TITLE: A Pilot Study of Zydelig in Patients with B-cell Malignancies as Post-Autologous Transplant Remission Maintenance

Protocol Number: **1630GCC**

IND Number: **101254**

Protocol Version and Date: Protocol version 3.0, August 22nd, 2017

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SYNOPSIS

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Synopsis

Concept and Rationale:
Autologous stem cell transplantation (ASCT) represents a potential curative treatment for patients with relapsed and/or refractory (R/R) B-cell lymphomas, and is presently the modality that yields the best chance of prolonged progression-free survival in this population of patients.

Unfortunately, approximately half of these patients suffer from relapsed disease and die from their disease within 1 to 3 years after transplantation, depending on the disease status before transplantation.
Treatment of relapsed B-cell lymphomas after ASCT is challenging, and there are no standard of care or guidelines for this problem.

Rituximab maintenance may have some limited role in follicular lymphoma post autologous transplantation, but most of these patients have been exposed to rituximab and meet the criteria of being resistant to rituximab. With the increased number of patients who are undergoing transplantation and with the improved non-relapse mortality, relapse after transplant has become a larger factor in terms of survival. Relapses occur mostly within the first 2 years after ASCT.

Zydelig (Idelalisib) is the 1st marketed PI3Kδ inhibitor that has been effective against indolent B-cell lymphomas (iNHL) with remarkable activity in heavily treated patients, leading to an overall response rate (ORR) of 57%, a median progression free survival (PFS) of 11 months and a median duration of response of 12.4 months.[1]
We propose to incorporate Zydelig into a maintenance paradigm post ASCT for patients with iNHL and transformed iNHL (tiNHL). The goal of this strategy is to increase the likelihood that patients are able to maintain a remission after ASCT at 1 and 2 years of follow-up.

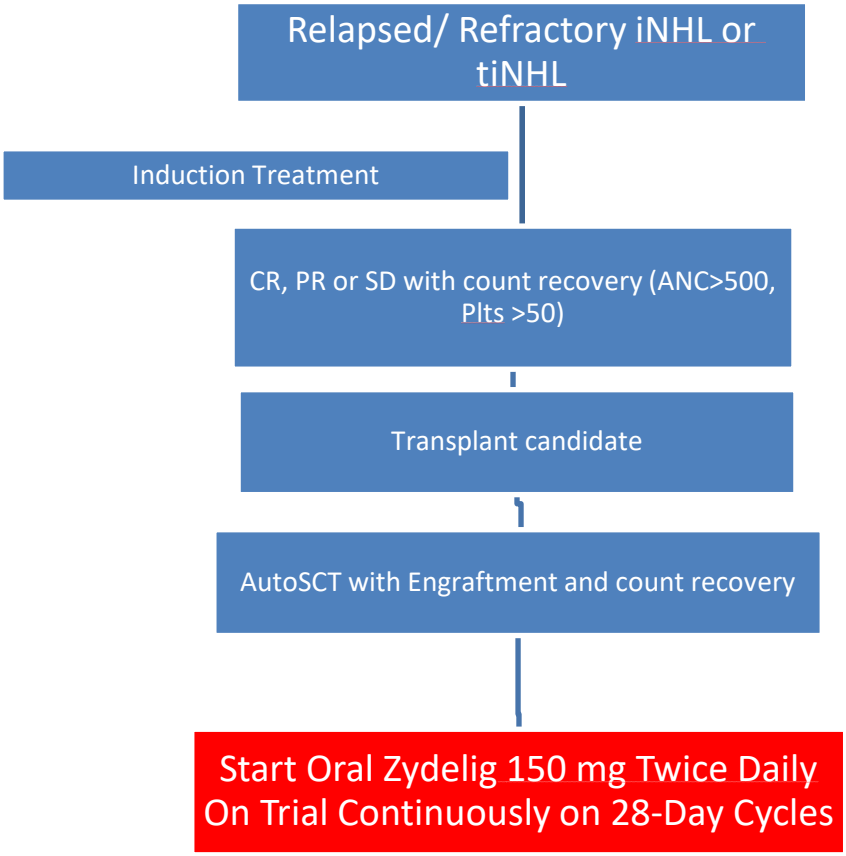
Mirroring the paradigm incorporating BCR/ABL TKI, lenalidomide and Sorafenib therapies in the post-transplant treatments of Ph+ ALL, MM, and FLT3 ITD AML respectively, we propose inhibiting the proliferation and survival of iNHL cells by blocking the B-cell receptor signaling (BCR) via inhibiting the downstream molecular target PI3Kδ with Zydelig in the post-transplant setting.

Primary Objective(s):
1. Determine the toxicity and safety of incorporating Zydelig into the post- ASCT maintenance setting for iNHL and tiNHL immediately after ASCT.

Secondary Objective(s):

1. Assess the efficacy of incorporating Zydelig into the post-ASCT maintenance setting for iNHL and tiNHL immediately after ASCT with a corresponding endpoint of 1-year PFS after the transplantation.
2. 2-year Progression Free Survival (PFS).
3. Non-relapse mortality (NRM).
4. Overall survival (OS).
5. Correlatives studies:
    a. To perform pharmacodynamics studies.
    b. To understand mechanism of resistance to Zydelig.
    c. To assess the effect of Zydelig on the immune system.

Study Design:



Number of Patients:
We will be studying a cohort of 34 patients with iNHL or tiNHL.

Main Criteria for Inclusion/Exclusion:
Inclusion Criteria - must meet all

1. iNHL as defined by follicular lymphoma (FL), marginal zone lymphoma (MZL), lymphoplasmacytic lymphoma/Waldenstrom disease (LPL/WM) and small lymphocytic lymphoma (SLL) or tiNHL as defined by large B cell transformation of any of the above entity.
2. Patients must be eligible to undergo high dose chemotherapy (HDT) followed by ASCT as a form of remission consolidation.
3. Patients without evidence of documented disease progression clinically or radiographically (stable disease [SD], partial remission [PR] or complete remission [CR]) who have had count recovery (ANC > 500 cells/mm^3, non-transfused platelet count > 20,000 K/mm^3) and are at least 30 days post ASCT, but no more than 120 days post ASCT.

Exclusion Criteria:

1. Lack of engraftment
2. Patients with active lymphoma CNS disease

3. Patients with active infection defined as requiring systemic antibiotic treatment and fever within 48 hours of screening.
4. Patients with progressive disease, as defined in protocol section 8.4
5. Patients who progressed while previously taking Zydelig
6. Patients with moderate to severe lung disease including:
   6.1. Patients requiring O2 supplementation
   6.2. Patients unable to walk 50 feet without stopping to rest
   6.3. Moderate to severe obstructive or restrictive disease of the lung

7. Patients with inflammatory bowel disease
8. Patients with active hepatic disease, liver cirrhosis, or known HBV/HCV infection
9. Patients with de novo diffuse large B-cell lymphoma
10. Patients with h/o PCP or CMV infections

Intervention and Mode of Delivery:
Oral Zydelig at 150 mg twice daily continuously on 28-day cycles.
Dose delays/modifications as below for Grade 2 or above for some hematological and non-hematological toxicities such hepatotoxicity, diarrhea/colitis/intestinal perforation, pneumonitis, infections, neutropenia and thrombocytopenia, or any other grade 3 non-hematologic toxicity considered at least possibly related to Zydelig.

Duration of Intervention and Evaluation:
iNHL and tiNHL patients will be eligible after ASCT.
Start of therapy would occur after engraftment, minimum at day 30 post ASCT and no later than 120 days post-ASCT.
Patients will continue on Zydelig up to one year or to progression/relapse/death or unacceptable toxicity, whichever occurs first.

HDT/ASCT will occur as soon as possible based on successful mobilization, collection and infusion of bone marrow or peripheral blood stem cells at a minimum of $2x10^6$ CD34+/Kg of weight.
Myeloablative transplant preparative regimen is based on institutional standards.
Engraftment will be defined as ANC over 500 cells/mm^3 and non-transfused platelet count of 20K/mm^3.
Standard supportive care in the post-transplant setting will be given.

Toxicities will be evaluated to include standard hematologic toxicities for solid tumors (i.e. count suppression etc.). Dose reductions will be pursued as described below for both hematologic and non-hematologic toxicities grade 2 and above

Initial dose will be 150 mg PO BID. Dose modifications for toxicities due to Zydelig will follow the package insert recommendations as below. For other severe or life-threatening toxicities related to Zydelig, withhold drug until toxicity is resolved. If resuming Zydelig after interruption for other severe or life-threatening toxicities, reduce the dose to 100 mg twice daily. Recurrence of other severe or life-threatening Zydelig-related toxicity upon rechallenge should result in permanent discontinuation of Zydelig. Toxicity, as well as graft failure will be monitored continuously throughout the trial.

Statistical Methods:
We are studying a cohort of 34 patients with iNHL or tiNHL. A single-stage open-label design will be used for the study. Please see section 14.0 Statistical Considerations for more information.

1. OBJECTIVES

1.1. Primary Objective

1.1.1. Determine the toxicity and safety of incorporating Zydelig into the post- ASCT maintenance setting for iNHL and tiNHL immediately after ASCT. Toxicity will be monitored continuously throughout the trial.

1.2. Secondary Objectives

1.2.1. Assess the efficacy of Zydelig into the post- ASCT maintenance setting for iNHL and tiNHL immediately after ASCT.

The corresponding endpoint is to report the 1-year PFS after the transplantation. PFS is defined as time to progression, relapse of the disease or death. The efficacy endpoint would be improvement of 1-year PFS after ASCT by 20% based on an approximate baseline PFS of 60% for iNHL and tiNHL.[1,2] The expected 1-year PFS will be around 80%.

Survival without progression or death will be determined using the Kaplan-Meier estimates at 1 year post ASCT.

1.2.2. 2-year PFS.

2-year PFS will be determined using the Kaplan-Meier estimates at 2 years post ASCT.

1.2.3. Non-relapse mortality (NRM).

NRM is defined as death in the absence of competing risks, relapse or progression of disease. This secondary endpoint will be characterized and presented as a cumulative incidence at 3 months and 12 months after SCT.

1.2.4. Overall survival (OS).

Survival without death will be determined and presented as Kaplan-Meier estimates at 1 and 2 years post ASCT.

1.2.5. Correlative studies.

See Appendix D.

2. BACKGROUND

2.1. Zydelig (Zydelig, GS-1101, Cal-101)

Zydelig is is an inhibitor of PI3Kinase delta which is highly expressed in malignant lymphoid B-cells. PI3Kδ inhibition results in apoptosis of malignant tumor cells. In addition, Zydelig inhibits several signaling pathways, including the B-cell receptor. Zydelig was recently approved by the U.S. Food and Drug Association (FDA) for the treatment of the following:

- relapsed chronic lymphocytic leukemia (CLL), in combination with rituximab, in patients for whom rituximab alone would be considered appropriate therapy due to other co-morbidities
- relapsed follicular B-cell non-Hodgkin lymphoma (FL) in patients who have received at least two prior systemic therapies
- relapsed small lymphocytic lymphoma (SLL) in patients who have received at least two prior systemic therapies.[1,2],[3-5]

2.2. Study Disease – Indolent B-cell Lymphomas/Transformed B-cell Lymphomas

Early published clinical trial of Zydelig in multiple relapsed and treated indolent B-cell lymphomas showed a respectable ORR of 57% (6% CR) a short median time to response of 1.9

months and a prolonged median duration of response of 12.5 months. Responses were seen in all lymphoma subtypes. The estimated median progression-free survival and overall survival were 11 months, and 20 months, respectively. The estimated survival rate at one year was 80%. This population of patients included patients who already had undergone HDT/ASCT, and these patients had no different responses to Zydelig compared to the other patients.[4]
There are some reports in the literature showing that the PI3K/Akt/mTOR signaling pathway might be activated in aggressive B-cell lymphoma.[6-10] Other PI3K inhibitors, such as SAR245408, showed some activity in 25% of aggressive B-cell lymphoma.[11]

2.3. Rationale

Autologous stem cell transplantation (ASCT) represents a potential curative treatment for patients with relapsed and/or refractory (R/R) B-cell lymphomas and is presently the modality that yields the best chance of prolonged survival without disease in this population of patients.
Unfortunately, approximately half of these patients suffer from relapsed disease and die from their disease in 1 to 3 years after transplantation depending, on the disease status before transplantation.

Treatment of relapsed B-cell lymphomas after ASCT is challenging, and there are no standard of care or guidelines for this problem.

Rituximab maintenance may have some limited role in follicular lymphoma post autologous transplantation, but most of these patients have been exposed to rituximab and meet the criteria of being resistant to rituximab. With the increased number of patients who are undergoing transplantation and with the improved non-relapse mortality, relapse after transplant has become a larger factor in terms of survival. Relapses occur mostly within the first 2 years after ASCT.

Zydelig is the 1st marketed PI3Kδ inhibitor that has been effective against indolent B-cell lymphomas (iNHL) with remarkable activity in heavily treated patients, leading to response rate (ORR) of 57%, a median progression free survival (PFS) of 11 months and a median duration of response of 12.4 months.[4]

We propose to incorporate Zydelig into a maintenance paradigm post ASCT for patients with iNHL and transformed iNHL (tiNHL). The goal of this strategy is to increase the likelihood patients are able to maintain a remission after ASCT at 1 and 2 years of follow-up.
Mirroring the paradigm incorporating BCR/ABL TKI and Sorafenib targeted therapies in the post-transplant treatments of Ph+ ALL and FLT3 ITD AML respectively, we propose inhibiting the proliferation and survival of iNHL cells by blocking the B-cell receptor signaling (BCR) via inhibiting the downstream molecular target PI3Kδ with Zydelig in the post-transplant setting.

2.4. Correlative Studies Background

Please refer to Appendix D

3. PATIENT SELECTION

3.1. Eligibility Criteria

3.1.1. Inclusion Criteria (must meet all)

1. Histologically documented (by HPI or pathology report) iNHL as defined by follicular lymphoma (FL), marginal zone lymphoma (MZL), lymphoplasmacytic lymphoma/Waldenstrom disease (LPL/WM) and small lymphocytic lymphoma (SLL) or tiNHL as defined by large B cell transformation of any of the above entities including chronic lymphocytic leukemia (CLL)
2. Patients must be eligible to undergo high dose chemotherapy (HDT) followed by ASCT as a form of remission consolidation
3. Patients without evidence of documented disease progression clinically or radiographically after ASCT (stable disease (SD), partial remission (PR) or complete remission (CR)) who have had count recovery (ANC > 500 cells/mm^3, non-transfused platelet count > 20,000 K/mm^3) and are at least 30 days post ASCT but no more than 120 days post ASCT

3.1.2. Prior Therapy

Patients may have received any prior therapy deemed necessary for them to be eligible to HDT/ASCT except for patients whom have progressed while on Zydelig. Patients who have responded to Zydelig previously are eligible for enrollment on the protocol.

3.1.3. Age >18

3.1.4. ECOG performance status <4 (see Appendix A).

3.1.5. Life expectancy of greater than four months.

3.1.6. Patients must have normal organ function as defined below (after the HDT/ASCT):

- total bilirubin $\leq$ 2x institutional upper limit of normal
- AST(SGOT)/ALT(SGPT) <2.5 X institutional upper limit of normal
- Creatinine $\leq$ 1.5x institutional upper limit of normal OR creatinine clearance $\geq$60 mL/min/1.73 m2 for patients with creatinine levels $\geq$ 1.5x upper limit of normal.

3.1.7. Because the effects of Zydelig on the developing human fetus are unknown, women of child-bearing potential and men must agree to use adequate contraception (hormonal or barrier method of birth control; abstinence) prior to study entry and for the duration of study participation. Female subjects of childbearing potential should have a negative pregnancy test within 72 hours prior to receiving the first dose of Zydelig. Male subjects must agree to use an adequate method of contraception starting with the first dose of the study drug Zydelig. Female and male participants must agree to use contraception for at least 30 days after the last dose of Zydelig. Women of childbearing potential is defined as women who continues to have menstrual periods, have not had a tubal ligation, or the removal of fallopian tubes, ovaries or uterus.

3.1.8. Ability to understand English and the willingness to sign a written informed consent document.

3.2. **Exclusion Criteria**

3.2.1 Patients who have had chemotherapy or radiotherapy within 2 weeks of first dose of Zydelig.

3.2.2 Patients receiving any other investigational agents within 30 days of receiving Zydelig

3.2.3 Patients who were previously exposed to Zydelig and experienced progression of disease.

3.2.4 History of allergic reactions attributed to compounds of similar chemical or biologic composition to Zydelig.

3.2.5 Patients with active and/or untreated CNS lymphoma will not be eligible.

3.2.6 Patients with inflammatory bowel disease.

3.2.7 Uncontrolled intercurrent illness including, but not limited to ongoing or active infection (defined as requiring systemic antibiotic treatment and fever within 48 hours of screening), symptomatic congestive heart failure (patients with NYHA score of III and above are excluded), unstable angina pectoris, cardiac arrhythmia, or psychiatric illness/social situations that would limit compliance with study requirements.

3.2.8 Women who are pregnant or nursing or plan to become pregnant or nurse during the course of the study.

3.2.9 Positive HIV status.

3.2.10 Patients with lack of count recovery as defined by ANC > 500 cells/mm^3, non-transfused platelet count > 20,000 K/mm^3.

3.2.11 Patients who are unable to swallow pills.

3.2.12 Patients with moderate to severe lung disease including:

- Patients requiring O2 supplementation
- Patients unable to walk 50 feet without stopping to rest
    - Obstructive lung disease as defined by pre-transplant FEV1 $\leq$ 60% of predicted.
    - Restrictive lung disease as defined by pre-transplant FVC < 60% of predicted.

3.2.13 Patients taking strong CYP3A4 inhibitors or inducers with Risk X (Avoid Combination) according to Lexicomp. Please see appendix C for more information.

3.2.14 Patients with active hepatic disease, liver cirrhosis, or known HBV/HCV infection.

3.2.15 Patients with de novo diffuse large B-cell lymphoma.

3.2.16 Patients with h/o PCP pneumonia or positive CMV viremia confirmed twice at least 1 day apart at screening.

3.3 Inclusion of Women and Minorities

Both men and women, and members of all races and ethnic groups are eligible for this trial.

4. REGISTRATION PROCEDURES

All patients must sign the IRB approved informed consent. Human protection committee approval of this protocol and consent form is required. Patients must be registered with the Study Coordinator/Coordinating Center Contact,Veronica Rodriguez. The following documents are to be submitted for review: signed informed consent, eligibility checklist completed and signed, all supporting documents that demonstrate eligibility requirements have been met such as lab results, pathology reports, medical history/progress note of Investigator. Please fax or email these documents to:Veronica Rodrigiez, Fax: 410-328-1975, Veronica.Rodriguez@umm.edu. Instructions concerning correlative/special studies will be conveyed at the time of registration. Upon review and verification of eligibility, an email or fax document will be sent to the registering center to confirm dose assignment.

5. TREATMENT PLAN

5.1 Zydelig Administration

Treatment will be orally administered on an inpatient and outpatient basis with the starting dose of 150 mg by mouth twice a day for continuous 28-day cycles. Treatment will continue until progression, intolerance, or patient/physician discretion to stop therapy. Zydelig will be started with count recovery (ANC over 500 cells/mm^3, non-transfused platelet count over 20,000 K/mm^3) in patients who are at least 30 days after induction and/or transplant but no more than 120 days post-transplant.

Reported adverse events and potential risks are described in Section 9. Appropriate dose modifications for Zydelig are described in Section 7. No investigational or commercial agents, or therapies other than those described below may be administered with the intent to treat the patient's malignancy.

Patients should swallow Zydelig tablets whole each morning and evening (i.e. every 12hours). Tablets may be taken with or without food. Patients should keep track of adherence to Zydelig therapy by using the “Patients Drug Diary” (see appendix B). This diary will be collected at the end of each cycle. At the time of collection, the diary will be reviewed by a staff member and the patient will be prompted to complete any blank entries before completion of the visit. Should a patient miss or vomit a dose of Zydelig within less than 6 hours of the planned dose, the patient should take it as soon as possible. Patients who miss or vomit a dose of Zydelig longer than 6 hours after the planned dose should wait until the next scheduled dose to resume taking Zydelig.

5.2 General Concomitant Medication and Supportive Care Guidelines

Because there is a potential for interaction of Zydelig with other concomitantly administered drugs through the cytochrome P450 system, the case report form must capture the concurrent

use of all other drugs, over-the-counter medications, or alternative therapies. The Principal Investigator should be alerted if the patient is taking any agent known to affect or with the potential to affect selected CYP450 isoenzymes.

Agents typically used in the supportive care of patients undergoing treatment for NHL should not be manipulated due to potential drug interactions, unless toxicity is observed.

For management of skin toxicity (rash); i.e., topical emollients, topical steroids or keratolytic creams can be used.

Avoid concurrent use of Zydelig with other drugs that may cause liver toxicity.

For management of grade ≥ 2 pneumonitis, diarrhea, or hepatotoxicity, Zydelig needs to be held. Systemic corticosteroids can be started at the discretion of the investigator.

Recent reports showed increased risk of Pneumocystis pneumonia (PCP) and Cytomegalovirus infection (CMV) associated with Zydelig. Because of these known risks, Trimethoprime-sulfamethoxazole (TMP-SMX) will be given as one double-strength tablet daily or three times per week, or as one single-strength tablet once daily. For patients who cannot take TMP-SMX, we will offer dapsone 100 mg tablet once a day or atovaquone suspension 1500 mg once a day. Blood CMV PCR will be monitored once a month; no prophylaxis is required. PCP prophylaxis and CMV monitoring will start once the patient starts taking Zydelig and will end 1 month after stopping Zydelig. Patients will be taken off the study drug if they develop PCP pneumonia, if CMV PCR becomes detectable in the blood or they develop CMV infection.

5.3 Duration of Therapy

In the absence of treatment delays due to adverse events, treatment may continue for 1 year or 12 cycles (28 days per cycle) after transplant or until one of the following criteria applies:

- Disease Progression
- Intercurrent illness that prevents further administration of treatment
- Unacceptable adverse event(s)
- Evidence of PCP pneumonia or CMV viremia, confirmedat 2 consecutive blood draws at least 1 day apart with any value ≥500IU/mL in plasma or evidence of documented CMV disease.
- Patient decides to withdraw from the study
- General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the investigator.

5.4 Duration of Follow-up

Patients will be followed for 24 months after end of study treatment or until death, whichever occurs first. Patients removed from study for unacceptable adverse events will be followed until resolution or stabilization of the adverse event.

5.5 Criteria for Removal from Study

Patients will be removed from study at the time of disease progression as determined by protocol section 8.4. Exclusions are made for relapse isolated to the CNS which is able to be managed through local therapy.

6. REQUIRED DATA/STUDY CALENDAR

Pre-Study Testing Intervals
To be completed within 16 DAYS before study treatment:
- All blood work
- History and physical

To be completed within 28 DAYS before study treatment:
- Any X-ray, scan of any type (e.g., CT or MRI) or ultrasound that is utilized for tumor measurement

To be completed within 42 DAYS before study treatment:
- Any X-ray, scan of any type (e.g., CT or MRI) or ultrasound that is not utilized for tumor measurement
- Bone marrow biopsy and aspirate (unilateral) is required if there washistory of bone marrow involvement.

	Prior to Treatment	**Cycle 1 Day 1**	**Cycle 1 Day 8 ± 3 days**	**Cycle 1 Day 15 ± 3 days**	**Day 1 of Each Subsequent Cycle ± 3 days [I]**	**Cycle 2 Day 15 ± 3 days**	**Cycle 3 Day 15 ± 3 days**	**End of Treatment* * ± 3 days**	**Time of Restaging and Post-treatment Follow-up*, [%]**
Tests & Observations									
History & Progress Note	**X**	**X**			**X**			**X**	**X**
Physical Examination	**X**	**X**			**X**			**X**	**X[J]**
Pulse, Blood Pressure	**X**	**X**			**X**			**X**	**X**
Height	**X**								
Weight	**X**	**X**			**X**			**X**	**X**
Performance Status	**X**	**X**			**X**			**X**	**X**
Drug Toxicity Assessment	**X**	**X**			**X**			**X**	
Solicited Abnormalities/AEs	**X**	**X[A]**			**X[A]**			**X**	
Laboratory Studies									
CBC, Diff, Platelets	**X**	**X**			**X**			**X**	**X**
Serum Creatinine, CrCl (est), BUN	**X**	**X**			**X**			**X**	**X**
Serum Electrolytes	**X**	**X**			**X**			**X**	**X**
AST, ALT, Alk Phos, Bilirubin	**X**	**X**		**X**	**X^**	**X**	**X**	**X**	**X**
Uric Acid, Phosphate, LDH	**X**	**X**			**X**			**X**	**X**
Blood CMV PCR	**X**	**X**			**X**			**X**	
Beta2-Microglobulin	**X**							**X**	

Serum or Urine BHCG	**X**[B]							**X**	
Thyroid Function Tests (T3,T4, TSH)	**X**[E]				**X**[E]			**X**	
Triglycerides	**X**[I]							**X**	
HIV~	**X**[C~]							**X**	
HBsAg~, Anti-HBc~Ab,HepC Ab~	**X~**							**X**	
ECG	**X**		**X**[F]					**X**	
Staging									
CT/MRI (chest/abd/pelvis) with Tumor Measurements	**X**							**X**	**X**[D]
CT Neck	**X**							**X**	**X**[D]
PET (or PET/CT)	**X**							**X**	**X**[D]
Bone Marrow Asp & Biopsy	**X**							**X**[G]	**X**[G]
Histologic Review	**X**							**X**[K]	
Correlative Samples	**X**[H]	**X**[H]						**X**[H]	**X**[H]

Table 1

* Restage every 3 cycles during treatment (i.e., cycles 3, 6, 9, 12, etc.), then every 3 months for 1 year, then every 6 months for another year.
** If off study prior to month 12 study treatment
% Starting at cycle 15 through cycle 24: Visit window +/- 4 weeks. Starting at cycle 27 through cycle 36: Visit window +/- 12 weeks.
^ Monitor ALT, AST, Alk Phos and bilirubin in all patients every 2 weeks (or 15 days) for the first 3 cycles of treatment, than every 4 weeks during subsequent cycles.
~ If done before the transplant, no need to repeat them.
A. Abnormalities/adverse events should be solicited, and severity graded, on day 1 of each cycle of treatment.
B. In women of childbearing potential (as defined in Section 3.1.7). A negative serum or urine HCG test is required within 14 days prior to study.
C. Patients with known HIV positivity are excluded.
D. CT, PET or PET/CT done PRN to follow measurable disease. Scan to be done with or without PET depending on the patient disease status.

E. Thyroid function tests every 3 cycles while on treatment and at completion of protocol therapy(Prior to treatment, C3D1, C6D1, C9D1, C12D1).
F. ECG on day 8 of cycle 1, and then as clinically indicated. The steady-state (day 8) ECG is a requirement of the FDA under the Alliance IND for Zydelig.
G. Repeat bone marrow aspirate and biopsy to confirm CR only if involved at baseline. Also a bone marrow aspirate/biopsy will be done if suspicion of bone marrow involvement.
H. See protocol 19.2 Time Points of appendix D Correlative Studies
I. Triglycerides Day 1 of cycles 3, 6, 9, 12 and then every 3 months until month 24. Then again at months 24, 30, & 36.
J. Physical Exam during follow-up.
K. Only if there is progression, as judged by the Investigator

7. DOSING DELAYS/DOSE MODIFICATIONS

Please refer to table 2 below.
Patients who experience a Grade 2 or 3 toxicity and recover to ≤ Grade 1 (or to pretreatment baseline level of toxicity) may continue treatment at the next lower dose level (i.e., Dose level 2 down to dose level 1).

Once the dose has been reduced, patients must remain at the reduced dose for 28 days. Dose escalation may occur at the discretion of the investigator and may occur every 28 days. Patients may have their dose de-escalated from level 2 to level 1, three times before being removed from treatment.

Please note:
- There are no dose escalations above 150 mg BID
- There are no dose reductions below 100 mg BID

Table 2

Dose Modification Schedule	
Dose Level	Dose of Zydelig
Level 2 (starting dose)	150 mg PO BID
Level 1	100 mg PO BID

Table 3

Dose Modifications for Toxicities Due to Zydelig

Pneumonitis	**Any symptomatic pneumonitis**		
	Discontinue Zydelig in patients with any severity of symptomatic pneumonitis		
ALT/AST	**>3.0-5.0 x ULN**	**>5-20 x ULN**	**>20 x ULN**
	Decrease Zydelig to 100 mg BID and monitor weekly until ≤1 x ULN.	Withhold Zydelig. Monitor at least weekly until ALT/AST are ≤1 x ULN, then may resume Zydelig at 100 mg BID.	Discontinue Zydelig permanently.
Bilirubin	**>1.5-3 x ULN**	**>3-10 x ULN**	**>10 x ULN**

	Decrease Zydelig to 100 mg BID. Monitor at least weekly until ≤1 x ULN.	Withhold Zydelig. Monitor at least weekly until bilirubin is ≤1 x ULN, then may resume Zydelig at 100 mg BID.	Discontinue Zydelig permanently.
Diarrhea*	**Moderate diarrhea**	**Severe diarrhea or hospitalization**	**Life-threatening diarrhea**
	Decrease Zydelig to 100 mg BID. Monitor at least weekly until resolved.	Withhold Zydelig. Monitor at least weekly until resolved, then may resume Zydelig at 100 mg BID.	Discontinue Zydelig permanently.
Neutropenia^	**ANC 1.0 to <1.5 Gi/L**	**ANC 0.5 to <1.0 Gi/L**	**ANC <0.5 Gi/L**
	Maintain Zydelig dose.	Decrease Zydelig to 100 mg BID. Monitor ANC at least weekly.	Interrupt Zydelig. Monitor ANC at least weekly until ANC ≥0.5 Gi/L, then may resume Zydelig at 100 mg BID.
Thrombocytopenia	**Platelets 50 to <75 Gi/L**	**Platelets 25 to <50 Gi/L**	**Platelets <25 Gi/L**
	Maintain Zydelig dose.	Decrease Zydelig to 100 mg BID Monitor platelet counts at least weekly.	Interrupt Zydelig. Monitor platelet count at least weekly. May resume Zydelig at 100 mg BID when platelets ≥25 Gi/L.
Pneumocystis pneumonia	**Any symptomatic pneumonia**		
	Discontinue Zydelig in patients with any severity of PCP		
CMV viremia/infection	**Any CMV viremia/infection**		
	Discontinue Zydelig in patients with any CMV viremia/infection		
Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; BID, twice daily; PCP, pneumocystis pneumonia; CMV, cytomegalovirus; ULN, upper limit of normal			

*Moderate diarrhea: increase of 4–6 stools per day over baseline. Severe diarrhea: increase of ≥7 stools per day over baseline.

^ G-CSF might be administered at the discretion of the investigator

7.1 Other Non-hematologic Toxicity

For other grade 3 non-hematologic toxicity considered at least possibly related to Zydelig, interrupt Zydelig until toxicity improves to ≤ grade 2, and then resume Zydelig with one dose level reduction for all subsequent cycles.

For other grade 4 non-hematologic toxicity, discontinue Zydelig.

8. CRITERIA FOR RESPONSE, PROGRESSION, AND RELAPSE

For purposes of this study, patients should be restaged every 3 cycles during treatment (i.e., cycles 3, 6, 9, 12, etc.), then every 3 months for 1 year, then every 6 months for another year.

The Revised Response Criteria for Malignant Lymphoma is adopted.[13]

8.1 Complete Response

Complete response (CR) is defined as the following:

• Complete disappearance of all detectable clinical evidence of disease and disease-related symptoms (if present before therapy).

• In patients where the CT or PET/CT scan was positive before therapy, a post-treatment residual mass of any size is permitted as long as it is PET/CT-negative.

• The spleen and/or liver, if considered enlarged before therapy on the basis of a CT or PET/CT, should be considered normal size by imaging studies, and nodules related to lymphoma should disappear. However, determination of splenic involvement is not always reliable because a spleen considered normal in size may still contain lymphoma, whereas an enlarged spleen may reflect variations in anatomy, blood volume, the use of hematopoietic growth factors, or other causes other than lymphoma.

• If the bone marrow was involved by lymphoma before treatment, the infiltrate must have cleared on repeat bone marrow biopsy. The biopsy sample on which this determination is made must be adequate (with a goal of > 20 mm unilateral core). If the sample is indeterminate by morphology, it should be negative by immunohistochemistry. A sample that is negative by immunohistochemistry, but demonstrating a small population of clonal lymphocytes by flow cytometry will be considered a CR until data becomes available demonstrating a clear difference in patient outcome.

8.2 Partial Response

Partial response (PR) is defined as the following:

• At least a 50% decrease in the sum of the product of the diameters (SPD) of up to six of the largest dominant nodes or nodal masses. These nodes or masses should be selected according to all of the following: a) they should be clearly measurable in at least two perpendicular dimensions; b) if possible, they should be from disparate regions of the body; and c) they should include mediastinal and retroperitoneal areas of disease whenever these sites are involved.

• No increase should be observed in the size of other nodes, liver, or spleen.

• 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.

• Bone marrow assessment is irrelevant for determination of a PR if the sample was positive before treatment. However, if positive, the cell type should be specified in the report (e.g., large-cell lymphoma or small neoplastic B cells). 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.

•For patients if the CT or PET/CT was positive before therapy, the post-treatment PET should be positive in at least one previously involved site.

8.3 Stable Disease

Stable disease (SD) is defined as when the patient fails to attain the criteria needed for a CR or PR, but does not fulfill those for progressive disease (see below). The CT or PET/CT should be positive at prior sites of disease, with no new areas of involvement on the post-treatment CT or PET/CT.

8.4 Progression or Relapse

Disease progression (PD) or relapse is defined as any one of the following:

• Lymph nodes should be considered abnormal if the long axis is > 1.5 cm, regardless of the short axis. If a lymph node has a long axis of 1.1 to 1.5 cm, it should only be considered abnormal if its short axis is > 1 cm. Lymph nodes ≤ 1 cm by ≤ 1 cm will not be considered as abnormal for relapse or progressive disease.

• Appearance of any new lesion > 1.5 cm in any axis during or at the end of therapy, even if other lesions are decreasing in size. Increased FDG uptake in a previously unaffected site should only be considered relapsed or progressive disease after confirmation with other modalities. In patients with no prior history of pulmonary lymphoma, new lung nodules identified by CT are mostly benign. Thus, a therapeutic decision should not be made solely on the basis of the CT or PET/CT without histologic confirmation.

• At least a 50% increase from nadir in the SPD of any previously involved nodes, or in a single involved node, or the size of other lesions (e.g., splenic or hepatic nodules). To be considered progressive disease, a lymph node with a diameter of the short axis of < 1 cm must increase by ≥ 50% and to a size of 1.5 x 1.5 cm, or > 1.5 cm in the long axis.

• At least a 50% increase in the longest diameter of any single previously identified node > 1 cm in its short axis.

• Lesions should be PET-positive if a typical FDG-avid lymphoma or one that was PET-positive before therapy unless the lesion is too small to be detected with current PET systems (< 1.5 cm in its long axis by CT).

8.5 Guidelines for Evaluation of Measurable Disease

Measurable extra nodal 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 not easily assessable (e.g., pleural effusions, bone lesions) will be recorded as present or absent only, unless, while an abnormality is still noted by imaging studies it is found to be histologically negative.

Clinical lesions will only be considered measurable when they are superficial (e.g., skin nodules, palpable lymph nodes).

Lesions on chest X-ray are acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung. However, CT or PET/CT is preferable.

Conventional CT and MRI should be performed with cuts of 10 mm or less in slice thickness contiguously. Spiral CT should be performed using a 5 mm contiguous reconstruction algorithm. This applies to the chest, abdomen, and pelvis. Head & neck and extremities usually require specific protocols.

Ultrasound should not be used to measure tumor lesions that are clinically not easily accessible when the efficacy endpoints of the study is objective response evaluation. It is a possible alternative to clinical measurements of superficial palpable nodes, subcutaneous lesions, and thyroid nodules. Ultrasound might also be useful to confirm the complete disappearance of superficial lesions usually assessed by clinical examination.

8.6 Particular Case of Waldenstrom Macroglobulinemia

Table 4

Categorical Response Definitions

Response category	Definition
Complete response (CR)	Absence of serum monoclonal IgM protein by immunofixation Normal serum IgM level Complete resolution of extramedullary disease, i.e., lymphadenopathy and splenomegaly if present at baseline Morphologically normal bone marrow aspirate and trephine biopsy
Very good partial response (VGPR)	Monoclonal IgM protein is detectable ≥90% reduction in serum IgM level from baseline* Complete resolution of extramedullary disease, i.e., lymphadenopathy/splenomegaly if present at baseline No new signs or symptoms of active disease
Partial response (PR)	Monoclonal IgM protein is detectable ≥50% but<90% reduction in serum IgM level from baseline* Reduction in extramedullary disease, i.e., lymphadenopathy/splenomegaly if present at baseline No new signs or symptoms of active disease
Minor response (MR)	Monoclonal IgM protein is detectable ≥25% but<50% reduction in serum IgM level from baseline* No new signs or symptoms of active disease

Categorical Response Definitions

Response category	Definition
Stable disease (SD)	Monoclonal IgM protein is detectable <25% reduction and <25% increase in serum IgM level from baseline* No progression in extramedullary disease, i.e., lymphadenopathy/splenomegaly No new signs or symptoms of active disease
Progressive disease (PD)	≥25% increase in serum IgM level* from lowest nadir (requires confirmation) and/or progression in clinical features attributable the disease

***** Sequential changes in IgM levels may be determined either by M protein quantitation by densitometry or total serum IgM quantitation by nephelometry
For more details, please refer to http://www.ncbi.nlm.nih.gov/pubmed/23150997[14]

9. ADVERSE EVENTS: LIST AND REPORTING REQUIREMENTS

9.1 Adverse Event Definitions

CTCAE term (AE description) and grade: The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.03 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 4.03. A copy of the CTCAE version 4.03 can be downloaded from the CTEP web site.

Attribution of the AE:
• Definite – The AE *is clearly related* to the study treatment.
• Probable – The AE *is likely related* to the study treatment.
• Possible – The AE *may be related* to the study treatment.
• Unlikely – The AE *is doubtfully related* to the study treatment.
• Unrelated – The AE *is clearly NOT related* to the study treatment.

The Definition of a Serious Adverse Event (SAE):

SAE is defined as any of the following:
• Any death that occurs while the patient is enrolled in the study or within 30 days of completing the study
• Immediately life-threatening adverse event
• Requires inpatient hospitalization
• Prolongation of an existing hospitalization
• Congenital anomaly/birth defect
• Medically important event
• Disability/incapacity (persistent or significant)
Progression of the cancer under study is not considered an adverse event, unless it results in hospitalization or death.

9.2 Adverse Events for Zydelig

The following is taken from the Investigator's Brochure (IB) 6th Edition for Zydelig. Please note that this section will be replaced by the CAEPR for Zydelig when it becomes available.

9.2.1 Treatment-Emergent Hematological and Non-hematological Adverse Events in ≥ 5% of All Subjects

Table 5
Adverse Reactions (≥ 10% of Subjects) in Patients with Indolent non-Hodgkin Lymphoma Treated with Zydelig 150 mg BID

	Zydelig Monotherapy N=146 (%)	
Adverse Reaction	**Any Grade**	**Grade ≥3**
Gastrointestinal disorders		
diarrhea [(a)]	68 (47)	20 (14)
nausea	42 (29)	2 (1)
abdominal pain [(b)]	38 (26)	3 (2)
vomiting	22 (15)	2 (1)
General disorders and administration site conditions		
fatigue	44 (30)	2 (1)
pyrexia	41 (28)	3 (2)
asthenia	17 (12)	3 (2)
peripheral edema	15 (10)	3 (2)
Infections and infestations		
upper respiratory tract infection	18 (12)	0
Respiratory, thoracic, and mediastinal disorders		
pneumonia [(c)]	37 (25)	23 (16)
cough	42 (29)	1 (1)
dyspnea	25 (17)	6 (4)
Skin and subcutaneous disorders		
rash [(d)]	31 (21)	4 (3)
night sweats	18 (12)	0
Nervous system disorders		
headache	16 (11)	1 (1)
Metabolism and nutrition disorders		
decreased appetite	24 (16)	1 (1)

Psychiatric disorders		
Insomnia	17 (12)	0

(a) Diarrhea includes the following preferred terms: diarrhea, colitis, enterocolitis, and gastrointestinal inflammation.
(b) Abdominal pain includes the following preferred terms: abdominal pain, abdominal pain upper, abdominal pain lower and abdominal discomfort.
(c)Pneumonia includes the terms: pneumonia, pneumonitis, interstitial lung disease, lung infiltration, pneumonia aspiration, respiratory tract infection, atypical pneumonia, lung infection, pneumocystis jiroveci pneumonia, bronchopneumonia, pneumonia necrotizing, lower respiratory tract infection, pneumonia pneumococcal, pneumonia staphylococcal, pneumonia streptococcal, pneumonia cytomegaloviral, and respiratory syncytial virus infection.
(d) Rash includes the following preferred terms: dermatitis exfoliative, rash, rash erythematous, rash macular, rash maculo-papular, rash pruritic, and exfoliative rash.

Treatment-emergent Laboratory Abnormalities in Patients with Indolent non-Hodgkin Lymphoma Treated with Zydelig 150 mg BID

	Zydelig Monotherapy N=146 (%)		
Laboratory Abnormality	**Any Grade**	**Grade 3**	**Grade 4**
Serum chemistry abnormalities			
ALT increased	73 (50)	20 (14)	7 (5)
AST increased	60 (41)	12 (8)	6 (4)
Hematology abnormalities			
neutrophils decreased	78 (53)	20 (14)	16 (11)
hemoglobin decreased	41 (28)	3 (2)	0
platelets decreased	38 (26)	4 (3)	5 (3)

Grades were obtained per CTCAE version 4.03.

Serious Adverse Events Reported as Possibly, Probably, or Definitely Related to Zydelig

Table 6

System Organ Class	**Adverse Event**
Blood and lymphatic system disorders	Anemia Febrile neutropenia Neutropenia Red cell aplasia Thrombocytopenia
Gastrointestinal disorders	Colitis Diarrhea Ischemic colitis Nausea Esophagitis Stomatitis Vomiting

General disorders and administration site conditions	Fatigue Fever Influenza-like symptoms Pyrexia
Hepatobiliary disorders	Cholecystitis Cholecystitis, acalculous Cholecystitis, acute
Infections and infestations	Abscess Brain abscess Cellulitis Cytomegalovirus infection Endocarditis Herpes zoster Herpes zoster, ophthalmic Meningitis Pneumonia Pneumonia fungal Pneumonia, Pneumocystis jiroveci Sepsis
Hepatotoxicity	ALT increased AST increased Hepatic enzyme increased Transaminase increased
Metabolism and nutrition disorders	Anorexia Fluid retention Hypercalcemia Tumor lysis syndrome
Renal and urinary disorders	Renal failure Renal failure, acute
Respiratory, thoracic, and mediastinal disorders	Atelectasis Hypoxia Pneumonia, organizing Pneumonitis Pulmonary embolism Pulmonary fibrosis
Skin and subcutaneous tissue disorders	Rash Rash, generalized Rash maculopapular

9.3 Adverse Event Characteristics/Evaluation

An investigator who is a qualified physician will evaluate all adverse events according to the NCI Common Terminology for Adverse Events (CTCAE), version 4.03. Any adverse event which changes CTCAE grade over the course of a given episode will have each change of grade recorded on the adverse event case report forms/worksheets.

All adverse events, regardless of CTCAE grade must also be evaluated for seriousness.

• CTCAE term (AE description) and grade: The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.03 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 4.03. A copy of the CTCAE version 4.03 can be downloaded from the CTEP web site (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm).

Table 7

V4.0 CTCAE Grading	**Grade 1**	**Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.**
	Grade 2	**Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL.**
	Grade 3	**Severe or Medically Significant but not immediately life-threatening; hospitalization or prolongation or hospitalization indicated; disabling; limiting self-care ADL.**
	Grade 4	**Life Threatening consequences; urgent intervention indicated.**
	Grade 5	**Death related to AE**
Seriousness	A serious adverse event is any adverse event occurring at any dose or during any use of the investigational condition that:	
	†**Results in death**; or	
	†**Is life threatening; or places the subject, in the view of the investigator, at immediate risk of death from the event as it occurred** (Note: This does not include an adverse event that, had it occurred in a more severe form, might have caused death.); or	
	†**Results in a persistent or significant disability/incapacity** (substantial disruption of one's ability to conduct normal life functions); or	
	†**Results in or prolongs an existing inpatient hospitalization** (hospitalization is defined as an inpatient admission, regardless of length of stay, even if the hospitalization is a precautionary measure for continued observation. (Note: Hospitalization [including hospitalization for an elective procedure] for a preexisting condition which has not worsened does not constitute a serious adverse event.); or	
	†**Is a congenital anomaly/birth defect** (in offspring of subject exposed to the investigational condition regardless of time to diagnosis);or	
	Other important medical events that may not result in death, not be life threatening, or not require hospitalization may be considered a serious adverse event when, based upon appropriate medical judgment, the event may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed previously (designated above by a †).	
Duration	Record the start and stop dates of the adverse event. If less than 1 day, indicate the appropriate length of time and units.	
Action Taken	Did the adverse event cause the study treatment to be discontinued?	
Relationship to Test Condition	Did the investigational condition cause the adverse event? The determination of the likelihood that the investigational condition caused the adverse event will be provided by an investigator who is a qualified physician. The investigator's signed/dated initials on the source document or worksheet that supports the causality noted on the AE form, ensures that a medically qualified assessment of causality was done. This initialed document must be retained for the required regulatory time frame. The criteria below are intended as reference guidelines to assist the investigator in assessing the likelihood of a relationship between the test drug and the adverse event based upon the available information. **The following components are to be used to assess the relationship between the investigational condition and the AE**; the greater the correlation with the components and their respective elements (in number and/or intensity), the more likely the investigational condition caused the adverse event (AE):	
	Exposure	Is there evidence that the subject was actually exposed to the investigational condition such as: reliable history, acceptable compliance assessment (pill count, diary, etc.), expected pharmacologic effect, or measurement of drug/metabolite in bodily specimen?
	Time	Did the AE follow in a reasonable temporal sequence from administration of the

	Course	investigational condition? Is the time of onset of the AE compatible with a study-induced effect (applies to trials with investigational medicinal product[s])?
	Likely Cause	Is the AE not reasonably explained by another etiology such as underlying disease, other drug(s)/vaccine(s), or other host or environmental factors?

• 'Expectedness': AEs can be 'Unexpected' or 'Expected' for expedited reporting purposes only. The following abnormalities/adverse events are considered "expected" and their presence/absence should be solicited, and severity graded, at baseline and for each cycle of treatment.

- ✓ Fatigue
- ✓ Skin rash
- ✓ Diarrhea
- ✓ Decreased neutrophils, hemoglobin and platelet count
- ✓ Increased serum ALT and AST
- ✓ Cough and pneumonitis
- ✓ Fever
- ✓ Infection

9.4 Serious Adverse Event Reporting

Investigators are responsible for monitoring the safety of patients who have entered this study and for alerting the UMGCCC DSM/QAC to any event that seems unusual, even if this event may be considered an unanticipated benefit to the patient. Any adverse event that meets the definition of serious which occurs at any time during the clinical study or within 30 days of receiving the last dose of study medication, whether or not related to the study drug will be reported as follows:

All SAE's, whether or not related to the study drug, will be reported via OnCore to the DSM/QAC according to the UMGCC DSM/QAC SOP.

Treatment-related toxicities and other adverse events will be monitored through standard medical practice, in addition to scheduled follow-ups as outlined in the treatment plan. Adverse events should be described according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events, v. 4.03 (Table 7).
(see http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm).

Any serious adverse event, or follow up to a serious adverse event (including death due to any cause other than progression of the cancer under study) that occurs to any subject from the time the consent is signed through end of study participationor the initiation of new anti-cancer therapy, whichever is earlier (whether or not related to protocol therapy) must be reported within 24 hours to the Coordinating Center (Attn: Dr. Jean Yared – FAX (410) 328-1975) using FDA Form 3500A (MedWatch form). The Coordinating Center will then report the event to the FDA using FDA Form 3500A (MedWatch Form).

Additionally, any serious adverse event considered by an investigator (who is a qualified physician) to be related to protocol therapy that is brought to the attention of the study team at any time outside of the time period specified in the previous paragraph also must

be reported immediately to the Coordinating Center using FDA Form 3500A (MedWatch Form).

Any unexpected grade 4 or 5 adverse event and any death during the study period must be reported using FDA Form 3500A (MedWatch form) to the Coordinating Center within one working day (24 hours) of discovery or notification. Please submit the adverse event report using FDA Form 3500A to:

Veronica Rodriguez
Room N9E12
22 S. Greene Street, Baltimore, MD 21201
Phone: 410-328-9747
Fax: 410-328-1975
Email: Veronica.Rodriguez@umm.edu

The event should also be reported locally to the site Institutional Review Board (IRB) per local policy.

Otherwise, unexpected serious adverse events must be reported within 15 days.

If the event meets the criteria for FDA mandatory IND safety reporting (serious AND unexpected), the Coordinating Center will report the event to the FDA using FDA Form 3500A (MedWatch form). Events which are assessed as "unexpected fatal or life-threatening" should be reported to FDA by the Coordinating Center as soon as possible, but no later than 7 calendar days following the initial receipt of the information. All other unexpected serious suspected adverse reactions suggesting significant risk to human subjects should be reported to FDA no later than 15 calendar days following the initial receipt of the information.

A copy of all 15 Day Reports and Annual Progress Reports are to be submitted as required by FDA, Pharmaceutical and Medical Devices agency (PMDA) or other local regulators.

All subjects with serious adverse events must be followed up for outcome/resolution for at least 90 days after stopping protocol therapy.

9.5 Routine Adverse Event Reporting

An investigator who is a qualified physician will evaluate all adverse events according to the NCI Common Terminology for Adverse Events (CTCAE), version 4.03. Any adverse event which changes CTCAE grade over the course of a given episode will have each change of grade recorded on the adverse event case report forms/worksheets.

All adverse events regardless of CTCAE grade must also be evaluated for seriousness.

9.6 Data Safety Monitoring Plan

It is the responsibility of the Principal Investigator to oversee the safety of study participants. This safety monitoring will include careful assessment and appropriate reporting of adverse events as noted above.

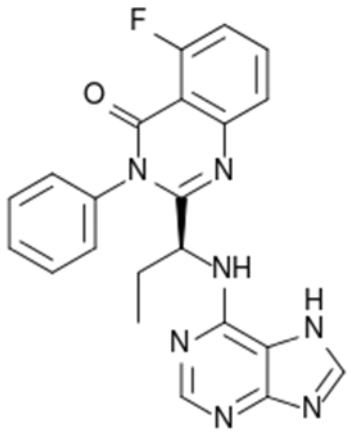
This study will be monitored by the UMGCCC Data and Safety Monitoring and Quality Assurance Committee and will follow the Data Safety and Monitoring Plan as outlined in the Clinical Investigator Handbook of the UMGCCC Clinical Research Office. Monitoring will be conducted as per the plan on file with the University of Maryland IRB (also available in the UMGCCC Clinical Investigator Handbook.

9.7 Secondary AML/MDS

AML/MDS events are now to be reported via AdEERS (in addition to your routine AE reporting mechanisms). In CTCAE v4.0, the event(s) may be reported as either: 1) Leukemia secondary to oncology chemotherapy, 2) Myelodysplastic syndrome, or 3) Treatment-related secondary malignancy. Any malignancy possibly related to cancer treatment (including AML/MDS) should also be reported via the routine reporting mechanisms outlined.

10. PHARMACEUTICAL INFORMATION

10.1 Zydelig (GS-1101, CAL-101) ()



The substance acts as a phosphoinositide 3-kinase inhibitor; more specifically, it blocks P110δ, the delta isoform of the enzyme phosphoinositide 3-kinase.

10.2 Availability

Zydelig (CAL-101) will be supplied and distributed by Gilead Sciences, Inc. Zydelig is supplied in bottles of 60 tablets of 100 mg and 150 mg strengths. The bottles of Zydelig are white high-density polyethylene with a child-resistant cap and a polyester or cotton coil. The tablet shape is plain-faced, modified oval. The tablets contain the inactive ingredients microcrystalline cellulose, hydroxypropyl cellulose, croscarmellose sodium, sodium starch glycolate, and magnesium stearate. The 100 mg tablets are orange film coated, and the 150 mg tablets are pink film coated. Tablets should be swallowed whole.

10.3 Storage and Stability

Zydelig tablets should be stored at a controlled room temperature of 25ºC (77ºF), with a range from 15ºC (59ºF) to 30ºC (86ºF). While stability of study drug tablets stored at

controlled room temperature has been confirmed, brief excursions to temperatures as low as –10°C or as high as 40°C (eg, during shipping) will not adversely affect the drug. Updated stability data will be provided to the sites, as appropriate.
At the end of the study, any remaining unused Zydelig should be destroyed according to local institutional procedures.

Preparation
Zydelig should be dispensed in the original container.

Administration
The prescribed dose of Zydelig should be taken orally. At each dose administration, the tablet number corresponding to the appropriate dose of study drug is to be swallowed whole with 100 to 200 mL (~ 4 to 8 ounces) of water. In case of breakage of the tablets in the oral cavity, additional water should be taken as a rinse.
Zydelig may be taken with or without food. There are no known dietary restrictions related to study drug use.

Overdose Precautions
In Phase 1 studies, an MTD for Zydelig was not reached when administering the drug continuously at dose levels of 350 mg/dose BID (700 mg per day). However, in this protocol, an overdose is defined as administration of more than the prescribed daily study drug (Zydelig) dose (ie, >300 mg in a single day).

In a subject who experiences an overdose, consideration should be given as to whether study drug administration should be temporarily interrupted. If the overdose ingestion is recent and substantial, and if there are no medical contraindications, use of gastric lavage or induction of emesis may be considered. Observation for any symptomatic side effects should be instituted, and biochemical and hematological parameters should be followed closely (consistent with the protocol or more frequently, as needed). Appropriate supportive management to mitigate adverse effects should be initiated.

Inadvertent Exposure and Spill Precautions
Based on available data from nonclinical studies, Zydelig does not appear to be acutely toxic, genotoxic, or irritative at levels that are likely to result from inadvertent exposure to the contents of broken tablets. However, personnel handling the drug should use reasonable precautions to avoid eye contact, skin contact, inhalation, or ingestion of the study drug product. For further information regarding inadvertent exposure and spill precautions, please consult the Zydelig investigator brochure.

10.4 Pharmacokinetics

Absorption
Following oral administration of a single dose of Zydelig in the fasted state, the median Tmax was observed at 1.5 hours. Idelalisib exposure increased in a less than dose-proportional manner over a dose range of 50 mg to 350 mg twice daily in the fasted state. Relative to fasting conditions, the administration of a single dose of Zydelig with a highfat meal increased idelalisib AUC 1.4-fold. Zydelig can be administered without regard to food.

Distribution
Idelalisib is greater than 84% bound to human plasma proteins with no concentration dependence. The mean blood-to-plasma ratio was 0.7. The population apparent central volume of distribution at steady state is 23 L

Metabolism and Elimination
Idelalisib is metabolized to its major metabolite GS-563117 via aldehyde oxidase and CYP3A. GS-563117 is inactive against PI3Kδ in vitro. Idelalisib undergoes minor metabolism by UGT1A4. The population apparent systemic clearance at steady-state is 14.9 L/hr. The population terminal elimination half-life of idelalisib is 8.2 hours. Following a single dose of 150 mg of [14C] idelalisib, 78% and 14% of the radioactivity was excreted in feces and urine, respectively. GS-563117 accounted for 49% of the radioactivity in the urine and 44% in the feces.

Specific Population
Age, Gender, Race and Weight
Population pharmacokinetic analyses indicated that age, gender, race, and weight had no effect on idelalisib exposure.

Patients with Renal Impairment
A pharmacokinetic study following a single dose of 150 mg of Zydelig was performed in healthy subjects and subjects with severe renal impairment (CrCl 15 to 29 mL/min). Creatinine clearance had no effect on idelalisib exposure. No dose adjustment is needed for patients with CrCl ≥15 mL/min.

Patients with Hepatic Impairement
A pharmacokinetic study of Zydelig was performed in healthy subjects and subjects with hepatic impairment. The geometric mean AUC increased up to 1.7-fold in subjects with ALT or AST or bilirubin values greater than the upper limit of normal (ULN) compared to subjects with normal AST or ALT or bilirubin values. Limited safety and efficacy data are available for patients with baseline AST or ALT greater than 2.5 x ULN or bilirubin greater than 1.5 x ULN, as these patients were excluded from Studies 1 and 2. Patients with baseline hepatic impairment should be monitored for signs of Zydelig toxicity.

Drug Interactions

In Vitro Studies
Idelalisib is a substrate for aldehyde oxidase, CYP3A, and UGT1A4 in vitro. Idelalisib inhibits CYP2C8, CYP2C19, CYP3A, and UGT1A1 and GS-563117 inhibits CYP2C8, CYP2C9, CYP2C19, CYP3A and UGT1A1 in vitro. Idelalisib and GS-563117 are not likely to inhibit CYP1A, CYP2B6, and CYP2D6. Idelalisib induces CYP2B6 and CYP3A4, but does not induce CYP1A2 in vitro. GS- 563117 does not induce these enzymes. Idelalisib and GS-563117 are substrates of P-glycoprotein (P-gp) and BCRP in vitro. Idelalisib is not a substrate of OATP1B1, OATP1B3, OAT1, OAT3, or OCT2. GS- 563117 is not a substrate of OATP1B1 or OATP1B3. Idelalisib inhibits P-gp, OATP1B1, and OATP1B3, and GS-563117 inhibits OATP1B1, OATP1B3 in vitro. Idelalisib is not likely to inhibit BCRP, OCT2, OAT1, or OAT3, and GS-563117 is not likely to inhibit P-gp, BCRP, OCT2, OAT1, or OAT3.

Effect of Other Drugs on Idelalisib

A single dose of 150 mg of Zydelig was administered alone and after rifampin (a strong CYP3A and P-gp inducer) 600 mg once daily for 8 days in healthy subjects. Rifampin decreased the geometric mean idelalisib AUC by 75% and the geometric mean Cmax by 58%. Avoid coadministration of Zydelig with strong CYP3A and P-gp inducers. A single dose of 400 mg of Zydelig was administered alone and after ketoconazole (a strong CYP3A and P-gp inhibitor) 400 mg daily for 4 days in healthy subjects. Ketoconazole increased the geometric mean idelalisib AUC by 1.8-fold. No changes in the geometric mean Cmax were observed. Patients taking concomitant CYP3A inhibitors should be monitored for signs of Zydelig toxicity

Effect of Idelalisib on Other Drugs

A single oral dose of midazolam 5 mg was administered alone and after Zydelig 150 mg for 15 doses in healthy subjects. The geometric mean midazolam Cmax increased by 2.4-fold and the geometric mean midazolam AUC increased by 5.4-fold. Avoid coadministration of Zydelig with CYP3A substrates, as Zydelig is a strong CYP3A inhibitor. A single dose of 10 mg of rosuvastatin (OATP1B1 and OATP1B3 substrate) was administered alone and after Zydelig 150 mg for 12 doses in healthy subjects. No changes in exposure to rosuvastatin were observed. A single dose of 0.5 mg of digoxin (P-gp substrate) was administered alone and after Zydelig 150 mg for 19 doses in healthy subjects. No changes in exposure to digoxin were observed.

10.5 Toxicity.

Hepatotoxicity

Fatal and/or serious hepatotoxicity occurred in 18% of patients treated with Zydelig monotherapy and 11% of patients treated with Zydelig in combination trials. Elevations in ALT or AST greater than 5 times the upper limit of normal have occurred. These findings were generally observed within the first 12 weeks of treatment and were reversible with dose interruption. After resumption of treatment at a lower dose, 26% of patients had recurrence of ALT and AST elevations. Discontinue Zydelig for recurrent hepatotoxicity. Avoid concurrent use of Zydelig with other drugs that may cause liver toxicity. Monitor ALT and AST in all patients every 2 weeks for the first 3 months of treatment, every 4 weeks for the next 3 months, then every 1 to 3 months thereafter. Monitor weekly for liver toxicity if the ALT or AST rises above 3 times the upper limit of normal until resolved. Withhold Zydelig if the ALT or AST is greater than 5 times the upper limit of normal, and continue to monitor AST, ALT and total bilirubin weekly until the abnormality is resolved.

Severe Diarrhea or Colitis

Severe diarrhea or colitis (Grade 3 or higher) occurred in 14% of patients treated with Zydelig monotherapy and 19% of patients treated with Zydelig in combination trials. Diarrhea can occur at any time. Avoid concurrent use of Zydelig and other drugs that cause diarrhea. Diarrhea due to Zydelig responds poorly to antimotility agents. Median time to resolution ranged between 1 week and 1 month across trials, following interruption of Zydelig therapy and in some instances, use of corticosteroids.

Pneumonitis

Fatal and serious pneumonitis occurred in patients treated with Zydelig. In randomized clinical trials of combination therapies, pneumonitis occurred in 4% of patients treated

with Zydelig compared to 1% on the comparator arms. Time to onset of pneumonitis ranged from <1 to 15 months. Patients taking Zydelig who present with pulmonary symptoms such as cough, dyspnea, hypoxia, interstitial infiltrates on a radiologic exam, or a decline by more than 5% in oxygen saturation should be evaluated for pneumonitis. If pneumonitis is suspected, interrupt Zydelig until the etiology of the pulmonary symptoms has been determined. Patients with pneumonitis thought to be caused by Zydelig have been treated with discontinuation of Zydelig and administration of corticosteroids.

Infections

Fatal and/or serious infections occurred in 21% of patients treated with Zydelig monotherapy and 36% of patients treated with Zydelig in combination trials. The most common infections were pneumonia, sepsis, and febrile neutropenia. Monitor patients for signs and symptoms of infection and interrupt Zydelig for Grade 3 or higher infection. Serious or fatal Pneumocystis jirovecii pneumonia (PJP) or cytomegalovirus (CMV) occurred in <1% of patients treated with Zydelig. Consider prophylaxis for PJP. Interrupt Zydelig in patients with suspected PJP infection of any grade, and permanently discontinue Zydelig if PJP infection of any grade is confirmed. Interrupt Zydelig in the setting of positive CMV PCR or antigen test until the infection has resolved. If Zydelig is subsequently resumed, patients should be monitored (by PCR) for CMV reactivation at least monthly.

Intestinal Perforation

Fatal and serious intestinal perforation occurred in Zydelig-treated patients. At the time of perforation, some patients had moderate to severe diarrhea. Advise patients to promptly report any new or worsening abdominal pain, chills, fever, nausea, or vomiting. Discontinue Zydelig permanently in patients who experience intestinal perforation

Severe Cutaneous Reactions

Fatal cases of Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) have occurred in patients treated with Zydelig. If SJS or TEN is suspected, interrupt Zydelig until the etiology of the reaction has been determined. If SJS or TEN is confirmed, permanently discontinue Zydelig. Other severe or life-threatening (Grade ≥3) cutaneous reactions, including dermatitis exfoliative, rash, rash erythematous, rash generalized, rash macular, rash maculo- papular, rash papular, rash pruritic, exfoliative rash, and skin disorder, have been reported in Zydelig-treated patients. Monitor patients for the development of severe cutaneous reactions and discontinue Zydelig.

Anaphylaxis

Serious allergic reactions, including anaphylaxis, have been reported in patients on Zydelig. In patients who develop serious allergic reactions, discontinue Zydelig permanently and institute appropriate supportive measures.

Neutropenia

Treatment-emergent Grade 3 or 4 neutropenia occurred in 25% of patients treated with Zydelig monotherapy and 46% of patients treated with Zydelig in combination trials. Monitor blood counts closely.

Embryo-fetal Toxicity

Based on findings in animals, Zydelig may cause fetal harm when administered to a pregnant woman. Idelalisib is teratogenic in rats, at systemic exposures 12 times those reported in patients at the recommended dose of 150 mg twice daily. Advise females of reproductive potential to avoid becoming pregnant while taking Zydelig. If contraceptive methods are being considered, use effective contraception during treatment, and for at least 1 month after the last dose of Zydelig.

11. CORRELATIVE STUDIES

Please see Appendix D

12. DATA REPORTING/REGULATORY CONSIDERATIONS

Clinical data will be entered into the OnCore® database by performing site personnel. Information can be entered into Oncore® in a way that is 21CRF11.10 (electronic medical records) compliant. OnCore® is equipped for HIPAA-compliant internet-based entry of protocol tracking and review information.

All study data will be collected by the research team at each and every study visit and recorded in the research record. This data will then be entered in to the OnCore® study database.

All source documents will be obtained and retained along with any study forms, and placed into the patient's research record.

ADMINISTRATIVE AND REGULATORY DETAILS

This study will be conducted in accordance with current U.S. Food and Drug Administration (FDA) Regulations, Good Clinical Practices (GCPs) and International Counsel on Harmonization (ICH) E6 Guidelines.

Under the terms of the Food and Drug Administration Modernization Act (FDAMA) and the Food and Drug Administration Amendments Act (FDAAA), the trial and its results will be submitted to the Clinical Trials Data Bank, http://www.clinicaltrials.gov.

Information posted will allow subjects to identify potentially appropriate trials for their disease conditions and pursue participation by calling a central contact number for further information on appropriate trial locations and trial site contact information.

Institutional Review Board (IRB)

This protocol will be submitted to the University of Maryland IRB. Study procedures will begin once IRB approval is secured. All amendments, instances of reportable new information (i.e. unanticipated problems, data breaches, etc.) and continuing review reports will be submitted to the University of Maryland IRB.

13. Clinical Trial Monitoring

Data safety and verification monitoring will be conducted in accordance with the Greenebaum Cancer Center Sponsor-Investigator Monitoring Standard Operating Procedure (SOP), the Code of Federal Regulations (CFR), and FDA and International Counsel on Harmonization (ICH) E6 Guidelines.

14. STATISTICAL CONSIDERATIONS

A true proportion of study subjects that are not removed from the study for toxicity or intolerance of 0.70 or higher will be considered satisfactory in this particular patient population. If the true proportion of severe toxicity -free patients is 50% or less, then Zydelig will not be considered a promising maintenance treatment post Autologous stem cell transplantation due to unacceptable toxicity.

A single-stage open-label design will be used for the study. With 34 eligible patients on the study, the Type I error or probability of declaring drug desirable if the proportion of subjects removed from study due to toxicity or intolerability is 0.50 or higher, is 0.075. The probability of rejecting the Zydelig as unacceptable due to severe toxicity compound if the proportion of subject who developed severe toxicity is less or equal to 30% rate is less than 20%. Hence, the study will have an adequate about 80% power. Addressing the safety of Zydelig, a maximum width 90% confidence interval for any grade 3 or higher toxicity will be about 32%, assuming that a total of 31 patients are enrolled. For instance, if 3 out of 31 patients (10%) develop grade 3 or higher non-hematologic toxicity, then a 90% confidence interval for the true toxicity rate is between 3% and 24%. For 31 patients in this study, if the true unknown probability of a rare toxicity is 10%, the probability of observing 1 or more toxicities is 96%, for 5% it is 80%, and if the true toxicity rate is 3% then the probability of observing one or more rare toxicities is 61%.

We plan to accrue 34 eligible patients to account for about 10% possible drop-out

14.1 Study Design/Primary Endpoints

This single cohort open-label study will accrue 34 patients with iNHL or tiNHL. The biologically active dose of Zydelig will be 1st used at 100/150 mg PO BID. Within patient dose reductions are allowed for hematologic and non-hematologic toxicities above grade 2. The proportion of patients removed from the study due to toxicity will be reported, along with all toxicities specified by type and grade.

Early stopping guideline for toxicity: Toxicity will be monitored continuously. If it becomes evident that the proportion of patients being removed from the study for toxicity convincingly exceeds 50%, the study will be halted for a safety consultation. The toxicity stopping rule will hold enrollment.

14.2 Sample Size/Accrual Rate

A sample size of 34 patients will be accrued and will be required to account for possible drop-out and inevaluability. The early stopping rule is defined above. Anticipated accrual is 1 patient per institution every 2 months. Therefore, accrual is anticipated to take from 20 to 36 months.

14.3 Stratification Factors

- Patients will be analyzed based on the indolent or aggressive type of NHL given that the two groups historically have different outcomes after AutoSCT.
- Patients will be analyzed based on average daily dose of Zydelig through the treatment duration to assess for dose dependence on progression rate.

14.4 Analysis of Secondary Endpoints

14.4.1 1-year PFS after ASCT.

PFS is defined as the time from the date of ASCT till progression or death whatever comes first. PFS function will be estimated using the Kaplan-Meier approach with 90% Confidence Interval.

Analysis of secondary objective(s):

The 1-year PFS will be estimated and reported using the Kaplan-Meier curve with the corresponding 90% confidence interval.

14.4.2 2-year PFS will be calculated with the same method as 1-year PFS (see 13.4.1).

14.4.3 Cumulative incidences of NRM at 3 months and 12 months by competing risks model and Grey's test.

14.4.4 The Cox regression model will be used to assess plausible risk factors for PFS and OS. The correlatives findings will be incorporated into time-to-event analyses using appropriate statistical models. Statistical analysis will be conducted by the BSS of the GCC.

14.4.5 Correlatives Studies

Please see Appendix C

15. REFERNCES

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16. Table 8 APPENDIX A Performance Status Criteria

ECOG Performance Status Scale	
Grade	Descriptions
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.

17. APPENDIX B
Patient Zydelig Diary

PATIENT MEDICATION DIARY – Zydelig

Today's date _____ Agent Zydelig

Patient Name_____ (*initials acceptable)* Patient Study ID _____

INSTSRUCTIONS TO THE PATIENT:

1. Complete one form for each 4 week-period while you take Zydelig.
2. You will take your dose of Zydelig twice a day. You will take 100 mg or 150 mg tablets, depending on the instructions from your doctor.
3. Record the date, the number of capsules of each size you took, and when you took them. Record doses as soon as you take them; do not batch entries together at a later time.
4. If you have any comments or notice any side effects, please record them in the comments column. If you make a mistake while you write, please cross it out with one line, put your initials next to it, and then write the corrected information next to your initials. Example: SB 9:30 am.
5. If you miss a dose of Zydelig, then you should take it as soon as you remember, as long as it is within 6 hours of the schedule. If not, then you should skip the missed dose.
6. Please return this form to your physician when you go for our next appointment.

		Time of daily dose		# of tablets taken		Comments
Day	Date	AM	PM	100 mg	150 mg	
1.						
2.						
3.						
4.						
5.						
6.						
7.						
8.						
9.						
10.						
11.						
12.						
13.						

14.						
15.						
16.						
17.						
18.						
19.						
20.						
21.						
22.						
23.						
24.						
25.						
26.						
27.						
28.						

Physician's Office Will Complete This Section:

1. Date patient started this cycle: _____

2. Date patient stopped this cycle: _____

3. Patient's dose cohort: _____

4. Total number of capsules taken this month (each size): _____

5. Physician/Nurse/Data Manager's Signature:_____

Patient's Signature: _____

18. Appendix C. Inhibitors and Inducers of CYP3A

Inhibitors and inducers of CYP3A enzymes are defined as follows. Further information can be found at the following website:
http://medicine.iupui.edu/clinpharm/ddis/main-table/.

Inhibitors of CYP3A	Inducers of CYP3A
Strong inhibitors	
indinavir nelfinavir ritonavir clarithromycin itraconazole ketoconazole nefazodone saquinavir suboxone telithromycin cobicistat boceprevir mibefradil telaprevir troleandomycin posaconazole	efavirenz nevirapine barbiturates glucocorticoids modafinil oxcarbazepine phenobarbital phenytoin pioglitazone rifabutin rifampin St. John's Wort troglitazone
Moderate inhibitors:	
aprepitant amprenavir amiodarone atazanavir ciprofloxacin cresemba crizotinib darunavir/ritonavir dronedarone erythromycin diltiazem fluconazole fosamprenavir grapefruit juice Seville orange juice verapamil Voriconazole [a] imatinib	
Weak inhibitors:	
cimetidine fluvoxamine	
All other inhibitors:	
chloramphenicol delavirdine diethyl-dithiocarbamate gestodene mifepristone norfloxacin norfluoxetine star fruit	

19. APPENDIX D CORRELATIVE STUDIES

19.1 Background and Overview

It is clear that some lymphomas become "addicted" to one or more oncogenic pathways, including the PI3K/Akt/mTOR axis. Patients with iNHL who are reliant on this pathway may be more responsive to Zydelig, which blocks PI3Kδ (1). However, there are no approved predictive biomarkers for PI3K/mTOR inhibitors' activity. A recent report demonstrated that PTEN, p-AKT, and p-p70S6K correlated with response to trastuzumab in patients with metastatic breast cancer, lending support to the importance of the activation status of key proteins of the PI3K/AKT/mTOR pathway as predictive biomarkers for response(2).

Similarly to other tyrosine kinase inhibitors, Zydelig activity is limited by de novo or acquired resistance (3). For example, p110α-mediated constitutive activation of PI3K has been shown to be a mechanism of resistance in this pathway through limiting the efficacy of p110δ-selective inhibition (4). The MEK1/2 (mitogen-activated kinase 1/2)/ERK1/2 (extracellular signal-regulated kinase 1/2) pathway is one of the most frequently dysregulated signaling cascades in cancer, including in hematological malignancies (5). While PI3K inhibition induces compensatory activation of p-ERK, co-inhibition of the PI3K and ERK pathway potentiates the activity of PI3K inhibitors in several malignancies, including T-cell lymphomas (6-8). Given that the nature of our study lacks adequate power to definitively evaluate these biomarkers, our goal in this pilot study is to assess the feasibility and potential signal from several candidate biomarkers for response and resistance to Zydelig.

As a PI3Kδ inhibitor, Zydelig has a profound effect on the immune system (9). It has been associated with colitis, pneumonitis, and hepatotoxicity suggestive of an autoimmune process. A recent report has demonstrated that inhibition of PI3Kδ in mice has a protective effect against several non-hematological cancers (10). The mechanism of action shown in this study was PI3Kδ-mediated inactivation of myeloid-derived suppressor cells (MDSCs) and regulatory T cells (Treg) resulting in upregulation of CD8+ T cells. In addition, PI3Kδ play a role in the anti-tumor response of the natural killer (NK) cells (11, 12). Given these interesting results, we will determine whether regulatory T cell, CD8+ T cell, CD4+ T cell, NK cell, and MDSC populations change in patients enrolled in this trial, immediately prior to Zydelig, and at 3 time points post starting Zydelig treatment (4 weeks, 12 weeks, and 6 months following the start of Zydelig).

Whole exome sequencing (WES) has emerged as a powerful method for correlating genetic mutations with treatment response. Cancers are often associated with genetic alterations that result in up- or down-regulation of particular signaling pathways that can now be further defined through WES. Van Allen et al. recently performed whole exome sequencing on samples from patients with urothelial carcinoma that showed that somatic mutations in *ERCC2*, a component of the nucleotide excision repair pathway, correlate with response to cisplatin (13). We propose to perform a similar approach using WES on formalin-fixed, paraffin-embedded (FFPE) tissue sections or frozen tissue blocks from enrolled, consented patients and to compare DNA from tissue samples to germline DNA that will be extracted from either peripheral blood mononuclear cells (PBMC) or histologically normal tissue. In addition, we will repeat a biopsy at the time of relapse and perform WES in order to assess for the acquisition of additional genetic alterations that might explain the mechanism of resistance.

In summary, correlative studies will be performed on samples from consenting patients to examine the following aims:

- Expression levels of p-AKT, PI3Kδ, PI3Kα, PTEN, p-p70S6K, and p-ERK pre- and post-Zydelig. Tumor samples (either bone marrow [BM] or lymph node [LN]) will be examined using immunohistochemistry (IHC).
- Flow cytometric characterization of circulating MDSCs, NK cells, regulatory T cells, CD4+ T cells, and CD8+ T cells pre-Zydelig and at 3 time points following the start of Zydelig (post-Zydelig) at weeks 4 and 12, and at 6 months.
- Whole exome sequencing of tumor and germline DNA pre-Zydelig and at relapse post-Zydelig.
- Participation in the correlative studies portion of this study is highly encouraged but optional.

19.2 Time Points

Peripheral blood and tumor samples for WES and IHC will be collected at 2 time points:

- Pre-treatment: FFPE or frozen tissue blocks samples taken from patients at time of transformation or relapse prior to starting Zydelig will be acquired. . Tissues obtained closer to starting Zydelig are highly preferred, but earlier biopsies for patients who will not have repeat biopsies just prior to study enrollment are acceptable. These samples will serve as a baseline for tracking acquired mutations or other genetic alterations associated with therapy resistance at relapse. The purpose of IHC and WES here is to evaluate biochemical and genetic markers for PI3K pathway activation and assessment of recurrent somatic mutations in lymphoma.

- Post-Zydelig treatment: Samples taken following relapse of lymphoma after SCT and Zydelig treatment should be strongly encouraged for all patients, especially for those who had a biopsy just prior to starting Zydelig. These samples will be compared to baseline samples for tracking acquired alterations in signaling pathways associated with therapy resistance at relapse. The purpose of IHC and WES here is to identify biochemical and genetic factors that may contribute to “escape” from Zydelig-mediated suppression of the PI3K/Akt/mTOR axis, and to assess for changes in recurrent somatic mutation profiles and clonal architecture compared to a prior biopsy.

For immunological studies, peripheral blood will be collected immediately prior to starting Zydelig and at the following time points after starting Zydelig: 4 weeks, 12 weeks, and 6 months.
All samples, except for frozen specimens intended for WES, will be shipped to Maciej Kmieciak, PhD at VCU Massey Cancer Center (19.6.4). Frozen tumor specimens intended for WES will be shipped to the Fehniger Lab at Washington University (19.7).
The Sample Collection Table 9outlines the sampling requirements for each time point and correlative endpoint.

19.3 Collection and Processing at Participating Sites for IHC and Immunologic Studies

Peripheral blood: 30 mL of whole blood will be drawn directly into 3 anticoagulated 10 mL blood collection tubes (containing sodium heparin or EDTA). Invert tubes 8-10 times to mix sample with anticoagulant. Samples will be labeled as specified in section 19.6.1 below and immediately

shipped at ambient temperature by overnight courier to VCU Massey Cancer Center (see 19.6.4 for shipping details). Samples must arrive at VCU Massey Cancer Center within 24 hours of blood draw. Coordinate with Dr. Maciej Kmieciak to ensure proper delivery on a business day.

Please note that an additional tube of blood may be required for WES at certain time points (see 19.4 below).

Tumor samples will be obtained by core needle biopsy (3-5 cores) or whole LN resection at each time point. Institutional procedures should be followed for the procurement of the tumor samples. Procured BM or LN samples for IHC should be placed in formalin and held at room temperature until shipping (see Section 19.6.2). **Please note** that processing of tissue for WES samples is different from that described in this section.

The Sample Collection Table 9 outlines the sampling requirements for each time point and correlative endpoint.

19.4 Collection and Processing at Participating Sites for WES Studies

For disease LN samples collected fresh, immediate snap freezing of an excisional biopsy piece or core biopsies is preferred. For disease bone marrow samples collected fresh, RBC lysis followed by centrifugation to form a cell pellet, and snap freezing is preferred. Peripheral blood samples will be processed as described in section 19.6, and sent immediately to VCU Massey Cancer Center for further processing (see 19.6.4 for shipping information). One tube of blood (10 mL) is required for each WES time point. Frozen specimens will be held in a freezer until shipped in batch on dry ice to Washington University. For FFPE tissue, tissue blocks or cores will be shipped to VCU Massey Cancer Center at room temperature in batch.

The Sample Collection Table 9 outlines the sampling requirements for each time point and correlative endpoint.

19.5 Sample Labeling for WES and IHC Studies

Each collected sample should be labeled as follows:

- Study number
- Patient sequence identification number
- Date of collection
- Time of collection
- Study time point (ie, pre-treatment or time post-treatment)

19.6 Shipping to VCU Massey Cancer Center

19.6.1 All blood samples (See Section19.6.4) for each patient must be shipped on dry ice by overnight courier immediately following collection. Samples must arrive within 24 hours of blood draw. Delivery must be coordinated with Dr. Maciej Kmieciak to ensure receipt of samples on a business day.

19.6.2 Fixed tumor samples should not be shipped until both pre- and post-treatment samples have been acquired (ie, batched for each patient). The samples should be shipped in formalin at room temperature by overnight courier as soon as possible after the post-treatment samples have been procured. If post-treatment samples will not be procured, proceed with shipping of the pre-treatment sample.

19.6.3 FFPE tissue, tissue blocks or cores should be shipped to VCU Massey Cancer Center in batch at room temperature by overnight courier.

19.6.4 Tumor and blood samples from all participating institutions will be shipped to the VCU Massey Cancer Center Clinical and Translational Research Laboratory (CTRL). The shipping date should be planned so that samples will arrive on a business day. Arrangements for delivery of samples being shipped within a 24-hour timeframe must be made in advance with the CTRL. Contact Dr Maciej Kmieciak in advance if any questions arise about timing of shipments.

Ship to:

Maciej Kmieciak, PhD
VCU Massey Cancer Center
Clinical and Translational Research Laboratory
401 College Street
Floor 1, Room G-111
Richmond, VA 23298-0037
Telephone (Office): 804-628-5337
Telephone (Lab): 804-628-5335
Email: mkmieciak@vcu.edu

The VCU Massey Cancer Center CTRL will process and analyze all tumor samples collected for the correlative studies for IHC, as well as all blood samples intended for flow cytometric evaluation. VCU Massey Cancer Center will process blood for PBMC isolation and ship snap frozen PBMC pellets for sequencing to Washington University (see 19.7). Any FFPE samples intended for WES analysis will be shipped from VCU Massey Cancer Center to Washington University in batch.

19.7 Shipping to Washington University

Frozen tissue samples will be shipped in batch to Washington University via Courier on dry ice. Samples should be labeled with the study UPN and sample information without including protected health information (PHI). Tracking numbers should be sent via email to addresses listed below prior to shipping, and all shipments should be received on a business day. Ship to:

Attention: Fehniger Lab / WU-Oncology
Southwest Tower Building, Room 634
4940 Parkview Place
St. Louis, MO 63110
Phone: 314 747 1547
Fax: 314 362 9333
E-mail: tfehnige@wustl.edu, tchappe@dom.wustl.edu, bjewell@dom.wustl.edu

19.8 Sample Processing at VCU Massey Cancer Center

17.8.1 FFPE tissue blocks and slides will be prepared, stained, and pathologically scored by Dr Kathryn Rizzo at VCU Massey Cancer Center. Validated antibodies for IHC staining include the following: PTEN (138G6) Rabbit mAb #9559 (Cell Signaling) (2), PI 3-kinase p110δ Antibody (A-8): sc-55589 (Santa Cruz) (15), PI3 Kinase p110α (C73F8) Rabbit mAb #4249 (Cell Signaling) (16), Phospho-Akt (Ser473) (736E11)

Rabbit mAb #3787 (Cell Signaling) (2), Phospho-p44/42 MAPK (Erk1/2) (Thr202/Tyr204) (D13.14.4E) XP® Rabbit mAb #4370 (Cell Signaling) (17), and Phospho-p70 S6 Kinase pThr389 Antibody PA1-526 (Cell Signaling) (2). Any FFPE samples intended for WES analysis will be shipped from VCU MCC to Washington University in batch.

19.8.2 Blood samples will be processed immediately after arrival at VCU Massey Cancer Center for isolation of PBMC using Ficoll-Hypaque according to manufacturer-specified protocol and as previously described (14). Cells obtained for the pre- and post-treatment samples will each be divided into 2 cryogenic tubes: tube A containing approximately 5 x 10^6 PBMC and tube B containing the remaining cells. For sequencing samples, 5 x 10^6 PBMC (tube A) will be pelleted, snap frozen, and shipped in batch to Washington University for nucleic acid isolation and sequencing.

19.8.3 Flow cytometry analysis of PBMC samples will be performed by VCU Massey Cancer Center to assess the circulating levels of MDSCs, NK cells, regulatory T cells, CD4+ T cells, and CD8+ T cells. Validated antibodies for flow cytometry staining in this study include the following: anti-human CD33 PE (Biolegend), anti-human CD11b PE/Cy7 (Biolegend), anti-human HLA-DR Antibody APC (Biolegend), anti-human Foxp3 PE (Bioscience), anti-human CD8a PE/Cy7 (Biolegend), anti-human CD4 FITC (Biolegend), anti-human CD25 APC (Biolegend), anti-human CD3 APC/Cy7 (Biolegend), anti-human CD56 PE (Biolegend), and Rat IgG2a K Isotype control PE (Bioscience) (18).

19.9 Sample Processing at Washington University

Genomic DNA (gDNA) will be isolated from FFPE or frozen tissue samples including diseased tissue and paired non-malignant tissue (QIAamp DNA mini kit, Qiagen). Quality control and mass assessments will be performed to ensure gDNA integrity prior to sequencing (Agilent bioanalyzer). From gDNA, Illumina sequencing libraries will be generated as described (19). Whole exome capture will be performed per manufacturer's instruction (Nimblegen V3). Illumina sequencing will be performed as described (19). Somatic calls will be made using the latest version of the somatic variant bioinformatic pipeline (The Genome Institute at Washington University), utilizing sequencing data from paired lymphoma and non-malignant tissue. Validation of variants may be confirmed using a custom-capture (Nimblegen), followed by Illumina sequencing approach (20).

19.10 Sample Tracking

Submission of all tumor samples will be logged into the appropriate fields in the database.

19.11 Pharmacokinetics assessment

Zydelig displayed in early trial linear pharmacokinetics (ie, not time dependent), a less-than dose-proportional increase in exposure, and achieved steady state by day 8. Zydelig twice-daily administration resulted in higher trough concentrations, as expected, vs once-daily dosing at the corresponding dose level.

Table 9

Sample Collection Table			
Sample	**Timepoints to be Collected**	**Volume/patient**	**Immediate Processing Instructions**
Tumor for IHC	1. Pre-Zydelig treatment 2. Post-Zydelig treatment	Biopsy (3-5 cores of tumor or whole LN)	Formalin at room temperature
Tumor for sequencing	1. Pre-Zydelig treatment 2. Post-Zydelig treatment	Fresh frozen or FFPE lymphoma tissue	Snap freeze and storage at -20 to -80°C
Blood for Flow Cytometry	1. Pre-Zydelig treatment 2. 4 wks post-Zydelig treatment[A] 3. 12 wks post-Zydelig treatment[B] 4. 6 mo post-Zydelig treatment[B]	3 tubes of 30 mL[C] (10 mL per tube)	Mix with anticoagulant and ship immediately to VCU Massey Cancer Center
Blood for Whole Exome Sequencing	1. Pre-Zydelig treatment 2. Post-Zydelig treatment[D]	1 tube of 10 mL[C]	Mix with anticoagulant and ship immediately to VCU Massey Cancer Center

A. Plus or minus 1 week.

B. Plus or minus 2 weeks.

C. A total of $5x10^6$ cells are required for the whole exome sequencing samples. Any extra cells can be discarded. If blood draw for flow cytometry and whole exome sequencing occurs on the same day, any "extra" cells from the WES collection tube may be combined in the sample for flow cytometry.

D. Treatment will be done at End of Treatment for all patients enrolled.

19.12 References (Correlative Studies)

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