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Protocol CA204006: A Phase 3, Randomized, Open Label Trial of Lenalidomide/dexamethasone With or Without Elotuzumab in Subjects with Previously Untreated Multiple Myeloma

Amendment Number 03 - Substudy
Site Number: All

Study Director/Central Medical Monitor
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[redacted]

This protocol amendment contains information that is confidential and proprietary to Bristol-Myers Squibb (BMS).

This amendment must be maintained with the referenced protocol.

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1 AMENDMENT INTRODUCTION AND RATIONALE

[redacted]

1.2 Research Hypothesis

At the time of progression the surface CS1 expression in the elotuzumab, lenalidomide, dexamethasone arm will be lower than at baseline.

2 OBJECTIVES

2.1 Primary Objective

- To describe the change from baseline to progression of the cell surface expression of CS1 from bone marrow-derived MM cells in both treatment arms.

2.2 Secondary Objectives

- To describe the level of cell surface CS1 from bone marrow-derived MM cells at the time of progression in both treatment arms.
- To describe sCS1 levels in serum and to evaluate change from baseline during therapy and at progression in both treatment arms.
- To describe the presence, and the change from baseline, on therapy, and at progression, of circulating MM cell numbers and their CS1 cell surface expression in both treatment arms.
- To describe the cell number and CS1 expression patterns between matched samples of bone marrow-derived MM cells and circulating MM cells at baseline and at progression in both treatment arms.

3 STUDY SITES

This study is a multi-center, non-randomized, correlative exploratory study that will be performed at approximately 15 North American and European sites that permit correlative exploratory studies to be conducted in compliance with all applicable laws, rules, and regulations.

4 SUBJECT SELECTION CRITERIA

To participate in this Correlative Sub-study Amendment, subjects will be asked to read, understand, and sign an informed consent form designed for the purpose of collecting samples for research purposes. Subjects must have consented to participate in the main clinical trial CA204006. There is no pre-determined enrollment goal for this study; participation in this substudy is strictly voluntary. **Subjects will be informed that they will not be excluded from the main clinical trial CA204006 if they do not wish to participate in the Correlative Sub-study Amendment.**

5 PROCEDURES

Subjects who consent to participate in this study and who voluntarily give written informed consent for collection of samples will have a bone marrow aspirate collected at screening (baseline) and again at time of progression. For each subject, approximately 10 mL of bone marrow aspirate will be collected at each time point; this is in addition to the volume required for the main study (1.5 mls -2.5 mls required for cytogenetic analysis, and approximately 1.5 -2.5 mls for creation of 10 slides [4 for ICON CL and 6 for FISH analysis]). A minimum of 3 mL is needed to conduct the procedures associated with the primary and secondary objectives. Additionally, peripheral blood will be collected allowing preparation of serum samples–at matched time points (screening and at time of progression) and evaluation of secondary and exploratory objectives. The collected samples will be delivered to designated laboratories for completion of the biomarker analyses and the isolation of $CD138^+$ plasma cells, which will be frozen and stored for exploratory analysis at a later date.

[redacted]

7 CONFIDENTIALITY

Bristol Myers Squibb will work to protect the confidentiality of research subjects who volunteer to participate in this correlative sub-study and to ensure that the analyses are conducted in compliance with all applicable laws, rules and regulations.

All samples are stored in a de-identified fashion; they are labeled only with a randomly generated bar code number.[2] The link between this bar code number and the coded identification number assigned to the study subject is maintained in a secure Bristol-Myers Squibb database and is not shared with either the laboratories, or the researchers, that analyze the samples.

Bristol-Myers Squibb **does not** receive subject's' names, phone numbers, addresses or National ID Numbers, such as an identity card numbers, passport numbers or US social security numbers, when collecting data from the clinical trial, and, cannot link the identity of subjects to the research analyses. Therefore, any data from the analyses that might be released into the public domain will be predominately aggregate data. For example, a scientific research publication or a presentation at a scientific meeting will not contain any information that would allow a person reading the article or attending the presentation to identify individual participants. This will minimize the chance that any information will be used as a basis for discrimination (e.g., when the subject applies for life or medical insurance).

8 SUBJECT RIGHTS

Study subjects can withdraw their consent to participate in the Correlative Sub-study Amendment at any time, and even after the sample has been shipped to the analysis lab. As long as the Investigator or Investigator's designee retains the clinical trial records, a study subject will be able to contact his/her Investigator or the Investigator's designee and ask for his/her sample to be withdrawn from the sub study and destroyed.

8.1 Record Retention

The Investigator must retain essential documents for the maximum period required by applicable regulations and guidelines.[7] or Institutional procedures, or for the period specified by the sponsor, whichever is longer. The Investigator must contact Bristol-Myers Squibb prior to destroying any records associated with the study.

Bristol-Myers Squibb will notify the Investigator when the trial records are no longer needed.

If the Investigator withdraws from the study (eg, relocation, retirement), the records shall be transferred to a mutually agreed upon designee (eg, another Investigator, IRB). Notice of such a transfer will be given in writing to Bristol-Myers Squibb.

9 WITHDRAWAL OF SUBJECTS FROM CORRELATIVE RESEARCH

Subjects have, at any time, the option to withdraw consent for participation from:

1. Only the Correlative Sub-study Amendment independent of the main clinical trial (CA204006);

OR

2. Both the main clinical trial (CA204006) and Correlative Sub-study Amendment.

Subjects who wish to withdraw their consent from the Correlative Sub-study Amendment (ie, have their samples destroyed) should contact the Investigator.

It is possible that subjects may decide to withdraw consent from the main clinical trial (CA204006) but continue with their consent for the Correlative Sub-study Amendment. In such cases the Investigator should inform subjects that their sample may be used for research.

If a subject requests to withdraw consent for the Correlative Sub-study Amendment after the time the Investigator is legally required to maintain the records linking the subject's sample and coded health information to their identity, and the records have been destroyed, the sample will become anonymous and unable to be withdrawn.

10 DESTRUCTION OF BONE MARROW SAMPLE AND RELATED MATERIAL

In the case of subjects who have withdrawn their consent for participation in the Correlative Sub-study Amendment the Investigator will notify Bristol-Myers Squibb Sample Bank. Bristol-Myers Squibb Sample Bank will destroy any remaining sample and any material obtained from the sample in accordance with BMS procedure for Sample Destruction. In the case of samples that have been partially analyzed, the remaining sample will be destroyed but Bristol-Myers Squibb shall be entitled to retain and use any research results obtained prior to the withdrawal of consent.

11 FLOW CHART/TIME AND EVENTS SCHEDULE

Table 11-1: Time and Event Schedule

Procedure	Visit Day: Screening	Visit Day: Cycle 3, Day 1	Visit Day: Time of Progression
Sub study Informed Consent	X[a]		
Bone Marrow Sample Collection	X[b]		X[c]
Serum Collection	X[b]	X	X[c]
Peripheral Blood Collection	X[b]	X	X[c]

[a] Informed consent for testing may be obtained at any time during the trial PRIOR to the collection of the sample.

[b] The sample can be collected up to 30 days prior to receiving first scheduled dose of drugs (Cycle 1/Day 1), regardless of study arm.

[c] The sample can be collected up to the start of new therapy.

12 SAMPLE COLLECTION AND PROCESSING

Following collection, the bone marrow aspirate sample will be shipped immediately at room temperature to the designated central laboratory Samples need to be received by the designated laboratory within 48 hours after collection to allow for completion of qualified assays and valid interpretation of results. The first 3mL of the collected sample will be used to conduct assays that comprise the primary, secondary objectives [redacted] The remainder of the sample will be processed by magnetic separation to isolate CD138+ plasma cells that will be immediately frozen and stored for future use to address the exploratory objectives. Peripheral blood will be collected and sent to two central laboratories to address objectives outlined in secondary and exploratory objectives. Serum collected will be prepared, frozen, and sent to BMS laboratories for evaluation of soluble proteins (including sCS1) as outlined in secondary objectives. Details for collection, processing, storing and shipping these samples will be provided in a separate procedure manual.

13 INFORMED CONSENT

Investigators must ensure that subjects, or, in those situations where consent cannot be given by subjects, their legally acceptable representative are clearly and fully informed about the purpose, potential risks and other critical issues regarding clinical studies in which they volunteer to participate. Freely given written informed consent must be obtained from every subject or, in those situations where consent cannot be given by subjects, their legally acceptable representative, prior to study participation.

The rights, safety, well-being of the study subjects are the most important considerations and should prevail over interests of science and society.

The following section contains Bristol-Myers Squibb procedures on obtaining informed consent from subjects or their legally acceptable representative prior to participating in a clinical trial. Procedures are described for all subjects including those who are unable to give informed consent. The relevant procedures must be used whenever they are applicable.

A separate informed consent will be obtained from study subjects who voluntarily agree to participate in the correlative sub study Amendment. The informed consent form for correlative sample collection reflecting this Amendment will be submitted for review and approval to the IRB/Ethics Committee charged with this responsibility.

13.1 Informed Consent Procedures

Preparation of the consent form is the responsibility of the Investigator and must include all elements required by ICH, GCP and applicable regulatory requirements, and must adhere to GCP and to the ethical principles that have their origin in the Declaration of Helsinki. The consent form must also include a statement that Bristol-Myers Squibb and regulatory authorities have direct access to subject records. Prior to the beginning of the study, the Investigator must have the IRB/IEC's written approval/favorable opinion of the written informed consent form and any other information to be provided to the subjects.

The Investigator must provide the subject or legally acceptable representative with a copy of the informed consent form and written information about the study in the language in which the subject is most proficient. The language must be non-technical and easily understood. The Investigator should allow time necessary for subject or subject's legally acceptable representative to inquire about the details of the study, then informed consent must be signed and personally dated by the subject or the subject's legally acceptable representative and by the person who conducted the informed consent discussion. The subject or legally acceptable representative should receive a copy of the signed informed consent and any other written information provided to study subjects prior to subject's participation in the trial

14 INSTITUTIONAL REVIEW BOARD/INDEPENDENT ETHICS COMMITTEE (IRB/IEC)

This amendment, the informed consent form for correlative sample collection and any advertisement for subject recruitment will be submitted for review and approval to the IRB/Ethics Committee charged with this responsibility. The investigator must have on file written and dated approval/favorable for this amendment from the IRB/Ethics Committee before this sample is collected.

[redacted]

AMENDMENT ACKNOWLEDGEMENT

I have read this Amendment and agree that it contains all necessary details for carrying out the changes described. I understand that it must be reviewed by the Institutional Review Board/Ethics Committee overseeing the conduct of the study and approved or given favorable opinion before implementation unless to eliminate an immediate hazard to subjects.

If this Amendment substantially alters the study design or increases potential risk to subjects, the consent form will be revised and submitted to the Institutional Review Board/Independent Ethics Committee for approval/positive opinion. I will use the new consent form for any new subjects prior to enrollment, and for subjects currently enrolled in the study if they are affected by the Amendment.

_____ _____

Investigator's printed name and signature *Date*

_____ _____

Medical Monitor/Study Director *Date*
(If required by applicable regulations and guidelines.)

Protocol Number: CA204006
Site Specific
Amendment Number: 03