NGM Biopharmaceuticals, Inc.

STATISTICAL ANALYSIS PLAN

Protocol Title:	A Phase 1/2 Dose-Finding Study Followed by Expansion Cohorts of NGM120, a GFRAL Antagonist Monoclonal Antibody Blocking GDF15 Signaling, in Subjects With Advanced Solid Tumors and Pancreatic Cancer Using Combination Therapy
Protocol Number:	NGM120 18-0402
Phase:	Phase 1/2
Sponsor:	NGM Biopharmaceuticals, Inc. 333 Oyster Point Boulevard South San Francisco, CA 94080
Author:	[redacted]
SAP Date:	06SEP2023
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APPROVAL SIGNATURE PAGE

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Document Version No	1.1
Date	06SEP2023

We, the undersigned, confirm that we have read, understood and agree to the content of this document and hereby authorize its approval.

[redacted]

Signature Date

[redacted]

Signature Date

TABLE OF CONTENTS

LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Only abbreviations and terms relevant to the SAP are repeated herein. The reader is referred to the protocol for the complete and comprehensive list of abbreviations and definitions of terms for the study.

ADT	Androgen deprivation therapies
AE	Adverse event
ALT	Alanine aminotransferase
ANOVA	Analysis of variance
ASA24	Automated Self-Administered 24-hour Dietary Assessment Tool
AUC	Area under the concentration-time curve
CACS	Cancer anorexia cachexia syndrome
C_{max}	Maximum observed concentration
CTCAE	Common Terminology Criteria for Adverse Events
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
EORTC-QLQ-CAX24	European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Cancer Cachexia 24
EOS	End of study
EOT	End of treatment
[redacted]	[redacted]
EW	Early withdrawal
[redacted]	[redacted]
GDF15	Growth differentiation factor 15
GFRAL	Glial cell line-derived neurotrophic factor receptor alpha-like
mCRPC	metastatic Castration Resistant Prostate Cancer
MedDRA	Medical Dictionary for Regulatory Activities
MTD	Maximum tolerated dose
OS	Overall survival
PCWG2	Prostate Cancer Working Group 2
PD	Pharmacodynamic(s)
PHQ-9	Patient Health Questionnaire
PK	Pharmacokinetic(s)

PRO	Patient reported outcomes
PSA	Prostate Specific Antigen
QxW	Once every x weeks
QTc	Corrected QT
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	Serious adverse event
SAP	Statistical analysis plan
SD	Standard deviation
SSE	Symptomatic skeletal events
TEAE	Treatment-emergent adverse event
T_{max}	Time to maximum observed concentration
TTPP	Time to PSA progression
ULN	Upper limit of normal
WOCBP	Woman of childbearing potential

1. INTRODUCTION

1.1. Preface

This document presents a statistical analysis plan (SAP) for NGM Biopharmaceuticals, Inc. NGM120 Clinical Study Protocol 18-0402 (A Phase 1/2 Dose-Finding Study Followed by Expansion Cohorts of NGM120, a GFRAL Antagonist Monoclonal Antibody Blocking GDF15 Signaling, in Subjects with Advanced Solid Tumors, and Pancreatic Cancer) Using Combination Therapy). Reference materials for this statistical plan include the NGM120 Clinical Study Protocol 18-0402 (Amendment Number: 6, Version 7.0, 07 APR 2022). The purpose of this SAP is to provide detailed descriptions of the statistical methods and data derivations other than pharmacokinetic (PK) related endpoints. The details of the analysis for PK data will be discussed in a separate document.

The SAP will be finalized and approved prior to database lock. Statistical programming may occur as study data accumulate in order to have analysis programs ready at the time of database lock.

1.2. Purpose of Analyses

The purposes of the planned analyses described in this SAP are to assess the safety and tolerability, as well as to obtain preliminary evidence of antitumor activity and anti-cachexia activity, of NGM120 monotherapy in subjects with select advanced solid tumors (Part 1), NGM120 in combination with gemcitabine and Abraxane for the management of metastatic pancreatic cancer (Part 2), and NGM120 in metastatic castration-resistant prostate cancer (mCRPC) patients who have progressed under 1 or more lines of ADT (Part 3). Results from the analyses completed will be included in the final clinical study report (CSR) for NGM120 18-0402, and may also be utilized for regulatory submissions, manuscripts, or other clinical development activities.

Post-hoc exploratory analyses not identified in this SAP may be performed to further examine the study data. These analyses will be clearly identified, where appropriate, in the final CSR. Additional analyses not prospectively identified in this SAP may also be completed for publications, or regulatory or funding inquiries. These analyses, if performed, may not be reported in the CSR, but will be fully documented in the document containing the additional analyses.

2. STUDY OBJECTIVES AND ENDPOINTS

Study objectives and endpoints defined in the protocol include safety, tolerability, immunogenicity, pharmacokinetic (PK), pharmacodynamic (PD), and health status/utility endpoints.

2.1. Study Objectives and Endpoints for Part 1

2.1.1. Primary Objective and Endpoint for Part 1

The primary objective of Part 1 is to determine the safety and tolerability of NGM120 in subjects with select solid tumors. The primary endpoint for Part 1 is the maximum tolerated dose (MTD) or maximum feasible dose (MFD) as evidenced by dose limiting toxicities (DLTs), adverse events (AEs), serious adverse events (SAEs), discontinuation of investigational product due to toxicity, and changes from baseline in laboratory parameters, electrocardiograms, vital signs, and local injection-site symptom assessment.

2.1.2. Secondary Objectives and Endpoints for Part 1

The secondary objectives and endpoints for Part 1 are described below.

Secondary Objectives for Part 1	Secondary Endpoints for Part 1
• To characterize the pharmacokinetics of NGM120 in subjects with select solid tumors	• Serum concentrations of NGM120 at specified time points • Pharmacokinetic parameters (including, but not limited to, maximum observed serum concentration [C_{max}], time to maximum observed concentration [T_{max}], area under the concentration-time curve [AUC], clearance, apparent volume of distribution, and apparent terminal half-life [$t_{1/2}$]).
• To characterize the immunogenicity against NGM120 in subjects with select solid tumors	• Percentage of subjects to develop antidrug antibodies and neutralizing antibodies
• To obtain preliminary evidence of antitumor and anticachexia efficacy of NGM120 in subjects with select solid tumors	• Percent change from baseline in tumor measurements • Body weight, body composition, and lean body mass changes • [redacted]
• Characterize changes in body weight and skeletal muscle index during therapy with NGM120	• Change in body weight • [redacted]

2.1.3. Exploratory Objectives for Part 1

The exploratory objectives and endpoints for Part 1 are described below.

Exploratory Objectives for Part 1	Exploratory Endpoints for Part 1
• [redacted]	[redacted]

2.2. Study Objectives and Endpoints for Part 2

2.2.1. Primary Objective and Endpoint for Part 2

The primary objective of Part 2 is to determine the safety and tolerability of NGM120 when administered in combination with gemcitabine+Abraxane for the management of metastatic pancreatic cancer. The primary endpoint for Part 2 is the maximum tolerated dose (MTD), maximum feasible dose (MFD), or optimal efficacious dose (OED) as evidenced by DLTs, AEs, SAEs, discontinuation of investigational product due to toxicity, PK/PD correlation, and changes from baseline in laboratory parameters, ECGs, vital signs, and local injection-site symptom assessment.

2.2.2. Secondary Objectives and Endpoints for Part 2

The secondary objectives and endpoints for Part 2 are described below.

Secondary Objectives for Part 2	Secondary Endpoints for Part 2
• To characterize the PK of NGM120 in subjects when administered in combination with gemcitabine+Abraxane for the management of metastatic pancreatic cancer	• C_{max}, T_{max}, AUC, clearance, apparent volume of distribution, and apparent $t_{1/2}$.
• To characterize the immunogenicity against NGM120 in subjects when administered in combination with gemcitabine+Abraxane for the management of metastatic pancreatic cancer	• Percentage of subjects to develop antidrug antibodies and neutralizing antibodies
• To obtain preliminary evidence of antitumor and anticachexia efficacy of NGM120 in subjects when administered in combination with gemcitabine+Abraxane for the management of metastatic pancreatic cancer	• Overall response rate, disease control, duration of response, progression-free survival, and overall survival • Body weight, body composition, and lean body mass changes • [redacted]
• Characterize changes in body weight and skeletal muscle index during therapy with NGM120	• Change in body weight • [redacted]

2.2.3. Exploratory Objectives and Endpoints for Part 2

The exploratory objectives and endpoints for Part 2 are described below.

Exploratory Objectives for Part 2	Exploratory Endpoints for Part 2
• [redacted]	[redacted]

Exploratory Objectives for Part 2	Exploratory Endpoints for Part 2
	• Correlation of GDF15 and other genetic polymorphism to response (applicable only to subjects who consent to providing an optional pharmacogenetic sample; analyses will be reported separately) • PK and PD relationship
• Characterize changes in functional status during therapy with NGM120	• Change in hand grip strength • Change in daily movement as measured by a wearable biometric sensor
• Collection of optional pharmacogenetic sample for future analysis	• Buccal swab collected

2.3. Study Objectives and Endpoints for Part 3

2.3.1. Primary Objective and Endpoint for Part 3

The primary objective of Part 3 is to determine the safety and tolerability of NGM120 when administered in mCRPC patients who have progressed under 1 or more lines of ADT. The endpoints for Part 3 are AEs, SAEs, discontinuation of investigational product due to toxicity, and changes from baseline in laboratory parameters, ECGs, vital signs, and local injection-site symptom assessment.

2.3.2. Secondary Objectives and Endpoints for Part 3

The secondary objectives and endpoints for Part 3 are described below.

Secondary Objectives for Part 3	Secondary Endpoints for Part 3
• To characterize the PK of NGM120 when administered in mCRPC patients who have progressed under 1 or more lines of ADT	• C_{max}, T_{max}, AUC, clearance, apparent volume of distribution, and apparent $t_{1/2}$.
• To characterize the immunogenicity against NGM120 when administered in mCRPC patients who have progressed under 1 or more lines of ADT	• Percentage of subjects to develop antidrug antibodies and neutralizing antibodies
• To obtain preliminary evidence of antitumor efficacy of NGM120 when administered in mCRPC patients who have progressed under 1 or more lines of ADT	• Prostate Specific Antigen (PSA) response defined as a reduction from baseline PSA level of at least 50%, maintained for at least 3 weeks. • Time to PSA progression (TTPP) defined as the time interval between the date of randomization and the date of first documented PSA progression. PSA progression is defined as: 1) If decline from baseline value: an increase of ≥25% (at least 2 ng/mL) over the nadir value, confirmed by a second PSA value at least 3 weeks apart; 2) If no decline from baseline value: an increase of ≥25% (at least 2 ng/mL) over the baseline value after 12

Secondary Objectives for Part 3	Secondary Endpoints for Part 3
	weeks of treatment, confirmed by a second PSA value at least 3 weeks apart. Early increase in PSA within 12 weeks, when followed by subsequent decline, is ignored in determining this endpoint • Progression-free survival defined as the time interval between the date of randomization and the date of the first documentation of any of the following events: - Radiological tumor progression by RECIST 1.1 or Prostate Cancer Working Group 2 (PCWG2) - Symptomatic progression - Pain progression - Death due to any cause • Objective tumor response in patients with measurable disease (RECIST 1.1) • Duration of tumor response • Symptomatic skeletal events (SSE) rate, occurrence of SSE (by clinical evaluation) is defined as: - The occurrence of a new symptomatic pathological fracture, or - The use of external beam radiation to relieve bone pain, or - The occurrence of spinal cord compression, or - Tumor-related orthopedic surgical intervention • Time to occurrence of SSE defined as the time interval between the date of randomization and the date of the occurrence of the first event defining a SSE. • 24-month OS defined as the time interval from the date of randomization to the date of death due to any cause within a 24-month time frame
• Health status/utility	• EuroQol 5 dimension 5 level (EQ-5D-5L) • Change in body weight

2.3.3. Exploratory Objectives and Endpoints for Part 3

The exploratory objectives and endpoints for Part 3 are described below.

Exploratory Objectives for Part 3	Exploratory Endpoints for Part 3
• [redacted]	[redacted]

3. STUDY METHODS

3.1. General Study Design and Plan

This is a multicenter, Phase 1/2, study consisting of 3 parts, with Part 1 as the Phase 1a portion of the study, Part 2 as the Phase 1b/2 portion, and Part 3 as the Phase 1b portion. Part 2 will start at the same time as Part 1 and run concurrently. Part 3 was implemented with protocol version 6.0.

Part 1 and Part 2 Dose-Finding and Dose Expansion

Part 1 and Part 2 of the study will be split into a dose-finding portion followed by a dose-expansion portion. The study has dose-finding and dose-expansion criteria that will need to be met before either expanding a cohort or initiating an expansion cohort. The details please refer to Section 4.5 and Section 4.6 of Protocol.

The dose-finding portion will consist of 2 cohorts in a 3+3 dose-finding design with 2 dose levels. Depending on the dose level/cohort a subject is enrolled to, the subject will receive a dose of either 100 mg or 30 mg of NGM120. Following completion of the final dose-finding meeting, another dose level of NGM120 may be investigated as selected by the Safety Review Committee. Therefore, depending on drug safety/tolerability profiles, a MTD or a MFD will be identified (Part 1 and Part 2). If the drug safety/tolerability is not limiting, OED (Part 2) will be identified based on PK/PD correlation in the consideration of maximal PD activity and adequate

drug exposure. Additional cohorts may be added, as new research and clinical data become available.

After all subjects in a dose-finding cohort complete their first cycle of treatment, the Safety Review Committee will be convened to evaluate the available safety, PK, and PD data. The Safety Review Committee will determine whether to proceed with another dose level or whether the MTD/MFD (Part 1 and Part 2) has been reached. Following selection of the NGM120 MTD/MFD (Part 1) or MTD/MFD/OED (Part 2), enrollment to the dose-expansion cohort may begin as determined by the Safety Review Committee.

Part 1 and Part 2 of the study have dose-finding and dose-expansion criteria (see Sections 4.5 and 4.6 of the protocol) that will need to be met before either expanding a cohort or initiating the expansion cohort.

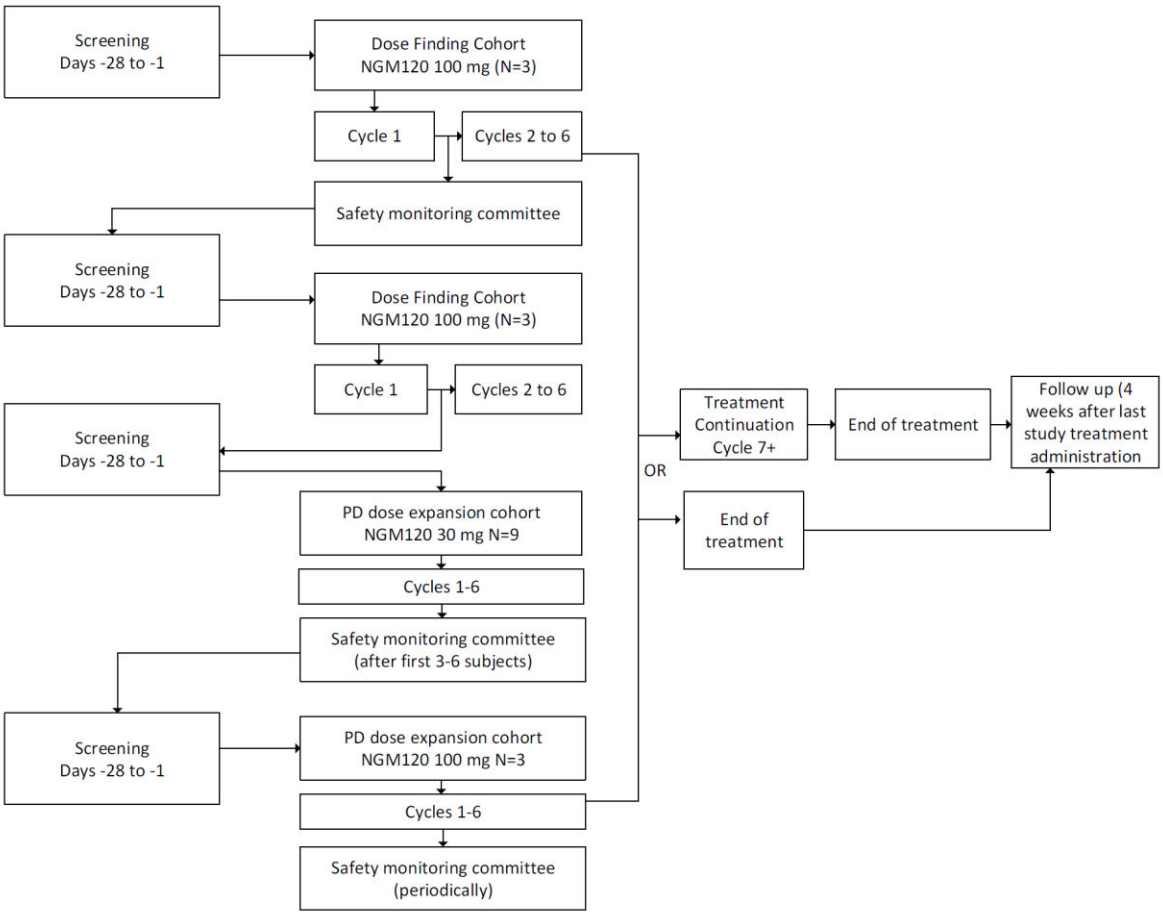
Number of Investigators and Study Centers:

Approximately 25 Investigators and study centers are expected to participate in this study in the United States.

3.2. Schedule of Study Procedures

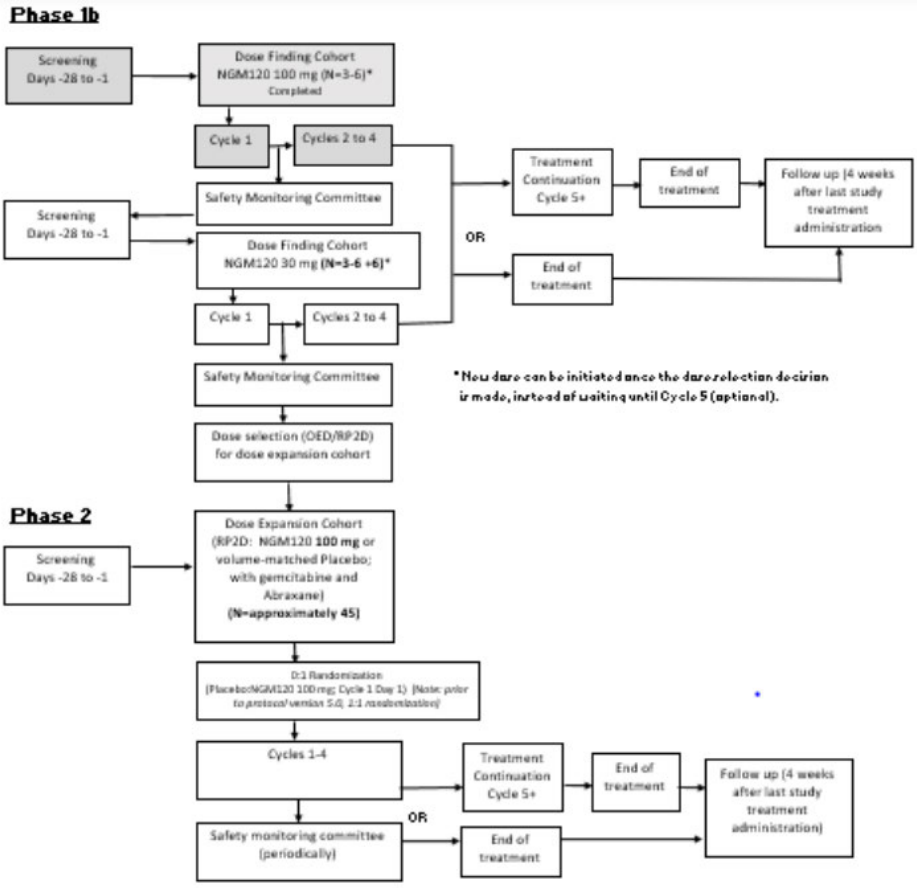
Comprehensive schedules of study procedures can be found in the study protocol. Specifically, the protocol includes 6 schedules: 1) Part 1, 2) Part 1 Treatment Continuation, 3) Part 2, 4) Part 2 Treatment Continuation, 5) Part 3, 6) Part 3 Treatment Continuation. These comprehensive schedules can be found in the protocol in Tables 1-1, 1-2, 1-3, 1-4, 1-5, and 1-6. In summary, Figures 1-1, 1-2, and 1-3 depict the study schema for Part 1, Part 2, and Part 3.

Figure 1-1. Study Schema of Part 1 (Phase 1a)



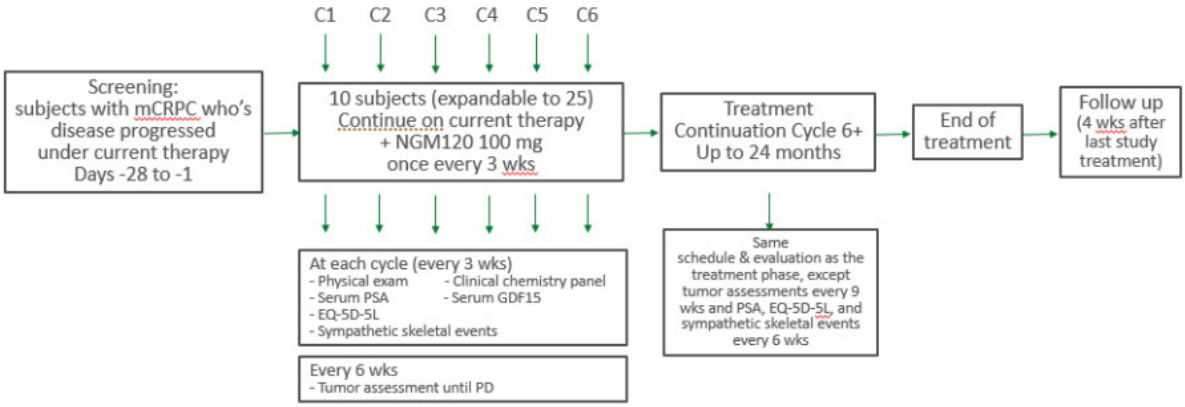
Note: For the 100 mg dose-expansion cohort, the Safety Review Committee will meet quarterly, or as needed (ad hoc).

Figure 1-2 Study Schema of Part 2 (Phase 1b/2)



Note: For the dose-expansion cohort, the Safety Review Committee will meet quarterly, or as needed (ad hoc).

Figure 1-3 Study Schema of Part 3 (Phase 1b)



3.3. Randomization and Blinding

Part 1 (dose-finding and dose-expansion cohorts) and Part 2 (dose-finding cohort) are open-label with all subjects receiving the same dose of study treatment depending on their enrolled cohort. Part 3 is open-label with all subjects receiving NGM120 100 mg Q3W.

Part 2 (dose-expansion cohort) will be single-blind (Sponsor unblinded). In the dose-expansion cohort of Part 2, subjects will be randomly allocated to treatment with either NGM120 100mg or a matching placebo Q4W. On Cycle 1 Day 1 (before study treatment administration) subjects will be assigned a unique number (randomization number) in ascending numerical order at the study center. The randomization number encodes the subject's assignment to 1 of 2 treatments (either NGM120 or placebo according to the randomization schedule generated prior to the study by the Sponsor-appointed vendor. In order to maintain the blind, the NGM120 and placebo injections will be provided to the study center already blinded with the NGM120 and placebo injections identical in physical appearance. The treatment each subject will receive will not be disclosed to the Investigator, study center staff, the subject, or study vendors. The Sponsor will be unblinded. Randomization will not be stratified by any factors.

4. SAMPLE SIZE

For Part 1, a standard sample size of 3 to 6 subjects will be entered per 3+3 dose level. This number of subjects is considered sufficient to proceed to another dose level. An additional 12 subjects will be enrolled for the dose-expansion cohorts and the total sample size for Part 1 will be approximately 15 to 21 subjects.

Part 2 will use the 3+3 design with 2 dose levels (100 mg and 30 mg) followed by an additional 60 subjects enrolled for the dose-level expansion. A standard sample size of 3 to 6 subjects will be entered per 3+3 dose level. Protocol version 5.0 expanded the NGM120 30 mg cohort to add 6 subjects based on emerging data (see Section 4.3 of protocol).

Based on a sample size of 30 subjects in the NGM120 arm of the Part 2 expansion cohort, the 95% Clopper-Pearson (Exact) CI are presented in Table 6-1.

Table 6.1 Confidence Intervals Based on Response (Part 2)

# of Response	Response Rate	95% Lower Confidence Limit	95% Upper Confidence Limit
6	0.2	0.0771	0.3857
7	0.23333	0.0993	0.4228
8	0.26667	0.1228	0.4589
9	0.3	0.1473	0.494
10	0.33333	0.1729	0.5281
11	0.36667	0.1993	0.5614
12	0.4	0.2266	0.594

For Part 3, 10 patients will be initially accrued before expansion to 25 subjects. At least 2 subjects with a 50% or higher magnitude of PSA reduction from baseline level and maintained for at least 3 weeks are required within the initial 10 subject cohort to continue the patient accrual, with a planned enrollment of 25 patients.

Based on N of 25, the 95% Clopper-Pearson (Exact) CI for Part 3 are presented in Table 6-2.

Table 6-2 Confidence Intervals Based on Response (Part 3)

# of Responses	Response Rate	95% Lower Confidence Limit	95% Upper Confidence Limit
5	0.2	0.0683	0.407
6	0.24	0.0936	0.4513
7	0.28	0.1207	0.4939
8	0.32	0.1495	0.535
9	0.36	0.1797	0.5748
10	0.4	0.2113	0.6133

5. GENERAL CONSIDERATIONS

5.1. Analysis Populations

Data for all subjects will be assessed to determine if subjects meet the criteria for inclusion in each analysis set. Classifications into analysis sets will be documented per standard operating procedures.

The following analysis sets have been defined for the analyses that are described in this SAP.

5.1.1. All Subjects

All subjects who have signed the written informed consent form. This population will be used for data listings when appropriate.

[redacted]

5.1.3. Full Analysis Set

The Full Analysis Set includes all subjects who receive at least 1 dose (full or partial) of study treatment.

5.1.4. [redacted]

[redacted]

5.2. [redacted]

[redacted]

5.3. Management of Analysis Data

5.3.1. Baseline

Unless otherwise specified, the baseline value is defined as the last measurement prior to administration of the first does of study drug.

5.3.2. Study Day

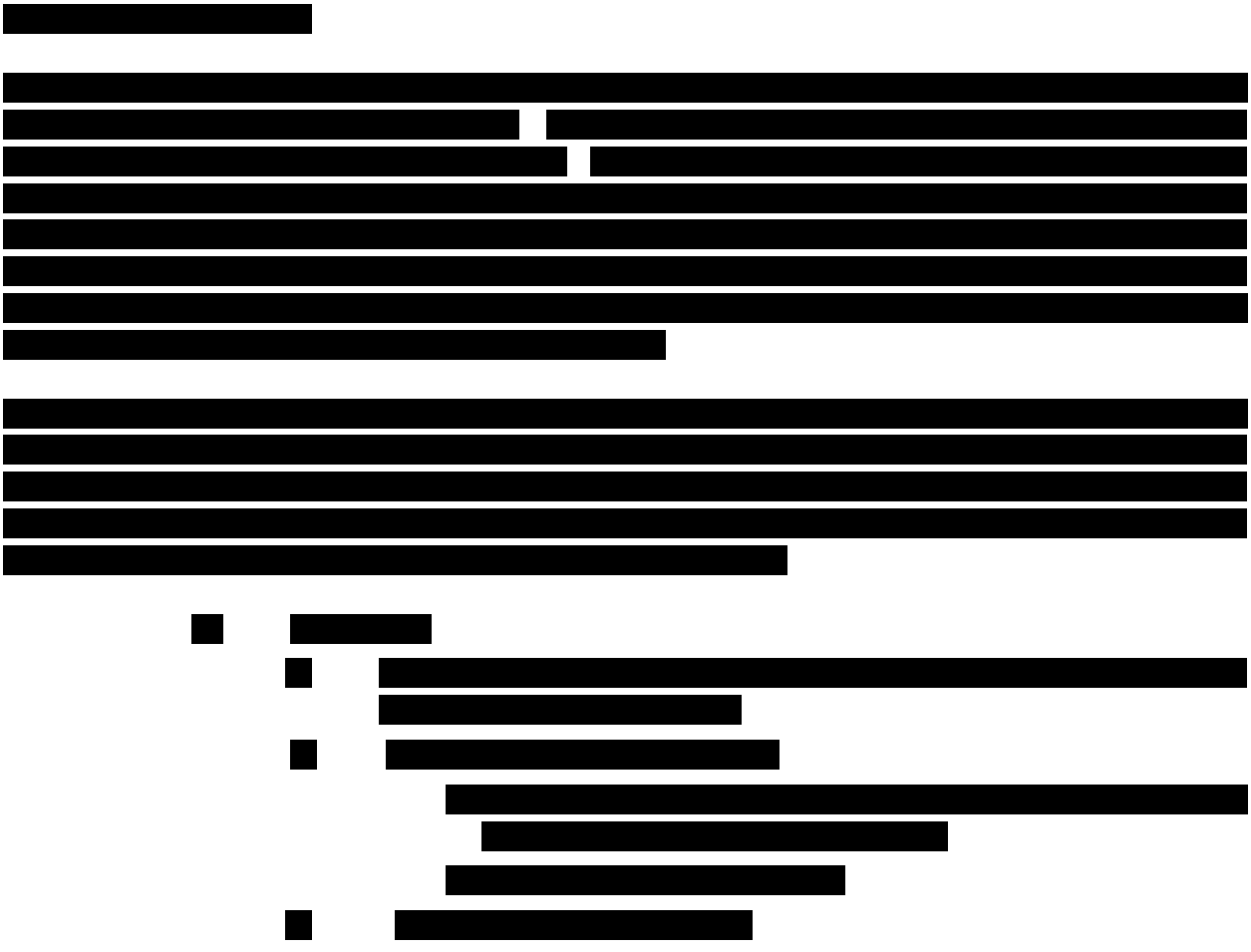
Study day is calculated as assessment date minus date of first dose of study drug + 1 if the assessment occurred after the date of first dose of study drug. For assessments that occurred before the first dose of study drug, study day is calculated as assessment date minus date of first dose of study drug. Date of first dose is defined as study Day 1.

5.3.3. Missing Data

Every effort will be made to collect all data. However, despite best efforts, missing or incomplete data may be reported. All missing or partial data will be presented in the patient data listing, as they are recorded on the electronic case report form (eCRF).

Subjects lost to follow-up or withdrawn will be included in statistical analyses up to the point of their last evaluation. Unless otherwise specified, as noted below, in general, no imputation of values for missing data will be performed.

5.3.3.1. Handling of Missing Date Values



[redacted]

The following conventions will be used to impute missing portions of other dates. Partial dates are not expected for death. If a partial date is present for dates related to disease history (diagnosis, histological confirmation, prior progression), the same rules as for AE and CM start date will be applied.

5.3.3.2. Missing Baseline Data

Every effort will be made to ensure that accurate baseline information is collected. Subjects will not be excluded from any of the analysis sets due to missing baseline. However, if a subject is missing baseline information, they will have missing change from baseline result.

5.3.3.3. Imputation Methods

Aside from imputation of partial and missing dates, as described above, all data will be observed cases, without imputation. The handling of PK data is discussed in a separate document for PK analysis.

5.3.4. Analysis Visit Windows, Unscheduled Visits, and Early Termination Visit

Safety analyses will be based on nominal visits as recorded on the eCRFs except the early termination/end of study visit. There will be no analysis visit windows calculated programmatically. The early termination visit data will be combined with the end of treatment/study visit and be summarized as the last assessment visit. In the derivation of maximum/minimum change from baseline values and worst post-baseline values unscheduled assessments will be used.

5.3.5. Pooling of Investigational Sites

The data from all study centers will be pooled together for analyses. No adjustment of center effect will be performed.

5.3.6. Protocol Deviations

The list of protocol deviations will be compiled and reviewed to identify major and minor deviations prior to database closure. These decisions will be documented in the study trial master file.

Any deviation from the protocol will be reviewed prior to database closure and a decision taken regarding evaluation for each analysis set. If no subjects have major protocol deviations, no adjustments to the analysis sets will be made.

5.3.7. Analysis Software

Data manipulation, tabulation of descriptive statistics, calculation of inferential statistics, and graphical representations will be performed primarily using SAS (release 9.4 or higher) for Windows. If the use of other software is warranted, the final CSR will detail what software was used and for what purposes.

5.3.8. Statistical Summaries: Descriptive and Inferential

Descriptive summaries of variables will be provided where appropriate. For continuous variables, the number of non-missing values (n), mean, standard deviation, median, minimum, and maximum will be tabulated by treatment. For categorical variables, the counts and proportions of each value will be tabulated by treatment. Kaplan-Meier estimates will be presented for time-to-event variables. Expansion of descriptive table categories within each treatment may occur if such elaborations are thought to be useful.

No formal statistical comparison will be conducted, for part 2 of the study with randomization, difference between NGM120 and placebo with the 95% confidence interval (CI) for the differences will be provided.

All study related data collected will be presented in listings. Study related data not subject to analysis according to this plan will not appear in any tables or graphs but will be included in the data listings.

5.3.9. Interim Analyses, Final Analysis, and Publication of Study Results

[redacted]

The final analysis will be completed after all subjects have completed the study and the final study database has been locked.

6. SUMMARY OF STUDY DATA

The summaries of study data will be conducted by Part 1, Part 2, and Part 3, separately. Part 1 will be summarized by NGM 120 dose levels (100 mg and 30 mg). For Part 2 data, the summaries will be separated by cohort (dose-finding (phase 1b) and dose-expansion (phase 2)) and by treatment group (NGM 120 vs. Placebo) for dose expansion cohort. Summary by dose within a cohort or cross cohorts may also be performed where appropriate.

6.1. Subject Disposition

Subject disposition will summarize the end of study information and include the number and percentage of subjects who completed the study and subjects who prematurely discontinued the study with reasons for withdrawal. The number and percentage of subjects who completed treatment and the reasons for not completing treatment will also be presented. All percentages will be based on the number of subjects in the Safety Analysis Set.

A by-subject listing of study completion information including the reason for premature study discontinuation, if applicable, will be presented. Also, a by-subject listing of treatment completion information including the reason for not completing treatment, if applicable, will be presented.

6.2. Analysis Sets

A summary of the number and percentage of subjects in each analysis set will be provided.

By-subject listings will be produced for subjects' status (Y/N) in each of the analysis sets.

6.3. Protocol Deviations

The study team will meet and review the protocol deviations data to determine whether a protocol deviation is major (i.e., important) or minor (i.e., not important). This will be done before database lock. A summary of the number and percentage of subjects with major protocol deviation will be provided. All protocol deviations will be included in a by-subject listing, with a flag to indicate if a deviation was considered major or minor. Separate by-subject listings will document if a subject (1) signed informed consent (IC) and (2) met all inclusion/exclusion eligibility criteria, and if any failed, the failed criterion number. All enrolled subjects will be included in this listing,

6.4. Demographics, Baseline and Disease Characteristics

Descriptive summaries of subject demographics and baseline variables include age, sex, race, ethnicity, body weight, height, BMI, site of metastatic disease, number of metastatic sites, prior therapy, stage of initial diagnosis, and time to initial cancer diagnosis will be provided for each analysis set.

Time to initial cancer diagnosis is defined as the duration between the date of initial cancer diagnosis and date of informed consent date.

6.5. Medical History

Medical history will be coded using Medical Dictionary for Regulatory Activities (MedDRA version 21.0 or above). Medical history will be summarized by the number and percentage of subjects for each System Organ Class (SOC) and Preferred Term (PT) for the Safety Analysis Set. Percentages will be based on the number of subjects in the Safety Analysis Set.

Medical history data will be presented in by-subject listings.

6.6. Prior and Concomitant Medications

Prior medications are defined as any medication that is taken prior to the day of first dose of study drug (i.e. start date before the first study treatment date). Concomitant medications are defined as any medication taken on or after the day of first dose of study drug throughout the study (i.e. end date either the same or after the first dose of study treatment, or still ongoing at the end of the study). A given medication may be classified both as a prior medication and as a concomitant medication.

Prior and concomitant medications will be coded using WHODDE+WHOHD (version 1Q2018 or above) and summarized in tables by Anatomical Therapeutic Chemical (ATC) and PT. Listings will also include verbatim term captured on the eCRF. For all medication tables, medications will be counted once per subject, regardless of the number of times it was reported on the eCRF.

The number and percentage of subjects using (1) prior medications and (2) concomitant medications will be summarized for the Safety Analysis Set.

All prior and concomitant medications will be presented in the same by-subject listing.

6.7. Treatment Compliance

The duration of treatment, the total administered dose, and the corresponding dose intensity – calculated as total administered dose as a proportion of total planned dose – will be summarized by treatment arm for the Safety Analysis Set. The total dose will be reported separately for each dose of NGM120 as well as for Abraxane and Gemcitabine. Descriptive statistics of the number of cycles where the study drug was received will also be summarized.

[redacted]

- [redacted]

6.8. Efficacy Analyses

The analyses of response data will be conducted for all subjects in the Efficacy Evaluable Set and/or the Full Analysis Set.

Tumor response will be evaluated by the investigators and by the central reader using RECIST 1.1 criteria. In Part 2, if the principal investigator believes the subject is experiencing clinical benefit from treatment, the subject may be treated beyond potential progression. Therefore, a PD followed by at least one SD/PR/CR assessment prior to the start of new anti-cancer treatment, if any, is considered pseudo-progression. The pseudo-progression will be ignored when assessing the best overall response. The analyses of responses data will be performed for the results from the central reader as the primary analyses and from the investigators as the sensitivity analyses.

The overall response of each tumour assessment will be classified as the following categories:

- Completed Response (CR)
- Partial Response (PR)
- Stable Disease (SD)
- Progression Disease (PD)
- Not Evaluable (NE)

Based on the RECIST 1.1 guidelines, the confirmed responses will be used for the tumor response analyses. The algorithm of confirmed responses is described in Table 7.

[redacted]

[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]

6.8.1. Best Overall Response

Best overall response (BOR) is the best tumor response recorded up until documentation of disease progression or death from any cause, or until the data cutoff date for ongoing patients for IA analysis, whichever occurs first.

The distribution (number and percentage) of BOR will be summarized.

6.8.2. Objective Response Rate

Objective response rate (ORR) will be calculated as the proportion of subjects who achieve a best overall response of confirmed CR or PR. Subjects who do not have a post-baseline tumor assessment for any reason will be considered non-responders and included in the denominator when calculating the response rate when the analysis is based on the full Analysis Set.

A 2-sided Clopper-Pearson 95% CI will be constructed for ORR. In addition, for part 2, the difference in ORRs between treatments will be provided and corresponding 95% CI will be calculated using Clopper-Pearson method.

6.8.3. Disease Control Rate

Disease Control Rate (DCR) will be calculated as the proportion of subjects who achieve a best overall response of confirmed CR or PR, or SD.

A 2-sided Clopper-Pearson 95% CI will be constructed for DCR in each treatment group. In addition, for part 2, the difference in DCRs between treatments will be provided and corresponding 95% CI will be calculated using Clopper-Pearson method.

6.8.4. Progression-Free Survival

Progression-free survival (PFS) is defined as the time from administration of the first study treatment to the date of the first confirmed progression by RECIST 1.1 or death due to any cause, whichever comes first for subjects in part 1 and part 2. PFS is defined as the time from administration of the first study treatment to the date of the first documentation of tumor progression by RECIST 1.1 or Prostate Cancer Working Group 2 (PCWG2), symptomatic progression, pain progression, or death due to any cause, whichever comes first for subjects in part 3.

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[redacted]	[redacted]	[redacted]

PFS will be analyzed using Kaplan-Meier methodology and Kaplan-Meier plots will be provided. The median PFS and its 2-sided 95% CI using the complementary log-log transformation method (SAS PROC LIFETEST CONFTYPE=LOGLOG) will be calculated. In addition, the 6, 12, 18, and 24 months PFS rate along with 95% CI will be estimated from the Kaplan-Meier estimate.

In addition, the hazard ratio between NGM120 and placebo for subjects in part 2 along with 95% CI will be obtained by fitting a Cox model with the treatment and sex as covariates.

6.8.5. Duration of Objective Response and Time to Objective Response

Duration of objective response (DOR) is defined as the time from first documentation of response (CR or PR) that is subsequently confirmed per RECIST v1.1 to the date of the first documentation of tumor progression or to death due to any cause, whichever occurs first for subjects in part 1 and part 2. DOR is defined as the time from first documentation of response (CR or PR) that is subsequently confirmed per RECIST v1.1 to the date of the first documentation of tumor progression by RECIST 1.1 or Prostate Cancer Working Group 2 (PCWG2), symptomatic progression, pain progression, or death due to any cause, whichever comes first for subjects in part3. Subjects who neither progress nor die, the duration of objective response will be censored at the same time they were censored for PFS definition (see Section 8.8.4).

DOR will be analyzed using Kaplan-Meier methodology and Kaplan-Meier plots will be provided for subjects who achieved confirmed PR or CR. The median DOR and its 2-sided 95% CI using the complementary log-log transformation method will be calculated.

Time to objective response is defined as the time from administration of the first study treatment to the date of the first documentation of response (CR or PR) that is subsequently confirmed per RECIST v1.1.

Summary statistics of time to objective response will be provided for subjects who achieved confirmed PR or CR.

6.8.6. Overall Survival

Overall Survival (OS) is defined as the date from start of the study treatment to the date of death due to any cause. A subject who has not died will be censored at last known date alive.

Subject survival status will be followed every 3 months for at least 24 months after the last study treatment administration.

OS will be analyzed using Kaplan-Meier methodology and Kaplan-Meier plots will be provided. The median OS and its 2-sided 95% CI using the complementary log-log transformation method will be calculated. The 6-, 12-, 18-, and 24-months OS rate along with 95% CI will be estimated from the Kaplan-Meier estimate, if applicable.

In addition, the hazard ratio between NGM120 and placebo for subjects in part 2 along with 95% CI will be obtained by fitting a Cox model with the treatment as unique covariate.

6.8.7. Sums of Diameters for Target Lesion

The maximum percent reduction (or minimum percent increase if there is no reduction) from baseline in the sums of diameters for target lesions, will be derived for each subject and will be graphically displayed with a waterfall plot, if appropriate. The change from baseline in sums of diameters for target lesions, at each response assessment will be graphically displayed with a spider plot, if appropriate.

6.8.8. Body Weight, Body Composition, Lean Body Mass

The subjects' weight and waist circumference will be measured. CT scan will also be performed to document the subject's lean body mass.

Actual values and changes from baseline for weight, waist circumference and lean body mass will be summarized descriptively at each scheduled visit.

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6.8.9. [redacted]

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6.8.9.1. [redacted]

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[redacted]d post-baseline timepoint using a shift table of the frequency count on observed data.

6.9. Exploratory Endpoints

6.9.1. [redacted]

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6.9.2. [redacted]

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6.9.3. [redacted]

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6.9.4. Symptomatic Skeletal Events (Part 3 only)

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6.9.5. [redacted]

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[redacted]

6.9.7. Immunogenicity and exploratory biomarkers

All immunogenicity and exploratory biomarkers analyses may be summarized with descriptive statistics using the Full Analysis Set.

6.10. Pharmacodynamic Analyses

The analyses of PD endpoints will be conducted for all subjects in the Full Analysis Set by treatment and by Study Part 1, Part 2, and Part 3. Actual values and changes from baseline for concentrations of PD markers will be summarized descriptively by visit. In addition, for subjects in part 2, the difference in the changes from baseline between NGM120 and placebo group will be estimated using MMRM model with the same covariates that described in section 8.8.8. The difference of the least square mean (lsmean) estimates between NGM120 and placebo along with the 95% CI at the scheduled visits with tumor assessment will estimated.

Correlation of baseline circulating PD level to response, correlation of baseline tumor PD expression from archival tissues to response, and also immunophenotypic changes of circulating immune cells, may be performed as exploratory analysis.

6.11. Safety Analyses

All safety analyses will be conducted by treatment and by Study Part 1, Part 2, and Part 3 using the Safety Analysis Set.

6.11.1. Adverse Events (AEs)

The Medical Dictionary for Regulatory Activities (MedDRA) nomenclature will be used to code adverse events. A treatment-emergent adverse event (TEAE) is an AE that begins or worsens after the time of start of first study-drug administration.

The number and percentage of subjects with any TEAEs will be summarized by SOC and PT. At each level of MedDRA (ex. at the PT level), subjects will be counted only once if they had more than one such event reported during the AE collection period. Multiple occurrences of the same event within a subject also will be counted once in the maximum intensity category (severe > moderate > mild) and in the maximum causal relationship category (definite > probable > possible > unknown > unlikely > unrelated)**.**

The following summary tables will be presented for TEAE data:

- Overall summary of TEAEs
- TEAEs by decreasing PT frequency
- TEAEs by SOC and PT
- Serious TEAEs by SOC and PT
- Drug-related TEAEs by SOC and PT
- TEAE leading to an injection site reaction

- TEAEs by highest relationship to study treatment by SOC and PT
- TEAEs by highest relationship to each drug for the combination treatment study treatment (Part 2) by SOC and PT
- TEAEs by maximum CTCAE grade by SOC and PT

The following listing will be presented:

- Deaths
- SAEs
- TEAEs leading to study discontinuation

AEs will be provided in by-subject listings, including both TEAE and non-TEAE events.

6.11.2. Laboratory Data

Descriptive statistics n, mean, standard deviation, median, minimum, and maximum will be used to present observed values and change from baseline of each laboratory parameter by scheduled study visit using the Safety Analysis Set. For categorical variables, number (n) and percentage (%) will be used. Unscheduled visits will not be summarized but are included in the by-subject listings. Shift tables from baseline clinical grade to worst post-baseline grade will also be presented for chemistry and hematology laboratory parameters, where deemed appropriate.

All laboratory data, including unscheduled visits, will be presented in a by-subject listing. Flags will be included in the listing identifying values below or above the normal range.

6.11.3. Urine Drug Screen

Urine drug screens data, including those from unscheduled visits, will be presented in the by-subject listings.

6.11.4. Tuberculosis Screen

Tuberculosis screens will be assessed with summaries of counts and percentages for positive and negative results, by scheduled study visit using the Safety Analysis Set. Unscheduled visits will not be summarized but are included in the by-subject listings.

6.11.5. Vital Signs

Descriptive statistics of observed values and change from baseline will be presented for each vital sign variable by scheduled study visit using the Safety Analysis Set. Vital signs collected include weight, temperature, pulse, respiratory rate, systolic blood pressure, diastolic blood pressure, BMI, and waist circumference. Unscheduled visits will not be summarized but are included in the by-subject listings.

All vital sign data, including unscheduled visits, will be presented in a by-subject listing.

6.11.6. ECG

Descriptive statistics of observed values and change from baseline will be presented for each electrocardiogram (ECG) parameter by scheduled study visit using the Safety Analysis Set. Unscheduled visits will not be summarized but are included in the by-subject listings.

All ECG data, including unscheduled visits, will be presented in a by-subject listing.

6.11.7. Physical Examination

Physical examination data will be presented in a by-subject listing.

6.11.8. ECOG performance status

The number and percentages of patients in groups by largest increase (worsening) in ECOG score from baseline to any post-baseline visits will be summarized.

A listing of all ECOG Performance status at all visits will be created.

7. [redacted]

8. CHANGES TO PLANNED ANALYSIS FROM STUDY PROTOCOL

The changes to the planned analysis in the protocol are listed below.

The method of the following analysis in the protocol "All PD/efficacy variables will be summarized with descriptive statistics by treatment/dose group. The treatment group comparison between gemcitabine and Abraxane with NGM120 and gemcitabine and Abraxane with placebo will be performed using an analysis of variance (ANOVA) or analysis of covariance (ANCOVA) model for continuous variables." will be change to MMRM model to accommodate the within subject variance across time.

"Change" instead of "percentage change" will be utilized to analyze the treatment effect in the biomarkers, skeletal muscle index, hand grip strength and daily movement.

9. REFERENCES

[1] Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, Dancey J, Arbuck S, Gwyther S, Mooney M, Rubinstein L, Shankar L, Dodd L, Kaplan R, Lacobe D, Verweij J. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer. January 2009;45(2):228-47.

[2] FACIT Administration and Scoring Guidelines (www.facit.org).

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