THE UNIVERSITY OF TEXAS
MD Anderson Cancer Center

Protocol Abstract Page

A Phase II Study of Carfilzomib in the Treatment of Relapsed/Refractory Mantle Cell Lymphoma
2013-0259

Core Protocol Information

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Full Title:	A Phase II Study of Carfilzomib in the Treatment of Relapsed/Refractory Mantle Cell Lymphoma
Protocol Phase:	Phase II
Version Status:	Terminated 12/21/2017
Version:	09
Document Status:	Final

Abstract

Objectives:

PRIMARY OBJECTIVE:

- To evaluate the efficacy of single agent carfilzomib in patients with relapsed/refractory MCL as measured by response rate.
- To further evaluate the toxicity of Carfilzomib in patients with MCL.

SECONDARY OBJECTIVES:

- To estimate the response duration, progression free survival, time to failure and overall survival.

Rationale: (Be as concise as possible)

Study Rationale

MCL is a distinct subset of B-cell non-Hodgkin's lymphoma (NHL) characterized by the t (11, 14) chromosomal translocation, which results in over-expression of cyclin D1 and deregulation of the cell cycle. MCL is not yet curable because most patients eventually relapse and succumb to progressive MCL. Therefore, novel therapeutic strategies are needed for the treatment of patients with MCL.
Carfilzomib, an irreversible proteasome inhibitor with selectivity for the chymotrypsin-like

active site, inhibits the proliferation of human tumor cells. In our laboratories, carfilzomib induced apoptosis of both established MCL cells and fresh primary MCL cells from patients in a dose-dependent manner. Carfilzomib significantly inhibited the growth of subcutaneous tumors and prolonged the long-term survival of the MCL-bearing SCID mice. Therefore, Carfilzomib is effective in vitro and in vivo in preclinical studies.35,36
Based on the above data and observations, we propose the current LOI for a phase II clinical trial using carfilzomib in relapsed refractory MCL. We hypothesize that this agent may result in a high CR and PR response rates and have significantly reduced side effects. This protocol aims to evaluate the safety of carfilzomib as single agent in patients MCL and to observe the response rate to this regimen.

Eligibility: (List All Criteria)

Inclusion:

1) Confirmed diagnosis of mantle cell lymphoma.

2) Patients must have relapsed or refractory MCL.

3) Understand and voluntarily sign an IRB-approved informed consent form.

4) Age >/= 18 years at the time of signing the informed consent.

5) Patients must have bi-dimensional measurable disease (bone marrow only involvement is acceptable).

6) Eastern Cooperative Oncology Group (ECOG) performance status of 2 or less

7) Serum bilirubin <1.5 mg/dl and Creatinine Clearance >/= 30 mL/min, platelet count >50,000/mm^3 and absolute neutrophil count (ANC) > 1,000/mm^3. [Patients who have bone marrow infiltration by MCL are eligible if their ANC is · 500/mm^3 (growth factor allowed) or their platelet level is equal to or > than 30,000/mm^3.]. AST (SGOT) and ALT (SGPT) < 2 x upper limit of normal or < 5 x upper limit of normal if hepatic metastases are present. Uric acid within normal limits.

8) Females of childbearing potential (FCBP)* must have a negative serum or urine pregnancy test within 30 days of initiation of therapy. * A female of childbearing potential is a sexually mature woman who: 1) has not undergone a hysterectomy or bilateral oophorectomy; or 2) has not been naturally postmenopausal for at least 24 consecutive months (i.e., has had menses at any time in the preceding 24 consecutive months).

9) FCBP must agree to use a highly-effective form of birth control while taking the study drug and for 1 month after the last dose of study drug. Highly-effective forms of birth control include implants, injectables, birth control pills with 2 hormones, some intrauterine devices (IUDs), or having a sterilized partner. The type of birth control used must be discussed with and approved by the attending physician prior to initiation of study drug.

10) Males must agree to use a condom with spermicide every time they have sex during the study and for 3 months after the last dose of study drug. They also must agree to not donate sperm during the study and for 3 months after the last dose of study drug.

11) Patients must be willing to receive transfusions of blood products.

Exclusion:

1) Any serious medical condition including but not limited to, uncontrolled hypertension, uncontrolled diabetes mellitus, active/symptomatic coronary artery disease, chronic obstructive pulmonary disease (COPD), renal failure, active hemorrhage, or psychiatric illness that, in the investigators opinion places the patient at unacceptable risk and would prevent the subject from signing the informed consent form.

2) Pregnant or breast feeding females.

3) Known HIV infection. Patients with active hepatitis B infection (not including patients with prior hepatitis B vaccination; or positive serum Hepatitis B antibody). Known hepatitis C infection is allowed as long as there is no active disease and is cleared by GI consultation

4) All patients with active central nervous system lymphoma.

5) Significant neuropathy (Grades 3 - 4, or Grade 2 with pain) within 14 days prior to enrollment.

6) Known history of allergy to Captisol® (a cyclodextrin derivative used to solubilize carfilzomib).

7) Contraindication to any of the required concomitant drugs or supportive treatments or intolerance to hydration due to preexisting pulmonary or cardiac impairment including pleural effusion requiring thoracentesis to ascites requiring paracentesis.

8) Patients with active pulmonary embolism or deep vein thrombosis (diagnosed within 30 days of study enrollment).

9) Patients with symptomatic bradycardia (heart rate < 50 bpm, hypotension, light-headedness, syncope).

10) Use of any standard/experimental anti-lymphoma drug therapy, including steroids, within 3 weeks of initiation of the study or use of any experimental non-drug therapy (e.g. donor leukocyte/mononuclear cell infusions) within 56 days of initiation of the study drug treatment. Prior allogeneic SCT within 16 weeks or autologous SCT within 8 weeks of initiation of therapy.

11) Patients with New York Health Association (NYHA) Class III and IV heart failure, myocardial infarction in the preceding 6 months, and conduction abnormalities, including but not limited to atrial fibrillation, atrioventricular (AV) block block, QT prolongation, sick sinus syndrome, ventricular tachycardia, as these patients may be at greater risk for cardiac complication, per carfilzomib labeling.

12) The patient has a prior or concurrent malignancy that in the opinion of the investigator, presents a greater risk to the patient's health and survival, than of the MCL, within the subsequent 6 months at the time of consent. Investigator discretion is allowed.

13) Acute active infection requiring treatment (systemic antibiotics, antivirals, or antifungals) within 14 days prior to enrollment.

14) Patients who have received any previous Carfilzomib treatment.

Are patients <18 years of age eligible to participate in this study? ○ **Yes** ● **No**

Studies that include children must meet the criteria for inclusion.
http://www.fda.gov/ohrms/dockets/AC/04/briefing/4028B1_05_NIH-Inclusion%20of%20Children.doc
http://www.hhs.gov/ohrp/policy/populations/children.html

Studies that exclude children must have appropriate justification. Please select all that apply:

Phase I or Phase II study targeting cancer that is very unusual in pediatrics (e.g., prostate, lung, breast, chronic lymphocytic leukemia, etc.)

Are participants >65 years of age eligible to participate in this study? ● **Yes** ○ **No**

Are pregnant women eligible to participate in this study? ○ **Yes** ● **No**

Will the recruitment population at M. D. Anderson include persons who are incarcerated at time of enrollment (e.g., prisoners) or likely to become incarcerated during the study?
○ **Yes** ● **No**

Disease Group:

Lymphoma

Treatment Agents/Devices/Interventions:

Carfilzomib

Proposed Treatment/Study Plan:

Is treatment assignment randomized? ○ **Yes** ● **No**

Is this a blinded or double-blinded study? ○ **Yes** ● **No**

This will be a single-center, phase II clinical trial in patients with relapsed refractory mantle cell lymphoma.

Carfilzomib will be given at a dose of 20*/56 mg/m^2 (* CFZ 20 mg/m2 IV on Days 1 and 2 in Cycle 1 followed by 56 mg/m^2 for each subsequent dose thereafter) on days 1 and 2, 8 and 9, 15 and 16 of a 28-day cycle (following cycle 12 carfilzomib will be given on days 1 and 2 and 15 and 16 only). The targeted enrollment according to our statistical design is 60 patients.

All patients shall be registered with CORe (Clinical Oncology Research System) at (713) 745-2673 prior to receiving therapy.

Carfilzomib will be administered intravenously (IV) at 20/56 mg/m^2.

Overall response rate (ORR) (≥ partial response [PR]) will be assessed by the Revised Response Criteria for Malignant Lymphoma, with secondary assessment of clinical benefit response (CBR = minimal response [MR] + ORR), time to progression (TTP), and duration of response (DOR).

Therapy will continue in 28-day cycles for a maximum of 36 cycles (3 years), until there is disease progression, unacceptable toxicity or the patient chooses to withdraw from therapy.

All patients will be asked to record the medications they take at home and to bring the medication record they use to the clinic with them when they return to see their physician or

research nurse. The patients will be provided with a specific medication form on which to record this information. Patients will also be asked to report any adverse events they experience during the course of the study. They will be given a form on which to record their information and this form will be returned on their next clinic visit to assist the research personnel in determining adverse events.

Carfilzomib for Injection is supplied as a lyophilized parenteral product in single-use vials. The lyophilized product is reconstituted with Water for Injection to a final carfilzomib concentration of 2.0 mg/mL prior to administration.

Table of Assessments

15 TABLE OF ASSESSMENTS

Assessment	Screening	Cycles 1 – 12 (cycle = 28 days)						Cycle 13 and higher	End of Treatment[16]	LTFU
	-30 days	Day 1* (+/- 3 days)	Day 2 (+/- 3 days)	Day 8 (+/- 3 days)	Day 9 (+/- 3 days)	Day 15 (+/- 3 days)	Day 16 (+/- 3 days)			
Medical/RX history[1]	X							Cycles 13 and higher, carfilzomib is given on days 1, 2 and 15 and 16 only. All other evaluations remain the same as cycles 1 - 12		
Physical exam, ECOG, BSA[2]	X	X		(X)[2]		(X)[2]			X	
Vital signs[3]	X	X	X	X	X	X	X		X	
Neurologic assessment[4]	X	X							X	
12-lead ECG	X								X	
Hematology[5]	X	X		(X)[5]		(X)[5]			X	
Full serum chemistries[6]	X	X		(X)[6]		(X)[6]			X	
Serum β2 microglobulin[6]	X									
Hepatitis B and C[6]	X									
Coagulation tests[7]	X								X	
Pregnancy test[8,9]	X	X[8]		(X)[8]		(X)[8]			X[8]	
Tissue and cytology Dx of MCL[11]	X									
CT chest/abd/pelvis/neck[10]	X	(X)[12]							X	
CXR[10]	X								X	
Echo/MUGA	X	(X)[18]								
Unilateral BMB and aspirate	X[13]	(X)[13]							X	
Colonoscopy/GI endoscopy	X[14]	(X)[14]							X	
Other imaging/PET[14]	X	(X)[14]							X	
Carfilzomib administration[10,15]		X	X	X	X	X	X			
Adverse events	→							→		→
Concomitant medications	→							→		→
Disease status and survival										X[17]

(X) Parentheses indicate that the particular test is situational at that time point, as specified in the respective footnote.
* + 3 day window does not apply to Day 1 of Cycle 1

1. Medical history: prior treatments for mantle cell lymphoma, significant medical conditions, neuropathy history
2. Physical examination: review of systems, height at baseline, weight, calculation of BSA at baseline and if significant weight loss or gain. Abbreviated PE on day 8 and 15 of cycle 1 and days 1 and 15 of cycles 2 and 3 followed by day one of each cycle or as clinically indicated.
3. Vital signs: systolic and diastolic blood pressure, respiration, pulse, oral temperature prior to and one hour following carfilzomib infusion during Cycle 1 days 1 and 2 and as clinically indicated. Monitor according to institutional guidelines with each dose of carfilzomib.
4. Neurologic exam: evaluate peripheral neuropathy and/or changes in preexisting neuropathy
5. Hematology: hemoglobin, hematocrit, WBC with complete manual differential (neutrophils [segmented and bands], lymphocytes, monocytes, eosinophils, basophils), RBCs, platelet count (for screening, historical panel may be used if within 14 days prior to initiation of therapy). Obtain and review prior to each dose of carfilzomib on days 1, 8 and 15 of Cycles 1 and 2 and on days 1 and 15 of Cycle 3. Obtain and review prior to dosing on day 1 of each subsequent cycle and as clinically indicated.
6. Full blood chemistry panel: BUN, creatinine, glucose, uric acid, bicarbonate, calcium, chloride, phosphorus, potassium, sodium, albumin, total protein, magnesium, total bilirubin, alkaline phosphatase, ALT, AST, LDH (for screening, historical panel may be used if within 14 days prior to1st day of study drug). Repeat on days 8 and 15 of cycle 1 and on days 1 and 15 of cycles 2 and 3, thereafter repeat on day 1 of each subsequent cycle. Serum β2 microglobulin, Hepatitis B and C at baseline.
7. Coagulation tests: prothrombin time, activated partial thromboplastin time, and international normalized ratio (historical panel may be used if within 14 days prior to 1st day of study drug)
8. Pregnancy tests for FCBP. Does not have to be performed on C1D1.
9. A female of childbearing potential (FCBP) is a sexually mature woman who: 1) has not undergone a hysterectomy or bilateral oophorectomy; or 2) has not been naturally postmenopausal for at least 24 consecutive months (i.e., has had menses at any time in the preceding 24 consecutive months).
10. Disease Assessment: Obtain bi-dimensional measurements. The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up.
11. A formalin-fixed paraffin embedded tumor block or slides must be sent MD Anderson's pathology department for confirmation of MCL diagnosis. However, prior to enrollment, a report from a local laboratory is acceptable. Not needed for patients with non-measurable disease. The Investigatorcan determine whether or not a tumor biopsy is needed.
12. Starting in Cycle 3, repeat every 2 cycles up to cycle 12 and then every 3 cycles. Perform only those evaluations with known or suspected sites of disease. If no change in persistent mass, a biopsy is to be performed if feasible.
13. Send baseline bone marrow aspirate for cytogenetics and lymphoma markers. FISH for IgH/cyclin D1 may be required to make a definitive diagnosis if bone marrow is inconclusive. Repeat only if initially positive and send bone marrow aspirate for lymphoma markers. Repeat bone marrow biopsy to confirm CR.
14. Baseline colonoscopy and other GI endoscopies are required only if this is the main area of disease response assessment. They do not need to be repeated on C1D1. If in CR by radiologic evaluation, bone marrow or blood test at any time, do colonoscopy with random biopsy and bone marrow biopsy and PET scan if necessary and possible to confirm CR.
15. Carfilzomib administration: See section 6 for pre-treatment therapy and study drug administration and section 7 for dose modification guidelines.
16. Approximately 30 days after discontinuation of all study drugs or before start of subsequent treatment (whichever occurs first)
17. Every 6 months for 1 year via telephone. For subjects who did not progress during treatment.
18. ECHO/MUGA can be done as needed at any other time with cardiac consultation. They do not need to be repeated on C1D1.

Study Enrollment:
The study population for this research will consist of participants from:

Only at MDACC

Estimated Accrual:

Total Accrual at MDACC: 60
Estimated monthly accrual at MDACC: 1-2

Accrual Comments:

Is this an NCI-Cancer Therapy Evaluation Protocol (CTEP)? No

Is this an NCI-Division of Cancer Prevention Protocol (DCP)? No

Statistical Considerations:

The primary objective for this phase II study is to estimate the efficacy and evaluate the toxicity

of the single agent Carfizomib when given to patients with relapse/refractory mantle cell lymphoma (MCL). The maximum number of patients will be enrolled is 60.

The overall response (OR: complete response + partial response) at 4 cycles and toxicity at 1 cycle will be monitored simultaneously using the Bayesian stopping boundaries calculated based on beta-binomial distribution. Independence is assumed between OR and toxicity. Toxicity is defined as the following toxicities observed during cycle 1 (28 days) of the treatment:

Non-hematologic:

- >/= Grade 2 neuropathy with pain
- >/=Grade 3 non-hematologic toxicity (excluding nausea, vomiting, diarrhea, hyperglycemia due to dexamethasone treatment and rash due to lenalidomide treatment)
- >/=Grade 3 nausea, vomiting, or diarrhea uncontrolled by maximal antiemetic/antidiarrheal therapy
- >/=Grade 4 fatigue persisting for > 7 days
- Treatment delay greater than 21 days for toxicity

Hematologic:

- Grade 4 neutropenia [absolute neutrophil count (ANC) < 500/mm3] lasting for > 7 days
- Febrile neutropenia (ANC < 1,000/mm3 with a fever >/=38.3·C)

Grade 4 thrombocytopenia (<25,000/mm3) that persists for >/= 7 days, despite holding treatment
Treatment delay greater than 21 days for toxicity

Based on the efficacy and toxicity data from a Phase II study of Velcade in relapse/refractory MCL and two Phase II ongoing studies of Carfizomib in multiple myeloma, we will consider that Carfizomib is promising in treating relapse/refractory MCL if the OR rate at 4 months is at least 45% and the toxicity rate at 1 month is below 30%. A sample size of 60 ensures that, if the trial is not terminated early, a posterior 90% credibility interval for OR ate at 4 months will have width of .21 at most, under the assumption of a 45% OR rate. The prior probabilities of OR and toxicity for the regimen are modeled by beta distributions (*Beta*(0.9, 1.1) and *Beta*(0.6, 1.4), respectively). Denoting the probabilities of OR and toxicity by $\{\theta_{OR}, \theta_{TOX}\}$, and they are compared to fixed targets of OR and toxicity rates. The following decision criteria will be applied:

1) stop if Prob$\{ \theta_{OR} < 0.45 \mid \text{data}\} > 0.95$, and
2) stop if Prob$\{ \theta_{TOX} > 0.30 \mid \text{data}\} > 0.95$

Patients will be monitored by a cohort size of 10 according to the following stopping boundaries for OR at 4 months and toxicity at one month. If the number of responses required for moving the trial to next stage has not been achieved, the patient enrollment will be halted until enough responses observed.

Number of patients evaluated	Stop if ≤ OR observed	Stop if ≥ toxicity observed
10	1	6
20	5	10
30	8	14
40	12	18
50	16	21
60	Always stop with this many patients	

The operating characteristics are summarized in the following tables (based on simulations from 10,000 trials).

True Toxicity Rate	True OR Rate	Prob(stop the trial early due to toxicity or futility)
0.10	0.25	0.928
	0.35	0.493
	0.45	0.103
	0.55	0.011
	0.65	0.001
0.20	0.25	0.928
	0.35	0.497
	0.45	0.111
	0.55	0.020
	0.65	0.009
0.30	0.25	0.936
	0.35	0.551
	0.45	0.206
	0.55	0.125
	0.65	0.116
0.40	0.25	0.967
	0.35	0.766
	0.45	0.587
	0.55	0.544

	0.65	0.539
0.50	0.25	0.995
	0.35	0.962
	0.45	0.932
	0.55	0.926
	0.65	0.925

The above stopping boundaries and operating characteristics are calculated using MultcLean (v.2.0.0) design software downloaded from http://biostatistics.mdanderson.org/SoftwareDownload. A sample size of 1000 was used for the historical (standard treatment) data for the Model Input to approximate the fix targets for OR and toxicity rates.

Summary statistics will be provided for continuous variables. Frequency tables will be used to summarize categorical variables. Logistic regression will be utilized to assess the effect of patient prognostic factors on the response rate and the toxicity rate. The distribution of time-to-event endpoints including overall survival and progression free survival will be estimated using the method of Kaplan and Meier. Comparison of time-to-event endpoints by important subgroups will be made using the log-rank test. Cox proportional hazard regression will be employed for multivariate analysis on time-to-event outcomes.

Toxicity data will be summarized by frequency tables for all patients. For the efficacy endpoints, intend-to-treat analysis will be applied to the eligible patients. For the toxicity endpoint, per-treated analysis will be performed to include any patient who received the treatment regardless of the eligibility nor the duration or dose of the treatment received.

Data Safety Monitoring Board / DSMB at MDACC:

Select the name of the data safety monitoring board (DSMB) monitoring this protocol:
Not Applicable

Please explain:
This protocol is not randomized or blinded.

Protocol Monitoring:

Does this protocol have a schedule for interim and final analysis? Yes

Provide a summary or schedule of interim analysis.

Patients will be monitored by a cohort size of 10 according to the following stopping boundaries for OR at 4 months and toxicity at one month. If the number of responses required for moving the trial to next stage has not been achieved, the patient enrollment will be halted until enough responses observed.

Number of patients evaluated	Stop if </= OR observed	Stop if >/= toxicity observed
10	1	6
20	5	10
30	8	14
40	12	18
50	16	21
60	Always stop with this many patients	

Protocol Monitoring Plan:

This study will be monitored by the MD Anderson IND Office and a protocol-specific monitoring plan will be followed.

Intellectual Property:

1. Does this study include any agents, devices, or radioactive compound (or drug) manufactured at MD Anderson Cancer Center or by a contract manufacturer? No

Investigational New Drugs (IND):

Does this protocol require an IND? Yes

Who is the IND Holder/Regulatory Sponsor?
MD Anderson Cancer Center
IND Number: 116699

Please "Compose" an Investigator's Brochure Cover Letter. For technical assistance, contact the PDOL Help Desk, 713-745-7365.

Investigational Device (IDE):

Does this study utilize an Investigational Device? N/A

Sponsorship and Support Information:

Does the Study have a Sponsor, Supporter or Granting Agency? Yes

Sponsor Name: Onyx
Support Type: Industry Funding
Agent Name(s): Carfilzomib

This Sponsor/Supporter/Granting Agency will receive data.

Radioactive Material:

Does this study involve the administration of radioisotopes or a radioisotope labeled agent? Click here for help	N/A

Biosafety:

Does this study involve the use of Recombinant DNA Technology?	No
Does this study involve the use of organisms that are infectious to humans?	No
Does this study involve human/animal tissue other than blood derived hematopoietic stem cells?	N/A

Questions should be addressed to the Transfusion Medicine Tissue Coordinator at 713-792-8630.

Laboratory Tests:

Is there any biomarker testing in this study being used to determine patient/participant eligibility, treatment assignment, or management of patient/participant care?

- ○ Yes
- ● No
- ○ Not Applicable For This Protocol

Manufacturing:

Will you manufacture in full or in part (split manufacturing) a drug or biological product at the M. D. Anderson Cancer Center for the proposed clinical study?	No

Student/Trainee Information:

Is this research being conducted as a partial fulfillment for completion of a degree?	No