Protocol Title:

An Open-Label Phase 2 Study of Ofatumumab (Arzerra®) in Combination with Oral GSK2110183 in the Treatment of Relapsed and Refractory Chronic Lymphocytic Leukemia (CLL)

SPONSOR:	**Princess Margaret Cancer Centre-University Health Network**
FUNDING SOURCE:	**GlaxoSmithKline Inc.**
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PRINCIPAL INVESTIGATOR SIGNATURE PAGE

Principal Investigator:	Dr. Christine I. Chen 610 University Avenue, Suite 5-220 Princess Margaret Cancer Centre Toronto, ON M5G 2M9	
	Signature of Investigator	Date
	Printed Name of Investigator	
	By my signature, I agree to personally supervise the conduct of this study and to ensure its conduct in compliance with the protocol, informed consent, IRB/EC procedures, instructions from GlaxoSmithKline Inc. representatives, the Declaration of Helsinki, ICH Good Clinical Practices guidelines, Health Canada and the applicable parts of the United States Code of Federal Regulations or local regulations governing the conduct of clinical studies.	

STUDY PERSONNEL

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Study Sponsor: **Study Location:**	Princess Margaret Cancer Centre – University Health Network 610 University Avenue Toronto, ON M5G 2M9
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Glossary of Abbreviations

ADR	Adverse Drug Reaction
AE	Adverse event
ALT (SGPT)	Alanine transaminase (serum glutamate pyruvic transaminase)
ANC	Absolute neutrophil count
APC	Antigen-presenting capability
AST (SGOT)	Aspartate transaminase (serum glutamic oxaloacetic transaminase)
AUC	Area under the curve
BUN	Blood urea nitrogen
CFR	Code of Federal Regulations
CLL	Chronic Lymphocytic Leukemia
Cmax	Maximal plasma concentration
Cmin	Minimal plasma concentration
CR	Complete response
CRF	Case report form
CT	Computed tomography
CTCAE	Common toxicity criteria
CYP	Cytochrome P450
DMC	Data Monitoring Committee
DSMB	Data Safety Monitoring Board
EC	Ethics Committee
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
FCBP	Female of child bearing potential
FDA	Food and Drug Administration
FISH	Fluorescence in situ hybridization
GCP	Good clinical practice
GCSF	Granulocyte colony stimulating factor, filgrastim (Neupogen)
IB	Investigator's Brochure
ICH	International Conference on Harmonization
IND	Investigational New Drug
IRB	Institutional Review Board
IWCLL	International Workshop on Chronic Lymphocytic Leukemia
LDH	Lactate dehydrogenase
MedDRA	Medical Dictionary for Regulatory Activity

NCI	National Cancer Institute
OD	Per day
OS	Overall survival
PD	Progressive disease
PO	Per os
PR	Partial response
RBC	Red blood cell (count)
RR	Response rate
SAE	Serious adverse event
SD	Stable disease
TLS	Tumor lysis syndrome
TSH	Thyroid stimulating hormone
TTP	Time to progression
WBC	White blood cell (count)
WHO	World Health Organization

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1. Protocol Synopsis

PROTOCOL TITLE: An Open-Label Phase 2 Study of Ofatumumab (Arzerra®) in Combination with Oral GSK2110183 in the Treatment of Relapsed and Refractory Chronic Lymphocytic Leukemia (CLL)	
DATE PROTOCOL FINAL:	**June 6, 2011**
INDICATION:	**Relapsed or refractory CLL, previously treated with at least one fludarabine-containing regimen**
STUDY PHASE:	**Phase II**

BACKGROUND AND RATIONALE:

Ofatumumab is a novel anti-CD20 monoclonal antibody with promising anti-tumor activity in CLL. In an international study of heavily pretreated CLL patients either refractory to both fludarabine and alemtuzumab (FA-ref) or refractory to fludarabine with bulky nodal disease (BF-ref), ofatumumab led to impressive single-agent response rates of 58% (FA-ref) and 47% (BF-ref) (Wierda 2010). In this study, toxicities were predictable and significant myelosuppression was uncommon (grade 3-4 neutropenia 6-14%). Although responses were rapid in onset (80% of responses occurring within 2 months), response durations were relatively short at a median of 7.1 months (FA-ref) and 5.6 months (BF-ref). Based on results from this study, ofatumumab received FDA approval for treatment of FA-ref patients with CLL. However, despite these encouraging preliminary data of single-agent ofatumumab, improvements in response rates, quality and duration of responses, will likely only be achieved with combination therapy.

GSK2110183 is a novel pan-AKT kinase inhibitor that potently inhibits growth in vitro of numerous hematologic cell lines, including CLL. The AKT pathway plays a centralized role in tumor differentiation, migration, proliferation and survival. Aberrant activation of the AKT pathway is frequently observed in CLL and may be associated with chemotherapy resistance and a higher capacity for proliferation (Longo 2007). AKT inhibition appears to cause CLL cell apoptosis primarily via effects on the microenvironment, such as counteracting the protective anti-apoptotic effect of stromal cells (Shehata 2010). Importantly, AKT inhibition in primary CLL samples leads to apoptosis of CLL B cells with preferential sensitivity of cells with high-risk features of unmutated IgVH status and CD38 positivity (Hofbauer 2010). In fludarabine-resistant samples with 17p13 deletion, AKT inhibition can lead to clear apoptosis, similar to that seen in fludarabine-sensitive samples. In an ongoing phase 1-2 trial of single agent GSK2110183 in relapsed and refractory patients with various hematologic malignancies, this oral agent was found to be very well-tolerated with minimal myelotoxicity. Dose-limiting toxicities in the phase 1 part were reversible liver enzyme abnormalities. The phase 2 part is ongoing and has thus far shown encouraging responses in myeloma and other lymphoproliferative disorders, including CLL.

The combination of ofatumumab and GSK2110183 is attractive for use in relapsed and refractory CLL as these two agents have markedly different mechanisms of action, non-overlapping toxicities, and activity in resistant disease. We propose the use of this combination in patients with CLL who have relapsed or are refractory to prior fludarabine-based therapy (single agent or combination therapy), with or without bulky nodal disease. The dose and schedule of ofatumumab will be identical to that used in the pivotal trial of single-agent ofatumumab and the

daily recommended phase 2 dose of GSK2110183 will be used. As neither ofatumumab nor GSK2110183 are myelosuppressive, the combination is anticipated to be well-tolerated in a relapsed or refractory CLL population where cytopenias are common. Currently, neither ofatumumab nor GSK2110183 are available for use in Canada. Although rituximab is approved for first line use as part of the FCR (fludarabine, cyclophosphamide, rituximab) regimen, retreatment using rituximab is not available. Furthermore, access to alemtuzumab in Ontario is restricted (no funding) and rarely available. As a result, there are limited options for therapy in CLL patients failing fludarabine therapy in Ontario and there is heavy demand from community oncologists and patients for clinical trials that provide novel therapies. Currently at Princess Margaret Cancer Centre, the largest tertiary care oncology centre in Canada, we have no competing trials for CLL patients who are relapsed or refractory to prior fludarabine-based therapy, and therefore accrual to this proposed study is anticipated to be rapid and efficient.

STUDY OBJECTIVES:

Primary:

1. To assess the efficacy (overall response rate, including complete and partial responses as per the IWCLL 2008 response criteria) of ofatumumab in combination with GSK2110183 in the treatment of patients with relapsed or refractory CLL who have received at least one prior fludarabine-containing regimen.

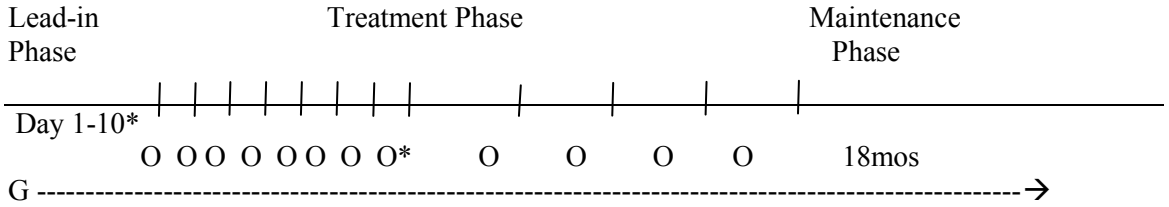
Secondary:

1. To assess the toxicity of ofatumumab in combination with GSK2110183 in patients with relapsed or refractory CLL.
2. To assess clinical efficacy endpoints such as progression-free and overall survival, stable disease, response duration, and time to next CLL therapy following therapy with ofatumumab in combination with GSK2110183.
3. To identify predictors of response using gene expression analysis and demonstrate target inhibition via flow-cytometry based pharmacodynamic studies.
4. To evaluate the pharmacokinetics of GSK2110183 after multiple single agent daily dosing and in combination with ofatumumab in first 10 eligible participants.

STUDY DESIGN:

This is a phase 2, open-label, single institution trial of combination of intravenous (IV) ofatumumab and oral GSK2110183 in patients with relapsed or refractory CLL. Patients must have received at least one prior line of therapy containing fludarabine (single-agent or combination therapy). During the initial 7 months Treatment Phase, ofatumumab will be administered weekly for 8 doses, then once every 4 week cycle for an additional 4 doses (dose and schedule identical to the pivotal phase 2 trial) (Wierda 2010) and GSK2110183 will be given daily PO (Treatment Phase). There will be an initial 10 day lead-in with GSK2110183 alone prior to initiation of ofatumumab to allow for evaluation of changes in cell surface expression due to GSK2110183 and for GSK2110183 pharmacokinetic studies (Lead-in Phase). The official Cycle 1 Day 1 will start on the date of first dose of ofatumumab. Cycle duration = 4 weeks. Patients will be assessed for safety, disease assessment, response, and survival on day 1 of each cycle during the Treatment Phase. The safety data will be reviewed by the Data Safety Monitoring Board (DSMB) during their biannual meeting. Enrollment will continue while DSMB response to the review of the safety data is awaited. All patients achieving SD, PR or CR by the end of the Treatment Phase will proceed to the Maintenance Phase. Patients with PD at any time, including by the end of Treatment Phase, will be taken off study. During the Maintenance Phase,

single-agent GSK2110183 will be administered daily for a maximum of 12 months (12 cycles). Maximum duration on any study drug is 18 months (18 cycles). During the Follow-up Phase, patients will be assessed for safety, disease assessment, response, and survival every 3 months through month 36 (year 3), or until subsequent CLL therapy or death, whichever comes first. Key indications for study withdrawal are progressive disease, intolerable toxicity, or completion of therapy.



G - GSK2110183 125mg OD continuously
O - Ofatumumab: The dosage regimen is 300mg Ofatumumab for the first infusion and 2,000 mg ofatumumab for all subsequent infusions. The infusion schedule is 8 consecutive weekly infusions, followed 4 weeks later by 4 consecutive monthly (i.e. every 4 weeks) infusions.
* PK sampling on Day 10 of lead-in phase and with 8th weekly dose of ofatumumab

STUDY ENDPOINTS

Primary:

- Overall Response Rate (ORR)

Secondary:

- Stable disease duration
- If responses are observed, response duration
- Progression-free survival
- Overall survival
- Toxicity (as graded per NCI CTC version 4.03)

STUDY DURATION:	**TOTAL SAMPLE SIZE:**
• Completion of 18 cycles (months) plus Lead-in of 10 days • At any time for unacceptable toxicity or patient request	31 response evaluable patients
DOSING REGIMEN (S):	**DRUG SUPPLIES:**
GSK2110183 125mg OD continuously in combination with Ofatumumab 300mg IV for the first infusion and 2000mg weekly x 7 doses, followed 4 weeks later by 4 consecutive monthly (i.e. every 4 weeks) doses.	GSK will supply GSK2110183 oral tablets and ofatumumab IV formulation

2 Schedule of Study Assessments *

Procedures	**Screening**	**Lead-in phase**			**Treatment Phase**						**Maintenance Phase**		**Follow-up**
	≤ 28 days from Lead-in Day 1	**(Days 1 to 10)**			Cycles 1 and 2				Cycles 3	Cycles 4-7	Cycle 8-18	Treatment discontinuation	Every 3 months up to 36 months
		Day 1	Day 8	Day 10	Day 1	Day 8	Day 15	Day 22	Day 1	Day 1	Day 1		
Informed Consent	**X**												
Demography	**X**												
Record prior medications, treatments, including prior anti-cancer therapies	**X**												
Physical Exam	**X**	**X**			**X**				**X**	**X**	**X**	**X**	**X**
Neurological symptoms questions assessment	**X**	**X**			**X**				**X**	**X**	**X**	**X**	**X**
ECOG	**X**	**X**			**X**				**X**	**X**	**X**	**X**	**X**
Height	**X**	**X**											
Weight	**X**	**X**			**X**				**X**	**X**	**X**	**X**	**X**
Vital Signs(BP, Pulse, RR, SaO2, temp)[1]	**X**	**X**			**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	
Tumor measurements by physical exam (lymphadenopathy, spleen/liver)	**X**	**X**			**X**				**X**	**X**	**X**	**X**	**X**
Bone marrow aspirate ± biopsy[2]	**X**		**X**									**X**	
CT chest, abdomen, pelvis[3]	**X**										**X**	**X**	
12-lead ECG[4]	**X**												
Adverse Events	**X**	**X**			**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**
Concomitant Therapy	**X**	**X**			**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	
Hematology[5]	**X**	**X**			**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**
Reticulocyte count	**X**												
HbA1C	**X**												
INR/PT	**X**												
PTT	**X**												
Direct Antiglobulin Test	**X**												
Beta 2 microglobulin	**X**												
CD4/CD8 cell count	**X**											**X**	
Chemistry[6]	**X**	**X**			**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**
Urinalysis	**X**												

Serum Pregnancy Test	**X**												
TSH	**X**								**X**[12]	**X**[12]	**X**[12]	**X**[12]	**X**
Hepatitis B&C[7]	**X**				**X**		**X**		**X**	**X**	**X**	**X**	**X**
Quantitative serum immunoglobulins[8]	**X**								**X**[8]	**X**[8]	**X**[8]	**X**[8]	**X**[8]
Peripheral blood for FISH	**X**[13]												
Pharmacokinetic blood sampling[9]				**X**			**X**						
Peripheral blood for correlative studies and ZAP70, and IgVH mutational status	**X**		**X**[10]										
Dispense GSK2110183 for next cycle[11]		**X**			**X**				**X**		**X**	**X**	
Ofatumumab infusions[14]					**X**	**X**	**X**	**X**		**X**			
Follow-up anti-cancer therapy													**X**
Follow-up survival													**X**

* An unscheduled visit can occur at any time during the study. The date for the visit and any data generated must be recorded on the appropriate CRF. Source documents for these unscheduled visits must also be maintained.
* Scheduled visits will have window period of +/- 4 days.

1. During the ofatumumab infusion, vital signs will be obtained preinfusion, at 30-minute intervals for the first hour during ofatumumab infusion, and then every hour until completion of infusion, including postinfusion. More frequent vital sign measurements should be performed if unstable, or if adverse events occur.
2. Bone marrow aspirate and biopsy to be performed routinely at baseline screening and at study discontinuation for morphology. BM aspirate samples (no biopsy) will be taken for correlatives at baseline screening and at study discontinuation (only if patient is progressing at time of study discontinuation). An additional bone marrow aspirate (no biopsy) will be performed on Day 8 of the lead-in phase (Window period of + 2 days to coincide with clinic days) for correlative studies only. Repeat bone marrows at any other time will only be performed to confirm CR.
3. All patients with baseline abnormalities on CT will undergo rescanning at end of cycle 6 (prior to the start of the Maintenance Phase), at study discontinuation, and to assess CR only. CT scans will not be performed routinely to assess partial response at any other time unless required at investigator discretion. Total estimated radiation per patient completing the study: 3-4.5 cGY (mSv)
4. Repeat ECG to be performed as required
5. Hematology includes CBC with differential WBC and platelet counts.
6. Chemistry includes sodium, potassium, chloride, CO2, calcium, magnesium, phosphorus, BUN, creatinine, fasting glucose, albumin, total protein, alkaline phosphatase, total bilirubin, AST, ALT, LDH, and uric acid. If total bilirubin levels ≥1.5 times upper normal limit are documented, a direct (conjugated) bilirubin will be evaluated. Please note that the glucose should be performed on a fasting blood sample (at least 8 hours fasting) (either separately from other chemistry or all scheduled chemistry must be performed fasting.)
7. Screening includes HbsAg, HbsAb, Hep B core total Ab, HCV. In addition, HBV DNA PCR testing every 2 weeks for the first month, every 4 weeks for months 2 and 3, and then every 3 months thereafter until 1 year after last dose of ofatumumab (only for patients with HBcAb (Hep B core Ab) test positive and HBV DNA test negative).
8. Quantitative serum immunoglobulins will be performed at screening and every 6 months from cycle 1 day 1 through month 36.

9. Peripheral blood sampling for pharmacokinetic studies will be performed on first 10 eligible participants; on Day 10 of the Lead-in Phase and Cycle 2 Day 22 of the Treatment Phase (with 8th weekly dose of ofatumumab): Predose (before GSK2110183 dose), 0.5, 1, 2, 3, 4, 6, 8, 10-12, 14-22, and 24hr after (10-12hr and 14-22hr samples only where collection times are feasible)
10. Scheduling must accommodate collection of correlative samples on Monday through Thursday only (Day 8)
11. Only enough GSK2110183 for 1 cycle of therapy may be provided to the patient.
12. TSH will be performed at screening and every 3 months from cycle 1 day 1 through month 36.
13. ZAP70 will be performed in Dr.Suzanne Trudel's laboratory at Ontario Cancer Institute and IgVH mutational status will be performed at the Manitoba Tumor Bank without cost. See Appendix 6.
14. Ofatumumab infusions can be divided over 2 days if required for the management of infusion related reaction.

3 Background and Rationale

3.1 Introduction

Ofatumumab is a novel anti-CD20 monoclonal antibody with promising anti-tumor activity in CLL. In an international study of heavily pretreated CLL patients either refractory to both fludarabine and alemtuzumab (FA-ref) or refractory to fludarabine with bulky nodal disease (BF-ref), ofatumumab led to impressive single-agent response rates of 58% (FA-ref) and 47% (BF-ref)(Wierda et al. 2010). In this study, toxicities were predictable and significant myelosuppression was uncommon (grade 3-4 neutropenia 6-14%). Although responses were rapid in onset (80% of responses occurring within 2 months), response durations were relatively short at a median of 7.1 months (FA-ref) and 5.6 months (BF-ref). Based on results from this study, ofatumumab received FDA approval for treatment of FA-ref patients with CLL. However, despite these encouraging preliminary data of single-agent ofatumumab, improvements in response rates, quality and duration of responses, will likely only be achieved with combination therapy.

GSK2110183 is a novel pan-AKT kinase inhibitor that potently inhibits growth in vitro; of numerous hematologic cell lines, including CLL. The AKT pathway plays a centralized role in tumor differentiation, migration, proliferation and survival. Aberrant activation of the AKT pathway is frequently observed in CLL and may be associated with chemotherapy resistance and a higher capacity for proliferation (Longo et al. 2007). AKT inhibition appears to cause CLL cell apoptosis primarily via effects on the microenvironment, such as counteracting the protective anti-apoptotic effect of stromal cells (Shehata et al. 2010). Importantly, AKT inhibition in primary CLL samples leads to apoptosis of CLL B cells with preferential sensitivity of cells with high-risk features of unmutated IgVH status and CD38 positivity (Hofbauer et al. 2010). In fludarabine-resistant samples with 17p13 deletion, AKT inhibition can lead to clear apoptosis, similar to that seen in fludarabine-sensitive samples. In an ongoing phase 1-2 trial of single agent GSK2110183 in relapsed and refractory patients with various hematologic malignancies, this oral agent was found to be very well-tolerated with minimal myelotoxicity. Dose-limiting toxicities in the phase 1 part were reversible liver enzyme abnormalities. The phase 2 part is ongoing and has so far shown encouraging responses in myeloma and other lymphoproliferative disorders, including CLL.

3.2 Rationale for Treatment in Chronic Lymphocytic Leukemia

3.2.1 Clinical study rationale:

The combination of ofatumumab and GSK2110183 is attractive for use in relapsed and refractory CLL as these two agents have markedly different mechanisms of action, non-overlapping toxicities, and activity in resistant disease. We propose the use of this combination in patients with CLL who have relapsed or are refractory to prior fludarabine-based therapy (single agent or combination therapy), with or without bulky nodal disease. The dose and schedule of ofatumumab will be identical to that used in the pivotal trial of single-agent ofatumumab and the daily recommended phase 2 dose of GSK2110183 will be used. As neither ofatumumab nor GSK2110183 are myelosuppressive, the combination is anticipated to be well-tolerated in a relapsed or refractory CLL population where cytopenias are common. Currently, neither ofatumumab nor GSK2110183 are available for use in Canada. Although rituximab is approved for first line use as part of the FCR (fludarabine, cyclophosphamide, rituximab) regimen, retreatment using rituximab is not available. Furthermore, access to alemtuzumab in Ontario is restricted (no funding) and rarely available. As a result, there are limited options for therapy in CLL patients failing fludarabine therapy in Ontario and there is heavy demand from community oncologists and patients for clinical trials that provide novel therapies. Currently at Princess Margaret Cancer Centre, the largest tertiary care oncology centre in Canada, we have no competing trials for CLL patients who are relapsed or refractory to prior fludarabine-based therapy, and therefore accrual to this proposed study is anticipated to be rapid and efficient.

3.2.2 Correlative studies rationale:

As a companion study to the proposed clinical trial, we will conduct experiments aimed at identifying predictors of response and pharmacodynamic studies to demonstrate target inhibition. Pharmacokinetic studies will be analyzed after multiple dosing of GSK2110183 alone and during combination GSK2110183 and ofatumumab to determine interactions in plasma levels of the two agents. See Appendix 6 for details of PD and PK studies.

4 Study Objectives and Endpoints

4.1 Objectives

4.1.1 Primary objectives

- To assess the efficacy (overall response rate, including complete and partial responses as per the IWCLL 2008 response criteria) of ofatumumab in combination with GSK2110183 in the treatment of patients with relapsed or refractory CLL who have received at least one prior fludarabine-containing regimen

4.1.2 Secondary study objectives

- To assess the toxicity of ofatumumab in combination with GSK2110183 in patients with relapsed or refractory CLL

- To assess clinical efficacy endpoints such as progression-free and overall survival, stable disease, response duration, and time to next CLL therapy following therapy with ofatumumab in combination with GSK2110183.

- To identify predictors of response using gene expression analysis and demonstrate target inhibition via flow-cytometry based pharmacodynamic studies (Appendix 6)

- To evaluate the pharmacokinetics of GSK2110183 after multiple single agent daily dosing and in combination with ofatumumab in first 10 eligible participants. (Appendix 6)

4.2 Endpoints

4.2.1 Primary Endpoint

- Overall response rate (includes partial and complete responses)

4.2.2 Secondary Endpoints

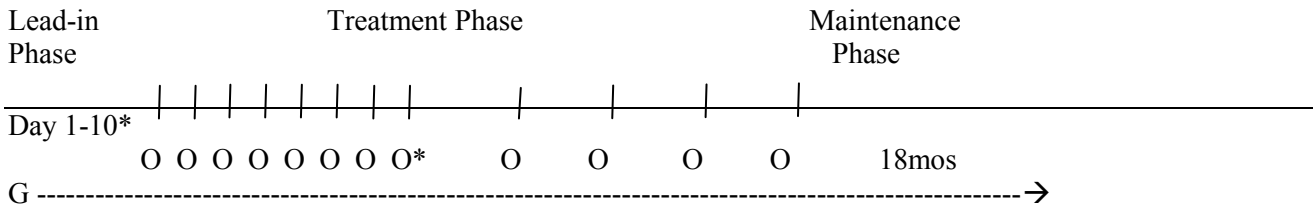
- Stable disease duration, and if responses are observed, response duration, progression-free and overall survival.
- Safety (type, frequency, severity, and relationship of adverse events to study therapy).

5 Investigational Plan

5.1 Overall design

This is a phase 2, open-label, single institution trial of combination IV ofatumumab and oral GSK2110183 in patients with relapsed or refractory CLL. During the initial 7 months Treatment

Phase, ofatumumab will be administered weekly for 8 doses, then once every 4 weeks cycle for an additional 4 doses (dose and schedule identical to the pivotal phase 2 trial, Wierda et al. 2010) and GSK2110183 will be given daily PO (Treatment Phase). There will be an initial 10 day lead-in with GSK2110183 alone prior to initiation of ofatumumab to allow for evaluation of changes in cell surface expression due to GSK2110183 and pharmacokinetic studies (Lead-in Phase). The official Cycle 1 Day 1 will start on the date of first dose of ofatumumab. Cycle duration = 4 weeks. Patients will be assessed for safety, disease assessment, response, and survival on day 1 of each cycle during the Treatment Phase. The safety data will be reviewed by the DSMB during their biannual meeting. Enrollment will continue while DSMB response to the review of the safety data is awaited. All patients achieving SD, PR or CR by the end of the Treatment Phase will proceed to the Maintenance Phase. Patients with PD at any time, including by the end of Treatment Phase, will be taken off study. During the Maintenance Phase, single-agent GSK2110183 will be administered daily for a maximum of 11 months (11 cycles). Maximum duration on any study drug is 18 months (18 cycles). During the Follow-up Phase, patients will be assessed for safety, disease assessment, response, and survival every 3 months through month 36 (year 3), or until subsequent CLL therapy or death, whichever comes first. Key indications for study withdrawal are progressive disease, intolerable toxicity or completion of therapy.



G - GSK2110183 125mg OD continuously

O – Ofatumumab: The dosage regimen is 300mg Ofatumumab for the first infusion and 2000 mg Ofatumumab for all subsequent infusions. The infusion schedule is 8 consecutive weekly infusions, followed 4 weeks later by 4 consecutive monthly (i.e. every 4 weeks) infusions.

* PK sampling on Day 10 of lead-in phase and with 8th weekly dose of ofatumumab (see Appendix 6)

5.1.1 Investigational Drug - Ofatumumab

Ofatumumab is a fully human monoclonal antibody (mAb), IgG1κ, targeting a unique CD20 epitope, resulting in increased binding affinity to CD20, prolonged dissociation rate and increased ability to bind and activate complement (C1q) at the cell surface. This generates a superior induction of tumor cell lysis by CDC activity, especially in cells with low CD20 density, as it is the case in CLL, with similar ADCC activity, compared to tumor cell lysis capability observed with rituximab (Teeling et al 2006).

In a phase I dose-ranging trial of ofatumumab 500mg (n=3), 1000mg (n=3), and 2000mg (n=27) given weekly x 4, 50% PR was observed with the highest dose amongst relapsed CLL patients. (Coiffier et al. 2008). Cmax, Cmin, AUC and t½ increased from dose 1 to 4 in all three arms. In the 2000mg dose group, objective response significantly correlated with Cmax, AUC and t½ after dose 4 and survival endpoints correlated with exposure. The MTD (maximum tolerated dose) was not reached and treatment was well tolerated. Adverse events were limited to grade 1-2 infusion reactions, grade 3-4 neutropenia occurred in only 6% of patients and non-opportunistic grade 1-2 infections were observed in 51% of patients.

A phase II study of 500mg and 1000mg ofatumumab in combination with fludarabine and cyclophosphamide (OFC) in frontline CLL patients is ongoing.

The investigational medical product, ofatumumab, is a liquid concentrate for solution for infusion presented in glass vials. Ofatumumab will be infused intravenously on day 1 (300mg) followed by an infusion of 2000 mg weekly for 7 doses, followed 4 weeks later by an infusion of 2000 mg every 4 weeks for 4 additional doses. Each cycle will be of 4 weeks in duration.

The ofatumumab infusions will be prepared in 1000mL sterile, pyrogen free 0.9% NaCl to yield a 0.3mg/mL and 2mg/mL ofatumumab concentration for the first and subsequent infusions, respectively.

5.1.2 GSK2110183

GSK2110183 is a novel member of the N-alkyl pyrazole class of orally available kinase inhibitors and has been shown to be a potent, pan-AKT inhibitor, with potency (K_i*) values for AKT 1, 2 and 3 kinases being 0.084, 2.0 and 2.6 nM, respectively. GSK2110183 exhibits a time-dependent inhibition of AKT with a dissociation half-life of 20 minutes. In vitro, GSK2110183 causes a concentration- and time-dependent reduction in phosphorylation of multiple proteins downstream of AKT such as GSK3, PRAS40, Forkhead (FOXO1/3a) and Caspase 9. Treatment of tumor cells with GSK2110183 resulted in a concentration-dependent increase in the nuclear translocation of the FOXO-3a transcription factor as a functional consequence of reduced phosphorylation of FOXO-3a. GSK2110183 has been shown to inhibit the proliferation of a range of tumor cell lines from multiple histologies including breast, hematological, colon, ovarian and prostate (EC_{50} <1 uM). AKT signaling is inhibited in cell lines both sensitive and less sensitive to GSK2110183, suggesting that resistance to GSK2110183 is not due to a lack of AKT kinase inhibition. GSK2110183 has been shown to induce cycle arrest at G1 phase or apoptosis in a concentration-dependent manner depending on the cellular context.

GSK2110183 is an oral, low nanomolar pan-AKT kinase inhibitor given once daily in a phase 1, first-time-in-human (FTIH), two-stage study of patients with various hematologic malignancies. This study identified the maximal tolerated dose as 125mg daily with a cohort expansion Part 2 at this dose. The most common adverse events (AEs) were GI disorders (nausea 35%, dyspepsia 35%, diarrhea 19%, vomiting 12%) with very few drug-related Grade 3 AEs. The most frequent Grade 3 AEs were liver function test abnormalities (AST and ALT). Myelosuppression is uncommon at the 125mg dose (Grade 3-4 neutropenia 13%). Although AKT2 is an integral part of the insulin signaling pathway and hyperglycemia and hyperinsulinemia may be expected, no clinically significant hyperglycemia was observed in this study. Since GSK2110183 inhibits multiple cytochrome P450 (CYP) enzymes in vitro, there is potential for significant drug-drug interactions and therefore a variety of agents are prohibited or are to be used with caution during GSK2110183 use.

Four strengths of GSK2110183 (hydrochloride salt), formulated as a white to almost white solid, are provided as capsules equivalent to 1, 5, 25 or 100mg of GSK2110183 (free form).

5.2 Screening and Eligibility

The Investigator or designee is responsible for keeping a record of all subjects who sign an Informed Consent Form for entry into the study. All subjects will be screened for eligibility. Screening procedures are outlined in Section 2, Schedule of Study Assessments and must take place within 28 days prior to initiation of therapy.

Approximately 31 subjects with relapsed or refractory CLL will be screened for enrollment and must meet the eligibility criteria below.

Subjects must meet the following inclusion/exclusion criteria to be eligible for the study.

Inclusion criteria

Patients must fulfil all of the following criteria to be eligible for admission to the study:

- A confirmed diagnosis of B-cell CLL by IWCLL 2008 criteria (Appendix 1)
- Patients must have evidence of disease progression as evidenced by rapid doubling of peripheral lymphocyte count, progressive lymphadenopathy or hepatosplenomegaly, worsening anemia or thrombocytopenia, or progressive constitutional symptoms [including fatigue, weight loss, night sweats, fever (without infection)]
- Must be relapsed or refractory to at least one prior fludarabine-containing regimen (no maximum number of prior regimens).
- Age $\geq$ 18 years.
- ECOG performance status of 0, 1 or 2 (Appendix 3)
- Signed the Informed Consent form
- Life expectancy of $\geq$ 6 months
- Able to swallow and retain oral medication
- Normal HbA1C $\leq$ 0.07
- Fasting blood sugar <7mmol/L

Exclusion criteria:

Subjects meeting **any** of the following criteria are excluded from this study:

- CLL therapy, including stem cell transplantation, within 4 weeks of study initiation. Corticosteroids alone may be administered up to seven days prior to the first dose of study drug.
- Treatment with any known non-marketed drug substance or experimental therapy within 5 terminal half-lives or 4 weeks prior to enrollment, whichever is longer, or currently participating in any other interventional clinical study
- Prior treatment with anti-CD20 monoclonal antibody or alemtuzumab within 3 months prior to start of therapy
- Known hypersensitivity to ofatumumab, GSK2110183, or any components therein.
- Anticoagulants are permitted only if the subject meets PTT and INR entry criteria while on anticoagulants (INR and PTT ≤1.5 times upper normal limit). Their use must be monitored in accordance with local institutional practice.
- Current use of any anti-platelet agent (e.g. dipyridamole, clopidogrel) other than aspirin (81mg daily).
- Current use of a prohibited medication based on potential drug-drug interaction – a complete list is found in Appendix 2
- Known CNS involvement with CLL
- Transformation to aggressive B-cell malignancy (e.g. large B-cell lymphoma, Richter's syndrome, prolymphocytic leukemia [PLL])
- "Active" autoimmune disease – prior history of autoimmune hemolysis (DAT positive or negative) or immune thrombocytopenia without current active autoimmune disease is allowed
- Subjects who have current active hepatic or biliary disease (with exception of patients with Gilbert's syndrome, asymptomatic gallstones, liver metastases or stable non-hepatitis B or C chronic liver disease per investigator assessment – please see below for Hepatitis B and C criteria)
- Previously diagnosed diabetes mellitus (Type 1 or 2)
- Other past or current malignancy. Subjects who have been free of malignancy for at least 5 years, or have a history of completely resected non-melanoma skin cancer, or successfully treated in situ carcinoma are eligible.

- Chronic or current infectious disease requiring systemic antibiotics, antifungal, or antiviral treatment such as, but not limited to, chronic renal infection, chronic chest infection with bronchiectasis, and tuberculosis.
- Any medical condition that would require long-term use (>1 month) of systemic corticosteroids during study treatment (excludes topical or inhaled corticosteroid use)
- History of significant cerebrovascular disease in the past 6 months or ongoing event with active symptoms or sequelae
- QTc $\geq$ 470 msec on screening ECG
- Clinically significant cardiac disease including unstable angina, acute myocardial infarction within six months prior to study entry, congestive heart failure (NYHA III-IV), and arrhythmia unless controlled by therapy, with the exception of extra systoles or minor conduction abnormalities.
- Significant concurrent, uncontrolled medical condition including, but not limited to, renal, hepatic, gastrointestinal, endocrine, pulmonary, neurological, cerebral or psychiatric disease which in the opinion of the investigator may represent a risk for the patient.
- Any major surgery within the prior 4 weeks.
- Known HIV positive.
- Positive serology for Hepatitis B (HB) defined as a positive test for HBsAg. In addition, if negative for HBsAg but HBcAb positive (regardless of HBsAb status), a HB DNA test will be performed and if positive the subject will be excluded. Consult with a physician experienced in the care and management of study patients with hepatitis B to manage and treat patients who are HBcAb positive. Initiate antiviral therapy, if required.
- Positive serology for hepatitis C (HC) defined as a positive test for HCAb, in which case reflexively perform a HC RIBA immunoblot assay on the same sample to confirm the result.
- Screening laboratory values:

  platelets $\leq 30 \times 10^9$/L

  neutrophils $\leq 0.7 \times 10^9$/L

estimated GFR <40mL/min as calculated by the Cockcroft Gault formula

total bilirubin ≥1.5 times upper normal limit (unless due to a known history of Gilbert's disease)

ALT ≥2.5 times upper normal limit

alkaline phosphatase ≥2.5 times upper normal limit

INR and PTT ≥1.5 times upper normal limit

- Pregnant or lactating women. Women of childbearing potential must have a negative pregnancy test at screening.
- Women of childbearing potential, including women whose last menstrual period was less than one year prior to screening, unable or unwilling to use adequate contraception from study start to one year after the last dose of protocol therapy.

  Adequate methods of contraception include use of an intrauterine device with an additional barrier method (**diaphragm with spermicidal gel or condoms with spermicide)**, double-barrier methods (diaphragm with spermicidal gel **and** condoms **with spermicide**), partner vasectomy, and total abstinence. Oral or depot hormonal contraceptives are not reliable due to potential drug-drug interactions. (The same contraceptive guidelines apply for male patients with a partner who is a woman of childbearing potential)
- Male subjects unable or unwilling to use adequate contraception methods from study start to one year after the last dose of protocol therapy.

5.3 Visit schedule and assessments

Screening Assessments and all on study scheduled visits and assessments are outlined in Section 2 Schedule of Study Assessments.

An unscheduled visit can occur at any time during the study. The date for the visit and any data generated must be recorded on the appropriate CRF. Source documents for these unscheduled visits must also be maintained.

At treatment discontinuation, subjects will undergo off study evaluations as per the Schedule of Assessments, Section 2. In addition, a safety assessment will be done approximately 28 days (+/- 4

days) post the last dose of protocol therapy. Thereafter, for patients who go off protocol treatment will be followed every three months to document time to relapse, next treatment, and death.

Pharmacokinetic sampling will take place on the following schedule (Appendix 6):

- Day 10 of the Lead-in Phase:
    - Predose (before GSK2110183 dose), 0.5, 1, 2, 3, 4, 6, 8, 10-12, 14-22, and 24hr after (10-12hr and 14-22hr samples only where collection times are feasible)

- Cycle 2 Day 22 of the Treatment Phase (with 8th weekly dose of ofatumumab):
    - Predose (before GSK2110183 dose), 0.5, 1, 2, 3, 4, 6, 8, 10-12, 14-22, and 24hr after (10-12hr and 14-22hr samples only where collection times are feasible)

5.3.1 Treatment assignments

All potential patients will be assessed by the study coordinator. Patients will be registered after completing an eligibility checklist. Protocol treatment is to begin within 7 working days of patient registration. Pre-study treatment evaluations will be performed as per Section 2, Schedule of Study Assessments.

5.4 Drug Administration

5.4.1 Dosing regimen - GSK2110183

GSK2110183 will be administered at a dose of 125mg orally daily as a single agent during the 10 day Lead-in Phase and then in combination with ofatumumab for 7 cycles/months (Treatment Phase), then as a single agent during the Maintenance Phase for an additional 11 cycles (max total duration 18 cycles/months). Subjects experiencing adverse events felt to be due to GSK2110183 may need study treatment modifications (See Section 5.5). Dose re-escalations for GSK2110183 are allowed at the discretion of the investigator and approval of the Study Medical Monitor.

5.4.2 Dosing regimen – Ofatumumab

Ofatumumab is a liquid concentrate for solution for infusion presented in glass vials. The ofatumumab infusions will be prepared in 1000mL sterile, pyrogen free 0.9% NaCl to yield a

0.3mg/mL and 2mg/mL ofatumumab concentration for the first and subsequent infusions, respectively.

The dosing of ofatumumab will initiate with an intravenous infusion of 300 mg on Day 1 followed by an infusion of 2000 mg2000mg weekly for 7 doses, followed 4 weeks later by an infusion of 2000 mg every 4 weeks for 4 additional doses. Each cycle will be of 4 weeks in duration.

Pre-medication before each ofatumumab infusion must be given within 30 minutes to 2 hours prior to the treatment:

Table 1 Pre-medication Requirements prior to Ofatumumab Infusions

Infusion #	**Acetaminophen (PO)** or equivalent	**Antihistamine (IV or PO)** diphenhydramine or equivalent	**Glucocorticoid (IV)** prednisolone or equivalent
1st	1000 mg	50 mg	50 mg
2nd	1000 mg	50 mg	50 mg
3rd -Nth	1000 mg	50 mg	0 – 50 mg*

*If the 2nd infusion has been completed without the subject experiencing any grade = 3 AEs, pre-medication with glucocorticoid may be reduced or omitted before the 3rd to Nth infusion at the discretion of the investigator.

During the ofatumumab infusion the patient should be monitored closely. Vital signs will be obtained preinfusion, at 30-minute intervals for the first hour during ofatumumab infusion, and then every hour until completion of infusion, including post-infusion. More frequent vital sign measurements should be performed if unstable, or if adverse events occur.

First Infusion of 300 mg Ofatumumab (CLL)

The first dose administered of ofatumumab in CLL should be 300 mg to minimize infusion reactions. The initial rate of the first infusion of 300 mg ofatumumab (0.3 mg/mL) should be 12 mL/h. If no infusion reactions occur the infusion rate should be increased every 30 minutes, to a maximum of 400 mL/h, according to Table 2. If this schedule is followed, the infusion duration will be approximately 4.6 hours.

Table 2 Infusion rate at 1st ofatumumab infusion (300 mg)

Time	mL/hour
0 – 30 minutes	12
31 – 60 minutes	25
61 – 90 minutes	50
91 – 120 minutes	100
121 - 150 minutes	200
151 - 180 minutes	300
181+ minutes	400

If an infusion reaction develops, the infusion should be temporarily slowed or interrupted. Upon restart, the infusion rate should be half of the infusion rate at the time the infusion was paused. If however, the infusion rate was 12 mL/hour before the pause, the infusion should be restarted at 12 mL/hour.

Thereafter, the infusion rate may be increased according to the judgment of the investigator, in the manner described in this section.

First Infusion of 2000 mg Ofatumumab

The initial rate of the first infusion of 2000 mg ofatumumab (2 mg/mL) should be 12 mL/h. If no infusion reactions occur the infusion rate should be increased every 30 minutes, to a maximum of 400 mL/h, according to Table 3. If this schedule is followed, the infusion duration will be approximately 5 hours.

Table 3 Infusion rate at 1st ofatumumab infusion (2000 mg)

Time	mL/hour
0 – 30 minutes	12
31 – 60 minutes	25
61 – 90 minutes	50
91 – 120 minutes	100
121 - 150 minutes	200
151 - 180 minutes	300
181+ minutes	400

If an infusion reaction develops, the infusion should be temporarily slowed or interrupted. Upon restart, the infusion rate should be half of the infusion rate at the time the infusion was paused. If, however, the infusion rate was 12 mL/hour before the pause, the infusion should be restarted at 12

mL/hour. Thereafter, the infusion rate may be increased according to the judgment of the investigator, in the manner described in this section.

Subsequent Infusions of 2000 mg Ofatumumab

If the previous infusion has been completed without grade ≥ 3 infusion-associated AEs, the subsequent infusion of the 2000 mg ofatumumab (2 mg/mL) can start at a rate of 25 mL/hour and should be doubled every 30 minutes up to a maximum of 400 mL/h, according to Table 4. Duration of the infusion will be approximately 4 hours if this schedule is followed. If the previous infusion has been completed with grade ≥ 3 infusion-associated AEs, the subsequent infusion should start at a rate of 12 mL/hour according to Table 2.

Table 4 Infusion rate at subsequent ofatumumab infusion

Time	mL/hour
0 – 30 minutes	25
31 – 60 minutes	50
61 – 90 minutes	100
91 – 120 minutes	200
121+ minutes	400

5.4.3. Management of Severe (Grade ≥3) Infusion Reactions to Ofatumumab

Infusion reactions tend to decrease with subsequent doses of ofatumumab. Most of the infusion / injection site reactions reported with ofatumumab have been mild or moderate; however, infusion reactions may be severe or even lead to death. If the investigator judges a grade ≥3 AE to be related to the infusion, the infusion must be interrupted and the appropriate clinical intervention begun. When the AE decreases to grade <3, the investigator may restart the infusion. Upon restarting the infusion, the infusion rate must be 12mL/hr for the first infusion or 25mL/hr for subsequent infusions, and may subsequently be increased according to the judgment of the investigator, as described in Table 3 and Table 4 (i.e. not more than doubled and no earlier than every 30 minutes).

If the severity of the AE does not resolve to grade <3 despite adequate clinical intervention, or the same AE increases to grade 3 on three occasions during one infusion, the subject should be withdrawn from treatment.

5.4.4 Record of administration

Accurate records will be kept in the source documents of all drug administration (including dispensing and dosing). Time and rate changes of Ofatumumab infusions will be recorded only during management of infusion related reaction.

5.5 Dose Continuation, Modification and Interruption

Subjects will be evaluated for AEs at each visit with the NCI CTCAE v4.03 (see Appendix 4: NCI CTCAE v4.03) used as a guide for the grading of severity. Sections below describe dose reduction steps, instructions for initiation of a new cycle of therapy and dose modifications during a cycle of therapy.

5.5.1 Dose Modification Steps for GSK2110183

GSK2110183 dose reductions should be taken one dose level at a time per the table below.

Dose levels for GSK2110183:

Dose level	Daily dose (mg)
Dose level 0 (starting dose)	125
Dose level -1	100
Dose level -2	75
Dose level -3	50
Dose level -4	25

5.5.2 Instructions for initiation of a New Cycle

A new course of treatment may begin on the scheduled Day 1 of a new cycle if:

- The ANC is $\geq 0.5 \times 10^9$/L;
- The platelet count is $\geq 30 \times 10^9$/L ;
- Any drug-related rash, diarrhea, dyspepsia, mucositis or infection that may have occurred has resolved to ≤ **grade 1** severity (see Section 5.5.3.2);
- Any drug-related toxicity that may have occurred has resolved to ≤ **grade 2** severity

If these conditions are not met on Day 1 of a new cycle, the subject will be evaluated weekly and a new cycle of treatment will not be initiated until the toxicity has resolved as described above. If the toxicity does not resolve to ≤ Grade 2 or baseline within 14 days, withdrawal from the trial is recommended. However, if the investigator agrees that further treatment will benefit the subject,

treatment can continue with at least one-level dose reduction once the toxicity resolves to ≤ Grade 1 or baseline.

If GSK2110183 dose reduction was taken during the previous cycle and the cycle was completed without requiring further dose modification, then the next cycle will start at the same reduced dose of GSK2110183. If ofatumumab or GSK2110183 dosing was omitted for the remainder of the previous cycle or if the new cycle is delayed due to toxicity newly encountered on the scheduled Day 1, then the new cycle will be started with a one-level dose reduction of GSK2110183, based upon which drug was felt by the investigator to be most responsible for the toxicity.

EXCEPTIONS:

For toxicities specific to either ofatumumab or GSK2110183, see Section 5.5.3

For hematopoietic toxicities (neutropenia, thrombocytopenia), only GSK2110183 will undergo dose reductions. Ofatumumab will not be dose-reduced for cytopenias.(see Section 5.5.3.1).

If GSK2110183 dosing is delayed for ANC < 0.5 x 10^9/L on Day 1 of a new cycle, the option of initiating GCSF support may be taken (see Section 5.5.4).

5.5.3 Instructions for dose modifications or interruption

5.5.3.1 Ofatumumab

Dose delay and dose reduction rules for ofatumumab are as follows and in the table below.

- There will be no ofatumumab dose reductions. Infusional reactions will mandate infusion rate modifications (Section 5.4.3).
- For treatment interruptions during a cycle, the 28-day schedule of each cycle will continue to be followed. Missed doses of ofatumumab are not made up.
- For treatment interruptions that delay the scheduled start of a new cycle, when toxicity has resolved as required to allow the start of a new cycle (Section 5.5.2), the restart day of therapy becomes Day 1 of the next cycle.
- There will be no dose reductions of ofatumumab for hematopoietic toxicity (neutropenia, thrombocytopenia). Only GSK2110183 will be dose-reduced for cytopenic toxicity (see Section 5.5.4)
- If GSK2110183 is held for toxicities at the ***start of a new cycle***, ofatumumab will also be held until toxicities resolve and allow the new cycle to initiate with both agents.

- If GSK2110183 is held for toxicities in the ***middle of a cycle***, ofatumumab may continue **without interruption**, providing the investigator feels that ofatumumab is not contributing to the toxicities.

NOTE: Discontinuation of ofatumumab for infusional adverse events will warrant patient removal from study. If the lowest dose level of GSK2110183 is not tolerated for GSK2110183-related toxicity, the patient may continue on study with ofatumumab alone.

5.5.3.2 GSK2110183

Dose delay and dose reduction rules for GSK2110183 are as follows and in the table below.

- GSK2110183 dose reduction steps are outlined in Section 5.5.1.
- For treatment interruptions during a cycle, the 28-day schedule of each cycle will continue to be followed. Missed doses of GSK2110183 are not made up.
- For treatment interruptions that delay the scheduled start of a new cycle, when toxicity has resolved as required to allow the start of a new cycle (Section 5.5.2), the restart day of therapy becomes Day 1 of the next cycle.
- If ofatumumab is held at the start of a new cycle, GSK2110183 should also be held.

5.5.4 Dose modifications for GSK2110183 (specific toxicities):

Table 1. Specific hematologic toxicities:

Neutropenia	**Intervention**
Grade 1 – 2	None
Grade 3 neutropenia with fever (temperature ≥ 38.5º C) or Grade 4 neutropenia	Hold (interrupt) both study drugs and follow CBC weekly. When neutropenia has resolved to ≤ grade 2, then resume GSK2110183 dose at next lower dose level (no dose reduction for ofatumumab). Instead of waiting for neutrophil recovery, there is an option to use GCSF 300ug SC OD until neutropenia has resolved to ≤ grade 2, then resume GSK2110183 dose at next lower dose level (no dose reduction for ofatumumab). If more than one event of Grade 3-4 neutropenia occurs (i.e. more than one dose reduction of GSK2110183 is undertaken), there is an option to use GCSF 300ug SC once or twice weekly continuously as secondary prophylaxis.

Thrombocytopenia	**Intervention**
Grade 1 – 3	None
Grade 4 (<25,000/uL)	Hold (interrupt) both study drugs and follow CBC weekly. When thrombocytopenia has resolved to ≤ grade 2, then resume GSK2110183 dose at next lower dose level (no dose reduction for ofatumumab).

Table 2. Specific non-hematologic toxicities:

Hyperglycemia	Intervention
Grade 1 – ULN-8.9 mmol/L	None
Grade 2 - >8.9-13.9 mmol/L	Monitor blood glucose weekly (either with portable glucometer or with chemistry testing). If Grade 2 hyperglycemia recurs, then decrease GSK2110183 by one dose level immediately and carry over into the subsequent cycle. If Grade 2 hyperglycemia recurs within new cycle, decrease GSK2110183 by one dose level immediately and carry over into the subsequent cycle. Continue dose reductions (max once per cycle) until no episodes of Grade 2 hyperglycemia are documented within the new cycle. If dose level -4 is reached and Grade 2 or higher hyperglycemia recurs, discontinue GSK2110183.
Grade 3 - >13.9-27.8 mmol/L	Check for ketoacidosis: If present, discontinue therapy and treat as for diabetic ketoacidosis. If no acidosis, hold drug and treat with oral hypoglycemics or insulin as needed. Monitor blood glucose daily (or more as per physician discretion). If no further grade 3 hyperglycemia recurs over 7 successive days of monitoring, GSK2110183 may be restarted at one dose level reduction. Repeat above instructions for recurrent Grade 3 hyperglycemia. If dose level -4 is reached and Grade 3 or higher hyperglycemia recurs, discontinue GSK2110183.
Grade 4 - >27.8 or acidosis	Discontinue GSK2110183

Table 3. Other specific toxicities:

Other specific toxicities	Intervention
Infection grade ≥1 or 2	Hold (interrupt dose). Follow weekly Categorize infection: If grade 1 or 2, resume when controlled at previous dose at the investigator's discretion.
Infection ≥ grade 3	If infection is grade 3, when it resolves to grade ≤1, restart therapy with 1 dose level reduction.
Diarrhea ≤ grade 2 (presumed secondary to drug – must rule out infectious causes)	Initiate loperamide 2mg po q2h while awake (max 16mg per 24 hour period). If diarrhea-free for >12 hours, discontinue loperamide. If diarrhea ≤ grade 2 recurs within the same cycle, hold (interrupt dose) and use loperamide as above. When diarrhea resolves to ≤ grade 1, drug may be resumed at a one dose level reduction.
Diarrhea ≥ grade 3 or associated with dehydration (presumed secondary to drug – must rule out infectious causes)	Hold (interrupt dose) for remainder of cycle and hydrate. If diarrhea resolves to ≤ grade 1**,** drug may be resumed with next cycle but at a one dose level reduction. If ≥ grade 3 diarrhea recurs, repeat above and reduce by one dose level again. If again ≥grade 3 diarrhea recurs, patient will be removed from study.

Dyspepsia ≤ grade 2	Initiate proton pump inhibitor or H2 blocker but proceed with current study drug dose. No dose reductions are required as long as symptoms resolve to ≤ grade 1. If dyspepsia ≤ grade 2 persists, decrease drug by one dose level. Continue with dose reductions if dyspepsia ≤ grade 2 persists. When symptoms resolve to ≤ grade 1, drug may be continued at the current dose level reduction.
Dyspepsia ≥ grade 3	Hold (interrupt dose) until symptoms are controlled. Add proton pump inhibitor or H2 blocker. When symptoms resolve to ≤ grade 1, drug may be resumed at a one dose level reduction.
Mucositis ≤ grade 2	Initiate bicarbonate mouthwashes and mycostatin mouthwash. If mucositis ≤ grade 2 persists, decrease drug by one dose level. Continue with dose reductions if mucositis ≤ grade 2 persists. When symptoms resolve to ≤ grade 1, drug may be continued at the current dose level reduction.
Mucositis ≥ grade 3	Hold (interrupt dose) until symptoms are controlled. Initiate bicarbonate mouthwashes and mycostatin mouthwash. When symptoms resolve to ≤ grade 1, drug may be resumed at a one dose level reduction.
Rash ≤ grade 2	Hold (interrupt dose) until rash has resolved to ≤grade 1, then resume previous dose. If ≤ grade 2 rash recurs, hold (interrupt dose) until rash has resolved to ≤grade 1, then resume dose at a one dose level reduction.
Rash grade 3	Hold (interrupt dose) for remainder of cycle. If rash has resolved to ≤grade 1, drug may be resumed at one dose level reduction. If grade 3 or higher rash recurs, patient will be removed from study.
Rash grade 4	Discontinue drug and patient will be removed from study.
Other non-hematologic toxicity assessed as study drug-related ≥ Grade 3	Hold dose and follow at least weekly. When toxicity resolves to ≤ **grade 2**, restart at next lower dose level.

Progressive Multifocal Leukoencephalopathy (PML)

Progressive multifocal leukoencephalopathy (PML) is a viral-induced demyelinating disease of the central nervous system usually occurring in the immunocompromised individual. JC virus infection resulting in PML and death has been reported in rituximab-treated subjects with hematologic malignancies or with systemic lupus erythematosus (SLE), an indication for which rituximab has not been approved. In the literature, PML has been reported to occur in 0.52% of CLL subjects and in approximately 5% of fludarabine-treated B-CLL subjects. One case of PML was reported in a very ill CLL subject treated with ofatumumab, previously treated with alemtuzumab and fludarabine and with very low CD4 cell count.

Investigators and nurses should pay careful attention for signs and symptoms consistent with a diagnosis of PML. Signs and symptoms of PML include visual disturbances, ocular movements, ataxia, and changes in mental status such as disorientation or confusion. These symptoms are not an exhaustive list and the investigator should exercise judgment in deciding to report signs and symptoms to sponsor promptly.

If a subject develops neurological signs or symptoms consistent with PML treatment should be halted and the subject referred to a neurologist for evaluation. At a minimum, blood JCV PCR and/or MRI will be performed and if either is positive perform Cerebrospinal Fluid (CSF) JCV PCR. If blood JCV PCR and MRI are negative, the investigator will contact the GSK for appropriate action to be taken. If blood JCV PCR and/or MRI are positive, the subject should proceed to the Follow-Up Period. All such subjects will be followed until resolution. Any subject with a diagnosis of PML will be withdrawn from ofatumumab. There are no known tests that can reliably determine who is at increased risk for developing PML. There are no known interventions that can reliably prevent PML or adequately treat PML if it occurs.

Hepatitis B Virus (HBV) reactivation

Hepatitis B Virus (HBV) reactivation can occur in patients receiving CD20-directed cytolytic antibodies, including ARZERRA (Ofatumumab), in some cases resulting in fulminant hepatitis, hepatic failure and death.

In patients who develop HBV reactivation while receiving ofatumumab, immediately discontinue ofatumumab and start appropriate treatment for HBV, discontinue any concomitant chemotherapy the patient is receiving until the HBV infection is controlled or resolved. Due to insufficient data, no recommendations can be made regarding the resumption of ofatumumab after resolution of HBV in patients who develop HBV reactivation.

The risk of HBV infection and hepatitis can occur in patients who have not been previously exposed to HBV.

5.5.5 Treatment compliance

At all times, when dispensing protocol therapy, the study coordinator will review the instructions with subjects. Subjects will be asked to maintain a diary to record the drug administration. Subjects will be asked to bring any unused drug and empty drug containers to the clinic at their next visit.

Research personnel will count and record the number of used and unused drug at each visit and reconcile with the patient diary.

5.6 Concomitant therapy

5.6.1 Recommended concomitant therapy

Subjects should receive full supportive care, including transfusions of blood and blood products, antibiotics, hematopoietic growth factors, and antiemetics when appropriate. All patients will take allopurinol 300mg PO daily beginning at least 3 days before the start of GSK2110183 Lead-in Phase and continuing through 14 days of Cycle 1 on the Treatment Phase (minimum 27 days) for tumor lysis syndrome (TLS) prophylaxis. Subjects should be instructed to maintain adequate hydration and maintain urinary output as an additional measure to prevent TLS. Based on a patient's reaction and laboratory parameters, TLS prophylaxis may be continued or restarted as needed at the Investigator's discretion.

5.6.2 Prohibited concomitant therapy

Concomitant use of other anti-cancer therapies, including radiation, or other investigational agents is not permitted while subjects are receiving protocol therapy. In addition, GSK2110183 inhibits multiple cytochrome P450 (CYP) enzymes in vitro with CYP3A4 and CYP2C8 showing the lowest IC50's. GSK2110183 shows metabolism dependent inhibition of CYP3A4 and induced CYP3A4 in cultured human hepatocytes and GSK2110183 inhibits the human uptake transporter OATP1B1, as well as the human efflux transporter BCRP. As a result, other medications that may interact with GSK2110183 are prohibited or should be used with caution are outlined in Appendix 2.

5.6.3. Meals and Dietary Restrictions

On all blood sampling days, subjects will fast for at least eight hours prior to the blood draw for fasting glucose testing and other blood tests as required by Schedule of study events. Fasting will consist of avoiding the oral ingestion of calorie – containing products; however, ingestion of water and other non-caloric beverages is permitted.

Patients should fast 1 hr. before and 2 hrs. after each GSK2110183 dose. In addition, subjects shall abstain from ingestion of any food or drink containing grapefruit and grapefruit juice, Seville

oranges, or pommelos within 7 days prior to the first dose of GSK2110183 until the end of the study.

5.7 Discontinuation of Study Treatment

Treatment will continue until to a maximum of 18 cycles (months) or the occurrence of any of the following events.

- Disease progression (see Appendix 5 for IWCLL Response Criteria). If a study patient meets progressive disease criteria, study meds may be continued at investigator's discretion and after approval from the Study Medical Monitor, if it benefits the study patient.
- Adverse event(s) that, in the judgment of the Investigator, may cause severe or permanent harm or which rule out continuation of the treatment regimen (see Section 6.1)
- Major violation of the study protocol.
- Withdrawal of consent
- Lost to follow up
- Death

5.7.1 Stopping Safety Criteria

5.7.1.1 Liver Chemistry Stopping Criteria

Liver chemistry threshold stopping criteria have been designed to assure subject safety and to evaluate liver event etiology during administration of investigational product and the follow-up period. The sponsor-investigator is to review all events which meet liver chemistry stopping criteria to determine if the event was due to;

- tumor lysis, disease related liver involvement
- concomitant chemotherapy
- other identified cause and to exclude drug induced liver injury (DILI) due to Ofatumumab

The criteria are relevant for all Ofatumumab studies because transient elevations in LFTs may be due to tumor lysis which is of clinical benefit, disease related liver involvement or due to other chemotherapy rather than drug induced liver injury from Ofatumumab. If the event is determined to be due to causes other than Ofatumumab DILI and improvement is observed after withdrawal of

Ofatumumab, rechallenge may be attempted if deemed appropriate by the sponsor-investigator and in addition to consent of the subject.

Investigational product will be stopped if any of the following liver chemistry stopping criteria is met:

1. ALT ≥8xULN
2. ALT ≥5xULN for more than 2 weeks
3. ALT ≥3xULN and bilirubin ≥2xULN (>35% direct bilirubin, bilirubin fractionation required‡)

‡ **NOTE:** *If serum bilirubin fractionation not immediately available, study drug should be discontinued if ALT > 3xULN and bilirubin >2xULN. Serum bilirubin fractionation should be performed if testing is available. If testing unavailable, record presence of detectable urinary bilirubin on dipstick, indicating direct bilirubin elevations and suggesting liver injury*.

When any of the liver chemistry stopping criteria is met, do the following:

- Immediately stop study treatment
- Hold Ofatumumab for two weeks, repeat liver chemistry testing at least twice weekly, and report to sponsor-investigator to discuss the possibility of re-challenging with Ofatumumab. *Note: The 2 week time point for stopping medication was chosen because it will distinguish from LFT elevations due to tumor lysis which should have resolved within this time period. Medication is interrupted and it is a clinical and patient decision if Ofatumumab may be re-started. The risk: benefit ratio is different in an oncology setting and an efficacious therapy may be life-saving.*

- Report SAE to GSK within 24 hours
    - All events of ALT > 3xULN **and** bilirubin > 2xULN (>35% direct bilirubin) (or ALT>3xULN and INR>1.5, if INR measured; INR measurement is not required and the threshold value stated will not apply to subjects receiving anticoagulants), termed 'Hy's Law', **must be reported as an SAE (excluding studies of hepatic impairment or cirrhosis)**.
    - NOTE: if serum bilirubin fractionation is not immediately available, study treatment should be discontinued if ALT > 3xULN **and** bilirubin > 2xULN. Serum bilirubin

fractionation should be performed if testing is available. If testing is unavailable, **record presence of detectable urinary bilirubin on dipstick**, indicating direct bilirubin elevations and suggesting liver injury.

Liver chemistry follow-up assessments are to be followed until liver chemistries resolve, stabilize or return to baseline values.

Liver Chemistry Follow-up Assessments; (these chemistry tests/ assessments below are to be performed at the time of the event and then continued and/or discontinued at the discretion/judgment of the sponsor-investigator; please refer to stopping criteria within this document below)

Viral hepatitis serology including:

- *Hepatitis A IgM antibody;*
- *Hepatitis B surface antigen and Hepatitis B Core Antibody (IgM);*
- *Hepatitis C RNA;*
- *Cytomegalovirus IgM antibody;*
- *Epstein-Barr viral capsid antigen IgM antibody (or if unavailable, obtain heterophile antibody or monospot testing);*
- *Hepatitis E IgM antibody*

- Serum creatine phosphokinase (CPK) and lactate dehydrogenase (LDH)
- Fractionate bilirubin, if total bilirubin >2xULN
- Obtain complete blood count with differential to assess eosinophilia
- Record the appearance or worsening clinical symptoms of hepatitis, or hypersensitivity, fatigue, decreased appetite, nausea, vomiting, abdominal pain, jaundice, fever, or rash
- Record use of concomitant medications, acetaminophen, herbal remedies, other over the counter medications, or putative hepatotoxins
- Increased alcohol use

The following assessments are required for subjects with ALT >3xULN and bilirubin >2xULN (.35% direct) but are optional for other abnormal liver chemistries:

- Anti-nuclear antibody, anti-smooth muscle antibody, and Type 1 anti-liver kidney microsomal antibodies
- Liver imaging (ultrasound, magnetic resonance, or computerized tomography) to evaluate liver disease.

Stopping Criteria:

- For subject meeting liver stopping criteria 1:
    - A repeat of liver chemistries within 24 hours, liver event follow-up assessments and close monitoring
    - A specialist or hepatology consultation is recommended
    - Monitor subjects twice weekly until liver chemistries (ALT, AST, alkaline phosphatase, bilirubin) resolve, stabilize or return to within baseline values.
- For subjects meeting criteria 2 or 3:
    - A repeat of liver chemistries within 24 to 72 hours for repeat liver chemistries and liver event follow-up assessments
    - Monitor subjects weekly until liver chemistries (ALT, AST, alkaline phosphatase, bilirubin) resolve, stabilize or return to within baseline values
- After holding Ofatumumab for two weeks:
    - If the treatment is exhibiting efficacy **and** the subject wants to continue therapy after being informed of the results of liver chemistry testing, then the Ofatumumab may be re-started.
    - Liver chemistries and follow-up assessments should be monitored at a minimum of every 2 weeks until resolution, stabilization, or a return to baseline values, at which point monitoring should be continued per protocol
- Subjects with ALT >3xULN **but** <5xULN **and** bilirubin <2xULN without hepatitis symptoms or rash, and who may be monitored weekly for at least 4 weeks, then the following actions should be taken:
    - Subjects can continue Ofatumumab

- Weekly repeat of liver chemistries until they resolve, stabilize, or return to baseline values, then monitor liver chemistries as per protocol assessment schedule

If at any time the subject meets any of the liver chemistry stopping criteria, then proceed as described above

If after 4 weeks of monitoring, ALT<3xULN and bilirubin<2xULN monitor twice monthly until liver chemistries normalize or return to within baseline values

5.7.1.2 QTc Withdrawal Criteria

A subject that meets the criteria below will be withdrawn from the study.

- QTcB or QTcF > 500 msec or uncorrected QT >600msec (machine or manual overread)
- If subject has bundle branch block then criteria is QTcB or QTcF > 530 msec

These criteria are based on an average QTc value of triplicate ECGs. If an ECG demonstrates a prolonged QT interval, obtain 2 more ECGs over a brief period, and then use the averaged QTc values of the 3 ECGs to determine whether the subject should be discontinued from the study.

5.8 Follow-Up

At treatment discontinuation, subjects will undergo a safety assessment approximately 28 days (+/- 4 days) post the last dose of protocol therapy. Thereafter, follow-up will be required every three months until next therapy, relapse or death, whichever comes first (see off study evaluations per the Schedule of Assessments, Section 2).

6 Adverse events

6.1 Adverse Events:

Any untoward medical occurrence in a subject or clinical investigation subject, temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

Events meeting the definition of an AE include:

- Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments e.g., ECGs, radiological scans, vital signs measurements), including those that worsen from baseline, and felt to be clinically significant in the medical and scientific judgment of the investigator

- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition
- New conditions detected or diagnosed after investigational product administration even though it may have been present prior to the start of the study
- Signs, symptoms, or the clinical sequelae of a suspected interaction
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either investigational product or a concomitant medication (overdose per se will not be reported as an AE/SAE)

"Lack of efficacy" or "failure of expected pharmacological action" per se will not be reported as an AE or SAE. However, the signs and symptoms and/or clinical sequelae resulting from lack of efficacy will be reported if they fulfill the definition of an AE or SAE.

Events that **do not** meet the definition of an AE include:

- Any clinically significant abnormal laboratory finding or other abnormal safety assessments that is associated with the underlying disease, unless judged by the investigator to be more severe than expected for the subject's condition.
- The disease/disorder being studied, or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the subject's condition
- Medical or surgical procedure (e.g., endoscopy, appendectomy); the condition that leads to the procedure is an AE
- Situations where an untoward medical occurrence did not occur (social and/or convenience admission to a hospital)
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen
- B cell depletion and hypogammaglobulinemia due to ofatumumab treatment

6.2 Serious Adverse Event (SAE) Definition

A serious adverse event is one that at any dose (including overdose):

- Results in death
- Is life-threatening[1]

- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability or incapacity[2]
- Is a congenital anomaly or birth defect
- Is an important medical event[3]

[1]"Life-threatening" means that the subject was at immediate risk of death at the time of the serious adverse event; it does not refer to a serious adverse event that hypothetically might have caused death if it were more severe.

[2]"Persistent or significant disability or incapacity" means that there is a substantial disruption of a person's ability to carry out normal life functions.

[3]Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in situations where none of the outcomes listed above occurred. Important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition above should also usually be considered serious. Examples of such events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse. A new diagnosis of cancer during the course of a treatment should be considered as medically important.

NOTE: Pregnancies must be reported to GSK; however are not to be reported as SAEs unless they meet serious criteria.

6.3 Adverse Drug Reaction Reporting

Toxicity will be scored using CTCAE Version 4.03 for toxicity and adverse event reporting (Appendix 4). A copy of the CTCAE Version 4.03 can be downloaded from the CTEP homepage (HTTP://CTEP.INFO.NIH.GOV). All appropriate treatment areas should have access to a copy of the CTCAE Version 4.03. All adverse clinical experiences, whether observed by the investigator or reported by the patient, must be recorded, with details about the duration and intensity of each episode, the action taken with respect to the test drug, and the patient's outcome. The investigator must evaluate each adverse experience for its relationship to the test drug and for its seriousness.

6.3.1 Laboratory and Other Safety Assessment Abnormalities Reported as AEs and SAEs

- Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., ECGs, radiological scans, vital signs measurements), including those that worsen from baseline, and felt to be clinically significant in the medical and scientific judgment of the investigator **are** to be recorded as AEs or SAEs.

- All events meeting liver stopping criteria must be recorded as an SAE.

- However, any clinically significant safety assessments that are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the subject's condition, are **not** to be reported as AEs or SAEs.

- B cell depletion, IgG below LLN, low CD19+ count, and hypogammaglobulinemia due to treatment with ofatumumab are **not** to be reported as AEs or SAEs.

- Infusion related AEs may lead to a prolonged infusion time. Overnight stay at the hospital due to slow infusion rate is **not** to be reported as a SAE.

The investigator must appraise all abnormal laboratory results for their clinical significance. If any abnormal laboratory result is considered clinically significant, the investigator must provide details about the action taken with respect to the test drug and about the patient's outcome.

6.3.2 Disease-Related Events and/or Disease-Related Outcomes Not Qualifying as SAEs

An event which is part of the natural course of the disease under study (i.e., disease progression) does not need to be reported as an SAE. However, if the progression of the underlying disease is greater than that which would normally be expected for the subject, or if the investigator considers that there was a causal relationship between treatment with investigational product or protocol design/procedures and the disease progression, then this must be reported as an SAE.

6.4 Investigator Reporting Responsibilities

The conduct of the study will comply with all Health Canada safety reporting requirements.

CTA Annual Reports

Annual Clinical Trial Application reports, under the old Health Canada regulatory framework, have been replaced by the annual updated Investigator's Brochure. Updated Investigator's Brochures, including all safety information and global status should be submitted annually. Additional information and any changes that have been incorporated in the updated Investigator's

Brochure should be highlighted for ease of review and evaluation. If an Investigator's Brochure is updated more frequently, it should be submitted as required.

All adverse experience reports must include the patient study number, age, sex, weight, severity of reaction (mild, moderate, severe), relationship to drug (probably related, doubtful relationship, definitely not related), date and time of administration of test medications and all concomitant medications and medical treatment provided. The investigator is responsible for evaluating all adverse events to determine whether criteria for "serious" and as defined above are present. The investigator is responsible for reporting adverse events to GSK as described below.

6.4.1 Expedited reporting by investigator to GlaxoSmithKline Inc.

Serious adverse events (SAE) are defined above. The investigator must inform GSK in writing of any SAE within 24 hours of being aware of the event. The date of awareness should be noted on the report. The written report must be completed and supplied to GSK by facsimile within 24 hours/1 business day at the latest on the following working day.

All SAEs regardless of relationship to investigational product will be collected from the first dose of investigational product up to a minimum of 6 months after the last dose of investigational product or until the end of the follow-up period whichever is longer. All SAEs regardless of causality will be collected until the end of the follow-up period. SAEs are no longer required to be reported if a subject begins treatment with another therapy.

From the time a subject consents to participate in and completes the study all SAEs assessed **as related to study participation** (e.g., protocol-mandated procedures, invasive tests, or change in existing therapy) or **related to GSK concomitant medication**, will be reported promptly to GSK.

Any SAE brought to the investigator's attention after the subject has completed the study and considered by the investigator as possibly related to investigational product must be reported to GSK.

The initial report must be as complete as possible, including details of the current illness and (serious) adverse event, and an assessment of the causal relationship between the event and the investigational product(s). Information not available at the time of the initial report (e.g., an end date for the adverse event or laboratory values received after the report) must be documented on a follow-

up report. A final report to document resolution of the SAE is required. GSK numbers for SAE reporting: Tel: 905-819-3057 Fax: 1-866-903-4718;
email: (Patricia Lavorata) patricia.x.lavorata@gsk.com.

In addition, the investigator or designated person will provide a brief safety update by email or telephone every 2 weeks to GSK for the duration during which study drug(s) are administered.

Pregnancy

Any pregnancy that occurs during study participation must be reported to GSK. To ensure subject safety, each pregnancy must be reported to GSK within 2 weeks of learning of its occurrence. The pregnancy must be followed up to determine outcome (including premature termination) and status of mother and child. Pregnancy complications and elective terminations for medical reasons must be reported as an AE or SAE. Spontaneous abortions must be reported as an SAE.

Any SAE occurring in association with a pregnancy, brought to the investigator's attention after the subject has completed the study and considered by the investigator as possibly related to the investigational product, must be promptly reported to GSK.

In addition, the investigator must attempt to collect pregnancy information on any female partners of male study subjects who become pregnant while the subject is enrolled in the study. Pregnancy information must be reported to GSK as described above.

6.4.2 Report of Adverse Events to the Institutional Review Board

The Principal Investigator is required to notify his/her Institutional Review Board (IRB) of a serious adverse event according to institutional policy.

6.4.3 Investigator Reporting to Health Canada

For drugs used in ***clinical trials in Canada***, only adverse drug reactions (ADRs) that are *both serious and unexpected* are subject to expedited reporting to Health Canada. Expedited reporting of reactions, which are serious but expected, is not required. Expedited reporting is not required for serious events from clinical investigations that are considered unrelated to the study product, whether or not the event is expected.

During a clinical trial the sponsor is required to inform Health Canada of any serious, unexpected adverse drug reaction that has occurred inside or outside Canada. ADR report must be filed in the cases:

- where the ADR is neither fatal nor life-threatening, within 15 days after becoming aware of the information
- where it is fatal or life-threatening, immediately where possible and, in any event, within 7 days after becoming aware of the information
- within 8 days after having informed Health Canada of the ADR, submit as complete as possible, a report which includes an assessment of the importance and implication of any findings

Each ADR which is subject to expedited reporting should be reported individually in accordance with the Health Canada / ICH Guidance Document E2A: Clinical Safety Data Management: Definitions and Standards for Expedited Reporting.

Ongoing safety information respecting a drug should be conveyed to Investigator(s) and their Research Ethics Board(s). For further information refer to the Health Canada / ICH Guidance Documents E6: Guideline for Good Clinical Practice and E2A: Clinical Safety Data Management: Definitions and Standards for Expedited Reporting.

How to file an ADR report to Health Canada:

A completed ADR Expedited Reporting Summary Form should be attached to the front of the completed ADR report (suggested ADR report format: Suspect Adverse Reaction Report - CIOMS form of the Council for International Organizations of Medical Sciences (CIOMS)).

The report should be submitted by fax to the appropriate Directorate.

6.5 Adverse event updates/IND safety reports

GSK shall notify the Investigator via an IND Safety Report of the following information:

- Any AE associated with the use of drug in this study or in other studies that is both serious and unexpected.
- Any finding from tests in laboratory animals that suggests a significant risk for human subjects including reports of mutagenicity, teratogenicity, or carcinogenicity.

The Investigator shall notify his/her IRB/EC promptly of these new serious and unexpected AE(s) or significant risks to subjects.

7 Response Assessment

Baseline lesion assessments must occur within ≤ 28 days of protocol therapy initiation or as indicated in Section 2, Schedule of Study Assessments. All patients will undergo baseline imaging with CT scans of neck, chest, abdomen and pelvis.

Efficacy assessments are scheduled to occur every 4 weeks (beginning of each cycle). Response and progression will be evaluated in this study using the 2008 IWCLL criteria for response in CLL **(Appendix 5**). Radiological methodologies, techniques and/or physical examination, established at baseline, for the assessment and measurement of each identified lesion must be used for all subsequent assessments. Repeat CT scanning will be required in patients with baseline CT abnormalities in order to confirm CR only and at study discontinuation.

8 Protocol Amendments/Deviations

8.1 Protocol amendments

Any amendment to this protocol must be agreed to by the Principal Investigator and reviewed by GSK. Written verification of IRB/EC approval will be obtained before any amendment is implemented.

8.2 Protocol deviations

When an emergency occurs that requires a deviation from the protocol for a subject, a deviation will be made only for that subject. A decision will be made as soon as possible to determine whether or not the subject (for whom the deviation from protocol was effected) is to continue in the study. The subject's medical records will completely describe the deviation from the protocol and state the reasons for such deviation. In addition, the Investigator will notify the IRB/EC/Health Canada in writing of such deviation from protocol.

Non-emergency minor deviations from the protocol will be permitted with approval of the Principal Investigator.

9 Data Management

9.1 Analyses and Reporting

Data will be analyzed and reported after accrual has been completed. All subsequent data collected will be analyzed and reported in a follow-up clinical report.

9.2 Data Monitoring Committee

The Data Safety Monitoring Board (DSMB) at Princess Margaret Cancer Centre will be composed of medical and statistical independent reviewers and will meet to review the efficacy and safety data and determine a risk/benefit analysis in this subject population. The purpose of the DSMB is to advise on serious safety considerations, lack of efficacy and any other considerations within the charge to the Committee. The DSMB may request additional meetings or safety reports as deemed necessary upon discussion with GSK and its representatives. The DSMB may stop the study following review of results from any report.

9.3 Study auditing

9.3.1 Investigator responsibilities

Investigator responsibilities are set out in the ICH guideline for Good Clinical Practice (GCP) and in accordance with the rules and regulations of Health Canada's Therapeutic Products Directorate.

Investigators or a designated member of the Investigator's staff must enter study data onto CRFs or other data collection system. The Investigator will permit study-related audits by IRB/EC review, and regulatory inspection(s) (e.g., Health Canada, FDA, EMEA, TPP), providing direct access to the facilities where the study took place, to source documents, to CRFs, or other data collection system to all other study related documents.

The Investigator, or a designated member of the Investigator's staff, must be available at some time during audits to review data and resolve any queries and to allow direct access to the subject's records (e.g., medical records, office charts, hospital charts, and study related charts) for source data verification.

10 Biostatistical Analysis

10.1 Overview

This is a phase II study to investigate the efficacy of ofatumumab in combination with oral GSK2110183 in patients with relapsed or refractory CLL. The protocol will accrue 31 response evaluable patients.

10.2 Endpoints

The primary and secondary objectives will be evaluated by analysis of efficacy endpoints (response rates, response duration), progression-free and overall survival, and toxicity.

Evaluable for toxicity - All patients will be evaluable for toxicity from the time of their first dose of GSK2110183. After 6 subjects have completed cycle 1 of the Treatment Phase (on combination ofatumumab and GSK2110183), an analysis to assess safety and tolerability will be conducted.

Evaluable for response - All patients who have received at least 1 dose of GSK2110183 during the initial Lead-in Phase will be considered evaluable for response. Duration of Response (DOR) is defined, for the subset of patients with a CR or PR, as the time from first documented evidence of CR or PR until first documented disease progression or death due to any cause. If sample size permits, duration of response will be summarized descriptively using Kaplan-Meier medians and quartiles. Only the subset of patients who show a CR or PR will be included.

Evaluable for survival - All patients will be evaluable for survival. Overall survival is defined as the length of time between the date of first dose of study treatment (GSK2110183) and death due to any cause. Progression Free Survival (PFS) is defined as the length of time between the date of first dose of study treatment (GSK2110183) and the earliest date of disease progression or death due to any cause. If the patient does not have a documented date of progression or death, then PFS will be censored at the date of last adequate assessment. For a patient who is alive at the time of the statistical analysis, the patient will be considered censored at the last date of known contact.

10.3 Statistical Methodology

10.3.1 Study Design

This is a single-stage phase 2 study evaluating the efficacy of combination ofatumumab and GSK 2110183. The protocol will accrue 31 response-evaluable patients. Patients who have received at least one dose of GSK2110183 will be evaluable for safety and response.

10.3.2 Sample Size, Significance Level and Power

In the pivotal trial of single-agent ofatumumab in fludarabine-refractory CLL which led to FDA approval (Wierda et al, 2010), the overall response rate in the BF-ref cohort which is used as the historical comparator for our current study population, was 47% (0.470). The proposed study will accrue 31 subjects in the sample size to decide whether the proportion responding, P, is less than or equal to 0.470 or greater than or equal to 0.670, a 20% increase in response rate. A 20% increase in response rate is generally considered a clinically significant change. If the number of responses is 19 or more, the hypothesis that $P \leq 0.470$ is rejected with a target error rate (α error) of 0.10 and an actual error rate of 0.079. If the number of responses is 18 or less, the hypothesis that $P \geq 0.670$ is rejected with a target error rate of 0.20 and an actual error rate of 0.192. Therefore, the significance level (i.e., the probability of rejecting H_o when it is true) is 0.10.

10.3.3 Statistical Analysis

Univariate analysis of response predictors will be performed using Fisher's exact test and Wilcoxon rank-sum test. Response predictors to be evaluated will include age, abnormal baseline serum laboratory values (e.g. LDH, beta-2 microglobulin, albumin, direct antiglobulin test, hemoglobin, lymphocytes, neutrophils, platelets, creatinine, ZAP70, CD38), clinical features (bulky adenopathy, organomegaly, RAI stage), disease status (relapsed or refractory), number of prior lines of therapy (1,2, vs 3 or more), FISH cytogenetics (17p/11q deletion vs none), IgVH status (mutated versus unmutated). Survival will be calculated using the Kaplan-Meier method. Statistical analyses will be applied using SAS 9.2.

10.4 Safety evaluation

Data from all subjects who receive any protocol therapy will be included in the safety analyses. Subjects who entered the study and did not receive any protocol therapy and had this confirmed, will not be evaluated for safety. Severity of adverse events will be graded by NCI Common Terminology criteria version 4.03. SAEs will be reported at a minimum of up to 6 months after the last dose or to the end of the follow-up period whichever is longer. If a subject starts other therapy, then SAEs will

no longer be required to be reported. Note: Causality must be assessed for each study drug separately. SAE forms used must allow for attribution for each study drug to be documented separately. A formal review of safety data after the first 6 patients have completed cycle 1 of the Treatment Phase will be performed before continuing accrual.

10.5 Patient Accrual and Study Duration

Accrual for this study is expected to be about 2 patients per month. Thus, patient accrual is expected to be complete within 18-24 months. Additional time will be required to allow the response data to mature.

All patients registered in the study will be accounted for. The number of patients who die or withdraw before treatment begins will be specified. The distribution of follow-up times will be described and the number of patients lost to follow-up will be given.

11 Regulatory Considerations

11.1 Institutional Review Board/Ethics Committee approval

The protocol for this study has been designed in accordance with the general ethical principles outlined in the Declaration of Helsinki. The review of this protocol by the IRB/EC and the performance of all aspects of the study, including the methods used for obtaining informed consent, must also be in accordance with principles enunciated in the declaration, as well as ICH Guidelines, Tri-Council Policy Statement on Ethical Conduct of Research Involving Humans (TCPS) and Part C Division 5 of the Food and Drug Regulations of Health Canada.

The Investigator will be responsible for preparing documents for submission to the relevant IRB/EC and obtaining written approval for this study. The approval will be obtained prior to the initiation of the study.

The approval for both the protocol and informed consent must specify the date of approval, protocol number and version, or amendment number.

Any amendments to the protocol after receipt of IRB/EC approval must be submitted by the Investigator to the IRB/EC for approval. The Investigator is also responsible for notifying the

IRB/EC of any serious deviations from the protocol, or anything else that may involve added risk to subjects.

Any advertisements used to recruit subjects for the study must be reviewed and approved by the IRB/EC prior to use.

11.2 Informed consent

The Investigator must obtain informed consent of a subject or his/her designee prior to any study related procedures as per GCPs as set forth in the TCPS and ICH guidelines.

Documentation that informed consent occurred prior to the subject's entry into the study and the informed consent process should be recorded in the subject's source documents. The original consent form signed and dated by the subject and by the person consenting the subject prior to the subject's entry into the study, must be maintained in the Investigator's study files.

11.3 Study records requirements

The Investigator must ensure that the records and documents pertaining to the conduct of the study and the distribution of the protocol therapy, that is copies of CRFs or other data collection system and source documents (original documents, data, and records [e.g., hospital records; clinical and office charts; laboratory notes; memoranda; subject's diaries or evaluation checklists; SAE reports, pharmacy dispensing records; recorded data from automated instruments; copies or transcriptions certified after verification as being accurate copies; microfiches; photographic negatives, microfilm, or magnetic media; x-rays; subject files; and records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the clinical study; documents regarding subject treatment and drug accountability; original signed informed consents, etc.]) be retained by the Investigator for as long as needed to comply with national and international regulations (generally 2 years after discontinuing clinical development or after the last marketing approval). In Canada records relating to clinical trials must be maintained for 30 years. These records must be made available to Health Canada within 2 days if there is a risk to the health of trial subjects, otherwise they must be made available within 7 days of a request from Health Canada.

The Investigator agrees to adhere to the document/records retention procedures by signing the protocol.

11.4 Premature discontinuation of study

The Principal Investigator, institution and GSK have the right to discontinue this study at any time for reasonable medical or administrative reasons. Possible reasons for termination of the study could be but are not limited to:

- Unsatisfactory enrollment with respect to quantity or quality.
- Inaccurate or incomplete data collection.
- Falsification of records.
- Failure to adhere to the study protocol.

Any possible premature discontinuation would be documented adequately with reasons being stated, and information would have to be issued according to local requirements (e.g., IRB/EC, regulatory authorities, etc.).

12 References

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Longo P, Laurenti L, Gobessi S, et al. The Akt signaling pathway determines the different proliferative capacity of chronic lymphocytic leukemia B-cells from patients with progressive and stable disease. Leukemia 2007;21:110-120.

Shehata M, Schnabl S, Demirtas D, et al. Reconstitution of PTEN activity by CK2 inhibitors and interference with the PI3-K/Akt cascade counteract the antiapoptotic effect of human stromal cells in chronic lymphocytic leukemia. Blood 116:2513-2521, 2010.

Teeling, J. L., et al. The Biological Activity of Human CD20 Monoclonal Antibodies Is Linked to Unique Epitopes on CD20. *J Immunol*. 2006;177:362-371.

Wierda W, Kipps T, Mayer J, et al: Ofatumumab as single-agent CD20 immunotherapy in fludarabine-refractory chronic lymphocytic leukemia. J Clin Oncol 28:1749-1755, 2010.

13 Appendices

Appendix 1: IWCLL Diagnostic Criteria for CLL 2008

(Hallek et al. Blood 2008;111:5446)

The diagnosis of B-CLL must have been made at some point in the past, prior to study entry. **All** of the following criteria must have been satisfied at the time of diagnosis:

- Persistent B lymphocytosis of ≥ 5 $x10^9$/L for the duration of at least 3 months. Morphologically, the lymphocytes must appear mature.
- Lymphocyte immunophenotyping shows the presence of B-cell markers CD19, CD20, CD23 with CD5 antigen (and absence of other pan-T cell markers)
- The B cell is monoclonal with regards to kappa or lambda light chain restriction

Greater than 55% prolymphocytes and/or 15 $x10^9$/L absolute prolymphocytes in the peripheral blood establishes a diagnosis of prolymphocytic leukemia and would be deemed ineligible for this study.

A bone marrow aspirate/biopsy is not necessary for the diagnosis of B-CLL but if done for diagnostic purposes.

Appendix 2. Drugs potentially affected by GSK2110183*

PROHIBITED DRUGS WHILE ON STUDY

CYP3A Substrate	Therapeutic Area
carbamazepine	Anticonvulsants
ergotamine, dihydroergotamine	Antimigraine
clarithromycin,	Antimicrobials
pimozide	Antipsychotics
amprenavir, atazanavir, indinavir, lopinavir, ritonavir, saquinavir	Antivirals
amiodarone, disopyramide, quinidine, bosentan	Cardiovascular Agents
cyclosporine, everolimus, sirolimus, tacrolimus	Immunosuppressive Agents
OAT1B1 Substrate	**Therapeutic Area**
caspofugin	Antifungal
atrasentan, methotrexate	Anti-cancer
BCRP Substrate	**Therapeutic Area**
topotecan	Anti-cancer

USE WITH CAUTION WHILE ON STUDY

CYP3A Substrate	Therapeutic Area
fentanyl,	Analgesics
alfentanil, ropivacaine	Anesthetics
losartan	Angiotensin II Inhibitors
ethosuxamide, trimethadione	Anticonvulsants
buspirone, roboxetine, sertraline, trazadone, venlafaxine	Antidepressants and Anxiolytics
emadastine, loratadine	Antihistamines
artemether, halofantrine, lumefantrine, quinine	Antimalarial
erythromycin, clindamycin, rifabutin, rifampin	Antimicrobials
eletriptan	Antimigraine
-dihydroergocriptine, bromocriptine	Antiparkinsonians
aripiprazole, bromperidol, clozapine, haloperidol, quetiapine	Antipsychotics
oxybutynin, tolterodine	Antispasmodics
bosentan, delavirdine, tipranavir, nelfinavir, amprenavir, atazanavir, delaviridine, efavirenz, fosamprenavir, indinavir, lopinavir, nelfinavir, nevirapine, ritonavir, saquinavir	Antivirals
amlodipine, barnidipine, diltiazem, dofetilide, eplerenone, felodipine, nifedipine, pranidipine, propafenone, verapamil, vesnarinone	Cardiovascular Agents
sildenafil, tadalafil, vardenafil	Erectile dysfunction treatments
aprepitant, lansoprazole	Gastrointestinal Agents
atorvastatin, lovastatin, simvastatin	HMG CoA reductase inhibitors
alprazolam, chlordiazepoxide, diazepam, flunitrazepam, midazolam, propofol, triazolam, zolipidem, zopiclone	Hypnotics and Sedatives

Appendix 2. Drugs potentially affected by GSK2110183*

PROHIBITED DRUGS WHILE ON STUDY

CYP3A Substrate	Therapeutic Area
carbamazepine	Anticonvulsants
ergotamine, dihydroergotamine	Antimigraine
clarithromycin,	Antimicrobials
pimozide	Antipsychotics
amprenavir, atazanavir, indinavir, lopinavir, ritonavir, saquinavir	Antivirals
amiodarone, disopyramide, quinidine, bosentan	Cardiovascular Agents
cyclosporine, everolimus, sirolimus, tacrolimus	Immunosuppressive Agents
OAT1B1 Substrate	**Therapeutic Area**
caspofugin	Antifungal
atrasentan, methotrexate	Anti-cancer
BCRP Substrate	**Therapeutic Area**
topotecan	Anti-cancer

USE WITH CAUTION WHILE ON STUDY

CYP3A Substrate	Therapeutic Area
fentanyl,	Analgesics
alfentanil, ropivacaine	Anesthetics
losartan	Angiotensin II Inhibitors
ethosuxamide, trimethadione	Anticonvulsants
buspirone, roboxetine, sertraline, trazadone, venlafaxine	Antidepressants and Anxiolytics
emadastine, loratadine	Antihistamines
artemether, halofantrine, lumefantrine, quinine	Antimalarial
erythromycin, clindamycin, rifabutin, rifampin	Antimicrobials
eletriptan	Antimigraine
□-dihydroergocriptine, bromocriptine	Antiparkinsonians
aripiprazole, bromperidol, clozapine, haloperidol, quetiapine	Antipsychotics
oxybutynin, tolterodine	Antispasmodics
bosentan, delavirdine, tipranavir, nelfinavir, amprenavir, atazanavir, delaviridine, efavirenz, fosamprenavir, indinavir, lopinavir, nelfinavir, nevirapine, ritonavir, saquinavir	Antivirals
amlodipine, barnidipine, diltiazem, dofetilide, eplerenone, felodipine, nifedipine, pranidipine, propafenone, verapamil, vesnarinone	Cardiovascular Agents
sildenafil, tadalafil, vardenafil	Erectile dysfunction treatments
aprepitant, lansoprazole	Gastrointestinal Agents
atorvastatin, lovastatin, simvastatin	HMG CoA reductase inhibitors
alprazolam, chlordiazepoxide, diazepam, flunitrazepam, midazolam, propofol, triazolam, zolipidem, zopiclone	Hypnotics and Sedatives

CYP3A Substrate	Therapeutic Area
pioglitazone, repaglinide, rosiglitazone	Hypoglycemic Agents
temsirolimus	Immunosuppressive Agents
tretinoin	Retanoids
CYP2C8 Substrate	**Therapeutic Area**
repaglinide	Hypoglycemic Agents
OATP Substrate	**Therapeutic Area**
atorvastatin, cerovastatom, fluvastatin, pravastatin, simvastatin, rosuvastatin	HMG CoA reductase inhibitors[2]

1. Please note some drugs may be listed more than once. This is due to the fact that they are substrates for both CYP and a transporter (e.g., OATP1B1, BCRP).
2. If patients are on a high dose of a HMG CoA reductase inhibitor, dose reduction should be considered. Monitoring for toxicities (such as rhabdomyolysis) should be considered.

USE WITH CAUTION WHILE ON STUDY

Other Drugs that could affect GSK2110183	Therapeutic Area
quinidine	Antiarrhythmics
fluvoxamine, fluoxetine, nefazodone, paroxetine	Antidepressants
fluconazole, itraconazole, ketoconazole, terbinafine, voriconazole	Antifungals
ciprofloxacin, clarithromycin, erythromycin, isoniazid, rifamycin class agents (e.g., rifampin, rifabutin, rifapentine), telithromycin, troleandomycin	Anti-infectives
amprenavir, atazanavir, delaviridine, efavirenz, fosamprenavir, indinavir, lopinavir, nelfinavir, nevirapine, ritonavir, saquinavir	Antivirals
phenobarbital, oxandrolone, tizanidine, gemfibrozil	Miscellaneous

* A copy of this information to be given to the study participants.

Appendix 3 – ECOG Performance Status Scale

SCORE	DESCRIPTION
0	Fully active, able to carry on all pre-disease performance without restriction.
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work.
2	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	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead.

Appendix 4 - NCI CTC Version 4.03

TOXICITY WILL BE SCORED USING NCI CTC VERSION 4.03 FOR TOXICITY AND ADVERSE EVENT REPORTING. A COPY OF THE NCI CTC VERSION 4.03 CAN BE DOWNLOADED FROM THE CTEP HOMEPAGE: (HTTP://CTEP.INFO.NIH.GOV**).**
ALL APPROPRIATE TREATMENT AREAS HAVE ACCESS TO A COPY OF THE CTC VERSION

Appendix 5 - IWCLL Response Criteria 2008 - Hallek. Blood 2008;111:5446

Complete Remission (CR)

CR requires all of the following criteria to be met for a period of at least 2 months after completion of therapy:

a) Peripheral blood lymphocytes < 4 x 10^9/L

b) Absence of significant lymphadenopathy (>1.5cm) by physical exam and appropriate radiology

c) No hepatomegaly or splenomegaly by physical exam and appropriate radiology

d) Absence of constitutional symptoms

e) Normal CBC as exhibited by:

- Neutrophils > 1.5 x10^9/L without need for exogenous growth factors
- Platelets >100 x10^9/L without need for platelet transfusion or exogeneous growth factors
- Hemoglobin > 110g/L (untransfused and without need for exogenous erythropoeitin)

f) Bone marrow to be done at least 2 months after the last treatment and if clinical and laboratory results (first 5 points under "Complete Remission") demonstrate that a CR has been achieved. The marrow sample must be at least normoceullar for age, with <30% of nucleated cells being lymphocytes. Lymphoid nodules should be absent. If marrow is hypocellular, a repeat sample should be taken after 4 weeks or when peripheral blood counts have recovered.

Complete Remission with incomplete bone marrow recovery (CRi)

This category describes patients who fulfill all the criteria for CR (including the marrow examinations) but who have persistent anemia or thrombocytopenia or neutropenia apparently unrelated to disease activity but related to drug toxicity.

Partial Remission (PR)

PR requires all the following criteria to be met for a period of at least 2 months:

a) ≥ 50% decrease in the peripheral blood lymphocytes from pre-treatment value
b) ≥ 50% reduction in the sum products of up to 6 lymph nodes, or in one lymph node diameter if only a single lymph node was present before therapy. To be determined by physical exam or CT scan (if abnormal at baseline)
c) No increase in any lymph node and no new enlarged node. In small lymph nodes (<2 cm), an increase of <25% is not considered to be significant.
d) ≥ 50% reduction in hepatomegaly and/or splenomegaly by physical exam or on CT scan (if abnormal at baseline)

In addition, one or more of the following must be present for at least 2 months:

e) Neutrophils ≥ 1.5 $x10^9$/L without need for exogenous growth factor support
f) Platelets > 100 $x10^9$/L or 50% improvement over baseline without need for exogenous growth factors
g) Hemoglobin > 110 g/L or 50% improvement over baseline (without transfusions or erythropoietin support)

Stable Disease (SD)

Not CR, PR or PD (equivalent to nonresponse)

Progressive Disease (PD)

At least one of the following:

a) Lymphadenopathy (any one event):
    a. Appearance of any new lesion, such as enlarged lymph nodes (>1.5cm), splenomegaly, hepatomegaly or other organ infiltrates)
    b. An increase by ≥ 50% in greatest determined diameter of any previous site
    c. A lymph node of 1 to 1.5cm must increase by 50% or more to a size greater than 1.5cm in the longest axis. A lymph node of more than 1.5cm must increase to more than 2.0cm in the longest axis

b) ≥ 50% increase in the size of the liver and/or spleen as determined by measurement below the costal margin or appearance of palpable hepatomegaly or splenomegaly not previously present

c) ≥ 50% increase in the absolute number of circulating lymphocytes with at least 5.0 $x10^9$/L

d) Transformation to a more aggressive histology (eg Richter's syndrome or prolymphocytic leukemia with >55% prolymphocytes).

e) Occurrence of cytopenias (neutropenia, anemia, or thrombocytopenia) attributable to CLL.

    a. During therapy: cytopenias cannot be used to define PD

    b. After therapy: The progression of any cytopenia (unrelated to autoimmune cytopenia), as documented by a decrease of Hb levels by more than 20g/L or to <100g/L, or by a decrease of platelet counts by >50% or to less than 100 x 10^9/L, which occurs at least 3 months after treatment, if the marrow biopsy demonstrates an infiltrate of clonal CLL cells.

Appendix 6 – Correlative and Pharmacokinetic Studies

Rationale of Correlative Studies

As a companion study to the proposed clinical trial, we will conduct experiments aimed at identifying predictors of response and pharmacodynamic studies to demonstrate target inhibition

Clinical Trial Specimens and Processing

Peripheral blood (PB) and bone marrow aspirate (BMA) samples are collected from subjects at screening and day 10 approximately 4 hours after dosing. Where feasible, samples are collected at approximately the same time of day for each patient. Approximately 10 mls of PB and BMA will be drawn from subjects into heparinized and EDTA tubes and sent directly to the lab at Princess Margaret Cancer Centre. One ml of PB and BMA will be set aside for flow based pharmacodynamic studies described below. The remaining sample will be processed and stored as follows: plasma will be prepared and banked; whole blood will be stained for CD38, ZAP-70 and CD20 (to assess for expression of the target of Ofatumumab) and analyzed by flow cytometry as described below; mononuclear cells (MNC)s from the remaining samples will be prepared by Ficoll-Hypaque gradient and the percentage of CLL cells will be determined by CD19 labeling and flow cytometry. Samples with <85% purity undergo enrichment by immunoselection with anti-CD19-conjugated immunomagnetic beads. Cytospin slides will be prepared and stored. The cells will then be counted and aliquoted as follows: $5x10^6$ cells in Trizol for RNA extraction to be used for microarray analysis, 100 x 10^6 cells in 9M Urea solution for potential use in proteomics studies and immediately frozen at -80^0C, the remaining cells are snap frozen or frozen in DMSO as viable cells at -80^0C.

Pharmacogenomic Studies:

Gene expression analysis will be obtained to address two aims: (i) expression profiles associated with response to the agents as a means of identifying biomarkers of response and (ii) understanding the cellular actions of the drug in CLL cells. These studies will be performed using Affy U133 Plus 2.0 microarrays from Affymetrix using standard

methods. Arrays failing more than one of five different quality control metrics defined by the BioConductor package array QCmetrics (MA plots, spatial distribution of feature intensities, boxplot distribution of probe intensities, heatmap representation of the distance between arrays, relative log expression and normalized unscaled standard error plots) will be excluded from further analysis. Expression intensities on 64 CEL files will be summarized and present/absent calls made using the MAS5 algorithm (BioConductor). A volcano plot will be used to identified probe sets with a greater than 2-fold difference in expression at day 10 with a p-value <0.05 using Benjamini and Hochberg False Detection Rate multiple test correction. The relative gene expression profiles among the patients with complete response (CR) or partial response (PR) will be compared to those with minimal response (MR), stable disease (SD) or progressive disease (PD).

Flow Cytometry Based Pharmacodynamic Studies:

Cells from PB and BM samples will be evaluated for target modulation and the effects of GSK2110183 on downstream signaling targets of AKT (baseline and 4 hours after dosing on day 10). Flow cytometry is a highly developed technique for the diagnosis of hematological malignancies, based on the correlated measurements of multiple surface immunophenotypic markers plus forward and orthogonal light scattering characteristics of cell subpopulations. However, with the recent introduction of techniques that measure the activation states of signaling pathways using phosphospecific antibodies, the scope of flow cytometry now extends into molecular therapeutic monitoring in the clinic. By using flow cytometry applications we will determine whether AKT is activated in CLL cells pre-treatment and whether administration of GSK2110183 inhibits its downstream targets in primary cells. Correlation with patient response will be determined. The results will be analyzed on an exploratory basis.

Flow Cytometry Protocol

We will use a triple antibody (Ab) combination (anti-CD19, anti-CD5, phospho-specific antibody) to analyze signaling in CLL cells. BM and PB samples will be subjected to red cell lysis and quality of the sample will be assessed by flow cytometry by measurements

of forward and side scatter, CD19/CD5 and 7AAD staining. Cells will be resuspended in stem span H3000 defined serum free medium and aliquoted to FACS tubes. To one set of tubes, 500 uM LY294002 (inhibitor of PI3K) or solvent control will be added and incubated at 37^0C for 30 min. Phosphorylation of AKT and its downstream targets (phopho-S6 and phospho-GSK3) will be evaluated by flow cytometry. By comparing with the solvent control we can establish whether there is constitutive activation of AKT in CLL samples at baseline vs day 10. To a second set of tubes we will activate AKT by BCR stimulation with goat anti-IgM $F(ab)_2$ fragment or PMA for 12 minutes and compared to solvent. We will determine whether the ability to activate AKT and its downstream targets *ex vivo* is inhibited in samples on day 10 of treatment compared to baseline. As an additional control to demonstrate that the cells are viable and signaling is intact we will also assess the effect on SYK phosphorylation a non-AKT dependent target of BCR signaling. The cells will be fixed and permeabilized using our recently developed protocol that optimizes the preservation of phenotypic features and intracellular phosphorylated epitopes. Briefly, samples are removed from the dry bath, fixed by adding methanol-free formaldehyde to give a final concentration of 4% for 10 min. The cells will be washed in cold wash buffer and then resuspended in 1 ml of cold freezing medium consisting of 10% glycerol, 20% fetal bovine serum in RPMI tissue culture medium, and stored at -20^0C and batched for antibody staining so that paired samples are analyzed together.

For intracellular phospho-specific antibody staining (phospho-AKT, phospho-S6, phospho-GSK3, phospho-Syk, and phospho-RAS S40), thawed cells will be washed and 0.5 million cell aliquots will be resuspended and permeablilized in 1 ml of 50% methanol in 0.9% NaCl and incubated on ice for 10 min. Cells will then be washed and the cell pellet resuspended and labeled with an antibody mix containing primary conjugated phospho-specific antibodies described above together with CD19/CD5 (to identifiy the CLL cells) and incubated at room temperature for 15 min. Approximately, 30,000 ungated events will be collected for each sample on a LSR II flow cytometer.

All patients will have bone marrow aspirate as well as peripheral blood samples drawn at baseline and during therapy for these studies.

DIRECTIONS FOR CORRELATIVE SAMPLING:

Correlative study samples:

Bone marrow: 10mL BM aspirate in a heparin tube (2 green-top tubes)

Peripheral blood: 10mL blood in a heparin tube (2 green-top tubes)

Schedule of correlative sample collections:

Aim to collect samples approximately 4 hours post-dosing of GSK2110183

When feasible, samples will be collected at the same time of day for each patient.

Baseline (Within 28 days prior to first dose of GSK2110183)

After 7 days of GSK2110183 (Lead-in phase) [Day 8 of the lead-in phase (Window period of + 2 days to coincide with clinic days)] – Monday through Thursday only

At study discontinuation – only for those patients who go off study for progressive disease

Label each tube with the following information:

- Patient initials Study code
- Study name – OFA + GSK183 CLL

Peripheral blood and bone marrow samples will be sent to:

Dr.Suzanne Trudel, Ontario Cancer Institute,

Princess Margaret Cancer Centre

8th Floor Rm 202

620 University Ave, Toronto, Ontario, Canada M5G 2C1

Call the lab at 416-946-4501 ext 6486 for sample pick-up.

For IgVH mutational analysis samples will be sent from Dr. Trudel's lab to Manitoba Tumor Bank:

CancerCare Manitoba
ATTN: Dr. James Johnston
675 McDermot Ave. Room Number: ON5049
Winnipeg, Manitoba
Canada R3E 0V9
Tel: 204-787-2137

DIRECTIONS FOR PHARMACOKINETIC SAMPLING:

Pharmacokinetic analyses will be done on blood samples from the first 10 eligible participants

Schedule of pharmacokinetic sample collections:

Peripheral blood sampling for PK studies will be performed on 2 days:

Day 10 of the Lead-in Phase:

- Predose (before GSK2110183 dose), 0.5, 1, 2, 3, 4, 6, 8, 10-12, 14-22, and 24hr after (10-12hr and 14-22hr samples only where collection times are feasible)

Cycle 2 Day 22 of the Treatment Phase (with 8th weekly dose of ofatumumab):

- Predose ((before GSK2110183 dose), 0.5, 1, 2, 3, 4, 6, 8, 10-12, 14-22, and 24hr after (10-12hr and 14-22hr samples only where collection times are feasible)

Venous blood samples (4 mls for each sample) will be collected into an EDTA (k2 or k3) tube at time points specified above.

Label each PK sampling tube with the following information:

- Patient initials
- Study number

- Study name – OFA + GSK183 CLL

PK study sample processing instructions:

Blood should be collected in K3EDTA, plasma should be stored at -20^{0}C

1. Sample Handling:

-At each time point collect 2 mL of blood into a K3EDTA tube.

-Immediately after the sample is obtained, gently invert the tube 5 to 8 times to thoroughly mix the anticoagulant

2. Samples should remain at room temperature prior to centrifugation and should be processed within 30 minutes of collection

- Centrifuge the sample at 2500 to 3000 rpm for 10 to 15 minutes at +2 to 8°C to achieve a clear plasma layer over the red cells

The speed and time may be varied according to the make and model of centrifuge used.

-Immediately transfer plasma to corresponding pre-labeled cryovials and store at -20°C.

1. Cyrovials will be shipped every two weeks
2. Back-up cyrovials will be stored at site and shipped if required.

Shipp to PPD:

Maria Edwards
PPD
2244 Dabney Road
Richmond VA, 23230, USA
Tel: (804) 254.8430; Fax: (804) 254.1104
e-mail:Maria.Edwards@ppdi.com

Appendix 7 – Neurological Symptoms questions

Patient to be asked these questions by the study nurse.

		YES	NO
1.	Does the subject report any new weakness?		
2.	Does the subject report any new difficulty with coordination or walking?		
3.	Does the subject report any new signs of confusion, impaired memory or attention?		
4.	Does the subject appear apathetic compared to previous contacts?		
5.	Does the subject report any new visual disturbances?		
6.	Has the subject had any new trouble speaking, either slurring speech, difficulty getting out words, difficulty understanding words, or difficulty comprehending spoken language:		
7.	Does the subject have any other new neurological symptoms, including but not limited to: New onset seizure New sensory loss New emotional liability		

If any of the above are answered "Yes" at any visit, the investigator will contact the medical monitor and the patient's symptoms will be treated by the investigator. If required, a neurologic referral can be considered.