Study Protocol

Title:	Serologic Response to a New Recombinant, Adjuvanted Herpes Zoster Vaccine in Patients with Chronic Lymphocytic Leukemia and Waldenstrom Macroglobulinemia Treated with First-Line BTK inhibitors – A Pilot Study
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Serologic Response to a New Recombinant, Adjuvanted Herpes Zoster Vaccine in Patients with Chronic Lymphocytic Leukemia and Waldenström Macroglobulinemia Treated with First-Line BTK Inhibitors – A Pilot Study

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Summary of Changes

Section	Change
General	Due to the COVID-19 pandemic, collection of the 1-year post-vaccination blood draw was not possible. The amendment will allow for a delayed blood collection and chart review at 24-months post-vaccination to replace the 1-year time point.

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PROTOCOL SUMMARY

Title: Serologic Response to a New Recombinant, Adjuvanted Herpes Zoster Vaccine in Patients with Chronic Lymphocytic Leukemia and Waldenström Macroglobulinemia Treated with First-Line BTK Inhibitors – A Pilot Study

Objectives:
The primary objective is to measure humoral response 4 weeks after vaccination with the Shingrix herpes zoster vaccine in patients with CLL and WM undergoing first-line treatment with BTK inhibitors.
The secondary objectives of the study are:

- To measure the humoral immune response at 24 months after the completion of vaccination with the Shingrix vaccine in patients ≥ 50 years with CLL and WM receiving first-line treatment with BTK inhibitors.
- To measure PBMC activation by ELISPOT and/or flow cytometry at 4 weeks and 24 months following vaccination with Shingrix, as a marker of cellular mediated immunity.
- To determine the rate of lymphoma progression while receiving BTK inhibitors.
- To correlate lymphoma progression while receiving BTK inhibitors and vaccine response at 4 weeks and 24 months following the vaccination.

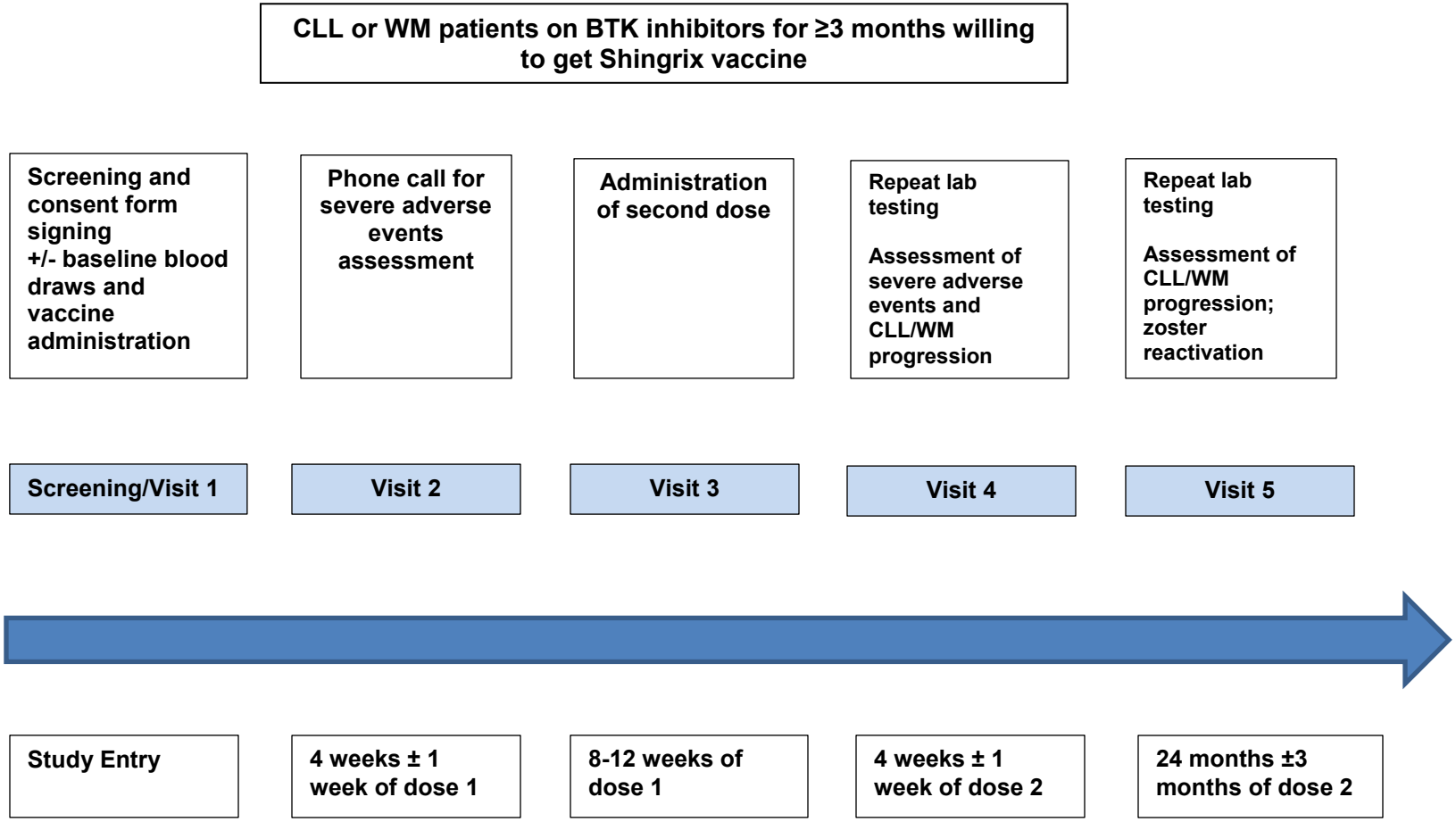
Study Population:
Male and Female, ≥ 50 years of age, with diagnosis of chronic lymphoid leukemia (CLL) or Waldenstrom's macroglobulinemia (WM). See full inclusion/exclusion criteria in section 3. 2.

Number of Subjects:
33

Description of Study Intervention:
Administration of Shingrix vaccine at baseline and 2 months and performance of blood draws at baseline, at 4 weeks and 24 months after the completion of vaccination to assess serological response.

Study Duration:
Approximately 26 months

STUDY DIAGRAM



1. PURPOSE OF THE STUDY AND BACKGROUND

1.1. Purpose of the study

Chronic lymphocytic leukemia (CLL) and Waldenstrom's macroglobulinemia (WM) are known risk factors for zoster reactivation, commonly called shingles. Although a recently FDA-approved recombinant, adjuvanted herpes zoster vaccine (Shingrix) is currently being offered to these populations, no study has specifically evaluated them in combination with BTK inhibitors.

The purpose of the study is to complete a single-arm trial evaluating if patients with CLL or WM, while on treatment with first-line BTK inhibitors, can achieve immunologic response to Shingrix. If effective, this will result in a new, well-tolerated shingles prevention strategy for these patients.

Primary objective:

- To measure the humoral immune response 4 weeks after the completion of vaccination with the Shingrix vaccine in patients ≥ 50 years with CLL and WM receiving first-line treatment with BTK inhibitors.

Secondary objectives include:

- To measure the humoral immune response at 24 months after the completion of vaccination with the Shingrix vaccine in patients ≥ 50 years with CLL and WM receiving first-line treatment with BTK inhibitors.
- To measure PBMC activation by ELISPOT and/or flow cytometry at 4 weeks and 24 months following vaccination with Shingrix, as a marker of cellular mediated immunity.
- To determine the rate of lymphoma progression while receiving BTK inhibitors.
- To correlate lymphoma progression while receiving BTK inhibitors and vaccine response at 4 weeks and 24 months following the vaccination.

1.2. Background

Varicella zoster is a ubiquitous virus in the United States that initially manifests as chicken pox in children. Once a person has been infected, the virus remains latent and can reactivate on various occasions, especially when immunity decreases. This herpes zoster reactivation, commonly called "shingles", is a painful condition which can lead to permanent nerve damage, pain, costly treatment and, on very rare occasions, death.

Herpes zoster reactivation is common in the general population, with rates averaging 3.2 cases/ 1000 person years. The incidence increases as people age, reaching 10.9 cases/ person years over the age of 80.[1] Since 2006, a live-attenuated vaccine has been indicated for people over 50 years of age to prevent zoster reactivation. Because of pre-existing immunosuppression, this vaccine is contraindicated in patients with hematologic malignancies, namely CLL and WM.

Yet, we know that these patients suffer from increased risk of developing zoster reactivation. A recent British study found that patients with hematologic malignancies had a 2.46-fold increased risk of developing shingles and among them, lymphoma was the most represented

subgroup.[2] An American database study showed similar results.[1]
In October 2017, the FDA approved the use of a new recombinant, adjuvanted vaccine to prevent shingles in patients over 50 years old. This vaccine has shown greater efficacy at creating immune response than the former live-attenuated vaccine in healthy patients, and has now become a better prevention option in patients over 50 years old.[3] In that population, the capacity to mount immune response was observed in almost 100% of patients one month after the last of the two doses.[3]

Patients with hematologic malignancies represent a distinct class of patients because of their baseline immune alterations, in part due to dysfunctions in the B-cell receptor (BCR) pathway.[4] Among indolent lymphomas, CLL has most frequently been associated with acquired immunodeficiency and infections are a major cause of morbidity and mortality in these patients.[5] Mechanisms for that state of immunodeficiency are diverse and not completely understood, but include, in addition to alterations in the BCR pathway, marked dysfunction of the immune system via alterations in T-cell repertoire and hypogammaglobulinemia.[6,7] As a result, immunogenicity to various vaccines is also reduced.[8,9,10,11]

Despite these characteristics, patients with hematologic malignancies receiving treatment with anti-CD20 monoclonal antibodies have been shown to achieve immune response to inactivated zoster vaccination[12] and a recent large phase 3 trial showed reduction in herpes zoster reactivation and persistent neurologic pain with the same vaccine.[13] However, among that population, patients with indolent lymphoma were those with the lowest response rate.[12] Patients with hematologic malignancies undergoing autologous stem cell transplants have also been shown to achieve serologic response to Shingrix in a recent study.[14]

Over the last few years, novel therapies have emerged for the treatment of CLL[15] and WM[16–18], including Bruton tyrosine kinase inhibitors of which ibrutinib and acalabrutinib are examples. Bruton tyrosine kinase (BTK) is thought to play an important role in the biology of these diseases.[19] Its constitutional activation leads to activation of several downstream pathways, including MAP kinase, AKT and NFkB, resulting in cell proliferation, differentiation and survival.[4]

BTK also plays a significant role in normal immune defense. Congenital lack of BTK activity results in X-linked agammaglobulinemia, a condition characterized by altered humoral immunity and impairment in T cell memory response. Affected patients present with severe infections caused by increased susceptibility to encapsulated bacteria and certain blood borne viruses.[19]

Some data indicate that CLL patients treated with BTK inhibitors manage to reconstitute partial immune response with increased levels of immunoglobulins, suggesting that the treatment helps control the immune alterations due to the disease rather than amplify them[20]. Despite this, immunogenicity to certain vaccines is difficult to achieve.[21,22]

To our knowledge, there are no prospective studies that have evaluated if patients while on treatment with single agent BTK inhibitors could achieve immune response to a zoster recombinant vaccine. We hypothesize that patients with CLL and WM while on treatment with BTK inhibitors can achieve a humoral response, albeit to a lesser level than the general population.

2. STUDY DESIGN

2.1. Overview

We are conducting a single-center, single-arm pilot clinical study. All subjects will be provided with the study vaccine.

Anticipated enrollment period: We anticipate meeting enrollment goals within 6 months.

Follow-up period: Patients will be treated and followed on study for 24 months post-completion of vaccination for assessment of lymphoma status and possible evaluation of persistent serologic response.

2.2. Rationale for Study Design

Evidence exists that patients over 50 years old in the general population and immunocompromised patients with hematologic conditions can achieve serologic response to Shingrix.[3] However, response seems to be less in patients with CLL or indolent lymphoma[13] and patients treated with BTK inhibitors have yet to be studied. Our study specifically targets that population through a simple trial that will address whether these patients can truly benefit from the vaccine.

The vaccine is indicated in our planned patient population, but we do not understand its efficacy and we do not know optimal timing for vaccination while on BTK inhibition. There is evidence of vaccine response in a subset of immunocompromised patients with minimal toxicity.[13,14] A placebo group was not included because it was perceived as possibly unethical to take away their possibility to receive the vaccine.

The decision was also made not to include a healthy control group since the primary objective of the study is to assess the response rate in our population, not to compare it with the general population. Moreover, a study with over 3000 healthy patients shows robust response data in almost 100% of subjects, which we can use to indirectly compare our response rates.[3] Prior studies in vulnerable populations have used the same design with valid results. Toxicity rates did not result any higher than in the general population in these studies. It is not expected to be higher in our population.

Assessment of serological response at four weeks was planned in our study in accordance with previous vaccination literature. This time point is known to represent the end of primary immunity response, which is a marker of immunologic response. Assessing a clinical endpoint (reactivation of herpes zoster) would have necessitated a larger cohort of patients followed for several years, which is not the objective of a pilot study. This could ultimately be done in further studies if response is noted in this trial.

Reassessment of serological response was originally planned at one year to evaluate the rate of persistent response. This time point was previously chosen in the general population, and subjects were found to have persistent immunity.[3] It was also assessed in a recent phase III trial evaluating response to another inactivated herpes zoster vaccine in immunocompromised patients undergoing autologous stem cell transplant. They were also found to have persistent response.[13] Due to the COVID-19 pandemic and closure of research laboratories the one year sample could not be collected. The sample will instead be collected at 24 months ± 3 months. A recent study demonstrated persistent response to the Shingrix vaccine in healthy adults up to 10

years after the initial dose[34], suggesting that the 24-month collection is a reasonable time point for reassessment.

This study is designed to obtain valid and comparable results to measure response to a vaccine in a vulnerable population in a fast and uncomplicated way.

2.3. Rationale for Dosage

The FDA approved the use of the new recombinant, adjuvanted herpes zoster vaccine (Shingrix) in October 2017. The vaccine is supplied as a single-dose vial of lyophilized varicella zoster virus glycoprotein E (gE) to be reconstituted with the accompanying vial of AS01B adjuvant suspension component. After reconstitution, a single dose of Shingrix is 0.5 mL and should be administered intramuscularly.

Two doses at 0 and 2 to 6 months are indicated.

3. CHARACTERISTICS OF THE RESEARCH POPULATION

3.1. Subject Characteristics

a) Number of Subjects:

Target accrual is 30 evaluable CLL or WM subjects receiving treatment with BTK inhibitors. Assuming a 10% drop out rate, we aim to enroll a total of 33 subjects. Participants will be replaced in case of drop out or failure to receive the second dose of the vaccine. Failure to have blood drawn for baseline and/or 4 weeks after vaccination will also warrant replacement.

Subjects will not be replaced if they fail to present to the blood draw 24 months post-vaccination.

In the case of a change of therapy between the first and second dose of the vaccine (including the addition of rituximab), patients will remain on study and will not be replaced. Their data will be included in the estimates of vaccine response in the intent-to-treat analysis but excluded from sub-group analyses.

Based on data from the University of Rochester Cancer Center pharmacy, as of May 2018, 150 CLL and WM patients are on BTK inhibitor therapy and there are approximately 20 new cases per month. A local CLL database confirms those numbers and shows that a total of about 50 patients are on single-agent, first-line ibrutinib as of January 2018. No patient was identified while collecting this data, with respect to patients' confidentiality.

Patients who have started BTK inhibitors come to clinic about every 3 months for routine visits. Based on those numbers, we expect the recruitment of 33 patients to be feasible within 6 months.

b) Gender and Age of Subjects:

Subjects must be at least 50 years old to participate. Patients under 50 years old are excluded as per the label of the vaccine. It is anticipated that most subjects will be in their sixth or seventh decade given the age distribution of CLL[23] and WM.[24] There is no upper age limit if the patient meets the other inclusion criteria.

We expect that only a minority of subjects will be diagnosed with WM as compared to CLL because it is a much rarer disease, with only 1400 new cases diagnosed each year in the United States.[25,26]

All genders are accepted. It is expected that there will be slightly more males than females included in the study as the male-to-female ratio in CLL is normally 1.3-1.7.[27] and about 60% of WM patients are males.[24]

c) **Racial and Ethnic Origin:**

We are not excluding any persons on the basis of racial background. The incidence of CLL in the United States is highest in Caucasians as compared with African Americans and Asian Pacific Islanders.[28] WM is also more common in Caucasians than in any other ethnic groups, particularly in Hispanics and in African Americans where it makes up only about 5% of the population.[25] This should be reflected in our study.

d) **Vulnerable Subjects:**

Vulnerable subjects should not be enrolled.

3.2. **Inclusion and Exclusion Criteria**

a) **Inclusion Criteria:**
Patients will be eligible if:

- They are at least 50 years of age;
- Have been diagnosed with chronic lymphocytic leukemia (CLL) OR Waldenström macroglobulinemia (WM);
- Have been on first-line BTK inhibitor (i.e. ibrutinib or acalabrutinib) for at least 3 months;
- Prior treatment with single agent rituximab is permitted if the last dose was administered more than one year ago;
- Have at least a one-year life expectancy;
- Have a history of varicella (chicken-pox) OR lived in the US or any endemic country for > 30 years'
- Prior radiation therapy is allowed

b) **Exclusion Criteria:**

Patients will be excluded from the study if they:

- Have a known hypersensitivity to a vaccine component;
- Have had herpes zoster reactivation within the past year;
- Received or were scheduled to receive a live virus vaccine in the period from 4 weeks prior to Dose 1 through 28 days post-second dose;
- Received or were scheduled to receive an inactivated vaccine in the period ranging from 7 days prior to Dose 1 through 7 days post- second dose;
- Are unable to give informed consent;
- Have an absolute lymphocyte count greater than 20,000 X 10^9/L;
- Are receiving treatment for CLL or WM with an additional agent other than a BTK inhibitor;

- Had rituximab treatment less than one year prior to study start;
- Had prior chemotherapy.

3.3. Discussion of Subject Population

Inclusion and exclusion were selected to include a homogeneous CLL and WM population treated with BTK inhibitors. Special consideration was taken to avoid disease heterogeneity in order to obtain valid results and this is why only patients who have been on a first-line BTK inhibitor for at least 3 months will be included.

The age limit was set at 50 years old as per the vaccine label.

Exclusion criteria were the result of contra-indications to the vaccine or to the inability to correctly undergo all steps in the research process. In our population, a considerable number of patients also received concomitant rituximab for a period of 6 months (weekly for 1 month and monthly until month 6) at treatment initiation in the context of a clinical trial. We decided not to exclude these patients, but to restrict their enrollment to those who have not had rituximab in the last 12 months. The 12-month time limit was set to minimize the prolonged side effects of rituximab on immunity, but to maximize the inclusion of patients. Data published by Anolik et al in 2006 showed that, although incomplete, B cell recovery occurred by 12 months.[29] Even though retrospective data shows that 38.9% of patients with non-Hodgkin's lymphoma develop new-onset hypogammaglobulinemia at a median of 1.4 years post-treatment with a median of 7 doses of rituximab[30] and multiple case reports of prolonged hypogammaglobulinemia, happened in the context of rheumatologic diseases or concomitant chemotherapy,[31–33] this data does not represent our population and thus cannot be applied to them. Currently, no such data exists for this population.

Exclusion of subjects with absolute lymphocyte counts greater than 20,000 cells/μL was decided empirically to avoid interference with the assays. An excessive number of lymphocytes could potentially interfere with the laboratory analyses.

4. SUBJECT IDENTIFICATION, RECRUITMENT AND CONSENT

4.1. Method of Subject Identification and Recruitment

CLL and WM subjects on BTK inhibitors will be primarily identified through the Strong Memorial Hospital pharmacy. Lymphoma physicians in the cancer center, all actively involved in research, will be made aware of the study. Subjects may be contacted by their regular team of providers or their regular visits will be used to expose the study by their lymphoma specialist. If patients express interest, a member of the research team will screen the patient, present the study in greater detail and have the patient consent.

Subsequent to consent, a chart review will be performed and captured data will be stored in a secure REDCap database. Privacy is maintained by institutional procedures, which require formal review by appropriate committees prior to any written or telephone correspondence with patients or families.

4.2. **Process of Consent**

Written consent will be obtained from each subject. Informed consent will be conducted by members of the clinical research team using an IRB-approved informed consent document. The study procedures, their timing, the time and effort asked from the participant, the immediate benefits and the risks associated with the study will be reviewed thoroughly in plain and simple language. The investigator will ensure that written informed consent is obtained from each subject by obtaining the signature and date on the informed consent document prior to the performance of protocol evaluations or procedures. If the informed consent is updated during the study, re-consent will be required from the participants.

If need be, additional time will be allowed to potential subjects to review the document to ensure adequate consent. It will be possible for them to leave with the consent form and review it whenever they feel is most appropriate.

Consent documents will be stored in a secure location at the cancer center as per regular procedures.

A translator and/or translated version of the protocol will be provided as needed.

All subjects will be notified of the delayed one-year blood draw and their permission requested to collect the blood sample and chart review at 24 months.

5. METHODS AND STUDY PROCEDURES

Screening procedures will take place after subjects have consented to study participation.

Subjects will be asked to return to the clinic at a later date to have the baseline blood tests performed and the vaccine administered. We will determine a selection of dates where a certain number of patients will be able to have both procedures performed on the same day.

Blood may also be drawn for baseline testing at the Cancer Center and subjects subsequently administered the vaccine at the outpatient pharmacy on screening day.

After consent, a brief chart and CLL database review will be performed to collect certain variables such as those listed below:

- Age
- Stage at diagnosis
- Date of diagnosis
- 17p deletion (yes/no)
- TP53 mutation (yes/no)
- Mutated status of IVHG (yes/no)
- 11q del (yes/no)
- Presence of trisomy 12 (yes/no)
- Del 13q (yes/no)
- Watch and wait period duration
- Date of BTK inhibitor therapy initiation
- History of zoster reactivation

- History of zoster vaccination
- Immunoglobulin levels before study start
- Use of rituximab in the past (yes/no)
    - Number of cycles
    - Date of last cycle

Prior to the first dose of the vaccine, blood will be collected to assess immunity via measurement of anti-gE and cellular-mediated immunity. Samples will be processed in the cancer center research laboratory. Peripheral blood mononuclear cells (PBMC) will be processed and cryopreserved for future cellular assays and serum will be banked for analysis of anti-gE.

At visit 2, four weeks post-first dose, subjects will be contacted by phone call to report any adverse events. A chart review for severe adverse events will also be performed.

As per the label of the vaccine, the second dose of the vaccine will be administered two months after the first one, at visit 3. One month subsequent to that second dose, at visit 4, a second blood draw will be performed to evaluate the subject's immunogenic response. The initial analyses will be repeated, and response will be measured using statistical methods described below. Safety will be assessed again in the same way as after the first dose. A chart review will be performed to assess CLL/WM progression on BTK inhibitor therapy as determined by subjects' regular team of providers during their latest visit.

These analyses will be repeated 24 months after the last dose of the vaccine to assess long term immunogenicity, at visit 5. A last chart review also be performed to assess incidence of zoster reactivation and disease progression as determined by their team of providers during the latest visit**.**

Table 1. Schedule of Study Procedures

Visit	**Screen***	**1***	**2**	**3**	**4**	**5**
		Dose 1	Safety assessment	Dose 2	Blood draw	Optional Blood draw
Visit window		0	Week 4 ± 1 week	Weeks 8-12	4 Weeks ± 1 week after Dose 2	24 months ± 3 months of Dose 2
Obtain informed consent	X					
Confirm eligibility	X					
Enroll	X					
Vaccine administration	X*	X*		X		
Lab work (anti-gE and CMI)	X*	X*			X	X
Safety assessment (patient-reported AEs			X		X	

and chart review)						

*Note: Administration of the first dose of the vaccine and completion of the lab assays will take place once, either at the screening visit OR at the first visit. If this is done at screening, then screening and visit one will happen within the same visit.
Subjects will be contacted through phone call OR in person at the clinic on for safety assessment.

5.1. **Treatment Dosage and Administration**

Vaccines will be acquired, stored and administered by the outpatient pharmacy as per the label and with respect to standard-of-care procedures.

Subjects will have a one-vial dose of the vaccine administered by staff from the outpatient pharmacy at that location, and surveillance for immediate adverse effects will be done according to regular procedures.

Cold compresses may be applied to the vaccinated area as needed.

Table 2. Study Drug

Agent	**Pre-medications; Precautions**	**Dose**	**Route**	**Schedule**
Shingrix vaccine	none.	0.5 µg	IM push	Months 0 and 2

5.2. **Efficacy Assessments**

Vaccine response, as determined by blood antibody levels to the varicella virus glycoprotein E subunit (anti-gE), will be measured by ELISA. This humoral response will be assessed four weeks after vaccination is complete. In patients who were seropositive before the study, a positive response will be defined as at least a four-fold increase in geometric mean concentration (GMC) of anti-VZV gE antibody as measured per ELISA. Humoral response in seronegative patients at baseline will be defined as at least a four-fold increase from the lower detection limit of the anti-gE antibody assay.

Secondary efficacy objectives include:

1. Measure humoral response at 24 months post-vaccination, which is defined as persistence of anti-gE antibody above test threshold at 24 months.
2. Measure cell-mediated response to vaccination at one month and 24 months after vaccination.
3. Evaluation of CLL/WM progression on BTK inhibitor as determined by treating oncologist at latest assessment, and correlation between progression on BTK inhibitor and vaccine response at 4 weeks and at 24 months post-second dose.

Cellular-mediated response will be determined by measuring PBMC activation (by ELISPOT or flow cytometry) following stimulation with varicella glycoprotein E peptide. PBMC activation at 4 weeks and 24 months post dose will be compared to pre-vaccination activation levels.

a. Safety Assessments

Subjects will be educated to recognize immediate adverse reactions to the vaccine. Patient-reported signs of allergic or hypersensitivity reactions will be assessed and managed by the study team as needed. Only severe adverse effects will be captured in this study. Subjects will be contacted 4 weeks ± 1 week after each dose of the vaccine for assessment and their chart will be reviewed at the same moment. Severe adverse effects are defined as any grades 3-5 adverse effects included in the CTCAE v5.0 classification.

The decision was made not to report all side effects because the safety of this vaccine has already been proven in large clinical trials, both in a general population of older adults and in immunocompromised patients, including lymphoma patients receiving chemotherapy. These thousands of patients did not experience significant toxicity from herpes zoster vaccination.[3,13] Moreover, clinically relevant concerns to vaccine administration are grade 3-5 toxicities, which will be captured in the study, both via patient-reported toxicity and through chart review.

b. Assessment of Subject Compliance

All study procedures (vaccine administration and blood draws) will be performed at Strong Memorial Hospital, which will ensure compliance.

c. Costs to the Subject

Cost and administration of the vaccine and all required laboratory testing is covered by the study. Collection and maintenance of research records, laboratory assays and storage of blood samples will also be covered by the study. There will be no direct cost to the subjects to be part of the research project.

d. Payment for Participation

Subjects will not receive payments for their participation in the study.

e. Return of Individual Research Results

Patients will not directly be notified of the results as there will be no direct clinical implications to the observed immunological response. However, that information will be made available through their hematologist after the study is finished.

6. CONCOMITANT AND DISALLOWED MEDICATIONS

Subjects will be required to have been on first-line BTK inhibitors for at least 3 months at study start. Prior dose reductions for toxicity will be allowed.

Subjects will not be asked to discontinue any medication to participate in the study. However, prior use of other medications designed to treat specifically CLL or WM (i.e. venetoclax) will not

be allowed. Change in medication as determined by treating oncologist will be allowed.

Other vaccination will be allowed during the study provided it does not interfere with the study assays. Administration of another inactivated vaccine (for example influenza or pneumococcal vaccine) will only be authorized outside that critical time period that ranges from 7 days prior to the first dose until 7 days post-second dose. We will encourage patients to receive the influenza vaccine and come back for the study protocol 7 days later should this interfere with our study.

7. SUBJECT WITHDRAWALS

Subjects will be advised in the written informed consent forms that they have the right to withdraw from the study at any time without prejudice. Withdrawal of consent can be submitted to any member of the research team, after which point no further data will be collected on these patients.

Subjects may be withdrawn by the investigator if they fail to present for the second dose of the vaccine or for the first control blood draws, or if they experience a severe adverse effect attributed to the first dose of the vaccine.

If therapy needs to be modified and subjects stop BTK inhibitor therapy between enrollment and their second vaccine dose, they will be offered the second dose and remain on study.

8. STUDY DRUG/DEVICE/BIOLOGIC ADMINISTRATION/ASSIGNMENT

8.1. Study Drug/Device/Biologic

- Shingrix will be acquired by the outpatient hospital pharmacy. The vaccine is supplied as a single-dose vial of lyophilized varicella zoster virus glycoprotein E (gE) to be reconstituted with the accompanying vial of AS01B adjuvant suspension component. After reconstitution, a single dose of Shingrix is 0.5 mL, to be administered intramuscularly. After reconstitution, each 0.5-mL dose is formulated to contain 50mcg of the recombinant gE antigen, 50mcg of MPL, and 50mcg of QS-21. Each dose also contains 20mg of sucrose (as stabilizer), 4.385mg of sodium chloride, 1mg of DOPC, 0.54mg of potassium dihydrogen phosphate, 0.25mg of cholesterol, 0.160mg of sodium dihydrogen phosphate dihydrate, 0.15mg of disodium phosphate anhydrous, 0.116mg of dipotassium phosphate, and 0.08mg of polysorbate 80. This is not an investigational drug and will be given as standard of care according to the FDA label. The vaccine will be provided for patients enrolled in the study.

8.2. Dosage of Study Drug/Biologic

Dosage of study drug: Shingrix vaccine 50 mcg of anti-gE protein and adjuvant product given at month 0 and month 2.

Should a vaccine-related SAE happen between doses 1 and 2, dose 2 may be omitted. There will be no other dose adjustment.

8.3. Accountability of Investigational Supplies

Vaccines will be obtained and administered through the outpatient hospital pharmacy and kept at that location until reconstitution and administration to the patients. The pharmacist will be responsible for receipt, storage, reconstitution and record keeping.

8.4. Subject Withdrawal of Study Drug

Subjects cannot continue to be followed in the study if they refuse to complete the vaccination process. However, the label of the vaccine specifies the second dose of the vaccine can be administered between 2 to 6 months subsequent to the first one. In that context, if subjects were to get the second dose within that period, they could still be included in the trial, provided data collection is still ongoing.

9. SAFETY AND REPORTABLE EVENTS

9.1. Serious Adverse Event

A serious adverse event is defined as any adverse medical experience that results in any of the following outcomes:

- death;
- is life-threatening;
- requires inpatient hospitalization or prolongation of existing hospitalization;
- results in persistent or significant disability/incapacity;
- is a congenital anomaly/birth defect; or
- requires medical or surgical intervention to prevent permanent impairment or damage.

The following attribution scale will be used:

- Definite: SAE is clearly related to the investigational agent
- Probable: SAE is likely related to the investigational agent
- Possible: SAE is possibly related to the investigational agent
- Unlikely: SAE is doubtfully related to the investigational agent
- Unrelated: SAE is clearly not related to the investigational agent

Serious adverse events, and deaths that occur during the patient's study participation will be recorded in the REDCap database. SAEs will be monitored from the first dose of study vaccine until 4 weeks (28 days) post-last dose of vaccine or withdrawal from participation. All SAEs should be monitored until they are resolved or are clearly determined to be due to a patient's stable or chronic condition or intercurrent illness(es).

9.2. Responsibilities for Reporting Serious Adverse Events

All serious adverse events will be reported in the REDCap database within 5 business days of learning of the event. SAE reports are expected to include sufficient detail so as to determine the severity, toxicity grade, expectedness and treatment. The report should be updated to document resolution or any sequelae. The research team will review these reports and determine if further action is required. We do not expect frequent SAEs in that study. Even in immunocompromised patients, previous studies have shown favorable safety profiles

with the use of that vaccine and no SAEs have been found to be clearly attributed to the vaccine.

10. RISK/BENEFIT ASSESSMENT

10.1. **Potential Risks**

The following risks have been most frequently reported in association to the recombinant zoster vaccine:

- pain (78.0%),
- redness (38.1%),
- swelling (25.9%);
- myalgia (44.7%),
- fatigue (44.5%),
- headache (37.7%),
- shivering (26.8%),
- fever (20.5%),
- and gastrointestinal symptoms (17.3%).

Unsolicited adverse events occurring within 30 days of vaccination were reported in 50.5% of subjects receiving Shingrix. Unsolicited adverse events that occurred in ≥1% of recipients of Shingrix and at a rate at least 1.5-fold higher than placebo included the following:

- chills (3.5% versus 0.2%),
- injection site pruritus (2.2% versus 0.2%),
- malaise (1.7% versus 0.3%),
- arthralgia (1.7% versus 1.2%),
- nausea (1.4% versus 0.5%),
- dizziness (1.2% versus 0.8%).

In addition to risks secondary to the vaccine itself, confidentiality breach is a risk associated with the chart review we will need to perform.

Risks associated with venipuncture include vasovagal episodes, ecchymoses at the site of blood removal, and extremely rare instances of infection.

10.2. **Protection Against Risks**

To minimize risks of discomfort associated to venipuncture and vaccine administration, cold compresses may be applied to the punctured/vaccinated areas as needed.

Should subjects experience an immediate severe adverse effect, they will receive appropriate routine care through personnel at the Cancer Center, which will be covered by patients' insurance.

10.3. **Potential Benefits to Subjects**

Subjects enrolled in this trial will receive the new recombinant, adjuvanted varicella zoster vaccine for free. Should our hypothesis prove true, these subjects will benefit from improved protection against shingles. There will be no financial compensation of subjects for participation in this research.

10.4. **Alternatives to Participation**

Participation in this study is voluntary. If a subject chooses not to participate, the vaccine could be administered outside of this clinical trial.

11. CONFIDENTIALITY OF DATA AND INFORMATION STORAGE

Study specific forms within REDCap will be used for web-based data management. Information abstracted from patient care records is obtained for research purposes only. Procedures are in place for maintaining confidentiality of all information collected as part of this study. Access to medical records and the REDCap study database is limited to the investigative staff. Data are managed by study number and will be analyzed anonymously. All reports are of a summary nature and no individual patients are identified. Non-computerized medical records are kept in a locked filing cabinet. Access to personal identifiers is based on a "need to know" basis, and this access is reviewed and documented by the PI.

11.1. **Investigator record Retention**

The investigator shall retain study drug disposition records and all source documentation (such as laboratory reports, inpatient or office patient records) for the maximum period required by the country and Institution in which the study will be conducted. If the investigator withdraws from the study (due to relocation, retirement, etc.), the records shall be transferred.

12. RESEARCH INFORMATION IN MEDICAL RECORDS

The patient's chart will mention that the vaccine was administered and may reference participation in the research study. The results from this study will not be reported in the patient's chart.

13. DATA ANALYSIS AND MONITORING

13.1. **Sample Size Determination**

The primary endpoint for assessing the immunological response to the vaccine has been defined in section 5.2. The target accrual will be 30 evaluable subjects receiving treatment with BTK inhibitor. Allowing for 10% drop-out due to subject participation or lab testing issues, this trial will accrue a total of 33 CLL or WM patients. Based on current estimates, the expected time to accrue these subjects is 6 months.

We expect that the response to vaccine will be significantly less than the 97% response rate seen in the healthy general population. The table below shows the exact Clopper-Pearson two-sided 90% confidence intervals for a range of likely observed response rates for a range of sample sizes. The upper bound of the 90% (two-sided) confidence interval corresponds to a (one-sided) 95% confidence interval. Therefore, with 30 evaluable subjects and observed response rate

<85%, we will have 95% confidence that the true immunological response rate is less than the general population response rate.

Table 3: Two-sided 90% Confidence Intervals for a range of potential response rates by sample size

Immunologic Response Rate (%)	Sample Size		
	20	**25**	**30**
25	10 – 46%	12 – 43%	13 – 41%
35	18 – 56%	19 – 53%	21 – 52%
45	26 – 65%	28 – 63%	29 – 61%
55	35 – 74%	37 – 72%	39 – 71%
65	44 – 82%	47 – 81%	48 – 79%
75	54 – 90%	57 – 88%	59 – 87%
85	66 – 96%	68 – 95%	70 – 94%

13.2. **Planned Statistical Analysis**

13.2.a **Primary Analysis**

The estimates of geometric mean antibody titers pre- and post-vaccination, mean fold-changes, and vaccine response rates will be described with 90% (two-sided) confidence intervals. These estimates will be important for designing a future vaccine trial in patients treated with BTK inhibitors with emergence of shingles as the primary outcome. Self-reported and chart-reviewed serious adverse events will be summarized in tabular format by type and grade.

13.2.b **Secondary and Exploratory Analyses**

As secondary analyses, the change in antibody titers pre and post-vaccination will be evaluated with the Wilcoxon Rank Signed Test for paired data. This test will provide some indication whether the within subject change in titer is statistically different from zero. The change in seroprotection rates pre and post vaccination will be assessed by the exact McNemar test for paired proportions.

As exploratory analyses, the association between baseline characteristics and the achievement of immunological response and change in antibody titers will be assessed using exact non-parametric statistical tests, such as exact Chi-Square test, Wilcoxon Rank Sum test, or Spearman rank correlation tests, depending on the scale of the variables involved. Baseline characteristics of particular interest have been described above and include age, stage at diagnosis, time since diagnosis, presence of high-risk or low-risk features, time since BTK inhibitor therapy initiation, history of zoster reactivation, IgG levels at study entry and use of rituximab therapy. These results will be reported along with descriptive statistics for the purpose of hypothesis generation in future trials.

The disease progression to BTK inhibitor at visit 4 and visit 5 will be determined from the closest assessment by treating oncologist. The association between vaccine response and disease progression at each time point will be assessed with Fisher's exact test.

Immunologic markers of immune response (anti-gE and cellular-mediated immunity markers) will be measured at three time points: baseline (before first vaccine dose), midpoint (4 weeks post-second vaccine dose), and endpoint (24 months post-second vaccine dose). A linear mixed model will be used to describe the change in immunologic markers over time, controlling for important baseline characteristics and including the subject as a random effect. Some markers may require transformation to approximate a normal distribution. This model will provide estimates for the shape of the effect of vaccination on these markers over the 24- month study interval, as well as inter versus intra-subject variation which will be important in the design of future trials.

13.3. **Data and Safety Monitoring**

For the current study, we will use the Wilmot Cancer Institute Data and Safety Monitoring Committee at the University of Rochester. The DSMC procedure guidelines are designed to adhere to Good Clinical Practice (GCP) based on Code of Federal Regulations, FDA policy, International Conference on Harmonization guidelines, and institutional RSRB policies. Compliance with GCP ensures that safety of human subjects is not compromised, the study is carefully conducted, protocol is strictly adhered to, and adverse events are properly reviewed and reported. According to GCP guidelines, responsibility for the protection of human subjects and proper conduct of clinical trials is shared among the principal investigator, clinical trial sponsor, institutional RSRB, and the DSMC.

Overall Framework for Safety Monitoring

Regular assessment of data quality (audit reports and accrual progress reports) and toxicities will enable the DSMC to assess whether significant risks are occurring that would warrant study closure. Cumulative reports of SAE's previously reported for expedited review and any new serious adverse event are also reviewed.

Study Investigators will conduct continuous review of data and patient safety. The Investigator will submit progress reports of these data to the Clinical Trials Monitoring Committee for review to its predetermined frequency. The review will include for each treatment arm/dose level: the number of patients enrolled, withdrawals, significant toxicities as described in the protocol, serious adverse events both expected and unexpected, dose adjustments, and responses observed. The PI maintains a database of all serious adverse events with toxicity grade and information regarding treatment required, complications, or sequelae. The Investigator will submit a copy of the SAE spreadsheet along with the Progress Report to the Clinical Trials Monitoring Committee for review. Actual review dates will be assigned when the 1st patient is accrued.

Any serious adverse event that is serious, related AND unexpected must be reported within 10 calendar days to both the Safety Coordinator and the RSRB (see RSRB guidelines). The DSMC Chair will determine whether further action is required, and when patient safety is of concern, an interim meeting may be called.

Serious adverse events that are related AND expected or unrelated AND unexpected will be reported to the Committee for review. SAE reports are expected to include sufficient detail so that the DSMC can determine the severity, toxicity grade, expectedness, treatment required, and a follow up report documenting resolution or if there are sequelae. Unless otherwise specified in the protocol, serious adverse events that require detailed reports (but not necessarily expedited) are expected, related, non-hematologic toxicities of grades 3, 4 or 5.

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