PROTOCOL

Androgen Receptor Targeting in Mantle Cell Lymphoma: A Pilot Trial of Enzalutamide

Trial of the Fred Hutchinson Cancer Research Center (FHCRC), the University of Washington (UW), and the Seattle Cancer Care Alliance (SCCA)

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SCHEMA

Registration

Baseline staging

Start enzalutamide monotherapy 160mg QD continuously

Restaging on q3 month basis

Continue therapy until intolerance, progressive disease, or the discretion of patient / clinician

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1.0 OBJECTIVES

1.1 Primary objectives

1.1.1 Perform a preliminary assessment of the efficacy of single-agent enzalutamide, based on overall response rate, in subjects with relapsed/refractory mantle cell lymphoma (MCL) or previously untreated MCL.

1.2 Secondary objectives

1.2.1 To evaluate the duration of disease control (progression free survival) in patients with MCL treated with enzalutamide.

1.2.2 To evaluate the safety profile of enzalutamide in MCL.

1.2.3 To gain preliminary data on clinical activity and toxicity of this regimen in male vs. female patients.

2.0 BACKGROUND

2.1 Mantle Cell Lymphoma (MCL)

MCL represents approximately 5-10% of non-Hodgkin lymphoma (NHL) diagnosed annually in the US and Europe, with an average incidence rate of approximately 0.5 cases per 100,000 person-years [1]. The average age at diagnosis is 70 and recent reports indicate, in contrast to other NHLs, the incidence of MCL is potentially on the rise [2]. Interestingly, and pertinent to this protocol, MCL demonstrates a clear male predominance with a male to female ratio ranging from 2-2.5:1 across multiple studies. Moreover, the aforementioned trend in increased incidence of MCL is largely accounted for by an annual percent increase in men (7.8%, vs 2.5% in women) [2]. The pathobiology underlying this gender-distribution imbalance is unknown, although anecdotal observations of decreased clinical aggressiveness of MCL in male patients who have been treated with androgen deprivation for prostate cancer (PCa) and in vitro evidence of relative androgen receptor (AR) overexpression in MCL cell lines implicate the AR signaling axis as a potential driver of leukemogenesis in MCL.

The clinicopathological features of MCL are intermediate between classically indolent and aggressive NHLs; demonstrating adverse features of aggressive lymphoma with frequent rapid disease progression, as well as adverse features of indolent lymphoma, being essentially incurable. As such, MCL presents uniquely challenging treatment paradigm which has garnered increased attention in basic and clinical research over the recent years. While these research efforts have led to approval of myriad new MCL-directed therapies (bortezomib, bendamustine, lenalidomide, ibrutinib) and improved clinical outcomes for patients afflicted with

this disease, MCL remains a largely incurable malignancy with a 3 year overall survival of 40-80% depending on age, gender and treatment regimen (i.e. chemoimunotherapy +/- ASCT) [3]. These data indicate that, despite improvements in therapeutic options for MCL, most patients will still relapse and eventually succumb to their malignancy. There exists, however, a subset of MCL patients that presents with an indolent form of the disease who are able to go months to years without MCL-directed therapy and whose long term prognosis is favorable. Defining patients with this indolent form of MCL at initial diagnosis is a clinical challenge and, thus far, there have been no clearly defined clinical or pathological features able to reproducible identify this subgroup; further prospective research is ongoing.

2.2 Enzalutamide and the AR axis in MCL

Sex steroid receptors are widely expressed in the hematopoietic system, and are characterized by sex-related differences, such as higher AR in leucocytes and macrophages from male donors [4, 5]. Steroid hormone signaling mediates pleomorphic effects, influencing dendritic cell, lymphocyte, NK cell, neutrophil, macrophage, platelet and red cell physiology [6-9], and resulting in gender-related differences in immune surveillance, cytokine production, and inflammatory responses [10]. Disease-specific differences in receptor expression have also been described, including aberrant methylation and expression of the AR in leukemia cells and non-Hodgkin's lymphomas (NHL) [11-13]. Of particular relevance to this protocol, the AR gene is preferentially hypermethylated (and therefore not expressed) in follicular and diffuse large B cell lymphomas, but remains unmethylated and open to transcription in MCL [14-15]. ER expression has also been demonstrated in human lymphomas, including Hodgkin's, Burkitt's and multiple myeloma cell lines[1] and ER signaling has been shown to modulate growth and proliferation in myeloma and Burkitt's cell lines[16, 17].

Preclinical studies at our institution have shown AR levels in MCL lines were ~2^6 fold higher than those in non-MCL cell lines or AR- PCa cell lines (Figure 1A). Additionally, expression of the AR target gene PSA in MCL cell lines was directly correlated with that of AR (Figure 1B) suggesting functional AR transactivation. Of note, lymphoma cell lines are known to express functional estrogen receptors, and although lower, AR transcript levels were within several fold of ER transcript levels in most MCL lines (Figure 1C).

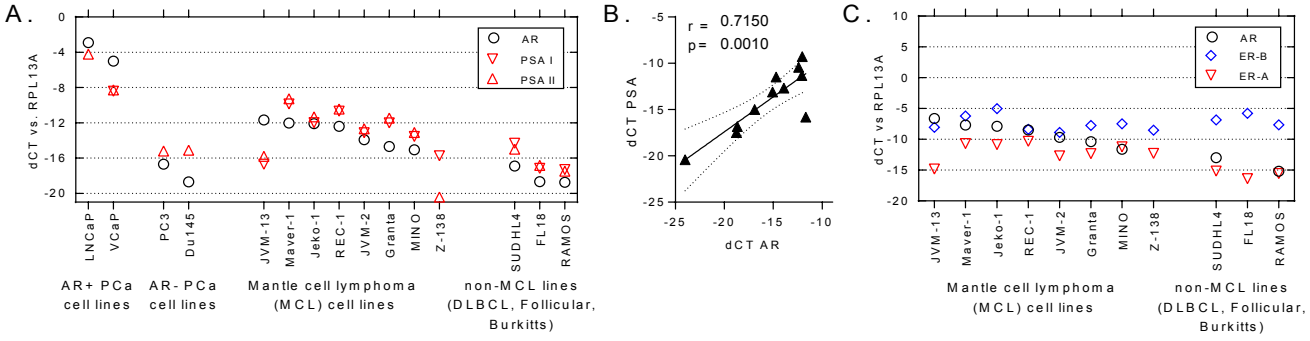

Figure 1. (A) Expression of AR (white squares) and PSA (red triangles) by qRT-PCR in prostate cancer, mantle cell lymphoma (MCL) and non-MCL lymphoma cell lines (normalized to the house-keeping gene RPL13A). (B) Linear regression of PSA and AR expression in the eight MCL lines and three non MLC lymphoma lines shown in A. (C) Concomitant expression levels of estrogen receptors alpha and beta in lymphoma lines.

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Treatment of 4 different AR+ MCL lines with the AR agonist R1881, the potent AR antagonist enzalutamide (Section 3.1 below) or the combination demonstrated somewhat limited stimulation by agonist, but consistent suppression of proliferation by enzalutamide (Figure 2). Minimal change was observed in an AR negative MCL line (Ramos), and the magnitude of suppression in AR+ male and female MCL lines (Granta and Jeko, resp.) was comparable to that observed in the AR+ LNCaP PCa cell line. We detected AR, PSA and ER transcripts in human MCL tumors in the ranges observed in the panel of MCL cell lines (Figure 3, left), as well as variable but detectable levels of AR protein by IHC (Figure 3, right). In addition to this compelling preclinical data, in collaboration with our institution's GU oncology group and others, we have identified a very small subset of patient with both MCL and PCa on androgen-blocking therapies who have been observed anecdotally to have a more indolent course with regard to their MCL (personal communication); further informing the potential therapeutic role of AR axis blockade in patients with MCL.

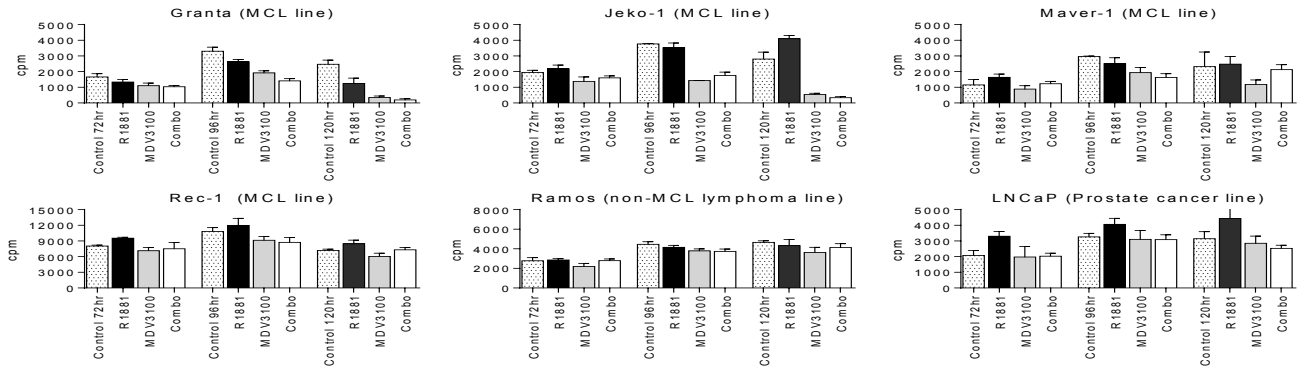

Figure 2 Response of 4 AR+ MCL lines to treatment with control (hatched bars), the AR agonist R1881 (black bars), Enzalutamide (MDV3100, gray bars) or the combination (white bars), at 24, 48 or 72 hours, compared to the AR- non MCL lymphoma cell line, Ramos, and the AR+ prostate cancer cell line LnCaP. Gender of patients from which cell lines

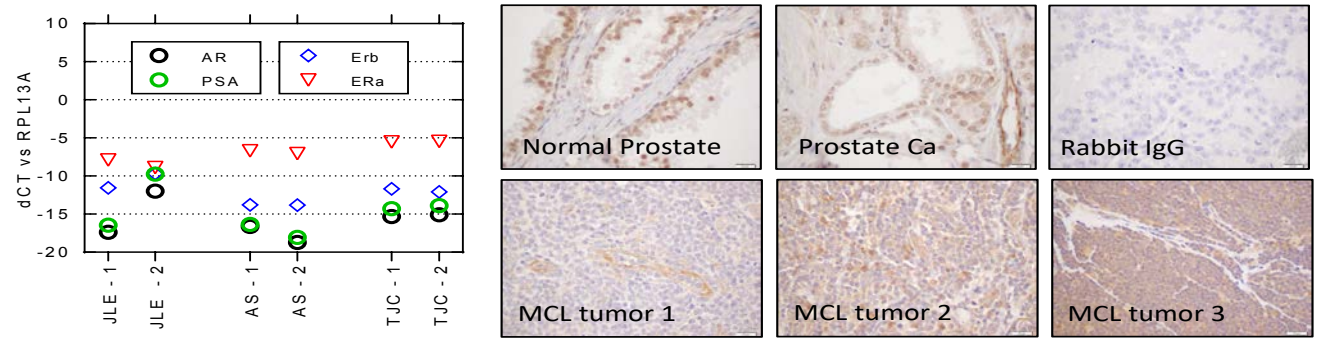

Fig 3. Left – Expression of AR, PSA, ERa and ERb by qrt-pcr in replicate RNA isolates from tumor cells of 3 MCL patients. **Right** - Expression of AR by IHC in normal prostate, prostate cancer, negative isotype control, and 3 human MCL tumors (AR SC C-19) (different patients than those shown on left).

2.3 Summary

Despite recent advances in treatment strategies, MCL remains a largely incurable disease prone to short-interval relapses, ultimately resulting in a significant

foreshortening of quality adjusted life years for those afflicted with the disease. Based on the strong male predominance of MCL, the clinical observation of MCL tumor control following standard androgen deprivation therapy, and our preliminary data suggesting a role for AR-axis activity in MCL, we hypothesize that the potent AR antagonist enzalutamide will yield anti-tumor activity in MCL, induce downstream biological effects consistent with inhibition of steroid receptor signaling, and thus provide an additional effective therapeutic modality toward improving patient outcomes in this challenging disease process.

3.0 DRUG INFORMATION

3.1 General Information

Enzalutamide (MDV3100) is an androgen receptor signaling inhibitor that targets several steps in the AR signaling pathway. Enzalutamide competitively inhibits binding of androgens to ARs, inhibits nuclear translocation of receptors and inhibits the association of the AR with DNA. Enzalutamide is currently FDA approved for the treatment of metastatic, castration-resistant prostate cancer (CRPC). As this medication has not previously been studied in patients with MCL, we will extrapolate dosing and adverse effect monitoring from clinical experience with enzalutamide in the setting of CRPC. Enzalutamide is sold and distributed by Astellas/Medivation, Inc. under the brand name Xtandi™.

3.2 Administration

Enzalutamide is provided as liquid-filled soft gelatin capsule for oral administration. Each capsule contains 40 mg of the active pharmaceutical ingredient. The approved therapeutic dose (CRPC) is 160 mg once daily (4 capsules, each 40 mg).

3.3 Toxicity

3.3.1 Adverse events

The safety and tolerability of enzalutamide have been evaluated in a combined safety analysis including metastatic CRPC patients from 2 large randomized, placebo-controlled phase 3 studies (MDV3100-03) [NCT01212991] and CRPC2 [NCT00974311]). These data are summarized below. Please refer to the current FDA-approved package insert and/or the *Physician Desk Reference* for complete details.

The most common adverse reactions (≥ 10%) in patients with CRPC treated with enzalutamide are asthenia/fatigue, back pain, decreased appetite, constipation, arthralgia, diarrhea, hot flush, upper respiratory tract infection, peripheral edema, dyspnea, musculoskeletal pain, weight decreased, headache, hypertension, and dizziness/vertigo.

3.3.2 Seizure

Seizure occurred in 0.9% of patients receiving enzalutamide who previously received docetaxel and in 0.1% of patients who were chemotherapy-naive. Patients will be informed of the increased risk of

seizure and advised to inform their provider of any seizure or loss of consciousness. Patients who have a prior seizure history or chronic use of drugs that lower the seizure threshold will not be enrolled. Enzalutamide will be permanently discontinued for any subjects who develop a seizure during treatment.

3.3.3 Hypertension

Hypertension was reported in 10.6% of patients receiving enzalutamide and 4.3% of patients receiving placebo. No patients experienced hypertensive crisis. Patients will be informed of hypertension risk..

3.3.4 Falls and fall related injuries

Falls occurred in 9% of patients treated with enzalutamide compared to 4% of patients treated with placebo. Falls were not associated with loss of consciousness or seizure. Fall-related injuries were more severe in patients treated with enzalutamide and included non-pathologic fractures, joint injuries, and hematomas. Patients will be informed of fall risk.

3.3.5 Infection

1% of patients treated with enzalutamide compared to 0.3% of patients treated with placebo died from infections or sepsis. However, this increase in infection rate was not seen across all trials involving enzalutamide. Patients will be informed of potential increased infection risk.

3.3.6 Laboratory Abnormalities

Grade 1-4 neutropenia occurred in 15% of patients on enzalutamide (1% Grade 3-4) and in 6% of patients on placebo (no Grade 3-4). The incidence of Grade 1-4 thrombocytopenia was similar in both arms; 0.5% of patients on enzalutamide and 1% on placebo experienced Grade 3- 4 thrombocytopenia. Grade 1-4 elevations in ALT occurred in 10% of patients on enzalutamide (0.3% Grade 3-4) and 18% of patients on placebo (0.5% Grade 3-4). Grade 1-4 elevations in bilirubin occurred in 3% of patients on enzalutamide and 2% of patients on placebo.

3.3.7 Hallucinations

1.6% of patients treated with enzalutamide were reported to have Grade 1 or 2 hallucinations compared to 0.3% of patients on placebo. Of the patients with hallucinations, the majority were on opioid containing medications at the time of the event. Hallucinations were visual, tactile, or undefined.

3.4 Pregnancy/Breast Feeding:

Enzalutamide is a pregnancy category X medication and is contraindicated in women who are pregnant or who are planning to become pregnant. A confirmed negative pregnancy test will be required for all female subjects prior to enrollment and both male and female subjects will be counseled on and required to employ effective use of barrier contraception from the start of therapy through a minimum

of 3 months after the last dose. Enzalutamide has not been studied in breast feeding mothers and its excretion characteristics in breast milk remain unknown. We will not enroll any patients who are actively breastfeeding.

3.5 Drug Interactions

3.5.1 Metabolism, CYP2C8:

Co-administration of a strong CYP2C8 inhibitor (gemfibrozil) increased the composite area under the plasma concentration-time curve (AUC) of enzalutamide plus N-desmethyl enzalutamide by 2.2-fold in healthy volunteers. In current study, co-administration of enzalutamide with strong CYP2C8 inhibitors will be avoided if possible and, if unavoidable, dose reductions will be made according to the manufacture guidelines and SCCA pharmacy assistance.

The effects of CYP2C8 inducers on the pharmacokinetics of enzalutamide have not been evaluated in vivo. Co-administration of enzalutamide with strong or moderate CYP2C8 inducers (e.g., rifampin) may alter the plasma exposure of enzalutamide and will be avoided in this trial if possible.

3.5.2 Metabolism, CYP34A:

Co-administration of a strong CYP3A4 inhibitor (itraconazole) increased the composite AUC of enzalutamide plus N-desmethyl enzalutamide by 1.3-fold in healthy volunteers. Co-administration of enzalutamide with strong CYP3A4 inducers (e.g., carbamazepine, phenobarbital, phenytoin, rifabutin, rifampin, rifapentine) may decrease the plasma exposure of enzalutamide and will be avoided if possible. The effects of CYP3A4 inducers on the pharmacokinetics of enzalutamide have not been evaluated in vivo. Selection of an alternative medication with no or minimal CYP3A4 induction potential is recommended by the manufacturer and this strategy will be utilized whenever possible.

Enzalutamide is a strong CYP3A4 inducer and a moderate CYP2C9 and CYP2C19 inducer in humans. Co-administration with drugs that are metabolized by CYP3A4 (e.g., alfentanil, cyclosporine, dihydroergotamine, ergotamine, fentanyl, pimozide, quinidine, sirolimus and tacrolimus), CYP2C9 (e.g., warfarin) and CYP2C19 (e.g., S-mephenytoin) will be avoided when possible and closely monitored when concurrent use is unavoidable.

3.6 Supplier

Enzalutamide used under this study will be provided by from Astellas/Medivation, Inc. and distributed by NCCN's vendor CRMG.

3.7 Drug Accountability

The investigator, or a responsible party designated by the investigator, must maintain a careful record of the receipt, disposition, and return of all drugs received for this study using the study specific Investigational Agent Accountability form.

3.7.1 Return of unused enzalutamide
Patients will be instructed to return unused enzalutamide. All unused drug will be destroyed per institutional Investigational Drug Services policy.

4.0 STAGING CRITERIA

When applicable, the Lugano staging criteria [18] (see Appendix A) will be used; staging should be the highest stage established, either at diagnosis or relapse of disease.

For patients from whom data are available, the mantle cell lymphoma international prognostic index (MIPI) [19] will be documented at the time of diagnosis and enrollment (see Appendix B).

5.0 ELIGIBILITY CRITERIA

5.1 Inclusion Criteria

5.1.1 Patients must have histologically confirmed relapsed/refractory or previously untreated mantle cell lymphoma (any stage).

5.1.2 Patients with untreated MCL should be asymptomatic or minimally symptomatic from their MCL and without aggressive clinicopathological features that would otherwise warrant immediate intensive therapy. These will generally be patients who qualify for an initial period of "watch and wait" per clinical discretion.

5.1.3 Patients must have metabolically active (PET scan positive, as defined in section 10.3), measurable disease (defined as lesions greater than 1.5 cm long axis that can be accurately measured in two dimensions by CT).

5.1.4 Patients must have an ECOG performance status of 0-2 (see Appendix C).

5.1.5 Patients must be 18 years of age or older.

5.1.6 Hematology values must be within the following limits independent of growth factor or transfusion support:

5.1.6.1 Absolute neutrophil count (ANC) $\geq 1000/mm^3$ or $\geq 750/ mm^3$ in the setting of marrow involvement by disease.

5.1.6.2 Platelets $\geq 50,000/mm^3$ or $\geq 30,000 /mm^3$ in the setting of marrow involvement by disease or splenomegaly due to disease.

5.1.7 Biochemical values within the following limits:

5.1.7.1 Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤ 3 x upper limit of normal (ULN)

5.1.7.2 Total bilirubin ≤ 1.5 x ULN unless bilirubin rise is due to Gilbert's syndrome or of non-hepatic origin

5.1.7.3 Creatinine clearance (CrCl) ≥ 30 mL/min (as calculated by Cockcroft-Gault Equation)

5.1.8 All patients must be informed of the investigational nature of this study and have given written consent in accordance with institutional and federal guidelines. Patient must sign an informed consent document indicating that they understand the purpose of and procedures required for the study, and are willing to participate in and comply with the guidelines of the study.

5.1.9 Women of childbearing potential and men who are sexually active must affirm they are practicing a highly effective method of barrier birth control during and after the study consistent with local regulations regarding the use of birth control methods for subjects participating in clinical trials. Men must agree to not donate sperm during or after the study. These restrictions apply throughout the treatment period and for three months after the last dose of enzalutamide.

5.1.10 Women of childbearing potential must have a negative serum (beta-human chorionic gonadotropin [β-hCG]) or urine pregnancy test at screening. Women who are pregnant or breastfeeding are ineligible for this study.

5.2 Exclusion Criteria

5.2.1 Uncontrolled illness including, but not limited to ongoing or active infection, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, or psychiatric illness/social situations that would limit compliance with study requirements within 6 months of enrollment.

5.2.2 Known active central nervous system lymphoma.

5.2.3 Known clinically significant heart disease as evidenced by:

- Myocardial infarction within 6 months of enrollment.
- Uncontrolled angina within 6 months of enrollment.
- Congestive heart failure NYHA Class III or IV, or a history of congestive heart failure NYHA Class III or IV in the past, unless a screening ECHO or MUGA within 3 months results in a left ventricular ejection fraction ≥45%.
- Clinically significant ventricular arrhythmias.
- History of Mobitz II second degree or third degree heart block without a permanent pacemaker in place.
- Bradycardia as indicated by a heart rate < 50 beats per minute at screening visit.
- Hypotension as indicated by SBP ≤ 85 on 2 consecutive measurements at screening visit.

- Uncontrolled hypertension as indicated by SBP > 170 mmHg or DBP > 105 mmHg on 2 consecutive measurements at screening visit.

5.2.3 Child Pugh class C hepatic dysfunction.

5.2.4 History of seizures.

5.2.5 Any life-threatening illness, medical condition, or organ system dysfunction which, in the investigator's opinion, could compromise the subject's safety, interfere with the absorption or metabolism of enzalutamide, or put the study outcomes at undue risk.

5.2.6 Patients with other prior malignancies except for adequately treated basal cell carcinoma, squamous cell carcinoma of the skin, breast or cervical cancer *in situ*, or other cancer from which the patient has been disease-free for 5 years or greater, unless approved by the protocol Investigator / Lead-Sub-Investigator.

5.2.7 Chemotherapy, immunotherapy, biologically targeted therapy, other investigational agent, or radiation therapy within 3 weeks of initiation of enzalutamide therapy. For patients with objectively progressive disease on a BTK-targeting agent whom in the opinion of the investigator would not tolerate a 21 day washout period, a >5 half-lives washout period will be allowed.

5.2.8 Prior allogeneic transplant with GVHD requiring ongoing immunosuppressive therapy.

5.2.9 HIV-positive individuals on combination antiretroviral therapy are ineligible because of the potential for pharmacokinetic interactions with enzalutamide.

5.2.10 Ongoing treatment with hormonal agents (e.g. finasteride, dutasteride, ketoconazole, hormonal birth control, estrogen replacement therapy, testosterone replacement therapy) or herbal products that may have hormonal activity (saw palmetto, black cohosh). Patients taking these agents are eligible for screening, but must be willing to undergo a washout period of 4 weeks prior to starting study treatment.

6.0 REGISTRATION

Patients must be registered prior to the start of protocol therapy. A completed eligibility checklist with source documentation, a copy of the signed consent form, and a signed HIPAA authorization are required for registration. All of the eligibility requirements according to Section 5 must have been met.

7.0 TREATMENT PLAN

7.1 Contact

For treatment or dose-modification related questions, please contact Dr. Martin at (206) 667-3132 or Dr. Gopal at (206) 606-2037. (MedCon may also be used to contact MDs at 206-543-5300.)

7.2 Administration of Enzalutamide

Enzalutamide is taken orally at a starting dose of 160 mg daily. Enzalutamide can be taken with or without food. Enzalutamide may be taken at any time during the day, but should be taken at the same time each day. A missed dose should be taken as soon it is remembered. If twelve or more hours have lapsed since a missed dose, participants should not take the missed dose; rather the participant should resume dosing at the next scheduled dose.

Drug	Dose	Route	Days	Duration
Enzalutamide	Starting dose of 160 mg, as four 40 mg capsules. Can be taken with or without food. Capsules should be swallowed whole with water. Do not chew, dissolve, or open capsules.	PO	Once daily	Until disease progression, intolerance, or decision of patient or treating physician

7.3 Prophylaxis

No prophylactic therapy is required for enzalutamide. Supportive care should be provided as clinically indicated.

7.4 Criteria for removal from protocol treatment:

- Documented progression of disease (see section 10.4).
- Development of seizures, or any therapy-related non-hematologic grade ≥ 4 toxicity or other serious adverse event as defined in section 12.0 will qualify for consideration of removal from protocol treatment.
- Development of any other unacceptable toxicity.
- Delay of treatment for more than 21 days due to toxicity.
- The patient may withdraw from the treatment at any time for any reason.
- Taking prohibited medications concurrent with enzalutamide therapy may result in removal from protocol treatment.

8.0 DOSAGE MODIFICATIONS

8.1 Toxicity Management, Dose Modification and Dose Delay

If a patient experiences a ≥ Grade 3 non-hematological toxicity related to the study drug or an intolerable side effect, treatment will be withheld for one week or until symptoms improve to ≤ Grade 2 or baseline, at which point treatment will

be resumed at the same dose or at a reduced dose (120 mg or 80 mg), based on clinician judgment.

8.2 Concomitant Therapy

Medications used during the course of the study should be documented.

8.2.1 Prohibited Concomitant Therapy:

The administration of concurrent medications intended to treat the primary cancer is not allowed during protocol therapy. This includes any chemotherapy, investigational agent, biologic agent or other anti-tumor agents.

The administration of concomitant medications with effects on drug metabolizing enzymes known to be involved in the metabolism of enzalutamide should be avoided where possible, as detailed in section 3.5 and summarized in the table below.

Class	Example Drugs	Recommendation
Strong CYP2C8 Inhibitors	Gemfibrozil	If co-administration with gemfibrozil cannot be avoid, reduce enzalutamide dose
Strong CYP2C8 Inducers	Rifampin	Avoid concomitant use
Strong CYP3A4 Inhibitors	Itraconazole	No initial dose adjustment
Strong/Moderate CYP3A4 Inducers	Carbamazepine, phenobarbital, phenytoin, rifabutin, rifamin, rifapentine, osentan, efavirenz, etravirine, modafinil, nafcillin, St. John's Wort	Avoid concomitant use
CYP3A4 Substrate	Alfentanil, cyclosporine, dihydroergotamine, ergotamine, fentanyl, pimozide, quinidine, sirolimus and tacrolimus	Avoid concomitant use of substrates with a narrow therapeutic index
CYP2C9 Substrate	Phenytoin, warfarin	Avoid concomitant use of substrates with a narrow therapeutic index
CYP2C19 Substrate	S-mephenytoin	Avoid concomitant use of substrates with a narrow therapeutic index
CYP2C8 Substrate	Pioglitazone	No dose adjustment

Patients should be strongly discouraged from taking any "alternative" or "naturopathic" medications since these agents may interact with study treatment. Concomitant use of these medications should be documented and evaluated by the treating investigator.

Hematopoietic growth factors and transfusions are allowed.

Localized radiation therapy will be allowed for symptom control as needed.

9.0 STUDY CALENDAR

- The first three treatment cycles will be 4 weeks (28 days). All subsequent cycles starting with Cycle 4 will be 12 weeks (84 days). Patients may be seen for additional optional mid cycle visits at the discretion of their provider.
- Study drug will be dispensed in a four week supply for the first three cycles, then in a 12 week supply for subsequent cycles

Required Studies	Screening (within 4 weeks of initiation of treatment)	During treatment	Post Therapy	Follow-up[10]
Physical				
Medical History	X			
Physical Exam	X	X[7]	X[9]	
Performance Status	X	X[7]	X[9]	
Clinical Disease Assessment	X	X[7]	X[9]	
Adverse Event Assessment	X	X[7]	X[9]	
EKG	X			
Lab				
CBC and differential	X	X[7]	X[9]	
Serum creatinine, total bilirubin, SGOT (AST), SGPT (ALT), electrolytes, calcium, glucose	X	X[7]	X[9]	
Albumin, LDH, B2M	X		X[9]	
Bone marrow studies	X[1]	X[1]		
Pregnancy test	X[2]			
Tissue collection, if feasible	X[11]			
PSA (prostate specific antigen)	X[3]	X[3]		
Total testosterone and estradiol	X[4]	X[4]		
Research Labs[5]	X[5]	X[5]	X[9]	
Radiology				
CT Chest, abdomen and pelvis (+ neck if clinical involvement)	X	X[8]		

FDG-PET (skull base to proximal femur)	X[6]	X[8]		

[1] Bone marrow studies include aspirate and unilateral or bilateral biopsy for standard analysis with additional correlative studies as specified in Section 14. Bone marrow studies should be performed at screening unless approved by the Investigator or Lead Sub-Investigator. If all bone marrow studies are negative at screening, these do not need to be repeated except in the case of progressive disease by CT imaging, if feasible. If bone marrow status is unknown or positive at screening, patients will need to a have bone marrow study to confirm a suspected CR.
[2] Pregnancy test is only required in women of childbearing potential. Pregnancy test will be repeated on the first day of study drug therapy if > 1 week has lapsed from initial screening pregnancy test and start of treatment.
[3] PSA is only required in men. To be drawn at screening, after 4 weeks of treatment (+/- 6 days), and at treatment discontinuation (+/- 6 days).
[4] Total testosterone and estradiol to be drawn at screening, after 4 weeks of treatment (+/- 6 days), and at treatment discontinuation (+/- 6 days).
[5]Research Labs include blood samples for serum hormone levels (DHT, DHEA, Androstenedione, Estrone). To be drawn at screening, after 4 weeks of treatment (+/- 6 days), after 12 weeks of treatment (+/- 6 days), and then every 12 weeks (+/- 6 days) during treatment. [6] May be obtained up to 8 weeks in advance of initiation of therapy (provided no additional anti-cancer therapies are administered during the interval). A Deauville score should be assigned.
[7] At the beginning of therapy (within 3 days), then every four weeks for the first 12 weeks (+/- 6 days), then at a minimum of every 12 weeks (+/- 6 days) while on therapy, depending on clinical course. For the first day of therapy, pre-entry H&P, PS, disease assessment, and adverse event assessment may be used (these do not need to be repeated within 3 days) and labs done within 14 days are acceptable.
[8] During treatment, restaging CT imaging will be performed every 12 weeks of therapy (+/- 7 days), or as indicated to evaluate clinical suspicion of disease progression. First restaging CT (three months after initiating therapy) should include PET imaging to ascertain metabolic response to therapy. Subsequently, restaging PET/CT should also be performed to confirm metabolic CR in patients with stable PR on 2 consecutive CT staging exams or in patients with a CR based on CT staging and baseline FDG-avid disease to determine metabolic CR and CR (resp.). A Deauville score should be assigned when restaging PET is performed.
[9] Post therapy evaluation will be completed 30 days (+/-7 days) after the last dose of enzalutamide or prior to initiation of new therapy, whichever comes sooner.
[10]Long-term follow-up should be performed according to the patient's physician's standard of care. This may be performed at patients' local physician's offices. Long-term follow-up will assess survival and disease progression; subjects may be contacted by the study team until five years out from study completion, subject withdrawal of consent, lost to follow-up, or study termination by the investigator, whichever occurs first.
[11] When appropriate, archival tissue or fresh samples from clinical biopsies may be used.

10.0 ENDPOINT DEFINITIONS AND CRITERIA FOR EVALUATION

10.1 Endpoint Definitions:

10.1.1 Primary endpoint:

Best overall response rate (ORR) which will include complete responses (CR) and partial responses (PR) as measured by standard criteria (Cheson *et al,* 2014) .

10.1.2 Secondary Endpoints:

1. Time to treatment failure (TTF)
2. Progression-free survival (PFS)
3. Overall survival (OS)
4. Adverse events (AEs) as measured by NCI-CTCAE 4.0.
5. Disease control rate (CR+PR+SD>3 months)

Clinical endpoints of ORR, CR, PR, TTF, PFS and AEs will be stratified by gender.

10.2 Selection of Indicator (Target) Lesions

Up to six of the largest dominant nodes or tumor masses selected according to all of the following:

- Clearly measurable in at least two perpendicular dimensions
  Abnormal lymph nodes are those that are either
  >1.5 cm in the greatest transverse diameter (GTD) regardless of the short axis diameter, or 1.0 cm in short axis diameter regardless of long axis
- If possible, they should be from disparate regions of the body
- Should include mediastinal and retroperitoneal areas of disease whenever these sites are involved
- Extranodal lesions within the liver or spleen must be at least 1.0 cm in two perpendicular dimensions.

10.3 PET Scans

Visual assessment currently is considered adequate for determining whether a PET scan is positive. A Deauville score should be reported. In brief, a positive scan is defined as focal or diffuse FDG uptake above background in a location incompatible with normal anatomy or physiology.

10.4 Response Criteria

Response will be defined by standard NCI criteria (Cheson *et al,* 2014) for lymphoid malignancies [18].

10.5 Progression-free Survival (PFS)

PFS will be measured as time from first study drug administration to the first occurrence of disease progression or death from any cause. Data for subjects without disease progression or death will be censored at the date of last disease assessment or date last known to be alive, respectively. The estimates will be formed using the all treated population. Progression-free survival will be calculated using assessments by investigators. Kaplan-Meier methodology will be used to estimate event-free curves and corresponding quartiles (including the median).

10.6 Assessment Inadequate, Objective Status Unknown

Progression has not been documented and one or more target lesions or other sites of disease have not been assessed or inconsistent methods of assessment were used.

10.7 Bone Marrow Status

Bone marrow status is evaluated as follows:

Positive: Unequivocal morphological, immunohistochemical, or immunophenotypic evidence of malignancy.

Negative: No aggregates or only a few well-circumscribed lymphoid aggregates without morphological, immunohistochemical, or immunophenotypic evidence of malignancy

Indeterminate: Does not qualify for either positive or negative status. *Note this typically consists of increased number or size of aggregates without morphological, immunohistochemical, or immunophenotypic atypia.

11.0 STATISTICAL CONSIDERATIONS

The primary objective of this pilot trial is to derive an estimate of the overall response rate (ORR, see section 10.4) in this population. Secondary clinical endpoints will include time to progression, progression-free survival, and safety. The study is not formally powered to reject a specified null hypothesis and as such the sample size is not based on the number of patients needed to reject the null hypothesis under a specified alternative. That said, with 20 patients the estimated ORR will be within 0.11 of the true ORR if the hypothesized ORR is 20%. An ORR of 20% will be taken as a benchmark for success for the primary endpoint of this pilot study. If the observed ORR is at least 20% (4 or more responses among the 20 patients), we would consider this treatment sufficiently meritorious to warrant further study in a future Phase II trial that will formally evaluate potential efficacy. If the true ORR is 10%, then the probability of 4 or more responses among 20 patients is only 0.13; if the true ORR is 30%, then the probability of 4 or more responses among 20 patients is 0.89. As stated above, the sample size for this trial is not based on specific null and alternative hypotheses. That said, if the assumed-true ORR with this regimen is 35%, then 20 patients will provide 86% power to observe a statistically significant (at the one-sided significance level of .15) improvement in ORR compared to the fixed ORR of 15%.

We will also be encouraged if patients have prolonged disease stability/lack of progression that may be observed with a cytostatic biological agent, though this secondary endpoint will deemed exploratory. For this secondary endpoint, a median PFS of ≥6 months would also be scored as a pilot success.

11.1 Stopping Rules

If we see no responses nor any evidence of disease stabilization (as defined above as stable disease ≥6mo) after the first 10 patients, then the trial will be halted for futility. If we see at least one response or capture at least one instance of disease

stabilization ≥6mo among the first 10 patients, then enrollment will continue to goal enrollment of 20 patients.

11.2 Anticipated Accrual

We expect to accrue approximately 1 patient per month and anticipate complete study accrual in 24 months.

11.3 Estimated Distribution of Study Population by Gender, Race and Ethnicity

Ethnic Category	Females	Males
American Indian/Alaska Native		
Asian	1	1
Native Hawaiian or Other Pacific Islander		
Black or African American	1	1
White	4	12
More than one race		
Unknown or not reported		
Racial Categories: Total of all subjects	6	14

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12.0 STUDY MONITORING AND REPORTING PROCEDURES

12.1 Adverse Event (AE) Reporting

AEs of Grade 3 and above, and Serious Adverse Events (SAEs) occurring at any grade will be monitored and recorded in study-specific case report forms (CRFs) from the time of the first dose of study treatment through 30 days following the end of study treatment, or until the patient receives an alternative anti-cancer therapy, whichever date comes first. AEs related to lymph node (tumor) biopsies that are done solely for research study screening purposes will be monitored, recorded, and reported according to the same standards, with the exception that assessment of study drug attribution will be excluded from reporting criteria.

The Investigator will assess AE grading, attribution, expectedness and whether the event is of interest to Astellas/Medivation Inc.

The NCI Common Terminology Criteria for Adverse Events v4.0 (CTCAE) will be used to classify and grade toxicities.

12.2 Definitions and Descriptions of Terms Used in AE Reporting

12.2.1 Adverse Event (AE)

An AE is any undesirable sign, symptom or medical condition or experience that develops or worsens in severity after starting the first dose of study treatment or any procedure specified in the protocol, even if the event is not considered to be related to the study.

Abnormal laboratory values or diagnostic test results constitute AEs only if they induce clinical signs or symptoms or require treatment or further diagnostic tests.

12.2.2 Serious Adverse Event (SAE) or Adverse Drug Reaction (ADR)

The term "Serious Adverse Event" (or "SAE") shall mean any adverse drug experience occurring at any dose that results in any of the following outcomes: death, is life-threatening (life-threatening means that the person was at immediate risk of death from the reaction as it occurred, i.e., it does not include a reaction which hypothetically might have caused death had it occurred in a more severe form), requires inpatient hospitalization or prolongation of an existing hospitalization, results in a persistent or significant disability or incapacity, results in a congenital anomaly or birth defect, results in cancer, or results in an important medical event. Important medical events which are AEs that may not result in death, be Life-Threatening, or require hospitalization may be considered SAEs when, based upon appropriate medical judgment, they may jeopardize the Study Participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

Disease progression should not be recorded as an adverse event or serious adverse event term; instead, signs and symptoms of clinical sequelae resulting from disease progression/lack of efficacy will be reported if they fulfill the serious adverse event definition.

12.2.3 Grade

Grade is defined as the severity of the adverse event. The CTCAE Version 4.0 must be used to determine the grade of the adverse event. If toxicity is not listed in the CTCAE use the following general criteria for grading.

0 – No adverse event or within normal limits
1 – Mild adverse event
2 – Moderate adverse event
3 – Severe adverse event
4 – Life-threatening or disabling adverse event
5 – Fatal adverse event

12.2.5 Attribution

Attribution is defined as the determination of whether an adverse event is related to a medical treatment or procedure. Attribution categories are as follows:

- *Unrelated* The adverse event is *clearly NOT related* to therapy
- *Unlikely* The adverse event is *doubtfully related* to therapy
- *Possible* The adverse event *may be related* to therapy
- *Probable* The adverse event is *likely related* to therapy
- *Definite* The adverse event is *clearly related* to therapy

12.2.6 Suspected Adverse Reaction
Any adverse event for which there is a reasonable possibility that the drug caused the adverse event.

12.2.7 Unexpected Adverse Event
An AE that is not consistent in nature or severity with the product information documented in the current Investigator's Brochure or package insert, or in the protocol, consent form, and/or prior reports.

Note: The following events are ***not*** identified as AEs in this study:

- Disease progression or relapse. However, clinical events associated with progression/relapse may be reportable as AEs.
- Medical or surgical procedures in and of themselves, including those that require hospitalization (e.g., surgery, endoscopy, biopsy procedures) are not considered AEs. However, an event or condition requiring such procedures may be an AE.
- Abnormal laboratory values will be identified and recorded As AEs only if clinical intervention is required as a result.

12.3 Expedited Reporting

Expedited reporting will be conducted in accordance with FHCRC/Cancer Consortium IRB policies, applicable FDA regulations under 21 CFR 312.32, including regulations pertaining to reporting of Serious and Unexpected Suspected Adverse Reactions, and agreement with NCCN.

12.4 Routine Reporting

Routine reporting will be conducted in accordance with FHCRC/Cancer Consortium IRB policies, applicable FDA regulations, and agreements with NCCN.

12.4 Serious Adverse Event Reporting to NCCN and Astellas/Medivation Inc.

Expedited reporting will be conducted in accordance with FHCRC/Cancer Consortium IRB policies, FDA regulations, and agreements with NCCN. Reportable events and required time frames include:

- SAEs/Suspected Adverse Reactions that are *fatal or life-threatening*, *unexpected*, and *possibly related to the study drug* will be reported to the FDA as an IND Safety Report (via narrative report or MedWatch form 3500A) within 7 calendar days of the Investigator's awareness of the event. Notification to the FDA will be submitted concurrently to NCCN and Astellas.
- SAEs/Suspected Adverse Reactions that are *unexpected* and *possibly related to the study drug* (but are *not* fatal or life-threatening) will be reported to the FDA as an IND Safety Report (via narrative report or MedWatch form

3500A) within 15 calendar days of the Investigator's awareness of the event. Notification to the FDA will be submitted concurrently to NCCN and Astellas.

- AEs that are *unexpected*, *possibly related to the study drug*, and *serious or suggest a risk of greater harm from the research than previously known* will be reported to the IRB within 10 calendar days of the Investigator's awareness of the event.

Initial reporting will occur in the time frames noted above, with follow-up information, if needed, submitted as available.

Expedited reports should be emailed or faxed to both:

- Astellas Pharma Global Development – United States
  Email: Safety-us@us.astellas.com
  Fax number: (888) 396-3750

- NCCN Oncology Research Program (ORP)
  Email: ORPReports@nccn.org
  Fax number: (215) 358-7699

The following minimum information is required:

- Study number/IIT regulatory identifier
- Subject number, sex and age
- The date of report
- A description of the SAE (event, seriousness of the event)
- Causal relationship to the study drug

Follow-up information for the event should be sent promptly (within 7 days) as necessary.

12.5 Reporting to the IRB

Local IRB guidelines and policies will be followed for reporting serious adverse events in a timely manner.

12.7 Data Safety and Monitoring Plan

All serious adverse events are communicated to the study Investigator and regulatory agencies as described above. A status report including accrual, adverse events, and death information will be reviewed by the Investigator and the Fred Hutchinson Cancer Research Center (FHCRC) Protocol Data Monitoring Committee (PDMC) annually. In addition, the study will be monitored by Clinical Research Support (CRS)according to the Fred Hutchinson/University of Washington Cancer Consortium data and safety monitoring plan (DSMP).

12.8 Records

Under the supervision of the investigators, research staff will maintain case report forms and secured databases on the relevant clinical and laboratory data. Records maintained in investigators' offices will be secured with access limited to study personnel. Authorization for access to medical records will be obtained from all patients in accordance with provisions of the Health Insurance Portability and Accountability Act (HIPAA).

13.0 ELEMENTS OF INFORMED CONSENT

All Institutional, NCI, State and Federal regulations concerning informed consent and peer judgment will be fulfilled. Written consent will be obtained from all patients entering the study.

14.0 CORRELATIVE STUDIES

14.1 Objectives

14.1.1 To determine whether pre-treatment expression of AR and ER in tumor, or levels of androgens and estrogens in serum associate with response to therapy in MCL patients treated with enzalutamide.

14.1.2 To determine whether lack of AR expression or presence of truncated AR splice variants associate with poor response to therapy in MCL patients treated with enzalutamide.

14.2 Methodology

14.2.1 Serial measurement of serum hormone levels as outlined in the study calendar.

14.2.2 Analysis of AR and ER expression by immunohistochemistry (IHC) on formalin fixed pre-treatment tumor biopsy samples as outlined in the study calendar.

14.2.3 Additionally, patients with circulating tumor cells, those undergoing clinical bone marrow evaluation, and those undergoing clinical tumor biopsies may have fresh tumor cells collected for evaluation of AR and ER transcript levels by RNA isolation as well as measurement of tumor steroid levels (in the case of tissue biopsy).

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Appendix A: Revised staging system for primary nodal lymphomas (Lugano classification)

Stage	Involvement	Extranodal (E) status
I	One node or a group of adjacent nodes	Single extranodal lesions without nodal involvement
II	Two or more nodal groups on the same side of the diaphragm	Stage I or II by nodal extent with limited contiguous extranodal involvement
II bulky*	II as above with "bulky" disease	Not applicable
III	Nodes on both sides of the diaphragm; nodes above the diaphragm with spleen involvement	Not applicable
IV	Additional noncontiguous extralymphatic involvement	Not applicable

* A single nodal mass of 10cm or greater than a third of the transthoracic diameter at any level of thoracic vertebrae as determined by CT

Appendix B: Mantle cell lymphoma international prognostic index (MIPI)

POINTS	AGE (YEARS)	ECOG PS	LDH:UHN RATIO	WBC (10^9/L)
0	<50	0 to 1	<0.67	<6.7
1	50-59		0.67-0.99	6.7-9.9
2	60-69	2 to 4	1.00-1.49	10.0-14.9
3	≥70		≥1.50	≥15.0

SCORE	RISK GROUP
0 to 3 points	Low risk
4 to 5 points	Intermediate risk
6 to 12 points	High risk

Appendix C: ECOG Performance Status

0 – Asymptomatic (Fully active, able to carry on all pre-disease activities without restriction)

1 – Symptomatic but completely ambulatory (Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature. For example, light housework, office work)

2 – Symptomatic, <50% in bed during the day (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 – Symptomatic, >50% in bed, but not bedbound (Capable of only limited self-care, confined to bed or chair 50% or more of waking hours)

4 – Bedbound (Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair)

5 – Death