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)
- Double hit lymphoma (DHL) defined as translocations of *MYC* and *BCL2* +/- *BCL6*, or translocations of *MYC* and *BCL6* without *BCL2* translocation but with IHC expression of BCL2 (≥50%) OR Double expressing lymphoma (DEL) defined as protein expression by IHC of both MYC (≥40%) and BCL2 (≥50%) in the absence of dual translocations.
- 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

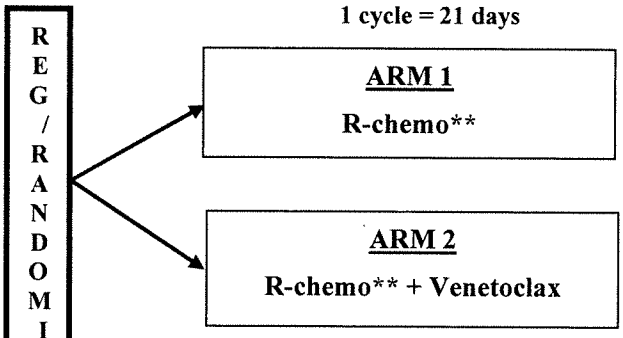
Required Initial Laboratory Values*

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**
AST and ALT	≤ 3 x ULN

**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/low-intermediate (0-2) vs. high-intermediate/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

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