

FAST FACTS

A051701 - RANDOMIZED PHASE II/III STUDY OF VENETOCLAX (ABT 199) PLUS CHEMOIMMUNOTHERAPY FOR MYC/BCL2 DOUBLE-HIT AND DOUBLE EXPRESSING LYMPHOMAS

Eligibility Criteria (Step 1)

1. Documentation of Disease

- a. Pathologic diagnosis of Diffuse Large B-cell lymphoma (DLBCL) or High grade B-cell lymphoma not otherwise specified (HGBCL NOS). Eligible subtypes include DLBCL NOS, EBV+ DLBCL, HBCL NOS, and DLBCL/HGBCL transformed from an underlying indolent B-cell lymphoma. Patients with T-cell/histiocyte rich large B-cell lymphoma and primary mediastinal B-cell lymphoma are not eligible.
- b. Double Hit Lymphoma (DHL) or Double Expressing Lymphoma (DEL)
 - i. DHL is defined as high grade B-cell lymphoma with one of the below:
 1. Translocations of MYC and BCL2
 2. Translocations of MYC and BCL2 and BCL6 (triple hit lymphoma)
 3. Translocations of MYC and BCL6 without BCL2 translocation BUT with IHC expression of BCL2 ($\geq 50\%$)
 - ii. DEL is defined as DLBCL or high grade B-cell lymphoma NOS with protein expression by IHC of both MYC ($\geq 40\%$) and BCL2 ($\geq 50\%$) in the absence of dual translocations of both MYC and BCL2 and/or *BCL6*. (Double Expressing Lymphoma, DEL). Local determination of FISH and 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.
 - c. The diagnosis of DLBCL/HGBCL and assessment of DEL/DHL will be performed per standardized guidelines at local institutions and patients will be enrolled based on local determination. Cases submitted as DHL must demonstrate the presence of a MYC translocation as well as a translocation of BCL2, BCL6, or both. 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.
 - Patients must have FDG-avid disease on PET/CT.

2. Prior Treatment

- a. No prior treatment for DLBCL/HGBCL is allowed with the exception of corticosteroids administered for palliation, or a single cycle of either R-CHOP or DA-EPOCH-R administered prior to enrollment. Corticosteroids or local radiation therapy are also allowed. Patients may have received intrathecal chemotherapy for CNS prophylaxis prior to registration. This single pre-registration cycle is being allowed to facilitate enrolling patients who required immediate initiation of therapy for rapidly progressing disease, or for patients where FISH or IHC results returned after initiation of chemotherapy rendered them protocol eligible.

Patients with DLBCL or HGBCL transformed from an underlying indolent lymphoma cannot have received prior chemotherapy, but prior anti-CD20 monoclonal antibody therapy or radiation therapy for an indolent B-cell lymphoma is allowed.

3. Not pregnant and not nursing, because this study involves an investigational agent whose genotoxic, mutagenic and teratogenic effects on the developing fetus and newborn are unknown.

Therefore, for women of childbearing potential only, a negative (if your test schedule specifically indicates a urine or serum pregnancy test, add that information at this point) pregnancy test done ≤ 14 days prior to registration is required.

4. **Age** 18-80 years

5. **ECOG Performance Status 0-2**

6. Required Initial Laboratory Values*:

Absolute Neutrophil Count (ANC) $\geq 1,000/\text{mm}^3$

Platelet Count $\geq 100,000/\text{mm}^3$

Creatinine ≤ 1.5 mg/dL OR

Calc. Creatinine Clearance ≥ 50 mL/min

Total Bilirubin ≤ 2.0 mg/dL**

AST and ALT ≤ 3 times institution upper limit of normal (ULN)

* Unless attributable to lymphoma

** Unless attributable to Gilbert's disease

7. Archival tissue must be available for submission in all patients for histopathology review, though participation in correlative substudies is optional.

8. Comorbid conditions

No active ischemic heart disease or congestive heart failure, and LVEF $\geq 45\%$

No known active HIV disease. Human immunodeficiency virus (HIV)-infected patients on effective anti-retroviral therapy with undetectable viral load within 6 months are eligible for this trial.

No known lymphomatous involvement of the CNS. A lumbar puncture or neuroimaging prior to study enrollment is not required in the absence of neurological signs or symptoms concerning for CNS involvement.

No active Hepatitis B or Hepatitis C infection. Patients with prior HBV exposure (positive HBV core antibody and/or surface antigen) are eligible if they have no detectable viral load, and are taking appropriate prophylactic antiviral therapy to prevent reactivation. Patients with history of HCV are eligible if they have been treated for HCV and have an undetectable HCV viral load.

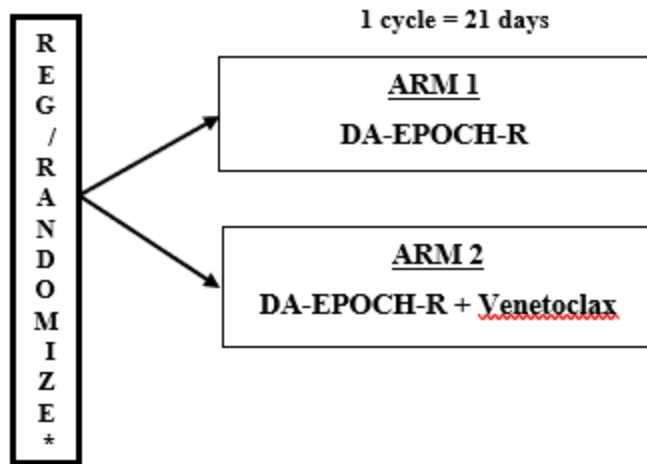
9. Concomitant medications

Chronic concomitant treatment with strong inhibitors of CYP3A4 is not allowed on this study. Patients on strong CYP3A4 inhibitors must discontinue the drug for 14 days prior to initiation of venetoclax. See Section 8.1.9 for more information.

Chronic concomitant treatment with strong CYP3A4 inducers is not allowed.

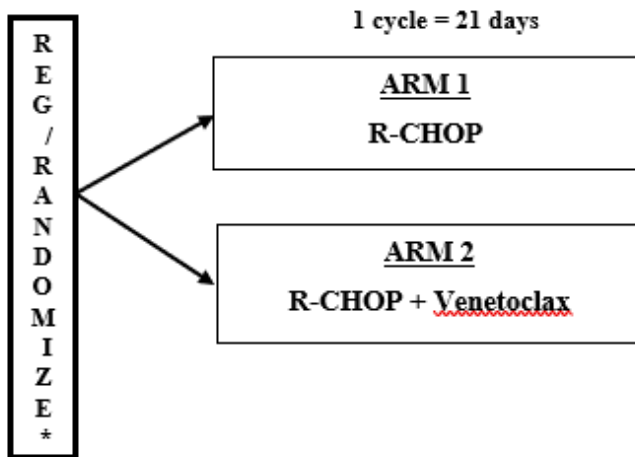
Patients must discontinue the drug 14 days prior to the start of venetoclax. See Section 8.1.10 for more information.

Schema for DHL Cohort



NOTE: The DHL cohort was permanently closed to accrual with Update #03.

Schema for DEL cohort



* Local determination of lymphoma subtype, DHL, or DEL, by FISH and IHC respectively, will be performed per standardized guidelines and will be acceptable for registration/randomization. Patients can receive a single cycle of R-CHOP or DA-EPOCH-R prior to registration/randomization, but that 21 day treatment cycle must be completed prior to beginning cycle 1 of protocol therapy. Patients will be stratified by IPI (low/low-intermediate (0-2) vs. high-intermediate/high (3-5)) score, and one prior cycle of R-chemo (yes vs. no).

Treatment is to continue for a total of 6 cycles, or until disease progression or unacceptable adverse event. Patients who received a single cycle of R-CHOP or DA-EPOCH-R prior to registration/randomization, will count that initial cycle towards the 6 total cycles and are to receive 5 cycles of therapy on protocol, or until disease progression or unacceptable adverse event. Patients will be followed for 10 years or until death, whichever comes first.

Please refer to the full protocol text for a complete description of the eligibility criteria and treatment plan.