Janssen Research & Development*

Millennium Pharmaceuticals, Inc.

Clinical Protocol

A Randomised, Open-Label, Multicentre Phase 3 Study of the Combination of Rituximab, Cyclophosphamide, Doxorubicin, VELCADE, and Prednisone (VcR-CAP) or Rituximab, Cyclophosphamide, Doxorubicin, Vincristine, and Prednisone (R-CHOP) in Patients With Newly Diagnosed Mantle Cell Lymphoma who are not Eligible for a Bone Marrow Transplant

Protocol 26866138-LYM-3002; Phase 3

JNJ-26866138 (VELCADE [Bortezomib] for Injection)**

EudraCT Number: 2007-005669-37

Amendment INT-6

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** *VELCADE is the exclusive trademark of Millennium Pharmaceuticals, Inc., registered in the United States and internationally.*

This study will be conducted under Food & Drug Administration IND regulations (21 CFR Part 312).

Issue/Report Date:	3 February 2014
Prepared by:	Janssen Research & Development, L.L.C.
Department:	Drug Development
Document No.:	EDMS-ERI-13160313:9.0 (**Legacy No.:** EDMS-PSDB-7480850)

Compliance: This study will be conducted in compliance with this protocol, Good Clinical Practice, and applicable regulatory requirements.

INVESTIGATOR AGREEMENT

I have read this protocol and agree that it contains all necessary details for carrying out this study. I will conduct the study as outlined herein and will complete the study within the time designated.

I will provide copies of the protocol and all pertinent information to all individuals responsible to me who assist in the conduct of this study. I will discuss this material with them to ensure that they are fully informed regarding the study drug, the conduct of the study, and the obligations of confidentiality.

Coordinating Investigator (where required):

Name (typed or printed): _____

Institution and Address: _____

_____

_____

_____

Signature: _____ Date: _____
(Day Month Year)

Principal (Site) Investigator:

Name (typed or printed): _____

Institution and Address: _____

_____

_____

_____

Telephone Number: _____

Signature: _____ Date: _____
(Day Month Year)

Sponsor's Responsible Medical Officer:

Name (typed or printed): Helgi van de Velde, M.D., Ph.D.

Institution: Janssen Research & Development

Signature: _____ Date: 21 FEB 2014
(Day Month Year)

Note: If the address or telephone number of the investigator changes during the course of the study, written notification will be provided by the investigator to the sponsor, and a protocol amendment will not be required.

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PROTOCOL AMENDMENTS

The original Protocol was issued 13 December 2007. Amendments are listed beginning with the most recent amendment.

Protocol Version	Issue Date
Original Protocol	13 Dec 2007
Amendment INT-1	1 Oct 2008
Amendment INT-2	26 Feb 2009
Amendment INT-3	16 Sep 2009
Amendment INT-4	23 Sep 2010
Amendment INT-5	9 Aug 2011
Amendment INT-6	3 Feb 2014

Amendment INT-6 (3 February 2014)

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

The overall reason for the amendment: The overall reason for the amendment is to provide clarification regarding long-term follow-up once the clinical cutoff has been reached for the primary endpoint and to add information regarding collection of second primary malignancy data.

Applicable Section(s)	Description of Change(s)
Rationale: Clarification is provided directing investigators to stop radiographic assessment of disease progression for subjects in short-term follow-up once clinical cutoff for the primary analysis has been reached.	
Synopsis Overview; Time/Events Schedule footnote f; 3.1. Study Design; 9.1.1. Overview; 9.1.4.1. Short-term Follow-up	Clarification added that upon notification by the sponsor that clinical cutoff for the primary analysis (295 PFS events) has been reached, radiographic assessment of disease progression will stop, and all subjects in short-term follow-up will enter the Long-term Follow-up Phase for assessment of survival status.
Rationale: Second primary malignancy is a possible risk associated with some chemotherapy treatments. Additional guidance is provided to investigators to help ensure that all cases of second primary malignancy are identified.	
Synopsis Safety Evaluation; Time/Events Schedule footnote s; 9.1.4.2. Long-term Follow-up; 9.6. Safety Evaluations; 12.2.1. All Adverse Events	Clarification added that instances of second primary malignancy will be documented for the duration of a subject's participation in the study, regardless of onset date and relationship to study drug.

PROTOCOL AMENDMENTS (CONTINUED)

Applicable Section(s)	Description of Change(s)
Rationale: Additional detail required to specify duration of the Long-term Follow-up Phase.	
Synopsis Efficacy Evaluations; Time/Events Schedule footnote g; 9.1.1. Overview; 9.1.4.2. Long-term Follow-up; 11.3. Efficacy Analyses	Long-term follow-up will continue until June 2017.
Rationale: Alignment with current sponsor requirements.	
Title Page: 1. Introduction	The company name has been updated to Janssen Research & Development. The protocol has been prepared by Janssen Research & Development, L.L.C. A statement has been added to the title page to explain the relationship between Janssen Research & Development and local operating companies.
5.2. Randomization and Blinding Procedures	Deleted reference to use of subject initials during randomization procedure.
12.2.1. All Adverse Events	Added clarification that in addition to reporting to investigators all serious adverse events that are unlisted and associated with the use of the drug, the sponsor will report this information to the head of the investigational institute where required.
12.2.3. Pregnancy	The timing for initial sponsor notification by the investigational staff of pregnancies in partners of male subjects is changed from within 1 working day of investigational staff knowledge of the event to within 24 hours of investigational staff knowledge of the event.
16.11. Use of Information	Alignment of text with current sponsor publication policy.
Rationale: Minor errors were noted	
Throughout the protocol	Minor grammatical, formatting, or spelling changes were made.

PROTOCOL AMENDMENTS (CONTINUED)

Amendment INT-5 (09 August 2011)

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

The overall reason for the amendment: The reasons for the amendment are to define criteria and appropriate boundaries for futility in the third interim analysis and to correct a footnote in the Time and Events table that was unintentionally changed in Amendment 3.

Applicable Section(s)	Text Changes (new text in **bold**, deleted text in ~~strikeout~~)	Description of change/ Rationale for Change
Throughout	Correction of minor typographical errors	
Time and Events Schedule, Footnote bb	Hematology samples on Days 1, 4, 8, and 11 of each cycle are required only for patients in Arm A prior to VELCADE dosing. For patients randomized to Arm B hematology samples will be taken on Day 1 and 11 of each cycle. No site visits are required on Day 4 and Day 8 of each cycle for patients randomized to Arm B. **Samples can be taken up to 24 hours prior to dosing day, provided the results are available before the dose of study medication is given. For pregnancy tests, if the pregnancy test during screening is within 28 days of Cycle 1 Day 1, it does not need to be repeated.**	This sentence was unintentionally omitted from Amendment 3 and is being restored as it is applicable to all protocol amendments.
Section 11.8, Interim Analyses	The third interim analysis has been planned for this study after at least 148 events have occurred in the ITT population. If, at the third interim analysis, pre-specified boundaries for PFS are met then the study will be terminated and superiority of the experimental arm (VcR-CAP) will be declared over the comparator arm (R-CHOP). **If the observed hazard ratio (R-CHOP vs VcR-CAP) for PFS in the third interim is equal to or less than 1.03 (a value of >1 favoring VcR-CAP), then the study may be terminated due to futility.** There will also be a review of the safety data at the third interim analysis.	To define criteria and appropriate boundaries for futility, in the event the conditional power falls below 30% at third interim analysis. Assuming that the observed hazard ratio (HR) is ≤1.03 at the third interim, the conditional power with future HR of 1.4 would be <30%, suggesting low probability of success at the end of the study. A stopping boundary with an observed HR of 1.03 at the third interim would only increase Type II error rate by <1%, having negligible impact on the overall power of the study. The proposed futility stopping boundary could lead to early study termination, but still maintain the overall study power if the study is not stopped.

PROTOCOL AMENDMENTS (CONTINUED)

Amendment INT-4 (23 September 2010)
This amendment is considered to be **substantial** based on the criteria set forth in Article 10(a) of Directive 2001/20EC of the European Parliament and the Council of the European Union.
The overall reason for the amendment: The amendment was based on the feedback from IDMC on the second interim analysis for safety and to provide more clarity and guidance on some aspects of the study.

Applicable Section(s)	Text Changes (new text in **bold**, deleted text in ~~strikeout~~)	Description of change / Rationale for Change
Throughout	Correction of minor typographical errors	
Synopsis, Overview of Study Design	Randomization can only occur **after central confirmation of diagnosis of MCL; except for potential patients in China, where central confirmation of sample adequacy on lymph node tissue is required**. ~~if an adequate lymph node tissue block has been submitted for central confirmation of diagnosis of MCL~~.	Confirmation of MCL as requirement prerandomization, with the exception of patients in China, added. Restriction to lymph node tissue for diagnosis of MCL removed, with exception of potential patients in China.
Time and Events Schedule procedure	~~Lymph node t~~**T**issue sample for biomarker study[v]	Restriction to lymph node tissue for diagnosis of MCL removed, with exception of potential patients in China.
Time and Events Schedule procedure	MCL ~~lymph node~~ biopsy tissue block or unstained slides **(preferably of lymph node origin)** for MCL confirmation[n]	Restriction to lymph node tissue for diagnosis of MCL removed, with exception of potential patients in China.
Time and Events Schedule procedures	**Hepatitis B screening[dd]**	Addition per IDMC recommendation.
Time and Events Schedule footnote dd	**HBsAg and anti-HBc testing to be performed**	Introduction of specific mandatory hepatitis B screening at recommendation of IDMC.
Time and Events Schedule footnote j	…..bone marrow aspirate can be used for the pharmacogenomics analysis (see footnote **p**~~y~~ below).	Corrected to refer to the corresponding footnote (ie, pharmacogenomics).

PROTOCOL AMENDMENTS (CONTINUED)

Applicable Section(s)	Text Changes (new text in **bold**, deleted text in ~~strikeout~~)	Description of change / Rationale for Change
Time and Events Schedule footnote n	Diagnosis of MCL (Stage II, III or IV) should be evidenced by ~~lymph node~~ histology and either……such as by cytogenetics, fluorescent in situ hybridization (FISH) or polymerase chain reaction (PCR). The ~~lymph node~~ biopsy sample **tissue block (preferably of lymph node origin)** and supportive data…..should be sent to the central laboratory during the screening visit ~~and the adequacy of this sample must be confirmed before randomization~~. ~~In some cases, a~~ **A** confirmation of MCL diagnosis ~~may be~~ **is** needed before the patient is randomized into the study **with the exception of China, where confirmation of sample adequacy, based on lymph node tissue, is required**. ……..In the event that there is no ~~lymph node~~ tissue block available, 10 unstained slides of 3-4 micron thickness PLUS 10 unstained slides of 10 micron thickness should be sent (these unstained slides are in addition to those required for pharmacogenomics testing).	Confirmation of MCL as requirement pre-randomization, with the exception of patients in China, added. Restriction to lymph node tissue for diagnosis of MCL removed, with exception of potential patients in China.
Time and Events Schedule footnote v	The primary ~~lymph node~~ **diagnosis** tissue (either block or slides) will also be used for pharmacogenomics testing per the patient's consent.	Restriction to lymph node tissue for diagnosis of MCL remove, with exception of potential patients in China.
Section 4.2, Inclusion Criteria	• Diagnosis of MCL (Stage II, III or IV) as evidenced by ~~lymph node~~ histology and either expression of cyclin D1…. – Paraffin embedded ~~lymph node~~ biopsy tissue block **(preferably of lymph node origin)** must be sent to the central laboratory for confirmation of **MCL diagnosis, prior to randomization. In China, a paraffin embedded lymph node biopsy tissue block must be sent for central confirmation of sample adequacy** prior to randomization. ~~In some instances a central confirmation of diagnosis may be required prior to randomization~~	Central pathology confirmation of MCL as requirement pre-randomization, with the exception of patients in China, added. Chinese patients require local pathology diagnosis of MCL and central confirmation of sample adequacy before randomization. Restriction to lymph node tissue for diagnosis of MCL removed, with exception of potential patients in China.
Section 4.2, Inclusion Criteria	Total bilirubin ≤~~2~~**1.5** x ULN	Changed to make consistent with other Velcade protocols and NCI-CTCAE v3.0 (excluding moderate and severe hepatic impairment).

PROTOCOL AMENDMENTS (CONTINUED)

Applicable Section(s)	Text Changes (new text in **bold**, deleted text in ~~strikeout~~)	Description of change / Rationale for Change
Section 5.2, Procedures	Patients can only be randomized if the **central laboratory has confirmed diagnosis of MCL or, in the case of patients in China, if the** lymph node tissue sample……to confirm the diagnosis of MCL. The IVRS will therefore be blocked after the screening call until the central laboratory has provided **the requisite** confirmation. ~~that the lymph node tissue block for analysis is adequate.~~	Confirmation of MCL as requirement pre-randomization, with the exception of patients in China, added. Restriction to lymph node tissue for diagnosis of MCL removed with the exception of potential patients in China.
Section 6.2, Dose Adjustments for Rituximab	**Carriers of hepatitis B should be closely monitored for clinical and laboratory signs of active HBV infection for several months following Rituximab therapy.**	Additional safety monitoring recommended for patients at risk of Hepatitis B re-activation.
Sections 8.3	8.3. ~~Permitted Medications and Supportive Therapies~~ **Prophylaxis for Hepatitis B Re-activation** **It is recommended that hepatitis B surface antigen positive patients receive lamivudine 100 mg/day (or equivalent prophylaxis) orally until 8 weeks after last chemotherapy.**	Recommended prophylaxis of hepatitis B re-activation during chemotherapy.
Section 8.4	8.4. ~~Excluded Medication~~ **Permitted Medications and Supportive Therapies**	This section was moved below to keep prophylactic treatments of herpes zoster (8.2) and hepatitis B (8.3) together.
Section 8.5	**8.5.** Excluded Medications	This section was created to move what was previously Section 8.4 (Excluded Medications)

PROTOCOL AMENDMENTS (CONTINUED)

Applicable Section(s)	Text Changes (new text in **bold**, deleted text in ~~strikeout~~)	Description of change / Rationale for Change
Sections 9.1.1, Overview; 9.1.2, Pretreatment Phase; 9.5, Pharmacogenomics Evaluations; 9.5.1.1, Somatic Mutational Status of Tissue; 9.5.1.3, Biomarkers; 9.5.2, Pharmacogenomics and Biomarker Samples; 9.5.3, DNA Storage for Future Analyses (Part 2); 10.3, Withdrawal From the Study; Attachment 5, Pharmacogenomics Sample Collection and Shipment Procedure	~~Lymph node~~	Deleted reference to lymph node tissue for diagnosis as restriction to lymph node for diagnosis of MCL is removed, with exception of potential patients in China.
Section 9.6, Safety Evaluation	Clinical Laboratory Tests **Calcium, alkaline phosphatase, phosphate, glucose, uric acid** • **Hepatitis B Screening** – **Hepatitis B surface antigen** – **Hepatitis B core antibody**	Added to address inconsistencies between the Time and Events Schedule and this section. Introduction of specific mandatory hepatitis B screening at recommendation of IDMC.
Section 13.4, Preparation and Handling	**Aseptic technique must be strictly observed throughout the reconstitution and handling of VELCADE since no preservative is present.** Each vial of VELCADE for Injection should be reconstituted ~~under a laminar flow biological cabinet (hood),~~ within 8 hours…..	Added to resolve reconstitution procedure of VELCADE according to the existing VELCADE prescribing guidelines (ie, Summary of Product Characteristics), relevant to the participating countries.

PROTOCOL AMENDMENTS (CONTINUED)

Amendment INT-3 (16 September 2009)
This amendment is considered to be **substantial** based on the criteria set forth in Article 10(a) of Directive 2001/20EC of the European Parliament and the Council of the European Union.
The overall reasons for the amendment: The IDMC recommendation for an additional interim analysis on safety has been added. To ensure the potential for feedback to the investigator regarding the quality of the samples sent for central review and whether they will be adequate for analysis. Provided clarity on what constitutes central MCL diagnosis. Changes to inclusion and exclusion criteria to include that a check of the quality of the lymph node sample be performed before the patient can be randomized and added in the potential to use steroids if they are waiting for the quality check of sample, and the patient has high burden disease. Clearer guidance is given on dose adjustments of cyclophosphamide and doxorubicin for hematologic toxicities. Implemented IDMC recommendations on herpes zoster prophylaxis. The sensitivity analysis on MCL diagnosed patients has been clarified.

Applicable Section(s)	Text Changes (new text in **bold**; deleted text in ~~strikeout~~)	Description of Change / Rationale for Change
Throughout	Correction of minor typographical errors or grammatical errors.	
Synopsis, Overview of Study Design	**Randomization can only occur if an adequate lymph node tissue block has been submitted for central confirmation of diagnosis of MCL.**	To clarify that in order for a patient to be randomized, a lymph node tissue sample must be submitted to central review for confirmation of MCL diagnosis.
Synopsis, Overview of Study Design; Section 3.1, Study Design; Section 9.1.1, Overview	The total study duration from randomization of the first patient until the last ~~PD~~ **PFS** event required…..enrollment and approximately 18 months for follow up).	Clarification that events for the efficacy analysis of the primary endpoint are defined as PFS, not PD.
Synopsis, Overview of Study Design; Section 3.1, Study Design	~~Two~~ **Three** interim analyses are planned for this study. The first interim analysis will occur after the first….is compared with the investigator assessment of the diagnosis.	Following the first interim analysis, the IDMC recommended to assess cumulative toxicity by reviewing safety data after 100 patients in each arm have completed or discontinued study treatment. This means the addition of a new interim analysis for the review of safety only. The study will now incorporate 3 interim analyses, instead of the originally planned 2- the first and second will be for safety only and the third, as was originally planned after 148 events, will be for safety and efficacy.

PROTOCOL AMENDMENTS (CONTINUED)

Applicable Section(s)	Text Changes (new text in **bold**; deleted text in ~~strikeout~~)	Description of Change / Rationale for Change
Synopsis, Overview of Study Design; Section 3.1 Study Design (Continued)	**Central review is defined as a review by an independent pathologist and in the event that there is insufficient tumor material available for pathological confirmation of MCL, an independent lymphoma expert will review relevant local diagnostic and clinical information to verify the diagnosis of MCL. Samples determined as negative for MCL diagnosis by the independent pathologist cannot be evaluated by the independent lymphoma expert and will not be considered MCL confirmed.**	Following the analysis of the MCL diagnosis by central pathology compared with the investigator assessment, there were a number of samples that were deemed indeterminate by central pathology due to insufficient sample availability for analysis. These patients had met the inclusion entry criteria for the diagnosis of MCL made by the investigator. In such cases, the diagnostic data used by the site will be presented to another independent lymphoma expert to verify the diagnosis.
	The concordance rate of the diagnosis of MCL will also be reviewed at 50% accrual. This ~~will~~ **may** be used to recalculate the sample size ~~so that only patients with MCL provide the required number of events required for the final analysis~~ **to ensure an adequate number of PFS events (approximately 280) in those subjects with a centrally confirmed MCL diagnosis at the time of the final analysis (295 PFS events in total).**	The IDMC agreed that a review of the concordance rate of the diagnosis of MCL should occur at 50% accrual. The adjustment of the sample size may be assessed after that review. The final analysis will occur after 295 events in the ITT population, however at that time, a sensitivity analysis will be performed on the efficacy in the population of patients with confirmed MCL by central review. This statement has been added to clarify that the sensitivity PFS analysis in the subset of subjects with centrally confirmed MCL diagnosis is adequately powered: 280 events provides approximately 80% power to detect a hazard ratio of 1.4 with a 2-sided log-rank test (α=0.05).

PROTOCOL AMENDMENTS (CONTINUED)

Applicable Section(s)	Text Changes (new text in **bold**; deleted text in ~~strikeout~~)	Description of Change / Rationale for Change
Synopsis, Overview of Study Design; Section 3.1, Study Design (Continued)	~~The~~ **A** second **interim analysis for safety will occur after 100 patients in each arm (200 patients in total) have either completed the study treatment or discontinued the study treatment, which allows sufficient exposure for review of cumulative toxicity.** The **third** interim analysis is planned after at least 148 events have occurred in **the intent-to-treat (ITT population).**	The study will now incorporate 3 interim analyses, instead of the originally planned 2- the first and second will be for safety only and the third, as was originally planned after 148 events, will be for safety and efficacy.
	If, at the **third** interim analysis, pre-specified boundaries for PFS are met then the study will be …over the comparator arm (R-CHOP). If pre-specified boundaries are not met at the **third** interim ~~stage~~ **analysis**, the final analysis of the study will occur after 295 events **have been observed in the ITT population.**	The study will now incorporate 3 interim analyses, instead of the originally planned 2- the first and second will be for safety only and the third, as was originally planned after 148 events, will be for safety and efficacy. To clarify that the required number of event are from the ITT population.
Synopsis, Overview of Study Design	The IDMC will review the data for the ~~two~~ **3** interim analyses and provide recommendations according to the charter.	The study will now incorporate 3 interim analyses, instead of the originally planned 2- the first and second will be for safety only and the third, as was originally planned after 148 events, will be for safety and efficacy.
Synopsis, Safety Evaluations	Blood samples for serum chemistry~~,~~ **and** hematology ~~and urinalysis~~ will be collected.	Urinalysis (other than for pregnancy testing) does not add any further value to the clinical and blood laboratory data on the safety analysis parameters in this study, therefore it is being removed to avoid further unnecessary investigations.
Synopsis, Statistical Methods; Section 11.1, Sample Size Determination	**If 280 PFS events are observed in the subset of subjects with a centrally confirmed diagnosis of MCL, the study can achieve approximately 80% power to detect a hazard ratio of 1.4 in this subset of patients with a 2-sided log-rank test (α=0.05).**	To clarify that the PFS sensitivity analyses in the subset of subjects with a confirmed MCL diagnosis is adequately powered.

PROTOCOL AMENDMENTS (CONTINUED)

Applicable Section(s)	Text Changes (new text in **bold**; deleted text in ~~strikeout~~)	Description of Change / Rationale for Change
Synopsis, Statistical Methods; Section 11.3, Efficacy Analyses	**For all efficacy endpoints, the primary analysis is to be performed in the ITT population. A sensitivity analysis will be performed in the subset of subjects with a centrally confirmed diagnosis of MCL. Approximately 280 events are expected in this subset of subjects at the time of the final analysis (295 PFS events in total), which can provide around 80% power to detect a hazard ratio of 1.4 using a 2-sided log-rank test (α=0.05).**	To clarify that, while primary efficacy analyses are to be performed in the ITT population, adequately powered sensitivity analyses are to be performed in those subjects with centrally confirmed MCL diagnosis.
Time and Events Schedule	Reordered letters in footnotes and added footnote u to the table	Previous version was missing 2 letters and footnote u was not cited in the table.
Time and Events Schedule Procedure	~~Urinalysis~~	Urinalysis (other than for pregnancy testing) does not add any further value to the clinical and blood laboratory data on the safety analysis parameters in this study, therefore it is being removed to avoid further unnecessary investigations.
	Lymph node ~~Archived or fresh~~ tissue sample ~~or slides~~ for biomarker study[v]	Archive tissue and slides are not the recommended tissue material for this analysis.
	Optional bone marrow sample for biomarker analysis (only need to consider if no tissue samples are available)[v]	To clarify when this option should be exercised.
	MCL **lymph node** biopsy **tissue block or unstained** slides for MCL confirmation[n]	To clarify that no archive tissue will be available as patients recruited in this study are newly diagnosed so no banked tissue will be stored.

PROTOCOL AMENDMENTS (CONTINUED)

Applicable Section(s)	Text Changes (new text in **bold**; deleted text in ~~strikeout~~)	Description of Change / Rationale for Change
Time and Events Schedule Footnote n	~~Biopsy samples and supportive materials for central …is not necessary before enrollment or treatment.~~ **Diagnosis of MCL (Stage II, III or IV) should be evidenced by lymph node histology and either expression of cyclin D1 (in association with CD20 and CD5) or evidence of t(11;14) translocation, such as by cytogenetics, fluorescent in situ hybridization (FISH) or polymerase chain reaction (PCR)**. **The** ~~pathology slides~~ **lymph node biopsy sample** and supportive data such as …..used for MCL diagnosis ~~will be collected for independent pathology confirmation of diagnosis and then~~ **should be sent to the central laboratory during the screening visit and the adequacy of this sample must be confirmed before randomization. In some cases, a confirmation of MCL diagnosis may be needed before the patient is randomized into the study. After study completion, the samples** will be returned to the study center. ~~These slides and supportive material are to be submitted before Day 1 of Cycle 2.~~ **In the event that there is no lymph node tissue block available, 10 unstained slides of 3-4 micron thickness PLUS 10 unstained slides of 10 micron thickness should be sent (these unstained slides are in addition to those required for pharmacogenomics testing).**	To provide clarity on the requirements of the diagnosis for MCL to ensure the correct study population is enrolled and to provide clarity on the tumor material required for central confirmation of diagnosis. To ensure the potential for feedback to the site regarding the quality of the samples sent for central review and whether they will be adequate for analysis. This has been implemented to ensure that no more patients are diagnosed as indeterminate due to insufficient material being sent to the central laboratory for confirmation of diagnosis.
Time and Events Schedule Footnote v	~~Patients must provide archival tumor material~~ **The primary lymph node tissue** (either block or slides) ~~for this study~~ **will also be used for pharmacogenomics testing per the patient's consent.** If this sample is ~~not available~~ **insufficient for pharmacogenomics testing**, the patient has the option to consent to a fresh ~~tumor~~ **lymph node** sample ~~collection~~.	To clarify when this option should be exercised.

PROTOCOL AMENDMENTS (CONTINUED)

Applicable Section(s)	Text Changes (new text in **bold**; deleted text in ~~strikeout~~)	Description of Change / Rationale for Change
Time and Events Schedule Footnote x	~~Samples~~ **The pregnancy test samples** can be taken up to 24 hours prior to dosing ~~day provided the results are available before the dose of study medication is given. For pregnancy tests, if the pregnancy test during screening is within 28 days of~~ **for screening pregnancy testing, a negative test up to 28 days prior to** Cycle 1 Day 1~~, it does not need to be repeated~~ **is acceptable.**	Reworded for clarity.
Time and Events Schedule, Footnote cc; Section 9.1.4.1, Short-term Follow-up; Section 9.2.1.3 Criteria for Response Categories	**When the patient is recorded to have an event of PD, a repeat CT scan to confirm PD must be undertaken at least 30 days after the scan that was used to determine PD. In the event a patient starts subsequent anti-lymphoma treatment, it is highly recommended that this repeat CT scan be performed before the patient starts treatment. The repeat CT scan must be done using i.v. and oral contrast and must be of the neck, chest, abdomen, and pelvis. If the patient is intolerant of i.v. contrast agents, the scan may be performed with only oral contrast.**	To ensure that patients are not lost to follow-up, censored inappropriately, and to minimize the discrepancy between the investigator determination of PD and independent review determination of PD.
Time and Events Schedule, Footnote cc	**At the time of the initial documentation of PD, a PD fax form together with documentation of PD (e.g., CT scan report) must be sent to the sponsor's medical representative within 24 hours.**	
Section 3.1, Study Design	This is a randomized, open-label, multicenter, prospective study to ….who have newly diagnosed MCL and who are ineligible ~~or not considered~~ for bone marrow transplantation.	This population is no longer permitted to enter the study. This was to be removed in INT-2 but due to a typographical error was not deleted in this part of the protocol. A note to file was issued to explain this.
	~~An IDMC has been commissioned for this study.~~	Removed redundant text.

PROTOCOL AMENDMENTS (CONTINUED)

Applicable Section(s)	Text Changes (new text in **bold**; deleted text in ~~strikeout~~)	Description of Change / Rationale for Change
Section 4.2, Inclusion Criteria	• Diagnosis of MCL (Stage II, III or IV) as evidenced by ….evidence of t(11;14)~~,~~ **translocation**, such….	Inadvertent omission in previous versions.
	– **Paraffin embedded lymph node biopsy tissue block must be sent to the central laboratory for confirmation of adequacy prior to randomization. In some instances a central confirmation of diagnosis may be required prior to randomization.**	To ensure the potential for feedback to the site regarding the quality of the samples sent for central review and whether they will be adequate for analysis. This has been implemented to ensure that no more patients are diagnosed as indeterminate due to insufficient material being sent to the central laboratory for confirmation of diagnosis.
Section 4.3, Exclusion Criteria; Section 8.4, Excluded Medications	– **Short course (maximum of 10 days; not exceeding 100 mg/day) prednisone or equivalent steroids are allowed to treat symptoms in subjects with advanced disease who enter the screening phase and are waiting to be randomized.**	To allow investigators to manage symptoms while waiting for the results of the sample adequacy test.
Section 5.2, Procedures	**Patients can only be randomized if the lymph node tissue sample sent to the central laboratory at screening has been evaluated as adequate for analysis to confirm the diagnosis of MCL. The IVRS will therefore be blocked after the screening call until the central laboratory has provided confirmation that the lymph node tissue block for analysis is adequate.**	To clarify that in order for a patient to be randomized, a lymph node tissue sample must be submitted to central review for confirmation of MCL diagnosis.
Section 6, Dosage and Administration	**However, careful evaluation of the toxicity (particularly hematologic toxicities) should occur when considering causality to study medication to ensure that the correct dose adjustments take place. For example, when considering causality for neutropenia in Arm A it is important to consider that cyclophosphamide or doxorubicin (or both) may be causal agent(s).**	To provide clearer guidance on causality and ensure that appropriate dose adjustments are made in cases of hematologic toxicity.
Section 6.3, Dose Adjustments for Cyclophosphamide	**In light of this, a patient can only start a cycle with cyclophosphamide if the ANC is ≥1.5 x 10^9 cells/L and platelets are ≥100 x 10^9 cells/L.** Replaced Table 2 relating to dose modifications of cyclophosphamide and doxorubicin for hematologic toxicities.	To provide clearer guidance on the dose adjustment for hematologic toxicities causally related to cyclophosphamide and doxorubicin.

PROTOCOL AMENDMENTS (CONTINUED)

Applicable Section(s)	Text Changes (new text in **bold**; deleted text in ~~strikeout~~)	Description of Change / Rationale for Change
Section 6.4, Dose Adjustments for Doxorubicin	The maximum dose given for each patient in this study will be 300 mg/m^2 (**it may be higher, for example, if the patients receive 8 cycles of treatment or have a large BSA. However, the total exposure should not exceed the lifetime cumulative dose limit)**.	The original maximum total exposure was based on average BSA and 6 cycles of exposure, but it is recognized that some patients with a high BSA or those that receive 8 cycles may have higher exposure. However in either case, the total maximum lifetime exposure must not be exceeded.
	Dose modifications for hematologic toxicities should be performed as indicated in Table 2.	To provide clearer guidance on the dose adjustment for hematologic toxicities causally related to cyclophosphamide and doxorubicin.
Section 6.7, Cycle Delay	• Platelet count ≥ ~~50~~**100** x 10^9 cells/L (prior platelet transfusion is allowed) **Patients with thrombocytopenia due to bone marrow infiltration from MCL are permitted to have platelets of ≥50 x 10^9 cells/L on the first day of each cycle**.	The platelet count has been increased at start of cycle to allow the patient a sufficient baseline to tolerate potential toxicity from cyclophosphamide. This ensures that patients are more likely to be able to receive maximum drug exposure of all study medications for each cycle.
	• ANC ≥~~1.0~~ **1.5** x 10^9 cells/L	The neutrophil count has been increased at start of cycle to allow the patient a sufficient baseline to tolerate potential toxicity from cyclophosphamide. This ensures that patients are more likely to be able to receive maximum drug exposure of all study medications for each cycle.
Section 8.2, Prophylactic Treatment for Herpes Zoster	**Prophylaxis for herpes zoster reactivation is mandatory during the Treatment Phase. Acceptable antiviral therapy includes acyclovir (e.g., 400 mg given orally, 3 times a day), famcyclovir (e.g., 125 mg given orally, twice a day), or valacyclovir (e.g., 500 mg given orally, twice a day).**	Recommendation by IDMC following the first interim analysis for safety. New section added and subsequent sections were renumbered.

PROTOCOL AMENDMENTS (CONTINUED)

Applicable Section(s)	Text Changes (new text in **bold**; deleted text in ~~strikeout~~)	Description of Change / Rationale for Change
Section 8.3, Permitted Medications and Supportive Therapies	Colony stimulating growth factors are ~~not~~ permitted ~~in the first cycle,~~ **anytime during the study for the prevention of neutropenia and also** ~~thereafter they can be preseribed~~ for the management of treatment-emergent toxicities.	G-CSF can be given for the prevention or treatment of neutropenia or febrile neutropenia.
Section 9.1.1, Overview	For the pharmacogenomic~~s~~ analysis, ~~archived~~ paraffin embedded ~~tumor~~ **lymph node** tissue blocks… will be collected. If ~~banked~~ paraffin embedded samples are not available, the patient has the option of consenting to a fresh ~~-~~**lymph node** tissue biopsy. This fresh ~~tumor~~ **lymph node** biopsy is optional and not required to participate in this study. If sufficient sample is available….required for central histology review for this study ~~may~~ **will** be utilized ~~in the absence of archived material~~. In the ~~absence~~ of ~~archival tumor~~ **sufficient lymph node** tissue blocks or fresh ~~tumor~~ **lymph node tissue** sample collection**,** the patient has the option to consent to a 5 mL bone marrow sample for the biomarker analyse**s.** Patients must provide paraffin…to a fresh ~~tumor~~ **lymph node tissue** biopsy, ~~(in the absence of archived material)~~, whole blood, bone marrow and serum sampling.	To clarify that no archive tissue will be available as patients recruited in the study are newly diagnosed so no banked tissue would be stored. Reworded sentences for clarity.
Section 9.1.2, Pretreatment Phase	**All patients must provide an adequate lymph node tissue block for central review prior to randomization.** Biopsy samples and supportive …..are required for the study.~~; however, confirmation is not necessary before enrollment or treatment.~~	Confirmation of MCL by central review is required prior to randomization into the study.
	In the event there is insufficient tumor material available for the independent pathologist confirmation of MCL, an independent lymphoma expert will review relevant local diagnostic and clinical information to verify the diagnosis of MCL. Samples determined as negative for MCL cannot be evaluated by the independent expert and will not be considered MCL confirmed.	To clarify that central review is conducted either by an independent pathologist or by an independent lymphoma expert in those cases where insufficient tumor material is available to the independent pathologist.

PROTOCOL AMENDMENTS (CONTINUED)

Applicable Section(s)	Text Changes (new text in **bold**; deleted text in ~~strikeout~~)	Description of Change / Rationale for Change
Section 9.1.2, Pretreatment Phase (Continued)	Representative ~~stained~~ **tissue block or unstained** microscope slides from a ~~prior~~ **lymph node** biopsy ~~that demonstrate the diagnosis of MCL,~~ and other supporting data… to the central pathologist. These materials must be sent to the central pathologist ~~before Day 1 of Cycle 2~~ **during screening and adequacy of these samples must be confirmed before the patient can be randomized**.	To ensure the potential for feedback to the site regarding the quality of the samples sent for central review and whether they will be adequate for analysis. This has been implemented to ensure that no more patients are diagnosed as indeterminate due to insufficient material being sent to the central laboratory for confirmation of diagnosis.
Section 9.1.4.1, Short-term Follow-up; Section 9.2.1.3, Criteria for Response Categories	**Death and events of progression constitute PFS, the primary endpoint for this study; it is therefore important that instances of PD, death or study discontinuation be reported to the sponsor as soon as possible. A PD fax form provided by the sponsor together with documentation of PD (e.g., CT scan report must be sent to the sponsor's medical representation within 24 hours of the event.**	To ensure that patients are not lost to follow-up, censored inappropriately, and to minimize the discrepancy between the investigator determination of PD and independent review determination of PD.
Section 9.5, Pharmacogenomics Evaluations	• Correlations of somatic… subunits from paraffin embedded **lymph node tissue** or fresh ~~frozen~~ **lymph node** tissue **or bone marrow** (additional genes associated with response to drug treatment may also be evaluated). • Evaluation of Ki-67, NF-kB and *PSMA5*,and other protein …in paraffin embedded **lymph node tissue** or fresh ~~frozen~~ **lymph node** tissue **or bone marrow** (e.g., p27, p53, cyclin D1, *CTAG1B, CYCLIN A, B, E, P21, ICAM, VCAM,*..... ~~A previously embedded paraffin tumor tissue sample, a whole …. 5- mL bone marrow sample), and three 5-mL serum samples (30 mL in total).~~ **Samples** will be collected from patients who give separate written informed consent…as described. ~~Archived paraffin-embedded tumor samples will be collected from all …. Ki-67, NF-kB and PSMA5 analyses .~~	To clarify that no archive tissue will be available as patients recruited in the study are newly diagnosed so no banked tissue would be stored. Reworded sentences for clarity.

PROTOCOL AMENDMENTS (CONTINUED)

Applicable Section(s)	Text Changes (new text in **bold**; deleted text in ~~strikeout~~)	Description of Change / Rationale for Change
Section 9.5, Pharmacogenomics Evaluations (Continued)	If sufficient sample is available, a portion of the ~~biopsy~~ **embedded paraffin lymph node tissue** required for central review ~~may~~ **will** be utilized for **the** analyses. ~~for proteasome and Ki-67 analyses in the absence of archival material~~. If there is ~~no archived tumor~~ **insufficient lymph node tissue** sample available, patients can optionally consent to undergo a biopsy to obtain fresh ~~tumor~~ **lymph node tissue** sample or to provide **a** 5 mL sample of bone marrow. Whole blood **(10 mL)** and **three 5 mL** serum samples will be collected…	Same as on previous page.
Section 9.5.1.1, Somatic Mutational Status of ~~Tumor~~ **Lymph Node** Tissue	~~Previously obtained paraffin-embedded,…. will be collected, if available. These tumor tissues may be from the time of the patient's initial tumor diagnosis or … study medication administration. If an archived tumor sample is not available, the …sample or provide a 5 mL bone marrow sample.~~ If sufficient sample is available, a portion of the **embedded paraffin lymph node** ~~biopsy~~ **tissue sample** required for central review ~~of the diagnosis of MCL may~~ **will** be utilized**.** ~~in the absence of archival material.~~ **If there is insufficient lymph node tissue sample available, patients can optionally consent to undergo a biopsy to obtain a fresh lymph node tissue sample or to provide a 5 mL sample of bone marrow.** Purified DNA from these ~~tumor~~ tissues will be examined….. Suspected drug target genes including …~~will~~ **may** be ~~prospectively~~ analyzed in ~~tumor~~ **lymph node** tissue of all patients in order within this clinical trial. DNA extracted from ~~archived tumor~~ **lymph node** tissue or bone marrow samples will be utilized for these analyses.	

PROTOCOL AMENDMENTS (CONTINUED)

Applicable Section(s)	Text Changes (new text in **bold**; deleted text in ~~strikeout~~)	Description of Change / Rationale for Change
Section 9.5.1.3, Biomarkers	**If sufficient sample is available, a portion of the embedded paraffin lymph node tissue sample required for central review will be utilized. If there is insufficient lymph node tissue sample available, patients can optionally consent to undergo a biopsy to obtain a fresh lymph node tissue or to provide a 5 mL sample of bone marrow.** ~~Paraffin-embedded, formalin-fixed tumor or fresh frozen tissue will also be~~ **These samples will be** subjected to immunohistochemical analysis to quantify the levels of Ki-67, p27, … prognostic proteins.	Same as on previous page.
Section 9.5.2, Pharmacogenomics and Biomarker Samples	~~Primary tumor (archived) tissue is an archived …. patients, if available. If archived tumor tissue is …..tumor tissue sample or a 5 mL bone marrow sample.~~ **If sufficient sample is available, a portion of the embedded paraffin lymph node tissue sample required for the central review will be utilized. If there is insufficient lymph node tissue sample available, patients can optionally consent to undergo a biopsy to obtain a fresh lymph node tissue sample or to provide a 5 mL sample of bone marrow.**	
Section 9.5.3, DNA Storage for Future Analyses (Part 2)	Patients will be asked to consent to …..~~archival paraffin~~ embedded ~~tumor~~ **lymph node tissue** or fresh **lymph node tissue** ~~frozen~~ samples….	
Section 9.6 Safety Evaluations	Blood samples for serum chemistry~~,~~ **and** hematology ~~and urinalysis~~ Removed urinalysis laboratory parameters	Urinalysis (other than for pregnancy testing) does not add any further value to the clinical and blood laboratory data on the safety analysis parameters in this study, therefore it is being removed to avoid further unnecessary investigations.
Section 10.3 Withdrawal From the Study	The DNA extracted from the patient's blood, bone marrow or fresh or ~~archived~~ paraffin embedded **lymph node** tissue will be retained…..	To clarify that no archive tissue will be available as these patients are newly diagnosed so no banked tissue will be stored.

PROTOCOL AMENDMENTS (CONTINUED)

Applicable Section(s)	Text Changes (new text in **bold**; deleted text in ~~strikeout~~)	Description of Change / Rationale for Change
Section 11.5, Pharmacogenomics Analyses	The pharmacogenomics exploratory statistical analysis will be performed 1) at the time of the ~~second~~ **third** interim analysis, if required; and 2) at the completion of the trial in order to inform subsequent lymphoma trials.	The IDMC recommended addition of 1 more interim analysis for safety.
Section 11.8, Interim Analyses	There will be ~~two~~ **3** interim analyses planned in the study. The first interim analysis will …when central review is compared with the investigator assessment of the diagnosis. **The concordance rate of the diagnosis of MCL when central review is compared with the investigator assessment of the diagnosis will also be reviewed at 50% accrual.** This ~~will~~ **may** be used to recalculate the sample size to ~~allow for~~ **ensure an** adequate number of **PFS** events ~~for~~ **(approximately 280) in those subjects with a centrally confirmed MCL diagnosis at the time of** the final analysis **(295 PFS events in total)**. If the observed difference is less than 95%, the sample size ~~will~~ **may** be adjusted to provide adequate **PFS** events ~~for~~ **(approximately 280) in those subjects with a centrally confirmed MCL diagnosis at the time of** the final analysis **(295 PFS events in total)**. There is no alpha adjustment for the ~~1st IA~~ **first 2 interim analyses** since no efficacy analyses will be performed.	Following the first interim analysis, the IDMC recommended to assess cumulative toxicity by reviewing safety data after 100 patients in each arm have completed or discontinued study treatment. This means the addition of a new interim analysis for the review of safety only. The study will now incorporate 3 interim analyses, instead of the originally planned 2- the first and second will be for safety only and the third, as was originally planned after 148 events, will be for safety and efficacy. The IDMC agreed that a review of the concordance rate of the diagnosis of MCL should occur at 50% accrual. The adjustment of sample size may be assessed after that review. To clarify that the PFS sensitivity analyses in those subjects with a centrally confirmed MCL diagnosis is adequately powered: 280 events provides 80% power to detect a hazard ration of 1.4 with a 2-sided log-rank test ($\alpha = 0.05$).

PROTOCOL AMENDMENTS (CONTINUED)

Applicable Section(s)	Text Changes (new text in **bold**; deleted text in ~~strikeout~~)	Description of Change / Rationale for Change
Section 11.8, Interim Analyses (Continued)	The second interim analysis **will review the safety data and be performed after 100 patients per arm have either completed or discontinued study treatment.** **The third interim analysis** has been planned for this study after at least 148 events have occurred **in the ITT population.** If, at the **third** interim analysis, pre-specified boundaries for PFS are met then the study will be ….over the comparator arm (R-CHOP). There will also be a review of the safety data at ~~2~~$^{~~nd~~}$ **the third** interim analysis. Assuming that 148 events are observed at the ~~second~~ **third** interim analysis, the alpha …for the final analysis is 0.049 (2-sided). If pre-specified boundaries are not met at the **third** interim stage, the final analysis of the study will occur after 295 events **in patients have been observed in the ITT population.**	To clarify that the required number of events are to be from the ITT population.

PROTOCOL AMENDMENTS (CONTINUED)

Applicable Section(s)	Text Changes (new text in **bold**; deleted text in ~~strikeout~~)	Description of Change / Rationale for Change
Attachment 5, Pharmacogenomics Sample Collection and Shipment Procedure	Paraffin Embedded **Lymph Node** Tissue~~, Stained and Unstained Slides,~~ (including bone marrow samples), Fresh ~~Frozen~~ **Lymph Node** Tissue ~~Archived~~ **Paraffin embedded lymph node** or fresh ~~frozen~~ **lymph node** tissue samples will be labeled …… on the tubes. A form will accompany each ~~archived~~ **lymph node** ….. as part of study specific materials (see Section 14.0). • Confirm that patient has a~~n archived~~ **a paraffin embedded lymph node** tissue sample. Determine location of ~~archival and~~ contact person. Determine if site is ….. block or fresh ~~frozen~~ **lymph node tissue** sample. • Send the paraffin embedded ~~tumor~~ **lymph node** sample from the primary biopsy or ~~tumor~~ **lymph node** resection specimen using the kit provided. • All ~~tumor~~ **lymph node tissue** blocks should be sent to the address specified by the central laboratory. • If the ~~-~~**lymph node** tissue block from the primary biopsy or ~~tumor~~ **lymph node tissue** resection… DO NOT package the ~~tumor~~ paraffin embedded **lymph node tissue** block in dry ice.	To clarify that no archive tissue will be available as these patients are newly diagnosed so no banked tissue will be stored.

PROTOCOL AMENDMENTS (CONTINUED)

Amendment INT-2 (26 February 2009)
This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20EC of the European Parliament and the Council of the European Union.
The overall reasons for the amendment: Modification of inclusion criterion restricting enrollment to patients who are truly not eligible for transplantation and the criterion for platelet counts was modified to include patients with lower baseline platelet counts secondary to mantle cell lymphoma. Exclusion criterion regarding serious medical conditions was clarified. Criteria for efficacy response were modified to make measurements operationally feasible and to comply with modified IWRC recommendations. Some laboratory tests considered not to be mandatory were eliminated. Adverse event collection wording was clarified to ensure the capture of adverse events relevant to the study. A new section for treatment of tumor lysis syndrome was added to ensure that appropriate measures are taken to prevent tumor lysis syndrome.

Applicable Section(s)	Text Changes (new text in **bold**; deleted text in ~~strikeout~~)	Description of Change / Rationale for Change
Abbreviations	Abbreviations were updated	
Synopsis, Overview of Study Design	The Treatment Phase will extend from randomization until 6 cycles of treatment have been given **(or 2 cycles beyond a response documented in Cycle 6)**.	Text added to be consistent with main body of the protocol.
Synopsis, Study Population	Patients must also be ineligible ~~or not considered~~ for bone marrow transplantation as determined by their treating physician.	To maintain a homogenous evaluable study population comprising patients who are truly not eligible for transplantation, the enrollment of those patients not considered for transplant will be terminated. All current patients falling into this category will be analyzed and evaluable per protocol.
Synopsis, Safety Evaluations	~~After 30 days after the last dose of study drug, only Grade3 and 4 adverse events will be reported until completion of the last study-related procedure.~~	Not needed in the synopsis and the wording has been revised in other sections.
Time and Events Schedule, ECOG performance status, vital signs, and BSA	Removed inappropriate cross out marks for ECOG and vital sign evaluations during Response Evaluation. Removed ~~X~~ for BSA evaluation during Short-term Follow-up.	Correction of typographical errors, ECOG and vital sign evaluations should be included during Response Evaluation period. BSA is not needed during Short-term Follow-up period.
Time and Events Schedule, Footnote h	**CT scans must be performed as part of the screening process, however if a previous scan is available, this may be used as the screening scan providing that it was performed no more than 56 days prior to randomization and meets the criteria required for study entry scans.**	To clarify that patients do not need to undergo a repeat scan for screening providing there is a scan that meets the entry criteria and is less than 56 days old.

PROTOCOL AMENDMENTS (CONTINUED)

Applicable Section(s)	Text Changes (new text in **bold**; deleted text in ~~strikeout~~)	Description of Change / Rationale for Change
Time and Events Schedule, Footnote m	Bone marrow aspirate and biopsy will be repeated… assessment that was positive, indeterminate, or insufficient~~, or not done~~.	Patients who do not have a bone marrow assessment at screening are not eligible for study entry
Time and Events Schedule, Footnote n	Hematology includes hemoglobin, ~~hematocrit~~,…	Hematocrit is not mandatory
Time and Events Schedule, Footnote o	Clinical chemistry at screening includes sodium, potassium, bicarbonate, ~~chloride~~, …calcium, and ~~magnesium (optional)~~	Removed tests from the list that are not mandatory
	All these evaluations, with the exception of **bicarbonate and** ß-2 microglobulin,….	To clarify that bicarbonate only needs to be measured at screening.
	~~ß-2 microglobulin needs only to be done at screening and at the time of documentation of PD~~	ß-2 microglobulin measurement is not needed at the time of PD, the rest of the sentence was redundant and therefore the entire sentence was deleted.
Time & Events Schedule, Footnote u	~~The total dose per day for each patient will be capped at 100 mg.~~	The dose of prednisone is not capped.
Time & Events Schedule, Footnote v	~~After 30 days after the last dose of study drug medication, only grade 3 and 4 adverse events will be collected.~~ **Adverse events occurring after 30 days following the last dose of study drug should be reported if considered related to study drug.**	To clarify that only adverse events considered related to study drug will be collected after treatment is terminated
Time & Events Schedule, Footnote w	~~ß-2 microglobulin will only be collected at the time of documentation of PD.~~	β-2 microglobulin is not needed at the time of PD.
Time & Events Schedule, Footnote ff	Hematology samples on Day **1,** 4, 8, 11…	Samples must be taken on the first day of each cycle.
	No site visits are required on Day 4 and Day 8 of each cycle for patients randomized to Arm B	To clarify that patients in Arm B do not need to attend for visits on Day 4 and Day 8 of each cycle.
Section 4.1, General Considerations	~~In addition, those patients for whom bone marrow transplantation is not available or who refuse a transplant as the treatment option for the frontline management of their MCL will be eligible to take part in this study.~~	Only those patients truly not eligible for transplantation will be allowed to enter study from this amendment onwards
Section 4.2, Inclusion Criteria	Diagnosis of MCL… as evidenced by **lymph node** histology….	To clarify that histology has to be confirmed on a lymph node biopsy and not other sites of disease

PROTOCOL AMENDMENTS (CONTINUED)

Applicable Section(s)	Text Changes (new text in **bold**; deleted text in ~~strikeout~~)	Description of Change / Rationale for Change
	Not eligible ~~or not considered~~ for bone marrow transplantation as assessed by the treating physician (e.g., **age or** the presence…. ~~Those patients who are eligible, but not considered for transplantation (e.g., due to costs or study site not performing transplantation) are no longer eligible to be enrolled into the study.~~	Those patients who are eligible, but not considered for transplantation (e.g., due to costs or study site not performing transplantation) are no longer eligible to be enrolled into the study.
	Platelets ≥100,000 cells/µL **or ≥75,000 cells/µL if thrombocytopenia is considered by the investigator to be secondary to MCL (e.g., due to bone marrow infilitration or sequestration from splenomegaly)**	Platelet count of ≥100,000 cells/µL can be too high for this patient population given that some patients with bone marrow involvement or splenomegaly due to MCL may have low platelet counts, but could benefit from therapy.
Section 4.3, Exclusion Criteria	Serious medical (**e.g., cardiac failure [New York Heart Association; NYHA Class III or IV, Attachment 12 or left ventricular ejection fraction; LVEF <50%], active peptic ulceration, uncontrolled diabetes mellitus)**…	To exclude those patients at high risk from severe toxicities associated with some of the study medication.
Section 6.1, Dose Adjustments for VELCADE	~~**The EMEA (European Medicines Agency) has contraindicated the use of VELCADE in subjects with acute diffuse infiltrative pulmonary disease and pericardial disease.**~~	This risk information was mistakenly incorporated into this document during the last update.
Section 8.1, Therapy for Tumor Lysis Syndrome	**For subjects at risk for tumor lysis syndrome, allopurinol treatment should be considered and special attention should be given to adequate hydration.**	New section added to ensure that appropriate measures are undertaken for the prevention of tumor lysis syndrome.

PROTOCOL AMENDMENTS (CONTINUED)

Applicable Section(s)	Text Changes (new text in **bold**; deleted text in ~~strikeout~~)	Description of Change / Rationale for Change
Section 9.1.2, Pretreatment Phase	All patients must undergo…….with **oral and** i.v.contrast…..~~(may be performed up to 28 days before randomization)~~; this may be performed using **only** oral contrast. **CT scans must be performed as part of the screening process, however if a previous scan is available, this may be used as the screening scan providing that it was performed no more than 56 days prior to randomization and meets the criteria required for study entry scans.**	To clarify that scans need to be done with both forms of contrast unless the patient is intolerant of i.v. contrast. Clarification of the requirements for CT scans during the Pretreatment Phase.
9.1.4.1, Short-term Follow-up	Following the End-of-Treatment visit, all patients will have efficacy assessments every 6 weeks (± 4 days) for 18 weeks ~~(±7 days)~~ and thereafter every 8 weeks **(± 7 days)**…..	Correction
	For safety assessments, after 30 days after last dose of study drug, only **adverse events considered related to study drug** will be reported.	To clarify which adverse events need to be reported after termination of treatment
9.1.4.2, Long-term Follow-up for Survival Status (Every 12 Weeks)	Only survival data, **adverse events considered related to study drug**,……Follow-up Phase	To clarify which adverse events need to be reported in long-term follow-up.
Section 9.2, Efficacy	During the study…….CT scans with **oral and** i.v. contrast	To clarify that scans need to be done with both forms of contrast unless the patient is intolerant of i.v. contrast
	~~For patients intolerant of i.v. contrast agents, the chest, and abdomen and pelvic CTs may be performed with oral contrast agents.~~	Removed redundant wording
Section 9.2.1.3, Criteria for Response Categories	All measurable lymph nodes and nodal masses ~~(including splenic and extranodal nodes and masses)~~ must have regressed….	Changes to the complete response criteria to make the measurements operationally feasible as assessable lesions are not measured or quantified. Previous wording did not allow for necessary measurements to be logistically possible.
	Non-measurable and assessable nodes ~~(including splenic and extranodal nodes and masses)~~ that were 1.1 to 1.5 …..(SPD) **as visually estimated**	

PROTOCOL AMENDMENTS (CONTINUED)

Applicable Section(s)	Text Changes (new text in **bold**; deleted text in ~~strikeout~~)	Description of Change / Rationale for Change
Section 9.2.1.3, Criteria for Response Categories (continued)	**All extranodal sites of disease must have completely disappeared.**	To comply with modified IWRC recommendations all extranodal sites of disease must have completely disappeared
	Any residual lymph node mass >1.5 cm in longest transverse dimension **or extranodal site of disease (irrespective of size)** must have regressed by more than 75%….	Changes to the unconfirmed complete response criteria make the measurements operationally feasible as assessable lesions are not measured or quantified. Previous wording did not allow for necessary measurements to be logistically possible.
	At least a 50% decrease in the sum of the product ~~of the product~~ of the diameters…	Deleted repeated wording.
	Non-measurable **nodes and** nodules must regress by ≥50% in their SPD or, for single **non-measurable** ~~nodules~~ **lesions**, in the greatest transverse diameter **as visually estimated.**	Clarification of partial response criteria
	A) ≥50% increase from nadir in the SPD of ~~any~~ all measurable sites of disease~~ >1.5 cm in the long axis and >1.0 cm in the short axis~~ at the time that progressive or relapsed disease is identified and the absolute change in at least ~~one~~ 1 dimension is ≥0.5 cm **for at least 1 lesion**; or B) ≥50% increase in the long axis of any measurable site of disease ~~>1.5 cm in the long axis and >1.0 cm in the short axis~~ at the time that progressive or relapsed disease is identified and the absolute change in the long axis is ≥0.5 cm.	Clarification of progressive disease criteria

PROTOCOL AMENDMENTS (CONTINUED)

Applicable Section(s)	Text Changes (new text in **bold**; deleted text in ~~strikeout~~)	Description of Change / Rationale for Change
Section 9.2.1.3, Criteria for Response Categories (continued)	2. A) ≥50% increase from nadir in the SPD of ~~any~~ **all** non-measurable sites of disease **(excluding truly assessable disease) as visually estimated** ~~that measures >1cm in 2 perpendicular dimensions at the time that progressive or relapsed disease is identified,~~ and the absolute change….is ≥0.5 cm **for at least 1 non-measured lesion as estimated visually**; or B) ≥50% increase in the long axis of any non-measurable site of disease **(excluding truly assessable disease)** ~~that measures >1cm in 2 perpendicular dimensions at the time that progressive or relapsed disease is identified,~~ and the absolute change in the long axis is ≥0.5 cm, **as estimated visually**. 3. ≥50% increase from nadir ~~the SPD of any other previously identified site of disease~~ **any truly assessable site of disease as visually estimated.** 4. Appearance of any new lymph node…..in short axis, **any new unequivocal extranodal site of disease (irrespective of size)**, or unequivocal … **5. Appearance of a new organ enlargement or unequivocal increase of an organ enlargement that was present since baseline.**	
Section 9.2.1.4, Reappearing Nodes	**Reappearing nodes (from a nadir of 0 cm x 0 cm): Any node(s) that reappear (measured or not measured) >1.5 x 1.0 cm or unequivocally reappearing extranodal lesions (irrespective of size and whether measured or not) should result in PD.**	New section added to provide clarity on how to classify reappearing nodes.
Section 9.3, Patient-Reported Outcomes	PRO questionnaires must be filled out during the Screening visit ~~(within 7 days prior to randomization)~~	PRO is part of the screening process, therefore the time window should not be 7 but 28 days.

PROTOCOL AMENDMENTS (CONTINUED)

Applicable Section(s)	Text Changes (new text in **bold**; deleted text in ~~strikeout~~)	Description of Change / Rationale for Change
Section 9.6, Safety Evaluations	~~The evaluation period will be defined as starting from signing the ICF to at least 30 days after the last dose of study drug. After 30 days after the last dose of study drug, only grade 3 and 4 adverse events will be reported until completion of the last study-related procedure.~~ **All adverse events, with the exception of progression of MCL, will be reported from the time a signed and dated informed consent form is obtained until 30 days following the last dose of study drug or until the start of subsequent systemic anti-lymphoma therapy, if earlier. Adverse events reported after 30 days following the last dose of study drug should also be reported if considered related to study drug**.	To ensure the capture of adverse events that are relevant to the study.
	Hematocrit removed from hematology panel	Clarification and updated based on changes in Time and Events Schedule
	~~In addition to the above laboratory parameters, chloride, bicarbonate, alkaline phosphatase, calcium, magnesium, phosphate, uric acid, glucose, and ß-2 microglobulin will be measured at screening and at relevant time points during the study…~~ **Please see Time and Events Schedule for exact time points of these and other assessments. Also included are ß-2 microglobulin and bicarbonate, which are measured only at screening.**	Reworded to provide clarity.
Section 11.8, Interim Analysis	**Assuming that 148 events are observed at the second interim analysis**, the alpha allocated for the interim is 0.003 (2-sided) and for the final analysis is 0.049 (2-sided).	Clarification

PROTOCOL AMENDMENTS (CONTINUED)

Applicable Section(s)	Text Changes (new text in **bold**; deleted text in ~~strikeout~~)	Description of Change / Rationale for Change
Section 12.2.1, All Adverse Events	~~After 30 days after the last dose of study drug, only grade 3 and 4 adverse events will be reported until completion of the last study-related procedure.~~ **All adverse events, with the exception of progression of MCL, will be reported from the time a signed and dated informed consent form is obtained until 30 days following the last dose of study drug or until the start of subsequent systemic anti-lymphoma therapy, if earlier. Resolution information after 30 days following the last dose of study drug should also be provided. Adverse events occurring after 30 days should also be reported if considered related to study drug**.	To ensure the capture of adverse events that are relevant to the study
Attachment 12	**Attachment 12: New York Heart Association Classification of Cardiac Disease**	Addition of new attachment in support of modified exclusion criterion (noted above).
Throughout the protocol	Minor grammatical, spelling, or format changes were made	Minor errors were noted.

PROTOCOL AMENDMENTS (CONTINUED)

Amendment INT-1 (1 October 2008)
This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20EC of the European Parliament and the Council of the European Union.

The original protocol, issued 13 Dec 2007, was named Protocol 26866138-LYM-3002 INT-1. This amendment corrects the name to Protocol 26866138-LYM-3002, and is Amendment INT-1.

Editorial changes and typographical errors were made and corrected throughout the document. New abbreviations were added to the abbreviations list. "Subject" was changed to "patient" for consistency.

Applicable Section(s)	Text Changes (new text in **bold**; deleted text in ~~strikeout~~)	Description of Change / Rationale for Change
Synopsis, Secondary Objectives Section 2, Secondary Objectives	To determine the duration of response (DoR), time to next treatment (TNT), and **treatment-free interval**	To add other variables of clinical benefit
Synopsis, Exploratory Objectives Section 2, Exploratory Objectives	**To evaluate medical resource utilization (MRU) information which may be used in future economic evaluation models**	MRU has been added as an exploratory objective to allow for formal analysis
Synopsis, Overview of Study Design Section 3.1, Study Design	Patients who are withdrawn from the study.…willing to continue study follow-up procedures **can** ~~should~~ be followed up as per protocol for PD.	As per the ICF, patients who withdraw consent are not mandated to provide any further data, however they may agree to provide further information such as outcome of adverse events or survival status but this is completely at their discretion.
Synopsis, Overview of Study Design Section 3.1, Study Design Section 6, Dosage and Administration Section 8.3, Subsequent Therapies Section 9.1.1, Study Procedures Overview Section 9.1.3, Treatment Phase	A clarification was made to these sections that patients with response first documented in Cycle 6 could receive 2 further cycles of therapy, for a total of 18 or 24 weeks of therapy	Ensure that all treatment arms are balanced and that all patients receive the same amount of study medication.

PROTOCOL AMENDMENTS (CONTINUED)

Applicable Section(s)	Text Changes (new text in **bold**; deleted text in ~~strikeout~~)	Description of Change / Rationale for Change
Synopsis, Overview of Study Design Section 3.1, Study Design	This will be used to recalculate the sample size ~~to allow for~~ **so that only patients with MCL provide the required** ~~an adequate~~ number of events for the final analysis	The study population is patients with MCL, however, MCL is a difficult diagnosis and can sometimes be misdiagnosed. It is critical for the final analysis that the total number of events includes only patients with a definitive diagnosis of MCL
Synopsis, Overview of Study Design Section 3.1, Study Design	~~A central review of this data by the IDMC will occur. If the concordance rate adequately meets a pre-specified target, a decision will be made to discontinue central confirmatory review of the diagnosis of MCL. If the concordance rate does not meet the pre-specified criteria, central histology review will continue and the sample size may have to be adjusted~~	Central review of diagnosis of MCL for each patient will continue throughout the whole study for all patients
Synopsis, Overview of Study Design	**An Independent Data Monitoring Committee (IDMC) will be formed and constituted according to regulatory agency guidelines. Detailed information regarding the composition of the IDMC and detailed IDMC procedures will be provided in the IDMC charter. The IDMC will review the data for the two interim analysis and provide recommendations according to the charter.**	Defines upfront that an IDMC will be constituted and review of data at interim stage will be conducted by IDMC.
Synopsis, Study Population Section 3.1, Study Design Section 4.2, Inclusion Criteria	Patients must also be ineligible **or not considered** for bone marrow transplantation as determined by their treating physician ~~and verified by the sponsor's study physician~~	Patients in centers where bone marrow transplantation is not conducted or where patients refuse transplantation as recommended by their treating physician but would otherwise receive chemotherapy can be eligible for study entry.
Synopsis, Dosage and Administration	**All patients will receive a minimum of 6 cycles of therapy irrespective of the treatment arm to which they are randomized. In both treatment arms, if a patient shows a documented response at cycle 6 efficacy assessment that has not been documented previously, they can be considered for two further cycles (as per the investigator discretion) to consolidate that response.** ~~Thereafter, study medication dose and schedule reduction for toxicity will be allowed during the study~~	It is recommended for both R-CHOP and VELCADE that responses should be consolidated with two further cycles of therapy.

PROTOCOL AMENDMENTS (CONTINUED)

Applicable Section(s)	Text Changes (new text in **bold**; deleted text in ~~strikeout~~)	Description of Change / Rationale for Change
Synopsis: Efficacy Evaluations	…progression-free survival (PFS), which is defined … the date of PD **or relapse if CR or CRu…**	To clarify definition of PFS
Synopsis: Efficacy Evaluations Section 9.2.2.2, Secondary Endpoints	The death due to PD will be considered … after last disease assessment (**or, at most, 1 missing disease assessment visit**)….	Provide clarity on which patients will be censored
Synopsis: Efficacy Evaluations	**Patients who withdraw from study (withdrawal from study or lost to follow up) or receive subsequent anti-lymphoma therapy without documented progression will be censored at the time of the last adequate disease assessment (before the start of such therapies). Patients who have not progressed and are still alive at the cutoff date for the final analysis will be censored at the last adequate disease assessment.**	Provide clarity on how the final data analysis will handle censoring of patients.
Synopsis: Efficacy Evaluations Section 9.2.2.2, Secondary Endpoints	ORR is defined as the proportion of patients who achieve CR, CRu, or PR ~~relative to the per-protocol population.~~ Disease response and progression will be evaluated according to the **modified** International Workshop to Standardize Response Criteria Group (IWRC) recommendations by radiographic imaging, **and other appropriate investigations** ~~physical examination, and other procedures as necessary~~	Provide clarity that the central radiology review and assessments will be based on radiology alone and that the IWRC has been modified for the purposes of this study to allow for appropriate assessments for patients with MCL. The investigator may use other procedures to make a clinical diagnosis. For example, the diagnosis of CR would require a confirmation of a negative bone marrow examination if positive at baseline.
Synopsis: Efficacy Evaluations Section 9.2.2.2, Secondary Endpoints	CR rate is defined as the proportion of patients who achieve CR and CRu ~~relative to the per-protocol population~~. Disease response and progression will be evaluated according to the **modified** International Workshop to Standardize Response Criteria Group (IWRC) recommendations by radiographic imaging **and other appropriate investigations**. ~~physical examination, and other procedures as necessary.~~	See above.

PROTOCOL AMENDMENTS (CONTINUED)

Applicable Section(s)	Text Changes (new text in **bold**; deleted text in ~~strikeout~~)	Description of Change / Rationale for Change
Synopsis, Efficacy Evaluations Section 9.2.2.2, Secondary Endpoints	Additionally, the CT scans or other radiographic evaluations will be locally assessed ~~by a radiologist~~ during the conduct of the study for the purpose of treatment decision-making.	Assessments will be made locally but not necessarily by a radiologist.
Synopsis, Efficacy Evaluations	~~The death due to PD will be considered as an event if the date of death is within 6 month after last disease assessment (or within one disease assessment period), otherwise, death will be censored at the date of last disease assessment~~	TTP does not include the event of death only progression
Synopsis, Safety Evaluations	The evaluation period will be defined as starting from ~~first study related procedure~~ **signing of informed consent** to …..only **grade 3 and 4** adverse events will be ~~collected~~ **reported** until completion	To clarify that all adverse events that are grade 3 and 4 will be collected
Synopsis, Safety Evaluations	In addition, 12-lead electrocardiograms (ECGs), **echocardiograms/multiple uptake acquisition (MUGA) scans**, vital signs…will be performed	Both Doxorubicin and VELCADE can give cardiac disorders and it is therefore considered important to document baseline left ventricular function or any cardiac abnormality.
Synopsis, Statistical Methods	For the secondary efficacy endpoints, the OS, ~~18-month survival, and~~ TTP, **and TNT** will be compared using stratified log-rank test. **The 18-month survival rate will be compared using the standard error estimated from the Greenwood formula.** The Kaplan-Meier method will be used to estimate the distribution of PFS, OS (**including the 18-month survival rate**), TTP, **and TNT** for each treatment.	To provide clarity in analysis of data
Synopsis, Statistical Methods	The duration of response and treatment-free interval ~~time to subsequent anti-lymphoma therapy~~ will be summarized descriptively **using the Kaplan-Meier method.**	See above.
Synopsis, Statistical Methods	TNT~~The time to subsequent anti-lymphoma therapy~~ will be summarized descriptively	Changed name of this secondary endpoint to time to next treatment (TNT)
Time and Events Schedule	Numerous changes have been made to keep the Time and Events Schedule consistent with changes made to the body of the protocol.	

PROTOCOL AMENDMENTS (CONTINUED)

Applicable Section(s)	Text Changes (new text in **bold**; deleted text in ~~strikeout~~)	Description of Change / Rationale for Change
Section 4.1, General Considerations Section 4.2, Inclusion Criteria	Patients must also be ineligible for bone …~~and verified with the sponsor study physician~~	Verification is no longer required as the data will be collected in eCRF.
Section 4.1, General Considerations	**In addition, those patients for whom bone marrow transplantation is not available or who refuse a transplant as the treatment option for the frontline management of their MCL will be eligible to take part in this study.**	Clarification of study entry criteria.
Section 4.2, Inclusion Criteria	Male or female patients 18 years or older **(the patient must be at least the legal age limit to be able to give informed consent within the jurisdiction the study is taking place).**	In some countries taking part in this study, the legal age limit to be able to give written consent is more than 18 years old.
Section 4.2, Inclusion Criteria	…such as by cytogenetics, fluorescent in situ hybridization (FISH) or polymerase chain reaction (PCR) **Patients with a diagnosis of Stage 1 MCL will not be permitted to enter study**	To clarify that Stage 1 is excluded.
Section 4.2, Inclusion Criteria	Female patients must be post menopausal …. **They must also be prepared to continue birth control measures for at least 6 months after terminating treatment.**	Vincristine recommendation in the SmPC.
Section 4.3, Exclusion Criteria	Active systemic infection requiring treatment **and patients with known diagnosis of HIV or active hepatitis B (carriers of Hepatitis B are permitted to enter study)**	Exclude high risk patients from study entry
Section 5.2, Procedures	**The IPI will be assessed according to the following risk factors: age, stage of disease, performance status, LDH level and number of extranodal sites (attachment 10). For stratification, the scores will then be categorized (low [0-1 factor], low-intermediate [2 factors], high- intermediate [3 factors] and high [4-5 factors]).** **The stage of disease at diagnosis will also be used for stratification and be assessed using the American Joint Committee on Cancer NHL staging system (Attachment 11).**	Provide detailed information and guidance on how to calculate the IPI and assess the stage of disease for this study.

PROTOCOL AMENDMENTS (CONTINUED)

Applicable Section(s)	Text Changes (new text in **bold**; deleted text in ~~strikeout~~)	Description of Change / Rationale for Change
Section 6, Dosage and Administration	**Study medication will be administered within 72 hours of randomization.**	Provide a time window and limit for the period between randomizing and delivering the first dose of study medication to the patient.
Section 6, Dosage and Administration	Study medication dose and schedule reduction…. **The time interval between sequential VELCADE doses must be at least 72 hours.**	Provide a sufficient time interval between the VELCADE doses.
Section 6, Dosage and Administration	Last 4 paragraphs of Section 6 were added in this amendment.	Provide clarity that if a patient discontinues one or two drugs for toxicity reasons, the patient is still to complete 6 cycles of therapy assigned to that arm to ensure that the patient is not withdrawn from study; and to provide an explanation that in the event of a toxicity, more than one drug may be found to be causally related and therefore more than one drug may need to have a dose adjusted or skipped
Section 6.1, Dose Adjustments for VELCADE	**Dose adjustments for VELCADE must follow the SmPC.**	
Section 6.1, Dose Adjustments for VELCADE	**The EMEA (European Medicines Agency) has contraindicated the use of VELCADE in subjects with acute diffuse infiltrative pulmonary disease and pericardial disease**.	Updated risk.
Section 6.1, Dose Adjustments for VELCADE	… VELCADE is to be held for up to 2 weeks until the patient has an ANC ≥ 750 cells/μL and a platelet count ≥ ~~30~~25,000 cells/μL	To ensure consistency in recommendations
	Dose re-escalations of VELCADE are not permitted after dose modifications for the above toxicities. **On any day of VELCADE administration during a cycle (other than day 1 of each cycle) the hematology results must be:** • Platelet count ≥ 25,000cells/μL • ANC ≥750cell/μL **If the above parameters are not met, the VELCADE dose can be held up to 2 days. Doses of study drug that need to be**	Provide clear guidance on the management of toxicities due to VELCADE and dose modification and to be consistent with the recommendation in the VELCADE SmPC.

PROTOCOL AMENDMENTS (CONTINUED)

Applicable Section(s)	Text Changes (new text in **bold**; deleted text in ~~strikeout~~)	Description of Change / Rationale for Change
	held within a cycle will be skipped, the dose will not be made up later in the cycle. **For VELCADE, cycle delays or study drug discontinuation are not required for lymphopenia of any grade.**	
Section 6.1.1, Velcade Dose Modifications for Neuropathic Pain or Peripheral Sensory Neuropathy	**Dose or schedule re-escalations are not permitted for VELCADE after modification for neuropathic pain or sensory peripheral neuropathy**.	See above.
Section 6.2, Dose Adjustments for Rituximab	~~In patients who develop viral hepatitis, rituximab should be discontinued and appropriate treatment including antiviral therapy initiated~~. **Hepatitis B virus reactivation with fulminant hepatitis, hepatic failure and death has been reported in some patients treated with rituximab. It is recommended to closely monitor carriers of hepatitis B. In patients who develop worsening of their status, rituximab should be discontinued and appropriate treatment initiated. Patients with active hepatitis should not receive rituximab**	Allow the inclusion of patients who are known to be carriers of Hepatitis B provided they are closely monitored. Patients with active hepatitis B are not to be included.
Section 6.3, Dose Adjustments for Cyclophosphamide	**The most common adverse events experienced with cyclophosphamide are hematological toxicities. Myelosuppression with leucopenia, anemia, and thrombocytopenia can occur. The lowest leukocyte and thrombocyte levels occur in the first to second week after treatment is started. Recovery usually occurs within 3-4 weeks after treatment is started**. Patients who develop hematological toxicities **thought to be causally related to cyclophosphamide** must have their dose adjusted on Day 1 of each cycle according to the following table:… **Following treatment with cyclophosphamide, hemorrhagic cystitis and hematuria can occur. These may necessitate interruption of dosing.**	Provide more guidance on the side effect profile of cyclophosphamide.

PROTOCOL AMENDMENTS (CONTINUED)

Applicable Section(s)	Text Changes (new text in **bold**; deleted text in ~~strikeout~~)	Description of Change / Rationale for Change
Section 6.4, Dose Adjustments for Doxorubicin	**Dose adjustments for Doxorubicin must follow the provided SmPC.** **Dose limiting toxicities of doxorubicin are myelosuppression and cardiotoxicity. Myelosuppresion includes leucopenia, anemia and thrombocytopenia reaching nadir at 10-14 days after treatment. Cardiotoxicity as an arrhythmia may occur directly after administration and ECG changes may last up to 2 weeks after administration. Cardiotoxicity may, however, occur several weeks or months after administration**	Provide more guidance on the side effect profile of doxorubicin.
Section 6.5, Dose Adjustments for Vincristine	**Dose adjustments for vincristine must follow the provided SmPC.** **Neurologic toxicity is the most common adverse event experienced with vincristine and it is related to dose and age**. In case of serious neurotoxicity, vincristine should not be administered, especially if there are signs of **paraesthesia or** paresis	Provide more guidance on when the dose of vincristine should be held in the event of a neurotoxic event.
Section 6.6, Dose Adjustments for Prednisone	Entire Section 6.6 is new addition to the protocol.	Allows for dose adjustment of high dose prednisone within the study if a patient develops an adverse event and is not tolerant of 100mg/m^2. But the patient still needs to receive a minimum amount of prednisone during the study.
Section 6.7, Cycle Delay	**The following parameters must be met on the first day of each cycle (other than cycle 1):** **·Platelet count ≥ 50 x 10^9 cells/L (prior platelet transfusion is allowed)** **·Hemoglobin ≥8g/dL (≥4.96mmol/L) (prior RBC transfusion or recombinant human erythropetin use is allowed)** **·ANC ≥1.0 x 10^9 cells/L** **·Nonhematologic toxicity must have recovered to Grade 1 or baseline.** **If the above parameters are not met, the start of the next cycle will be held on a weekly basis for a maximum of 3 weeks for recovery to the specified levels**	Provide clarity on what the minimum requirements are at the beginning of each cycle prior to study drug administration.

PROTOCOL AMENDMENTS (CONTINUED)

Applicable Section(s)	Text Changes (new text in **bold**; deleted text in ~~strikeout~~)	Description of Change / Rationale for Change
Section 7, Compliance	**Patients will be given diary cards to complete for the prednisone dosing at home on Days 2-5. The patients must bring these to the site on every visit so that the diary cards can be checked by study site personnel for compliance.**	To highlight that compliance and drug accountability will be ensured for the prednisone dosing that the patient will be self medicating on Days 2-5.
Section 8.1, Permitted Medications and Supportive Therapies	All supportive therapies **(such as any antinausea medication, MESNA for the prevention of hemorrhagic cystitis or antiviral prophylaxis for herpes) …**	To provide clarity that any supportive care required for the patient can be given with the exceptions listed.
Section 9.1.1, Study Procedures Overview	If sufficient sample is available, a portion of the biopsy required **for central histology review** for this study may be utilized…	Clarify which tissue sample is being referenced
Section 9.1.1, Study Procedures Overview	**In the absence of archival tumor tissue blocks or fresh tumor sample collection, the patient has the option to consent to a 5 mL bone marrow sample for the biomarker analyses.**	To clarify that the 5 mL bone marrow sample for biomarker analysis is optional and not mandatory.
Section 9.1.2, Pretreatment Phase	All patients must sign informed consent … in Sections 4.2 and 4.3 before **randomization** ~~before the first dose of investigational product can be administered~~	To clarify when informed consent must be signed.
	All patients must undergo … (may be performed up to 28 days before randomization); this may be performed ~~with~~ **using** oral contrast….	To clarify that oral contrast should be used instead of IV if the patient is intolerant of IV contrast.
	Evaluation of other sites …. before ~~first dose of study medication~~ randomization.	To clarify when sites of disease need to be evaluated
	These materials must be sent to the central pathologist after the patient receives the ~~first dose of study medication on Day 1 Cycle 1~~ **before Day 1 of Cycle 2**.	To clarify when the material required for central review must be sent to the central laboratory.
Section 9.1.3, Treatment Phase	**Treatment must start within 72 hours of randomization**	Provide a time window and limit within which the patient has to receive study medication.
	All patients who~~, on Day 1 Cycle 1 of the treatment phase, continue to~~ meet the eligibility requirements as assessed during screening will be randomized in the study and start treatment **within 72 hours of randomization** with the assigned study medication.	Provide clarity on when the patient must meet eligibility criteria.
Section 9.1.3, Treatment Phase	This visit will be performed 30 days (**with a maximum window of +7 days**) after the last dose…	Provide a maximum time limit for when the end of treatment visit can occur.

PROTOCOL AMENDMENTS (CONTINUED)

Applicable Section(s)	Text Changes (new text in **bold**; deleted text in ~~strikeout~~)	Description of Change / Rationale for Change
Section 9.1.4, Follow-up	For both short-term and long-term follow-up, time windows were added to visits	Provide maximum time limits within which the visits should occur
Section 9.1.4, Follow-up	For both short-term and long-term follow-up, clarified that **grade 3 and 4** adverse events will be reported.	After treatment only grade 3 and 4 adverse events need to be collected.
Section 9.1.4.1, Short-term Follow-up	Following the End-of-Treatment visit, all patients will have efficacy assessments **every 6 weeks (± 4 days) for 18 weeks (± 7 days)**	To provide a time window for when patients should be contacted.
Section 9.1.4.2, Long-term Follow-up for Survival Status (Every 12 Weeks)	Patients will be contacted every **12 weeks (± 7 days)** until death, via telephone or office visit to assess survival status.	To provide a time window for when patients should be contacted.
	Only survival data, **grade 3 and 4** adverse events and information on subsequent anti-lymphoma therapies will be collected in the long-term follow-up phase.	To clarify that information on subsequent anti-lymphoma therapy will also be collected.
Section 9.2, Efficacy	During the study, disease response will be assessed using CT scans with **IV** contrast of the neck, chest, abdomen and pelvis (**at minimum**, oral contrast should be used if IV contrast is contraindicated	Emphasize that all CT scans should be done with IV contrast in the first instance and oral to be used in the event that IV is contraindicated.
Section 9.2, Efficacy	…review of hematology and clinical chemistry results **may also occur at the site level, but for the purpose of the central review, only radiographic evaluations will be assessed**.	Clarification
Section 9.2.1.2, Definitions of Measurable and Assessable Disease	Measurable sites of disease are defined as **lymph nodes or** lymph node masses, ~~splenic nodules, hepatic nodules, and other~~ **or** extranodal sites of lymphoma.	Many patients will have extranodal sites of lymphoma and for MCL it is important to allow that these sites of disease be evaluable for response.
Section 9.2.1.2, Definitions of Measurable and Assessable Disease	Measurement must be determined by radiological imaging ~~or physical examination~~	Measurable lesions can only accurately be measured by radiological imaging.

PROTOCOL AMENDMENTS (CONTINUED)

Applicable Section(s)	Text Changes (new text in **bold**; deleted text in ~~strikeout~~)	Description of Change / Rationale for Change
Section 9.2.1.2, Definitions of Measurable and Assessable Disease	**Up to 10 measurable sites of disease** ~~Dominant lymph node masses include up to 6 nodal masses~~ that are clearly measurable… **will be followed for each patient**. Measurable sites of disease ~~The dominant nodal masse~~s should be chosen such that they are representative of the patient's disease (**this includes splenic and extranodal disease**). If there are **lymph nodes or** lymph node masses… should always be included ~~in the dominant masses~~. In addition, **selection of measurable lesions** ~~the dominant masses~~ should be from as disparate regions of the body as possible. ~~Extranodal sites of disease cannot be chosen as dominant lymph node masses~~	For MCL and assessments in frontline setting, the distinction between dominant and non dominant lesions are irrelevant as all sizeable lesions that fit the definition of measurable (maximum 10) should be potentially considered for study evaluation
Section 9.2.1.2, Definitions of Measurable and Assessable Disease	~~All other measurable sites of disease that are not included as dominant lymph node masses are considered nondominant measurable disease.~~ ~~·Up to 10 measurable sites of disease (the total number of dominant lymph node masses and nondominant sites of disease) will be followed for each patient~~. All other sites of disease will be considered assessable, ~~even if they are >1 cm in 2 perpendicular dimensions.~~	For MCL, there is extensive extranodal involvement and the wording has been adapted to allow for the selection of extranodal sites of disease as measurable disease to be monitored, this will be more representative of the disease.
Section 9.2.1.3, Criteria for Response Categories	All **measurable** lymph nodes and nodal masses (**including splenic and extranodal nodes and masses**) must have regressed… ~~≥~~>1.5 cm before therapy). *New bullet next*: **Non-measurable and assessable nodes ~~and any~~** ~~Previously involved nodes~~ (**including splenic and extranodal nodes and masses**) that were 1.1 to 1.5 cm …	Clarify that splenic, hepatic and extranodal sites of disease can be used as measurable lesions and that all measurable sites of disease must fulfil these criteria. The ≥ is changed to > as a typographical correction. Provide clarity on how much all other nodes than those selected as measurable nodes should regress by in order for the criteria of CR to be met. This is a frontline study so there will be no previously measured lesions available

PROTOCOL AMENDMENTS (CONTINUED)

Applicable Section(s)	Text Changes (new text in **bold**; deleted text in ~~strikeout~~)	Description of Change / Rationale for Change
Section 9.2.1.3, Criteria for Response Categories	At least a 50% decrease in sum of the product of the diameters (SPD) of ~~up to six of the largest dominant nodes or nodal masse~~ **the measurable sites of disease**	Criteria for PR have been changed to align with the changes in CR.
	~~At least 50% or greater decrease in the SPD of nondominant measurable sites of disease~~	
	No increase should be observed in ~~the size of other nodes, liver, or spleen~~ **any site of disease that meet the criteria for relapsed or progressive disease**	
	Non-measurable ~~Splenic and hepatic~~ nodules must regress by ≥50% in their SPD or, for single nodules, in the greatest transverse diameter	
	~~With the exception of splenic and hepatic nodules, involvement of other organs is usually assessable and no measurable disease should be present~~	
	No new sites of disease should be observed **that meet the criteria for relapsed or progressive disease**	
	Progressive Disease (after PR/SD) or Relapsed Disease (after CR/Cru)	Changes are made to incorporate extranodal disease as measurable disease, so the PD criteria have been changed to reflect this.
	Progressive **or relapsed** disease requires **any** one of the following:	
	In #1, ~~dominant node or nodal mass~~ replaced with **measurable site of disease**	
	In #2, any ~~measured extranodal~~ site of disease replaced with any **non-measurable site**	
	#3, ≥50% increase from nadir in the SPD of **any other previously identified site of disease** ~~non-measured site of disease that was followed from baseline, as visually determined~~	

PROTOCOL AMENDMENTS (CONTINUED)

Applicable Section(s)	Text Changes (new text in **bold**; deleted text in ~~strikeout~~)	Description of Change / Rationale for Change
	#4. Appearance of any new lymph node site of disease that measures >1.5 cm in long axis and >1.0 cm in short axis, or ~~any measurable extranodal site of disease that measures >1 cm in 2 perpendicular dimensions~~ unequivocal evidence of a new site of assessable disease (for example effusions, acites, masses with indistinct borders, new involvement of the bone marrow).	
	#5. Deleted.	
	Disease that is only assessable (e.g., pleural effusions, bone lesions) will be recorded as **no change, increased, decreased, or new**, ~~present or absent only~~, unless, while an abnormality…	To be consistent with CRF data collection
Section 9.2.2.2, Secondary Endpoints	CR rate is defined as the proportion of patients who achieve CR and CRu ~~relative to the per-protocol population. Disease response and progression will be evaluated according to the International Workshop to Standardize Response Criteria Group (IWRC) recommendations by radiographic imaging, physical examination, and other procedures as necessary~~	Correction of typographical error, this sentence is repeated from above.
Section 9.2.2.2, Secondary Endpoints	TTP **will be analysed in the ITT population and** is defined as….	Clarify to which study population the analysis will apply.
Section 9.2.2.2, Secondary Endpoints	**OS will be analysed in the ITT population**	Clarify to which study population the analysis will apply.
Section 9.2.2.2, Secondary Endpoints	TNT ~~subsequent anti-lymphoma therapy~~ will be assessed… to the start of **anti-lymphoma therapy subsequent to study treatment** ~~alternative therapy~~. Patients who do not receive alternate therapy… analysis **at the date of the last visit**. ~~death or at the last known date alive~~	Define time to next treatment
Section 9.2.2.2, Secondary Endpoints	**Treatment-free interval will be assessed, for those patients who have terminated study treatment, from the end of the study treatment to the start of anti-lymphoma therapy subsequent to the study treatment. Patients who do not receive alternate therapy will be censored in the analysis at the date of the last visit.**	Define treatment-free interval

PROTOCOL AMENDMENTS (CONTINUED)

Applicable Section(s)	Text Changes (new text in **bold**; deleted text in ~~strikeout~~)	Description of Change / Rationale for Change
Section 9.3, Patient Reported Outcomes	~~Time windows for eligible assessment will be +/- 2 weeks of the scheduled assessment.~~	
Section 9.4, Medical Resource Utilization	MRU data associated with …. will be collected for all patients **during the study**…. ~~This will be collected at the beginning of each cycle; the data entered will relate to the previous cycle~~	
Section 9.5, Pharmacogenomics Evaluations	A previously embedded paraffin tumor sample, a whole blood sample (10 mL), (**in the absence of paraffin tumor, a fresh tumor sample** or 5 mL bone marrow sample), and three 5 mL serum samples…	See below.
Section 9.5, Pharmacogenomics Evaluations	…a portion of the biopsy required ~~for this study~~ **for the central review of diagnosis of MCL** may be utilized for proteasome and Ki-67 analyses in the absence of archival material. **If there is no archived tumor sample available, patients can optionally consent to undergo a biopsy to obtain fresh tumor sample or to provide a 5 mL sample of bone marrow**. Whole blood, ~~bone marrow~~ and serum samples	For the biomarker part of the study changes are made to clarify that the only mandatory requirement is the provision of the archived tumour sample. The consent to provide a 10ml whole blood sample plus the three 5 mL serum samples is optional.
Section 9.5.1.1, Somatic Mutational Status of Tumor Tissue	…the patient has the option to consent to collection of a fresh tumor tissue sample **or provide a 5 mL bone marrow sample**. If sufficient sample is available, a portion of the biopsy required ~~for this study~~ **for the central review of the diagnosis of MCL** may be utilized in the absence of archival material. ~~A bone marrow sample will also be collected from all patients at baseline.~~	See above.
Section 9.5.1.1, Somatic Mutational Status of Tumor Tissue	DNA extracted from archived tumor tissue ~~and~~/or bone marrow samples will be utilized for these analyses	See above.
Section 9.5.1.3, Biomarkers	Paraffin embedded, formalin-fixed tumor or fresh frozen tissue will also be subjected to immunohistochemical analysis to quantify the levels of Ki-67, **p27, p65 subunit of** NF-Kb	Clarification
Section 9.5.2, Pharmacogenomics and Biomarker Samples	If archived tumor tissue is not available for mutation testing, the patient can still be entered into the study and has the option of providing a fresh tumor tissue sample~~. A~~ **or a 5 mL** bone marrow sample. ~~and~~ A whole blood sample will be collected…	See explanation under Section 9.5

PROTOCOL AMENDMENTS (CONTINUED)

Applicable Section(s)	Text Changes (new text in **bold**; deleted text in ~~strikeout~~)	Description of Change / Rationale for Change
Section 9.6, Safety Evaluations	After 30 days after the last dose…only **grade 3 and 4** adverse events will be reported…	To clarify that all adverse events that are grade 3 and 4 will be collected
Section 9.6, Safety Evaluations	ß -2 microglobulin will be measured at screening **and at relevant time points during the study, eg efficacy assessment timepoints and whenever PD is documented.**	ß -2 microglobulin is potentially a prognostic indicator, collection of these samples allows for future subanalyses
Section 9.6, Safety Evaluations	During short-term follow-up, only LDH **will be measured** ~~is required~~	Grammatical correction
Section 9.6, Safety Evaluations	Urinalysis (**if not all parameters are captured by the laboratory performing the tests, the investigator should report whichever ones are available**)	Not all of these tests are routinely done by all the laboratories, however it is important to capture as much information as is analysed.
Section 9.6, Safety Evaluations	Electrocardiogram (ECG)/**Echocardiography or Multiple Uptake Gated (MUGA) scans**	Both Doxorubicin and VELCADE can give cardiac disorders and it is therefore considered important to document baseline left ventricular function or any cardiac abnormality.
Section 9.6, Safety Evaluations	**Echocardiography or MUGA scans will be performed as mandatory at screening but thereafter optionally according to clinical need. The purpose is to document baseline ventricular and septal parameters as well as baseline ventricular function. Any follow-up test method should be the same as the screening method.**	To ensure consistency in follow-up measurements and assessments of cardiac status.
Section 10.3, Withdrawal From the Study	The DNA extracted from the patient's blood, bone marrow or **fresh** or archived paraffin embedded tissue will be retained and used in accordance	Clarification
Section 11.1, Sample Size Determination	The median PFS… is 18 months[36]	Reference added.
Section 11.3, Efficacy Analyses	The overall response rate and overall complete response rate will be obtained… using the **Cochran-Mantel-Haenszel (CMH)** chi-square test	Clarification as to which chi-square test will be used
Section 11.3, Efficacy Analyses	The duration of response and **treatment-free interval** ~~time to subsequent anti-lymphoma therapy~~ will be summarized.	Change of secondary endpoint to treatment-free interval

PROTOCOL AMENDMENTS (CONTINUED)

Applicable Section(s)	Text Changes (new text in **bold**; deleted text in ~~strikeout~~)	Description of Change / Rationale for Change
Section 11.8, Interim Analyses	If the observed concordance rate is ≥95% … ~~and central histological review of the diagnosis of MCL will be discontinued.~~ If the observed difference is less than 95% … ~~and central confirmation of the diagnosis of MCL will continue.~~	Central review of histological diagnosis will continue irrespective of concordance rate.
Section 11.8, Interim Analyses	**The first interim analysis will also review the safety data collected to date. Safety data will be reviewed after at least one cycle for the first 100 treated patients, irrespective of whether they complete treatment within that first cycle.**	To clarify that the first IA will also review the safety data in the intent-to-treat population.
	….of the experimental arm (VcR-CAP) will be declared over the comparator arm (R-CHOP). **There will also be a review of the safety data at 2nd interim analysis.**	Clarify that the 2nd IA will also have a review of the safety data.
Section 11.9, Independent Data Monitoring Committee	…to evaluate safety data and results of the prospectively defined interim analyses of efficacy **and central histological review**.	Clarify that the IDMC will review both interim analyses data.
Section 12.2.1, Procedures	PD or relapse will not be reported as an adverse event, **however, unexpected clinical signs or symptoms must be reported, even if they are eventually attributable to PD or relapse**.	Provide clarity on what should be reported.
Section 12.2.3, Pregnancy	Any patient who becomes pregnant during the study must be promptly withdrawn from **treatment within** the study	Clarify that if the patient becomes pregnant they should not receive any more treatment but should in fact be followed up for outcome.
Section 13.1, Physical description of study drugs	Vincristine is supplied as a lyophilized powder or **as United States Pharmacopeia (USP), sterile, preservative–free, single use only, solution available for intravenous use in 2 mL vial.**	Clarification on Vincristine information
Section 13.2, Packaging	Packaging information was updated for all study medication.	Providing clarity
Section 13.2, Packaging	Prednisone 5 mg and **20** mg tablets….	Correcting typographical error
Section 13.4, Preparation and Handling	Prednisone should be stored at ~~Store at Controlled Room Temperature 15º to~~ **room temperature**	To ensure compliance as prednisone will be self medicated by the patient at home

PROTOCOL AMENDMENTS (CONTINUED)

Applicable Section(s)	Text Changes (new text in **bold**; deleted text in ~~strikeout~~)	Description of Change / Rationale for Change
Section 13.4, Preparation and Handling	Cyclophosphamide is a cyto~~static~~**toxic** agent. As with all cyto~~static~~**toxic** agents, caution is required when preparing and handling cyclophosphamide. Cyto~~static~~**toxic** agents….	Clarify the classification of agents.
	Doxorubicin is a cyto~~static~~**toxic** agent. As with all cyto~~static~~**toxic** agents, caution is required when preparing and handling doxorubicin. Cyto~~static~~**toxic** agents….	
	Vincristine is a cyto~~static~~**toxic** agent. As with all cyto~~static~~**toxic** agents, caution is required when preparing and handling Vincristine. Cyto~~static~~**toxic** agents….	
Section 13.5, Drug Accountability	Patients will be given diary cards to complete for the prednisone dosing at home on days 2-5. The patients must bring these to the site on every visit so that the diary cards can be checked by study site personnel for compliance.	To highlight that compliance and drug accountability will be ensured for the prednisone dosing that the patient will be self medicating on days 2-5
Section 15.2.3, Informed Consent	date a separate pharmacogenomics informed consent form indicating agreement to participate in pharmacogenomics and **biomarker** research.	Clarification
Attachment 5	Change in shipping address	Samples will be received and handled through J&JPRD, Department of Pharmacogenomics. Samples will be distributed from the repository at JJPRD to the vendor identified to perform the protocol specified analyses.
Attachment 7	Deleted last page	The questionnaire has been updated and no longer includes the last page.
Attachment 10 and Attachment 11	Added to the protocol.	

A Randomised, Open-Label, Multicentre Phase 3 Study of the Combination of Rituximab, Cyclophosphamide, Doxorubicin, VELCADE, and Prednisone (VcR-CAP) or Rituximab, Cyclophosphamide, Doxorubicin, Vincristine, and Prednisone (R-CHOP) in Patients With Newly Diagnosed Mantle Cell Lymphoma who are not Eligible for a Bone Marrow Transplant

SYNOPSIS

OBJECTIVES

Primary Objectives

To determine which regimen rituximab, cyclophosphamide, doxorubicin, VELCADE, and prednisone (VcR-CAP) or rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) provides greater benefit in patients with newly diagnosed mantle cell lymphoma (MCL), as assessed by significant prolongation of progression-free survival (PFS).

Secondary Objectives

The secondary objectives are:

- To determine overall survival (OS)
- To determine time to progression (TTP)
- To determine the 18-month survival rate
- To determine overall response (CR+CRu+PR) and CR (CR + CRu) rates
- To determine the duration of response, time to next treatment (TNT), and treatment-free interval
- To evaluate the safety of VcR-CAP compared to R-CHOP

Exploratory Objectives

- To evaluate patient-reported outcomes (PROs) utilizing the European Organisation for Research and Treatment of Cancer-quality of life questionnaire (EORTC-QLQ-C30), EQ-5D, and Brief Fatigue Inventory (BFI) instruments
- To evaluate medical resource utilization (MRU) information which may be used in future economic evaluation models
- To identify patient populations that are more or less likely to respond to VcR-CAP or R-CHOP through the evaluation of biomarker analyses

OVERVIEW OF STUDY DESIGN

This is a randomized, open-label, multicenter, prospective study to compare the efficacy and safety of the combination of VcR-CAP to that of R-CHOP in patients who have newly diagnosed MCL of Stage II, III, or IV and who are ineligible to undergo bone marrow transplantation.

At least 486 patients will be randomized into one of 2 arms (Treatment Arm A or Treatment Arm B) in a 1:1 ratio taking into account the following stratification factors: International Prognostic Index (IPI) and stage of disease at diagnosis.

Treatment Arm A: (VcR-CAP) rituximab 375 mg/m^2 intravenous (i.v.) on Day 1, cyclophosphamide 750 mg/m^2 i.v. on Day 1, doxorubicin 50 mg/m^2 i.v. on Day 1, VELCADE 1.3 mg/m^2 i.v. on Days 1, 4, 8 and 11, prednisone 100 mg/m^2 per os (p.o.) on Day 1 to Day 5 of a 21 day (3 week) cycle for 6 cycles (or 8 cycles if a response is first documented at Cycle 6 assessment).

Treatment Arm B: (R-CHOP) rituximab 375 mg/m^2 i.v. on Day 1, cyclophosphamide 750 mg/m^2 i.v. on Day 1, doxorubicin 50 mg/m^2 i.v. on Day 1, vincristine 1.4 mg/m^2 (maximum total of 2 mg) i.v. on Day 1, prednisone 100 mg/m^2 p.o. on Day 1 to Day 5 of a 21 day (3 week) cycle for 6 cycles (or 8 cycles if a response is first documented at Cycle 6 assessment).

SYNOPSIS (CONTINUED)

Patient participation will include a Screening Phase, a Treatment Phase, a Short-term Follow-up Phase, and a Long-term Follow-up Phase. The Screening Phase will be up to 28 days (56 days for bone marrow evaluation) prior to randomization. Randomization can only occur after central confirmation of diagnosis of MCL except for potential patients in China, where central confirmation of sample adequacy on lymph node tissue is required. The Treatment Phase will extend from randomization until 6 cycles of treatment have been given (or 2 cycles beyond a response documented in Cycle 6). The Short-term Follow-up Phase will extend from the End-of-Treatment Phase to PD (progressive disease) (or relapse if the patient achieves a CR or CRu), initiation of alternate antineoplastic therapy, decision by the patient to completely withdraw from the study or refusal to take part in any further study related procedures or follow-up, or death. The Long-term Follow-up Phase will be used to assess survival and will document when the patient has died. Patients who are withdrawn from the study due to adverse events, or reasons other than above and are willing to continue study follow-up procedures can be followed up as per protocol for PD. Upon notification by the sponsor that clinical cutoff for the primary analysis (295 PFS events) has been reached, radiographic assessment of disease progression will stop, and all subjects in short-term follow-up will enter the Long-term Follow-up Phase.

Patients will be randomized and assigned to either Treatment Arm A or B. They will receive 6 cycles of therapy; if a documented response is noted at Cycle 6 assessment that has not been previously observed, the patients can receive a further 2 cycles to consolidate the response. Patients may receive less therapy or deviate from the planned treatment dose and schedule due to adverse events, as specified by the dose and schedule modifications and cycle delays defined in the protocol.

The total study duration from randomization of the first patient until the last PFS event required for the final analysis is expected to be approximately 42 months (approximately 24 months for enrollment and approximately 18 months for follow up).

Three interim analyses are planned for this study. The first interim analysis will occur after the first 100 patients have been randomized into the study and will assess safety and the concordance rate of the diagnosis of MCL when central review is compared with the investigator assessment of the diagnosis. Central review is defined as a review by an independent pathologist and in the event that there is insufficient tumor material available for pathological confirmation of MCL, an independent lymphoma expert will review relevant local diagnostic and clinical information to verify the diagnosis of MCL. Samples determined as negative for MCL diagnosis by the independent pathologist cannot be evaluated by the independent lymphoma expert and will not be considered MCL confirmed. The concordance rate of the diagnosis of MCL will also be reviewed at 50% accrual. This may be used to recalculate the sample size to ensure an adequate number of PFS events (approximately 280) in those subjects with a centrally confirmed MCL diagnosis at the time of the final analysis (295 PFS events in total). A second interim analysis for safety will occur after 100 patients in each arm (200 patients in total) have either completed the study treatment or discontinued the study treatment, which allows sufficient exposure for review of cumulative toxicity**.** The third interim analysis is planned after at least 148 events have occurred in the intent-to-treat (ITT) population.

If, at the third interim analysis, pre-specified boundaries for PFS are met then the study will be terminated and superiority of the experimental arm (VcR-CAP) will be declared over the comparator arm (R-CHOP). If pre-specified boundaries are not met at the third interim analysis, the final analysis of the study will occur after 295 events have been observed in the ITT population.

An Independent Data Monitoring Committee (IDMC) will be formed and constituted according to regulatory agency guidelines. Detailed information regarding the composition of the IDMC and detailed IDMC procedures will be provided in the IDMC charter. The IDMC will review the data for the 3 interim analyses and provide recommendations according to the charter.

SYNOPSIS (CONTINUED)

STUDY POPULATION

Male and female patients who have a confirmed molecular diagnosis of MCL (Stage II, III or IV) and have had no other prior treatments for their disease will be eligible to take part in the study. Patients must also be ineligible for bone marrow transplantation as determined by their treating physician.

DOSAGE AND ADMINISTRATION

Patients randomized to Treatment Arm A will receive rituximab 375 mg/m^2 i.v. on Day 1, cyclophosphamide 750 mg/m^2 i.v. on Day 1, doxorubicin 50 mg/m^2 i.v. on Day 1, VELCADE 1.3 mg/m^2 (i.v.) on Days 1, 4, 8 and 11, prednisone 100 mg/m^2 p.o. on Day 1 to Day 5 of a 21 day (3 week) cycle for 6 cycles (VcR-CAP). VELCADE will be administered as a 3 to 5 second intravenous bolus before the other medications are administered. Thereafter, rituximab will be administered followed by the other study medications as per the directions provided in the respective product labels.

Patients randomized to Treatment Arm B will receive rituximab 375 mg/m^2 i.v. on Day 1, cyclophosphamide 750 mg/m^2 i.v. on Day 1, doxorubicin 50 mg/m^2 i.v. on Day 1, vincristine 1.4 mg/m^2 (maximum total of 2 mg) i.v. on Day 1, prednisone 100 mg/m^2 p.o. on Day 1 to Day 5 of a 21 day (3 week) cycle for 6 cycles (R-CHOP). All study medications will be administered according to the directions provided in the respective product labels.

All patients will receive a minimum of 6 cycles of therapy irrespective of the treatment arm to which they are randomized. In both treatment arms, if a patient shows a documented response at Cycle 6 efficacy assessment that has not been documented previously, they can be considered for 2 further cycles (as per the investigator discretion) to consolidate that response.

EFFICACY EVALUATIONS/CRITERIA

The primary endpoint is progression-free survival (PFS), which is defined as the interval between the date of randomization and the date of PD or relapse if CR or CRu or death, whichever is first reported, in the intent-to-treat (ITT) population. Death due to PD will be considered as an event if the date of death is within 6 months after last disease assessment (or, at most, 1 missing disease assessment visit), otherwise, death will be censored at the date of last disease assessment. Patients who withdraw from study (withdrawal from study or lost to follow-up) or receive subsequent anti-lymphoma therapy without documented progression will be censored at the time of the last adequate disease assessment (before the start of such therapies). Patients, who have not progressed and are still alive at the cutoff date for the final analysis, will be censored at the last adequate disease assessment.

Secondary endpoints are:

- ORR is defined as the proportion of patients who achieve CR, CRu, or PR. Disease response and progression will be evaluated according to the modified International Workshop to Standardize Response Criteria for Non-Hodgkin's Lymphoma (IWRC) recommendations by radiographic imaging and other appropriate investigations.

  The computed tomography (CT) scans or other radiographic evaluations will be centrally assessed by independent radiology review to confirm disease response for the purpose of the efficacy analyses. Additionally, the CT scans or other radiographic evaluations will be locally assessed during the conduct of the study for the purpose of treatment decision-making.

  CR rate is defined as the proportion of patients who achieve CR and CRu. Disease response and progression will be evaluated according to the modified IWRC recommendations by radiographic imaging and other appropriate investigations.

- Duration of response (CR, CRu, or PR) will be calculated from the date of initial documentation of a response to the date of first documented evidence of PD (or relapse for patients who experience CR or CRu on this study).

SYNOPSIS (CONTINUED)

- TTP is defined as the duration from the date of randomization until the date of first documented evidence of PD (or relapse for patients who experience CR or CRu on this study).
- OS is measured from the date of randomization to the date of the patient's death. If the patient is alive or the vital status is unknown, the date of death will be censored at the date that the patient is last known to be alive. Long-term follow-up will continue until June 2017.
- 18-month survival is defined as estimated survival rate at 18 months (Kaplan-Meier estimate).
- TNT is measured from the date of randomization to the start date of any anti-lymphoma treatment subsequent to the study treatment. Those patients without subsequent treatment will be censored at the date of the last visit.
- Treatment-free interval is measured from the end of the study treatment to the start date of any anti-lymphoma treatment subsequent to the study treatment. Those patients without subsequent treatment will be censored at the date of the last visit.

PHARMACOGENOMICS EVALUATIONS

Pharmacogenomics evaluations in this study will help to identify patient populations that are more or less likely to respond to VcR-CAP or R-CHOP through the evaluation of a defined set of biomarkers. Analysis of selected somatic and germline mutations are mandatory where health authorities have approved of this testing, and will require a separate patient informed consent.

SAFETY EVALUATIONS

All patients who receive treatment will be considered evaluable for toxicity. The evaluation period will be defined as starting from signing of informed consent to at least 30 days after the last dose of study drug. Blood samples for serum chemistry and hematology will be collected. In addition, 12-lead electrocardiograms (ECGs), echocardiograms/multiple uptake gated acquisition (MUGA) scans, vital signs, and physical examinations will be performed. Instances of second primary malignancy will be documented for the duration of a subject's participation in the study, regardless of onset date and relationship to study drug.

STATISTICAL METHODS

The sample size calculation for the study population is based on the following assumptions. The median PFS of R-CHOP is 18 months. Assuming that VcR-CAP improves this median PFS by 40%, i.e., from 18 months to 25 months, a total number of 295 (PD or death) events provides 80% power (alpha = 0.05, 2-sided) to detect such improvement. Assuming a 24 month accrual and 18 month follow-up, a total of 486 patients is needed for the study (243 per arm).

If 280 PFS events are observed in the subset of subjects with a centrally confirmed diagnosis of MCL, the study can achieve approximately 80% power to detect a hazard ratio of 1.4 in this subset of patients with a 2-sided log-rank test (α=0.05).

Demographic and baseline characteristics will be summarized according to treatment group.

Stratified log-rank test will be used to compare PFS between the 2 treatment arms in the primary efficacy analysis.

For the secondary efficacy endpoints, the OS, TTP, and TNT will be compared using stratified log-rank test. The 18-month survival rate will be compared using the standard error estimated from the Greenwood formula. The Kaplan-Meier method will be used to estimate the distribution of PFS, OS (including the 18-month survival rate), TTP, and TNT for each treatment.

ORR and CR rate will be obtained and comparison of the rates will be performed between 2 treatment arms using the Cochran-Mantel-Haenszel (CMH) chi-square test. The 95% confidence interval for the difference of response rate between 2 treatment arms will be given.

SYNOPSIS (CONTINUED)

The duration of response and treatment-free interval will be summarized descriptively using the Kaplan-Meier method. There will be no formal comparison of these endpoints between treatment groups because they are not statistically comparable.

TNT will be summarized descriptively. There will be no formal comparison of these endpoints between treatment groups because they are not statistically comparable.

For all efficacy endpoints, the primary analysis is to be performed in the ITT population. A sensitivity analysis will be performed in the subset of subjects with a centrally confirmed diagnosis of MCL. Approximately 280 events are expected in this subset of subjects at the time of the final analysis (295 PFS events in total), which can provide around 80% power to detect a hazard ratio of 1.4 using a 2-sided log-rank test (α=0.05).

Detailed tabulations of safety data (adverse events, vital signs, physical examinations and clinical laboratory tests) will be provided for all patients who receive study drug. The number and percent of patients with treatment-emergent adverse events will be summarized. Summary of other safety parameters by treatment group will be provided where appropriate.

TIME AND EVENTS SCHEDULE

Procedure	Screening	Cycles 1- 6 (and 7-8, if applicable)				Response Evaluation[d] Days 11-21 of Cycles 2, 4, 6 (and 8, if applicable)	Early Withdrawal/ End-of-Treatment Phase[e]	Short-term Follow-up[f] until PD/initiation alternate therapy/withdrawal	Long-term Follow-up[g] until death
		Day1	Day4	Day 8	Day 11				
Informed consent	X								
Inclusion/ Exclusion	X								
Demographics/Medical history	X								
Complete physical examination	X					X	X		
Limited physical examination[aa]		X[a]	X	X	X			X	
ECOG performance status	X	X[a]				X	X	X	
Vital signs		X[a]	X	X	X	X	X	X	
Weight/Height		X[a]					X	X	
BSA		X[a]							
ECG	X	X[a]					X		
Echocardiogram/MUGA scan[y]	X								
Neck and chest CT with oral and i.v. contrast[h]	X					X	X	X	
Abdomen and pelvis CT with oral and i.v. contrast[h]	X					X	X	X[cc]	
Evaluation of other sites of disease[i]	X					X	X	X[cc]	
Bone marrow aspirate and biopsy	X[j]					X[k]	X[k]	X[k]	
Hematology[l]	X	X[x]	X[bb]	X[bb]	X[bb]	X	X		
Clinical Chemistry[m]	X	X[x]				X	X	X[t]	
Serum/Urine β-HCG pregnancy test (for females)	X	X[a, x]					X		
Hepatitis B Screening[dd]	X								
PRO (EORTC-QLQ-C30, EQ5D, BFI)[o]	X	X					X		
Medical resource utilization[z]		X					X	X	

NOTE: Footnotes are provided at the end of the table (Continued)

TIME AND EVENTS SCHEDULE (CONTINUED)

Procedure	Screening	Cycles 1- 6 (and 7-8, if applicable)				Response Evaluation[d] Days 11-21 of Cycles 2, 4, 6 (and 8, if applicable)	Early Withdrawal/ End-of-Treatment Phase[e]	Short-term Follow-up[f] until PD/initiation alternate therapy/withdrawal	Long-term Follow-up[g] until death
		Day1	Day4	Day 8	Day 11				
FACT/GOG neurotoxicity questionnaire[u]	X	X					X		
Tissue sample for biomarker study[v]	X								
Optional bone marrow sample for biomarker analysis (only need to consider if no tissue samples are available)[v]	X								
Whole blood sample for pharmacogenomics and future testing (10 mL)[p]		X							
Serum sample collection (5 mL blood)[q]		X							
MCL biopsy tissue block or unstained slides (preferably of lymph node origin) for MCL confirmation[n]	X								
Concomitant medications/procedures	X	X	X	X	X	X	X	X[w]	X[w]
Adverse events	X	X	X	X	X	X	X	X[s]	X[s]
Survival									X
Rituximab dosing		X							
Prednisone dosing		X[r]							
Doxorubicin dosing		X							
Vincristine dosing[b]		X							
Cyclophosphamide dosing		X							
VELCADE dosing[c]		X	X	X	X				

NOTE: Footnotes are provided at the end of the table (Continued)

TIME AND EVENTS SCHEDULE (CONTINUED)

ALC = absolute lymphocyte count, ALT = alanine transaminase, ANC = absolute neutrophil count, AST = aspartate transaminase, β-HCG = beta-human chorionic gonadotropin, BFI = Brief Fatigue Inventory, BSA = body surface area, BUN = blood urea nitrogen, CR = complete response, CT = computed tomography, EORTC-QLQ-C30 = European Organisation for Research and Treatment of Cancer-quality of life questionnaire, FACT = Functional Assessment of Cancer Therapy; FISH = fluorescent in situ hybridization, GOG = Gynecologic Oncology Group, i.v. = intravenous, LDH = lactate dehydrogenase, MCL = mantle cell lymphoma, PCR = polymerase chain reaction, PD = progressive disease, PR = partial response, PRO = patient-reported outcomes, WBC = white blood cell

[a] To be performed prior to first dose in Cycle 1 Day 1, height at screening only

[b] Vincristine dosing for patients randomized to Treatment Arm B only

[c] VELCADE dosing for patients randomized to Treatment Arm A only

[d] Disease response assessments must be completed between Day 11 (after VELCADE administration for patients randomized to Arm A) and Day 21 inclusive. These disease response assessment results must be available before the first dose in the next cycle

[e] This visit is required for all patients. It should take place 30 days after the last dose of study medication with a window of +7 days. Early withdrawal is defined as stopping treatment before 6 complete cycles are given. If the patient requires alternate antineoplastic therapy in the interim period following the last dose of study medication and the End of Treatment visit then this visit should be completed earlier, i.e., just prior to initiation of alternate antineoplastic therapy

[f] Short-term Follow-up visits to assess disease progression will be required if treatment is discontinued prior to PD. Short-term Follow-up visits will be completed every 6 weeks for 18 weeks with a window of ±4 days and then every 8 weeks thereafter until PD with a window of ±7 days. The interval between Short-term Follow-up visits should be maintained at 6 or 8 weeks as required; if a visit occurs earlier or later than the scheduled visit date then the next visit date should be rescheduled to maintain the required interval from the previous visit. Upon notification by the sponsor that clinical cutoff for the primary analysis (295 PFS events) has been reached, radiographic assessment of disease progression will stop, and all subjects in short-term follow-up will enter the Long-term Follow-up Phase.

[g] Long-term Follow-up (physician visit or telephone contact) to assess survival will be required for all patients following PD or start of alternate antineoplastic therapy until death. Long-term Follow-up will be completed every 12 weeks with a window of ±7 days. The interval between Long-term Follow-up visits should be maintained at 12 weeks; if a visit occurs earlier or later than the scheduled visit date then the next visit date should be rescheduled to maintain the required interval from the previous visit. Long-term follow-up will continue until June 2017.

[h] May be performed with only oral contrast, if patient is intolerant of i.v. contrast agents. CT scans must be performed as part of the screening process, however if a previous scan is available, this may be used as the screening scan providing that it was performed no more than 56 days prior to randomization and meets the criteria required for study entry scans.

[i] Evaluation of other sites of disease may be performed by radiological imaging, physical examination, or other procedures as necessary, and should be performed throughout the study using the same method of assessment per patient. The physical examination scheduled on Day 1 of the immediately following cycle may be used. The hematology and clinical chemistry results from the nearest visit to the disease response assessments may be used for the disease response assessments during the rest periods of Cycles 2, 4 and 6. For patients consenting to the pharmacogenomics part of the study, one 5 mL sample of bone marrow will also be collected if the patient provides consent. This sample will be collected in addition to the clinically defined aspirate but will be collected at the same time.

[j] May be performed up to 56 days before first dose of study medication, 5 mLs of the bone marrow aspirate can be used for the pharmacogenomics analysis (see footnote p below).

[k] Bone marrow aspirate and biopsy will be repeated once during the study for confirmation of CR within 30 days of initial documentation of CR in patients with a screening bone marrow assessment that was positive, indeterminate, or insufficient.

[l] Hematology includes hemoglobin, platelets, complete WBC, ANC, and ALC.

[m] Clinical chemistry at screening includes sodium, potassium, bicarbonate, BUN/urea, creatinine, calcium, AST, ALT, total bilirubin, alkaline phosphatase, albumin, LDH, phosphate, uric acid, glucose, and ß-2 microglobulin. All these evaluations, with the exception of bicarbonate and ß-2 microglobulin, have to be repeated also at efficacy assessment time points and at the end-of-treatment or early withdrawal. On Day 1 of each cycle beginning with Cycle 2, clinical chemistry includes sodium, potassium, BUN/urea, creatinine, AST, ALT, total bilirubin, albumin, and LDH.

(continued)

TIME AND EVENTS SCHEDULE (CONTINUED)

[n] Diagnosis of MCL (Stage II, III or IV) should be evidenced by histology and either expression of cyclin D1 (in association with CD20 and CD5) or evidence of t(11;14) translocation, such as by cytogenetics, fluorescent in situ hybridization (FISH) or polymerase chain reaction (PCR). The biopsy sample tissue block (preferably of lymph node origin) and supportive data such as flow cytometry, cytogenetics, FISH, and PCR used for MCL diagnosis should be sent to the central laboratory during the screening visit. A confirmation of MCL diagnosis is needed before the patient is randomized into the study with the exception of China, where confirmation of sample adequacy, based on lymph node tissue, is required. After study completion, the samples will be returned to the study center. In the event that there is no tissue block available, 10 **unstained** slides of 3-4 micron thickness **PLUS** 10 **unstained** slides of 10 micron thickness should be sent (these **unstained** slides are in addition to those required for pharmacogenomics testing).

[o] To be completed before any other scheduled assessments are performed or treatment given.

[p] Patient participation in the pharmacogenomics component of the study is optional. A 10 mL blood sample will be collected only from patients who give informed consent for the pharmacogenomics component of this study. A pharmacogenomics blood sample drawn at a different visit does not constitute a protocol violation and will not require a protocol waiver.

[q] Cycles 1, 2 and 3 only. Cycle 1 sampling should be done before drug administration.

[r] Prednisone on Day 1 through Day 5 of each cycle.

[s] Adverse events occurring after 30 days following the last dose of study drug should be reported if considered related to study drug; however, all cases of second primary malignancy will be reported for the full duration of a subject's participation in the study, regardless of onset date and relationship to study drug.

[t] Only LDH will be collected during short-term follow-up.

[u] FACT/GOG will not be captured in the eCRF or clinical database but will be used as source document.

[v] The primary diagnosis tissue (either block or slides) will also be used for pharmacogenomics testing per the patient's consent. If this sample is insufficient for pharmacogenomics testing, the patient has the option to consent to a fresh lymph node sample. If neither of these samplings are possible, the patients have the option to consent to giving a 5 mL bone marrow sample for biomarker analysis instead. If this is the case then it is possible to use 5 mL of the bone marrow sample drawn at screening (required for assessing the MCL involvement in the bone marrow), if sufficient sample is available.

[w] During the Short-term and Long-term Follow-up Phases, this will only include documentation of subsequent therapy and procedures for the treatment of MCL. No need to collect other concomitant medications 30 days after last dose

[x] The pregnancy test samples can be taken up to 24 hours prior to dosing; for screening pregnancy testing, a negative test up to 28 days prior to Cycle 1 Day 1 is acceptable.

[y] Echocardiography or MUGA scan is mandatory at baseline, thereafter it can be repeated optionally at any time during the study if clinically relevant either at an assessment visit or at unscheduled visit

[z] Medical resource utilization collected throughout study.

[aa] Limited physical examination includes cardiac, pulmonary and abdominal examination with examination and documentation of any clinically relevant abnormalities.

[bb] Hematology samples on Days 1, 4, 8, and 11 of each cycle are required only for patients in Arm A prior to VELCADE dosing. For patients randomized to Arm B hematology samples will be taken on Day 1 and 11 of each cycle. No site visits are required on Day 4 and Day 8 of each cycle for patients randomized to Arm B. Samples can be taken up to 24 hours prior to dosing day, provided the results are available before the dose of study medication is given. For pregnancy tests, if the pregnancy test during screening is within 28 days of Cycle 1 Day 1, it does not need to be repeated.

[cc] When the patient is recorded to have an event of PD, a repeat CT scan to confirm PD must be undertaken at least 30 days after the scan that was used to determine PD. In the event a patient starts subsequent anti-lymphoma treatment, it is highly recommended that this repeat CT scan be performed before the patient starts treatment. The repeat CT scan must be done using i.v. and oral contrast, and must be of the neck, chest, abdomen, and pelvis. If the patient is intolerant of i.v. contrast agents, the scan may be performed with only oral contrast. At the time of the initial documentation of PD, a PD fax form together with documentation of PD (e.g., CT scan report) must be sent to the sponsor's medical representative within 24 hours.

[dd] HBsAg and anti-HBc testing to be performed.

TIME AND EVENTS SCHEDULE (CONTINUED)

DOSE AND ADMINISTRATION TABLE

Patients will be randomized to either Treatment Arm A or Treatment Arm B

	Rituximab	Cyclophosphamide	Doxorubicin	Prednisone	Vincristine	VELCADE
Treatment Arm A (VcR-CAP)	Day 1	Day 1	Day 1	Days 1- 5		Days 1, 4, 8, 11
Treatment Arm B (R-CHOP)	Day 1	Day 1	Day 1	Days 1- 5	Day 1	

Rituximab - 375 mg/m^2, i.v.

Cyclophosphamide - 750 mg/m^2, i.v.

Doxorubicin - 50 mg/m^2, i.v.

Vincristine - 1.4 mg/m^2, i.v. (max. total 2 mg)

Prednisone – 100 mg/m^2, p.o.

VELCADE - 1.3 mg/m^2, i.v.

For Treatment Arm A, VELCADE must be administered first, followed by rituximab. Thereafter, other study medications will be administered according to the directions provided in the respective product labels.

Each cycle is 21 days.

Maximum number of 6 cycles per arm or 2 cycles beyond a documented response.

ABBREVIATIONS

ADL	activities of daily living
ALC	absolute lymphocyte count
ALT	alanine aminotransferase
ANC	absolute neutrophil count
ASCT	autologous stem cell transplant
AST	aspartate aminotransferase
BFI	Brief Fatigue Inventory
BSA	body surface area
CHOP	cyclophosphamide-doxorubicin-prednisone-vincristine
CMH	Cochran-Mantel-Haenszel
CRF	case report form
CR	complete response
CRu	complete response, unconfirmed
CT	computed tomography
CVAD	cyclophosphamide, vincristine, doxorubicin, and dexamethasone
CVP	cyclophosphamide, vincristine, and prednisone (only included once in document)
DCF	data correction form
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eDC	electronic data capture
EORTC-QLQ	European Organisation for Research and Treatment of Cancer-Quality of Life Questionnaire
FACT	Functional Assessment of Cancer Treatment
FDA	United States Food and Drug Administration
FISH	fluorescence immunohistochemisty
GCP	Good Clinical Practice
GOG	Gynecologic Oncology Group
J&JPRD	Johnson & Johnson Pharmaceutical Research & Development, L.L.C.
ICH	International Conference on Harmonisation
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
IPI	International Prognostic Index
IRB	Institutional Review Board
IRC	Institutional Review Committee
IVRS	Interactive voice response system
IWRC	International Workshop to Standardize Response Criteria for Non-Hodgkin's Lymphoma
LDH	lactate dehydrogenase
MCL	mantle cell lymphoma
MedDRA	Medical Dictionary for Regulatory Activities
MRU	medical resource utilization
MUGA	multiple uptake gated acquisition
NCI-CTCAE	National Cancer Institute Common Toxicity Criteria for Adverse Events
NHL	non-Hodgkin's lymphoma
ORR	overall response rate
OS	overall survival
PD	progressive disease
PFS	progression-free survival
PR	partial response
PRO	patient-reported outcomes
QALY	quality-adjusted life years
QOL	quality of life
R-CHOP	rituximab-cyclophosphamide-doxorubicin-prednisone-vincristine
SmPC	Summary of Product Characteristics

ABBREVIATIONS (CONTINUED)

SPD	sum of the product of the diameters
TNT	time to next treatment
TTP	time to progression
ULN	upper limit of normal
VcR-CAP	VELCADE-Rituximab-Cyclophosphamide-Doxorubicin-Prednisone
WBC	white blood cell count

1. INTRODUCTION

VELCADE® (Bortezomib for Injection) is being codeveloped by Millennium Pharmaceuticals, Inc. (Millennium) and Janssen Research & Development.

The term sponsor used throughout this document refers to the entities listed in the Contact Information page(s), which will be provided as a separate document.

1.1. Background

Mantle cell lymphoma (MCL) is an incurable subtype of non-Hodgkin's lymphoma (NHL) that was recognized as a unique clinicopathologic entity in the 1990's. It is relatively uncommon representing, 6% of all NHL cases in the Western world. At the molecular level, MCL is uniquely characterized by over expression of the cell cycle regulator protein cyclin D1. This is due to the chromosomal translocation t(11;14)(q13;q32), which puts the cyclin D1 gene, B-cell leukemia/lymphoma 1 (bcl-1), under the control of the immunoglobulin heavy chain enhancer with subsequent overexpression of cyclin D1.[3-5] In association with overexpression of cyclin D1, other markers such as CD20 and CD5 are also evident in MCL. A variety of other molecular abnormalities commonly found in MCL are also important prognostic indicators. These include reduced expression of p27, a cyclin-dependent kinase (CDK) inhibitor, and inactivating p53 mutations, both of which are associated with poor survival in MCL.[6] The intracellular levels of both p27 and p53 primarily are regulated by proteasomal degradation, and VELCADE is known to increase the levels of both of these proteins. Therefore, modulation of these key cell cycle regulators may be an important part of the mechanism of action of VELCADE in MCL.

It is often said to incorporate the worst aspects of both the aggressive and indolent lymphomas. The disease progresses quickly, like the aggressive lymphomas, but it is incurable, like the indolent lymphomas.[7-9] The result is a median survival of about 3 years from diagnosis, the shortest median survival of all NHL subtypes. This is in marked contrast to the median survival of about 7 years in follicular lymphoma, and the 40% to 50% cure rate in diffuse large B-cell lymphoma.[10-11]

At initial diagnosis, most patients with MCL, predominantly males over 60 years of age, present with advanced stage disease (Stage III or IV), with extranodal involvement frequently occurring in the gastrointestinal tract, bone marrow, liver, lungs, and soft tissues.[7,12]

Once the disease has progressed, the prognosis is dismal, and following relapse, the median survival is approximately 18 months and, like all lymphomas, the expected survival is progressively shorter with each subsequent relapse.[13-15] In a recent study of the treatment of patients with relapsed or refractory MCL, VELCADE, as a single agent, has been shown to provide substantial clinical benefit in the form of durable responses and prolonged time to alternative therapy in the relapsed setting. Additionally, patients who were refractory to their previous line of therapy were shown to respond to single agent VELCADE, some achieving a complete response (CR).

In the frontline setting, even despite intensive therapies such as rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) showing substantial response rates (CR rates of up to 48%), these favorable clinical responses were not associated with prolonged progression free survival (median 16.6 months).[36] The aim, therefore, of introducing VELCADE into the frontline treatment option for MCL is not only to improve response rates but also to prolong PFS, translating into a prolonged survival for these patients.

Hence, MCL represents a serious and life-threatening malignancy for which there is an unmet medical need for newly diagnosed patients.

Current initial therapy for the treatment of MCL is similar to that for other aggressive lymphomas and includes cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) or hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone alternating with methotrexate and cytarabine (Hyper-CVAD), often in combination with rituximab (R-CHOP or R-Hyper CVAD); however, many chemotherapeutic regimens have been evaluated. Younger patients with good performance status are frequently considered for more intensive induction therapy with combinations such as R-Hyper CVAD and consolidation therapy with autologous stem cell transplant (ASCT) also is considered; however, this degree of intensive therapy is not an option for most patients with MCL

because of their age and comorbidities.[16,17] In addition, there is still no consensus that more intensive therapy is beneficial in the treatment of MCL. Randomized studies have not demonstrated a benefit with the addition of an anthracycline to CVP (cyclophosphamide, vincristine, and prednisone) or fludarabine in terms of response rate or survival, and stem cell transplant (SCT) does not appear to be curative in relapse or at first remission.[18,19,20] Response rates in the frontline setting in excess of 90% have been achieved in small-uncontrolled studies of intensive chemotherapeutic regimens with or without ASCT. In 1 randomized study, rituximab was shown to improve overall and complete response rates when added to CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone) in previously untreated patients, although this did not result in increased progression-free survival (PFS).[21-24] Anthracycline based therapies in combination with rituximab are now recognized by all international experts as the treatment of-choice in the first-line therapy of MCL, although durable responses are still inadequate.

1.1.1. VELCADE

VELCADE has proven clinical efficacy in MCL. Potential mechanisms of action may include inhibition of MCL tumor growth by cell cycle arrest and induction of cell death, both of which involve inhibition of nuclear factor kB (NFkB) activation. Cell cycle arrest occurred in G1 with rapid induction of apoptosis. In addition, G1 cell cycle arrest was associated with inhibition of cyclin D1 expression. Other mechanisms of action of VELCADE also may be active in MCL. Reduced expression of p27, and loss of normal p53 function are both associated with a poor prognosis in MCL. The intracellular levels of p27 and p53 are both modulated by proteasomal degradation. Therefore, it is possible that inhibition of the proteasome by VELCADE results in increased intracellular levels of p27 and p53, and that this contributes to VELCADE's activity in MCL.

At least 5 MCL studies have demonstrated the efficacy of single agent VELCADE in relapsed/ refractory MCL. A total of 283 patients with MCL were evaluated for safety and efficacy. Data from these studies confirmed the intrinsic activity of single agent VELCADE in patients with MCL.

One study, the largest study in this setting, recruited 155 patients and demonstrated that single agent VELCADE (1.3 mg/m^2 administered on Days 1, 4, 8, and 11) provides a clinical benefit in the form of durable response rates with a substantial time to next treatment. In addition, updated data for survival now show that the median overall survival (OS) is 23.5 months from the time of documented relapse, and 35.4 months in those patients achieving a response. VELCADE is now approved for the treatment of relapsed MCL in 23 countries globally, including the US.

1.2. Overall Rationale for the Study

The next logical step, therefore, was to assess whether this benefit can be translated in the frontline setting and provide the durable response rates with significant improvement in PFS and survival that the R-CHOP combination is currently lacking.

Two studies have been initiated to assess the safety of combining VELCADE with R-CHOP; one is a Phase 2 study to evaluate the combination of R-CHOP plus VELCADE in patients with newly diagnosed B lymphomas. Patients were randomized between 2 schedules of VELCADE: Arm A (Days 1, 4, 8, 11), Arm B (Days 1, 8). For the first 24 patients (step 1), VELCADE was administered at 1 mg/m² in Arm A and 1.3 mg/m² in Arm B. For the next 24 patients (step 2), it was increased to 1.3 mg/m² and 1.6 mg/m² respectively. The safety profile to date has demonstrated that Grade 3-4 thrombocytopenia occurred in 14% of cycles (35% Arm A, 0% Arm B, 14% step 2). Of the 48 patients evaluable for response, 40 achieved CR/CRu (18/20 in Arm A, 22/28 in Arm B). Five patients achieved partial response (PR) (1 Arm A, 4 Arm B). After 1-year median follow up, OS was 100% and event-free survival of 80%. Although the hematologic toxicities in both arms were acceptable, higher neurological toxicities were observed at higher doses (1.3 mg/m^2 Days 1, 4, 8, 11, and 1.6 mg/m^2 on Days 1 and 8). Nine patients developed Grade 2 neuropathy mostly in Arm B and 9 patients developed Grade 3-4 neuropathy in both arms. This study recommended that the combination of VELCADE and vincristine should not be administered concomitantly.[2]

Another study of R-CHOP plus VELCADE combination has been initiated in patients with newly diagnosed diffuse large B cell lymphoma (DLBCL).[1] 40 patients have been recruited into this study which shows that treatment

was generally well tolerated, however, peripheral neuropathy occurred in 22 patients (55%), with 45% Grade 1, 5% Grade 2, and 5% Grade 3.

VELCADE is approved for the treatment of relapsed MCL, and is currently being assessed in the frontline setting in combination with R-CHOP. In line with the above recommendation, the aim of this study is to substitute vincristine with VELCADE in the R-CHOP combination and to compare the efficacy of the two combinations. No data exists to isolate the contribution of the efficacy of vincristine in R-CHOP regimen in the treatment of MCL (studies in lymphoma with single agent vincristine are over 30 years old, MCL has been recognized as a unique disease entity only in the last 10 years), however, given the durable responses seen in the Phase 2 study, it is expected that VELCADE will provide added benefit in the frontline setting to patients with newly diagnosed MCL who are ineligible for bone marrow transplant.

An Independent Data Monitoring Committee (IDMC) will be constituted for this study.

2. OBJECTIVES

Primary Objective

To determine which regimen of chemotherapy rituximab, cyclophosphamide, doxorubicin, VELCADE, and prednisone (VcR-CAP) or rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) provides greater benefit in newly diagnosed MCL patients with Stage II, III, or IV disease, as assessed by significant prolongation of PFS.

Secondary Objectives

The secondary objectives are:

- To determine OS
- To determine time to progression (TTP)
- To determine the 18-month survival rate
- To determine overall response (CR+CRu+PR) and CR rates (CR+CRu)
- To determine the duration of response, time to next treatment (TNT), and treatment-free interval
- To evaluate the safety of VcR-CAP compared to R-CHOP

Exploratory Objectives

- To evaluate patient-reported outcomes (PROs) utilizing the European Organisation for Research and Treatment of Cancer quality of life questionnaire (EORTC-QLQ-C30), EQ-5D, and Brief Fatigue Inventory (BFI) instruments

- To evaluate medical resource utilization (MRU) information which may be used in future economic evaluation models
- To identify patient populations that are more or less likely to respond to VcR-CAP or R-CHOP through the evaluation of biomarker analyses

3. OVERVIEW OF STUDY DESIGN

3.1. Study Design

This is a randomized, open-label, multicenter, prospective study to compare the efficacy and safety of the combination of VcR-CAP to that of R-CHOP in patients who have newly diagnosed MCL and who are ineligible for bone marrow transplantation.

At least 486 patients will be randomized into 1 of 2 arms (Treatment Arm A or Treatment Arm B) in a 1:1 ratio taking into account the following stratification factors: International Prognostic Index (IPI) and stage of disease at diagnosis.

Treatment Arm A: **(VcR-CAP)** rituximab 375 mg/m^2 intravenous i.v. on Day 1, cyclophosphamide 750 mg/m^2 i.v. on Day 1, doxorubicin 50 mg/m^2 i.v. on Day 1, VELCADE 1.3 mg/m^2 i.v. on Days 1, 4, 8, and 11, prednisone 100 mg/m^2 per os (p.o.) on Day 1 to Day 5 of a 21 day (3 week) cycle for 6 cycles (or 8 cycles if a response is first documented at Cycle 6 assessment).

Treatment Arm B: (R-CHOP) rituximab 375 mg/m^2 i.v. on Day 1, cyclophosphamide 750 mg/m^2 i.v. on Day 1, doxorubicin 50 mg/m^2 i.v. on Day 1, vincristine 1.4 mg/m^2 (maximum total of 2 mg) i.v. on Day 1, prednisone 100 mg/m^2 p.o. on Day 1 to Day 5 of a 21 day (3 week) cycle for 6 cycles (or 8 cycles if a response is first documented at Cycle 6 assessment).

Patient participation will include a Screening Phase, a Treatment Phase, a Short-term Follow-up Phase, and a Long-term Follow-up Phase. The Screening Phase will be up to 28 days (56 days for bone marrow evaluation) prior to randomization. The Treatment Phase will extend from randomization until 6 cycles of treatment have been given (or 2 cycles beyond a response documented in Cycle 6). The Short-term Follow-up Phase will extend from the End-of-Treatment Phase to progressive disease (PD; or relapse if patient achieves a CR or CRu), initiation of alternate antineoplastic therapy, decision by the patient to completely withdraw from the study and refuse any further study related procedure, or death. Patients who are withdrawn from the study treatment due to adverse events, or reasons other than above and are willing to continue study follow-up procedures can be followed per protocol for PD or death.

The Long-term Follow-up Phase will be used to assess survival and will document when the patient has died. Upon notification by the sponsor that clinical cutoff for the primary analysis (295 PFS events) has been reached, radiographic assessment of disease progression will stop, and all subjects in short-term follow-up will enter the Long-term Follow-up Phase.

Patients will be randomized and assigned to either Treatment Arm A or B. They will receive a maximum of 6 cycles of therapy or 2 cycles beyond a documented response if the response is first documented at Cycle 6 assessment and not previously (up to 24 weeks). Patients may receive less therapy or deviate from the planned treatment dose and schedule due to adverse events, as specified by the dose and schedule modifications defined in the protocol.

The total study duration from randomization of the first patient until the last PFS event required for the final analysis is expected to be approximately 42 months (approximately 24 months for enrollment and approximately 18 months for follow up).

Three interim analyses are planned for this study. The first interim analysis will occur after the first 100 patients have been randomized into the study and will assess safety and the concordance rate of the diagnosis of MCL when central review is compared with the investigator assessment of the diagnosis. Central review is defined as a review by an independent pathologist and in the event that there is insufficient tumor material available

for pathological confirmation of MCL, an independent lymphoma expert will review relevant local diagnostic and clinical information to verify the diagnosis of MCL. Samples determined as negative for MCL diagnosis by the independent pathologist cannot be evaluated by the independent lymphoma expert and will not be considered MCL confirmed. The concordance rate of the diagnosis of MCL will also be reviewed at 50% accrual. This may be used to recalculate the sample size to ensure an adequate number of PFS events (approximately 280) in those subjects with a centrally confirmed MCL diagnosis at the time of the final analysis (295 PFS events in total). A review of this data will occur by the IDMC (See Section 11.8).

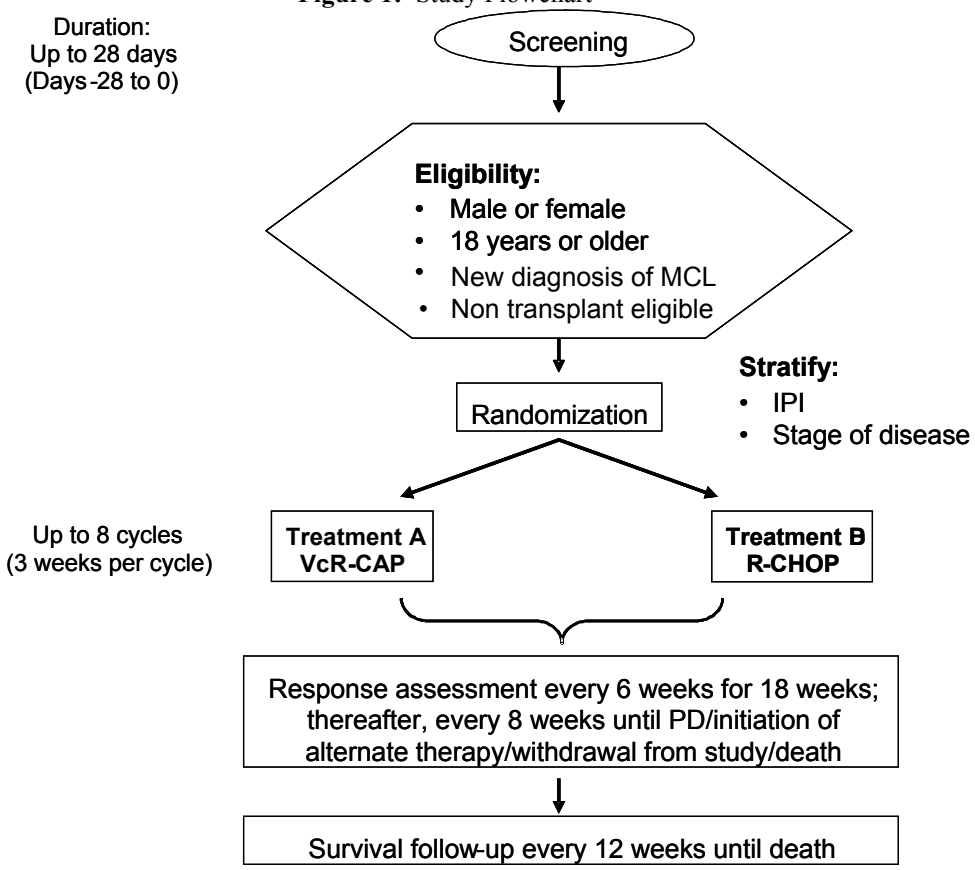
A second interim analysis for safety will occur after 100 patients in each arm (200 patients in total) have either completed the study treatment or discontinued the study treatment, which allows sufficient exposure for review of cumulative toxicity.

The third interim analysis is planned after at least 148 events have occurred in the ITT population. If, at the third interim analysis, pre-specified superiority boundaries for PFS are met then the study will be terminated and superiority of the experimental arm (VcR-CAP) will be declared over the comparator arm (R-CHOP). If the pre-specified futility boundaries for PFS are met, then the study may be terminated due to futility. If pre-specified boundaries are not met at the third interim analysis, the final analysis of the study will occur after 295 events have been observed in the ITT population.

The sample size calculation for the study population is based on the following assumptions. The median PFS of R-CHOP is 18 months. Assuming that VcR-CAP improves this median PFS by 40%, i.e., from 18 months to 25 months, a total number of 295 events provides 80% power (α=0.05, 2-sided) to detect such improvement. Assuming a 24 month accrual and 18 month follow-up, a total of 486 patients are needed for the study (243 per arm).

A flowchart of study procedures is provided in Figure 1.

Figure 1: Study Flowchart



3.2. Study Design Rationale

This study is designed to compare and establish superiority of the efficacy and safety of VcR-CAP to that of R-CHOP. The study is justified because there is a high unmet need for the treatment of patients who develop MCL and regimens that improve the clinical outcome and prognosis of patients with this disease are required. To date, no known treatments are curative, and median survival from first diagnosis is 3 years. A major goal for new treatments is to meaningfully improve PFS. The proposed study is designed to demonstrate a 40% improvement of PFS from 1 of the commonly used regimens in the treatment of frontline MCL, R-CHOP. The use of VELCADE in combination with vinca-alkaloids (in this case, vincristine) poses a risk of increased neurotoxicity and therefore the next logical step would be to substitute vincristine with VELCADE in this combination. Single agent VELCADE provides durable response rates and substantial clinical benefit, and it is hypothesized that this same regimen would also be as active in the frontline setting. The dose and regimen used in this study are therefore the same as that in the Phase 2 study of single agent VELCADE in

relapsed/ refractory MCL, i.e., 1.3 mg/m^2 on Days 1, 4, 8 and 11 of a 21 day cycle.

Rationale for Biomarker Evaluations

Molecular markers identified through pharmacogenomics and biomarker evaluations can facilitate more efficient drug development through their ability to identify patient subpopulations more or less likely to respond to drug treatment or experience a treatment-related adverse event. In this study, exploratory analyses focus on specific hypotheses to identify subpopulations of MCL patients that are sensitive or resistant to VcR-CAP or R-CHOP. Prior studies of prognostic molecular markers for MCL[25,26] and of specific response markers for rituximab[27,28] or VELCADE[29,30] allow the nomination of a specific series of candidate proteins and target gene polymorphisms/mutations. Additional candidate selections were based on identification of target-signaling pathway-related genes, genes previously shown to have differential responses to VELCADE treatment and prognostic markers of MCL. Experimental results will be correlated with clinical endpoints in order to determine if these specific candidate markers identify study populations that are more or less sensitive to study treatments.

Patient-Reported Outcomes

Patient-reported outcomes are included in clinical trials because some treatment effects are known only to the patient. There are no observable or physical measures for these concepts. These most often refer to a patient's symptoms or ability to function. In addition, patients provide a unique perspective on treatment effectiveness. When used to measure study endpoints, PRO instruments can augment what is known about the products based on the clinician perspective or physiologic measures. This is important because improvements in clinical measures of a condition may not necessarily correspond to improvements in how the patient functions or feels. PRO, when properly scaled, can be used in calculating quality-adjusted life years (QALY) for economic evaluation models to meet health authority requirements for reimbursement purposes. Formal assessment of the patient's perspective may provide valuable information that can be lost when that perspective is filtered through a clinician's evaluation of the patient's response to clinical interview questions. A self-administered structured

interview technique minimizes measurement error, ensures consistency without influence from a third party's interpretation.

4. STUDY POPULATION

4.1. General Considerations

Male and female patients who have a confirmed molecular diagnosis of MCL Stage II, III, or IV and have had no other prior treatments for their disease will be eligible to take part in the study. Patients must also be ineligible for bone marrow transplantation as determined by their treating physician.

4.2. Inclusion Criteria

Patients must satisfy all of the following criteria before entering the study:

- Male or female patients 18 years or older (the patient must be at least the legal age limit to be able to give informed consent within the jurisdiction the study is taking place)
- Diagnosis of MCL (Stage II, III or IV) as evidenced by histology and either expression of cyclin D1 (in association with CD20 and CD5) or evidence of t(11;14) translocation such as by cytogenetics, fluorescent in situ hybridization (FISH) or polymerase chain reaction (PCR). Patients with a diagnosis of Stage I MCL will not be permitted to enter study.
  - Paraffin embedded biopsy tissue block (preferably of lymph node origin) must be sent to the central laboratory for confirmation of MCL diagnosis prior to randomization. In China, a paraffin embedded lymph node biopsy tissue block must be sent for central confirmation of sample adequacy, prior to randomization.
- At least 1 measurable site of disease
- No prior therapies for MCL
- Not eligible for bone marrow transplantation as assessed by the treating physician (e.g., age or the presence of co-morbid conditions that may have a negative impact on the tolerability to transplantation).
- Eastern Cooperative Oncology Group (ECOG) status ≤2 (Attachment 1)
- Absolute neutrophil count (ANC) ≥1500 cells/μL
- Platelets ≥100,000 cells/μL or ≥75,000 cells/μL if thrombocytopenia is considered by the investigator to be secondary to MCL (e.g., due to bone marrow infiltration or sequestration from splenomegaly).
- Alanine transaminase ≤3 x upper limit of normal (ULN)
- Aspartate transaminase ≤3 x ULN

- Total bilirubin ≤1.5 x ULN
- Calculated creatinine clearance ≥20 mL/min. (Attachment 2)
- Female patients must be post menopausal for at least 1 year (must not have had a natural menses for at least 12 months), surgically sterile, or practicing an effective method of birth control (e.g., prescription oral contraceptives, contraceptive injections, intrauterine device, double-barrier method, contraceptive patch, male partner sterilization) and have a negative serum βHCG or urine pregnancy test at screening. They must also be prepared to continue birth control measures for at least 6 months after terminating treatment.
- Male patients must agree to use an acceptable method of contraception (for themselves or female partners as listed above) for the duration of the study.
- All patients (or their legally acceptable representatives) must have signed an informed consent document indicating that they understand the purpose of and procedures required for the study and are willing to participate in the study.
- In order to participate in the pharmacogenomics component of this study, patients (or their legally acceptable representative) must have signed the informed consent form for pharmacogenomics research indicating willingness to participate in the pharmacogenomics component of the study. Acquisition of tumor sample collections is required for all patients (where available); all other sample collections are optional.

4.3. Exclusion Criteria

Potential patients who meet any of the following criteria will be excluded from participating in the study:

- Prior treatment with VELCADE
- Prior antineoplastic (including unconjugated therapeutic antibodies), experimental or radiation therapy, radioimmunoconjugates or toxin immunoconjugates for the treatment of MCL. In the event that a patient has received doxorubicin for the treatment of any condition, other than MCL, the maximum dose and exposure received prior to entry into this study should not exceed 150 mg/m^2.
  - Short course (maximum of 10 days; not exceeding 100 mg/day) prednisone or equivalent steroids are allowed to treat symptoms in subjects with advanced disease who enter the screening phase and are waiting to be randomized.
- Major surgery (at the discretion of the treating physician and in consultation with the sponsor's medical monitor) within 2 weeks before randomization

- Peripheral neuropathy or neuropathic pain of Grade 2 or worse (as per the investigators assessment)
- Diagnosed or treated for a malignancy other than MCL within 1 year of randomization, or who were previously diagnosed with a malignancy other than MCL and have any radiographic or biochemical marker evidence of malignancy. Patients with completely resected basal cell carcinoma, squamous cell carcinoma of the skin, or in situ malignancy are not excluded.
- Active systemic infection requiring treatment and patients with known diagnosis of HIV or active hepatitis B (carriers of hepatitis B are permitted to enter study)
- History of allergic reaction attributable to compounds containing boron, mannitol, or hydroxybenzoates
- Known anaphylaxis or immunoglobulin E (IgE)-mediated hypersensitivity to murine proteins or to any component of rituximab including polysorbate 80 and sodium citrate dihydrate
- Female or male patients of child-bearing potential who will not use adequate contraception during the course of the study.
- Serious medical (e.g., cardiac failure [New York Heart Association; NYHA Class III or IV, Attachment 12 or left ventricular ejection fraction [LVEF] <50%], active peptic ulceration, or uncontrolled diabetes mellitus), or psychiatric illness likely to interfere with participation in this clinical study
- Concurrent treatment with another investigational agent.

5. RANDOMIZATION AND BLINDING

5.1. Overview

Randomization will be used to minimize the risk of bias in the assignment of patients to treatment, to increase the likelihood that known and unknown patient attributes (e.g., demographics and baseline characteristics) are evenly balanced across treatment groups, and to enhance the validity of statistical comparisons across treatment groups.

The sponsor and the sites will be blinded to all data reviewed by the IDMC.

5.2. Procedures

Patients will be assigned in a 1:1 ratio to 1 of the 2 treatment groups based on a computer-generated randomization schedule prepared by the sponsor before the study. The sponsor and the investigational sites will be blinded to all data reviewed by the IDMC.

Permuted blocks central randomization will be implemented in conducting this study. The randomization will be stratified by two stratification factors: International Prognostic Index (IPI) and stage of disease at diagnosis. The stratified randomization minimizes the imbalance in the distribution of treatment numbers within the levels of each individual stratification factors.

The IPI will be assessed according to the following risk factors: age, stage of disease, performance status, lactate dehydrogenase (LDH) level and number of extranodal sites (Attachment 10). For stratification, the scores will then be categorized (low [0-1 factor], low-intermediate [2 factors], high-intermediate [3 factors] and high [4-5 factors]).

The stage of disease at diagnosis will also be used for stratification and be assessed using the American Joint Committee on Cancer NHL staging system[39] (Attachment 11).

The patient number and treatment code will be assigned after phoning into the Interactive Voice Response System (IVRS). The caller must use their own user ID and PIN, and then give the requested patient details (e.g., patient's date of birth). Based on this information, the IVRS will assign a unique patient number and treatment code, which will dictate the treatment assignment for that patient.

Patients can only be randomized if the central laboratory has confirmed diagnosis of MCL or, in the case of patients in China, if the lymph node tissue sample sent to the central laboratory at screening has been evaluated as adequate for analysis to confirm the diagnosis of MCL. The IVRS will therefore be blocked after the screening call until the central laboratory has provided the requisite confirmation.

6. DOSAGE AND ADMINISTRATION

Study medication will be administered within 72 hours of randomization.

Active VELCADE be reconstituted as per the prescribing information.

Patients randomized to Treatment Arm A (VcR-CAP) will receive rituximab 375 mg/m^2 i.v. on Day 1, cyclophosphamide 750 mg/m^2 i.v. on Day 1, doxorubicin 50 mg/m^2 i.v. on Day 1, VELCADE 1.3 mg/m^2 i.v. on Days 1, 4, 8, and 11, prednisone 100 mg/m^2 p.o. on Day 1 to Day 5 of a 21 day

(3 week) cycle for 6 cycles (or 8 cycles if a response is first documented at Cycle 6 assessment).

Patients randomized to Treatment Arm B (R-CHOP) will receive rituximab 375 mg/m^2 i.v. on Day 1, cyclophosphamide 750 mg/m^2 i.v. on Day 1, doxorubicin 50 mg/m^2 i.v. on Day 1, vincristine 1.4 mg/m^2 (maximum total of 2 mg) i.v. on Day 1, prednisone 100 mg/m^2 p.o. on Day 1 to Day 5 of a 21 day (3 week) cycle for 6 cycles (or 8 cycles if a response is first documented at Cycle 6 assessment).

VELCADE will be administered as a 3 to 5 second intravenous bolus before the other medications are administered. Rituximab will then be administered. Thereafter, all other study medications will be administered according to the directions provided in the respective Summary of Product Characteristics (SmPC). Study medication dose and schedule reduction for toxicity will be allowed during the study, using the criteria defined in Section 6.1. The time interval between sequential VELCADE doses must be at least 72 hours.

A dose and administration schedule is provided following the Time and Events Schedule. The amount (in mg) of all study medications to be administered will be determined by body surface area (BSA), an example of a standard nomogram can be found in Attachment 3. Body surface area will be calculated on Day 1 of each cycle. The total calculated dose of VELCADE may be rounded to the nearest decimal point (e.g., a calculated dose of 2.47 mg can be rounded to 2.5 mg). If a patient experiences a >5% change in weight from the weight used in the previous BSA calculation, then the BSA and dose should be recalculated. Full doses of all study medications should be given based on the patient's actual BSA measured on Day 1 of every cycle, only the doses of vincristine should be capped.

If a patient discontinues any of the study medications assigned to them for any reason, including toxicity, the patient must not be withdrawn from study but continue on the other therapies in the allocated arm until the completion of 6 cycles (or 8 cycles if there is a response documented at Cycle 6 not previously documented).

Dose adjustments and modifications may be necessary for the causal agent as assessed by the investigator. However, as this study incorporates the use of a

number of chemotherapeutic agents given in combination, it may be difficult to isolate the causal agent and dose adjustments for more than one agent may be required at any given time.

Treatment-emergent adverse events of R-CHOP combination therapy predominantly comprise hematoxicities (such as neutropenia, leukopenia, thrombocytopenia and anemia). Nonhematoxicologic disorders such as asthenia, sensory disturbance, mucositis, alopecia, sepsis, dyspnea, back pain, hyperglycemia, hypersensitivity and cardiac disorders have all also been reported when treatment with R-CHOP has been administered. It is not always easy to assess the role of any one agent in these events and therefore it is at the investigator's discretion to decide if only one agent is causal and take action as described below or that the adverse event is as a result of more than one agent which should result in action being taken on the part of more than one agent.

It is expected that the combination of VcR-CAP in treatment Arm A, would result in a similar profile with a higher rate of hematologic toxicities compared to nonhematologic toxicities. However, careful evaluation of the toxicity (particularly hematologic toxicities) should occur when considering causality to study medication to ensure that the correct dose adjustments take place. For example, when considering causality for neutropenia in Arm A, it is important to consider that cyclophosphamide or doxorubicin (or both) may be causal agent(s).

6.1. Dose Adjustments for VELCADE

Dose adjustments for VELCADE must follow the SmPC.

Before each dose of study drug, the patient will be evaluated for possible toxicities that may have occurred after the previous dose(s). Toxicities will be assessed according to the National Cancer Institute Common Toxicity Criteria for Adverse Events (NCI CTCAE), Version 3.0. Previously established or new toxicities observed at any time, with the exception of VELCADE-related neuropathic pain or peripheral sensory neuropathy, are to be managed as follows:

- If the patient experiences ≥ Grade 3 neutropenia with fever, Grade 4 neutropenia lasting more than 7 days, a platelet count <10,000 cells/μL, or any ≥ Grade 3 nonhematologic toxicity considered by the investigator to be related to VELCADE, then study drug is to be held.
  - For nonhematologic toxicities, VELCADE is to be held for up to 2 weeks until the toxicity returns to Grade 2 or better.
  - For hematologic toxicities, VELCADE is to be held for up to 2 weeks until the patient has an ANC ≥750 cells/μL and a platelet count ≥25,000 cells/μL.
- If, after VELCADE has been held, the toxicity does not resolve, as defined above, then study drug must be discontinued.
- If the toxicity resolves, as defined above, and VELCADE is to be restarted, the dose must be reduced by approximately 25%, as follows:
  - If the patient was receiving 1.3 mg/m^2, reduce the dose to 1.0 mg/m^2.
  - If the patient was receiving 1.0 mg/m^2 following a previous dose reduction, reduce the dose to 0.7 mg/m^2.
  - If the patient was receiving 0.7 mg/m^2 following previous dose reduction, discontinue VELCADE. Dose reductions below 0.7 mg/m^2 are not permitted.

Dose re-escalations of VELCADE are not permitted after dose modifications for the above toxicities.

On any day of VELCADE administration during a cycle (other than Day 1 of each cycle) the hematology results must be:

- Platelet count ≥25,000 cells/μL
- ANC ≥750 cells/μL

If the above parameters are not met, the VELCADE dose can be held up to 2 days. Doses of study drug that need to be held within a cycle will be skipped; the dose will not be made up later in the cycle.

For VELCADE, cycle delays or study drug discontinuation are not required for lymphopenia of any grade.

6.1.1. VELCADE Dose Modifications for Neuropathic Pain or Peripheral Sensory Neuropathy

Patients who experience VELCADE-related neuropathic pain or peripheral sensory neuropathy are to be managed as presented in Table 1. Dose or schedule re-escalations are not permitted for VELCADE after modification for neuropathic pain or sensory peripheral neuropathy.

Table 1: Management of Patients With VELCADE-Related Neuropathic Pain or Peripheral Sensory Neuropathy

Neuropathic Pain (NCI CTCAE Grade [Version 3.0])		Peripheral Sensory Neuropathy (NCI CTCAE Grade [Version 3.0])				
		0	1	2	3	4
		Normal	Asymptomatic; Loss of deep tendon reflexes or paresthesia (including tingling) but not interfering with function	Sensory alteration or paresthesia (including tingling) interfering with function, but not interfering with ADL	Sensory alteration or paresthesia interfering with ADL	Disabling
0	None	No action	No action	*Reduction by 1 dose level*	Hold; reduction by 2 dose levels; schedule Δ required	Discontinue VELCADE
1	Mild pain not interfering with function	No action	No action	*Reduction by 1 dose level*	Hold; reduction by 2 dose levels; schedule Δ required	Discontinue VELCADE
2	Moderate pain: pain or analgesics interfering with function, but not interfering with ADL	*Reduction by 1 dose level*	*Reduction by 2 dose levels*	Hold; *reduction by 2 dose levels*	Hold; reduction by 2 dose levels; schedule Δ required	Discontinue VELCADE
3	Severe pain: pain or analgesics severely interfering with ADL	Hold; reduction by 2 dose levels; schedule Δ required	Hold; reduction by 2 dose levels; schedule Δ required	Hold; reduction by 2 dose levels; schedule Δ required	Discontinue VELCADE	Discontinue VELCADE
4	Disabling	Discontinue VELCADE	Discontinue VELCADE	Discontinue VELCADE	Discontinue VELCADE	Discontinue VELCADE

ADL = activities of daily living
Hold = Interrupt VELCADE until the toxicity returns to Grade 1 or better.
Schedule Δ Required = Schedule change from VELCADE twice weekly (Days 1, 4, 8, 11,) to once weekly (Days 1, 8) required.
For patients who have already been treated with 1.3 mg/m^2 of VELCADE, "reduction by 1 dose level" means reduction to 1 mg/m^2 of VELCADE, and "reduction by 2 dose levels" means reduction to 0.7 mg/m^2 of VELCADE (+ schedule Δ if indicated by the table). For patients who have been treated with 1 mg/m^2 of VELCADE, "reduction by 1 dose level" means reduction to 0.7 mg/m^2 of VELCADE; in case of "reduction by 2 dose levels" a reduction to 0.7 mg/m^2 of VELCADE always combined with a schedule Δ should be applied. For patients previously treated with 0.7 mg/m^2 of VELCADE, in case of "reduction by 1 dose level" and "reduction by 2 dose levels" a schedule Δ should be applied.

According to the table above, for example, if a patient had peripheral sensory neuropathy with objective sensory loss or paresthesia that interfered with function but not activities of daily living (ADL) (Grade 2) and mild

neuropathic pain not interfering with function (Grade 1), then the VELCADE dose is to be reduced by 1 dose level.

Neuropathic symptoms are more prominent than abnormalities on the clinical examination. The neurotoxicity-directed questionnaire Functional Assessment of Cancer Therapy/Gynecologic Oncology Group (FACT/GOG-Ntx) (see Attachment 4) is provided as a safety checklist to help determine the presence and intensity of neuropathic pain or peripheral neuropathy using the patients' reports. The FACT/GOG-Ntx questionnaire should be completed by all patients at the Screening visit, before dosing on Day 1 of each cycle, and at the End-of-Treatment Visit and be reviewed by the study staff to assist with the evaluation of the onset and intensity of peripheral neuropathy and other neurotoxicities that may possibly require intervention or dose modification.

6.2. Dose Adjustments for Rituximab

Dose adjustments for rituximab must follow the provided SmPC.

Patients who develop severe infusion reactions should have rituximab infusion discontinued and supportive care measures as medically indicated (e.g., i.v. fluids, vasopressors, oxygen, bronchodilators, diphenhydramine, and acetaminophen). In most cases, the infusion can be resumed at a 50% reduction in rate (e.g., from 100 mg/hr to 50 mg/hr) when symptoms have completely resolved.

Patients requiring close monitoring during first and all subsequent infusions include those with pre-existing cardiac and pulmonary conditions and those with prior clinically significant cardiopulmonary adverse events.

Hepatitis B virus reactivation with fulminant hepatitis, hepatic failure and death has been reported in some patients treated with rituximab. It is recommended to closely monitor carriers of hepatitis B. In patients who develop worsening of their status, rituximab should be discontinued and appropriate treatment initiated. Patients with active hepatitis B should not receive rituximab. Carriers of hepatitis B should be closely monitored for clinical and laboratory signs of active HBV infection for several months following rituximab therapy.

6.3. Dose Adjustments for Cyclophosphamide

Dose adjustments for cyclophosphamide must follow the provided SmPC.

The most common adverse events experienced with cyclophosphamide are hematologic toxicities. Myelosuppression with leukopenia, anemia, and thrombocytopenia can occur. The lowest leukocyte and thrombocyte levels occur in the first to second week after treatment is started. Recovery usually occurs within 3-4 weeks after treatment is started. In light of this, a patient can only start a cycle with cyclophosphamide if the ANC is $\geq 1.5 \times 10^9$ cells/L and platelets are $\geq 100 \times 10^9$ cells/L. Patients who develop hematologic toxicities thought to be causally related to cyclophosphamide must have their dose adjusted on Day 1 of each cycle according to the table below:

Table 2. Dose Modifications of Cyclophosphamide and Doxorubicin for Hematologic Toxicities

ANC (µL) and neutropenia	Platelet count (µL)	Dose given
≥1,500/µL	>100,000/µL	100% of the designated dose
>500/µL and no febrile neutropenia	>50,000/µL	100% of the designated dose after recovery of ANC to 1,500/µL and platelets to 100,000/µL
<500/µL and/or febrile neutropenia (ANC <500/µL + fever ≥38.5°C)	N/A	Initiate G-CSF for all subsequent cycles
<500/µL and/or febrile neutropenia (ANC <500/µL + fever ≥38.5°C despite growth factors	<50,000	25% dose reduction for subsequent cycles
Recurrence of <500/µL and/or febrile neutropenia (ANC <500/µL + fever ≥38.5°C despite growth factors	Recurrence of <50,000/µL	Additional 25% dose reduction for subsequent cycles
Third episode of <500/µL and/or febrile neutropenia (ANC <500/µL + fever ≥38.5°C despite growth factors and 2 dose reductions	Third episode of <50,000/µL	Discontinue

ANC = absolute neutrophil count; G-CSF = granulocyte colony stimulating factor, N/A = not applicable.
Note: Dose reductions due to low platelet counts are not required in patients with thrombocytopenia due to bone marrow infiltration from MCL.

Following treatment with cyclophosphamide, hemorrhagic cystitis and hematuria can occur. These may necessitate interruption of dosing.

6.4. Dose Adjustments for Doxorubicin

Dose adjustments for Doxorubicin must follow the provided SmPC.

The recommended lifetime cumulative dose limit of doxorubicin is 450-550 mg/m^2. The maximum dose given for each patient in this study will be 300 mg/m^2 (it may be higher, for example, if the patients receive 8 cycles of treatment or have a large BSA. However, the total exposure should not exceed the lifetime cumulative dose limit).

Dose limiting toxicities of doxorubicin therapy are myelosuppression and cardiotoxicity. Myelosuppression includes leukopenia, anemia and thrombocytopenia reaching nadir at 10-14 days after treatment. Cardiotoxicity as an arrhythmia may occur directly after administration and electrocardiogram (ECG) changes may last up to 2 weeks after administration. Cardiotoxicity may, however, occur several weeks or months after administration.

Doxorubicin is metabolized by the liver and excreted in bile. Impairment of liver function results in slower excretion of the drug and consequently increased retention and accumulation in the plasma and tissues, resulting in enhanced clinical toxicity.

Doxorubicin dosage must be reduced if hepatic function is impaired according to the following table:

Serum Bilirubin Levels	Recommended Dose
1.2 – 3.0 mg/dl (20.5 – 51.0 μmol/l)	50% normal dose
Over 3.0 mg/dl (>51.0 μmol/l)	25% normal dose

Dose modifications for hematologic toxicities should be performed as indicated in Table 2.

6.5. Dose Adjustment for Vincristine

Dose adjustments for vincristine must follow the provided SmPC.

If the liver function is abnormal on the first day of treatment, the vincristine dose is 100% with a bilirubin concentration of less than 25 μmol/l, 50% with

a bilirubin concentration of 25-50 µmol/l and 25% with a bilirubin concentration of more than 50 µmol/l. (see also dose adjustments for doxorubicin above in the event of liver abnormality).

Neurologic toxicity is the most common adverse event experienced with vincristine and it is related to dose and age. In case of serious neurotoxicity, vincristine should not be administered, especially if there are signs of paraesthesia or paresis. Upon a decrease of the symptoms after stopping administration of vincristine, treatment may be resumed at 50% of the dose.

6.6. Dose Adjustments for Prednisone

Dose adjustments for prednisone must follow the provided SmPC.

A dose above 80 mg/day of prednisone constitutes treatment with high dose steroid.

By definition, high dose prednisone will be used in this study at 100 mg/m^2. Patients administered high dose prednisone should be monitored carefully as there is a relatively higher risk of developing or exacerbating some conditions e.g., bacterial infections, viral infections, systemic mycoses, hypertension, diabetes mellitus, gastrointestinal conditions such as peptic ulcers and diverticulitis.

In the event that the patient develops an adverse event related to prednisone and are not able to tolerate 100 mg/m^2 of prednisone as required per protocol, the dose should be adjusted to a level specific to that patient, but should be no less than 80 mg per day (so that the patient still receives a high dose of prednisone).

In exceptional circumstances, a patient may not tolerate sudden steroid withdrawal at the end of 5 days of prednisone therapy. In such an instance, a tapering regimen of prednisone (reducing by 20 mg per day) can prescribed to the patient after sponsor approval.

6.7. Cycle Delay

After the rest period of each cycle (Day 11 to Day 21), the start of a NEW cycle can be delayed on a weekly basis (for a maximum of 3 weeks) until recovery of toxicity to a level allowing continuation of therapy. Delay of a new cycle for more than 3 weeks can only occur if there is clear clinical benefit observed and after approval by the sponsor. Otherwise, if there is a

delay in the start of a new cycle of more than 3 weeks due to insufficient recovery from toxicity, patients will discontinue study drug and have procedures performed as outlined in the End-of-Treatment Visit outlined in Section 9.1.3.

The following parameters must be met on the first day of each cycle (other than Cycle 1):

- Platelet count ≥100 x 10^9 cells/L (prior platelet transfusion is allowed)
- Hemoglobin ≥8 g/dL (≥4.96 mmol/L; prior RBC transfusion or recombinant human erythropoietin use is allowed)
- ANC ≥1.5 x 10^9 cells/L

Nonhematologic toxicity must have recovered to Grade 1 or baseline.

Patients with thrombocytopenia due to bone marrow infiltration from MCL are permitted to have platelets of ≥50 x 10^9 cells/L on the first day of each cycle.

If the above parameters are not met, the start of the next cycle will be held on a weekly basis for a maximum of 3 weeks for recovery to the specified levels.

7. COMPLIANCE

The dose of VcR-CAP or R-CHOP to be administered will be calculated using BSA (Attachment 3). The dose of each study drug to be administered will be documented in the source documents and case report form (CRF). Health care professionals will administer all study drugs.

Study personnel will maintain a log of all study drug administered. Drug supplies for each patient will be inventoried and accounted for.

Patients will be given diary cards to complete for the prednisone dosing at home on Days 2-5. The patients must bring these to the site on every visit so that the diary cards can be checked by study site personnel for compliance.

8. CONCOMITANT THERAPY

All therapies (prescriptions or over-the-counter medications, including vitamins and herbal supplements; non-pharmacologic therapies such as electrical stimulation, acupuncture, special diets, exercise regimens) different

from the study drug must be recorded in the concomitant therapy section of the CRF and in the source documents.

The sponsor must be notified in advance (or as soon as possible thereafter) of any instances in which prohibited therapies are administered.

8.1. Therapy for Tumor Lysis Syndrome

For subjects at risk for tumor lysis syndrome, allopurinol treatment should be considered and special attention should be given to adequate hydration.

8.2. Prophylactic Treatment for Herpes Zoster

Prophylaxis for herpes zoster reactivation is mandatory during the Treatment Phase. Acceptable antiviral therapy includes acyclovir (e.g., 400 mg given orally, 3 times a day), famcyclovir (e.g., 125 mg given orally, twice a day), or valacyclovir (e.g., 500 mg given orally, twice a day).

8.3. Prophylaxis for Hepatitis B Re-activation

It is recommended that hepatitis B surface antigen positive patients receive lamivudine 100 mg/day (or equivalent prophylaxis) orally until 8 weeks after last chemotherapy.

8.4. Permitted Medications and Supportive Therapies

All concomitant medications for medical conditions other than MCL are permitted, as clinically indicated.

All supportive therapies (such as any antinausea medication, MESNA for the prevention of hemorrhagic cystitis or antiviral prophylaxis for herpes) other than anticancer treatment needed for the management of patients enrolled in this study are permitted. Colony stimulating growth factors are permitted anytime during the study for the prevention of neutropenia and also for the management of treatment-emergent toxicities.

The following are supportive therapies that may be used if needed during this study:

- Loperamide is recommended for the treatment of diarrhea, starting at the time of the first watery stool. The loperamide dose regimen should be according to standard practice.
- Platelet and red blood cell transfusions are permitted, as necessary.

Premedication for rituximab infusion (e.g., acetaminophen, diphenhydramine, and steroids) should be considered before each infusion of rituximab. Premedication may attenuate infusion reactions.

8.5. Excluded Medications

The following medications and supportive therapies and procedures are prohibited at all times during the study:

- Any antineoplastic agent other than VELCADE, rituximab, cyclophosphamide, doxorubicin, vincristine or prednisone with the exception of medications that may have antineoplastic activity but are taken for other reasons, e.g., megestrol (Megace®), Cox-2 inhibitors, and bisphosphonates.
  - Short course (maximum of 10 days; not exceeding 100 mg/day) prednisone or equivalent steroids are allowed to treat symptoms in subjects with advanced disease who enter the screening phase and are waiting to be randomized.
- Any experimental agent other than that defined in the protocol
- Radiation therapy

8.6. Subsequent Therapies

Administration of any other antineoplastic therapy after completion of 6 cycles (or 2 cycles beyond a documented response of study drug administration (including maintenance or consolidation therapy) is not allowed until PD (or relapse if the patient achieves a CR or CRu) is established according to the criteria as described in the disease response criteria in Section 9.2.

Administration of any other antineoplastic therapy, to patients who discontinue study drug before completion of 6 cycles (or 8 cycles if a response is first documented in Cycle 6) of study drug administration for reasons other than PD, is strongly discouraged until PD is established.

After PD is established, subsequent therapy is left to the investigator's discretion. Subsequent therapy for MCL (including start and end date and best response) should be documented in the appropriate section of the CRF.

9. STUDY EVALUATIONS

9.1. Study Procedures

9.1.1. Overview

Patient participation will include a pretreatment (Screening Phase), a Treatment Phase, a Short-term and a Long-term Follow-up Phase. The Screening Phase can be up to 28 days prior to randomization. Bone marrow results obtained up to 56 days prior to randomization will be allowed.

The Treatment Phase will extend from randomization until completion of 6 cycles of treatment (or 8 cycles if a response is first documented in Cycle 6) or a decision to discontinue protocol treatment (distinguished from withdrawing consent to participate in the study), or decision by the patient to withdraw consent from the study.

The Short-term Follow-up Phase will extend from the End-of-Treatment Phase to PD, initiation of alternate antineoplastic therapy, decision by the patient to completely withdraw from the study or refusal to participate in any further study related procedures or follow-up, or death. Long-term Follow-up Phase will be used to assess survival and will document when the patient has died. Upon notification by the sponsor that clinical cutoff for the primary analysis (295 PFS events) has been reached, radiographic assessment of disease progression will stop, and all subjects in short-term follow-up will enter the Long-term Follow-up Phase. Long-term follow-up will continue until June 2017.

The total study duration from randomization of the first patient until the last PFS event required for the final analysis is expected to be approximately 42 months (approximately 24 months enrollment and approximately 18 months follow up). Patients on study (in the screening or treatment phase) at this time will continue to complete the planned protocol.

For the pharmacogenomics analysis, paraffin embedded tissue blocks obtained from biopsy or surgical resection specimens obtained at the time of diagnosis or subsequently, but before treatment on this study, will be collected. If paraffin embedded samples are not available, the patient has the option of consenting to a fresh tissue biopsy. This fresh biopsy is optional and not required to participate in this study. If sufficient sample is available, a portion of the biopsy required for central histology review for this study

will be utilized. In the absence of sufficient tissue blocks or fresh tissue sample collection, the patient has the option to consent to a 5 mL bone marrow sample for the biomarker analyses.

In countries where health authorities have approved pharmacogenomics and biomarker testing, patients must sign a separate informed consent form indicating their willingness to participate in the pharmacogenomics and biomarker analyses described in Section 9.5. Patients must provide paraffin embedded tissue (if available) and have the option of consenting to a fresh tissue biopsy, whole blood, bone marrow and serum sampling.

The Time and Events Schedule summarizes the frequency and timing of efficacy, safety, and other measurements.

The total volume of blood drawn for pharmacogenomics analysis will be 10 mL for whole blood collection, 15 mL for serum and 5 mL for bone marrow for biomarker analysis.

9.1.2. Pretreatment Phase

Screening procedures must be performed within 28 days prior to randomization.

All patients must sign informed consent prior to conduct of any study procedures, and satisfy all the inclusion criteria and none of the exclusion criteria listed in Sections 4.2 and 4.3 before randomization.

All patients must provide an adequate tissue block for central review prior to randomization.

Separate informed consent for the pharmacogenomics research component will be obtained during the Screening Phase.

All patients must undergo a neck, chest, abdominal and pelvic computed tomography (CT) scan with oral and i.v. contrast; this may be performed using only oral contrast if patient is intolerant of i.v. contrast agents. CT scans must be performed as part of the screening process, however if a previous scan is available, this may be used as the screening scan providing that it was performed no more than 56 days prior to randomization and meets the criteria required for study entry scans.

Evaluation of other sites of disease, as relevant, by radiological imaging, physical examination, or other procedures as necessary may be performed up to 28 days before randomization. Subsequent assessments performed throughout the study must use the same method of assessment per patient.

The CT scans or other radiological evaluations will be centrally assessed by independent radiology review to confirm disease response for the purpose of the final efficacy analyses. All details regarding shipping of radiology images will be provided in the study manual.

All patients must undergo a bone marrow aspirate and biopsy (may be performed up to 56 days before first dose of study medication).

Refer to the Time and Events Schedule for a complete list of procedures to be performed during the screening phase.

Biopsy samples and supportive materials for central confirmation of MCL diagnosis are required for the study. A central pathologist independent of the sponsor will confirm the diagnosis of MCL. In the event there is insufficient tumor material available for the independent pathologist confirmation of MCL, an independent lymphoma expert will review relevant local diagnostic and clinical information to verify the diagnosis of MCL. Samples determined as negative for MCL by the independent pathologist cannot be evaluated by the independent lymphoma expert and will not be considered MCL confirmed.

Representative tissue block or unstained microscope slides from a biopsy and other supporting data, such as flow cytometry data (not simply summary interpretations of the data), FISH, cytogenetics, and PCR will be sent to the central pathologist. These materials must be sent to the central pathologist during screening and adequacy of these samples must be confirmed before the patient can be randomized.

9.1.3. Treatment Phase

Treatment must start within 72 hours of randomization.

The Treatment Phase will start on Day 1 of Cycle 1 and finish on Day 21 of Cycle 6 (or Cycle 8 if a response is first documented in Cycle 6) or until early discontinuation of the allocated study medication (End-of-Treatment Visit).

All patients who meet the eligibility requirements as assessed during screening will be randomized in the study and start treatment within 72 hours of randomization with the assigned study medication.

Patients will not receive additional study medication per protocol beyond Day 11, Cycle 6 unless there is a documented response at Cycle 6, in which case 2 additional cycles of therapy can be given.

Patients will be evaluated throughout the Treatment Phase for possible toxicities and delays in dosing. Dose modifications will be made as required according to the dose-modification rules outlined in Section 6. Patients who discontinue investigational treatment due to toxicity will have End-of-Treatment procedures completed and enter the Short-term Follow-up Phase.

Throughout the Treatment Phase, the investigator will assess the patient's response to therapy using efficacy measurements and disease response criteria described in Sections 9.2.

Refer to the Time and Events Schedule for a complete list of procedures to be performed.

End-of-Treatment Visit:

All patients must complete an End-of-Treatment visit.

This visit will be performed 30 days (with a maximum window of +7 days) after the last dose of investigational product is administered (approximately 20 days after the end of Cycle 6) and will include End-of-Treatment procedures.

Refer to the Time and Events Schedule for a complete list of procedures to be performed.

9.1.4. Follow-up

9.1.4.1. Short-term Follow-up

Following the End-of-Treatment Visit, all patients will have efficacy assessments every 6 weeks (±4 days) for 18 weeks and thereafter every 8 weeks (±7 days) until PD/withdrawal from study/initiation of alternate therapy/death. When the patient is recorded to have an event of PD, a repeat CT scan to confirm PD must be undertaken at least 30 days after the scan

that was used to determine PD. In the event a patient starts subsequent anti-lymphoma treatment, it is strongly recommended that this repeat CT scan be performed before the patient starts treatment. The repeat CT scan must be done using i.v. and oral contrast and must be of the neck, chest, abdomen and pelvis. If the patient is intolerant of i.v. contrast agents, the scan may be performed with only oral contrast.

Death and events of progression constitute PFS, the primary endpoint for this study; it is therefore important that instances of PD, death or study discontinuation be reported to the sponsor as soon as possible. A PD fax form provided by the sponsor together with documentation of PD (e.g., CT scan report) must be sent to the sponsor's medical representation within 24 hours of the event.

The interval between Short-term Follow-up visits should be maintained at 6 or 8 weeks as required; if a visit occurs earlier or later than the scheduled visit date then the next visit date should be modified to maintain the required interval from the previous visit. Patients who experience progressive disease or start alternate antineoplastic therapy will enter Long-term Follow-up until time of death. Upon notification by the sponsor that clinical cutoff for the primary analysis (295 PFS events) has been reached, radiographic assessment of disease progression will stop, and all subjects in short-term follow-up will enter the Long-term Follow-up Phase.

For safety assessments, after 30 days after the last dose of study drug, only adverse events considered related to study drug will be reported. Refer to the Time and Events Schedule for a complete list of procedures to be performed.

9.1.4.2. Long-term Follow-up for Survival Status (Every 12 Weeks)

Patients will be contacted every 12 weeks (±7 days) until death, via telephone or office visit to assess survival status. The interval between Long-term Follow-up visits should be maintained at 12 weeks; if a visit occurs earlier or later than the scheduled visit date then the next visit date should be rescheduled to maintain the required interval from the previous visit.

If a patient decides to discontinue study treatment prior to disease progression, the end-of-treatment assessments should be performed, after

which they will enter short-term follow-up until PD or start of alternate antineoplastic therapy, and then long-term follow-up every 12 weeks until death. Long-term follow-up will continue until June 2017.

Only survival data, adverse events considered related to study drug, instances of second primary malignancy (regardless of relationship to study treatment), and information on subsequent anti-lymphoma therapies will be collected in the Long-term Follow-up Phase.

9.2. Efficacy

Efficacy will be assessed by central review of radiology.

During the study, disease response will be assessed using CT scans with oral and i.v. contrast of the neck, chest, abdomen and pelvis (at a minimum oral contrast should be used if i.v. contrast is contraindicated). Evaluation of other sites of disease by radiological imaging, physical examination, or other procedures as necessary (to be performed throughout the study using the same method of assessment per patient), and review of hematology and clinical chemistry results may also occur at the site level, but for the purpose of the central review, only radiographic evaluations will be assessed.

9.2.1. Evaluations

9.2.1.1. Radiographic Image Assessment

An Independent Radiographic Organization will perform the collection, qualification, and independent assessment of the radiographic images obtained during this study based on a pre-specified Independent Review Committee (IRC) charter. Image Acquisition Guidelines and Investigator Site Operations Manual will be provided to all clinical sites as separate documents to facilitate the consistent and quality acquisition of imaging data across all clinical sites. All clinical sites and imaging centers will be qualified by the Independent Radiographic Organization according to their ability to obtain quality images before they can enroll patients in the study.

9.2.1.2. Definitions of Measurable and Assessable Disease

Eligible patients must have at least 1 measurable site of disease.

Measurable sites of disease are defined as lymph nodes or lymph node masses or extranodal sites of lymphoma. Each measurable site of disease must be greater than 1.5 cm in the long axis and greater than 1.0 cm in the

short axis and clearly measurable in two perpendicular dimensions. All other sites of disease are considered assessable, but not measurable. Measurement must be determined by radiological imaging.

- Up to 10 measurable sites of disease that are clearly measurable in 2 perpendicular dimensions and >1.5 cm in the long axis and >1.0 cm in the short axis will be followed for each patient. Measurable sites of disease should be chosen such that they are representative of the patient's disease (this includes splenic and extranodal disease). If there are lymph nodes or lymph node masses in the mediastinum or retroperitoneum larger than 1.5 cm in 2 perpendicular dimensions, at least 1 lymph node mass from each region should always be included. In addition, selection of measurable lesions should be from as disparate regions of the body as possible.
- All other sites of disease will be considered assessable.

Assessable disease includes objective evidence of disease that is identified by radiological imaging, physical examination, or other procedures as necessary but is not measurable as defined above. Examples of assessable disease include bone lesions, mucosal lesions in the gastrointestinal tract, effusions, pleural, peritoneal or bowel wall thickening, disease limited to bone marrow, and groups of lymph nodes that are not measurable but are thought to represent lymphoma. In addition, if more than 10 sites of disease are measurable, these other sites of measurable disease may be included as assessable disease.

9.2.1.3. Criteria for Response Categories

The response criteria being used to assess efficacy are based on the International Workshop to Standardize Response Criteria for Non-Hodgkin's Lymphoma (IWRC)[24] as modified for this protocol. The criteria that must be met for each disease response category, CR, CRu, PR, SD, disease relapse and progression, are provided below.

Complete Response (CR) requires ALL of the following:

- Complete disappearance of all detectable clinical and radiological evidence of disease and disease-related symptoms and normalization of biochemical abnormalities definitely assignable to lymphoma (e.g., LDH) if present before therapy.
- All measurable lymph nodes and nodal masses must have regressed on CT to normal size (≤1.5 cm in their greatest transverse diameter for nodes >1.5 cm before therapy).

- Non-measurable and assessable nodes that were 1.1 to 1.5 cm in their greatest transverse diameter before treatment must have decreased to ≤1 cm in their greatest transverse diameter after treatment, or by more than 75% in the sum of the products of the greatest diameters (SPD), as visually estimated.
- The spleen or liver, if considered enlarged due to involvement with lymphoma before therapy on the basis of a physical examination or CT scan, should not be palpable on physical examination and should be considered normal size by imaging studies. Similarly, other organs considered to be enlarged before therapy due to involvement by lymphoma such as kidneys, must have decreased in size.
- If the bone marrow was involved by lymphoma, indeterminate or not adequately assessed during screening, an adequate aspirate and biopsy of the same site must be clear of lymphoma.
- All extranodal sites of disease must have completely disappeared.

Unconfirmed Complete Response (CRu) requires:

That the first and fourth criteria for CR be satisfied, however:

- Any residual lymph node mass >1.5 cm in longest transverse dimension or extranodal site of disease (irrespective of size) must have regressed by more than 75% of the product of the longest perpendicular dimensions compared to the pretreatment baseline.
- The bone marrow aspirate may be indeterminate (contain increased number or size of lymphoid aggregates without cytologic or architectural atypia).

If there are residual masses in a patient who would otherwise be considered to have achieved a CR or CRu, the patient should be classified as a partial responder.

Partial Response (PR) requires ALL of the following:

- At least a 50% decrease in sum of the product of the diameters (SPD) of the measurable sites of disease.
- No increase should be observed in any site of disease that meet the criteria for relapsed or progressive disease.
- Non-measurable nodes and nodules must regress by ≥50% in their SPD or, for single non-measurable lesions, in the greatest transverse diameter, as visually estimated.

- Bone marrow assessment is irrelevant for determination of a PR if the sample was positive before treatment. However, patients who achieve a CR by the above criteria, but who have persistent morphologic bone marrow involvement will be considered partial responders. When the bone marrow was involved before therapy and a clinical CR was achieved, but with no bone marrow assessment after treatment, patients should be considered partial responders.
- No new sites of disease should be observed that meet the criteria for relapsed or progressive disease.

Stable disease (SD) is defined as the following:

- A patient is considered to have SD when he or she fails to attain the criteria needed for a CR or PR, but does not fulfill those for progressive disease (see below).

Progressive Disease (after PR/SD) or Relapsed Disease (after CR/CRu)

Progressive or relapsed disease requires any one of the following:

1. A) ≥50% increase from nadir in the SPD of all measurable sites of disease at the time that progressive or relapsed disease is identified and the absolute change in at least 1 dimension is ≥0.5 cm for at least 1 lesion; or B) ≥50% increase in the long axis of any measurable site of disease at the time that progressive or relapsed disease is identified and the absolute change in the long axis is ≥0.5 cm.

2. A) ≥50% increase from nadir in the SPD of all non-measurable sites of disease (excluding truly assessable disease), as visually estimated, and the absolute change in at least 1 dimension is ≥0.5 cm for at least 1 non-measured lesion as estimated visually; or B) ≥50% increase in the long axis of any non-measurable site of disease (excluding truly assessable disease), and the absolute change in the long axis is ≥0.5 cm, as estimated visually.

3. ≥50% increase from nadir in any truly assessable site of disease, as visually estimated.

4. Appearance of any new lymph node site of disease that measures >1.5 cm in long axis and >1.0 cm in short axis, any new unequivocal extranodal site of disease (irrespective of size), or unequivocal evidence of a new site of assessable disease (for example effusions, ascites, masses with indistinct borders, new involvement of the bone marrow).

5. Appearance of a new organ enlargement or unequivocal increase of an organ enlargement that was present since baseline.

Measurable extranodal disease should be assessed in a manner similar to that for nodal disease. For these recommendations, the spleen is considered nodal disease. Disease that is only assessable (e.g., pleural effusions, bone lesions) will be recorded as no change, increased, decreased, or new, unless, while an abnormality is still noted by imaging studies or physical examination, it is found to be histologically negative.

When the patient is recorded to have an event of PD, a repeat CT scan to confirm PD must be undertaken at least 30 days after the scan that was used to determine PD. In the event a patient starts subsequent anti-lymphoma treatment, it is strongly recommended that this repeat CT scan be performed before the patient starts treatment. The repeat CT scan must be done using i.v. and oral contrast and must be of the neck, chest, abdomen and pelvis. If the patient is intolerant of i.v. contrast agents, the scan may be performed with only oral contrast.

Death and events of progression constitute PFS, the primary endpoint for this study; it is therefore important that instances of PD, death or study discontinuation be reported to the sponsor as soon as possible. A PD fax form provided by the sponsor together with documentation of PD (e.g., CT scan report) must be sent to the sponsor's medical representation within 24 hours of the event.

9.2.1.4. Reappearing Nodes

Reappearing nodes (from a nadir of 0 cm x 0 cm): Any node(s) that reappear (measured or not measured) >1.5 x 1.0 cm or unequivocally reappearing extranodal lesions (irrespective of size and whether measured or not) should result in PD.

9.2.2. Efficacy Criteria

9.2.2.1. Primary Endpoint

The primary endpoint is PFS, which is defined as the interval between the date of randomization and the date of PD or death, whichever is first reported, in the intent-to–treat (ITT) population. The death due to PD will be considered as an event if the date of death is within 6 month after last disease

assessment (or within one disease assessment period), otherwise, death will be censored at the date of last disease assessment.

9.2.2.2. Secondary Endpoints

ORR is defined as the proportion of patients who achieve CR, CRu, or PR. Disease response and progression will be evaluated according to the IWRC recommendations by radiographic imaging and other appropriate investigations.

The CT scans or other radiographic evaluations will be centrally assessed by independent radiology review to confirm disease response for the purpose of the efficacy analyses. Additionally, the CT scans or other radiographic evaluations will be locally assessed during the conduct of the study for the purpose of treatment decision-making.

CR rate is defined as the proportion of patients who achieve CR and CRu.

Duration of response (CR, CRu, or PR) will be calculated from the date of initial documentation of a response to the date of first documented evidence of PD (or relapse for patients who experience CR or CRu on this study).

TTP will be analysed in the ITT population and is defined as the duration from the date of randomization until the date of first documented evidence of PD (or relapse for patients who experience CR or CRu on this study). The death due to PD will be considered as an event if the date of death is within 6 months after last disease assessment (or, at most, 1 missing disease assessment visit), otherwise, death will be censored at the date of last disease assessment.

OS is measured from the date of randomization to the date of the patient's death. If the patient is alive or the vital status is unknown, the date of death will be censored at the date that the patient is last known to be alive. OS will be analyzed in the ITT population.

TNT will be assessed, for all patients, from the initiation of study treatment to the start of anti-lymphoma therapy subsequent to study treatment. Patients who do not receive alternate therapy will be censored in the analysis at the date of the last visit.

Treatment-free interval will be assessed, for those patients who have terminated study treatment, from the end of the study treatment to the start of anti-lymphoma therapy subsequent to the study treatment. Patients who do not receive alternate therapy will be censored in the analysis at the date of the last visit.

Eighteen-month survival is defined as survival rate at 18 months (Kaplan-Meier estimate).

9.3. Patient-Reported Outcomes

Three PRO instruments, the EQ-5D (Attachment 7), the EORTC QLQ-C30 Version 3.0 (Attachment 8), and the BFI (Attachment 9) will be used. The EORTC questionnaire to assess the quality of life of cancer patients QLQ-C30 Version 3.0 is composed of multi-item and single scales. These include five functional scales (physical, role, emotional, social, and cognitive), three symptoms (fatigue, nausea and vomiting and pain) and a global health status/QoL scale and six single items (dyspnea, insomnia, appetite loss, constipation, diarrhea and financial difficulties). All scales and single items meet the standards for reliability. The reliability and validity of the questionnaire is highly consistent across different language and cultural groups. The time recall period is the past week. The average time to complete the EORTC QLQ-C30 questionnaire is approximately 10 to 15 minutes.

Because oncology therapies may positively or negatively affect a patient's quality of life, a common methodologic approach is used to quantify this effect by "quality-adjusting" survival in comparative treatment groups. The result, quality-adjusted life-years (QALYs), is a measure of both the length and quality of life and is used as a measure of benefit in cost-utility analysis. General PRO instruments such as the EORTC QLQ-C30 are not designed to measure patient preferences (or utilities) in a way that is suitable for calculating QALYs. Therefore, a separate validated instrument, in this case the EuroQOL EQ-5D, will be used to quantify utilities to calculate QALYs for a cost-utility analysis[31,32,33,34,35]. The EQ-5D is a standardized instrument for use as a measure of health outcome. Applicable to a wide range of health conditions and treatments, it provides a simple descriptive profile and a single index value for health status. It is cognitively simple, taking only a few minutes to complete.

The BFI was developed for patients with fatigue due to cancer and cancer treatment. It was validated among patients with mostly hematologic malignancies including acute and chronic leukemias and lymphoma.[38] It assesses severity of fatigue and the impact of fatigue on daily functioning including general activity, mood, walking, work, relationships, and enjoyment in the past 24 hours. This time interval can be changed to the past week if more appropriate. It is a single-page, 9-item questionnaire that can be completed within 5 minutes.

Patients are eligible for the PRO assessment in this study if they fulfill the eligibility criteria and, more importantly, complete the baseline PRO questionnaire before randomization. Patients will be informed in the consent form that they will have their PRO assessment regularly while involved in this trial. PRO will be an exploratory endpoint and evaluated in a longitudinal design for all patients entered in this study.

PRO questionnaires must be filled out at the Screening visit; on Day 1 of every treatment cycle before other assessments are performed or study drugs are administered; and at the End-of-Treatment visit. The questionnaire will be handed out to the patients by the investigator or a study nurse prior to seeing the doctor for clinical evaluations. Patients will be asked to fill out the questionnaires as completely and accurately as possible. The CRFs will include a question on whether the PRO forms have been filled in and if not, the reason why. Data collection procedures should be followed using the EORTC guidelines.

Missing data may hamper assessment of PRO in clinical trials. This may be because centers do not collect the questionnaires at the appropriate time (unit non-response), and because patients may miss questions within the questionnaires (item non-response). The latter problem occurs less than 2% on average and should not be a problem. The former problem will be minimized by ensuring that participating centers are properly informed and motivated about PRO assessment. During the study, compliance with completing PRO questionnaires will be investigated at each time point.

9.4. Medical Resource Utilization

MRU data associated with medical encounters related to MCL or adverse effects of the treatment will be collected for all patients during the study. Specifically, MRU is evaluated based on the number of medical care encounters such as hospital admissions, reason, type, duration, type of adverse events involved, outpatient visits, diagnostic tests and procedures, and concomitant medications. The MRU data will be used to conduct economic analyses.

9.5. Pharmacogenomics Evaluations

There are 2 parts to the pharmacogenomics component of this study. This section of the study is to help identify patient populations that are more or less likely to respond to VcR-CAP or R-CHOP through the evaluation of a defined set of biomarkers including:

- Correlations of somatic mutations in specific proteasome subunits from paraffin embedded tissue or fresh tissue or bone marrow (additional genes associated with response to drug treatment may also be evaluated).
- Evaluation of Ki-67, NF-kB and *PSMA5*,and other protein prognostic markers of disease or drug activity in paraffin embedded tissue or fresh tissue or bone marrow (e.g., p27, p53, cyclin D1, *CTAG1B, CYCLIN A, B, E, P21, ICAM, VCAM, BID, BCL-XL, BAK, BCL2, ROS, BAX, CASPASES, CHK-1, PSMB8, LMP1, IL-32, PERK, GAS-5, P2RY5, CCNB1IP1, CR2, PTB, AKT1, CD40, JUN, eIF,* and *Noxa/Mcl-1*, STK17A, STK17B, CSEIL, DRAK1, DRAK2, TOSO, TNFRSFS, TNFS4, TANK, TRAF5, TRAF6, DED, ALK, Topoisomerase II, Repp86, IL10R, SPARC, CDC14A, RAS family, FADD, DAXX, RIPK1, RAIDD, PRAD1, BCL1)

Samples will be collected from patients who give separate written informed consent for this component of the study (where local regulations permit) (Attachment 5). This will allow for biomarker research, as described. If sufficient sample is available, a portion of the embedded paraffin tissue required for the central review of diagnosis of MCL will be utilized for the analyses. If there is insufficient tissue sample available, patients can optionally consent to undergo a biopsy to obtain a fresh tissue sample or to provide a 5 mL sample of bone marrow. Whole blood (10 mL) and three 5 mL serum samples will be collected from patients that optionally consent to these collections. Results of the exploratory analyses will be presented in a

separate report. Details of the analyses will be presented in the Statistical Analysis Plan.

9.5.1. Analyses Related to the Trial (Part 1)

Patients will be asked to consent to the pharmacogenomics and biomarker tests described below.

9.5.1.1. Somatic Mutational Status of Tissue

If sufficient sample is available, a portion of the embedded paraffin tissue sample required for central review will be utilized. If there is insufficient tissue sample available, patients can optionally consent to undergo a biopsy to obtain a fresh tissue or to provide a 5 mL sample of bone marrow. Purified DNA from these tissues will be examined to detect abnormalities (mutations, deletions, amplifications) in selected genes.

Genetic variability in drug target genes may influence drug binding and subsequently, response to treatment. Suspected drug target genes including *PSMB1, 2, 5, 6, 8* and *9* may be analyzed in tissue of all patients in order to determine any associations with response within this clinical trial.

In addition, other genes (such as those listed in Attachment 6) may be analyzed in the MCL population through a candidate gene approach with sufficient single nucleotide polymorphism (SNP)/mutation coverage in relation to PFS, disease response, duration of response, and OS with the goal of identifying a "classifier" that will associate with response to drug treatment. Suspected target genes and genes that have been involved in the signaling pathways affected by VELCADE will be included in the gene set. Prognostic markers of MCL will also be included. Other genes may be analyzed on identifiable samples if these genes are hypothesized to be relevant to VELCADE or the indications for which it is developed between the time that the clinical protocol has been issued and the samples have been made non-identifiable. DNA extracted from tissue or bone marrow samples will be utilized for these analyses.

9.5.1.2. Analysis of Whole Blood Samples

Genetic variability in drug target genes may influence drug binding and subsequently, patient response. For example, the efficacy of rituximab has been shown to be significantly associated with germline genetic variants in the Fcγ Receptor 3A (FCGR3A/FCGR2A) gene, indicating that functions of

non-neoplastic cells can play a prominent role in FL.[29, 30] Suspected drug target genes for VELCADE (PSMB1, 2, 5, 7, 8, and 9) and CHOP may be analyzed by genotyping of DNA extracted from lymphocytes found in whole blood collected from the patients.

Genetic variability in absorption, distribution, metabolism, and elimination (ADME) genes may also have implications in terms of patient-to-patient response, drug-drug interactions, and safety outcomes. Drug metabolism studies in preclinical animal models, in vitro systems, and in human liver microsomes indicate an important contribution of CYP2C19 and CYP3A and to a lesser extent CYP2D6, to clearance of VELCADE. These and the following candidate ADME genes will only be genotyped if considered appropriate depending on clinical trial results, developments in the scientific literature, and availability of assays designed to detect polymorphisms within these genes:

ABCB1 (MDR1), ABCB4 (MDR3), ABCC1 (MRP1), ABCC2 (MRP2), ADH, AHR, ALDH, ARNT, CYP1A1, CYP1A2, CYP1B1, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2D6, CYP2E1, CYP3A4, CYP3A5, CYP4B1, EPHX1, EPHX2, FMO1-4, GSTM1, GSTP2, GSTT1, MEH, MPO, NAT1, NAT2, NFE2L2, NR1I2 (PXR), SULT1A1, SULT1A2, SULT2A1 TPMT, UGT1A1, UGT1A3, UGT1A4, UGT1A6, UGT1A7, UGT1A8, UGT1A9, UGT2B15, UGT2B4, UGT2B7.

9.5.1.3. Biomarkers

If sufficient sample is available, a portion of the embedded paraffin tissue sample required for central review will be utilized. If there is insufficient tissue sample available, patients can optionally consent to undergo a biopsy to obtain a fresh tissue or to provide a 5 mL sample of bone marrow. These samples will be subjected to immunohistochemical analysis to quantify the levels of Ki-67, p27, p65 subunit of NF-kB and PSMA5 prognostic proteins. Other markers may also be analyzed including p53, cyclin D1, and markers of NF-kB activation. Clinical or preclinical studies have also implicated the following molecules in the efficacy of VELCADE: *CTAG1B, CYCLIN A, B, E, P21, NFKB, ICAM, VCAM, BID, BCL-XL, BAK, BCL2, ROS, BAX, CASPASES, CHK-1, PSMA5, PSMB8, LMP1, IL-32, PERK, GAS-5, P2RY5, CCNB1IP1, CR2, PTB, AKT1, CD40, JUN, eIF,* and *Noxa/Mcl-1*, *STK17A, STK17B, CSEIL, DRAK1, DRAK2, TOSO, TNFRSFS, TNFS4, TANK,*

TRAF5, TRAF6, DED, ALK, Topoisomerase II, *Repp86, IL10R, SPARC, CDC14A,* RAS family*, FADD, DAXX, RIPK1, RAIDD, PRAD1,* and *BCL1*. The protein levels of these or related biomarkers may also be evaluated and correlated with clinical outcomes.

Patients will be asked to optionally provide a serum sample before dosing in Cycles 1, 2, and 3 for serum protein analyses to look at the effects of study treatment on circulating levels of prognostic markers such as *VEGF* and *bFGF* as well as candidate response markers. Additional analyses may include mass spectrometry or other protein based evaluation of differences between serum samples from patients sensitive and insensitive to drug treatment. These additional analyses will proceed only if considered appropriate depending on clinical trial results, developments in the scientific literature, and availability of assays to reliably detect differences in clinical samples.

9.5.2. Pharmacogenomics and Biomarker Samples

Pharmacogenomics and biomarker sample collections will be applicable only for those countries where the health authorities have approved of this testing. The following samples will be taken for pharmacogenomics and biomarker analysis from patients who gave informed consent for this part of the study.

If sufficient sample is available, a portion of the embedded paraffin tissue sample required for central review will be utilized. If there is insufficient tissue sample available, patients can optionally consent to undergo a biopsy to obtain a fresh tissue or to provide a 5 mL sample of bone marrow. A whole blood sample will be collected from all patients that optionally consent. Serum samples will be collected from patients who optionally consent to serum protein analyses.

Refer to the Time and Events Schedule for a complete list of procedures to be performed.

9.5.3. DNA Storage for Future Analyses (Part 2)

Patients will be asked to consent to storage of DNA samples from whole blood, bone marrow or embedded tissue or fresh tissue samples for optional future testing of genes related to VELCADE, MCL or other similar cancers that may be treated with VELCADE. This analysis will include genes listed within this protocol and others that are later found to be relevant to the drug

or cancer. These markers can add value in characterizing any observed outcomes not foreseen in the clinical development. Analysis of variants within these genes may help to guide future development decisions for this compound. The DNA samples and relevant clinical data will be held in a non-identifiable format, in which case no link will be made between the genetic information and an individual patient.

9.6. Safety Evaluations

All patients who receive treatment will be considered evaluable for toxicity. All adverse events, with the exception of progression of MCL, will be reported from the time a signed and dated informed consent form is obtained until 30 days following the last dose of study drug or until the start of a subsequent systemic anti-lymphoma therapy, if earlier. Adverse events reported after 30 days following the last dose of study drug should also be reported if considered related to study drug, and all instances of second primary malignancy should be reported for the full duration of a subject's participation in the study, regardless of onset date or relationship to study drug.

All Grade 3 or 4 adverse events considered related to study drug must be followed until recovery to Grade 0 or 1. Neuropathic and cardiac adverse events of Grade 2 or higher will be followed until improvement to Grade 0 or 1. The unresolved aforementioned events will be followed for a maximum of 6 months.

The study will include the following evaluations of safety and tolerability according to the time points provided in the Time and Events Schedule:

Adverse Events

All adverse events will be recorded, with the details of the duration and the severity of each episode, the action taken with respect to the study drug, investigator's evaluation of its relationship to the study drug, and the patient outcome. The intensity (severity) of adverse events will be assessed using NCI CTCAE Version 3.0.

All serious adverse events (life-threatening, resulting in death, prolonged hospitalization, resulting in persistent disability, congenital anomaly/birth defect) must be reported to the IRB for review and also to the Sponsor within 24 hours by FAX.

Specific details on adverse event reporting are provided in Section 12.

Clinical Laboratory Tests

All laboratory tests should be performed at the laboratory facilities associated with the investigational site. Laboratory certificates or accreditation and normal ranges of the laboratory facility at the site must be submitted before the enrolment of any patient at the site.

If the patient has their laboratory assessments conducted at a laboratory facility other than the one associated with the investigational site, the investigator must submit laboratory certificates or accreditation and normal ranges for that facility as well.

Blood samples for serum chemistry and hematology will be collected. The investigator must review the laboratory report, document this review, and any clinically relevant changes in laboratory values must be recorded in the adverse event section of the CRF. For example, laboratory abnormalities leading to an action regarding study drug (dose change, temporary stop, delay of the start of a cycle or permanent stop) or the start of concomitant therapy should be reported. For each laboratory abnormality reported as an adverse event, the following laboratory values should be reported in the laboratory section of the CRF: the value indicative of the onset of each toxicity grade; the most abnormal value observed during the adverse event and the value supporting recovery to Grade 0 or 1 or to baseline values.

The following tests will be performed:

- Hematology Panel

  -hemoglobin
  - ANC and absolute lymphocyte count (ALC)
  -platelet count
  -white blood cell (WBC) count

- Serum Chemistry Panel

  -sodium
  -potassium
  -blood urea nitrogen (BUN)/urea
  -creatinine
  -aspartate aminotransferase (AST)
  -alkaline phosphatase
  -glucose
  -alanine aminotransferase (ALT)
  -LDH
  -total bilirubin
  -albumin
  -calcium
  -phosphate
  -uric acid

- Hepatitis B Screening

  -hepatitis B surface antigen
  -hepatitis B core antibody

Please see Time and Events Schedule for exact time points of these and other assessments. Also included are β-2 microglobulin and bicarbonate, which are measured only at screening. During short-term follow-up, only LDH will be measured.

- Serum/urine pregnancy test for women of childbearing potential only

Electrocardiogram (ECG)/Echocardiogram or Multiple Uptake Gated Acquisition (MUGA) scans

Twelve-lead ECGs will be recorded at a paper speed of 25 mm/sec so that the different ECG intervals (RR, PR, QRS, QT) can be measured manually. The ECG will be recorded until 4 regular consecutive complexes are available.

ECG interval estimates can be measured either manually or taken from the automated ECG recorder. ECGs will be recorded at the times specified in the Time and Events schedule.

Echocardiogram or MUGA scans will be performed as mandatory at screening but thereafter optionally according to clinical need. The purpose is to document baseline ventricular and septal parameters as well as baseline ventricular function. Any follow-up test method should be the same as the screening method.

Vital Signs

Pulse and blood pressure will be recorded at the times specified in the Time and Events Schedule.

Physical Examination

A complete physical examination will be conducted at the times specified in the Time and Events Schedule. During treatment cycles, the patient will undergo a limited examination, which will include any symptom related examinations required.

10. PATIENT COMPLETION/WITHDRAWAL

10.1. Completion

A patient will be considered as having completed the study Treatment Phase if he/she has completed all assessments at the End-of-Treatment visit of the Treatment Phase.

Completion of the posttreatment follow-up phases will occur after the patient has completed all of the required follow-up assessments or has been lost to follow-up and is censored.

10.2. Discontinuation of Treatment

If a patient must be discontinued from treatment before the end of the prescribed treatment regimen, this will not result in automatic withdrawal of the patient from the study.

A patient should be discontinued from study treatment if:

- The patient experiences overt disease progression or relapse
- The investigator believes that for safety reasons (i.e., adverse event) it is in the best interest of the patient to stop treatment
- The patient becomes pregnant
- The patient refuses further study drug
- A serious protocol violation has occurred, as determined by the principal investigator or the sponsor

The reason(s) a patient discontinues treatment will be recorded on the CRF. If a patient discontinues treatment before the end of the treatment phase, an end of treatment assessment must be obtained within 30 days after the last dose of study drug and follow-up continued for scheduled assessments.

10.3. Withdrawal From the Study

A patient will be withdrawn from the study for any of the following reasons:

- Lost to follow-up
- Withdrawal of consent
- Death

In case a patient is lost to follow-up, every possible effort must be made by the study site personnel to contact the patient and determine the reason for discontinuation. The measures taken to follow-up must be documented.

When a patient withdraws before completing the study, the reason for withdrawal must be documented in the CRF and in the source documents. Study drug assigned to the withdrawn patient will not be re-assigned to another patient. Patients who withdraw will not be replaced.

If a patient discontinues treatment before the end of the Treatment Phase, end-of-treatment and follow-up assessments will be obtained.

A patient who withdraws from the main part of the study will have the following options regarding pharmacogenomics research:

- The DNA extracted from the patient's blood, bone marrow or fresh or paraffin embedded tissue will be retained and used in accordance with the patient's original pharmacogenomics informed consent
- The patient may withdraw consent for pharmacogenomics research, in which case the DNA sample/s will be destroyed and no further testing will take place. To initiate the sample destruction process, the investigator must notify the sponsor site contact to request sample destruction. The sponsor site contact will, in turn, contact the pharmacogenomics representative for sample destruction. Upon request, the investigator will receive written confirmation from the sponsor that the sample has been destroyed

Withdrawal From Pharmacogenomics Research Only

The patient may also withdraw consent for pharmacogenomics research while remaining in the clinical study. If a patient withdraws consent for pharmacogenomics research, any DNA extracted from the patient’s samples will be destroyed. The sample destruction process will proceed as described above. After the clinical study is over, the sample will be made non-identifiable and therefore will not be destroyed. If the sample has

already undergone conversion to the non-identifiable format, the sponsor will notify the investigator in writing.

11. STATISTICAL METHODS

11.1. Sample Size Determination

The sample size calculation for the study population is based on the following assumptions. The median PFS of Treatment Arm B (R-CHOP) is 18 months.[36] Assuming that treatment Arm A (VcR-CAP) can improve the median PFS by 40%, i.e. from 18 months to 25 months, a total number of 295 events (PD or death) provides 80% power (α=0.05, 2-sided) to detect such improvement. Assuming a 24 month accrual and 18 month follow-up, a total of 486 patients is needed for the study (243/arm).

If 280 PFS events are observed in the subset of subjects with a centrally confirmed diagnosis of MCL, the study can achieve approximately 80% power to detect a hazard ratio of 1.4 in this subset of patients with a 2-sided log-rank test (α=0.05).

11.2. Study Populations

Intent-to-treat (ITT) Population

The intent-to-treat (ITT) population is defined as all patients who are randomized to treatment. Patients in this population will be analyzed according to the treatment to which they were randomized

Per-protocol (PP) Population

The per-protocol (PP) population is defined as all patients who are randomized to treatment and undergo at least 1 postbaseline disease assessment. Patients in this population will be analyzed according to the treatment to which they were randomized.

Safety Population

The safety population is defined as all patients who receive at least one dose of study drug. The safety population will be analyzed according to the treatment actually received.

Biomarker Population

The biomarker population is defined as patients whose biomaterial is available and who have consented to participate in the study's biomarker and pharmacogenomics evaluations or future research.

11.3. Efficacy Analyses

Stratified log-rank test will be used to compare PFS between the 2 treatment arms in the primary efficacy analysis.

For the secondary efficacy endpoints, the OS, 18-month survival, TTP, and TNT, will be compared using stratified log-rank test. The Kaplan-Meier method will be used to estimate the distribution of PFS, OS, 18-month survival, and TTP for each treatment.

Long-term follow-up will continue until June 2017.

The ORR and overall CR rate will be obtained and comparison of the rates will be performed between 2 treatment arms using the Cochran-Mantel-Haenszel (CMH) chi-square test. The 95% confidence interval for the difference of response rate between 2 treatment arms will be given.

The duration of response and treatment-free interval will be summarized descriptively. There will be no formal comparison of these endpoints between treatment groups because they are not statistically comparable.

For all efficacy endpoints, the primary analysis is to be performed in the ITT population. A sensitivity analysis will be performed in the subset of subjects with a centrally confirmed diagnosis of MCL. Approximately 280 events are expected in this subset of subjects at the time of the final analysis (295 PFS events in total), which can provide around 80% power to detect a hazard ratio of 1.4 using a 2-sided log-rank test (α=0.05).

11.4. Patient-Reported Outcomes Analyses

Patient-reported outcome assessments using the EORTC QLQ-C30, the EQ5D, and BFI will be analyzed to determine if response to the treatment and side effects of the treatment are accompanied by measurable changes in the PROs. The analyses will be performed on summary scores as well as on subscales and individual symptoms, with specific analytical methods outlined in a formal statistical analysis plan developed prior to database lock.

The primary analytical focus for the PRO will be the global health status/quality of life subscale of the EORTC QLQ-C30. The change in PRO scores between baseline and each postbaseline assessment will be described overall and according to the response to treatment. The secondary PRO

analytical focus including the remaining EORTC QLQ-C30 subscales and individual item scores, and the BFI item scores. The change in scores will be tabulated.

The EORTC QLQ-C30 questionnaire will be scored according to the algorithm described in the EORTC QLQ-C30 scoring manual. All scales and single items are scored on categorical scales and linearly transformed to 0-100 scales where:

- A high score for a symptom scale or item represents a high level of symptoms or problems.
- A high score for a functional scale represents a high or healthy level of functioning.
- A high score for the global health status/QoL represents high QoL.

The nine items of the BFI are measured on 0-10 numeric rating scales, with higher scores representing greater severity of fatigue and interference with daily functioning. A global fatigue score can be obtained by averaging all the items on the BFI.

The analysis of the PRO scores will be performed as a repeated-measures analysis using all available time points. The analysis will use mixed model analysis of variance.

In PROs, if necessary, missing data will be imputed using the last observation carried forward (LOCF) method. For PROs, if a multi-item subscale has a missing item, then the average of the remaining items will be used as the Scale score, as long as at least half the items in that Scale are present. For example, for Fatigue in EORTC QLQ-30, if Item 12 is missing, the average score of Items 10 and 18 will be used.

11.5. Pharmacogenomics Analyses

The pharmacogenomics exploratory statistical analysis will be performed 1) at the time of the third interim analysis, if required; and 2) at the completion of the trial in order to inform subsequent lymphoma trials.

Impact of Somatic Tumor Mutations in 100-Gene Set on Efficacy

For a gene with well-characterized, simple mutational spectra in tumors (e.g., p53), mutational status will be expressed as a categorical variable (mutated/not mutated) using standard, well-established gene-specific

classification schemes. For genes that do not have well-characterized mutational spectra, the impact of individual mutations and haplotypes (e.g., combinations of mutations) will be examined. The impact of mutational status, individual mutations, or haplotypes, as appropriate, will be tested using standard categorical tests or standard survival methods, depending on the endpoint, with modifications to allow for haplotyping testing, if required. Analyses will be performed within each treatment group and race.

Analysis of Whole Blood Samples

For genes with well-established genotype-to-phenotype mapping, the impact of predicted phenotype on response will be examined. For genes that do not have well-established genotype-to-phenotype mapping, the impact of the mutations taken individually and in haplotypes will be examined. The impact of predicted phenotype, individual mutations, or haplotypes, as appropriate, will be tested using standard categorical tests or standard survival methods, depending on the endpoint, with modifications to allow for haplotyping testing, if required. Analyses will be performed within each treatment group and race.

Impact of Changes in Protein Levels of Key Genes in Tumor Cells and Efficacy-Related Endpoints

Protein levels of prognostic markers such as p21cip1 and p27kip1 quantified by immunohistochemistry (IHC) and fluorescence in situ hybridization (FISH) will be measured as scores on an ordinal scale. The impact of protein expression level on response endpoints will be tested using standard categorical tests or survival analysis methods, as appropriate. The relationship between protein expression patterns (patterns of proteins, peptides, or small molecule components) in serum to clinical outcome will also be explored before and after treatment. Changes from baseline in protein levels after treatment will be categorized as increased, no change, or decreased, and tabulated against the response-related endpoints. Response related endpoints will be summarized by change from baseline using descriptive statistics and graphics, if appropriate. Impact of change from baseline will be tested using standard categorical or survival methods, as appropriate. Analyses will be performed within each treatment group.

11.6. Medical Resource Utilization Analyses

Frequencies of hospitalization, outpatient visits, reasons, types, durations, types of adverse events if involved, blood product transfusions, antibiotic use, and other concomitant medication will be calculated and tabulated.

11.7. Safety Analyses

All safety analyses will use data for the safety population. The safety parameters to be evaluated are the incidence, intensity, and type of adverse events, clinically significant changes in the patient's physical examination findings, vital signs measurements, and clinical laboratory results. Exposure to investigational product and reasons for discontinuation of study treatment will be tabulated.

Adverse Events

Detailed tabulations of safety data will be provided for all patients who receive study drug. The original terms used in the CRFs by investigators to identify adverse events will be coded using the Medical Dictionary for Regulatory Activities Terminology (MedDRA) dictionary. Treatment-emergent adverse events are adverse events that occur after the first dose of study drug, through the Treatment Phase, and for 30 days following the last dose of study drug; any event that is considered study-drug-related regardless of the start date of the event; or any event that is present at baseline but worsens in severity or is subsequently considered drug-related by the investigator. The number and percent of patients with treatment-emergent adverse events will be summarized according to intensity (NCI CTCAE, Version 3.0) and drug relationship as well as categorized by System Organ Class and preferred term by treatment group.

Clinical Laboratory Tests

Laboratory data will be summarized according to the type of laboratory test. Descriptive statistics will be calculated for each laboratory analyte at baseline and at each scheduled time point. The laboratory data for patients with any post baseline results outside the reference range will be summarized, when appropriate, by use of the NCI-CTCAE Version 3.0.

Vital Signs and Physical Examination

Changes in vital signs and physical examination parameters will be summarized over time and any abnormal values will be tabulated.

11.8. Interim Analyses

There will be 3 interim analyses planned in the study.

The first interim analysis will occur after the first 100 patients have been randomized into the study and will assess the safety and concordance rate of the diagnosis of MCL when central review is compared with the investigator assessment of the diagnosis. The concordance rate of the diagnosis of MCL when central review is compared with the investigator assessment of the diagnosis will also be reviewed at 50% accrual. This may be used to recalculate the sample size to ensure an adequate number of PFS events (approximately 280) in those subjects with a centrally confirmed MCL diagnosis at the time of the final analysis (295 PFS events in total). Based on publications the concordance rate of the diagnosis of MCL between central and investigator review of pathology is estimated at 91%.[37]

If the observed concordance rate is ≥95% (95% CI: 89%, 98%), the sample size for the study will not be changed. If the observed difference is less than 95%, the sample size may be adjusted to provide adequate PFS events (approximately 280) in those subjects with a centrally confirmed MCL diagnosis at the time of the final analysis (295 PFS events in total). There is no alpha adjustment for the first 2 interim analyses since no efficacy analyses will be performed.

The first interim analysis will also review the safety data collected to date. Safety data will be reviewed after at least one cycle for the first 100 treated patients, irrespective of whether they complete treatment within that first cycle.

The second interim analysis will review the safety data and be performed after 100 patients per arm have either completed or discontinued study treatment.

The third interim analysis has been planned for this study after at least 148 events have occurred in the ITT population. If, at the third interim analysis, pre-specified boundaries for PFS are met then the study will be terminated and superiority of the experimental arm (VcR-CAP) will be declared over the comparator arm (R-CHOP). If the observed hazard ratio (R-CHOP vs VcR-CAP) for PFS in the third interim is equal to or less than 1.03 (a value of >1 favoring VcR-CAP), then the study may be terminated

due to futility. There will also be a review of the safety data at the third interim analysis.

The type I error adjustment for the interim is based on O'Brien-Fleming spending function. Assuming that 148 events are observed at the third interim analysis, the alpha allocated for the interim is 0.003 (2-sided) and for the final analysis is 0.049 (2-sided).

If pre-specified boundaries are not met at the third interim stage, the final analysis of the study will occur after 295 events in patients have been observed in the ITT population.

11.9. Independent Data Monitoring Committee

An IDMC will be formed and constituted according to regulatory agency guidelines (such as United States Food and Drug Administration [FDA] guidelines) to evaluate safety data and results of the prospectively defined interim analyses of efficacy. The IDMC will meet following completion of the interim analysis. The review will consist of a review of the concordance rate of histological review, efficacy data, and safety data. Detailed information regarding the composition of the IDMC and detailed IDMC procedures will be documented in the IDMC charter.

11.10. Independent Radiology Review

An Independent Radiology Review body will review the results of the study mandated radiological procedures.

12. ADVERSE EVENT REPORTING

Timely, accurate, and complete reporting and analysis of safety information from clinical studies are crucial for the protection of patients, investigators, and the sponsor, and are mandated by regulatory agencies worldwide. The sponsor has established Standard Operating Procedures (SOPs) in conformity with regulatory requirements worldwide to ensure appropriate reporting of safety information; all clinical studies conducted by the sponsor or its affiliates will be conducted in accordance with those procedures.

12.1. Definitions

12.1.1. Adverse Event Definitions and Classifications

Adverse Event

An adverse event is any untoward medical occurrence in a clinical study patient administered a pharmaceutical product. An adverse event does not necessarily have a causal relationship with the treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product. (Definition per International Conference on Harmonisation [ICH])

This includes any occurrence that is new in onset or aggravated in severity or frequency from the baseline condition, or abnormal results of diagnostic procedures, including laboratory test abnormalities.

Note: The sponsor collects adverse events once the signed and dated informed consent form has been obtained.

Serious Adverse Event

A serious adverse event as defined by ICH is any untoward medical occurrence that at any dose meets any of the following conditions:

- Results in death
- Is life-threatening
  (The patient was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death if it were more severe.)
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity, or
- Is a congenital anomaly/birth defect

Note: Medical and scientific judgment should be exercised in deciding whether expedited reporting is also appropriate in situations other than those listed above. For example, important medical events may not be immediately life threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the outcomes listed in the definition above. Any adverse event is considered a serious adverse event if it is associated with clinical signs or symptoms judged by the investigator to have a significant clinical impact.

Unlisted (Unexpected) Adverse Event

An unlisted adverse event, the nature or severity of which is not consistent with the applicable product reference safety information. For an investigational product, the expectedness of an adverse event will be determined by whether or not it is listed in the Investigator's Brochure. For a comparator product with a marketing authorization, the expectedness of an adverse event will be determined by whether or not it is listed in the SmPC.

Associated With the Use of the Drug

An adverse event is considered associated with the use of the drug if the attribution is possible, probable, or very likely by the definitions listed in Section 12.1.2.

12.1.2. Attribution Definitions

Not related

An adverse event that is not related to the use of the drug.

Doubtful

An adverse event for which an alternative explanation is more likely, e.g., concomitant drug(s), concomitant disease(s), or the relationship in time suggests that a causal relationship is unlikely.

Possible

An adverse event that might be due to the use of the drug. An alternative explanation, e.g., concomitant drug(s), concomitant disease(s), is inconclusive. The relationship in time is reasonable; therefore, the causal relationship cannot be excluded.

Probable

An adverse event that might be due to the use of the drug. The relationship in time is suggestive (e.g., confirmed by dechallenge). An alternative explanation is less likely, e.g., concomitant drug(s), concomitant disease(s).

Very likely

An adverse event that is listed as a possible adverse reaction and cannot be reasonably explained by an alternative explanation, e.g., concomitant drug(s), concomitant disease(s). The relationship in time is very suggestive (e.g., it is confirmed by dechallenge and rechallenge).

12.2. Procedures

12.2.1. All Adverse Events

All adverse events, with the exception of progression of MCL, will be reported from the time a signed and dated informed consent form is obtained until 30 days following the last dose of study drug or until the start of a subsequent systemic anti-lymphoma therapy, if earlier. Resolution information after 30 days following the last dose of study drug should also be provided. Adverse events occurring after 30 days following the last dose of study drug should also be reported if considered related to study drug, and all instances of second primary malignancy will be collected for the full duration of a subject's participation in the study, regardless of onset date and relationship to study drug. Serious adverse events, including those spontaneously reported to the investigator within 30 days after the last dose of study drug, must be reported using the Serious Adverse Event Report Form. The sponsor will evaluate any safety information that is spontaneously reported by an investigator beyond the time frame specified in the protocol.

PD or relapse will not be reported as an adverse event, however, unexpected clinical signs or symptoms must be reported, even if they are eventually attributable to PD or relapse.

All events that meet the definition of a serious adverse event will be reported as serious adverse events, regardless of whether they are protocol-specific assessments.

All adverse events, regardless of seriousness, severity, or presumed relationship to study therapy, must be recorded using medical terminology in the source document and the CRF. Whenever possible, diagnoses should be given when signs and symptoms are due to a common etiology (e.g., cough, runny nose, sneezing, sore throat, and head congestion should be reported as "upper respiratory infection"). Investigators must record in the CRF their opinion concerning the relationship of the adverse event to study therapy. All measures required for adverse event management must be recorded in the source document and reported according to sponsor instructions.

The sponsor assumes responsibility for appropriate reporting of adverse events to the regulatory authorities. The sponsor will also report to the investigator (and the head of the investigational institute where required) all

serious adverse events that are unlisted and associated with the use of the drug. The investigator (or sponsor where required) must report these events to the appropriate Independent Ethics Committee/Institutional Review Board (IEC/IRB) that approved the protocol unless otherwise required and documented by the IEC/IRB.

Patients (or their designees, if appropriate) must be provided with a "study card" indicating the name of the investigational study drug, the study number, the investigator's name, a 24-hour emergency contact number, and, if applicable, excluded concomitant medications.

12.2.2. Serious Adverse Events

All serious adverse events occurring during clinical studies must be reported to the appropriate sponsor contact person by investigational staff within 24 hours of their knowledge of the event.

Information regarding serious adverse events will be transmitted to the sponsor using the Serious Adverse Event Report Form, which must be completed and signed by a member of the investigational staff, and transmitted to the sponsor within 1 working day. The initial report of a serious adverse event should be made by facsimile (fax) or may be made by telephone report in exceptional circumstances.

All serious adverse events that have not resolved by the end of the study, or that have not resolved upon discontinuation of the patient's participation in the study, must be followed until any of the following occurs:

- The event resolves
- The event stabilizes
- The event returns to baseline, if a baseline value is available
- The event can be attributed to agents other than the study drug or to factors unrelated to study conduct
- When it becomes unlikely that any additional information can be obtained (patient or health care practitioner refusal to provide additional information, lost to follow-up after demonstration of due diligence with follow-up efforts)

The cause of death of a patient in a clinical study, whether or not the event is expected or associated with the investigational agent, is considered a serious adverse event. Any event requiring hospitalization (or prolongation of

hospitalization) that occurs during the course of a patient's participation in a clinical study must be reported as a serious adverse event, except hospitalizations for the following:

- A standard procedure for protocol treatment administration will not be recorded as a serious adverse event (hospitalization or prolonged hospitalization for a complication of study treatment will be reported as a serious adverse event)
- The administration of blood or platelet transfusion (hospitalization or prolonged hospitalization for a complication of the transfusion will be reported as a serious adverse event)
- A procedure for a protocol/ disease related investigations (e.g., surgery, scans, endoscopy, sampling for laboratory tests, bone marrow sampling) (hospitalization or prolonged hospitalization for a complication of the procedure performed will be reported as a serious adverse event)
- Prolonged hospitalization for technical, practical or social reasons in absence of an adverse event
- Surgery or procedure planned before entry into the study (must be documented in the CRF)

12.2.3. Pregnancy

While pregnancy, in itself, is not an adverse event, all initial reports of patient pregnancy must be reported to the sponsor by the investigational staff within 24 hours of their knowledge of the event using a Serious Adverse Event Report Form (see Section 12.2.2, Serious Adverse Events) or Pregnancy Notification Form. Any patient who becomes pregnant during the study must be promptly withdrawn from treatment within the study. Because the study drug may have an effect on sperm, or if the effect is unknown, pregnancies in partners of male patients included in the study will be reported by the investigational staff within 24 hours of their knowledge of the event using the pregnancy notification form.

Follow-up information regarding the outcome of the pregnancy and any postnatal sequelae in the infant will be required.

12.3. Contacting Sponsor Regarding Safety

The names (and corresponding telephone numbers) of the individuals who should be contacted regarding safety issues or questions regarding the study are listed on the Contact Information page(s), which will be provided as a separate document.

13. STUDY DRUG INFORMATION

13.1. Physical Description of Study Drug(s)

VELCADE for Injection is an antineoplastic agent available for i.v. use only. Each single-dose vial contains 3.5 mg of bortezomib as a sterile lyophilized powder in a 10 mL glass vial, and inactive ingredient: 35 mg mannitol.

Cyclophosphamide injection is supplied in vials of 1 g. Each vial contains cyclophosphamide monohydrate equivalent to 1000 mg anhydrous cyclophosphamide.

Rituximab is a sterile, clear, colorless, preservative-free liquid concentrate for i.v. infusion administration in single use vials. The product is formulated for i.v. infusion administration in 9.0 mg/mL sodium chloride, 7.35 mg/mL sodium citrate dihydrate, 0.7 mg/mL polysorbate 80, and Sterile Water for Injection.

Prednisone is supplied as scored tablets containing either 5 mg or 20 mg of active product.

Doxorubicin injection for intravenous administration is supplied in a vial containing 25 mL of sterile solution. Each vial contains 50 mg of active product at a concentration of 2 mg/mL.

Vincristine is supplied as a lyophilized powder or as United States Pharmacopeia (USP), sterile, preservative–free, single use only, solution available for intravenous use in 2 mL vial. Each vial contains 1 mg of active product.

13.2. Packaging

VELCADE will be provided as a sterile lyophilized powder in a single-use 10 mL glass vial. Each vial contains the equivalent of 3.5 mg of VELCADE in the form of a mannitol boronic ester. Each vial is secured into a blister package. Blisters will be placed into a carton. Each carton will be labeled with a clinical label.

Cyclophosphamide is supplied in commercially packaged vials. Two vials will be labeled with a clinical label and placed into a carton. Each carton will be labeled with a clinical label.

Rituximab is supplied in the commercially-packaged vial. Vials may contain either 10 mL or 50 mL of active solution. Each carton will be labeled with a clinical label.

Prednisone 5 mg and 20 mg tablets are supplied in the commercially packaged blister containing 10 tablets. Each blister is secured into a child resistant wallet. Each child resistant wallet will be labeled with a clinical label.

Doxorubicin is supplied as individual packaged vials. Each vial will be labeled with a clinical label and placed into a carton. Each carton will be labeled with a clinical label. Doxorubicin will be supplied as a 0.2% injection containing 2 mg/ml doxorubicin hydrochloride. Each vial will contain 50 mg doxorubicin hydrochloride in a 25 mL solution.

Vincristine is supplied as individual packaged vials. Each vial will be labeled with a clinical label and placed into a carton. Each carton will be labeled with a clinical label.

13.3. Labeling

Study drug labels will contain information to meet the applicable regulatory requirements. The investigational products will be labeled as open-label material.

Each vial, blister, and carton of VELCADE will contain a study specific label with a unique identification number.

Each vial and carton of cyclophosphamide will contain a study specific label with a unique identification number.

Each vial and carton of rituximab will contain a study specific label with a unique identification number.

Each blister card of prednisone will contain a study specific label with a unique identification number.

Each vial and carton of doxorubicin will contain a study specific label with a unique identification number.

Each vial and carton of vincristine will contain a study specific label with a unique identification number.

13.4. Preparation and Handling

VELCADE

Vials containing lyophilized VELCADE for Injection should be stored below 30ºC. Vials should be stored in their carton to protect from light.

VELCADE is cytotoxic. As with all cytotoxic drugs, caution is required when preparing and handling VELCADE. Cytotoxic drugs should only be handled by staff specially trained in the safe handling of such preparations. The use of gloves and other appropriate protective clothing is recommended.

VELCADE will be supplied in sterile, single-use vials containing 3.5 mg of VELCADE. Aseptic technique must be strictly observed throughout the reconstitution and handling of VELCADE since no preservative is present. Each vial of VELCADE for Injection should be reconstituted within 8 hours before dosing, with 3.5 mL of normal (0.9%) saline, sodium chloride injection, so that the reconstituted solution contains VELCADE at a concentration of 1 mg/mL. Dissolution is completed in approximately 10 seconds. The reconstituted solution is clear and colorless, with a final pH of 5 to 6. Reconstituted VELCADE should be administered promptly and in no case more than 8 hours after reconstitution. In case of skin contact, wash the affected area immediately and thoroughly with soap and water and diluted hydrogen peroxide for 15 minutes. If product contacts eye, immediately flush eye thoroughly with water for at least 15 minutes. Always contact a physician after any form of body contact. All materials that have been used for preparation should be disposed of according to standard practices. A log must be kept of all disposed materials.

Cyclophosphamide

Cyclophosphamide should be stored below 25ºC. Store in the supplied container. After reconstitution, store at 2 to 8ºC and protect from light. Cyclophosphamide is a cytotoxic agent. As with all cytotoxic agents, caution is required when preparing and handling cyclophosphamide. Cytotoxic agents should only be handled by staff specially trained in the safe handling of such preparations. The use of gloves and other appropriate protective clothing is recommended.

Refer to the approved package insert for the preparation of cyclophosphamide.

Rituximab

Store vials in a refrigerator (2° to 8°C). Keep the container in the outer carton in order to protect from light.

The prepared infusion solution of MabThera is physically and chemically stable for 24 hours at 2° to 8°C and subsequently 12 hours at room temperature. From a microbiological point of view, the prepared infusion solution should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2° to 8°C, unless dilution has taken place in controlled and validated aseptic conditions.

Refer to the approved package insert for the preparation of rituximab.

Prednisone

Prednisone should be stored at room temperature below 30ºC.

Doxorubicin

Store between 2º to 8ºC. Protect from light. Doxorubicin is a cytotoxic agent. As with all cytotoxic agents, caution is required when preparing and handling. Cytotoxic agents should only be handled by staff specially trained in the safe handling of such preparations. Cytotoxic preparations must not be handled by pregnant employees. Careful and ample precautions must be observed in the removal of material used for reconstituting cytotoxic medications.

It is necessary to avoid any contact with the liquid. During preparation, it is necessary to use a strictly aseptic working method; the protection measures are the use of gloves, an oral mask, safety glasses, and protective clothing. The use of a vertical laminar hood is recommended. It is advisable to wear gloves during the administration of the product.

Doxorubicin will be administered as an intravenous infusion over 1 to 3 hours because bolus injections (1 to 2 minutes) cause higher peak plasma concentrations and therefore are probably more cardiotoxic.

Refer to the approved package insert for the preparation of doxorubicin.

Vincristine

Store vials in a refrigerator (2° to 8°C). Vincristine is a cytotoxic agent. As with all cytotoxic agents, caution is required when preparing and handling vincristine. Cytotoxic agents should only be handled by staff specially trained in the safe handling of such preparations. Cytotoxic preparations must not be handled by pregnant employees. Careful and ample precautions must be observed in the removal of material used for reconstituting cytotoxic medications.

The use of gloves and other appropriate protective clothing is recommended.

Vincristine can be diluted in physiological saline solution (0.9% wt/vol sodium chloride) to a concentration of 0.01 - 1 mg/ml.

Vincristine will be administered intravenously as a bolus injection of at least 1 minute.

For additional information refer to the approved package insert for vincristine.

13.5. Drug Accountability

The clinical investigator is responsible for ensuring that all study drug received at the site is inventoried and accounted for throughout the study. The dispensing of study drug to the patient, and the return of study drug from the patient (if applicable), must be documented on the drug accountability form. Patients or their legally acceptable representative, where applicable, must be instructed to return all original containers, whether empty or containing study drug. Study drug returned by study patients will be stored and disposed of according to the sponsor's instructions. Site staff must not combine contents of the study drug containers.

Study drug must be handled strictly in accordance with the protocol and the container label and will be stored in a limited access area or in a locked cabinet under appropriate environmental conditions. Unused study drug, and study drug returned by the patient (if applicable), must be available for verification by the sponsor's site monitor during on-site monitoring visits. The return to the sponsor of unused study drug, or used returned study drug for destruction, will be documented on the Drug Return Form. When the site

is an authorized destruction unit and study drug supplies are destroyed on site, this must also be documented on the Drug Return Form.

Hazardous materials such as used ampoules, needles, syringes and vials containing hazardous liquids, should be disposed of immediately in a safe manner and therefore will not be retained for drug accountability purposes. The immediate destruction of these drug supplies should be documented in the drug accountability records on site.

Study drug should be dispensed under the supervision of the investigator, a qualified member of the investigational staff, or by a hospital/clinic pharmacist. Study drug will be supplied only to patients participating in the study. Returned study drug must not be dispensed again, even to the same patient. Study drug may not be relabeled or reassigned for use by other patients. The investigator agrees neither to dispense the study drug from, nor store it at, any site other than the study sites agreed upon with the sponsor.

Patients will be given diary cards to complete for the prednisone dosing at home on days 2-5. The patients must bring these to the site on every visit so that the diary cards can be checked by study site personnel for compliance.

14. STUDY-SPECIFIC MATERIALS

The investigator will be provided with the following supplies:

- A copy of the current Investigator Brochure for VELCADE
- A copy of the SmPC for all study medications
- A copy of the NCI CTCAE Version 3.0

15. ETHICAL ASPECTS

15.1. Study-Specific Design Considerations

All patients will receive an active drug combination.

All participating patients will receive full supportive care and will be followed closely for safety and efficacy throughout the trial. Efficacy assessments will occur according to the internationally accepted response criteria. Safety assessments will occur through regular clinic visits including laboratory analyses. An IDMC will follow safety and efficacy during the trial at regular intervals and in a pre-specified interim analysis.

IEC/IRB approval for the pharmacogenomics research component of the clinical study and for the pharmacogenomics informed consent form must be obtained. IEC/IRB approval can be obtained for the protocol independent of approval for pharmacogenomics research.

All information, including but not limited to information regarding VELCADE or the sponsor's operations (e.g., patent application, formulas, manufacturing processes, basic scientific data, prior clinical data, and formulation information) supplied by the sponsor to the investigator and not previously published, and any data, including pharmacogenomics research data, generated as a result of this study, are considered confidential and remains the sole property of the sponsor. The investigator agrees to maintain this information in confidence and use this information only to accomplish this study, and will not use it for other purposes without the sponsor's prior written consent.

The results of the study will be reported in a Clinical Study Report generated by the sponsor and will contain all data from all investigational sites. Results of any pharmacogenomics analyses performed after the Clinical Study Report has been issued will be reported in a separate report and will not require a revision of the Clinical Study Report. Study patient identifiers will not be used in publication of pharmacogenomics results. Any work created in connection with performance of the study and contained in the data that can benefit from copyright protection (except any publication by the investigator as provided for below) shall be the property of the sponsor as author and owner of copyright in such work.

The total blood volume will be approximately 180 mL during the Treatment Phase and 15 mL in each study visit in short-term follow-up.

15.2. Regulatory Ethics Compliance

15.2.1. Investigator Responsibilities

The investigator is responsible for ensuring that the clinical study is performed in accordance with the protocol, current ICH guidelines on Good Clinical Practice (GCP), and applicable regulatory and country-specific requirements.

Good Clinical Practice is an international ethical and scientific quality standard for designing, conducting, recording, and reporting studies that involve the participation of human patients. Compliance with this standard provides public assurance that the rights, safety, and well being of study patients are protected, consistent with the principles that originated in the Declaration of Helsinki, and that the clinical study data are credible.

15.2.2. Independent Ethics Committee or Institutional Review Board (IEC/IRB)

Before the start of the study, the investigator (or sponsor where required) will provide the IEC/IRB with current and complete copies of the following documents:

- Final protocol and, if applicable, amendments
- Sponsor-approved informed consent form (and any other written materials to be provided to the patients)
- Investigator's Brochure (or equivalent information) and amendments
- Sponsor-approved patient recruiting materials
- Information on compensation for study-related injuries or payment to patients for participation in the study, if applicable
- Investigator's curriculum vitae or equivalent information (unless not required, as documented by IEC/IRB)
- Information regarding funding, name of the sponsor, institutional affiliations, other potential conflicts of interest, and incentives for patients
- Any other documents that the IEC/IRB requests to fulfill its obligation

This study will be undertaken only after the IEC/IRB has given full approval of the final protocol, amendments (if any), the informed consent form, applicable recruiting materials, and patient compensation programs, and the sponsor has received a copy of this approval. This approval letter must be dated and must clearly identify the IEC/IRB and the documents being approved.

Approval for the pharmacogenomics research component of the clinical study and for the pharmacogenomics informed consent form must be obtained from the IEC/IRB. Approval for the protocol can be obtained independent of approval for pharmacogenomics research.

During the study the investigator (or sponsor where required) will send the following documents to the IEC/IRB for their review and approval, where appropriate:

- Protocol amendments
- Revision(s) to informed consent form and any other written materials to be provided to patients
- If applicable, new or revised patient recruiting materials approved by the sponsor
- Revisions to compensation for study-related injuries or payment to patients for participation in the study, if applicable
- Investigator's Brochure amendments or new edition(s)
- Summaries of the status of the study at intervals stipulated in guidelines of the IEC/IRB (at least annually)
- Reports of adverse events that are serious, unlisted, and associated with the investigational drug
- New information that may adversely affect the safety of the patients or the conduct of the study
- Deviations from or changes to the protocol to eliminate immediate hazards to the patients
- Report of deaths of patients under the investigator's care
- Notification if a new investigator is responsible for the study at the site
- Any other requirements of the IEC/IRB

For protocol amendments that increase patient risk, the amendment and applicable informed consent form revisions must be submitted promptly to the IEC/IRB for review and approval before implementation of the change(s).

At least once a year, the IEC/IRB will be asked to review and re-approve this clinical study. This request should be documented in writing.

At the end of the study, the investigator (or sponsor where required) will notify the IEC/IRB about the study completion.

15.2.3. Informed Consent

Each patient (or a legally acceptable representative) must give written consent according to local requirements after the nature of the study has been fully explained. The consent form must be signed before performance of any study-related activity. The consent form that is used must be approved by both the sponsor and by the reviewing IEC/IRB. The informed consent should be in accordance with principles that originated in the Declaration of Helsinki, current ICH and GCP guidelines, applicable regulatory requirements, and sponsor policy.

Before entry into the study, the investigator or an authorized member of the investigational staff must explain to potential patients or their legally acceptable representatives the aims, methods, reasonably anticipated benefits, and potential hazards of the study, and any discomfort participation in the study may entail. Patients will be informed that their participation is voluntary and that they may withdraw consent to participate at any time. They will be informed that choosing not to participate will not affect the care the patient will receive for the treatment of his/her disease. Patients will be told that alternative treatments are available if they refuse to take part and that such refusal will not prejudice future treatment. Finally, they will be told that the investigator will maintain a patient identification register for the purposes of long-term follow-up if needed and that their records may be accessed by health authorities and authorized sponsor staff without violating the confidentiality of the patient, to the extent permitted by the applicable law(s) or regulations. By signing the informed consent form the patient or legally acceptable representative is authorizing such access, and agrees to allow his or her study physician to recontact the patient for the purpose of obtaining consent for additional safety evaluations, if needed, or to obtain information about his or her survival status.

The patient or legally acceptable representative will be given sufficient time to read the informed consent form and the opportunity to ask questions. After this explanation and before entry into the study, consent should be appropriately recorded by means of either the patient's or his/her legally acceptable representative's dated signature. After having obtained the consent, a copy of the informed consent form must be given to the patient.

Patients will be asked to consent to participate in a pharmacogenomics research component of the study (where local regulations permit). After informed consent for the clinical study is appropriately obtained, the patient or his/her legally acceptable representative will be asked to sign and personally date a separate pharmacogenomics informed consent form indicating agreement to participate in pharmacogenomics and biomarker research. A copy of the signed pharmacogenomics informed consent form will be given to the patient. Refusal to participate will not result in ineligibility for the clinical study.

If the patient or legally acceptable representative is unable to read or write, an impartial witness should be present for the entire informed consent process (which includes reading and explaining all written information) and should personally date and sign the informed consent form after the oral consent of the patient or legally acceptable representative is obtained.

When prior consent of the patient is not possible and the patient's legally acceptable representative is not available, enrollment procedures should be described in the protocol with documented approval/favorable opinion by the IEC/IRB to protect the rights, safety, and well being of the patient and to ensure compliance with applicable regulatory requirements. The patient or legally acceptable representative must be informed about the study as soon as possible and give consent to continue.

15.2.4. Privacy of Personal Data

The collection and processing of personal data from patients enrolled in this study will be limited to those data that are necessary to investigate the efficacy, safety, quality, and utility of the investigational study drug(s) used in this study.

These data must be collected and processed with adequate precautions to ensure confidentiality and compliance with applicable data privacy protection laws and regulations. Appropriate technical and organizational measures to protect the personal data against unauthorized disclosures or access, accidental or unlawful destruction, or accidental loss or alteration must be put in place. Sponsor personnel whose responsibilities require access to personal data agree to keep the identity of study patients confidential.

The informed consent obtained from the patient (or his/her legally acceptable representative) includes explicit consent for the processing of personal data and for the investigator to allow direct access to his or her original medical records for study-related monitoring, audit, IRB/IEC review, and regulatory inspection. This consent also addresses the transfer of the data to other entities and to other countries.

The patient has the right to request through the investigator access to his/her personal data and the right to request rectification of any data that are not correct or complete. Reasonable steps should be taken to respond to such a request, taking into consideration the nature of the request, the conditions of the study, and the applicable laws and regulations.

For those patients who gave consent to store DNA samples for future genetic research (Part 2), samples and corresponding relevant clinical data will be made nonidentifiable by the removal of personal identifiers. Samples will be stored until used up. Only research related to the drug or the indications for which the drug is developed will be done on stored samples. For data generated on identifiable samples (Part 1), the sponsor will provide the individual raw data, through the investigator, to patients who submit a written request. The sponsor cannot make decisions as to the significance of any findings resulting from this pharmacogenomics research, and cannot, therefore, provide genetic counseling. Genotypic data generated on nonidentifiable samples (Part 2) cannot be returned to individual patients.

15.2.5. Country Selection

Unless explicitly addressed as a specific ethical consideration in Section 15.1, Study-Specific Ethical Considerations, this study will only be conducted in those countries where the intent is to register for marketing authorization.

16. ADMINISTRATIVE REQUIREMENTS

16.1. Protocol Amendments

Neither the investigator nor the sponsor will modify this protocol without a formal amendment. All protocol amendments must be issued by the sponsor, and signed and dated by the investigator. Protocol amendments must not be implemented without prior IEC/IRB approval, or when the relevant competent authority has raised any grounds for non-acceptance, except when

necessary to eliminate immediate hazards to the patients, in which case the amendment must be promptly submitted to the IEC/IRB and relevant competent authority. When the change(s) involves only logistic or administrative aspects of the study, the IRB (and IEC where required) only needs to be notified.

During the course of the study, in situations where a departure from the protocol is unavoidable, the investigator or other physician in attendance will contact the appropriate sponsor representative by fax or telephone (see Contact Information pages provided separately). If possible, this contact will be made before implementing any departure from the protocol. In all cases, contact with the sponsor must be made as soon as possible to discuss the situation and agree on an appropriate course of action. The data recorded in the CRF and source documents will reflect any departure from the protocol, and the source documents will describe this departure and the circumstances requiring it.

16.2. Regulatory Documentation

16.2.1. Regulatory Approval/Notification

This protocol and any amendment(s) must be submitted to the appropriate regulatory authorities in each respective country, if applicable. A study may not be initiated until all local regulatory requirements are met.

16.2.2. Required Prestudy Documentation

The following documents must be provided to the sponsor before shipment of study drug to the investigational site:

- Protocol and amendment(s), if any, signed and dated by the investigator
- A copy of the dated and signed written IEC/IRB approval of the protocol, amendments, informed consent form, any recruiting materials, and if applicable, patient compensation programs. This approval must clearly identify the specific protocol by title and number and must be signed by the chairman or authorized designee.

- Name and address of the IEC/IRB including a current list of the IEC/IRB members and their function, with a statement that it is organized and operates according to GCP and the applicable laws and regulations. If accompanied by a letter of explanation, or equivalent, from the IEC/IRB, a general statement may be substituted for this list. If an investigator or a member of the investigational staff is a member of the IEC/IRB, documentation must be obtained to state that this person did not participate in the deliberations or in the vote/opinion of the study.
- Regulatory authority approval or notification, if applicable
- Signed and dated statement of investigator (e.g., Form FDA 1572), if applicable
- Documentation of investigator qualifications (e.g., curriculum vitae)
- Completed investigator financial disclosure form from the investigator
- Signed and dated clinical trial agreement, which includes the financial agreement
- Any other documentation required by local regulations

The following documents must be provided to the sponsor before enrollment of the first patient:

- Completed investigator financial disclosure forms from all subinvestigators
- Documentation of subinvestigator qualifications (e.g., curriculum vitae)
- Photocopy of the site signature log, describing delegation of roles and responsibilities at the start of the study
- Name and address of any local laboratory conducting tests for the study, and a dated copy of current laboratory normal ranges for these tests
- Local laboratory documentation demonstrating competence and test reliability (e.g., accreditation/license), if applicable.

16.3. Patient Identification, Enrollment, and Screening Logs

The investigator agrees to complete a patient identification and enrollment log to permit easy identification of each patient during and after the study. This document will be reviewed by the sponsor site contact for completeness.

The patient identification and enrollment log will be treated as confidential and will be filed by the investigator in the trial center file. To ensure patient confidentiality, no copy will be made. All reports and communications

relating to the study will identify patients by initials and assigned number only.

The investigator must also complete a patient-screening log, which reports on all patients who were seen to determine eligibility for inclusion in the study.

16.4. Source Documentation

At a minimum, source documentation must be available for the following to confirm data collected in the CRF: patient identification, eligibility, and study identification; study discussion and date of informed consent; dates of visits; results of safety and efficacy parameters as required by the protocol; record of all adverse events; concomitant medication; study drug; and date of study completion, and reason for early discontinuation if applicable.

It is recommended that the author of an entry in the source documents be identifiable.

At a minimum, the type and level of detail of source data available for a study patient should be consistent with that commonly recorded at the site as a basis for standard medical care. Specific details required as source data for the study will be reviewed with the investigator before the study and will be described in the monitoring guidelines (or other equivalent document).

16.5. Case Report Form Completion

Case report forms are provided for each patient in printed or electronic format.

Electronic Data Capture (eDC) will be used for this study. The study data will be recorded directly into the electronic CRF or transcribed by study personnel from the source documents onto an electronic CRF, and transmitted in a secure manner to the sponsor within 2 days of the patient's visit. The electronic file will be considered as the CRF. Worksheets may be used for the capture of some data to facilitate completion of the CRF. Any such worksheets will become part of the patients' source documentation.

All data relating to the study must be recorded in CRFs prepared by the sponsor. Data must be entered into CRFs in English. Designated site personnel must complete CRFs as soon as possible after a patient visit, and

the forms should be available for review at the next scheduled monitoring visit.

Every effort should be made to ensure that all subjective measurements (e.g., pain scale information or other questionnaires) to be recorded in the CRF are completed by the same individual who made the initial baseline determinations. The investigator must verify that all data entries in the CRFs are accurate and correct.

All CRF entries, corrections, and alterations must be made by the investigator or other authorized study-site personnel. If necessary, queries will be generated in the eDC tool. The investigator or an authorized member of the investigational staff must adjust the eCRF (if applicable) and complete the query.

If corrections to a CRF are needed after the initial entry into the CRF, this can be done in 3 different ways:

- Site personnel can make adjustments in the eDC tool at their own initiative or as a response to an auto query (generated by the eDC tool)
- Site manager (SM) can generate a query (field Data Correction Form [DCF]) for resolution by the investigational staff
- Clinical data manager (CDM) can generate a query for resolution by the investigational staff

PRO questionnaires will be provided as printed forms. All printed forms must be filled out legibly in black ballpoint pen or typed. The appropriate pages must be signed and dated by the investigator. Corrections to PROs must be made in such a way that the original entry is not obscured. Correction fluid or tape must NOT be used. The correct data must be inserted, dated, and initialed by the investigator or an authorized member of the investigational staff. The investigational staff must not write on No Carbon Required (NCR) copies of questionnaires left at the investigational site once the original is transmitted to the sponsor. Completed questionnaires will be continuously submitted according to the sponsor's instructions and reviewed by the sponsor to determine their acceptability. If necessary, DCFs will be generated and transmitted to the study site. The investigator or an authorized member of the investigational staff must complete, sign, and date the DCFs.

16.6. Data Quality Assurance

Steps to be taken to ensure the accuracy and reliability of data include the selection of qualified investigators and appropriate study centers, review of protocol procedures with the investigator and associated personnel before the study, and periodic monitoring visits by the sponsor. Written instructions will be provided for collection, preparation, and shipment of blood, plasma, and urine samples.

Guidelines for CRF completion will be provided and reviewed with study personnel before the start of the study. The sponsor will review CRFs for accuracy and completeness during on-site monitoring visits and after transmission to the sponsor; any discrepancies will be resolved with the investigator or designee, as appropriate. After upload of the data into the clinical study database they will be verified for accuracy.

16.7. Record Retention

In compliance with the ICH/GCP guidelines, the investigator/institution will maintain all CRFs and all source documents that support the data collected from each patient, as well as all study documents as specified in ICH/GCP Section 8, Essential Documents for the Conduct of a Clinical Trial, and all study documents as specified by the applicable regulatory requirement(s). The investigator/institution will take measures to prevent accidental or premature destruction of these documents.

Essential documents must be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or until at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents will be retained for a longer period if required by the applicable regulatory requirements or by an agreement with the sponsor. It is the responsibility of the sponsor to inform the investigator/institution as to when these documents no longer need to be retained.

If the responsible investigator retires, relocates, or for other reasons withdraws from the responsibility of keeping the study records, custody must be transferred to a person who will accept the responsibility. The sponsor must be notified in writing of the name and address of the new custodian.

Under no circumstance shall the investigator relocate or dispose of any study documents before having obtained written approval from the sponsor.

If it becomes necessary for the sponsor or the appropriate regulatory authority to review any documentation relating to this study, the investigator must permit access to such reports.

16.8. Monitoring

The sponsor will perform on-site monitoring visits as frequently as necessary. The monitor will record dates of the visits in a study center visit log that will be kept at the site. The first post-initiation visit will usually be made as soon as possible after enrollment has begun. At these visits, the monitor will compare the data entered into the CRFs with the hospital or clinic records (source documents). The nature and location of all source documents will be identified to ensure that all sources of original data required to complete the CRF are known to the sponsor and investigational staff and are accessible for verification by the sponsor site contact. If electronic records are maintained at the investigational site, the method of verification must be discussed with the investigational staff.

Direct access to source documentation (medical records) must be allowed for the purpose of verifying that the data recorded in the CRF are consistent with the original source data. Findings from this review of CRFs and source documents will be discussed with the investigational staff. The sponsor expects that, during monitoring visits, the relevant investigational staff will be available, the source documentation will be accessible, and a suitable environment will be provided for review of study-related documents. The monitor will meet with the investigator on a regular basis during the study to provide feedback on the study conduct.

16.9. Study Completion/Termination

16.9.1. Study Completion

The study is considered completed with the last visit of the last patient participating in the study. The final data from the investigational site will be sent to the sponsor (or designee) following completion of the final patient visit at that site, in the time frame specified in the Clinical Trial Agreement.

16.9.2. Study Termination

The sponsor reserves the right to close the investigational site or terminate the study at any time. Investigational sites will be closed upon study completion. An investigational site is considered closed when all required documents and study supplies have been collected and a site closure visit has been performed.

The investigator may initiate site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of an investigational site by the sponsor or investigator may include but are not limited to:

- Failure of the investigator to comply with the protocol, the sponsor's procedures, or GCP guidelines
- Inadequate recruitment of patients by the investigator

16.10. On-Site Audits

Representatives of the sponsor's clinical quality assurance department may visit the site at any time during or after completion of the study to conduct an audit of the study in compliance with regulatory guidelines and company policy. These audits will require access to all study records, including source documents, for inspection and comparison with the CRFs. Patient privacy must, however, be respected. The investigator and staff are responsible for being present and available for consultation during routinely scheduled site audit visits conducted by the sponsor or its designees.

Similar auditing procedures may also be conducted by agents of any regulatory body either as part of a national GCP compliance program or to review the results of this study in support of a regulatory submission. The investigator should immediately notify the sponsor if they have been contacted by a regulatory agency concerning an upcoming inspection.

16.11. Use of Information and Publication

All information, including but not limited to information regarding VELCADE or the sponsor's operations (e.g., patent application, formulas, manufacturing processes, basic scientific data, prior clinical data, formulation information) supplied by the sponsor to the investigator and not previously published, and any data, including pharmacogenomics research

data, generated as a result of this study, are considered confidential and remain the sole property of the sponsor. The investigator agrees to maintain this information in confidence and use this information only to accomplish this study, and will not use it for other purposes without the sponsor's prior written consent.

The investigator understands that the information developed in the clinical study will be used by the sponsor in connection with the continued development of VELCADE, and thus may be disclosed as required to other clinical investigators or regulatory agencies. To permit the information derived from the clinical studies to be used, the investigator is obligated to provide the sponsor with all data obtained in the study.

The results of the study will be reported in a Clinical Study Report generated by the sponsor and will contain all data from all investigational sites. Results of any pharmacogenomics analyses performed after the Clinical Study Report has been issued will be reported in a separate report and will not require a revision of the Clinical Study Report. Study patient identifiers will not be used in publication of pharmacogenomics results. Any work created in connection with performance of the study and contained in the data that can benefit from copyright protection (except any publication by the investigator as provided for below) shall be the property of the sponsor as author and owner of copyright in such work.

Consistent with Good Publication Practices and International Committee of Medical Journal Editors guidelines, the sponsor shall have the right to publish such primary (multicenter) data and information without approval from the investigator. The investigator has the right to publish study site-specific data after the primary data are published. If an investigator wishes to publish information from the study, a copy of the manuscript must be provided to the sponsor for review at least 60 days before submission for publication or presentation. Expedited reviews will be arranged for abstracts, poster presentations, or other materials. If requested by the sponsor in writing, the investigator will withhold such publication for up to an additional 60 days to allow for filing of a patent application. In the event that issues arise regarding scientific integrity or regulatory compliance, the sponsor will review these issues with the investigator. The sponsor will not mandate modifications to scientific content and does not have the right to

suppress information. The investigator will recognize the integrity of a multicenter study by not publishing data derived from the individual site until the combined results from the completed study have been published in full, within 12 months after conclusion, abandonment, or termination of the study at all sites, or the sponsor confirms there will be no multicenter study publication. Authorship of publications resulting from this study will be based on the guidelines on authorship, such as those described in the Uniform Requirements for Manuscripts Submitted to Biomedical Journals, which state that the named authors must have made a significant contribution to the design of the study or analysis and interpretation of the data, provided critical review of the paper, and given final approval of the final version.

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ATTACHMENTS

Attachment 1:
ECOG Performance Status

0 Normal activity. Fully active, able to carry on all pre-disease performance without restriction.

1 Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework, office work).

2 In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.

3 In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.

4 100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.

5 Dead.

Attachment 2:
Creatinine Clearance Calculation

Creatinine clearance for men and women will be calculated according to the Cockcroft-Gault formula as follows:

In men: $$\frac{\left[\left(140 - age\right) \times weight\left(kg\right)\right]}{\left[72 \times creatinine\left(mg / dL\right)\right]}$$

In women: $$\frac{\left[\left(140 - age\right) \times weight\left(kg\right)\right]}{\left[72 \times creatinine\left(mg / dL\right)\right]} \times 0.85$$

Note: Age (in years), weight (in kg), serum-creatinine (in mg/dL)
72 (normalized to 72 kg body weight and a body surface of 1.73 m^2)

Attachment 3:
Body Surface Area Calculation

BSA should be calculated using a standard nomogram. An example nomogram follows:

$$\text{BSA} = \sqrt{\frac{Ht(inches) \times Wt(lbs)}{3131}}$$

or

$$\text{BSA} = \sqrt{\frac{Ht(cm) \times Wt(kg)}{3600}}$$

Attachment 4:
FACT/GOG-Neurotoxicity Questionnaire, Version 4.0

By circling one (1) number per line, please indicate how true each statement has been for you during the past 7 days.

ADDITIONAL CONCERNS	Not at all	A little bit	Some-what	Quite a bit	Very much
I have numbness or tingling in my hands……	0	1	2	3	4
I have numbness or tingling in my feet……	0	1	2	3	4
I feel discomfort in my hands……..	0	1	2	3	4
I feel discomfort in my feet……	0	1	2	3	4
I have joint pain or muscle cramps……	0	1	2	3	4
I feel weak all over……	0	1	2	3	4
I have trouble hearing……	0	1	2	3	4
I get a ringing or buzzing in my ears……	0	1	2	3	4
I have trouble buttoning buttons……	0	1	2	3	4
I have trouble feeling the shape of small objects when they are in my hand……	0	1	2	3	4
I have trouble walking……	0	1	2	3	4

Attachment 5:
Pharmacogenomics Sample Collection and Shipment Procedure

Supplies and Preparation of Pharmacogenomics Whole Blood Samples

The central laboratory will provide the investigational site with prelabeled EDTA collection tubes. Detailed information is provided in the laboratory manual from the central laboratory.

Pharmacogenomics Whole Blood samples should be prepared as follows:

- Invert the tube 10 to 15 times immediately after collection, to prevent coagulation.
- DO NOT centrifuge sample.
- Blood samples collected and shipped within 24 hours can be shipped at ambient temperature (see sample shipment below).
- When there is a delay of more than 24 hours between collection and shipment, samples should be stored at 4°C at the investigational site for at most 5 calendar days, and shipped in ambient or cooled condition (but not on dry ice). Freezing of the blood should be avoided.

Pharmacogenomics Whole Blood Sample Shipment

- Once collected, the blood samples should be shipped within 24 hours to the central laboratory. Detailed information will be provided in the laboratory manual from the central laboratory. In general, the following guidelines should be adhered to:
- If possible, ambient/cooled shipment should be arranged with other clinical study samples. If this is not possible, a separate shipment for these blood samples should be organized, using the courier recommended by the central laboratory.
- Notify courier at least 24 hours in advance of the planned shipment. Provide courier with the appropriate account number to be used, if applicable.
- DO NOT package the samples in dry ice.
- Label the package with the study number and all other information required by the central laboratory.
- Include a return address (which includes the investigator's name) on the outside of each shipping container.
- Comply with all courier regulations for the shipment of biological specimens (include all paperwork).
- Retain all documents indicating date, time, and signature/s of person/people making the shipment, in the study files.
- The blood samples should be shipped to the name and address indicated in the central laboratory manual.

Attachment 5: (Continued)
Pharmacogenomics Sample Collection and Shipment Procedure

- The central laboratory provides a biweekly electronic update of the sponsor specific DNA repository to:

  Dr. Stephan Francke
  Johnson & Johnson Pharmaceutical Research & Development
  Department of Pharmacogenomics
  1000 Route 202
  Raritan, NJ 08869
  Tel: (908) 218-6596
  Fax: (908) 429-0695
  Email: sfranck1@prdus.jnj.com

- The central laboratory forwards extracted DNA samples either on request of the Department of Pharmacogenomics or at the end of the study to the address above.

*NOTE: If there are changes regarding the courier or location to which samples are shipped during the course of the clinical study, written notification will be provided to the investigator and will not require (a) protocol amendment(s).

Paraffin Embedded Tissue (including bone marrow samples), Fresh Tissue

Paraffin embedded or fresh tissue samples will be labeled with the specimen type, the study number, Case Report Form identification number (CRF ID #) and date of collection. No personal identifiers (name, initials, address, etc.) will be written on the tubes. A form will accompany each tissue sample being shipped and will be used to record the following information: the study number, CRF ID #, date of collection and comments. Forms will be provided as part of study specific materials (see Section 14.0).

- Confirm that patient has a paraffin embedded tissue sample. Determine location of contact person. Determine if site is able to generate slides or if they prefer to send the entire paraffin embedded block or fresh tissue sample.
- Send the paraffin embedded sample from the primary biopsy or resection specimen using the kit provided.
- All lymph blocks should be sent to the address specified by the central laboratory.
- If the tissue block from the primary biopsy or tissue resection specimen cannot be sent, please prepare ten 6-micron slides and send to the address specified by the central laboratory. Please see the laboratory manual for specimen processing labeling and shipping instructions. Please also prepare ten, 15-micron sections and place in an Ependorf tube if the tumoral content is greater than 80%, alternatively ten, 10 micron sections are placed on uncharged uncoated glass slides if the tumoral content is less than 80%. Send the samples to the address specified by the central laboratory.

Pharmacogenomics Tissue Sample Shipment

Notify courier at least 24 hours in advance of the planned shipment. Provide courier with the appropriate account number to be used, if applicable.

DO NOT package the paraffin embedded tissue block in dry ice.

Label the package with the study number and all other information required.

Include a return address on the outside of each shipping container. Send to the address specified by the central laboratory.

Attachment 5: (Continued)
Pharmacogenomics Sample Collection and Shipment Procedure

The central laboratory will send the paraffin blocks and samples for IHC to the following address:

Dr. Stephan Francke
Johnson & Johnson Pharmaceutical Research & Development
Department of Pharmacogenomics
1000 Route 202
Raritan, NJ 08869
Tel: (908) 218-6596
Fax: (908) 429-0695
Email: sfranck1@prdus.jnj.com

The central laboratory will send the samples for somatic analyses to the following address:

Dr. Stephan Francke
Johnson & Johnson Pharmaceutical Research & Development
Department of Pharmacogenomics
1000 Route 202
Raritan, NJ 08869
Tel: (908) 218-6596
Fax: (908) 429-0695
Email: sfranck1@prdus.jnj.com

Comply with all courier regulations for the shipment of biological specimens (include all paperwork).

Retain all documents indicating date, time and signature/s of person/people making the shipment, in the study files.

Serum for Protein Analysis

- One 5 mL blood sample should be drawn into a serum separator (red top) tube at each of the 3 specified visits.
- Protocol number, CRF ID #, and date of collection will identify the tubes. No personal identifiers (name, initials, address etc.) are to be placed on the tube.
- The sample should be spun down accordingly to separate serum and plasma.
- The sample is to be aliquoted into two 2 mL Sarstedt tubes. The 2 tubes are to be labeled with the protocol number, patient ID, CRF ID #, date of collection and type of tube.
- Once collected, sample should be shipped frozen within 24 hours to the central laboratory.
- Samples are to be stored at –70°C and shipped on dry ice. Storage at –20°C may be permitted, if required.
- The central laboratory will ship serum samples to the address specified above.

Attachment 6:
Candidate Gene List for Part 1 of Pharmacogenomics

AKT1, ALK, ALOX5, ATM, ATR, BAD, BAK1, BAX, BCL1, BCL2, BCL2A1, BCL2L1, BIK, BIRC2, BIRC3, BIRC4, CASP3, CASP7, CASP8, CASP9, CASP12P1, CCNA2, CCNB1, CCND1, CCNE1, CDC14A, CD40, CDC28, CDKN1A ($p21^{Cip1}$), CDKN1B ($p27^{Kip1}$), CDKN2B, CHUK, CSEIL, CTAG2, CTNNB1, DAXX, DED, DRAK1, DRAK2, E2F1, EIF2AK2, FADD, FAS, FASLG, FCGR2A, FOS, HRAS, HSPB1, HSPCA, ICAM1, IFI44, IGF1, IGF1R, IGFBP3, IκB, IKBKB, IKBKG (IKK), IL1A, IL6, IL10R, IL32, IRS1, JAK2, JUN, KRAS, MAPK, MAPKAPK2, MAPK8, MAP3K1, MAP3K14, MCL1, MDM2, MKI67, MYC, MYCN, NFKB1, NFKB1A, NFKB2, NOLC1, NOXA, NUDT6, PARP1, PRAD1, PRKDC, PSMA5, PSMB1, PSMB2, PSMB5, PSMB6, PSMC6, PSMB8, PSMB9, PSMB10, PSMD9 (p27), PTGS2, PTTG1, RASGRF1, RAF1, RAIDD, RAS family, REL, RELA, Repp86, RIPK1, SELE, SPARC, SPP1, STAT3, STIP1, STK17A, STK17B, TANK, TAP1, TAT, TNF, TNFRSFS, TNFS4, Topoisomerase II, TOSO, TP53, TRAF5, TRAF6, TTF1, VCAM1, VEGF.

Attachment 7:
Health Questionnaire

EQ - 5D

Health Questionnaire

English version for the US

Attachment 7: (Continued)
Health Questionnaire

By placing a checkmark in one box in each group below, please indicate which statements best describe your own health state today.

Mobility

I have no problems in walking about	☐
I have some problems in walking about	☐
I am confined to bed	☐

Self-Care

I have no problems with self-care	☐
I have some problems washing or dressing myself	☐
I am unable to wash or dress myself	☐

Usual Activities *(e.g. work, study, housework, family or leisure activities)*

I have no problems with performing my usual activities	☐
I have some problems with performing my usual activities	☐
I am unable to perform my usual activities	☐

Pain/Discomfort

I have no pain or discomfort	☐
I have moderate pain or discomfort	☐
I have extreme pain or discomfort	☐

Anxiety/Depression

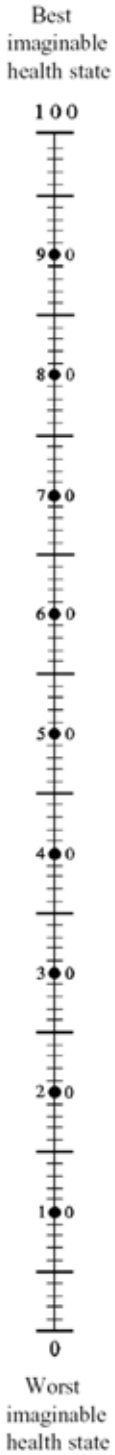
I am not anxious or depressed	☐
I am moderately anxious or depressed	☐
I am extremely anxious or depressed	☐

Attachment 7: (Continued)
Health Questionnaire

To help people say how good or bad a health state is, we have drawn a scale (rather like a thermometer) on which the best state you can imagine is marked 100 and the worst state you can imagine is marked 0.

We would like you to indicate on this scale how good or bad your own health is today, in your opinion. Please do this by drawing a line from the box below to whichever point on the scale indicates how good or bad your health state is today.

Your own health state today



Attachment 8:
EORTC QLQ-C30

EORTC QLQ-C30 (version 3)

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

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

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

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

Please go on to the next page

Attachment 8: (Continued)
EORTC QLQ-C30

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

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

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

1	2	3	4	5	6	7
Very poor						Excellent

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

1	2	3	4	5	6	7
Very poor						Excellent

Attachment 9:
Brief Fatigue Inventory

Brief Fatigue Inventory

STUDY ID# _____ HOSPITAL # _____

Date: ____/____/____ Time: _____

Name _____ _____ _____
Last First Middle Initial

Throughout our lives, most of us have times when we feel very tired or fatigued. Have you felt unusually tired or fatigued in the last week? Yes ☐ No ☐

1. Please rate your fatigue (weariness, tiredness) by circling the one number that best describes your fatigue right NOW.

0 1 2 3 4 5 6 7 8 9 10
No Fatigue — As bad as you can imagine

2. Please rate your fatigue (weariness, tiredness) by circling the one number that best describes your USUAL level of fatigue during past 24 hours.

0 1 2 3 4 5 6 7 8 9 10
No Fatigue — As bad as you can imagine

3. Please rate your fatigue (weariness, tiredness) by circling the one number that best describes your WORST level of fatigue during past 24 hours.

0 1 2 3 4 5 6 7 8 9 10
No Fatigue — As bad as you can imagine

4. Circle the one number that describes how, during the past 24 hours, fatigue has interfered with your:

A. General activity
0 1 2 3 4 5 6 7 8 9 10
Does not interfere — Completely Interferes

B. Mood
0 1 2 3 4 5 6 7 8 9 10
Does not interfere — Completely Interferes

C. Walking ability
0 1 2 3 4 5 6 7 8 9 10
Does not interfere — Completely Interferes

D. Normal work (includes both work outside the home and daily chores)
0 1 2 3 4 5 6 7 8 9 10
Does not interfere — Completely Interferes

E. Relations with other people
0 1 2 3 4 5 6 7 8 9 10
Does not interfere — Completely Interferes

F. Enjoyment of life
0 1 2 3 4 5 6 7 8 9 10
Does not interfere — Completely Interferes

Attachment 10:
Calculating the International Prognostic Index for MCL

Score 1 for each of the following:

Age > 60years

MCL Stage III or IV at diagnosis

EGCO performance status >1

More than one extranodal site involvement

LDH above normal limits

Score range will be 0 - 5

Attachment 11:
American Joint Committee on Cancer, NHL Staging System

Stage I	Involvement of a single lymph node region or localized involvement of a single extralymphatic organ or site
Stage II	Involvement of two or more lymph node regions on the same side of the diaphragm or localized involvement of a single associated extralymphatic organ or site and its regional nodes with or without other lymph node regions on the same side of the diaphragm
Stage III	Involvement of lymph node regions on both sides of the diaphragm (III) that may also be accompanied by localized involvement of an extralymphatic organ or site , by involvement of the spleen or both
Stage IV	Disseminated (multifocal) involvement of one or more extralymphatic organs with or without associated lymph node involvement, or isolated extralymphatic organ involvement with distant (no regional) nodal involvement

Attachment 12:
New York Heart Association Classification of Cardiac Disease

The following table presents the NYHA classification of cardiac disease:

Class	Functional Capacity	Objective Assessment
I	Patients with cardiac disease but without resulting limitations of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea, or anginal pain.	No objective evidence of cardiovascular disease.
II	Patients with cardiac disease resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea, or anginal pain.	Objective evidence of minimal cardiovascular disease.
III	Patients with cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes fatigue, palpitation, dyspnea, or anginal pain.	Objective evidence of moderately severe cardiovascular disease.
IV	Patients with cardiac disease resulting in inability to carry on any physical activity without discomfort. Symptoms of heart failure or the anginal syndrome may be present even at rest. If any physical activity is undertaken, discomfort is increased.	Objective evidence of severe cardiovascular disease.

Source: The Criteria Committee of New York Heart Association. Nomenclature and Criteria for Diagnosis of Diseases of the Heart and Great Vessels. 9th Ed. Boston, MA: Little, Brown & Co; 1994:253-256.

LAST PAGE