Official Title:	**A Randomized Open-Label Phase 1/2 Study of INCB001158 Combined With Subcutaneous (SC) Daratumumab, Compared to Daratumumab SC, in Participants With Relapsed or Refractory Multiple Myeloma**
NCT Number:	NCT03837509
Document Date:	Statistical Analysis Plan: 19 April 2022

Statistical Analysis Plan

INCB 01158-206

A Randomized Open-Label Phase 1/2 Study of INCB001158 Combined With Subcutaneous (SC) Daratumumab, Compared to Daratumumab SC, in Participants With Relapsed or Refractory Multiple Myeloma

Product:	**INCB001158**
IND Number:	[redacted]
EudraCT Number:	**2018-004076-35**
Sponsor:	**Incyte Corporation** **1801 Augustine Cut-Off** **Wilmington, DE 19803** **United States**
Protocol Version:	**Protocol Amendment 3 dated 01 DEC 2021**
CRF Approval Date:	**09 JUL 2021**
SAP Version:	**Original**
SAP Author:	[redacted] [redacted]**, Biostatistics**
Date of Plan:	**19 APR 2022**

This study is being conducted in compliance with Good Clinical Practice, including the archiving of essential documents.

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LIST OF ABBREVIATIONS

Abbreviation	Term
AE	adverse event
BID	twice daily
BOIN	Bayesian optimal interval
[redacted]	[redacted]
CR	complete response
CRF	case report form
CTCAE	Common Terminology Criteria for Adverse Events
[redacted]	[redacted]
DLT	dose-limiting toxicity
[redacted]	[redacted]
DOR	duration of response
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
FAS	full analysis set
FLC	free light chain
[redacted]	[redacted]
IMiD	immunomodulatory drug
IMWG	International Myeloma Working Group
irAE	immune-related adverse event
IV	intravenous
MedDRA	Medical Dictionary for Regulatory Activities
MM	multiple myeloma
MR	minimal response
MRD	minimal residual disease
NCI	National Cancer Institute
NE	not evaluable
[redacted]	[redacted]
ORR	objective response rate
OS	overall survival
PC	plasma cell
PD	progressive disease
PFS	progression-free survival
PI	proteasome inhibitor

Abbreviation	Term
[redacted]	[redacted]
PO	orally
PR	partial response
PT	preferred term
QTcF	QT interval corrected using Fridericia's formula
RAR	response adaptive randomization
R-ISS	Revised International Staging System
RP2D	recommended Phase 2 dose
SAP	Statistical Analysis Plan
SC	subcutaneous
sCR	stringent complete response
SD	stable disease
SI	Standard International
[redacted]	[redacted]
SOC	system organ class
SPD	sum of the products of the maximal perpendicular diameters of measured lesions
TEAE	treatment-emergent adverse event
[redacted]	[redacted]
TTR	time to response
[redacted]	[redacted]
VGPR	very good partial response
WHO	World Health Organization

1. INTRODUCTION

This is an open-label, dose-escalation Phase 1 and randomized Phase 2 study to evaluate the safety and antitumor activity of INCB001158 in combination with daratumumab SC, compared with daratumumab SC alone, in participants with relapsed or refractory MM who have received at least 3 prior lines (including IMiD, PI, and anti-CD38 therapies) but not more than 5 prior lines of therapy.

Phase 1 will consist of dose-escalation using a BOIN design and will determine the RP2D of INCB001158 in combination with daratumumab SC; efficacy will also be explored.

Phase 2 will consist of a randomized expansion phase to compare the RP2D of INCB001158 in combination with daratumumab SC to daratumumab SC alone using an RAR design. INCB001158 monotherapy will also be explored.

Section 2 of the Protocol provides a detailed description of the investigational products INCB001158 and daratumumab SC, target patient population, rationale for doses to be examined, and potential risks and benefits of treatment with INCB001158 and daratumumab SC.

The purpose of this SAP is to provide details of the statistical analyses that have been outlined in the INCB 01158-206 Protocol. [redacted]

2. STUDY INFORMATION, OBJECTIVES, AND ENDPOINTS

2.1. Protocol and Case Report Form Version

This SAP is based on INCB 01158-206 Protocol Amendment 3 dated 01 DEC 2021 and CRFs approved 09 JUL 2021. Unless superseded by an amendment, this SAP will be effective for all subsequent Protocol amendments and eCRF versions.

2.2. Study Objectives and Endpoints

Table 1 presents the objectives and endpoints.

Due to early termination decision following recruitment challenge (no safety-related concerns), primary safety analyses but no efficacy analyses will be performed due to insufficient number of participant enrolled in Phase 2.

Table 1: Objectives and Endpoints

Objectives	Endpoints
Primary	
Phase 1: To determine the safety, tolerability, and RP2D of INCB001158 in combination with daratumumab SC.	Safety and tolerability determined by monitoring the frequency, duration, and severity of AEs.
Phase 2: To compare the ORR of the RP2D of INCB001158 in combination with daratumumab SC to daratumumab SC monotherapy.	ORR, defined as the proportion of participants with a documented response PR or better, as per IMWG criteria.
Secondary	
Phase 1: To determine the efficacy of INCB001158 in combination with daratumumab SC.	ORR, defined as the proportion of participants with a documented response PR or better, as per IMWG criteria.
Phase 2: To determine the safety and tolerability of INCB001158 monotherapy at RP2D, and to compare the safety and tolerability and RP2D of INCB001158 in combination with daratumumab SC to daratumumab SC monotherapy	Safety and tolerability determined by monitoring the frequency, duration, and severity of AEs.
Phase 1: To determine the efficacy of INCB001158 in combination with daratumumab SC. **Phase 2:** To estimate the efficacy of INCB001158 monotherapy, and to compare the efficacy of INCB001158 in combination with daratumumab SC to daratumumab SC monotherapy.	• TTR, defined as the time from the first dose of study drug to the first documented response PR or better, as per IMWG criteria. • DOR, defined as time from first documented response PR or better, as per IMWG criteria, until date of disease progression or death, whichever occurs first. • PFS, defined as the duration from the date of first dose of study drug until either PD, as per IMWG criteria, or death, whichever occurs first. • MRD, defined as the percentage of MRD-negative participants. • OS, defined as the time from the first dose of study drug to death from any cause.

Table 1: Objectives and Endpoints (Continued)

Objectives	Endpoints
[redacted]	

3. STUDY DESIGN

This is an open-label, dose-escalation Phase 1 and randomized Phase 2 study to evaluate the safety and antitumor activity of INCB001158 in combination with daratumumab SC, compared with daratumumab SC alone, in participants with relapsed or refractory MM who have received at least 3 prior lines (including IMiD, PI, and anti-CD38 therapies) but not more than 5 prior lines of therapy.

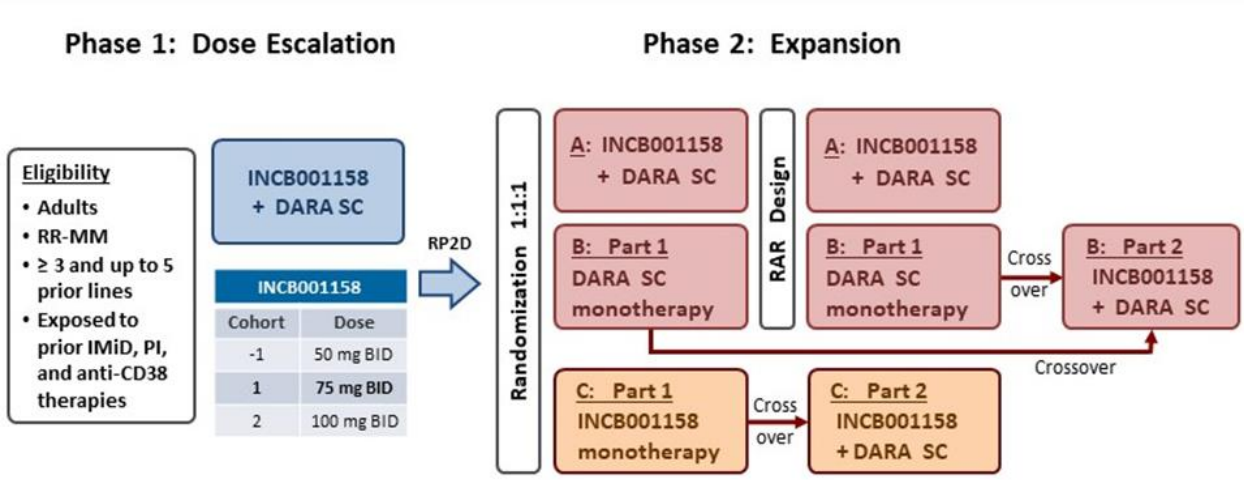
Phase 1 will consist of dose-escalation using a BOIN design and will determine the RP2D of INCB001158 in combination with daratumumab SC; efficacy will also be explored.

Phase 2 will consist of a randomized expansion phase to compare the RP2D of INCB001158 in combination with daratumumab SC to daratumumab SC alone using an RAR design. INCB001158 monotherapy will also be explored.

As a result of an early-termination decision following a recruitment challenge (no safety-related concerns), primary safety analyses but no efficacy analyses will be performed due to an insufficient number of participants enrolled in Phase 2.

The study design schema is presented in Figure 1.

Figure 1: Study Design Schema



3.1. Randomization

Refer to Protocol Amendment 3 dated 01 DEC 2021 for a full description of randomization.

3.2. Control of Type I Error

Refer to Protocol Amendment 3 dated 01 DEC 2021 for a full description of control of Type I error.

3.3. Sample Size Considerations

Refer to Protocol Amendment 3 dated 01 DEC 2021 for a full description of the sample size considerations.

3.4. Schedule of Assessments

Refer to Protocol Amendment 3 dated 01 DEC 2021 for a full description of all study procedures and assessment schedules for this study.

4. DATA HANDLING DEFINITIONS AND CONVENTIONS

The term "study drug" refers to INCB001158 only, and "study treatment" refers to INCB001158, daratumumab SC, or the combination of INCB001158 and daratumumab SC.

4.1. Scheduled Study Evaluations and Study Periods

4.1.1. Day 1

Day 1 is the date that the first dose of study treatment (INCB001158 or daratumumab SC) is administered to the participants.

4.1.2. Study Day

If a visit/reporting date is on or after Day 1, then the study day at the visit/reporting date will be calculated as

Day # = (visit/reporting date – Day 1 date + 1).

If the visit/reporting date is before Day 1, then the study day at the visit/reporting date will be calculated as

Day # = (visit/reporting date – Day 1 date).

A study day of –1 indicates 1 day before Day 1.

4.1.3. Baseline Value

Baseline is the last nonmissing measurement obtained before the first administration of study treatment (INCB001158 or daratumumab SC), unless otherwise defined.

When scheduled assessments and unscheduled assessments occur on the same day and the time of the assessment or time of first dose is not available, use the following convention to determine baseline:

- If both a scheduled and an unscheduled visit are available on the day of the first dose and the time is missing, use the scheduled assessment as baseline.
- If all scheduled assessments are missing on the day of the first dose and an unscheduled assessment is available, use the unscheduled assessment as baseline.

4.1.4. Handling of Missing and Incomplete Dates

In general, values for missing dates will not be imputed unless methods for handling missing dates are specified in this section or relevant sections. The original reported dates collected on the eCRF should be used in all relevant listings. The following rules will be used for handling partial dates for analyses requiring dates.

A partial disease diagnosis date will be handled as follows in calculations:

- If only the day is missing, then the first day of the month will be used.
- If both the month and day are missing, then 01 JAN of the year will be used.
- If the diagnosis date is completely missing, then no imputation will be done.

A missing or partial date of the last dose will be handled as follows:

- If only the day is missing, then the earlier date of the last day of the month or the date that the participant discontinued treatment will be used.
- If both the month and day are missing, then the earlier date of 31 DEC of the year or the date that the participant discontinued treatment will be used.
- Otherwise, the date that the participant discontinued treatment will be used as the date of the last dose.

For relevant efficacy endpoints, a partial date of the death date will be handled as follows in the calculation:

- If mmyyyy for the last known alive date = mmyyyy for the death date, then the death date will be set to the day after the last known alive date.
- If mmyyyy for the last known alive date < mmyyyy for the death date, then the death date will be set to the first day of the death month.
- Otherwise, the partial death date will not be imputed.

4.1.5. Cycle Length and Duration

Cycle 1 Day 1 is the day that the first dose of study treatment is administered. The scheduled cycle length is 28 days. INCB001158 will be administered on a continuous dose schedule.

Daratumumab SC administration will be once weekly for Cycles 1 and 2, once every 2 weeks for Cycles 3 to 6, and once every 4 weeks thereafter.

The estimated duration of study participation contains up to 28 days for screening, continuous treatment in consecutive 28-day cycles as long as participants are receiving benefit and have not met any criteria for study withdrawal, and every 8 to 12 weeks for follow-up.

4.2. Variable Definitions

The following variables will only be calculated if not reported on the eCRF.

4.2.1. Prior and Concomitant Medication

Prior medication is defined as any nonstudy medication started before the first dose of INCB001158 or daratumumab SC.

Concomitant medication is defined as any nonstudy medication that is started accordingly:

- Before the date of first administration of INCB001158 or daratumumab SC and is ongoing throughout the study or ends on/after the date of first study drug administration.
- On/after the date of first administration of INCB001158 or daratumumab SC and is ongoing or ends during the course of study.

A prior medication could also be classified as "both prior and concomitant medication" if the end date is on or after first dose of INCB001158 or daratumumab SC. In the listing, it will be indicated whether a medication is only prior, only concomitant, or both prior and concomitant.

For the purposes of analysis, all medications will be considered concomitant medications unless the medications can unequivocally be defined as not concomitant.

Additional rules that will be applied for the analysis and classification of prior and concomitant medications are given below:

- Consider the following cases as prior medication.
  - The end date is before the first dose date.
  - If the day of end date is missing, and the last day of the month is before the first dose date.
  - If the month of end date is missing, and the last day of the year is before the first dose date.
- Consider the following cases as concomitant medication.
  - The start date is after the first dose date.
  - If the day of start date is missing, and the first day of the month is on or after the first dose date.
  - If the month of start date is missing, and the first day of the year is on or after the first dose date.
- All other cases will be considered as both prior and concomitant medication.

5. STATISTICAL METHODOLOGY

5.1. General Methodology

Unless otherwise noted, SAS® software (SAS Institute Inc, Cary, NC; v9 or later) will be used for the generation of all tables, graphs, and statistical analyses. Descriptive summaries for continuous variables will include but not be limited to the number of observations, mean, standard deviation, median, minimum, and maximum. Descriptive summaries for categorical variables will include the number and percentage of participants in each category.

Interim analyses are planned for this study as defined in Section 9.

5.2. Study Phases and Treatment Groups

All summaries will be presented by dose level for Phase 1 and by treatment group for Phase 2. Note that separate listings will be provided for Phase 1 and Phase 2.

5.2.1. Phase 1: Dose Escalation

In Phase 1, INCB001158 (50-100 mg PO BID) in combination with daratumumab SC will be administrated in 28-day treatment cycles.

5.2.2. Phase 2: Expansion

Participants will be randomized 1:1:1 to Treatment Groups A, B, or C as follows:

- Treatment Group A: INCB001158 + daratumumab SC
- Treatment Group B: daratumumab SC monotherapy (Part 1), then crossover to INCB001158 + daratumumab SC (Part 2)
- Treatment Group C: INCB001158 monotherapy (Part 1), then crossover to INCB001158 + daratumumab SC (Part 2)

Treatments will be administrated in 28-day cycles for Treatment Groups A, B, and C.

5.3. Analysis Populations

5.3.1. Enrolled

This population will include all participants who sign the ICF.

5.3.2. Full Analysis Set

The FAS will include all participants who received at least 1 dose of INCB001158 or daratumumab SC. Participants will be analyzed according to the treatment to which they have been initially assigned.

This population will be used for summaries of demographics, baseline characteristics, participant disposition, safety, and exposure.

5.3.3. DLT Evaluable Population for Phase 1

The DLT evaluable population includes participants who have received at least 42 of 56 doses for the 28-day cycle regimen (representing ≥ 75% of the dose planned) of INCB001158 or who have a DLT.

Note that the DLT evaluable population will exclude participants in the randomized part (Phase 2) of the study.

6. BASELINE, EXPOSURE, AND DISPOSITION

Appendix A provides a list of data displays. Sample data displays are included in a separate document.

All summaries will be presented by dose level for Phase 1 and by treatment group for Phase 2.

6.1. Demographics, Baseline Characteristics, and Disease History

6.1.1. Demographics and Baseline Characteristics

The following demographics and baseline characteristics will be summarized for the FAS: age, sex, race, ethnicity, weight, and height.

6.1.2. Baseline Disease Characteristics and Disease History

The following baseline disease characteristics and disease history will be summarized for the FAS: ECOG performance status, time since diagnosis, Durie Salmon stage of initial diagnosis, R-ISS stage at initial diagnosis, Durie Salmon stage of current diagnosis, R-ISS stage at current diagnosis, and current myeloma type.

Time since diagnosis will be calculated as follows:

Time since diagnosis (years) = (Day 1 date – date of diagnosis + 1) / 365.25.

6.1.3. Prior Therapy

The number of prior therapy regimens for the disease under study will be summarized for all participants in the FAS. The component drugs of prior therapy regimens will be coded using the WHO Drug Dictionary. The number and percentage of participants who received each drug will be summarized by WHO drug class and WHO drug preferred term. The regimen name, component drugs, start and stop dates, purpose of the regimen, best response, reason for discontinuation, and date of relapse/progression will be listed.

The number of participants who received prior radiation will be summarized for the FAS. The radiotherapy type, body site, and start and stop dates will be listed.

The number of participants who had prior surgery or surgical procedure for the malignancies under study will be summarized for the FAS. The date and description of the surgery/procedure will be listed.

6.1.4. Medical History

For participants in the FAS, medical history will be summarized. This summary will include the number and percentage of participants with medical history events for each body system/organ class as documented on the eCRF.

6.2. Disposition of Participants

The number and percentage of participants who were screened, who failed screening, who were enrolled, who were treated, who were ongoing with study treatment, who completed study treatment, who discontinued study treatment with a primary reason for discontinuation, who were still in the study, who completed the study, and who withdrew from the study with a primary reason for withdrawal will be summarized for the FAS. The number of participants enrolled by country and site will also be provided.

6.3. Protocol Deviations

Protocol deviations recorded on the eCRF will be listed.

6.4. Exposure

6.4.1. Exposure to INCB001158

For participants in the Phase 1 and Phase 2 combined FAS, exposure to INCB001158 will be summarized descriptively as the following using information entered on the Dose INCB001158 eCRF:

- **Total actual dose (mg):** total actual dose taken of INCB001158.
- **Duration of treatment (days):** date of last dose of INCB001158 – date of first dose of INCB001158 + 1.
- **Average daily dose (mg):** total actual INCB001158 dose taken (mg) divided by the duration of treatment with INCB001158 (days).

6.4.2. Exposure to Daratumumab SC

For participants in the Phase 1 and Phase 2 combined FAS, exposure to daratumumab SC will be summarized descriptively as the following using information entered on the Daratumumab Dosing eCRF:

- **Number of infusions:** number of administered, nonzero infusions of daratumumab.
- **Average dose (mg):** total actual daratumumab dose (mg) divided by the number of infusions of daratumumab.
- **Dose administered per cycle (mg):** the actual dose of daratumumab administered (mg) per cycle.

6.5. Study Drug Compliance

For participants in the FAS, overall compliance (%) for INCB001158 will be calculated as follows:

overall compliance (%) = 100 × [total dose actually taken] / [total prescribed dose].

The total prescribed dose is defined as the sum of the doses prescribed by the investigator, accounting for dose modifications.

The total actual dose taken will be calculated based on information entered on the Drug Accountability eCRF. If there are dispensed drugs that have not been returned yet, the actual dose taken starting from the dispense date of the unreturned drugs will be imputed by the dose taken as reported on the Dose INCB001158 eCRF.

6.6. Prior and Concomitant Medication

Prior medications and concomitant medications will be coded using the WHO Drug Dictionary. The number and percentage of participants in the FAS for each prior and concomitant medication will be summarized by WHO drug class and PT.

A listing of post-treatment anticancer treatments will also be provided.

7. EFFICACY

Appendix A provides a list of data displays. Sample data displays are included in a separate document.

7.1. General Considerations

The primary endpoint of the Phase 2 portion of the Protocol is ORR, defined as the proportion of participants with CR, VGPR, or PR, according to IMWG criteria in the randomized FAS. Due to the small sample size of participants enrolled in Phase 2 at the time of study termination, only listings of the efficacy data will be provided.

7.2. Efficacy Hypotheses

As a result of an early-termination decision following a recruitment challenge (no safety-related concerns), efficacy analyses will not be performed due to an insufficient number of participants enrolled in Phase 2. Listings of the efficacy data will be provided for participants in Phase 1 and Phase 2. Details of the efficacy hypotheses may be found in the Protocol.

7.3. Analysis of the Efficacy Parameters

7.3.1. Primary Efficacy Analysis

Objective response rate is defined as the proportion of participants with at least 1 confirmed response of CR, VGPR, or PR, according to IMWG criteria.

Objective response rate in Phase 2 was the planned primary endpoint. Due to the small number of participants in Phase 2, only listings of the response assessment data will be provided. Therefore, ORR will not be calculated and will not be presented in the CSR.

The IMWG criteria are presented in Table 2. Per IMWG uniform response criteria, all response categories and PD require 2 consecutive assessments except for radiographic or bone marrow assessments. If a participant discontinues treatment without a PD, receives a subsequent anticancer therapy and then responds, this will not be included as a responder for ORR.

Table 2: International Uniform Response Criteria Consensus Recommendations

Response	Response Criteria
sCR	• CR as defined below, plus • Normal FLC ratio, and • Absence of clonal PCs by immunohistochemistry, immunofluorescence,[a] or 2- to 4-color flow cytometry
CR[b]	• Negative immunofixation on the serum and urine, and • Disappearance of any soft tissue plasmacytomas, and • < 5% PCs in bone marrow
VGPR[b]	• Serum and urine M-component detectable by immunofixation but not on electrophoresis, or • ≥ 90% reduction in serum M-protein plus urine M-protein < 100 mg/24 hours

Table 2: International Uniform Response Criteria Consensus Recommendations (Continued)

Response	Response Criteria
PR	• ≥ 50% reduction of serum M-protein and reduction in 24-hour urinary M-protein by ≥ 90% or to < 200 mg/24 hours • If the serum and urine M-protein are not measurable, a decrease of ≥ 50% in the difference between involved and uninvolved FLC levels is required in place of the M-protein criteria • If serum and urine M-protein are not measurable, and serum free light assay is also not measurable, ≥ 50% reduction in bone marrow PCs is required in place of M-protein, provided baseline bone marrow PC percentage was ≥ 30% • In addition to the above criteria, if present at baseline, a ≥ 50% reduction in the size (SPD) of soft tissue plasmacytomas is also required
MR	• ≥ 25% but ≤ 49% reduction of serum M-protein and reduction in 24-hour urine M-protein by 50% to 89% • In addition to the above criteria, if present at baseline, 25% to 49% reduction in the size of soft tissue plasmacytomas is also required • No increase in size or number of lytic bone lesions (development of compression fracture does not exclude response)
SD	• Not meeting criteria for CR, VGPR, PR, MR, or PD
PD[c]	Increase of 25% from lowest response value in any one of the following: • Serum M-component (absolute increase must be ≥ 0.5 g/dL) • Urine M-component (absolute increase must be ≥ 200 mg/24 hours) • Only in participants without measurable serum and urine M-protein levels: the difference between involved and uninvolved FLC levels (absolute increase must be > 10 mg/dL) • Only in participants without measurable serum and urine M-protein levels and without measurable disease by FLC levels, bone marrow PC percentage (absolute percentage must be ≥ 10%) • Bone marrow PC percentage: the absolute percentage must be > 10% • Definite development of new bone lesions or soft tissue plasmacytomas or definite increase in the size of existing bone lesions or soft tissue plasmacytomas (SPD) • Development of hypercalcemia (corrected serum calcium > 11.5 mg/dL) that can be attributed solely to the PC proliferative disorder

Note: All response categories (CR, sCR, VGPR, PR, and PD) require 2 consecutive assessments made at any time before the institution of any new therapy; CR, sCR, VGPR, PR, and SD categories also require no known evidence of progressive or new bone lesions if radiographic studies were performed. VGPR and CR categories require serum and urine studies regardless of whether disease at baseline was measurable on serum, urine, both, or neither.

Note: Radiographic studies are not required to satisfy these response requirements. Bone marrow assessments need not be confirmed. For PD, serum M-component increases of more than or equal to 1 g/dL are sufficient to define relapse if starting M-component is ≥ 5 g/dL.

[a] Presence/absence of clonal cells is based upon the kappa/lambda ratio. An abnormal kappa/lambda ratio by immunohistochemistry or immunofluorescence requires a minimum of 100 PCs for analysis. An abnormal ratio reflecting presence of an abnormal clone is kappa/lambda of > 4:1 or < 1:2.

[b] Clarifications to IMWG criteria for coding CR and VGPR in participants in whom the only measurable disease is by serum FLC levels: CR in such participants indicates a normal FLC ratio of 0.26 to 1.65 in addition to CR criteria listed above. VGPR in such participants requires a > 90% decrease in the difference between involved and uninvolved FLC levels.

[c] Clarifications to IMWG criteria for coding PD: Bone marrow criteria for PD are to be used only in participants without measurable disease by M-protein and by FLC levels; "25% increase" refers to M-protein, FLC, and bone marrow results, and does not refer to bone lesions, soft tissue plasmacytomas, or hypercalcemia, and the "lowest response value" does not need to be a confirmed value.

7.3.2. Secondary Efficacy Analyses

7.3.2.1. Best Overall Response

The best overall response, according to IMWG criteria, will be listed for each participant in the FAS.

7.3.2.2. Time to Response

Time to response is defined as the number of days from the randomization in Phase 2 (or first dose of study drug in Phase 1) to the first documented response of PR, VGPR, or CR (as per IMWG criteria). Time to response will be listed for the FAS.

7.3.2.3. Duration of Response

Duration of response is defined as the number of days from earliest date of PR, VGPR, or CR (as per IMWG criteria) until the earliest date of disease progression, relapse, or death due to any cause. Duration of response will be listed for the FAS.

7.3.2.4. Progression-Free Survival

Progression-free survival is defined as the number of days from the date of first dose of study drug in Phase 1 (or from randomization date in Phase 2) until either PD, as per IMWG criteria, or death, whichever occurs first.

Censoring rules for PFS are described in Table 3.

Table 3: Evaluation and Censoring of Progression-Free Survival

Situation	Outcome	Date of Progression or Censoring
No baseline tumor assessments	Censored	Date of randomization or Day 1 (for Phase 1)
No valid postbaseline response assessments	Censored	Date of randomization or Day 1 (for Phase 1)
Progression documented between scheduled response assessments	Progressed	Date of first overall response of PD
No progression	Censored	Date of last valid efficacy/disease assessment (not NE and not missing)
Study withdrawal for undocumented progression	Censored	Date of last valid efficacy/disease assessment (not NE and not missing)
Study withdrawal for toxicity or other reason	Censored	Date of last valid radiologic assessment (not NE and not missing)
New anticancer treatment started	Censored	Date of last valid efficacy/disease assessment (not NE and not missing) on/before starting a new anticancer treatment
Death before first progressive response assessment	Progressed	Date of death
Death between adequate response assessments	Progressed	Date of death
Death or progression after 2 or more missed assessments	Censored	Date of last valid efficacy/disease assessment (not NE and not missing)

7.3.2.5. Overall Survival

Overall survival will be listed for the FAS and is defined as the number of days from randomization in Phase 2 (or first dose of study drug in Phase 1) to death due to any cause. Date of death will be determined using the Death Report, the Survival Follow-Up, and the Participant Status eCRFs. Participants who are lost to follow-up or still alive at the time of analysis will be right-censored at the earlier of the date the participant was last known alive and the clinical data cutoff date for the analysis. The last known alive date is defined as the later of the last study visit and the date the participant was last known alive from the Survival Follow-Up and Participant Status eCRFs.

8. SAFETY AND TOLERABILITY

Appendix A provides a list of data displays. Sample data displays are included in a separate document.

8.1. General Consideration

Summary tables may be replaced with listings when appropriate. For instance, an AE frequency table may be replaced with a listing if it only contains a few unique PTs reported on relatively few participants.

Unless otherwise stated, table summaries will be limited to TEAEs.

8.2. Adverse Events

8.2.1. Adverse Event Definitions

A TEAE is any AE either reported for the first time or worsening of a pre-existing event after the first dose of study drug. Analysis of AEs (as discussed below) will be limited to TEAEs, but data listings will include all AEs regardless of their timing in relation to study drug administration. For purposes of analysis, all AEs will be considered TEAEs unless the AE can unequivocally be defined as not treatment-emergent.

Adverse events will be tabulated by MedDRA PT and SOC. Severity of AEs will be graded using the NCI CTCAE v5. The CTCAE reporting guidelines and grading details are available on the Cancer Therapy Evaluation Program website.

The subset of AEs considered by the investigator to be related to study drug will be considered to be treatment-related AEs. If the investigator does not specify the relationship of the AE to study drug, the AE will be considered to be treatment-related. The incidence of AEs and treatment-related AEs will be tabulated. In addition, serious TEAEs will also be tabulated.

A grading (severity) scale is provided for each AE term. If the toxicity is not included in the CTCAE v5 criteria, it will be rated on a scale of 1 to 5 as follows: 1 = mild, 2 = moderate, 3 = severe, 4 = life threatening, and 5 = death related to AE. All toxicities will be graded based on the worst level reached, not the level they may have reached if they had not been treated. When the intensity of an AE changes over time for a reporting period (eg, between visits), each change in intensity will be collected as an AE until the event resolves. Only the worst grade will be reported in AE summaries. Also, Grade 3 or higher AEs will be summarized.

Any missing onset date, causality, or severity must be queried for resolution. Unresolved missing causality and severity will be handled according to the following rules:

- An unresolved missing causality will be considered treatment-related.
- An unresolved missing severity will be identified as an unknown severity.

8.2.2. Dose-Limiting Toxicities

Participants in the DLT evaluable population with DLTs and the type of DLT will be listed by dose level and treatment group. An AE for a participant will be identified as a DLT if the event is recorded as a Protocol-defined DLT on the Adverse Event eCRF.

8.2.3. Adverse Events of Special Interest

Adverse events of special interest include irAEs that are seen with immunotherapy and potential inhibition of the urea cycle (based on urinary orotic acid, plasma ammonia, and BUN/urea assessments).

An overall summary of irAEs will include number (%) of participants reporting any irAEs.

8.2.4. Adverse Event Summaries

An overall summary of AEs by dose level for Phase 1 and by treatment group for Phase 2 using the FAS population as applicable will include the following:

- Number (%) of participants reporting any TEAEs
- Number (%) of participants reporting any serious TEAEs
- Number (%) of participants reporting any Grade 3 or higher TEAEs
- Number (%) of participants who had a fatal TEAE
- Number (%) of participants who had a TEAE related to INCB001158
- Number (%) of participants who had a TEAE related to daratumumab SC
- Number (%) of participants who had a TEAE related to INCB001158 and/or daratumumab SC
- Number (%) of participants who had a Grade 3 or higher TEAE related to INCB001158
- Number (%) of participants who had a Grade 3 or higher TEAE related to daratumumab SC
- Number (%) of participants who had a Grade 3 or higher TEAE related to INCB001158 and/or daratumumab SC
- Number (%) of participants who had a serious TEAE related to INCB001158
- Number (%) of participants who had a serious TEAE related to daratumumab SC
- Number (%) of participants who had a serious TEAE related to INCB001158 and/or daratumumab SC

- Number (%) of participants who had a TEAE leading to temporary interruption of INCB001158
- Number (%) of participants who had a TEAE leading to INCB00158 dose reduction
- Number (%) of participants who had a TEAE leading to permanent discontinuation of INCB001158
- Number (%) of participants who had an irAE

The following summaries will be produced by MedDRA term for the Phase 1 and Phase 2 FAS population (if 10 or fewer participants appear in a table, a listing may be appropriate):

- Summary of TEAEs by SOC and PT
- Summary of TEAEs by PT in decreasing order of frequency
- Summary of Grade 3 or higher TEAEs by PT in decreasing order of frequency
- Summary of serious TEAEs by PT in decreasing order of frequency
- Summary of INCB001158 treatment-related TEAEs by PT in decreasing order of frequency
- Summary of Grade 3 or higher INCB001158 treatment-related TEAEs by PT in decreasing order of frequency
- Summary of TEAEs with a fatal outcome by SOC and PT
- Summary of TEAEs leading to INCB001158 dose reduction by PT in decreasing order of frequency
- Summary of TEAEs leading to INCB001158 dose interruption by PT in decreasing order of frequency
- Summary of TEAEs leading to discontinuation of INCB001158 by PT in decreasing order of frequency

8.3. Clinical Laboratory Tests

8.3.1. Laboratory Value Definitions

Laboratory values and change from baseline values will be summarized descriptively by visit. The baseline value will be determined using the nonmissing values collected before the first dose using the priority defined in Table 4. The last record before administration in the highest priority will be considered the baseline record. For baseline laboratory candidates with the same date and time in the same priority category, additional rules may be provided after consultation with the medical monitor to delineate which value will be defined as baseline.

Table 4: Identification of Baseline Record

Priority	Laboratory Visit	Central or Local Laboratory
1	Scheduled	Central
2	Scheduled	Local
3	Unscheduled	Central
4	Unscheduled	Local

Laboratory test values will be assessed for severity based on the numerical component of CTCAE v5.

8.3.2. Laboratory Value Summaries

All test results and associated normal ranges from central laboratories will be reported in SI units. Any laboratory test results and associated normal ranges from local laboratories will be converted to SI units.

When there are multiple nonmissing laboratory values for a participant's particular test within a visit window, the convention described in Table 5 will be used to determine the record used for by-visit tabulations and summaries.

Table 5: Identification of Records for Postbaseline By-Visit Summaries

Priority	Laboratory Visit	Central or Local Laboratory	Proximity to Visit Window	Tiebreaker
1	Scheduled	Central	In-window	Use smallest laboratory sequence number
2	Scheduled	Local	In-window	
3	Unscheduled	Central	In-window	
4	Unscheduled	Local	In-window	
5	Scheduled	Central	Out-of-window	
6	Scheduled	Local	Out-of-window	

For coagulation and urinalysis laboratory values, listings will be provided.

Numeric chemistry and hematology laboratory values will be summarized descriptively in SI units, and non-numeric test values will be tabulated when necessary.

Severity grades will be assigned to laboratory test values based on the numerical component of CTCAE v5. The number of participants who experienced worsening of laboratory abnormalities will be summarized by maximum severity.

In cases where differentials of hematology parameters are obtained without corresponding absolute count data, efforts will be made to investigate if the conversion to an absolute value will lead to additional abnormalities. This will be discussed with the clinical team regarding appropriate documentation and action.

8.4. Vital Signs

Values at each scheduled visit, change, and percent change from baseline for vital signs, including systolic blood pressure, diastolic blood pressure, pulse, temperature, respiratory rate, and weight, will be summarized descriptively.

Normal ranges for vital sign values are defined in Table 6. For participants exhibiting vital sign abnormalities, the abnormal values will be listed along with their assigned treatment group. Alert vital signs are defined as an absolute value outside the defined normal range and percentage change greater than 25%. Note that the definition of alert vital signs does not apply for body temperature and weight. The abnormal values for participants exhibiting alert vital sign abnormalities will be listed.

Table 6: Normal Vital Sign Values

Parameter	High Threshold	Low Threshold
Systolic blood pressure	≤ 155 mmHg	≥ 85 mmHg
Diastolic blood pressure	≤ 100 mmHg	≥ 40 mmHg
Pulse	≤ 100 bpm	≥ 45 bpm
Temperature	≤ 38ºC	≥ 35.5ºC
Respiratory rate	≤ 24 breaths/min	≥ 8 breaths/min

8.5. Electrocardiograms

Twelve-lead ECGs including PR, RR, QT, QRS, and QTcF intervals will be obtained for each participant during the study. Values at each scheduled visit, change, and percentage change from baseline will be summarized for each ECG parameter. Baseline will be determined as the average of all nonmissing values before the first administration of INCB001158 or daratumumab SC.

Electrocardiogram results will be reviewed for clinically notable abnormalities according to the investigator. Electrocardiogram values will also be considered abnormal if the absolute percentage change from baseline is more than 25% (30% for QRS interval). Participants exhibiting ECG abnormalities will be listed with study visit and assigned treatment group. Outliers of QT and QTcF values, defined as absolute values > 450 milliseconds, > 500 milliseconds, or change from baseline > 30 milliseconds, will be summarized.

9. INTERIM ANALYSES

As a result of an early-termination decision following a recruitment challenge (no safety-related concerns), primary safety analyses but no efficacy analyses will be performed due to an insufficient number of participants enrolled in Phase 2. No formal interim analysis will be performed.

10. CHANGES AND MODIFICATIONS TO THE ANALYSIS PLAN

All versions of the SAP are listed in Table 7.

Table 7: Statistical Analysis Plan Versions

SAP Version	Date
Original	19 APR 2022

10.1. Changes to Protocol-Defined Analyses

As a result of an early-termination decision following a recruitment challenge (no safety-related concerns), primary safety analyses but no efficacy analyses will be performed due to an insufficient number of participants enrolled in Phase 2. Listings of efficacy data will be provided.

10.2. Changes to the Statistical Analysis Plan

Not applicable.

APPENDIX A. PLANNED TABLES AND LISTINGS

This appendix provides a list of the planned tables and listings for the Clinical Study Report. Shells are provided in a separate document for tables that are not in the Standard Safety Tables v1.11.

The lists of tables and listings are to be used as guidelines. Modifications of the lists that do not otherwise affect the nature of the analysis will not warrant an amendment to the SAP.

Note that separate listings will be provided for the Phase 1 FAS and the Phase 2 FAS and will include ".1" and ".2", respectively, at the end of the listing number.

Tables

Table No.	Title	Population	Standard
Baseline and Demographic Characteristics			
1.1.1	Summary of Participants Screened and Screen Failures	Enrolled	
1.1.2	Analysis Populations	FAS	X
1.1.3	Summary of Participant Disposition	FAS	X
1.1.4	Summary of Number of Participants Enrolled by Country and Site	FAS	X
1.2.1	Summary of Demographics and Baseline Characteristics	FAS	X
1.3.1	Summary of Baseline Disease Characteristics	FAS	X
1.4.1	Summary of Prior Therapy for Disease Under Study	FAS	
1.4.2	Summary of Prior Radiation Therapy	FAS	
1.4.3	Summary of Prior Surgical Procedures	FAS	
1.4.4	Summary of Prior Medications	FAS	X
1.4.5	Summary of Concomitant Medications	FAS	X
1.5.1	Summary of General Medical History	FAS	X
Exposure and Safety			
3.1.1	Summary of Exposure and Duration of Exposure to INCB001158	FAS	X
3.1.2	Summary of Exposure and Duration of Exposure to Daratumumab SC	FAS	X
3.1.3	Summary of Study Drug Compliance to INCB001158	FAS	X
3.2.1	Overall Summary of Treatment-Emergent Adverse Events	FAS	X
3.2.2	Summary of Treatment-Emergent Adverse Events by MedDRA System Organ Class and Preferred Term	FAS	X
3.2.3	Summary of Treatment-Emergent Adverse Events by MedDRA Preferred Term in Decreasing Order of Frequency	FAS	X
3.2.4	Summary of Grade 3 or Higher Treatment-Emergent Adverse Events by MedDRA Preferred Term in Decreasing Order of Frequency	FAS	X
3.2.5	Summary of INCB001158 Treatment-Related Treatment-Emergent Adverse Events by MedDRA Preferred Term in Decreasing Order of Frequency	FAS	X
3.2.6	Summary of Grade 3 or Higher INCB001158 Treatment-Related Treatment-Emergent Adverse Events by MedDRA Preferred Term in Decreasing Order of Frequency	FAS	
3.2.7	Summary of Treatment-Emergent Adverse Events With a Fatal Outcome by MedDRA System Organ Class and Preferred Term	FAS	X

Table No.	Title	Population	Standard
3.2.8	Summary of Treatment-Emergent Adverse Events Leading to INCB001158 Dose Reduction by MedDRA Preferred Term in Decreasing Order of Frequency	FAS	
3.2.9	Summary of Treatment-Emergent Adverse Events Leading to INCB001158 Dose Interruption by MedDRA Preferred Term in Decreasing Order of Frequency	FAS	
3.2.10	Summary of Treatment-Emergent Adverse Events Leading to Discontinuation of INCB001158 by MedDRA Preferred Term in Decreasing Order of Frequency	FAS	
3.3.1.1	Summary of Laboratory Values - Hematology	FAS	X
3.3.1.2	Summary of Laboratory Values - Chemistry	FAS	X
3.3.3.4	Treatment-Emergent Worsening of Laboratory Abnormalities - Hematology	FAS	X
3.3.3.5	Treatment-Emergent Worsening of Laboratory Abnormalities - Chemistry	FAS	X
3.4.1	Summary of Systolic Blood Pressure	FAS	X
3.4.2	Summary of Diastolic Blood Pressure	FAS	X
3.4.3	Summary of Pulse	FAS	X
3.4.4	Summary of Respiratory Rate	FAS	X
3.4.5	Summary of Body Temperature	FAS	X
3.4.6	Summary of Body Weight	FAS	X
3.5.1	Summary of PR Interval (ms) From 12-Lead ECG	FAS	X
3.5.2	Summary of QRS Interval (ms) From 12-Lead ECG	FAS	X
3.5.3	Summary of QT Interval (ms) From 12-Lead ECG	FAS	X
3.5.4	Summary of QTcF Interval (ms) From 12-Lead ECG	FAS	X
3.5.5	Summary of RR Interval (ms) From 12-Lead ECG	FAS	X
3.5.6	Summary of Heart Rate (bpm) From 12-Lead ECG	FAS	X
3.5.7	Summary of Outliers of QT and QTcF Interval Values (ms) From 12-Lead ECG	FAS	X

Listings

Listing No.	Title
2.1.2.x	Participant Enrollment and Disposition Status
2.2.1.x	Participant Inclusion and Exclusion Criteria Violations
2.2.2.x	Protocol Deviations
2.3.1.x	Analysis Populations
2.4.1.x	Demographics and Baseline Characteristics
2.4.2.x	Baseline Disease Characteristics
2.4.3.x	Prior Radiation Treatment
2.4.4.x	Prior Therapy for Disease Under Study
2.4.5.x	Prior Surgery or Surgical Procedure
2.4.6.x	Medical History
2.4.7.x	Prior and Concomitant Medications
2.4.8.x	Post-Treatment Anticancer Therapy
2.5.1.x	Study Drug Administration for INCB001158
2.5.2.x	Study Drug Compliance for INCB001158
2.5.3.x	Study Drug Administration for Daratumumab SC
2.6.1.x	Overall Response Assessments and Best Overall Response Under IMWG Criteria
2.6.2.x	Efficacy Endpoints (TTR, DoR, PFS, and OS)
2.6.3.x	ECOG Status
2.6.4.x	Clinical Laboratory Values – Chemistry, SPEP
2.6.5.x	Clinical Laboratory Values – Immunology
2.6.6.x	Clinical Laboratory Values – Immunology, Free Light Chains
2.6.7.x	Clinical Laboratory Values – Immunology, Immunofixation
2.6.8.x	Clinical Laboratory Values – Immunology, SPEP
2.6.9.x	Clinical Laboratory Values – Urinalysis, UPEP
2.7.1.x	Adverse Events
2.7.2.1	Dose-Limiting Toxicities
2.7.3.x	Serious Adverse Events
2.7.4.x	Fatal Adverse Events
2.7.5.x	Adverse Events Leading to Discontinuation of INCB001158
2.7.6.x	Investigator-Identified Immune-Related Adverse Events
2.8.1.1.x	Clinical Laboratory Values – Hematology
2.8.1.2.x	Clinical Laboratory Values – Chemistry
2.8.1.3.x	Clinical Laboratory Values – Coagulation and Urinalysis
2.8.1.4.x	Clinical Laboratory Values – Orotic Acid
2.8.1.5.x	Abnormal Clinical Laboratory Values – Hematology
2.8.1.6.x	Abnormal Clinical Laboratory Values – Chemistry
2.8.1.7.x	Clinical Laboratory Values – Endocrine
2.8.2.1.x	Vital Signs
2.8.2.2.x	Abnormal Vital Sign Values
2.8.3.1.x	12-Lead ECG Values