ALLIANCE A059102: A RANDOMIZED PHASE II US INTERGROUP STUDY OF CHO(E)P VS CC-486-CHO(E)P VS DUVELISIB-CHO(E)P IN PREVIOUSLY UNTREATED CD30 NEGATIVE PERIPHERAL T-CELL LYMPHOMAS (PTCL)

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Background:

While PTCL is treated for curative intent, 5-year (yr) overall survival (OS) remains 20-25% with CHOP based therapy. For pts <60 yrs old, the addition of etoposide to CHOP has been associated with improved outcomes. Brentuximab vedotin in combination with chemotherapy demonstrated an OS benefit in PTCL with CD30 >10% by immunohistochemistry, and most significantly improved outcomes in anaplastic large cell lymphoma. This served as proof of principle that biomarker driven therapy can lead to improved outcomes in this rare disease (Horwitz et al Lancet 2019). Duvelisib is a gamma delta PI3 kinase inhibitor with a 50% overall response rate in PTCL and a trend toward a higher response rate in PTCL with a T-follicular helper (TFH) phenotype (Brammer et al. Blood 2021). Azacitidine is a hypomethylating agent that has shown a 75% overall response rate (ORR) in PTCL with TFH phenotype. CC-486, oral azacitidine, has been safely combined with CHOP and showed a 75% ORR with a higher ORR in PTCL with TFH phenotype (Ruan et al. Blood 2021).

Methods:
A051902 is a 3 arm randomized phase II US intergroup study in previously untreated PTCL with CD30 expression <10% comparing standard chemotherapy (CHOP or CHOEP) to CHOP/CHOEP with duvelisib 25mg PO BID or CHOP/CHOEP with azacitidine 300mg PO. Pts will be stratified by age (>60, ≤60) and TFH phenotype. Pts over age 60 will receive CHOP and those ≤60 will receive CHOEP. Prior to the

randomized study, there is a safety lead-in study for the first 12 pts combining duvelisib 15mg BID with CHOP/CHOEP. The primary endpoint of the phase II study is complete remission (CR) rate by the Lugano 2014 criteria. The phase II study is powered for a 25% improvement in CR rate (45% vs 70%) in an experimental arm compared to CHOP/CHOEP with a 90% power and type I error rate of 10%. The phase II will enroll 159 pts (53 per arm). Key eligibility: 1. untreated PTCL (nodal T-cell lymphoma with TFH phenotype, follicular T-cell lymphoma, PTCL-NOS, angioimmunoblastic T-cell lymphoma, enteropathy associated T-cell lymphoma, monomorphic epitheliotropic intestinal T-cell lymphoma) with CD30 expression <10%, 2. Stage I-IV, PS 0-2. Pts with transformed mycosis fungoides or anaplastic large cell lymphoma are excluded.

Standard CHOP and CHOEP are administered every 21 days with growth factor support. Azacitadine 300mg will be taken on days -6 to -1 prior to cycle 1 and then on days 8 to 21 for cycles 1-5. Duvelisib 25mg BID will be taken continuously.

Correlative studies include evaluation of TFH phenotype (by immunohistochemistry, gene expression profiling and DNA sequencing) and cell free DNA evaluation to predict outcomes as well as patient reported outcomes. The study was activated 7/30/2021 and the safety lead-in portion is currently enrolling.

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