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

Eligibility Criteria

- Pathologic diagnosis of Diffuse Large B-cell lymphoma (DLBCL) or High grade B-cell lymphoma (HGBCL)
- High grade B-cell lymphoma with translocations of *MYC* and *BCL2* (Double Hit Lymphoma, DHL), or DLBCL or high grade B-cell lymphoma NOS with protein expression by IHC of both MYC (≥40%) and BCL2 (≥50%) in the absence of dual translocations (Double Expressing Lymphoma, DEL).
- 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.
- Not pregnant and not nursing
- Age ≥ 18 years
- ECOG Performance Status 0-2
- No active ischemic heart disease or congestive heart failure, and LVEF ≥ 45%
- No active HIV disease
- No known lymphomatous involvement of the CNS
- No active Hepatitis B or Hepatitis C infection
- No chronic concomitant treatment with strong inhibitors of CYP3A4
- No chronic concomitant treatment with strong CYP3A4 inducers

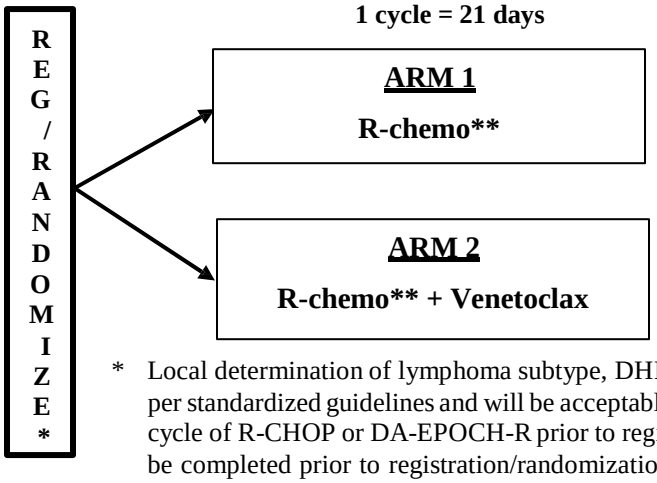
Required Initial Laboratory Values*

Platelet Count	≥ 100,000mm^3
Absolute Neutrophil Count (ANC)	≥ 1,000/mm^3
Creatinine	≤ 1.5 mg/dL
OR Calc. Creatinine Clearance	≥ 50 mL/min
Total Bilirubin	≤ 2.0 mg/dL**

**Unless attributable to lymphoma*

***Unless attributable to Gilbert's disease*

Schema



* 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 registration/randomization. Patients will be stratified by subtype (DEL vs. DHL) the IPI (low/intermediate (0-2) vs. high (3-5)) score, and one prior cycle of R-chemo (yes vs. no).

** The R-chemo backbone will be R-CHOP in patients with DEL, and DA-EPOCH-R in patients with DHL. 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 R-chemo +/- venetoclax 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.

3.0 PATIENT SELECTION

For questions regarding eligibility criteria, see the Study Resources page. Please note that the Study Chair cannot grant waivers to eligibility requirements.

3.1 On-Study Guidelines

This clinical trial can fulfill its objectives only if patients appropriate for this trial are enrolled. All relevant medical and other considerations should be taken into account when deciding whether this protocol is appropriate for a particular patient. Physicians should consider the risks and benefits of any therapy, and therefore only enroll patients for whom this treatment is appropriate.

Physicians should consider whether any of the following may render the patient inappropriate for this protocol:

- Psychiatric illness which would prevent the patient from giving informed consent.
- Medical condition such as uncontrolled infection (including HIV), uncontrolled diabetes mellitus or cardiac disease which, in the opinion of the treating physician, would make this protocol unreasonably hazardous for the patient.
- Patients who cannot swallow oral formulations of the agent(s).

In addition:

- Women and men of reproductive potential should agree to use an appropriate method of birth control throughout their participation in this study due to the teratogenic potential of the therapy utilized in this trial. Appropriate methods of birth control include abstinence, oral contraceptives, implantable hormonal contraceptives or double barrier method (diaphragm plus condom). Birth control must continue for 12 months after the last day of treatment.

3.2 Eligibility Criteria (Step 1)

Use the spaces provided to confirm a patient's eligibility by indicating Yes or No as appropriate. It is not required to complete or submit the following page(s).

When calculating days of tests and measurements, the day a test or measurement is done is considered Day 0. Therefore, if a test were done on a Monday, the Monday one week later would be considered Day 7.

A female of childbearing potential is a sexually mature female who: 1) has not undergone a hysterectomy or bilateral oophorectomy; or 2) has not been naturally postmenopausal for at least 12 consecutive months (i.e., has had menses at any time in the preceding 12 consecutive months).

___ **3.2.1 Documentation of Disease**

- Pathologic diagnosis of Diffuse Large B-cell lymphoma (DLBCL) or High grade B-cell lymphoma (HGBCL)
- High grade B-cell lymphoma with translocations of *MYC* and *BCL2* (Double Hit Lymphoma, DHL), or DLBCL or high grade B-cell lymphoma NOS with protein expression by IHC of both MYC (≥40%) and BCL2 (≥50%) in the absence of dual translocations (Double Expressing Lymphoma, DEL). Local determination of FISH and IHC will be performed per standardized guidelines and will be acceptable for study entry.
- 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. Given the heterogeneity in diagnostic work-up and interpretation, all local determinations will be followed by central confirmation in real time. Diagnostic slides and stains (or recuts/blocks) from all cases will be submitted to a central reference laboratory (Cleveland Clinic Laboratories). Immunostains will be reviewed or repeated (if unavailable or technically unsatisfactory) to confirm DE status. All DE cases will also be investigated for DH status, if not already performed. To exclude DH status, FISH for translocations of *BCL2* (break apart probes), *BCL6* (break apart probes), and *MYC* (break apart and *IGH/MYC* dual fusion probes*) must* be performed (either by referring site or at the central laboratory). Any missing information from the referring site will be supplemented by the central lab on required submitted unstained slides or blocks. Cases submitted as DH will be accepted as such upon review of submitted laboratory report.

___ **3.2.2 Prior Treatment**

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. 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.

3.2.3 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.

___ **3.2.4 Age ≥ 18 years**

___ **3.2.5 ECOG Performance Status 0-2**

___ **3.2.6 Required Initial Laboratory Values*:**

Absolute Neutrophil Count (ANC) ≥ 1,000/mm^3
Platelet Count ≥ 100,000/mm^3

Creatinine ≤ 1.5 mg/dL OR
Calc. Creatinine Clearance ≥ 50 mL/min
Total Bilirubin ≤ 2.0 mg/dL**

* *Unless attributable to lymphoma*
** *Unless attributable to Gilbert's disease*

___ **3.2.7** Archival tissue must be available for submission in all patients for histopathology review, though participation in correlative substudies is optional.

___ **3.2.8 Comorbid conditions**

No active ischemic heart disease or congestive heart failure, and LVEF ≥ 45%

No active HIV disease. Patients with history of HIV are eligible if they 1) have an undetectable viral load within the prior 6 months, or 2) have a detectable viral load with a CD4 count ≥ 200

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.

___ **3.2.9 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 protocol therapy. 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 study treatment. See Section 8.1.10 for more information.