. The reason for dose delay of bemarituzumab is to be recorded on each subject's CRF(s).

Bemarituzumab is to be administered prior to all other study treatment. After cycle 1, bemarituzumab dose should be recalculated only if the weight changes > 10% from baseline. If the dose is recalculated, the weight used for the recalculated dose should function as the new baseline.

If dose reductions or interruptions that do not fall within these guidelines are being considered by the investigator, these will require discussion with the Sponsor or designee.

Corneal Events

Any subject with a corneal event which occurs within 100 days of last receiving a dose of bemarituzumab, regardless if deemed related or not related to bemarituzumab, should be evaluated by an ophthalmologist. Any subject who reports pain or irritation of the eye or change in vision should be evaluated by an ophthalmologist. Refer to Table 6-5 for additional guidance.

Table 6-5. Bemarituzumab Dose Modification Guidelines for Adverse Events

CTCAE Grade	Interruption/Delay	Specific Management	Re-start guidance	Permanent Discontinuation
Corneal Toxicity[a] (refer to Table 11-8 for details regarding grading)				
1	n/a		n/a	n/a
2	Clinical judgement required. If subject has not been seen by ophthalmologist for the grade 2 event, treatment should either be held/delayed until ophthalmologic evaluation or, if not associated with a change in vision, subject may receive a maximum of one dose prior to ophthalmologic evaluation.	• Refer to ophthalmologist for evaluation • Treatment as deemed appropriate by the ophthalmologist. • Bemarituzumab may be continued or held, based on ophthalmologic findings.	If held/delayed, resume at full dose if event has improved to grade ≤ 1.	Discontinue if grade 3 or higher event recurs with restart of the drug.
3	Immediate interruption/delay until event has improved to grade ≤ 1	• Refer to ophthalmologist for evaluation urgently. • Treatment as deemed appropriate by the ophthalmologist. • Close follow up by ophthalmologist until event has improved to grade ≤ 1.	Resume at full dose if event has improved to grade ≤ 1.	Discontinue treatment if event does not improve to grade ≤ 1 Discontinue if grade 3 or higher event recurs with restart of the drug.
4	n/a	• Refer to ophthalmologist for evaluation urgently. • Treatment as deemed appropriate by the ophthalmologist. • Close follow up by ophthalmologist until event has improved to grade ≤ 1.	n/a	Discontinue bemarituzumab

Table 6-5. Bemarituzumab Dose Modification Guidelines for Adverse Events

CTCAE Grade	Interruption/Delay	Specific Management	Re-start guidance	Permanent Discontinuation
Infusion-related Reaction				
1	Decrease rate of infusion by 50%	• Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable. • Treat per institutional guidelines.	n/a	n/a
2	Immediate interruption/delay until event has improved to grade ≤1	• Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable. • Treat per institutional guidelines. Additional appropriate medical therapy may include but is not limited to IV fluids, antihistamines, NSAIDs, acetaminophen, and opioids	• After all symptoms have resolved: – administer premedication (eg, antihistamines, corticosteroids, and acetaminophen) 1.5 hours (± 30 minutes) prior to infusion using institutional standards – resume bemarituzumab at reduced infusion rate (50% or less of standard rate)	If grade 2 infusion-related reaction recurs despite adequate premedication, permanently discontinue bemarituzumab.
3	Immediate interruption	• Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable. • Hospitalization may be indicated. • Treat per institutional guidelines. Additional appropriate medical therapy may include but is not limited to IV fluids, antihistamines, NSAIDs, acetaminophen, and opioids, oxygen, vasopressors, corticosteroids, and epinephrine, in cases of anaphylaxis.	• If grade 3 infusion-related reaction resolves to grade ≤ 1 within 6 hours of onset, consider: – administer premedication (eg, antihistamines, corticosteroids, and acetaminophen) 1.5 hours (+ 30 minutes) prior to infusion using institutional standards – resume bemarituzumab at reduced infusion rate (50% or less of standard rate)	If grade 3 infusion-related reaction does not resolve to grade ≤ 1 within 6 hours of onset, permanently discontinue bemarituzumab.

CTCAE Grade	Interruption/Delay	Specific Management	Re-start guidance	Permanent Discontinuation
Infusion-related Reaction				
4	Immediate interruption	• Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable. • Hospitalization may be indicated. • Treat per institutional guidelines. Additional appropriate medical therapy may include but is not limited to IV fluids, antihistamines, NSAIDs, acetaminophen, opioids, oxygen, vasopressors, corticosteroids, and epinephrine. In cases of anaphylaxis, epinephrine should be used immediately.	n/a	Permanently discontinue bemarituzumab

Table 6-5. Bemarituzumab Dose Modification Guidelines for Adverse Events

CTCAE Grade	Interruption/Delay	Specific Management	Re-start guidance	Permanent Discontinuation
All other bemarituzumab-related adverse events				
1 or 2	n/a	Treat per institutional guidelines.	n/a	n/a
3 (first or second occurrence)	Delay or miss dose until recovery to baseline or grade 1	Treat per institutional guidelines.	If recovery to baseline or grade 1, may resume at full dose. • Parts 1, 2, and 4: Recovery timeframe 21 days from onset of event • Part 3: Recovery timeframe 28 days from onset of event	n/a
• Grade 3 (third occurrence) • For Parts 1, 2, and 4: grade 3 which does not recover to baseline or grade 1 within 21 days of onset of event • For Part 3: grade 3 which does not recover to baseline or grade 1 within 28 days of onset of event • Any grade 4	Immediate interruption	Treat per institutional guidelines.	n/a	Permanently discontinue bemarituzumab

CTCAE = Common Terminology Criteria for Adverse Events; IV = intravenous; n/a = not applicable; NSAIDs = nonsteroidal anti-inflammatory drugs.
[a] Ocular adverse events that are not corneal toxicity should follow dose modifications for all other bemarituzumab-related adverse events.

6.2.2.2 Non-Amgen Non-Investigational Product

6.2.2.2.1 Docetaxel

Dose adjustments for docetaxel are permitted and should be made in accordance with the relevant local guidelines and the latest version of the local prescribing information with the consideration of the recommendations provided below, which are based on the USPI.

Subjects who are dosed initially at 75 mg/m^2 and who experience either febrile neutropenia, neutrophils less than 500 cells/mm^3 for more than 1 week, severe or cumulative cutaneous reactions, or other grade 3 or 4 non-hematological toxicities during docetaxel treatment should have treatment withheld until resolution of the toxicity, and then resumed at 55 mg/m^2. Subjects who develop ≥ grade 3 peripheral neuropathy should have docetaxel treatment discontinued. Given adverse events related to nail toxicity may be additive in the context of the combined use of bemarituzumab and docetaxel, in the event of an occurrence of a grade 3 nail infection, paronychia or onycholysis, docetaxel must be held until resolution to grade < 1. Docetaxel should not be administered to subjects until ANC recovery to ≥ 1500 cells/mm^3 prior to each dose of docetaxel.

Concomitant use of docetaxel and drugs that inhibit CYP3A4 may increase exposure to docetaxel and should be avoided. In subjects receiving treatment with docetaxel (Parts 1 and 2), close monitoring for toxicity and docetaxel dose reduction should be considered if systemic administration of a potent CYP3A4 inhibitor (such as ketoconazole, itraconazole, clarithromycin, indinavir, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin, and voriconazole) cannot be avoided. Refer to the docetaxel regional prescribing information for additional information.

The reason for dose change of docetaxel is to be recorded on each subject's CRFs.

6.2.2.2.2 Carboplatin, Paclitaxel, Nab-Paclitaxel, and Pembrolizumab

For carboplatin, paclitaxel, nab-paclitaxel, and pembrolizumab dose modifications might be permitted to mitigate the adverse reactions according to institutional standards or local package inserts, which the investigator may elect to follow over the guidance provided herein.

Dosing interruptions are permitted for logistical reasons not related to study therapy and the reason for the interruption should be documented in the eCRF. Subjects should resume study therapy within 21 days of dose interruption.

Neurotoxicity

Subjects receiving paclitaxel and developing grade 3 or 4 neuropathy for 7 days of longer should have paclitaxel dose reduced by 20% for subsequent doses.

Subjects receiving nab-paclitaxel and developing grade 3 or 4 neuropathy should have nab-paclitaxel withheld and should resume nab-paclitaxel and carboplatin at reduced doses when neuropathy improves to grade 1 or completely resolves. On first occurrence the dose reduction for nab-paclitaxel and carboplatin AUC should be 25%, an additional 25% for the second recurrence, and discontinuation of treatment if a third recurrence should occur.

Renal impairment

Alterations in renal function may require carboplatin dose recalculation.

Hepatic impairment

Alterations in hepatic function may require paclitaxel dose recalculation.

Hematologic toxicity

In the initial phase of combination therapy treatment with pembrolizumab, paclitaxel or nab-paclitaxel, and carboplatin should be delayed until ANC is $\geq 1.5 \times 10^9$/L and platelet count is platelet count $\geq 100 \times 10^9$/L. Subjects receiving paclitaxel and developing febrile neutropenia during the prior cycle should have paclitaxel and carboplatin dose reduced by 20-25% for subsequent courses and/or institution of hematopoietic stimulating agents. The carboplatin dose should be reduced by 25% in subjects with platelet count nadir of $< 50 \times 10^9$/L and/or neutrophil nadir of $< 0.5 \times 10^9$/L. An additional dose reduction of 25% may be considered at second occurrence, and consider discontinuing nab-paclitaxel and carboplatin therapy if a subject qualifies for a third dose reduction. Dose reductions for hematologic toxicity should be maintained for subsequent cycles.

For subjects receiving nab-paclitaxel and developing febrile neutropenia or ANC $< 0.5 \times 10^9$/L for $>$ 7 days or delay of next cycle by $>$ 7 days for thrombocytopenia $< 50 \times 10^9$/L withhold nab-paclitaxel and carboplatin treatment until counts recover to an ANC of at least 1.5×10^9/L and platelet count of at least 100×10^9/L on day 1, or to an ANC of at least 0.5×10^9/L and platelet count of at least 50×10^9/L of day 8 or 15 of the cycle. If treatment is resumed then reduce nab-paclitaxel and carboplatin by 25% at first occurrence, and additional 25% at second occurrence, and consider discontinuing

nab-paclitaxel and carboplatin therapy if a subject qualifies for a third dose reduction. Dose reductions for hematologic toxicity should be maintained for subsequent cycles.

Pembrolizumab immune-related toxicity

No dose reduction for pembrolizumab is recommended. In general, pembrolizumab should be withheld for grade ≥ 3 immune-mediated adverse reactions, and permanently discontinued for life-threatening (grade 4) immune-mediated adverse events, recurrent severe (grade 3) immune-mediated reactions that require systemic immunosuppressive treatment, or an inability to reduce corticosteroid dose to 10 mg or less of prednisone or equivalent per day within 12 weeks of initiating steroids.

Allergic Reaction

If a subject experiences grade 1 or 2 allergic reaction to carboplatin, premedication should be given according to institutional practice prior to subsequent further study drug administration. If a grade 1 or 2 allergic reaction persists into the next cycle, escalation of the appropriate premedication should be done according to institutional practice prior to administration of carboplatin. For subjects experiencing grade 3 or 4 allergic reactions, treatment with carboplatin should be discontinued.

Refer to Section 6.7.2.1 for infusion reaction prophylaxis and other supportive care guidance.

6.2.3 Hepatotoxicity Stopping and Rechallenge Rules

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.

6.3 Preparation/Handling/Storage/Accountability

Guidance and information on drug accountability for the investigational product will be provided to the site.

6.4 Measures to Minimize Bias: Randomization and Blinding

6.4.1 Method of Treatment Assignment

Subjects who meet eligibility criteria according to the specific study part and enroll in the study will be assigned to treatment with bemarituzumab combination with other anti-cancer therapy or bemarituzumab monotherapy.

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

6.4.2 Blinding

This is an open-label study; procedures to blind treatment assignment are not applicable.

6.5 Treatment Compliance

When subjects are dosed at the site, they will receive bemarituzumab, chemotherapy, and pembrolizumab (depending on the study part) directly from the investigator or designee, under medical supervision. The date and time of each dose administered in the clinic will be recorded in the source documents and recorded in the CRF.

6.6 Treatment of Overdose

The effects of overdose for bemarituzumab are unknown, and there is no available antidote. For overdose information on pembrolizumab or the chemotherapy agents please refer to the Regional Prescribing Information.

In the event of an overdose, subjects should receive appropriate supportive medical care and be followed until resolution/stabilization of any clinical issues. A blood sample should be collected to determine bemarituzumab serum concentration as soon as possible after overdose.

Any instance of overdose (suspected or confirmed and irrespective of whether or not it involved investigational product in the study) must be communicated to the sponsor (or a specified designee) using the eCRF page within 24 hours of its occurrence.

Any overdose associated with clinical symptoms will be recorded as an adverse event or serious adverse event, as appropriate. Details of any signs or symptoms and their management should be recorded, including details of any treatments administered for the overdose. All overdoses with clinical symptoms meeting the serious adverse event criteria must be reported as described in Section 8.4.6.

6.7 Prior and Concomitant Treatment

6.7.1 Prior Treatment

All prior medications must be recorded in the designated eCRF. This includes prior therapies that were being taken/used from 3 months prior to enrollment through informed consent and all prior anticancer therapies for advanced or metastatic squamous-cell non-small-cell lung cancer dating back to initial diagnosis.

For prior therapies for advanced or metastatic squamous-cell non-small-cell lung cancer, collect therapy name, setting, dose, unit, frequency, start date, stop date, best response, and reason for discontinuation. For anticancer therapies consisting of multiple individual

components, information for each component should be collected. For all other prior therapies, collect therapy name, indication, dose, unit, frequency, route, start date, and stop date.

6.7.2 Concomitant Treatment

Throughout the study, investigators may prescribe any concomitant medications or treatments deemed necessary to provide adequate supportive care except for those listed in Section 6.1.6.

To mitigate the risk of corneal toxicities, prophylactic use of ocular lubricants and eyelid hygiene is recommended. Ocular lubricants (eg, preservative-free artificial tears) should be self-administered 3 times daily throughout the treatment period and for 28 (+ 3) days after the last dose. They may be polyvinyl alcohol-, or liquid polyol-based. If preservative free is not available, formulations with preservatives are allowed. Avoid viscous lubricants which can cause blurriness.

Concomitant therapies are to be collected from informed consent through the end of LTFU period. For concomitant therapies, including vaccines, collect therapy name, indication, dose, unit, frequency, route, start date, and stop date (for SARS-CoV-2 vaccines collect indication also).

For subsequent therapies taken for advanced or metastatic squamous-cell non-small-cell lung cancer, collect drug name, start date, and stop date.

6.7.2.1 Supportive Care

Subjects can receive supportive care according to local guidelines for blood product support, anti-emetics, antibiotics, antivirals, analgesics for pain control, other prophylactic treatments, etc. Hematopoietic stimulating agents may be used if indicated. For subjects on anticoagulant therapy, close monitoring of coagulation parameters is recommended.

7. Discontinuation of Study Treatment and Subject Discontinuation/Withdrawal

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 Section 7.1.

7.1 Discontinuation of Study Treatment

Subjects (or a legally authorized representative) can decline to continue receiving investigational product and/or other protocol-required therapies and/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 (see Section 1.3) 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 and/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.

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 Subject Discontinuation/Withdrawal 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. 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. Subjects who are withdrawn or removed from treatment or the study will not be replaced.

If a subject withdraws from the study, they 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 (Section 1.3) 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 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 they repeatedly fail 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, they 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 should 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 Section 1.3).

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 (Section 1.3), is essential and required for study conduct.

8.1 General Study Periods

8.1.1 Screening, Enrollment, and/or Randomization

Consent for Tissue Collection for FGFR2b Overexpression Status

Subjects must consent to provision of archival tissue (or fresh biopsy if archival tissue not available within last 5 years) for IHC-confirmed FGFR2b overexpression. For a subject to be eligible for study participation in Parts 2, 3, and 4, positive FGFR2b overexpression status must be demonstrated based on a tumor sample either archival or fresh. Archival or fresh biopsy specimen may be re-tested if eligibility is not met with the first specimen submitted.

Screening

The main study informed consent must be obtained before completing any screening procedure (other than the tissue collection for FGFR2b overexpression status) or discontinuation of standard therapy for any disallowed therapy. For Parts 2, 3, and 4 only, positive FGFR2b overexpression status must be confirmed prior to subjects entering screening. After the subject has signed the informed consent form, the site will register the subject in the IRT and screen the subject in order to assess eligibility for participation. The screening window is up to 28 days.

All screening evaluations must be completed and reviewed to confirm that potential subjects meet all eligibility criteria. 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 2 times.

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, unless directed by Amgen. Subjects rescreening

within 28 days of the signing of the original informed consent only need to repeat the assessment(s) that did not originally meet the eligibility criteria; all other initial screening assessments do not need to be repeated. If the rescreening period begins more than 28 days after the original signing of the informed consent form, all screening procedures, including informed consent, must be repeated.

8.1.2 Treatment Period

Visits will occur per the Schedule of Activities (Section 1.3). On-study visits may be completed within 72 hours prior to dosing. The date of the first dose of protocol-required therapies is defined as day 1. All subsequent doses and study visits will be scheduled based on the day 1 date. Administration of protocol-required therapies is to be administered last during each visit that it is required.

8.1.3 Safety Follow-up

Upon permanent discontinuation from the study treatment for any reason, a SFU visit will be performed approximately 28 (+3) days after the last dose of study treatment.

8.1.4 Long-term Follow-up

Long-term follow up will be conducted every 3 months (± 1 month) up to 2 years from the subject's first dose of bemarituzumab.

Vital status, disease status (until radiographic disease progression), and subsequent ophthalmological medications and anticancer treatment (ie, subsequent therapies taken for lung cancer) will be collected. Visits may be conducted by telephone. A comprehensive ophthalmologic examination should be completed if symptoms are reported by the subject up to 100 days after the last dose of bemarituzumab.

A complete list of assessments that will be conducted during LTFU are designated in the Schedule of Activities (Section 1.3).

8.1.5 End of Study

A subject is considered to have completed the study if they have completed the study including the last visit or the last follow up shown in the Schedule of Activities (Section 1.3).

8.2 General Assessments

8.2.1 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.

8.2.2 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.

8.2.3 Medical History

The Investigator or designee will collect a complete medical and surgical history that started within 5 years prior to enrollment through first dose of study treatment. Medical history will include information on the subject's concurrent medical conditions. The current toxicity grade will be collected for each condition that has not resolved. Record all findings on the medical history CRF.

Ophthalmologic history is to be recorded on the targeted ophthalmologic CRF.

In addition to the medical history above, squamous non-small-cell lung cancer history must date back to the original diagnosis, and is to be recorded on the cancer medical history CRF. Local tumor biomarker testing results (if completed) will be collected in the appropriate eCRF.

8.2.4 Physical Examination

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

8.2.5 Physical Measurements

Height in centimeters and weight in kilograms should be measured without shoes.

8.2.6 Substance Use History

Obtain a detailed history of prior and/or concurrent use of alcohol and tobacco.

8.2.7 Performance Status

Eastern Cooperative Oncology Group performance status will be collected at the timepoints indicated in the Schedule of Activities (Section 1.3). The ECOG criteria for this protocol are further defined in Section 11.10.

8.3 Efficacy Assessments

Radiological Imaging Assessment

The extent of disease will be evaluated by contrast-enhanced computed tomography (CT)/magnetic resonance imaging (MRI) according to RECIST v1.1. In order to reduce radiation exposure for subjects, low dose CT should be utilized whenever possible.

Screening scans:

The screening scans should be performed within 28 (+ 3) days prior to cycle 1 day 1 and include clinical examination and appropriate imaging techniques (preferably CT scans with appropriate slice thickness per RECIST v1.1; MRIs are acceptable). If there are multiple screening scans, the one closest to the enrollment date will be used as baseline.

Radiological assessment must include CT/MRI of the chest, abdomen, and pelvis, as well as assessment of all other known sites of disease. Tumor response assessment will be performed by the investigator per RECIST v1.1 guidelines (Section 11.9).

All subjects with brain metastasis must have MRI of the brain performed. All brain scans for subjects with brain metastasis are required to be MRI unless MRI is contraindicated, and then CT with contrast is acceptable. Brain imaging (MRI or CT) of the brain should be performed if signs or symptoms suggestive of CNS metastases are present.

Subsequent scans:

All subsequent scans should be performed in the same manner (eg, with the same contrast, MRI field strength) as at screening preferably on the same scanner. If the imaging modality must be altered (eg, unscheduled assessment) consultation with the Amgen medical monitor is recommended.

During treatment and follow-up, radiological imaging of the chest, abdomen, pelvis, as well as all other known sites of disease, will be performed independent of treatment cycle as specified in the Schedule of Activities (see Section 1.3). Imaging may also be performed more frequently if clinically necessitated at the discretion of the managing physician. Radiologic imaging and tumor assessment will be performed until start of new anticancer therapy, disease progression, death, withdrawal of consent, or end of study, whichever occurs first.

Determination of disease response for clinical management and response evaluation will be performed at the clinical sites per RECIST v1.1. Confirmation of response by a repeat scan is required after 4 weeks from the first documentation of response. Scans may be submitted to a central imaging core laboratory for archival, and, if needed, response assessment including RECIST v1.1, and/or exploratory analysis (eg, volumetric and viable tumor measurements).

8.4 Safety Assessments

Planned time points for all safety assessments are listed in the Schedule of Activities (see Section 1.3).

8.4.1 Vital Signs

The following measurements must be performed: systolic/diastolic blood pressure, heart rate, respiratory rate, and temperature. Allow subject to sit for 3-5 minutes before taking blood pressure measurement. 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. Record all measurements on the vital signs CRF.

8.4.2 Electrocardiograms (ECGs)

Parts 1, 2, and 4 only:

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 the most recumbent position possible. The ECG must include the following measurements: Heart rate, QRS, QT, Q-T corrected (QTc), and PR intervals. The principal investigator (PI) or designated site physician will review all ECGs. Once signed, the original ECG tracing will be retained with the subject's source documents. At the request of the sponsor, a copy of the original ECG will be made available to Amgen.

Part 3 only:

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 the most recumbent position possible. Electrocardiograms should be performed in a standardized method, in triplicate, and run consecutively. Each triplicate, which consists of three 10-second tracings, should be completed within a total of 5 minutes from the start of the first to the completion of the third, prior to blood draws or other invasive procedures. Each ECG must include the following measurements: QRS, QT, QTc, RR, and PR intervals.

- Baseline ECGs should be collected at 3 timepoints ≥ 5 minutes apart, with each baseline ECG performed in triplicate, and with at least 5 minutes between the end of each triplicate and the start of the next (total 9 ECGs)
- Each post-dose ECG should be performed in triplicate (total 3 ECGs)

Baseline is defined as screening. The PI or central reader will review all ECGs. Electrocardiograms will be transferred electronically to an ECG central vendor eg, for storage or for analysis per Amgen instructions. 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 or designee. Standard ECG machines should be used for all study-related ECG requirements. In certain circumstances Amgen or designee may be able to provide a standard ECG machine if a site is unable to provide one.

8.4.3 Clinical Laboratory Assessments

Refer to Section 11.2 for the list of clinical laboratory tests to be performed and to the Schedule of Activities (Section 1.3) for the timing and frequency.

The investigator is responsible for reviewing laboratory test results and recording any clinically relevant changes occurring during the study in the Events 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.

All protocol-required laboratory assessments, as defined in Section 11.2, must be conducted in accordance with the laboratory manual and the Schedule of Activities (Section 1.3).

8.4.4 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.

8.4.5 Other Safety

8.4.5.1 Ophthalmologic Examinations

Ophthalmologic examinations will be performed according to the Schedule of Activities (Section 1.3). Ophthalmologic adverse events of any grade up to 100 days after the last dose of bemarituzumab should be reported to Amgen by the investigator and evaluated by an ophthalmologist.

The ophthalmologic examination should include distance corrected visual acuity of each eye separately with acuity recorded as the logMAR equivalent (see Section 11.12), slit lamp examination of the anterior segment, tonometry (intraocular pressure measurement), and ocular surface staining (eg, fluorescein). In addition, a dilated retinal examination or 3 field retinal photographs should be performed at screening and at every other ophthalmic examination. Additionally, optical coherence tomography (OCT) of the macula is required for subjects diagnosed with, or with suspected retinal pigment epithelium (RPE) detachment. All assessments are to be done according to local practice.

Distance corrected visual acuity will be assessed using Snellen or Landolt C Chart and acuity must be recorded as logMAR equivalent. The same method should be used at screening and throughout the study. Other visual acuity charts may be utilized, but must be agreed with the Amgen medical monitor.

Ophthalmologic examinations should be performed regardless of dose delays per the schedule of activities (See Section 1.3). The ophthalmological examination may be repeated at any time, as clinically indicated, up to 100 days after the last dose of bemarituzumab. After the SFU visit if the subject has any persistent ophthalmologic findings, ophthalmologic assessments should continue until resolution of findings, withdrawal of consent, death, or lost to follow up. Ocular adverse events should be monitored by an ophthalmologist until resolution.

The following measures will be implemented for ophthalmologic adverse events:

- Monitoring through ophthalmologist visits at baseline and Q6W (- 5 days) for the first 24 weeks, and then every 8 weeks (-5 days) thereafter
- Ophthalmologic adverse event management guidance for the investigator (refer to Table 6-5)

If any clinically significant changes are noted compared to the previous examination or, if the subject has any grade 2 or higher ocular signs or symptoms, the subject should be evaluated by an ophthalmologist.

8.4.6 Adverse Events and Serious Adverse Events

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.

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

8.4.6.1.1 Adverse Events

The adverse event grading scale to be used for this study will be the Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0 and is described in Section 11.4, except for ocular adverse events which will be graded according to the study-specific ocular toxicity grading (see Appendix 11, Section 11.11).

The investigator is responsible for ensuring that all adverse events observed by the investigator or reported by the subject that occur after first dose of investigational product or after study-required activity and/or procedures through the end of SFU visit are reported using the Events eCRF (refer to Section 8.4.6.6 for collection of ocular adverse events after the SFU visit).

Adverse events within 28 (+ 3) days after the last day of study treatment are expected to be recorded. Adverse events of any grade occurring up to 14 days after the pre-screening procedure of tumor biopsy acquisition for the FGFR2b assay should be reported as adverse events if they are deemed related to the pre-screening procedure by the investigator.

8.4.6.1.2 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 pre-screening or main study informed consent through 28 (+ 3) days after the last study treatment or through the SFU visit for the protocol required reporting period, whichever occurs late, are reported using the Events eCRF. Serious adverse events of any grade occurring up to 14 days after the pre-screening procedure of tumor biopsy acquisition for the FGFR2b assay should be reported as serious adverse events if they are deemed related to the pre-screening procedure by the investigator.

All serious adverse events will be collected, recorded and reported to the sponsor or designee immediately and no later than 24 hours of the investigator's awareness of the event, as indicated in Section 11.4. The investigator will submit any serious adverse event data to the sponsor immediately and no later than 24 hours of it being available.

Since the criteria the CTCAE grading scale differs from the regulatory criteria for serious adverse events, if adverse events correspond to grade 4 CTCAE toxicity grading scale criteria (eg, laboratory abnormality reported as grade 4 without manifestation of life-threatening status), it will be left to the investigator's judgment to also report these

abnormalities as serious adverse events. For any adverse event that applies to this situation, comprehensive documentation of the event's severity must be recorded in the subject medical records.

8.4.6.1.3 Serious Adverse Events After the Protocol Required Reporting Period

During the long-term follow-up period, if the investigator becomes aware of serious adverse events suspected to be related to investigational product or any fatal adverse event (regardless of causality) after the protocol-required reporting period (as defined in Section 8.4.6.1.2) is complete, then these serious adverse events will be reported to Amgen immediately and no later than 24 hours following the investigator's awareness of the event on the Events CRF.

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 (including any fatal cases) suspected to be related to investigational product, then these serious adverse events will be reported to Amgen immediately and no later than 24 hours following the investigator's awareness of the event on the Events CRF.

Serious adverse events reported after the end of the study 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 records after the subject ends the study.

8.4.6.2 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.

8.4.6.3 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 immediately and no later than 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 Events CRF.

8.4.6.4 Regulatory Reporting Requirements for Safety Information

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.

For studies in which the treatment assignment is blinded, to comply with worldwide reporting regulations for serious adverse events, the treatment assignment of subjects who develop serious, unexpected, and related adverse events may be unblinded by Amgen before submission to regulatory authorities. Aggregate analyses may also be unblinded by the Safety Assessment Team, as appropriate. Investigators will receive notification of related serious adverse events reports sent to regulatory authorities in accordance with local requirements.

Amgen will prepare a single Development Safety Update Report (DSUR) (also referred to as Annual Safety Report [ASR] in the EU) for the Amgen Investigational Product. In order to ensure that consolidated safety information for the trial is provided, this single

DSUR will also include appropriate information on any other investigational products used in the clinical trial, if applicable.

8.4.6.5 Safety Monitoring Plan

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

8.4.6.6 Adverse Events of Special Interest

Selected adverse events known as bemarituzumab Events of Special Interest are ocular adverse events of any grade or seriousness occurring up to 100 days after the last dose of bemarituzumab and should be collected as adverse events. Any ophthalmological events not resolved at the SFU visit must be followed until resolution or no further improvement is expected based on an ophthalmology assessment. Ocular adverse events (including corneal adverse events) should be graded using the Ocular Toxicity Grading scale provided in Section 11.11.

Subjects should be assessed for possible bemarituzumab Events of Special Interest prior to each dose.

8.4.6.7 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 6 months after protocol-required therapies. During the LTFU period, local laboratory results performed in walk-in clinics or health centers are acceptable if the subject does not have a scheduled clinic visit.

If a pregnancy is reported, the investigator is to inform Amgen immediately and no later than 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, and ectopic pregnancy) are considered serious adverse events.

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

Pregnancy Testing

A highly sensitive (serum) pregnancy test should be completed at screening and within 72 hours of 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 11-3). Refer to Section 11.5 for contraceptive requirements.

Additional pregnancy testing should be performed on day 1 of every cycle (Parts 1 and 2) or day 1 of every other cycle (Part 3) during treatment, 28 (+ 3) days after discontinuing protocol-required therapies, and monthly (28 [± 3] days) pregnancy testing up to and inclusive of 75 (+3) days from the last bemarituzumab dose. If the patient continues on docetaxel upon bemarituzumab discontinuation, a one-time pregnancy test will be performed upon the patient's discontinuation of docetaxel during the SFU period.

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

8.5 Pharmacokinetic Assessments

Whole blood samples will be collected for measurement of serum concentrations of bemarituzumab as specified in the Schedule of Activities (Section 1.3). 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.

8.6 Pharmacogenetic Assessments

If the subject consents to the optional pharmacogenetic portion of this study, DNA analyses may be performed. These optional pharmacogenetic analyses focus on inherited genetic variations to evaluate their possible correlation to the disease and/or responsiveness to the therapies used in this study. This optional assessment is separate from genomic analysis of somatic mutations in the tumor and circulating tumor DNA (ctDNA) samples included as part of the main study. The goals of the optional studies include the use of genetic markers to help in the investigation of cancer and/or to identify subjects who may have positive or negative response to investigational product. No additional samples are collected for this part of the study. For subjects who consent to this/these analysis/analyses, DNA may be extracted. The final disposition of samples will be described in Section 11.6.

8.7 Antibody Testing Procedures

Blood sample(s) for antibody testing are to be collected according to the time points specified in the Schedule of Activities (Section 1.3) for the measurement of anti-bemarituzumab antibodies. Samples testing positive for binding antibodies may be further characterized.

Subjects who test positive for antibodies at the final scheduled antibody time point and have clinical sequelae that are considered potentially related to an anti-bemarituzumab antibody response will also be asked to return for additional follow-up testing. This testing is to occur approximately every 3 months from the final scheduled antibody time point and continue until: (1) antibodies are no longer detectable; or (2) the subject has been followed for a period of at least 1 year (± 4 weeks) post administration of bemarituzumab. More frequent testing or testing for a longer period of time may be requested in the event of safety-related concerns.

Refer to the Schedule of Activities (Section 1.3), as applicable, for specific time points, and the laboratory manual for detailed collection and handling instructions.

8.8 Biomarkers

Biomarkers are objectively measured and evaluated indicators of normal biologic processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention.

8.8.1 Biomarker Samples at Pre-Screening and Screening

FGFR2b

Tumor Tissue

Provision of archival tumor biopsy/resection (bone biopsies and cytology samples are excluded) formalin fixed and embedded in paraffin (within 5 years, or fresh biopsy if archival sample is not available) is required for assessment of FGFR2b overexpression status by IHC. Unstained slides or blocks are acceptable. Block return may not be possible in every country. A positive FGFR2b overexpression status result is required for enrollment in study Parts 2, 3, and 4 and subjects must consent to tumor tissue collection and testing in pre-screening. For Part 1, tissue collection will be performed during screening and FGFR2b IHC testing will be performed retrospectively. Primary tumor and metastatic sites of specimen collection are allowed. If fresh tissue samples need to be collected, these samples should be obtained following local standard of care procedures that are not expected to present any additional significant risk to the health, safety, and welfare of the subject.

Subjects for Parts 2, 3, and 4 will be selected for enrollment based on FGFR2b overexpression status, as determined by an IHC clinical trial assay (CTA) at a central Clinical Laboratory Improvement Amendments (CLIA)-certified laboratory (Roche Tissue

Diagnostics, Tucson, Arizona, US) that meets US regulatory requirements. Timing of sample collection is described in the Schedule of Activities (Section 1.3).

The CTA used to select subjects is the VENTANA FGFR2b (FPR2-D) assay, an IHC test to determine the FGFR2b overexpression status (positive or negative) in neoplastic tissue. Samples that are deemed positive for FGFR2b overexpression status exhibit any moderate (2+) to strong (3+) membrane staining in tumor cells.

Subjects who are deemed negative for FGFR2b overexpression status (absence of moderate to strong membrane staining) using IHC will not be eligible for enrollment in Parts 2, 3, or 4. It is the responsibility of each investigator to obtain an adequate tumor specimen for analysis of FGFR2b positivity for enrollment. Blocks are preferred, if available, but in lieu of blocks, unstained slides are recommended. The tumor specimen submitted should be of sufficient quantity to allow for IHC analysis; see the Laboratory Manual for details. Tumor slide or tumor block specimen processing, labeling, and shipping instructions are detailed in the Laboratory Manual that will be distributed with the specimen collection kit.

Once tumor specimens are received, analysis will be performed as efficiently as possible, and FGFR2b overexpression status results will be communicated back to the investigator or designee.

PD-L1 testing will be performed on leftover tissue, if available, as listed in the Schedule of Activities (Section 1.3).

8.8.2 Biomarker Development

Samples will be collected to develop or address biomarker hypotheses related to bemarituzumab activity (eg, to evaluate potential biomarkers that may correlate with treatment response). These samples may also be used for developing methods that enable better understanding of the disease.

Blood and tissue will be collected for biomarker development at the time points specified in the Schedule of Activities (Section 1.3), if allowed according to local regulations and agreed by EC/ IRB. Blood samples will be collected and assessed for ctDNA mutational profiles for potential association with clinical endpoints. Circulating tumor DNA plasma analysis will include the mandatory paired analysis of subject blood samples to identify and select out germline variants, to help refine and determine tumor-specific mutations. The ctDNA assessments are used for profiling of somatic mutations. Germline mutational results will not be reported. Biomarker assessment can be done only if the

biomarker research is allowed according to local regulations and agreed by the local EC/IRB.

When tumor samples or optional biopsy samples are available, including screening/pre-screening tissue, they will also be used for DNA, RNA, and protein expression analysis including somatic (tumor) mutations in order to correlate expression with response. Exploratory genomic analyses of tumor tissue, or biopsies, will include the paired sequencing analysis of subject blood cell pellet samples to identify and select out germline variants, to help refine and determine tumor-specific mutations. Germline mutational results will not be reported. None of these samples will be used for screening of hereditary traits.

8.8.2.1 Biomarker Future Research

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.

If consent is provided by subjects, any remaining samples collected at the time points specified in the Schedule of Activities (Section 1.3), including samples collected for biomarkers assessments, may be used for future research as described in Section 11.6. No additional samples will be collected for biomarker development/future research.

Amgen or another third-party manufacturer may attempt to develop test(s) designed to identify subjects most likely to respond positively or negatively to investigational product(s) to investigate and further understand cancer.

9. Statistical Considerations

9.1 Statistical Hypotheses

No statistical hypothesis will be tested.

9.2 Sample Size Determination

It is anticipated that up to 180 subjects will be enrolled in this study, consisting of a maximum of 18 subjects in Part 1 and a maximum of 150 subjects in Parts 2, 3, and 4 combined. The 150 subjects includes the possibility of 2 cohorts at 2 dose levels of bemarituzumab, consisting of 10 to 30 subjects in each of Parts 2 and 4. Three to 6 Japanese subjects per dose level will be enrolled in Part 1, Part 2, and/or Part 4, either as part of the initial dose level evaluation, or as backfill once the RP3D has been

determined. The planned regions for this study will include North America, Asia, Europe, and Australia.

With 3, 6, or 9 subjects in a dose level cohort in Part 1, there is approximately 58%, 82%, and 93% probability, respectively, of observing at least 1 DLT if the true DLT rate is 25%.

With a minimum of 10 subjects each in Parts 2, 3, and 4, there is an approximate 95% probability of observing at least 1 DLT if the true DLT rate is 25%, the lower end of the acceptable toxicity interval. Up to 30 subjects may be enrolled to gain further safety and preliminary efficacy data.

9.3 Populations for Analysis

The following populations are defined:

Population	Description
Enrolled	All subjects enrolled.
Safety	All subjects who received at least 1 dose of bemarituzumab.
DLT	All subjects that are enrolled in Part 1 who received at least one dose of bemarituzumab and Docetaxel; and met either of the following: 1) experienced a DLT, or 2) completed the 21-day DLT period, 3) received 100% of their planned dose.

9.3.1 Covariates

The relationship between covariates and endpoints may be explored and specified in the statistical analysis plan if appropriate.

9.3.2 Subgroups

Subgroups may be explored and specified in the statistical analysis plan if appropriate.

9.4 Statistical Analyses

The statistical analysis plan 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 8.1.5.

9.4.1 Planned Analyses

9.4.1.1 Interim Analysis and Early Stopping Guidelines

Part 3 may enroll simultaneously with Parts 1, 2, and 4; and Parts 2 and 4 may enroll simultaneously. Therefore, the timing of the DLRMs described below may be adjusted so data from multiple study parts can be reviewed at a single meeting. Interim analyses will be based on as-is database snapshots (ie, data that have gone through routine data cleaning).

9.4.1.1.1 Part 1

During DLRMs, Amgen, in consultation with the site investigators, will review all available cumulative data (safety, tolerability, laboratory, PK, and efficacy) by cohort prior to making dose escalation or dose de-escalation recommendations. Adverse events and DLTs observed in all subjects will be evaluated continually and fully integrated into all DLRMs and considered in all enrollment and dosing decisions. A DLRM will occur during dose escalation and after dose escalation is complete (21 days following last subject enrolled in dose escalation).

The guidelines for dose escalation or de-escalation to the next dose level are determined by using a mTPI-2 design (see Section 6.2.1).

9.4.1.1.2 Parts 2, 3, and 4

Amgen, in consultation with site investigators, will review the data as detailed above 4 months after the 10th subject has been enrolled, in each of Parts 2, 3, and 4.

Additional administrative analyses may be performed for Parts 2, 3, and 4 before the primary analysis in order to plan for additional studies.

9.4.1.2 Primary Analysis

The primary analysis will be based on a cleaned database lock and will occur 12 months after the last subject has been enrolled.

9.4.1.3 Final Analysis

A final analysis will be based on a cleaned database lock will occur after all subjects have ended the study.

9.4.2 Methods of Analyses

9.4.2.1 General Considerations

Data will be summarized by study part, and by dose level within Part 1. Descriptive statistics on continuous data will include means, medians, standard deviations and ranges, while categorical data will be summarized using frequency counts and

percentages. Unless otherwise specified, data will be summarized using the Safety Analysis Set.

Confidence intervals (CI) for proportions will be estimated using an exact method proposed by Clopper-Pearson (Clopper and Pearson, 1934). Kaplan-Meier (KM) methods will be used to estimate the median and percentiles for time to event endpoints with CI calculated by using the Brookmeyer and Crowley method (Brookmeyer and Crowley, 1982). Kaplan-Meier methods will be used to estimate landmarks for time to event endpoints (eg, 1-year OS) with the Greenwood formula (Kalbfleisch and Prentice, 1980) used to estimate the standard error used in CI calculation.

9.4.2.2 Efficacy Analyses

Endpoint/ Estimand	Statistical Analysis Methods
Primary	Not applicable
Secondary	Listings of secondary efficacy endpoints will be produced for all subjects. The proportion of subjects with an objective response will be estimated along with a 95% CI. The same method will be used to summarize disease control rate. For subjects treated at the RP3D, KM curves, KM quartiles with 95% CIs, and KM estimates with 95% CIs at landmark time points will be estimated for the following endpoints: duration of objective response (for only responding subjects), PFS, and OS.
Exploratory	Will be described in the statistical analysis plan finalized before database lock

9.4.2.3 Safety Analyses

9.4.2.3.1 Analyses of Primary Safety Endpoint(s)

Endpoint	Statistical Analysis Methods
Primary	The incidence of DLTs, treatment-emergent adverse events, clinical laboratory abnormalities, vital signs, and corneal findings will be tabulated. Subject incidence of DLTs will be tabulated by planned dose level for Part 1.

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 grade ≥ 3 events, fatal adverse events, serious adverse events, adverse events leading to discontinuation from investigational product or other protocol-required therapies, and adverse events of special interest will also be provided.

9.4.2.3.3 Laboratory Test Results

The analyses of safety laboratory endpoints will include summary statistics and shifts in grades of safety laboratory values between baseline and the worst on-study value.

9.4.2.3.4 Vital Signs

The analyses of vital signs will include summary statistics and shifts in vital sign values between baseline and the worst on-study value.

9.4.2.3.5 Physical Measurements

The analyses of physical measurements will include summary statistics.

9.4.2.3.6 Electrocardiogram

In Parts 1, 2, and 4 the ECG measurements will be 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.

In Part 3, ECG parameters will be summarized with descriptive statistics. In addition, the maximum post-baseline and maximum change from baseline in QT interval will be categorized and the number and percentage of subjects in each group will be summarized. ECG data will be listed and select parameters may be plotted.

9.4.2.3.7 Antibody Formation

The incidence and percentage of subjects who develop anti-bemarituzumab antibodies at any time will be tabulated.

9.4.2.3.8 Exposure to Investigational Product

The number of days on investigational product, the total dose of investigational product, and dose intensity will be summarized using descriptive statistics.

9.4.2.3.9 Exposure to Non-investigational Product

The number of days on non-investigational product, the total dose of non-investigational product, and dose intensity will be summarized using descriptive statistics.

9.4.2.3.10 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.

9.4.2.4 Other Analyses

Bemarituzumab serum concentration and pharmacokinetic parameters for bemarituzumab including, but not limited to, AUC, C_{max} and C_{trough} will be determined and tabulated. Pharmacokinetic data collected from this study in combination with PK data collected from other bemarituzumab studies will be used for population PK analysis. Additional analysis will be performed to evaluate relationships between bemarituzumab exposure and selected safety or efficacy or any relevant biomarker endpoints. Details and results of these exploratory analyses will be described in separate reports.

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11. Appendices

11.1 Appendix 1. List of Abbreviations

Abbreviation	Explanation
ADCC	antibody dependent cell-mediated cytotoxicity
ANC	absolute neutrophil count
ALT	alanine aminotransferase
ASR	Annual Safety Report
AST	aspartate aminotransferase
AUC	area under the concentration time curve
BIL	bilirubin
BOR	best overall response
$C_{avg,ss}$	area under the serum concentration versus time curve during the dosing interval at steady state divided by the dosing interval
CFR	Code of Federal Regulations
C_{max}	maximum observed concentration
CNS	central nervous system
CLIA	Clinical Laboratory Improvement Amendments
COVID-19	coronavirus disease 2019
CR	complete response
CRF	case report form
CRO	contract research organization
CrCl	creatinine clearance
CT	computed tomography
CTA	clinical trial assay
CTCAE	Common Terminology Criteria for Adverse Events
ctDNA	circulating tumor DNA
C_{trough}	observed concentration at the end of a dose interval
$C_{trough,ss}$	target trough steady state plasma concentration
C1D1	cycle 1 day 1
DAB	3,3′-Diaminobenzidine
DILI	drug induced liver injury
DLT	dose limiting toxicity
DLRM	Dose Level Review Meeting
DLRT	Dose Level Review Team
DSUR	Development Safety Update Report
EC	Ethics Committee
ECG	electrocardiogram

ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
EDC	electronic data capture
EMR	Electronic Medical Record
EoT	end of treatment
eSAE	electronic Serious Adverse Event
ESMO	European Society for Medical Oncology
EU	European Union
FDA	Food and Drug Administration
FDG	fluorodeoxyglucose
FFPE	formalin fixed paraffin embedded
FGF	fibroblast growth factor
FGFR	fibroblast growth factor receptor
FGFR2b	fibroblast growth factor receptor isoform 2b
FIH	first-in-human
FISH	fluorescence in situ hybridization
FRS2	FGFR substrate-2
FSH	follicle-stimulating hormone
GC	gastric cancer
GCP	Good Clinical Practice
GEJ	gastroesophageal junction
GFR	glomerular filtration rate
GSO	Global Safety Officer
HER2	human epidermal growth factor receptor 2
HIV	human immunodeficiency virus
HR	hazards ratio
ICF	informed consent form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IgG	Immunoglobulin G
IHC	immunohistochemistry
IND	Investigational New Drug
INR	international normalized ratio
IV	intravenous
IVD	in vitro diagnostic
IRB	Institutional Review Board
IRT	interactive response technology
ITT	Intent-to-treat

KM	Kaplan-Maier
LTFU	long-term follow-up
MedDRA	Medical Dictionary for Regulatory Activities
mOS	median overall survival
mPFS	median Progression Free Survival
MRI	magnetic resonance imaging
mTPI	modified toxicity probability interval method
NA	not applicable
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NE	not evaluable
NSCLC	Non-small Cell Lung Cancer
NYHA	New York Heart Association
OCT	ocular coherence tomography
ORR	objective response rate
OS	overall survival
PD	progressive disease
PD-L1	programmed death-ligand 1
PET	positron emission tomography
PFS	progression-free survival
PI	principal investigator
PK	pharmacokinetic
PR	partial response
PT	prothrombin time
Q2W	every 2 weeks
Q3W	every 3 weeks
Q6W	every 6 weeks
QTL	quality tolerance limit parameter
QTc	corrected QT interval
QTcF	Fridericia's correction formula
RECIST v1.1	Response Evaluation Criteria in Solid Tumors version 1.1
RP3D	recommended phase 3 dose
RPT	retinal pigment epithelium
rSDR/V	remote Source Data Review and Verification
SAP	Statistical Analysis Plan
SARS CoV-2	severe acute respiratory syndrome coronavirus 2
SD	stable disease
SFU	safety follow-up

SMQ	Standard MedDRA Query
SPC	Summary of Product Characteristics
SoA	Schedule of Activities
SqNSCLC	Squamous non-small-cell lung cancer
TBL	total bilirubin
TKI	tyrosine kinase inhibitor
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 central laboratory and the local laboratory. Additional analyte test results may be reported by the local or central laboratory, in accordance with standard laboratory procedures (eg, components of a hematology panel).

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

Additional 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				
Chemistry	Coagulation	Urinalysis[a]	Hematology	Other Labs
Albumin ALP AST (SGOT) ALT (SGPT) BUN or Urea Calcium Chloride Creatinine (and CrCl) Direct bilirubin Uric acid LDH Magnesium Phosphate Potassium Bicarbonate or carbon dioxide Sodium Total bilirubin Total protein Glucose	PT or INR APTT	Appearance Color pH Specific gravity Ketones Protein Glucose Bilirubin Nitrite Urobilinogen Occult blood	RBC Hemoglobin Hematocrit Platelets WBC ANC CBC with differential: • Neutrophils • Eosinophils • Basophils • Lymphocytes • Monocytes	Serum or urine Pregnancy Total cholesterol Amylase[b] Lipase[b]
CENTRAL LABORATORY				
Bemarituzumab PK[c] Anti-bemarituzumab antibody Tumor biopsy		Biomarkers: PD-L1, ctDNA, tumor profiling FGFR2b by IHC		

ALP = alkaline phosphatase; ALT = alanine aminotransferase; ANC = absolute neutrophil count; APTT = activated partial thromboplastin time; AST = aspartate aminotransferase; BUN = blood urea nitrogen; CBC = complete blood count; CrCl = creatinine clearance; ctDNA = circulating tumor DNA; FGFR2b = fibroblast growth factor receptor isoform 2b; IHC = immunohistochemistry; INR = international normalized ratio; LDH = lactate dehydrogenase; PD-L1 = programmed death-ligand 1; PK = pharmacokinetics; PT = prothrombin time; RBC = red blood cell count; SGOT = serum glutamic-oxaloacetic transaminase; SGPT = serum glutamic-pyruvic transaminase; WBC = white blood cell count

[a] If findings are clinically significant, a microscopic evaluation should be performed per institutional standard.
[b] Collected only at screening and as clinically indicated.
[c] Results will not be reported to sites as they are potentially unblinding.

If the subject is being followed for possible drug induced liver injury (DILI), the following analytes may be tested at the local laboratory depending on the clinical situation (see Appendix 7 [Section 11.7]).

Table 11-2. DILI Potential Analyte Listing

Chemistry	Total bilirubin, direct bilirubin, ALP, LDH, AST (SGOT), ALT (SGPT), creatine kinase, ferritin, gamma-glutamyl transferase, haptoglobin
Hematology	Hemoglobin, Platelets, RBC Morphology, RBC Count, WBC Count, WBC Differential
Coagulation	PT, INR, APTT
Immunology	5 Prime Nucleotidase, Alpha-1 Antitrypsin, Antinuclear Antibodies, Anti-Smooth Muscle Antibody, Anti-Soluble Liver Ag/Liver-Pancreas Ag, Cytomegalovirus IgG Antibody, Cytomegalovirus IgM Antibody, Endomysial IgA Antibody, Epstein-Barr Virus EDA IgG Antibody, Epstein-Barr Virus NA IgG Antibody, Epstein-Barr Virus VCA IgG Antibody, Epstein-Barr Virus VCA IgM Antibody, Hepatitis A Virus IgG Antibody, Hepatitis A Virus IgM Antibody, Hepatitis B Core Antibodies, Hepatitis B Core IgM Antibody, Hepatitis B Surface Antigen, Hepatitis B Virus DNA Genotyping, Hepatitis B Virus Surface Antibody, Hepatitis C Antibodies, Hepatitis C Virus RNA Genotyping, Hepatitis D Virus Antibody, Hepatitis D RNA, Hepatitis E RNA, Hepatitis E IgG Antibody, Hepatitis E IgM Antibody, Herpes Simplex Virus Type 1_2 IgG AB, Herpes Simplex Virus Type 1_2 IgM AB, Human Herpes Virus 6 DNA, Human Herpes Virus 7 DNA, Human Herpes Virus 8 DNA, Immunoglobulin G, Liver Kidney AB 1, Parvovirus IgM/IgG Antibody, Serum Caeruloplasmin, Tissue Transglutaminase IgA Antibody, Toxoplasma IgM/IgG, Varicella Zoster Virus Antibody
Toxicology	Acetaminophen

ALP = alkaline phosphatase; ALT = alanine aminotransferase; APTT = activated partial thromboplastin time; AST = aspartate aminotransferase; DILI = drug-induced liver injury; EDA = early antigen; Ig = immunoglobulin; INR = international normalized ratio; LDH = lactate dehydrogenase; NA = nuclear antigen; PT = prothrombin time; RBC = red blood cell; SGOT = serum glutamic-oxaloacetic transaminase; SGPT = serum glutamic pyruvic transaminase; VCA = viral capsid antigen; WBC = white blood cell

11.3 Appendix 3. Study Governance Considerations

Dose Level Review Meetings (DLRM)

A DLRM is conducted to review and interpret safety data for the purposes of making recommendations about dose-level escalation, dose level de-escalation, subject group/cohort continuation, or cohort expansion; making recommendations about non-dose escalation subject group/cohorts (eg, expanded, highest dose and/or final subject group/cohort); and evaluating safety signals for purposes of applying Dose Group/Cohort Stopping Rules. The required DLRT members are the medical monitor, global safety officer (GSO), and site investigators. The DLRT will include all site investigators or only actively screening and enrolling site investigators. The medical monitor, GSO, and site investigators are the only voting DLRT members. The following non-voting Amgen representatives may also be part of the DLRT: clinical study manager, biostatistician, or pharmacokinetic scientist.

The medical monitor must be in attendance and cannot be represented by a voting designee or delegate. Voting designees can be identified as appropriate by the GSO or site investigator(s). A site investigator may identify a delegate (eg, sub-Investigator) who is listed in the Delegation of Authority. If a site investigator does this, the site investigator must provide written agreement with the designee or delegate's vote.

For a DLRM to occur, the medical monitor must attend, and the GSO or delegate must attend. In addition, a quorum of site investigators must be present (may occur at more than one meeting). A quorum is defined as greater than or equal to 50% of the participating investigators or their qualified designee. The DLRM will be rescheduled if these requirements are not met.

All available study data, including demographics, investigational product administration, medical history, concomitant medications, adverse events, electrocardiogram (ECG), vital signs, and laboratory results will be reviewed. Data to be reviewed will be cleaned, queried, unqueried.

Dose level review meetings voting will occur as follows: there will be a total of 3 votes, 1 for the medical monitor, 1 for the GSO or delegate, and 1 for all of the site investigators or delegates combined. Regardless of how many site investigators there are, all of the site investigators combined will have a total of 1 vote decided by a majority of the investigators (defined as greater than or equal to 50%).

Dose Level Review Meetings recommendations to escalate to the next planned subject group/cohort must be by unanimous vote. If the voting members of the DLRT are not able to reach a unanimous recommendation on whether to escalate to the next planned subject group/cohort then this should be reflected in the DLRM Memo. Other recommendations, such as expanding a subject group/cohort or lowering a dose will be made by a majority vote.

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 International Council for Harmonisation (ICH) Good Clinical Practice (GCP) Guidelines
- Applicable ICH laws and regulations

The protocol, protocol amendments, 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. 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 protocol amendments and changes to the informed consent document that Amgen distributes to the site. 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.

During the course of the study, if new information becomes available that alters the benefit-risk of the study or the study drug, Amgen will follow applicable regulations to notify investigators, the IRB/IEC, and regulatory authorities, as appropriate.

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

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 authorized 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.

If important new information becomes available that may be relevant to the subject's consent during their participation in the study, subjects will 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.

[If a potential subject is illiterate or visually impaired and does not have a legally authorized representative, the investigator must provide an impartial witness to read the ICF to the subject and must allow for questions. Thereafter, both the subject and the witness must sign the ICF to attest that informed consent was freely given and understood. (Refer to ICH GCP guideline, Section 4.8.9.)]

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.

The 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.

Subject data should be kept in a secure location. Access to subject data will be limited to authorized individuals, 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.

Amgen complies with all relevant and applicable laws and regulations that protect personal information in order to ensure subject confidentiality and privacy. Subjects are designated by a unique subject identification number in the Sponsor's systems. The Sponsor uses access-controlled systems to house, review and analyze subject data. These systems are backed-up regularly to minimize the risk of loss of subject data; procedures are also defined for data recovery in the event of data loss. The Sponsor has standard operating procedures in place that restrict access to subject data to those who require access to this data based on their role and have also completed the required training. These procedures also outline the process for revoking access to such data when it is no longer needed. In the event of a security breach, the Sponsor has procedures in place for notification of privacy incidents and to address these incidents, via its Business Conduct Hotline.

Publication Policy

All publications (eg, manuscripts, abstracts, oral/slide presentations, book chapters) based on this study must be prepared in accordance with Amgen's publications policy and submitted to Amgen for review. 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, or the acquisition, analysis, or interpretation of data for the work; (2) drafting the work 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.

The sponsor or designee 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.

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 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.

Quality tolerance limit parameters (QTLs) will be predefined in the QTL definitions table to identify possible systematic issues that can impact participant safety and/or reliability of the study results. These predefined parameters will be monitored during the study. Important deviations from the QTL threshold limits for these parameters and remedial actions taken will be summarized in the clinical study report.

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 they have 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 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 or certain demographic information, such as gender, race, and ethnicity).

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 patients 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 2 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 a separate 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 preexisting 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 squamous 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 NSCLC). Note: The term “disease progression” should not be used to describe the adverse event. • 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. Also, “lack of efficacy” or “failure of expected pharmacological action” also constitutes 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 preexisting 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 preexisting 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 Case Report Form (CRF).
- The investigator must assign the following mandatory 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
  - Assessment of seriousness;
  - Severity (or toxicity defined below);
  - Assessment of relatedness to investigational product(s), and/or study-required activity and/or procedures;
  - Action taken; and
  - Outcome of event.
- If the severity of an adverse event worsens from the date of onset to the date of resolution, record a single event for each increased level of severity on the Event CRF
- It is not acceptable for the investigator to send photocopies of the subject's medical records to sponsor/responsible contact research organization (CRO) in lieu of completion of the Events CRF.
- 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(s) protocol-required therapies, device(s), 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 they have reviewed the adverse event/serious adverse event and has provided an assessment of causality. For sites reporting serious adverse events via electronic data capture (EDC), the investigator or sub investigator must confirm causality in EDC within 72 hours of the serious adverse event being entered on the Events CRF.
- 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. In this case, for sites reporting serious adverse events via EDC, the investigator or sub-investigator must reconfirm causality in the EDC

system within 72 hours of the serious adverse event being entered on the Events CRF.

- 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 will provide [Amgen] with a copy of any postmortem findings including histopathology.
- New or updated information will be recorded in the originally completed Events CRF.
- The investigator will submit any updated serious adverse event data to Amgen immediately and no later than 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) immediately and no later than 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 system has been taken off-line, then the site can report this information on the paper-based Serious Adverse Event Contingency Report Form (see Figure 11-1).
- Once the study has ended, serious adverse event(s) (including any fatal cases) suspected to be related to investigational product will be reported to Amgen 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 (paper-based form)

A Study # 20210102 AMG 552	**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

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

1. SITE INFORMATION

Site Number	Investigator	Country

Reporter	Phone Number	Fax Number
	( )	( )

2. SUBJECT INFORMATION

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

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

3. 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?	**Outcome of Event** Resolved Not resolved Fatal Unknown	Check only if event is related to study procedure eg, biopsy
				☐Yes ☐No		AMG 552 Bemarituzumab: None / Year		
				☐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 552 Bemarituzumab	☐ blinded ☒ open label							Lot # _____ ☐ Unknown Serial # _____ ☐ Unavailable / Unknown
<<IP/Device>>	☐ blinded ☐ open label							Lot # _____

FORM-056006 Confidential Clinical Trials Page 1 of 3 Amgen Proprietary - For Internal Use Only Version 7.0 Effective Date: 1 February 2016

A Study # 20210102 AMG 552	**Electronic Serious Adverse Event Contingency Report Form** **For Restricted Use**

								☐ Unknown Serial #
								☐ Unavailable / Unknown

	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 # 20210102** **AMG 552**	**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 males and females of childbearing potential are outlined in Section 5.2. Contraceptive use and methods should be consistent with local regulations for subjects participating in clinical studies.

Male and female subjects of childbearing potential should be advised of the pregnancy prevention requirements and the potential risk to the fetus if they become pregnant or father a child during treatment and for 6 months after the last dose of protocol-required therapies.

Definition of Females of Childbearing Potential

A female is considered fertile following menarche and until becoming postmenopausal unless permanently sterile. Permanent sterilization methods include documented hysterectomy, bilateral salpingectomy, and bilateral oophorectomy. Females with documented permanent infertility due to an alternate medical cause (eg, Mullerian agenesis, androgen insensitivity, gonadal dysgenesis), can be considered not of childbearing potential.

Note: Bilateral tubal ligation/occlusion is not considered a permanent sterilization method.

Note: Documentation from the following sources is acceptable to provide confirmation of each sterilization method: 1) review of subject's medical records; 2) subject's medical examination; or 3) subject's medical history interview.

A postmenopausal female is defined as:

- A woman of ≥ 55 years with no menses for 12 months without an alternative medical cause OR
- A woman age < 55 years with no menses for at least 12 months and with a follicle-stimulating hormone (FSH) level within the definition of "postmenopausal range" for the laboratory involved. In the absence of 12 months of amenorrhea, confirmation with more than 1 FSH measurement is required.

Contraception Methods for Female Subjects

Highly Effective Contraceptive Methods

- Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation (oral, intravaginal, or transdermal)
- Progestogen-only hormonal contraception associated with inhibition of ovulation (oral, injectable, or implantable)
- Intrauterine device

- Intrauterine hormonal-releasing system
- 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 6 months after the last dose of protocol-required therapies

The female partner should consider using a method of contraception for female subjects stated above (a female condom should not be used 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.

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 6 months of protocol-required therapies.
- Information will be recorded on the Pregnancy Notification Form (see Figure 11-3). The form must be submitted to Amgen Global Patient Safety immediately and no later than 24 hours of the site's awareness 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 consent 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 6 months after the last dose of protocol-required therapies. 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 elective termination of a pregnancy for medical reasons will be reported as an adverse event or serious adverse event. Abnormal pregnancy outcomes (eg, spontaneous abortions, stillbirth, fetal death, congenital anomalies) 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.
- 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 while pregnant (see Section 7.1 for details).

Male Subjects With Partners Who Become Pregnant or Were Pregnant at the Time of Enrollment

- In the event a male subject fathers a child during treatment, and for an additional 6 months after the last dose of protocol-required therapies, the information will be recorded on the Pregnancy Notification Form. The form (see Figure 11-3) must be submitted to Amgen Global Patient Safety immediately and no later than 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).
- Males with pregnant partners or whose partners become pregnant during treatment and for an additional 6 months after last dose of protocol-required therapies must practice sexual abstinence or use a condom through 6 months after discontinuing protocol-required therapies.
- The investigator will attempt to obtain a signed consent 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 consent 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 4 months after the last dose of protocol-required therapies.

- Information will be recorded on the Lactation Notification Form (see below) and submitted to Amgen Global Patient Safety immediately and no later than 24 hours of the investigator's awareness of the event.
- Study treatment will be discontinued if female subject breastfeeds during the study as described in exclusion criterion 222.
- With the female subjects signed consent 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 4 months after the last dose of protocol-required therapies.

Figure 11-3. Pregnancy and Lactation Notification Forms

Amgen Proprietary - Confidential

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: 20210102

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
				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 Proprietary - Confidential

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: 20210102

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
				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

When permitted by local regulations, any blood or tissue sample collected according to the Schedule of Activities (Section 1.3) can be analyzed for any of the tests outlined in the protocol and for any tests necessary to minimize risks to study subjects. This includes testing to ensure analytical methods produce reliable and valid data throughout the course of the study. This can also include, but is not limited to, investigation of unexpected results, incurred sample reanalysis, and analyses for method transfer and comparability.

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

When permitted by local regulations and if informed consent is provided by the subject, Amgen can do additional testing on remaining samples (ie, residual and back-up) to investigate and better understand the cancer, the dose response and/or prediction of response to bemarituzumab or docetaxel, characterize the antibody response, 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 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 (BIL) glucuronidation (eg, indinavir, atazanavir)
- Alpha-1 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.

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

Table 11-3. 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	> 3x ULN at any time	> 2x ULN
		OR
INR	--	> 1.5x (for subjects not on anticoagulation therapy)
	OR	AND
AST/ALT	> 8x ULN at any time > 5x ULN but < 8x ULN for ≥ 2 weeks > 5x ULN but < 8x ULN and unable to adhere to enhanced monitoring schedule > 3x 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 > 3x ULN (when baseline was < ULN)
	OR	
ALP	> 8x 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 Rechallenge of Amgen Investigational Product and Other Protocol-required Therapies After Potential Hepatotoxicity

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

If signs or symptoms recur with rechallenge, then Amgen investigational product and other protocol-required therapies are to be permanently discontinued. Subjects who clearly meet the criteria for permanent discontinuation (as described in Table 11-3) are never to be rechallenged.

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 immediately and no later than 24 hours of discovery or notification of the event (ie, before additional etiologic investigations have been concluded)
- The appropriate case report form (CRF) (eg, Events 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 11-3 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, BIL (total and direct), and INR within 24 hours
- In cases of TBL > 2x ULN or INR > 1.5, retesting of liver tests, BIL (total and direct), and INR is to be performed every 24 hours until laboratory abnormalities improve

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

Initiate investigation of alternative causes for elevated AST or ALT and/or elevated TBL. 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. Protocol-specific Anticipated Serious Adverse Events

Anticipated serious adverse events are events that are anticipated to occur in the study population at some frequency independent of investigational product exposure and do not need to be reported individually as a United States Food and Drug Administration (FDA) Investigational New Drug (IND) safety report by the sponsor. Identification and reporting of anticipated serious adverse events is the responsibility of the sponsor; the investigator is responsible for reporting adverse events and serious adverse events as described in Section 8.4.6 and Section 11.4.

Anticipated Serious Adverse Events for Study 20210102

MedDRA Preferred Term[a]
Lung cancer
Disease progression

[a] Exact Preferred Term according to Medical Dictionary for Regulatory Activities (MedDRA) Version 24

11.9 Appendix 9. Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST v 1.1 Eisenhauer et al, 2009)

11.9.1 Definitions

11.9.1.1 Measurable Disease

The presence of at least 1 measurable lesion. If the measurable disease is restricted to a solitary lesion, its neoplastic nature should be confirmed by cytology/histology.

11.9.1.2 Measurable Lesions

11.9.1.2.1 Measurable Non-nodal Tumor Lesions

Non-nodal lesions with clear borders that can be accurately measured in at least 1 dimension with longest diameter ≥ 10 mm in computed tomography (CT)/ magnetic resonance imaging (MRI) scan with slice thickness no greater than 5 mm. When slice thickness is greater than 5 mm, the minimum size of measurable lesion should be twice the slice thickness.

11.9.1.2.2 Nodal Lesions

Lymph nodes are to be considered measurable if ≥ 15 mm in short axis when assessed by CT/MRI (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.

11.9.1.2.3 Cystic Lesions

Cystic lesions thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above for non-nodal lesions.

11.9.1.2.4 Bone lesions with identifiable soft tissue components

Bone lesions with identifiable soft tissue components, that can be evaluated by cross sectional imaging techniques such as CT or MRI can be considered as measurable lesions if the soft tissue component meets the definition of measurability described above for non-nodal lesions.

11.9.1.2.5 Clinically Measured Lesions

Visible or palpable lesions can be considered measurable if ≥ 10 mm in longest diameter for non-nodal or ≥ 15 mm in shortest diameter for lymph nodes. Lesions should be measured radiologically if more accurate, if not then measured by calipers.

11.9.1.2.6 Irradiated Lesions

Tumor lesions situated in a previously irradiated area, or in an area subjected to other loco-regional therapy, are not measurable unless there has been demonstrated progression that is measurable in the lesion prior to enrollment.

11.9.1.2.7 Non-measurable Lesions

All other lesions, including small lesions (longest diameter $<$ 10 mm or pathological lymph nodes with $\geq$ 10 mm to $<$ 15 mm short axis with CT scan slice thickness no greater than 5 mm) are considered non-measurable. (When slice thickness is greater than 5 mm, the minimum size of measurable lesion should be twice the slice thickness).

Other examples of lesions usually considered to be non-measurable include:

- Lesions with prior local treatment: tumor lesions situated in a previously irradiated area, or an area subject to other loco-regional therapy, should not be considered measurable unless there has been demonstrated progression in the lesion.
- Categorically, clusters of small lesions, bone lesions without a soft tissue component, inflammatory breast disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonitis and leptomeningeal disease are non-measurable.

11.9.2 Methods of Measurement

All measurements should be taken and recorded in metric notation, using a ruler or calipers. The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and throughout the trial. 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 will be 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.

11.9.2.1 CT/MRI

Contrast-enhanced CT or MRI should be used to assess all lesions. Optimal visualization and measurement of metastasis in solid tumors requires consistent administration (dose and rate) of intravenous (IV) contrast as well as timing of scanning. CT and MRI should be performed with $\leq$5 mm thick contiguous slices. The longest diameter of selected lesions should be measured in the plane in which the images were acquired. Ideally, the same scanner or at least type of scanner should be used and the image acquisition protocol should be followed as closely as possible to prior scans.

11.9.2.2 PET-CT

At present, the low dose or attenuation correction CT portion of a combined positron emission tomography (PET)-CT is not always of optimal diagnostic CT quality for use with Response Evaluation Criteria in Solid Tumors (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 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.

11.9.2.3 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 1 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.

11.9.2.4 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.

11.9.2.5 Tumor markers

Tumor markers alone cannot be used to assess response. If markers are initially above the upper normal limit, they must normalize in a subject with a radiological CR for a subject to be considered a CR.

11.9.2.6 Cytology, Histology

These techniques can be used to differentiate between partial response (PR) and CR in rare cases if required by protocol (for example, residual lesions in tumor types such as germ cell tumors, where known residual benign tumors can remain).

When effusions are known to be a potential adverse effect of treatment (eg, with certain taxane compounds or angiogenesis inhibitors), the cytological confirmation of the

neoplastic origin of any effusion that appears or worsens during treatment can be considered if the measurable tumor has met criteria for response or stable disease in order to differentiate between response (or stable disease) and progressive disease (PD).

11.9.2.7 FDG-PET

While fluorodeoxyglucose (FDG)-PET response assessments need additional study, it is sometimes reasonable to incorporate the use of FDG-PET scanning to complement CT scanning in assessment of progression (particularly possible 'new' disease). New lesions on the basis of FDG-PET imaging can be identified according to the following algorithm:

- Negative FDG-PET at baseline, with a positive FDG-PET at follow-up is a sign of PD based on a new lesion.
- No FDG-PET at baseline and a positive FDG-PET at follow-up: If the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, this is PD. If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT, additional follow-up CT scans are needed to determine if there is truly progression occurring at that site (if so, the date of PD will be the date of the initial abnormal FDG-PET scan). If the positive FDG-PET at follow-up corresponds to a pre-existing site of disease on CT that is not progressing on the basis of the anatomic images, this is not PD.
- FDG-PET may be used to upgrade a response to a CR in a manner similar to a biopsy in cases where a residual radiographic abnormality is thought to represent fibrosis or scarring.
- Note: A ‘positive’ FDG-PET scan lesion means one which is FDG avid with an uptake greater than twice that of the surrounding tissue on the attenuation corrected image.

11.9.3 Lesion Evaluation

11.9.3.1 Baseline documentation of “Target” and “Non-target” lesions

11.9.3.1.1 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) and suitability for accurate repeated measurements. All other measurable lesions will be followed as non-target lesions.
- Lymph nodes are considered 1 organ, thus a maximum of 2 measurable lymph nodes may be identified as target lesions.
- 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 of diameters. The baseline sum of diameters will be used as reference by which to characterize objective tumor response.

11.9.3.1.2 Non-Target Lesions

All other lesions (or sites of disease) including pathological lymph nodes should be identified as non-target lesions and should be recorded at baseline. These lesions should be followed as "present," "absent," "unequivocal progression," or "not evaluable" throughout the study. In addition, it is possible to record multiple non-target lesions involving the same organ as a single item on the case report form (eg, "multiple enlarged pelvic lymph nodes" or "multiple liver metastases").

11.9.4 Response Criteria

Table 11-4. Evaluation of Target Lesions

Complete Response (CR)	Disappearance of all target non-nodal lesions. Any target lymph node must have reduction in short axis to < 10 mm, NOT total disappearance.
Partial Response (PR)	At least a 30% decrease in the sum of the diameters of target lesions, taking as reference the baseline sum of 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. If a subject is missing lesion data at a disease assessment and yet progressive disease criteria is met despite the missing data, the subject will be classified as PD.
Stable Disease (SD)	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD
Not Evaluable (NE)	When inadequate or no imaging/measurement is done at a particular time point, the subject's response is not evaluable (NE) at that time point.

Table 11-5. Evaluation of Non-target Lesions

Complete Response (CR):	Disappearance of all non-nodal non-target lesions and normalization of tumor marker level. All non-target lymph nodes must be non-pathological in size (< 10 mm short axis).
Non-CR/Non-PD	Persistence of one or more non-target lesions(s) and/or maintenance of tumor marker level above the normal limits.
Progressive Disease (PD)	Unequivocal progression of existing non-target lesions[a]. If a subject is missing lesion data at a disease assessment and yet unequivocal progression is met despite the missing data, the subject will be classified as PD.
Not Evaluable (NE)	When inadequate or no imaging is done at a particular time point, the subject's response is not evaluable (NE) at that time point.

SD = Stable Disease; PR = partial response.
[a] To achieve "unequivocal progression" on the basis of the non-target disease, there must be an overall level of substantial worsening in non-target disease such that, even in presence of SD or PR in target disease, the overall tumor burden has increased sufficiently to merit discontinuation of therapy. A modest "increase" in the size of 1 or more non-target lesions is usually not sufficient to qualify for unequivocal progression status.

11.9.5 Evaluation of Best Overall Response

The subject's best response assignment will depend on the findings of both target and non-target disease and will also take into consideration the appearance of new lesions. Best overall response (BOR) will be based on all post-baseline disease assessments that occur prior to the initiation of subsequent anticancer treatment. At least 5 weeks from the first dose of investigational product must elapse without radiological disease progression to meet the minimum criteria for stable disease (SD) duration in order to assign a BOR of SD. In general, subjects not classifiable under the RECIST v1.1 response categories due to inadequate data or early death will be classified as non evaluable (NE) for BOR but will be counted in the denominator of all response rate calculations.

Table 11-6. Time Point Overall Response

Target Lesions	Non-target Lesions	New Lesions	Overall Response
Subjects with Target (± Non-target) Disease			
CR	CR or NA	No	CR
CR	Non-CR/non-PD or NE	No	PR
PR	CR or Non-CR/Non-PD or NE or NA	No	PR
SD	CR or Non-CR/Non-PD or NE or NA	No	SD
PD	Any	Any	PD
Any	PD	Any	PD
Any	Any	Yes	PD
NE	CR or Non-CR/Non-PD or NE or NA	No	NE
Subjects with Non-target Disease Only			
NA	CR	No	CR
NA	Non-CR/Non-PD	No	SD (Non-CR/Non-PD)[a]
NA	CR or Non-CR/Non-PD	NE	SD (Non-CR/Non-PD)[a]
NA	PD	Any	PD
NA	Any	Yes	PD
NA	NE	No	NE

CR = complete response; PD = progressive disease; PR = partial response; NA = not applicable; NE = Not evaluable; SD = stable disease.

[a] Per RECIST v1.1, "SD (Non-CR/Non-PD)" is preferred over "SD" for Non-Target disease since SD is increasingly used as endpoint for assessment of efficacy in some trials so to assign this category when no lesions can be measured is not advised.

Table 11-7. Best Overall Response When Confirmation of Complete Response (CR) and Partial Response (PR) Required

Overall Response First Time Point	Overall Response Second Time Point	Best Overall Response
CR	CR	CR
CR	PR	SD, PD or PR[a]
CR	SD	SD provided minimum criteria for SD duration met, otherwise, PD
CR	PD	SD provided minimum criteria for SD duration met, otherwise, PD
CR	NE	SD provided minimum criteria for SD duration met, otherwise, NE
PR	CR	PR
PR	PR	PR
PR	SD	SD
PR	PD	SD provided minimum criteria for SD duration met, otherwise, PD
PR	NE	SD provided minimum criteria for SD duration met, otherwise, NE
NE	NE	NE

CR = complete response; PD = progressive disease; PR = partial response; NE = Not evaluable; SD = stable disease.

[a] If a CR is truly met at first time point, then any disease at a subsequent time point, even disease meeting PR criteria relative to baseline, makes the disease PD at that point (since disease must have reappeared after CR). Best response would depend on whether minimum duration for SD was met. However, sometimes "CR" may be claimed when subsequent scans suggest small lesions were likely still present and in fact that subject had PR, not CR at the first time point. Under these circumstances, the original CR should be changed to PR and the best response is PR.

11.9.6 Special Notes on Response Assessment

- Target lesions that become "too small to measure" - While on study, all lesions (nodal and non-nodal) recorded at baseline should have their measurements recorded at each subsequent evaluation, even when very small (eg, 2 mm). However, sometimes lesions or lymph nodes which are recorded as target lesions at baseline become so faint on CT scan that the radiologist may not feel comfortable assigning an exact measure and may report them as being 'too small to measure'. When this occurs, it is important that a value be recorded on the case report form. If it is the opinion of the radiologist that the non-lymph node lesion has likely disappeared, the measurement should be recorded as 0 mm. If the lesion is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned (Note: It is less likely that this rule will be used for lymph nodes since they usually have a definable size when normal and are frequently surrounded by fat such as in the retroperitoneum; however, if a lymph node is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned in this circumstance as well). This default value is derived from the 5 mm CT slice thickness (but should not be changed with varying CT slice thickness). The measurement of these lesions is potentially non-reproducible, therefore providing this default value will prevent false responses or progressions based upon measurement

error. To reiterate, however, if the radiologist is able to provide an accurate measure, that should be recorded, even if it is below 5 mm.

- New lesions - The term “new lesion” always refers to the presence of a new finding that is definitely tumor. If a new lesion is identified via a modality other than CT or MRI, CT or MRI confirmation is recommended unless the new lesion is deemed unequivocally tumor. New findings that are not definitively tumor but may be benign (infection, inflammation, etc.) are not selected as new lesions, until that time when the review is certain they represent tumor.
  - If a new lesion is equivocal, for example because of its small size, continued therapy and follow-up evaluation will clarify if it represents truly new disease. If additional imaging confirms there is definitely a new lesion, then progression should be declared using the date of the initial scan.
  - A lesion identified on a follow-up study in an anatomical location that was not scanned at baseline is considered a new lesion and will indicate disease progression, regardless of any response that may be seen in target or non-target lesions present from baseline.
- 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.
- Lesions that split or coalesce on treatment - When non-nodal lesions "fragment," the longest diameters of the fragmented portions should be added together to calculate the target lesion sum and identified as a fragment of the original lesion. Similarly, as lesions coalesce, a plane between them may be maintained that would aid in obtaining maximal diameter measurements of each individual lesion. If the lesions have truly coalesced such that they are no longer separable, the vector of the longest diameter in this instance should be the maximal longest diameter for the "coalesced lesion".
- “Symptomatic deterioration” alone does not qualify as objective progression. If objective progression was not previously documented, then every effort should be made to document objective progression even after discontinuation of treatment.
- In some circumstances it may be difficult to distinguish residual disease from scar or normal tissue. When the evaluation of CR depends on this determination, it is recommended that the residual lesion be further investigated by fine needle aspirate/biopsy or FDG-PET, to confirm the CR status.
- If a lesion disappears and reappears at a subsequent timepoint it should continue to be measured. However, the patient’s response at the point in time when the lesion reappears will depend upon the status of his/her other lesions. For example, if the patient’s tumor had reached a CR status and the lesion reappeared, then the patient would be considered PD at the time of reappearance. In contrast, if the tumor status was a PR or SD and 1 lesion which had disappeared then reappears, its maximal diameter should be added to the sum of the remaining lesions for a calculated response: in other words, the reappearance of an apparently ‘disappeared’ single

lesion amongst many which remain is not in itself enough to qualify for PD: that requires the sum of all lesions to meet the PD criteria.

11.10 Appendix 10. ECOG Performance Status and NYHA Classification

Eastern Cooperative Oncology Group (ECOG) Performance Scale

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

Source: Oken et al, 1982.

New York Heart Association Functional Classification

Class I — No limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, or dyspnea.

Class II — Slight limitation of physical activity. Comfortable at rest, but ordinary physical activity results in fatigue, palpitation, or dyspnea.

Class III — Marked limitation of physical activity. Comfortable at rest, but less than ordinary activity causes fatigue, palpitation, or dyspnea.

Class IV — Unable to carry out any physical activity without discomfort. Symptoms of cardiac insufficiency may be present even at rest. If any physical activity is undertaken, discomfort is increased.

11.11 Appendix 11. Ocular Toxicity Grading

Table 11-8. Ocular Toxicity Grading

Corneal Event	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**
Corneal punctate epitheliopathy*	Mild[a](non confluent) AND worsening from baseline	Moderate[b] (non-confluent) AND worsening from baseline	Severe[c] (confluent) AND worsening from baseline	NA
Corneal epithelial defect	NA	<3mm in largest diameter	≥3mm in largest diameter	Persistent epithelial defect (any size)
Ulcerative keratitis	NA	NA	Corneal ulcer without perforation in the affected eye	Perforation in the affected eye
Limbal stem cell dysfunction/deficiency	NA	NA	Any presence	NA
Decrease in visual acuity (corneal-related)[d]	1 - 2 lines of decreased vision from baseline	3 - 4 lines of decreased vision from baseline	5 - 6 lines of decreased vision from baseline	> 6 lines of decreased vision from baseline
Retinal Events	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**
Retinal tear	No retinal detachment and treatment not indicated	No retinal detachment and treatment indicated	NA	NA
Retinal detachment	NA	NA	Macular sparing rhegmatogenous detachment	Macula-off rhegmatogenous retinal detachment
Retinal pigment epithelial detachment	NA	Not involving the macula	Macula involving	NA
Retinal vascular disorders	NA	Retinal vascular disorder without neovascularization	Retinal vascular disorder with neovascularization	NA

Other ocular events	Grade 1	Grade 2	Grade 3	Grade 4
All other adverse ocular events, specify[d]	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated; 1 - 2 lines of decreased vision from baseline	Moderate; minimal, local,Q or noninvasive intervention indicated; limiting instrumental ADL: 3 - 4 lines of decreased vision from baseline	Severe or medically significant but not immediately sight-threatening; limiting self-care ADL; 5 - 6 lines of decreased vision from baseline	Sight-threatening consequences; urgent intervention indicated; > 6 lines of decreased vision from baseline

ADL = activities of daily living
* May include punctate keratitis, punctate epithelial erosions (PEE)
[a] Equivalent to +1 fluorescein staining
[b] Equivalent to +2 fluorescein staining
[c] Equivalent to +3-4 fluorescein staining
[d] For guidance on selecting the number of lines in decreased vision from baseline, please refer to Table 11.12. LogMAR Conversion Table for Visual Acuity.

11.12 Appendix 12. LogMAR Conversion Table for Visual Acuity*

Snellen Notation				Decimal Notation (eg, Landolt C or Han Chun Suk)	Visual Angle Notation (min of arc)	LogMAR
20 ft	6 m	5 m	4 m			
20/10	6/3	5/2.5	4/2	2.00	0.50	-0.30
20/15	6/4.5	5/3.75	4/3	1.33	0.75	-0.12
20/20	6/6	5/5	4/4	1.00	1.00	0.00
20/25	6/7.5	5/6.25	4/5	0.80	1.25	+0.10
20/30	6/9	5/7.5	4/6	0.67	1.50	+0.18
20/40	6/12	5/10	4/8	0.50	2.00	+0.30
20/50	6/15	5/12.5	4/10	0.40	2.50	+0.40
20/70	6/21	5/17.5	4/14	0.29	3.50	+0.54
20/100	6/30	5/25	4/20	0.20	5.00	+0.70
20/200	6/60	5/50	4/40	0.10	10.00	+1.00
20/400	6/120	5/100	4/80	0.05	20.00	+1.30
20/800	6/240	5/200	4/160	0.03	40.00	+1.60

*Visual acuity must be tested with the patient's prescribed lenses, as applicable. If the precise visual acuity result is not depicted on this table, please choose the closest value. If the result is equidistant between two values on this table, please choose the worse visual acuity line. For example, if the visual acuity using Landolt C is 0.90 (decimal notation), this is halfway between Snellen 20/20 (1.00 in decimal notation) and 20/25 (0.80 in decimal notation), and therefore the examiner would select 20/25, with corresponding logMAR of +0.10.
Source: https://www.aao.org/bcscsnippetdetail.aspx?id=3550b1ca-1740-4e7f-8712-70905c99eb26

11.13 Appendix 13. Country-specific Requirements

This appendix provides language for country-specific changes in the execution of the study in accordance with local regulatory requirements.

The summary of changes outlined below specify requirements for sites and subjects participating in the European Union. The country specific requirements for Japan will be outlined in a separate country specific supplement.

Table 11-9. Poland Summary of Changes

Protocol Section	Text in Protocol	Text For Poland
Section 11.2, Appendix 2. Clinical Laboratory Tests, Table 11-1. Analyte Listing, Chemistry	Bicarbonate or carbon dioxide	Add: Bicarbonate or carbon dioxide **(Optional)**

Table 11-10. France Summary of Changes

Protocol Section	Text in Protocol	Text for France
Section: 5.1, Inclusion Criteria, Criterion #102	Age ≥ 18 years old (or legal adult within country, whichever is older) at the time that the Informed Consent Form (ICF) is signed	Added: Age ≥ 18 years old (or legal adult within country, whichever is older)**, is not considered vulnerable per local regulations (ie, under guardianship, curatorship, or safeguard of justice) and/or is affiliated to a social security scheme (if applicable)** at the time that the Informed Consent Form (ICF) is signed
Section: 5.1, Inclusion Criteria, Criterion #107	Subject may or may not have received prior therapy for locally advanced and unresectable or metastatic disease depending on the study Part. • For Parts 1 and 2, subjects may have progressed on, or recurred after at least 1 prior systemic therapy.	Replaced: Subject may or may not have received prior therapy for locally advanced and unresectable or metastatic disease depending on the study Part. • For Parts 1 and 2, subjects **must** have progressed on, or recurred after at least 1 prior systemic therapy.
Section: 5.2, Exclusion Criteria, Other Medical Conditions, Criterion #204	Impaired cardiac function or clinically significant cardiac disease including: unstable angina within 6 months prior to first dose of study treatment, acute myocardial infarction < 6 months prior to first dose of study treatment, New York Heart Association (NYHA) class II-IV congestive heart failure,	Added: Impaired cardiac function or clinically significant cardiac disease including: unstable angina within 6 months prior to first dose of study treatment, acute myocardial infarction < 6 months prior to first dose of study treatment, New York Heart Association (NYHA) class II-IV congestive heart failure, uncontrolled hypertension (defined as an average systolic blood pressure > 160 mmHg or

	uncontrolled hypertension (defined as an average systolic blood pressure > 160 mmHg or diastolic > 100 mm Hg despite optimal treatment, uncontrolled cardiac arrythmias requiring anti-arrhythmic therapy other than beta blockers or digoxin, active coronary artery disease, Fridericia's correction formula (QTc) ≥ 470.	diastolic >100 mm Hg despite optimal treatment, uncontrolled cardiac arrythmias requiring anti-arrhythmic therapy other than beta blockers or digoxin, active coronary artery disease, Fridericia's correction formula **for men, subjects with corrected QT interval (QTc) ≥ 450 will be excluded; whereas for women, subjects with** QTc ≥ 470 **will be excluded.**
Section: 5.2, Exclusion Criteria, Prior/Concomitant Therapy, Criterion #217	Any anticancer therapy or immunotherapy within 4 weeks prior to enrollment; • Palliative radiotherapy is allowed, provided it has been completed more than 14 days prior to the first dose of study treatment • All treatment-related toxicity needs to be resolved to grade ≤ 1 prior the first dose of study treatment, with exception of alopecia or toxicities considered irreversible (defined as having been present and stable > 21 days) which are not otherwise described in the exclusion criteria • Exception for Part 2 and 4 expansion only: subjects can receive 1 dose of each non-investigational anticancer therap(ies) in the respective study part, if initiation of treatment is deemed urgent by the investigator	Replaced: Any anticancer therapy or immunotherapy within 4 weeks prior to enrollment; • Palliative radiotherapy is allowed, provided it has been completed more than 14 days prior to the first dose of study treatment • **The maximal grade for irreversible** toxicities **to be considered for participation is grade 3.** All **subjects with grade 2 or 3 toxicities from prior anti-cancer therapy that are** considered irreversible (defined as having been present and stable **for ≥ 5 months) may be allowed if** not otherwise described in the exclusion criteria, **and if there is an agreement to allow participation of those subjects by both the investigator and the sponsor.** • Exception for Part 2 and 4 expansion only: subjects can receive 1 dose of each non-investigational anticancer therap(ies) in the respective study part, if initiation of treatment is deemed urgent by the investigator
Section: 6.2.1. Dose Cohort Study Escalation/De-escalation and Stopping Rules, Enrollment Stopping Rules	• At any point during the study, throughout Parts 1, 2, 3, and 4, enrollment will be paused at the occurrence of 2 or more grade 4 or one or more grade 5 adverse events unless the events are clearly attributed to causes other than bemarituzumab. If limited information is available at the time the	Replaced: At any point during the study, throughout Parts 1, 2, 3, and 4, enrollment will be paused at the occurrence of 2 or more grade 4 or one or more grade5 adverse events unless the events are clearly attributed to causes other than **the investigational intervention of bemarituzumab alone or** bemarituzumab **in combination with other anti-cancer therapies.** If limited

	investigator reports the event to the sponsor, enrollment may continue while the sponsor collects additional information about the grade 4 or 5 event to determine the underlying cause. The DLRT will be reconvened to review the safety data and determine appropriate next steps that may include, but not be limited to, informing investigators and IRBs/IECs, implementing safety/toxicity management, informing health authorities, voluntarily putting the clinical trial on hold, or proceeding with enrollment.	information is available at the time the investigator reports the event to the sponsor, enrollment may continue while the sponsor collects additional information about the grade 4 or 5 event to determine the underlying cause. The DLRT will be reconvened to review the safety data and determine appropriate next steps that may include, but not be limited to, informing investigators and IRBs/IECs, implementing safety/toxicity management, informing health authorities, voluntarily putting the clinical trial on hold, or proceeding with enrollment. **Events commonly associated with non-investigational therapy (see below for examples) or progression of underlying disease and investigator assessed as not possibly related to bemarituzumab will not count towards enrolment stopping rules.** **Examples of events commonly associated with non-investigational therapies in this study:** • **In Parts 1 and 2, events commonly associated with docetaxel: hematologic toxicity (neutropenia, anemia, thrombocytopenia), severe fluid retention, enterocolitis, peripheral neuropathy.** • **In Part 4, events commonly associated with the combination of pembrolizumab, carboplatin, and nab-paclitaxel/paclitaxel: hematologic toxicity (neutropenia, anemia, thrombocytopenia) and immune related adverse events (pneumonitis, colitis, nephritis, endocrinopathies).**
Section: 6.7.2, Concomitant Treatment, Paragraph 5 (new)	Not applicable.	Added: **Investigators should refer to the local prescribing information (in particular contraindications, warnings and precautions) of any protocol-required therapies when considering the use of concomitant medication (eg, for carboplatin caution should be used when considering concomitant phenytoin, fosphenytoin, loop**

	diuretics, and other potentially nephrotoxic or ototoxic drugs).

Amendment 3

Protocol Title: A Phase 1b Study Evaluating the Safety, Tolerability, Pharmacokinetics, and Efficacy of Bemarituzumab Monotherapy and Combination with other Anti-Cancer Therapy in Subjects with Squamous-Cell Non-Small-Cell Lung Cancer (FORTITUDE-201)

Amgen Protocol Number (Bemarituzumab [AMG 552]) 20210102

EudraCT/EU CT number: 2021-004058-47/2023-505456-22

NCT number: NCT05267470

Amendment Date: 27 April 2023

Rationale:

Protocol is being amended to update EU CT number and include the European Economic Area (EEA) country specific supplements within the protocol appendices. The country specific supplements contain specific changes previously approved and apply only to subjects in the specified EEA country.

Superseding Amendment 2

Protocol Title: Phase 1b Study Evaluating the Safety, Tolerability, Pharmacokinetics, and Efficacy of Bemarituzumab Monotherapy and Combination with other Anti-Cancer Therapy in Subjects with Squamous-Cell Non-Small-Cell Lung Cancer (FORTITUDE-201)

Amgen Protocol Number: 20210102

EudraCT Number: 2021-004058-47

NCT Number: NCT05267470

Amendment Date: 28 October 2022

Rationale:

A superseding version of the protocol amendment 2 (PA2) was created to address typographical and orthographical errors that have been identified throughout the PA2 document:

- Updated criterion 232 in exclusion criteria section (Section 5.2) to correct immunosuppressive doses of systemic medications to more than (>)10 mg/day, rather than less than (<)10 mg/day.
- Corrected Q3W definition in schedule of activities (Section 1.3) Table 1-3

Amendment 2

Protocol Title: A Phase 1b Study Evaluating the Safety, Tolerability, Pharmacokinetics, and Efficacy of Bemarituzumab Monotherapy and Combination with Other Anti-Cancer Therapy in Subjects with Squamous-Cell Non-Small-Cell Lung Cancer (FORTITUDE-201)

Amgen Protocol Number: 20210102

EudraCT Number: 2021-004058-47

NCT Number: NCT05267470

Amendment Date: 27 September 2022

Rationale:

The key driver for this amendment is addition of the preliminary safety data from Part 1 of this study supporting further exploration of the combination of bemarituzumab with docetaxel in later lines of therapy and addition of the new part of the study, Part 4, exploring bemarituzumab in combination with double platinum-based chemotherapy and programmed death-ligand 1(PD-L1) inhibitor in first-line. Additionally, updates were incorporated that originated from a program wide update to align this protocol with other bemarituzumab protocols, where applicable. Based on this, the key revisions incorporated in the amendment are listed below, and a complete list of changes can be found in later section of this summary of change document:

- Updated overall design section of the protocol and other applicable protocol sections to reflect the addition of Part 4 of the study evaluating bemarituzumab in combination with carboplatin, paclitaxel or nab paclitaxel, and pembrolizumab in subjects with previously untreated metastatic or locally advanced squamous non-small-cell lung cancer (SqNSCLC), with consequential changes to the study schema.
- Updated study rationale and other applicable sections of the protocol to reflect information regarding bemarituzumab in combination with anti-cancer therapies.
- Updated number of subjects to be enrolled in the study from 108 to 180 with the addition of Part 4.
- Updated background information about bemarituzumab to provide most recent results of Study FPA144-004.
- Updated Benefit/Risk Assessment to reflect preliminary safety data from Part 1 supporting further exploration of bemarituzumab in combination with docetaxel at the

dose level 2 and to add a rationale supporting exploration of bemarituzumab combination with doublet platinum-based chemotherapy and PD-L1 inhibitor in first-line.

- Protocol language has been aligned, where applicable, to other ongoing bemarituzumab protocol amendments, to ensure consistency regarding applicable requirements. Updates to the protocol template have also been reflected in this amendment to ensure compliance with current regulatory requirements.
- Administration, typographical, and formatting changes were made throughout the protocol.

Amendment 1

Protocol Title: A Phase 1b Study Evaluating the Safety, Tolerability, Pharmacokinetics, and Efficacy of Bemarituzumab Monotherapy and Combination with Docetaxel in Subjects with Squamous-Cell Non-Small-Cell Lung Cancer (FORTITUDE-201)

Amgen Protocol Number Bemarituzumab 20210102

Amendment Date: 02 March 2022

Rationale:

This protocol is being amended to implement changes requested by regulatory/health authorities; and to include globally applicable changes from the French country-specific supplement (CSS), program level, and other Bema study level updates. Language is being included throughout to update/clarify the protocol. Changes including, but not limited to, the following were incorporated into the protocol:

- Updated the schedule of assessments (SoA) to specify the time at which pharmacokinetic (PK) samples are to be collected for Part 1 and 2 combinational therapies; to include inform consent language for screening of Part 1 only; to add language on reporting of during long-term follow-up (LTFU); to clarify that total cholesterol levels for the chemistry panel are required only at screening; to clarify the times pharmacokinetic samples are to be collected for Part 1 and 2 combination therapy; Additional updates to the archival tissue/fresh biopsy, vital assessments, and computerized tomography (CT)/Magnetic resonance imaging (MRI) sections in the SoA were also made.
- Updated language regarding tumor biopsy assessments, safety follow-up, and ocular toxicity grading scale in respective sections
- Updated dose-limiting toxicity (DLT) definition to specify that DLTs should be considered possibly related to study drug and not concomitant chemotherapy and disease progression or intercurrent illness
- Updated the dose modification and enrollment stopping rules
- Updated inform consent language regarding the screening process for Part 1

- Updated serious adverse events language to clarify that all serious adverse events related to the investigational product need to be recorded during LTFU and reported to Amgen
- Updated both inclusion and exclusion eligibility criteria sections
- Updated pregnancy testing language to clarify that repeat pregnancy test are required 28 (+3) days after discontinuing protocol-required therapies, and monthly (28 [± 3] days) pregnancy testing up to and inclusive 75 (+3) days from the last bemarituzumab dose
- Updated safety assessment sections to modify vital sign and ophthalmologic examination language
- Updated efficacy assessment section to remove reference to imaging manual
- Added new pharmacogenetic assessment section (section 8.6)
- Biomarker language was updated throughout various sections
- Administrative and editorial changes have been made throughout the protocol for clarification