Alliance Central Protocol Operations Program Office
125 S. Wacker Dr., Suite 1600
Chicago, IL 60606
P: 773-702-9171
F: 312-345-0117
www.AllianceforClinicalTrialsinOncology.org

September 1, 2023

Re: Amendment Disapproval of Update #03 to Protocol **A051701:** *"Randomized phase II/III study of venetoclax (ABT 199) plus chemoimmunotherapy for MYC/BCL2 double-hit and double expressing lymphomas"*

[redacted], MD
Cancer Therapy Evaluation Program
National Cancer Institute
9609 Medical Center Dr.
Bethesda, MD 20892

Dear Dr. [redacted]:

Thank you for your review of Update #03 to Protocol A051701, *"Randomized phase II/III study of venetoclax (ABT 199) plus chemoimmunotherapy for MYC/BCL2 double-hit and double expressing lymphomas"* (Version Date: 06/05/2023).

Attached please find the revised protocol for the resubmission of Update #03 (Version Date: 09/01/2023). The study team has addressed the comments from the reviewers below, and the protocol has been updated accordingly.

Sincerely,

[redacted], MD
[redacted]
Alliance for Clinical Trials in Oncology

I. Comments Requiring a Response – Major Issues:

#	Section	Comments
1.	3.2.1	When this BIQSFP award was approved, the plan was to evaluate the first 100 patients for concordance with local pathology reads to determine if the central review remained necessary. When that was done, it was found that the overall disagreement rate was 6/100. That evidence suggested that concordance was excellent and central testing was not required for protection of the study primary endpoints. Instead, the decision was made to continue the central review because at that time it was already clear that the DHL cohort was subject to comparatively excess toxicity due to use of DA-EPOCH-R backbone compared to the DEL cohort using R-CHOP backbone. Therefore, CTEP decided that central review was needed to protect DEL patients from being misassigned to the more toxic regimen where efficacy was not definitely known to be better than R-CHOP. This is no longer the case since the DA-EPOCH-R regimen is no longer being used. The Concordance data from the first 100 patients demonstrates that the local reads are all that are needed to preserve the trial primary endpoint integrity now that the trial is only enrolling DEL. The low rate of including non-DEL is already accounted for by the statistical design. There will be no further BIQSFP funding for this protocol. Please remove central review as requested in the last consensus review. **PI Response: The central review has been removed from throughout the protocol, and it has been clarified that this only applied to Phase II.**

II. Comments Requiring a Response– Administrative & Editorial Issues:

#	Section	Comments
2.	6.2	Please elaborate on what studies will be conducted on Whole Blood collected in EDTA vs Streck tube at registration and at different cycles/end of treatment. **PI Response: The EDTA tube collected pre-treatment will be used for plasma isolation and storage for future possible soluble serum biomarker studies. Germline DNA will be isolated from the isolated mononuclear cells.** **Serial Streck tube collections will be used to isolate cell free DNA to be used for MRD assessment in the laboratory of Dr. Ash Alizadeh**.

III. Company Comments – Requiring a Response:

#	Section	Comments
3.	7.1 7.2, 7.3	Please do not remove the following language: "but patients who start on rituximab should receive rituximab (or rituximab hyaluronidase) throughout, while patients who begin on a rituximab biosimilar should receive the biosimilar throughout." **PI Response: This language has been added back.**

IV. Recommendations:

#	Section	Comments
4.	Schema	Per change memo - In the schema diagrams, the box for Arm 2 has been updated to read: "R-CHOP** + Venetoclax." – please clarify the "**" reference as there is no ** footnote in the schema. **PI Response: The ** represents a typo in the change memo, which has been corrected. The update correctly reads R-CHOP + Venetoclax in the schema box for Arm 2. There is no footnote.**
5.	13.1	"R-Chemo" to "R-CHOP" change was not made in the first sentence or the second paragraph as suggested by the change memo. **PI Response: The use of R-chemo is appropriate in this sentence since the sentence refers to the original DHL and DEL cohorts, which used different chemotherapy backbones in the phase II portion of the study. The update closing the DHL is described in the following paragraph, where the chemotherapy regimen is referred to exclusively as R-CHOP.**

ALLIANCE FOR CLINICAL TRIALS IN ONCOLOGY

PROTOCOL UPDATE TO ALLIANCE A051701

RANDOMIZED PHASE II/III STUDY OF VENETOCLAX (ABT 199) PLUS CHEMOIMMUNOTHERAPY FOR MYC/BCL2-DOUBLE EXPRESSING LYMPHOMAS

NCI-supplied agent(s): Venetoclax (NSC #766270, IND [redacted]); IND holder: CTEP/DCTD/NCI
Commercial agent(s): Rituximab (NSC #687451), Etoposide (NSC #141540), Prednisone (NSC #10023), Vincristine (NSC #67574), Cyclophosphamide (NSC #26271), Doxorubicin (NSC #123127)

[X] **Update:**	[ ] **Status Change:**
[X] Eligibility changes	[ ] Activation
[X] Therapy / Dose Modifications / Study Calendar changes	[ ] Closure
[X] Informed Consent changes	[ ] Suspension / temporary closure
[X] Scientific / Statistical Considerations changes	[ ] Reactivation
[ ] Data Submission / Forms changes	
[X] Editorial / Administrative changes	
[X] Other: Updated CTSU language	

Because the CIRB is the IRB of record for this study, no recommended level of IRB review is provided by the Alliance. This amendment must be implemented within 30 days after posting. Please refer to the CIRB amendment application and CIRB guidelines for further instructions.

UPDATES TO THE PROTOCOL:

Cover Page

- The title has been updated to remove "double hit" lymphoma as this cohort is now closed.
- [redacted] has replaced [redacted] as the Primary Statistician.
- [redacted] has replaced [redacted] as the Data Manager.

Study Resources

- The URL for Expedited Adverse Event Reporting has been updated.
- The address and contact information for the Alliance Biorepository has been updated.

CTSU Contact Information

The table has been updated with the current CTSU template language.

Schema

- The title has been updated to remove "double hit" lymphoma.
- Under the Eligibility Criteria, "FDG-avid disease on PET/CT" has been added.
- Under the Eligibility Criteria, the age criterion has been changed to "Age 18-80 years."
- The schema has been separated into two different diagrams for the DEL and DHL cohorts.
- In the schema diagrams, the box for Arm 2 has been updated to read: "R-CHOP + Venetoclax."
- In footnote *, "prior to registration/randomization" has been changed to "prior to beginning cycle 1 of protocol therapy."

Section 1.0 (Background)

- In Section 1.1, the first paragraph has been updated.
- Section 1.2 has been revised to include updated data, a description of excess toxicity on the experimental arm of the initial DHL cohort, and a paragraph providing background to excess toxicity of full dose chemotherapy in patients over 80 years old.

Section 2.3 (Secondary objective(s))

- Section 2.3.5 has been revised to read: "To determine whether cell of origin and intensity of the MYC and BCL2 protein expression on diagnostic tumor biopsy correlate with PFS, EFS, and OS."
- The following has been added to the end of Section 2.3.6: "(phase II only)."

Section 3.2 (Eligibility Criteria [Step 1])

- In Section 3.2.1 (Documentation of Disease), the following changes have been made:
    - In the bullet point beginning "DEL is defined…", in the first sentence, "and/or *BCL6*" has been added. The last two sentences have been revised to read: "IHC will be performed per standardized guidelines and will be acceptable for study entry, but local IHC and FISH results for *MYC* must be submitted for central review in order to determine eligibility if enrolling as DEL based on local results during phase II. Central pathology review is no longer required as of Update #03."
    - The bullet point beginning "The diagnosis of DLBCL/HGBCL…" the references to central pathology review have been removed.
    - In the bullet point beginning "The diagnosis of DLBCL/HGBCL…", the last two sentences of the have been revised to read: Cases submitted as a DEL must demonstrate appropriate IHC protein expression of MYC and BCL2, and be negative for translocations of *MYC* along with translocations of *BCL2* and/or *BCL6* by FISH. Patients with *MYC* translocations and no translocations of either *BCL2* or *BCL6* are eligible for the DEL cohort.
    - The following bullet point has been added: "Patients must have FDG-avid disease on PET/CT."
- Section 3.2.4 has been revised to read: "Age 18-80 years"

Section 4.0 (Patient Registration)

This section has been updated with the current CTSU template language.

Section 4.4 (Patient Registration Requirements)
The following has been added to the bullet point: "(Phase II only. Central pathology review is no longer required as of Update #03)."

Section 4.6 (Stratification Factors, Grouping Factors, and Treatment Assignments)
The first sentence has been revised to read: "All patients registered will be assigned to one of the two treatment arms (Arm 1, R-chemo versus Arm 2, R-CHOP plus Venetoclax) in a 1:1 ratio utilizing a permuted block schedule."

Section 5.0 (Study Calendar)

- In the third paragraph, the second sentence has been revised as follows: "For patients who have received a single cycle of chemotherapy prior to protocol enrollment, PET/CT ~~and bone marrow biopsy~~ does not need to be repeated if performed before or during the pre-registration cycle."
- Under Staging, the "Central histologic review" row has been removed, and footnote **** and the former footnote 7 have been removed from below the table. Subsequent footnotes have been re-numbered accordingly.
- In the first column, under Staging, the bone marrow biopsy has been made optional.
- In the first column, under Staging, the parenthetical phrase after "CSF cytology and flow cytometry" has been revised to read: "(only if optional LP is performed)."
- In footnote **, in the first and third sentences, "1 week" has been changed to "3 weeks."
- In footnote ****, in the second sentence, "and *BCL6*" has been added to the list of translocations required for registration.
- In footnote ****, the following has been added to the fourth sentence: "along with translocations of *BCL2* and/or *BCL6*" and the following fifth sentence has been added: "Patients with MYC translocations and without translocations of *BCL2* and/or *BCL6* are eligible for the DEL cohort."
- In footnote †, "+/- venetoclax" has been removed from the first sentence.
- In footnote 3, the second sentence has been revised as follows: "In cycle 1 on protocol, TLS labs will be checked ~~on day 4~~ prior to the first dose of venetoclax…"
- In footnote 7, the following sentence has been added: "Submitted slides should include H&E, CD20, CD10, BCL2, BCL6, MYC, MUM1, and Ki-67."
- In footnote 8, in the second sentence, "can be performed" has been changed to "should be performed."
- In footnote 8, in the third sentence, "1 to 3 weeks" has been changed to "3 weeks," and "(+/- 3 days)" has been changed to "(+/- 7 days)."

Section 6.1 (Data Collection and Submission)

- This section has been updated with the current CTSU template language.
- In Section 6.1.1, the third paragraph has been revised as follows: "Radiology reports at registration, interim restaging ~~after cycle 3~~, end of treatment, and at the time of progression (where available)."

Section 6.2 (Specimen collection and submission)

- The former second paragraph regarding real time histopathology review has been removed.
- The "Mandatory for all patients" submissions have been removed from the table.
- Footnotes ** and *** have been removed from below the table.

Section 7.0 (Treatment Plan/Intervention)

- In the first two sentences "14 days" has been changed to "21 days."

- In the fifth paragraph, the third and fourth sentences have been revised to read: "Patients will be randomized to either Arm 1 (R-chemotherapy) or Arm 2 (R-CHOP and venetoclax). The R-chemotherapy in Arm 1 will be R-CHOP for subjects with DEL and DA-EPOCH-R for subjects with DHL."

Section 7.1 (Arm 1 [DEL]: R-CHOP)

- In Section 7.1.1, under the table, footnote * has been revised as follows: "An FDA-approved rituximab biosimilar ~~for DLBCL~~ or rituximab hyaluronidase may be substituted per institutional standards or as required by patient insurance coverage, but patients who start on rituximab should receive rituximab (or rituximab hyaluronidase) throughout, while patients who begin on a rituximab biosimilar should receive the biosimilar throughout. Rituximab hyaluronidase is administered by subcutaneous injection ~~may be substituted for IV rituximab~~ at the standard dose of 1400 mg, per institutional standard."
- In Section 7.1.1, in the last paragraph, "(+/- 2 days)" has been changed to "(+/- 3 days)."
- In Section 7.1.2, the following has been added in the first bullet point: "Biosimilars are allowed."
- In Section 7.1.3, the first paragraph has been revised to read: "CNS prophylaxis with intrathecal methotrexate may be included at the discretion of the treating investigator. If CNS prophylaxis is administered, the dose and schedule is at the discretion of the treating investigator. IV methotrexate is not allowed." In the second paragraph, "lumber" has been corrected to "lumbar."

Section 7.2 (Arm 1 [DHL]: DA-EPOCH-R)

- In the table in Section 7.2.1, the prednisone dose has been changed from "100 mg" to "60 mg/m^2" PO twice daily.
- In Section 7.2.1, under the table, footnote * has been revised as follows: "An FDA-approved rituximab biosimilar ~~for DLBCL~~ or rituximab hyaluronidase may be substituted per institutional standards or as required by patient insurance coverage, but patients who start on rituximab should receive rituximab (or rituximab hyaluronidase) throughout, while patients who begin on a rituximab biosimilar should receive the biosimilar throughout. Rituximab hyaluronidase is administered by subcutaneous injection ~~may be substituted for IV rituximab~~ at the standard dose of 1400 mg, per institutional standard."
- In Section 7.2.1, in the second to last paragraph, "(+/- 2 days)" has been changed to "(+/- 3 days)."
- In Section 7.2.2, the following has been added in the fourth bullet point: "Biosimilars are allowed."
- In Section 7.2.3, the first paragraph has been revised to read: "CNS prophylaxis with intrathecal methotrexate may be included at the discretion of the treating investigator. If CNS prophylaxis is administered, the dose and schedule is at the discretion of the treating investigator. IV methotrexate is not allowed." In the second paragraph, "lumber" has been corrected to "lumbar."

Section 7.3 (Arm 2 [DEL and DHL]: R-CHOP-Venetoclax)

- The section title has been updated to include "and DHL."
- In Section 7.3.1, under the table, footnote * has been revised as follows: "An FDA-approved rituximab biosimilar ~~for DLBCL~~ or rituximab hyaluronidase may be substituted per institutional standards or as required by patient insurance coverage, but patients who start on rituximab should receive rituximab (or rituximab hyaluronidase) throughout, while patients who begin on a rituximab biosimilar should receive the biosimilar throughout. Rituximab hyaluronidase is administered by subcutaneous injection ~~may be substituted for IV rituximab~~ at the standard dose of 1400 mg, per institutional standard."
- In Section 7.3.1, in the last paragraph, "(+/- 2 days)" has been changed to "(+/- 3 days)."

- In Section 7.3.2, in the first bullet point, "at least" has been added to the first sentence, and the following third sentence has been added: "Febuxostat may be substituted in allopurinol allergic or intolerant patients."
- In Section 7.3.2, the following has been added as the second bullet point: "Sulfamethoxazole/ trimethoprim DS tablet PO three times weekly, or SS tablet once daily (or alternate PJP prophylaxis)."
- In Section 7.3.2, the following has been added in the third bullet point: "Biosimilars are allowed."
- In Section 7.3.3, the first paragraph has been revised to read: "CNS prophylaxis with intrathecal methotrexate may be included at the discretion of the treating investigator. If CNS prophylaxis is administered, the dose and schedule is at the discretion of the treating investigator. IV methotrexate is not allowed." In the second paragraph "lumber" has been corrected to "lumbar."

Section 7.4 (Arm 2 [DHL]: DA-EPOCH-R-Venetoclax)

The following note has been added: "**NOTE:** Accrual to the DHL cohort was permanently closed as of Update #03.

Section 8.2 (Dose Modifications for Venetoclax)

- The fourth paragraph has been revised as follows: "If venetoclax dose reductions beyond dose level -3 is required ~~or venetoclax is held for > 4 weeks~~, venetoclax will be discontinued."
- In Section 8.2.1, the DA-EPOCH-R column has been removed, and Dose Level -3 has been added to the table.
- In Section 8.2.2, the following changes have been made:
    - In the "Grade 3 or 4 neutropenia with infection and/or fever" row, the first sentence of the first bullet point has been revised to read: "If patient is currently receiving venetoclax, hold remaining doses of venetoclax for the cycle," and the following has been added as the third bullet point: "Reduce dose of venetoclax by one dose level with the next cycle."
    - In the "Grade 4 thrombocytopenia and Grade 3 thrombocytopenia with bleeding" row, the first sentence of the first bullet point has been revised to read: "If patient is currently receiving venetoclax, hold remaining doses of venetoclax for the cycle," and the former third bullet point has been replaced with the following: "Reduce dose of venetoclax by one dose level with the next cycle."
    - Footnote * has been removed.
- In Section 8.2.3, the following changes have been made:
    - In the "Grade 3 or 4 non-hematologic toxicity at least possible related to venetoclax" row, the first bullet point has been revised to read: "Hold remaining doses of venetoclax for the cycle. Missed doses of venetoclax will not be made up," and the following has been added as the second bullet point: "Reduce venetoclax dose by one dose level with the next cycle."
    - In the "Grade 2 non-hematologic toxicity at least possibly related to venetoclax" row, the second sentence of the first bullet point has been revised to read: "After resolution, resume the same dose of venetoclax," and the following has been added as the second bullet point: "If the same grade 2 toxicity recurs, hold remaining doses for the cycle and resume the next cycle reduced by one dose level."

Section 8.3 (Dose Modifications for DA-EPOCH-R)

- Above the "Criteria for Dose Adjustment of DA-EPOCH-R" table, the phrase "(with our without venetoclax)" has been removed.
- In the third row of the "Criteria for Dose Adjustment of DA-EPOCH-R" table, the first bullet point has been revised to read: "Reduce DA-EPOCH-R by one dose level," and the last three bullet points have been removed.

- In the "DA-EPOCH-R Dose Adjustments for Intra-Patient Dose Modification" table, footnote ‡ has been removed.

Section 8.4 (Other Dose Modifications for R-CHOP and DA-EPOCH-R)

- In Section 8.4.2 (Neuropathy), the following changes have been made:
  - The first bullet point has been revised to read: "If grade 2 peripheral sensory neuropathy develops, reduce vincristine by 25%. If grade 2 peripheral neuropathy persists at next cycle, reduce vincristine to 50% of starting dose. Dose will not be re-escalated. If greater than 2 dose reductions are required, the vincristine should be discontinued. If patient experiences grade 3 peripheral sensory neuropathy, hold vincristine until recovery to grade 1 or less and then resume at 50% of starting dose. If grade 3 peripheral sensory neuropathy recurs, permanently discontinue vincristine. For grade 4 peripheral sensory neuropathy, permanently discontinue vincristine."
  - The second bullet point has been revised to read: "Motor neuropathy: If patient experiences grade 2 motor neuropathy, reduce vincristine by 25%. If grade 2 toxicity persists at next cycle, reduce to 50% of starting dose. If more than 2 dose reductions are required, the vincristine should be discontinued. If patient experiences grade 3 motor neuropathy, hold vincristine until recovery to grade 1 or less and then resume at 50% of starting dose. If grade 3 motor neuropathy recurs, permanently discontinue vincristine. If grade 4 toxicity develops, permanently discontinue vincristine."
- In Section 8.4.3 (Ileus and Constipation), the last four sentences have been revised to read: "If ileus or constipation require hospitalization despite maximal supportive care, the next dose of vincristine should be reduced to 50% of starting dose. If ileus or constipation again requires hospitalization, the dose should be reduced to 25% of starting dose. If greater than 2 dose reductions are required, the vincristine should be discontinued. If symptoms do not recur at the reduced dose, the vincristine may be re-escalated at 25% increments with subsequent cycles."
- Section 8.4.6 (Other toxicities on R-CHOP) has been added.

Section 9.1 (Routine Adverse Event Reporting)

Section 9.1.1 has been updated with the current CTSU template language.

Section 13.0 (Statistical Considerations)

The sentence beginning "The text in Sections 13.1-13.4…" has been removed.

Section 13.1 (Study Design)

- In the first paragraph, the first sentence has been revised to read: "This is a randomized, open label, multi-center phase II/III trial designed to evaluate efficacy of Venetoclax in combination with R-CHOP in newly diagnosed adult patients with diffuse large b-cell lymphoma (DLBCL) and high grade b-cell lymphoma (HGBCL) with translocations of *MYC* and *BCL2* and/or *BCL6*…"
- The following note has been added to the end of the first paragraph: "**NOTE:** as of Update #03, central pathologic review is no longer included."
- In the second paragraph, "R-chemo" has been changed to "R-CHOP" and the last sentence has been revised as follows: "The study will only proceed to the phase III component if there is evidence of extended PFS in ~~both cohorts or in~~ the DEL cohort ~~only~~."
- The third paragraph has been revised to reflect the updated design.
- The former fourth paragraph has been removed.

Section 13.2 (Endpoints)

- In Section 13.2.1, in the third paragraph, "in phase II" has been added to the first sentence, and the following note has been added: "**NOTE:** Central review is no longer included in the phase III portion of the study as of Update #03."
- In Section 13.2.2, in the second paragraph, "during phase II" has been added to the first sentence, and the following note has been added: "**NOTE:** Central pathology review is no longer included as of Update #03."

Section 13.3 (Updated Statistical Design and Analysis Plans for Primary and Key Secondary Endpoints [Update #03])

This section has been completely revised to reflect the updated design. The original design as well as the design that was modified in Update #02 are provided in Appendix VII for reference.

Section 13.4 (Sample size, accrual time, and study duration)

This section has been completely revised to reflect the updated design.

Section 13.5 (Justification and Statistical Considerations for the Update #02 Sample Size Adjustment)

This section has been removed and is now in Appendix VII. Subsequent sections have been re-numbered accordingly.

Section 13.5 (Supplementary analysis plans)

In the fifth paragraph, the first sentence has been revised to read: "Agreement between local and central results for DEL status will be closely monitored throughout the accrual period for the phase II component of the study as part of a monitoring rule included in Section 13.6."

Section 13.6 (Monitoring the study)

The following note has been added to the end of the second paragraph: "**NOTE:** Central pathology review is no longer included as of Update #03."

Section 13.8 (Inclusion of Women and Minorities)

- The table has been updated to reflect the updated sample size.
- The ethnic and racial categories have been removed to align with the current Alliance model protocol template.

UPDATES TO THE MODEL CONSENT:

Official Study Title

The title has been updated to remove "double hit" lymphoma.

What am I being asked to do?

The references to double hit lymphoma have been removed.

Why is this study being done?

The reference to double hit lymphoma has been removed.

What is the usual approach to my lymphoma?
The reference to dose adjusted EPOCH-R has been removed.

What will happen if I decide to take part in this study?
In the first paragraph, the references to dose adjusted EPOCH-R have been removed.

What are the study groups?

- In the Group 1 and Group 2 bullet points, the references to dose adjusted EPOCH-R have been removed.
- In the Group 1 and Group 2 bullet points, the last sentences have been updated to read: "There will be about 145 people in this group" to reflect the updated sample size.
- In the Group 2 bullet point, the fifth sentence of the first paragraph has been revised to read: "Venetoclax is a pill taken by mouth on days…" and the last sentence of the second paragraph has been revised to read: "After the first dose of Venetoclax, you may have to wait for 6 to 12 hours for the blood draw."

What exams, tests, and procedures are involved in this study?
Under "Some exams, tests, and procedures are a necessary part of the research…" the first bullet point regarding the sample required for diagnosis confirmation has been removed.

What risks can I expect from taking part in this study?

- Under Drug Risks, after "Study Group 1 and Study Group 2," the reference to dose adjusted EPOCH-R has been removed.
- Under Drug Risks, the risk tables for dose adjusted EPOCH-R have been removed.

Who will see my medical information?
Cleveland Clinic has been removed from the list of organizations.

Replacement protocol and model consent documents have been issued.

ATTACH TO THE FRONT OF EVERY COPY OF THIS PROTOCOL

Research Study Informed Consent Document

Study Title for Participants: Testing the addition of a new anti-cancer drug, venetoclax, to usual chemotherapy for high grade B-cell lymphomas

Official Study Title for Internet Search on http://www.ClinicalTrials.gov: A051701, "Randomized phase II/III study of venetoclax (ABT 199) plus chemoimmunotherapy for MYC/BCL2 double-expressing lymphomas," (NCT**03984448**)

Overview and Key Information

What am I being asked to do?

We are asking you to take part in a research study. This study has public funding from the National Cancer Institute (NCI), part of the National Institutes of Health (NIH) in the United States Department of Health and Human Services. We do research studies to try to answer questions about how to prevent, diagnose, and treat diseases like cancer.

We are asking you to take part in this research study because you have double expressing lymphoma. Double expressing lymphomas are diffuse large B-cell lymphomas that have the MYC and BCL2 proteins on the surface of the cancer cells, which also predicts for aggressive behavior.

Taking part in this study is your choice.

You can choose to take part or you can choose not to take part in this study. You also can change your mind at any time. Whatever choice you make, you will not lose access to your medical care or give up any legal rights or benefits.

This document has important information to help you make your choice. Take time to read it. Talk to your doctor, family, or friends about the risks and benefits of taking part in the study. It's important that you have as much information as you need and that all your questions are answered. See the "Where can I get more information?" section for resources for more clinical trials and general cancer information.

This study is conducted by the Alliance for Clinical Trials in Oncology, a national clinical research group supported by the National Cancer Institute. The Alliance is made up of cancer doctors, health professionals, and laboratory researchers, whose goal is to develop better treatments for cancer, to prevent cancer, to reduce side effects from cancer, and to improve the quality of life of cancer patients.

Why is this study being done?

This study is being done to answer the following question:

Can we lower the chance of your lymphoma returning or getting worse by adding a new drug to the usual combination of drugs?

We are doing this study because we want to find out if this approach is better or worse than the usual approach for your lymphoma. The usual approach is defined as care most people get for double expressing lymphoma.

What is the usual approach to my lymphoma?

The usual approach for patients who are not in a study would be the usual chemotherapy regimen used in this trial (R-CHOP) without the addition of the study drug venetoclax. The usual chemotherapy regimens are FDA approved. For patients who get the usual approach for this cancer, about 40 out of 100 are free of cancer after 5 years.

What are my choices if I decide not to take part in this study?

- You may choose to have the usual approach described above.
- You may choose to take part in a different research study, if one is available.
- You may choose not to be treated for cancer.
- You may choose to only get comfort care to help relieve your symptoms and not get treated for your cancer.

What will happen if I decide to take part in this study?

If you decide to take part in this study, you will either get the usual chemotherapy (R-CHOP) for up to 18 weeks, or you will get the usual chemotherapy (R-CHOP) plus the study drug venetoclax for up to 18 weeks. The chemotherapy regimen known as R-CHOP includes the following drugs: rituximab (R), cyclophosphamide (C), doxorubicin (H), vincristine (O), and prednisone (P).

After you finish your study treatment, your doctor will continue to follow your condition and watch you for side effects for up to 5 years after you registered to the study. You will have clinic visits every 3 months for 2 years, then every 6 months until 5 years after you are registered to the study. After 5 years, your doctor will follow up with you either in clinic or by phone every 6 months for up to 10 years after you registered to the study.

What are the risks and benefits of taking part in this study?

There are both risks and benefits to taking part in this study. It is important for you to think carefully about these as you make your decision.

Risks

We want to make sure you know about a few key risks right now. We give you more information in the "What risks can I expect from taking part in this study?" section.

If you choose to take part in this study, there is a risk that the study approach may not be as good as the usual approach at treating your lymphoma.

There is also a risk that you could have side effects from the study drugs. These side effects may be worse and may be different than you would get with the usual approach for your cancer.

Some of the most common side effects that the study doctors know about are:

- Fatigue
- Nausea
- Diarrhea
- Constipation
- Loss of appetite

There may be some risks that the study doctors do not yet know about.

Benefits

There is evidence that both the usual approach and the study approach are effective in the treatment of your type of cancer. It is not possible to know now if the study drug will extend your life or extend your time without disease compared to the usual approach. This study will help the study doctors learn things that will help people in the future.

If I decide to take part in this study, can I stop later?

Yes, you can decide to stop taking part in the study at any time.

If you decide to stop, let your study doctor know as soon as possible. It's important that you stop safely. This may mean slowly stopping the study drugs so that there is not a sudden unsafe change, risk to your health. If you stop, you can decide if you want to keep letting the study doctor know how you are doing.

Your study doctor will tell you about new information or changes in the study that may affect your health or your willingness to continue in the study.

Are there other reasons why I might stop being in the study?

Yes. The study doctor may take you off the study if:

- Your health changes and the study is no longer in your best interest.
- New information becomes available and the study is no longer in your best interest.
- You do not follow the study rules.

- For women: You become pregnant while on the study.
- The study is stopped by the Institutional Review Board (IRB), Food and Drug Administration (FDA), or study sponsor (National Cancer Institute (NCI)). The study sponsor is the organization who oversees the study.

It is important that you understand the information in the informed consent before making your decision. Please read, or have someone read to you, the rest of this document. If there is anything you don't understand, be sure to ask your study doctor or nurse.

What is the purpose of this study?

The purpose of this study is to compare the usual treatment alone to using venetoclax plus the usual treatment. The addition of venetoclax to the usual treatment may or may not increase the chance of your cancer going into remission and not returning. But, it could also cause side effects, which are described in the risks section below.

This study will help the study doctors find out if this different approach is better than the usual approach. To decide if it is better, the study doctors will be looking to see if the study drug increases the life of patients by 6 months or more compared to the usual approach.

What are the study groups?

This study has 2 study groups.

- **Group 1**

  If you are in this group, you will get the usual chemotherapy used to treat your type of cancer (R-CHOP). You will get most of these drugs through a vein in the arm, and one drug by mouth as a pill. The IV drugs in R-CHOP (rituximab, cyclophosphamide, doxorubicin, and vincristine) are administered on day 1 of each 21-day cycle. The prednisone pills with R-CHOP are taken by mouth on days 1 through 5 of every cycle. This study has 6 cycles.

  There will be about 145 people in this group.

- **Group 2**

  If you are in this group, you will get a study drug called venetoclax plus the usual chemotherapy used to treat your type of cancer (R-CHOP). You will get most of these drugs through a vein in the arm, and two drugs by mouth. The IV drugs in R-CHOP (rituximab, cyclophosphamide, doxorubicin, and vincristine) are administered on day 1 of each 21-day cycle. The prednisone pills with R-CHOP are taken by mouth on days 1 through 5 of every cycle. Venetoclax is a pill taken by mouth on days 4 through 8 of cycle 1 and days 1 through 5 of cycles 2 through 6. This study has 6 cycles. You will be asked to complete a daily drug diary to track doses of venetoclax taken or missed.

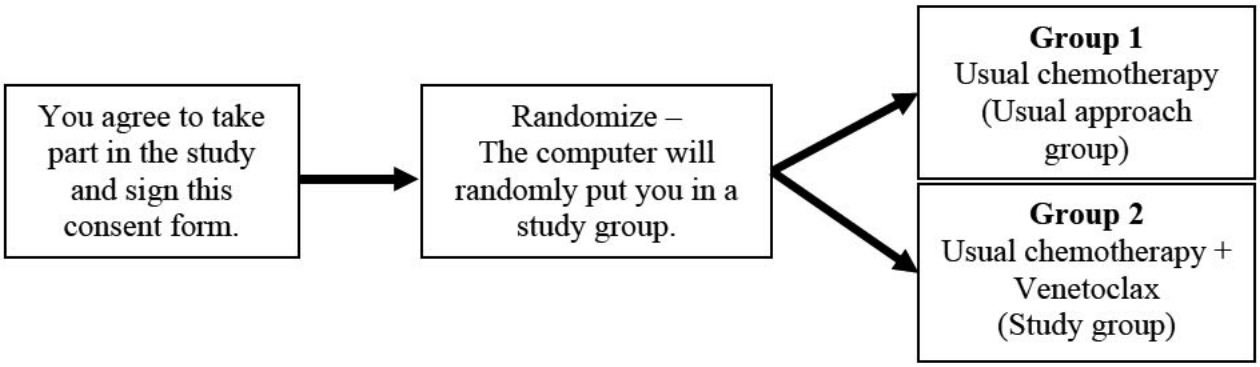
If you are in this group, you should drink 6-8 glasses of water a day beginning 2 days before the first dose of each cycle. You should avoid chewing, crushing, or breaking the venetoclax. Venetoclax should be swallowed intact with meals. After the first dose of Venetoclax, you may have to wait for 6 to 12 hours for the blood draw.

You will not be able to get additional doses of the drug, venetoclax. This drug is not approved by the FDA for treatment of your disease.

There will be about 145 people in this group.

We will use a computer to assign you to one of the study groups. This process is called "randomization." It means that your doctor will not choose and you cannot choose which study group you are in. You will be put into a group by chance. You will have an equal chance of being in Group 1 or Group 2.

Another way to find out what will happen to you during this study is to read the chart below. Start reading at the left side and read across to the right, following the lines and arrows.



What exams, tests, and procedures are involved in this study?

Before you begin the study, your doctor will review the results of your exams, tests, and procedures. This helps your doctor decide if it is safe for you to take part in the study. If you join the study, you will have more exams, tests, and procedures to closely monitor your safety and health. Most of these are included in the usual care you would get even if you were not in a study.

Listed below are exams, tests, and procedures that need to be done as part of this study to monitor your safety and health, but may not be included in the usual care. We will use them to carefully follow the effects of the study treatment, including preventing and managing side effects.

These exams, tests, and procedures to monitor your safety and health include:

- Blood tests on Day 1 of each cycle and twice per week for three weeks between cycles
- Bone marrow biopsy before you begin the study and when you finish study treatment

Some exams, tests, and procedures are a necessary part of the research study, but would not be included in usual care. Listed below are procedures that will be done for research purposes only.

- If you choose to take part in this study, you will be asked to complete questionnaires as part of this study. The questionnaires will be used to find out more about how you feel during study treatment and side effects of the treatments, and you will complete them on your own mobile device. Your answers will be visible to the study staff for research purposes. Your doctor may ask you some of the same questions in person during your clinical visits. You don't have to answer any question that makes you feel uncomfortable.

Questionnaires (Electronic surveys): For this study, you will be asked to complete the questionnaires on your personal smartphone or electronic device, which can be used to enter your answers to the questions. If you need help installing and/or using the questionnaire application (or "app") on your phone or tablet, ask for help at your study site. Someone may help you enter your answers in the device if you need.

The use of your own electronic device on a cellular network may result in a small cost to your data plan. You will not be reimbursed for any costs to your data plan. Regardless of the device you use, your answers and personal information will not be stored on the device.

Your survey answers will be sent to the research database and will be kept private as described in the section below called, "Who will see my medical information?" Your e-mail address will only be used for this survey and will not be used for mail or marketing purposes. The Alliance will not keep your email address.

If using your phone or a tablet is not possible or if you prefer not to use your own device, you will not be able to participate in this part of the study, but you will still be able to participate in the main study.

You will be asked to complete questionnaires at the following times:

- Weekly for the first 6 weeks and then every 3 weeks thereafter while on active treatment
- During your clinical visits on day 1 of each cycle

What risks can I expect from taking part in this study?

General Risks

If you choose to take part in this study, there is a risk that the study approach may not be as good as the usual approach for your lymphoma at inducing remission and preventing your lymphoma from coming back.

You also may have the following discomforts:

- Spend more time in the hospital or doctor's office.
- Be asked sensitive or private questions about things you normally do not discuss.
- May not be able to take part in future studies.

The drugs used in this study could be very harmful to an unborn or newborn baby. There may be some risks that doctors do not yet know about. It is very important that you check with your study doctor about what types of birth control or pregnancy prevention to use during the study and for 12 months after you have completed the study.

This study will use a sample of your tissue. Generally, your hospital will keep some of your tissue. This tissue may be used to help treat your cancer in the future. Because this study will need to use some of this tissue, there is a small risk that it could be used up.

Bone Marrow Biopsy Risks

There may be some temporary pain or discomfort associated with bone marrow biopsies at the site where the needle is inserted. The side effects associated with obtaining bone marrow samples include pain at the site of the procedure, as well as possible bleeding, bruising or swelling. Pain can be treated with regular pain medications. There is also a very small chance that you could develop an infection at the site of the procedure.

Blood Collection Risks

There can be mild pain, or some bleeding or bruising when blood is drawn. Rarely, an infection can happen where the needle was placed. Feeling dizzy or fainting can also happen, but may only last a few minutes after blood is drawn.

Side Effect Risks

The drugs used in this study may affect how different parts of your body work such as your liver, kidneys, heart, and blood. The study doctor will test your blood and let you know if changes occur that may affect your health.

There is also a risk that you could have other side effects from the study drugs.

Here are important things to know about side effects:

1. The study doctors do not know who will or will not have side effects.
2. Some side effects may go away soon, some may last a long time, and some may never go away.
3. Some side effects may make it hard for you to have children.
4. Some side effects may be mild. Other side effects may be very serious and even result in death.

You can ask your study doctor questions about side effects at any time. Here are important ways to make side effects less of a problem:

- If you notice or feel anything different, tell your study doctor. He or she can check to see if it is a side effect.
- Your study doctor will work with you to treat your side effects.
- Your study doctor may adjust the study drugs to try to reduce side effects.

This study is looking at a combination of the usual drugs used to treat this type of cancer plus a study drug. This different combination of drugs may increase your side effects or may cause new side effects.

Drug Risks

The tables below show the most common and most serious side effects doctors know about. Keep in mind that there might be other side effects doctors do not yet know about. If important new side effects are found, the study doctor will discuss these with you.

Study Group 1 and Group 2 – Possible side effects of R-CHOP are listed in the tables below. These drugs are part of the usual approach for treating this type of cancer:

Possible Side Effects of R-CHOP (Rituximab, Cyclophosphamide, Doxorubicin, Vincristine, and Prednisone)

COMMON, SOME MAY BE SERIOUS In 100 people receiving R-CHOP (Rituximab, Cyclophosphamide, Doxorubicin, Vincristine, and Prednisone), more than 20 and up to 100 may have:
• Hair loss • Constipation, nausea, vomiting, loss of appetite • Chills, fever • Sores in mouth • Reaction during or following infusion of the drug • Infection, especially when white blood cell count is low • Anemia which may require blood transfusions • Tiredness • Absence of menstrual period which may decrease the ability to have children • Blood in urine • Red colored urine, saliva, or sweat • Pain or redness at the site of injection or area of previous radiation • Numbness and tingling of arms and legs • Weakness and difficulty walking • In children and adolescents: decreased height • Loss of bone tissue • Mood swings • Skin changes, acne • Swelling of the body, tiredness, bruising • Swelling of lower legs

- High blood pressure which may cause headaches, dizziness, blurred vision
- Pain
- Increased appetite and weight gain
- Weight gain in the belly, face, back and shoulders

OCCASIONAL, SOME MAY BE SERIOUS

In 100 people receiving R-CHOP (Rituximab, Cyclophosphamide, Doxorubicin, Vincristine, and Prednisone), from 4 to 20 may have:

- Damage to the bone marrow (irreversible) which may cause infection, bleeding, may require transfusions
- Damage to the bone which may cause joint pain and loss of motion
- Loss or absence of sperm which may lead to an inability to father children
- Stuffy nose
- Fluid around the heart
- Heart attack or heart failure which may cause shortness of breath, swelling of ankles, cough or tiredness which may occur years after the dose
- Swelling of the body which may cause shortness of breath
- Swelling and redness at the site of the medication injection or area of previous radiation
- Sores in the throat or stomach
- Diarrhea
- Hepatitis, or liver damage which may cause yellow eyes and skin
- Allergic reaction which may cause rash, low blood pressure, wheezing, shortness of breath, swelling of the face or throat
- Cancer of the bone marrow (leukemia) caused by chemotherapy
- Damage to organs which may cause infection, bleeding, may require transfusions
- A tear or hole
- Darkening of the nail beds or skin or hands and feet
- Loss of nails
- Drooping eyelids
- Hoarseness
- Cloudiness of the eye, visual disturbances
- Glaucoma
- Non-healing wound
- Diabetes
- Kidney stones
- Heartburn
- Bruising, bleeding
- Abnormal heartbeat
- Sores in eye
- A tear or hole in the bowels that may require surgery
- Kidney damage which may require dialysis
- Cough

• Scarring of the lungs • Blockage of internal organs which may cause shortness of breath, wheezing, vomiting • Increased sweating • Itching, rash, blisters on the skin • Severe skin rash with blisters and peeling which can involve mouth and other parts of the body • Low blood pressure which may cause feeling faint

RARE, AND SERIOUS In 100 people receiving R-CHOP (Rituximab, Cyclophosphamide, Doxorubicin, Vincristine, and Prednisone), 3 or fewer may have:
• A new cancer including cancer of bone marrow (leukemia) caused by chemotherapy • Swelling of the brain which may cause dizziness and confusion • Infection, especially when white blood cell count is low • Bruising, bleeding • Severe blood infection • Seizure • Bleeding from sores in the stomach • Broken bones • Damage to the brain caused by a virus which may result in tiredness, weakness, changes in thinking, and disability. This is called progressive multifocal leukoencephalopathy (PML). • Heart stops beating.

Study Group 2 - In addition to side effects listed above, people who are in Group 2 may also have some side effects from venetoclax. These side effects are listed below.

Possible Side Effects of Venetoclax

COMMON, SOME MAY BE SERIOUS In 100 people receiving venetoclax (ABT-199), more than 20 and up to 100 may have:
• Anemia which may require blood transfusion • Diarrhea, nausea • Tiredness • Infection, especially when white blood cell count is low

OCCASIONAL, SOME MAY BE SERIOUS In 100 people receiving venetoclax (ABT-199), from 4 to 20 may have:
• Constipation, vomiting • Fever • Bruising, bleeding • Pain in joints • Headache

• Cough • High blood pressure which may cause headaches, dizziness, blurred vision

RARE, AND SERIOUS In 100 people receiving venetoclax (ABT-199), 3 or fewer may have:
• Kidney damage which may require dialysis

Additional Drug Risks

The study drug could interact with other drugs. Drugs that are metabolized by the protein CYP3A4 may not be allowed to be taken on this study. Your study doctor will give you a drug information handout and wallet card that lists these possible interactions. Share this information with your family members, caregivers, other health care providers, and pharmacists.
Rarely, there are problems getting enough supplies of the study drug. If that happens, your doctor will talk with you about your options.

Participants receiving venetoclax should avoid eating grapefruit, Seville oranges, starfruit or their juices. Participants receiving venetoclax should also avoid getting live vaccines.

What are my responsibilities in this study?

If you choose to take part in this study you will need to:

- Keep your study appointments.
- Tell your doctor about:
  - all medications and supplements you are taking
  - any side effects
  - any doctors' visits or hospital stays outside of this study
  - if you have been or are currently in another research study.
- Write down in your medication diary when you take the study drug at home.

For women: Do not get pregnant or breastfeed while taking part in this study. **For men:** Do not father a baby while taking part in this study. **For all:** Tell your study doctor right away if you think that you or your partner have become pregnant during the study or within 12 months after your last dose of study drug.

What are the costs of taking part in this study?

You and/or your insurance plan will need to pay for the costs of medical care you get as part of the study, just as you would if you were getting the usual care for your cancer. This includes:

- the costs of tests, exams, procedures, and drugs that you get during the study to monitor your safety, and prevent and treat side effects. This includes the blood tests on Day 1 of each cycle and between cycles and the bone marrow biopsies before you begin the study and when you finish study treatment.

- your insurance co-pays and deductibles.
- the costs of getting the study agents ready and giving it to you.
- the costs of the usual chemotherapy regimen.

Talk to your insurance provider and make sure that you understand what your insurance pays for and what it doesn't pay for if you take part in this clinical trial. Also, find out if you need approval from your plan before you can take part in the study.

You will be asked to take oral drugs including sulfamethoxazole/trimethoprim, acyclovir, omeprazole, and allopurinol to prevent side effects. Some insurance companies may not cover these costs. You are encouraged to talk with your insurance provider about coverage for these drugs.

Ask your doctor or nurse for help finding the right person to talk to if you are unsure which costs will be billed to you or your insurance provider.

If you are in Group 2, you or your insurance provider will not have to pay for the venetoclax while you take part in this study.

Taking part in this study may mean that you need to make more visits to the clinic or hospital than if you were getting the usual approach to treat your cancer. You may:

- Have more travel costs.
- Need to take more time off work.
- Have other additional personal costs.

You will not be paid for taking part in this study. The research may lead to new tests, drugs, or other products for sale. If it does, you will not get any payment.

What happens if I am injured because I took part in this study?

If you are injured as a result of taking part in this study and need medical treatment, please talk with your study doctor right away about your treatment options. The study sponsors will not pay for medical treatment for injury. Your insurance company may not be willing to pay for a study-related injury. Ask them if they will pay. If you do not have insurance, then you would need to pay for these medical costs.

If you feel this injury was caused by medical error on the part of the study doctors or others involved in the study, you have the legal right to seek payment, even though you are in a study. Agreeing to take part in this study does not mean you give up these rights.

Who will see my medical information?

Your privacy is very important to us. The study doctors will make every effort to protect it. The study doctors have a privacy permit to help protect your records if there is a court case. However, some of your medical information may be given out if required by law. If this should happen, the study doctors will do their best to make sure that any information that goes out to others will not identify who you are.

Some of your health information, such as your response to cancer treatment, results of study tests, and medicines you took, will be kept by the study sponsor in a central research database. However, your name and contact information will not be put in the database. If information from this study is published or presented at scientific meetings, your name and other personal information will not be used.

There are organizations that may look at your study records. Your health information in the research database also may be shared with these organizations. They must keep your information private, unless required by law to give it to another group.

Some of these organizations are:

- The study sponsor and any company supporting the study now or in the future.
- The NCI Central IRB, which is a group of people who review the research with the goal of protecting the people who take part in the study.
- The FDA and the groups it works with to review research.
- The NCI and the groups it works with to review research.
- The NCI's National Clinical Trials Network and the groups it works with to conduct research (including the Imaging and Radiation Oncology Core (IROC)).

In addition to storing data in the study database, data from studies that are publicly funded may also be shared broadly for future research with protections for your privacy. The goal of this data sharing is to make more research possible that may improve people's health. Your study records may be stored and shared for future use in public databases. However, your name and other personal information will not be used.

Some types of future research may include looking at your information and information from other patients to see who had side effects across many studies or comparing new study data with older study data. However, right now we don't know what research may be done in the future using your information. This means that:

- You will not be asked if you agree to take part in the specific future research studies using your health information.
- You and your study doctor will not be told when or what type of research will be done.
- You will not get reports or other information about any research that is done using your information.

Where can I get more information?

You may visit the NCI web site at http://cancer.gov/ for more information about studies or general information about cancer. You may also call the NCI Cancer Information Service to get the same information at: 1-800-4-CANCER (1-800-422-6237).

A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

You can talk to the study doctor about any questions or concerns you have about this study or to report side effects or injuries. Contact the study doctor (*insert name of study doctor[s]*) at (*insert telephone number, and email address if appropriate*).

For questions about your rights while in this study, call the (*insert name of organization or center*) Institutional Review Board at (*insert telephone number*).

Optional studies that you can choose to take part in

This part of the consent form is about optional studies that you can choose to take part in. They are separate from the main study described above. These optional studies will not benefit your health. The researchers leading this optional study hope the results will help other people with cancer in the future. The results will not be added to your medical records and you or your study doctor will not know the results.

Taking part in these optional studies is your choice. You can still take part in the main study even if you say "no" to any or all of these studies. There is no penalty for saying "no." You and your insurance company will not be billed for these optional studies. If you sign up for, but cannot complete any of these studies for any reason, you can still take part in the main study.

Circle your choice of "yes" or "no" for each of the following studies.

Optional sample collections for known laboratory studies and/or storage for possible future studies

Researchers are trying to learn more about cancer and other health problems using blood and tissue samples from people who take part in clinical trials. By studying these samples, researchers hope to find new ways to prevent, detect, treat, or cure diseases.

Some of these studies may be about how genes affect health and disease. Other studies may look at how genes affect a person's response to treatment. Genes carry information about traits that are found in you and your family. Examples of traits are the color of your eyes, having curly or straight hair, and certain health conditions that are passed down in families. Some of the studies may lead to new products, such as drugs or tests for diseases.

Unknown future studies

If you choose to take part in this optional study, leftover tissue samples that were collected under the study will be stored for future use and blood will be collected and stored for future use. Storing samples for future studies is called "biobanking." The biobank is being run by the Alliance for Clinical Trials in Oncology and is supported by the NCI. This is a publicly funded study. Samples from publicly funded studies are required to be shared as broadly as possible. However, we will protect your privacy. The goal of this is to make more research possible that may improve people's health.

The biobank is a public research resource. It has controlled access. This means that researchers who want to get samples and data from it must submit a specific research request. The request identifies who they are and what their planned research project is. Before getting the samples and data, the researchers must agree to keep the data private, only use it for their planned research project, and never use it to try to identify you.

Right now, we don't know what research may be done in the future using your blood and tissue samples. This means that:

- You will not be asked if you agree to take part in the future research studies.
- You and your study doctor will not be told when or what type of research will be done.
- You will not get reports or other information about any research that is done using your samples.

Unknown future research studies may include sequencing of all or part of your DNA. This is called genomic sequencing. Sequencing allows researchers to identify your genetic code. Changes in your genetic code may just be in your tumor tissue. These are called somatic changes. Changes may also be in your normal tissue and passed down through your family. For example, these genetic changes may be passed down to your children in the same way that eye and hair color are passed down. These are called germline changes. If only tumor tissue is sequenced, we will not know if a genetic change in your tumor is also in your normal tissue. This is why sometimes both normal tissue and tumor tissue are sequenced. This helps researchers understand if a genetic change happened only in your cancer tissue, or in your normal tissue as well.

What is involved in this optional sample collection?

If you agree to take part, here is what will happen next:

1. About 2 tablespoons of blood will be collected from a vein in your arm before you begin the study and about 2 teaspoons of blood will be collected from a vein in your arm at the end of cycle 1, the end of cycle 2, the end of treatment, and then every 3 months for 2 years from the end of treatment. A sample from the tissue that was collected at the time of your diagnosis will be sent to the biobank.
2. Your sample will be stored in the biobank. There is no limit on the length of time we will keep your samples and research information. The samples will be kept until they are used for research or destroyed.

3. Researchers can only get samples from the biobank after their research has been approved by experts. Researchers will not be given your name or contact information.
4. Some of your genetic and health information may be placed in central databases for researchers to use. The databases will not include your name or contact information.

What are the risks in this optional sample collection?

- The most common risks related to drawing blood from your arm are brief pain and maybe a bruise.
- Generally, hospitals will keep some of your tissue. This tissue may be used to help treat your cancer in the future. There is a small risk that when this tissue sample is submitted to the biobank for this optional sample collection, your tissue could be used up.
- Your medical and genetic information is unique to you. There is a risk that someone outside of the research study could get access to your study records or trace information in a database back to you. They could use that information in a way that could harm you. Researchers believe the chance that someone could access and misuse your information is very small. However, the risk may increase in the future as people find new ways of tracing information.
- In some cases, this information could be used to make it harder for you to get or keep a job and get or keep health insurance. There are laws against the misuse of genetic information, but they may not give full protection. For more information about the laws that protect you, ask your study doctor or visit: https://www.genome.gov/10002328/

How will information about me be kept private?

Your privacy is very important to the study researchers and biobank. They will make every effort to protect it. Here are just a few of the steps they will take:

1. They will remove identifiers, such as your initials, from your sample and information. They will replace them with a code number. There will be a master list linking the code numbers to names, but they will keep it separate from the samples and information.
2. Researchers who study your sample and information will not know who you are. They also must agree that they will not try to find out who you are.
3. Your personal information will not be given to anyone unless it is required by law.
4. If research results are published, your name and other personal information will not be used.

What are the benefits to taking part in this optional sample collection?

You will not benefit from taking part.

The researchers, using the samples from you and others, might make discoveries that could help people in the future.

Are there any costs or payments to this optional sample collection?

There are no costs to you or your insurance. You will not be paid for taking part in this study. The research may lead to new tests, drugs, or other products for sale. If it does, you will not get any payment.

What if I change my mind about this optional sample collection?

If you decide you no longer want your samples to be used, you can call the study doctor, (*insert name of study doctor for main trial*), at (*insert telephone number of study doctor for main trial*), who will let the biobank know. Then, any sample that remains in the biobank will be destroyed or returned to your study doctor. This will not apply to any samples or related health information that have already been given to or used by researchers.

What if I have questions about this optional sample collection?

If you have questions about the use of your samples for research, contact the study doctor, (*insert name of study doctor for main trial*), at (*insert telephone number of study doctor for main trial*).

Please circle your answer below to show if you would or would not like to take part in each optional study:

Samples for unknown future studies:

I agree that my samples and related health information may be kept in a biobank for use in future health research.

1) YES NO

Contact for Future Research

I agree that my study doctor, or someone on the study team, may contact me or my doctor to see if I wish to participate in other research in the future.

2) YES NO

This is the end of the section about optional studies.

My signature agreeing to take part in the study

I have read this consent form or had it read to me. I have discussed it with the study doctor and my questions have been answered. I will be given a signed and dated copy of this form. I agree to take part in the main study. I also agree to take part in any additional studies where I circled "yes".

Participant's signature

Date of signature

Signature of person(s) conducting the informed consent discussion

Date of signature