INTRODUCTION

- PKCβ isoforms have been implicated in the progression of many cancer types, including lymphoma, glioblastoma, breast, prostate, and colorectal cancers
- Suppresses signaling via PKCβ and PI3K/AKT
  - Inhibits phosphorylation of downstream signal proteins, e.g., pGSK3β
- Promote apoptosis and suppresses tumor growth, proliferation and angiogenesis
- Kinase Inhibitor
  - PKCβ: IC50 = 6nM

ENGINE STUDY DESIGN

- Phase 3, randomized (1:1), double-blind, placebo-controlled, multicenter study in patients with treatment naive high-risk DLBCL
- Approximately 235 patients will be enrolled in the US and China
- 66 events to provide 90% power to detect a HR of 0.45 for OS in subjects who are positive for the DGM1 biomarker, when using a stratified log-rank statistic having one-sided alpha of 0.025

OBJECTIVES

- Primary Objective is to compare the effect of R-CHOP plus enzastaurin versus R-CHOP plus placebo on overall survival (OS) in treatment-naive subjects with high-risk DLBCL who possess the DGM1 biomarker. Note: Both DGM1+ and DGM1− patients will be enrolled but primary analysis will include only DGM1+ patients.
- Secondary objectives are to compare combination phase CR & ORR in DGM1+ patients; determine OS of enzastaurin + R-CHOP in DGM1− patients; and evaluate safety profile of enzastaurin + R-CHOP

ENGINE STUDY KEY ELIGIBILITY

Key Inclusion Criteria:

- 18 years and older
- Histologically confirmed CD20-positive DLBCL (MYC & BCL2 and/or BCL6 rearrangements eligible)
- ECOG PS 0, 1 or 2
- International Prognostic Index (IPI) score ≥3
- DGM1+ or DGM1− (with high-risk patients selected)
- Adequate organ function
  - Total bilirubin ≤ 1.5x ULN
  - ALT & AST ≤ 1.5x ULN (< 5x ULN if liver involvement)
  - Creatinine Clearance ≥ 50 mL/min by Cockcroft- Gault equation
  - Platelet ≥ 75 x 10⁹/L (≥ 50 x 10⁹ if BM involvement)
  - Hgb ≥ 10 g/dL (≥ 8 g/dL if BM involvement)
  - ANC ≥ 1.5 x 10⁹/L (≥ 1.0 x 10⁹ if BM involvement)

Key Exclusion Criteria:

- History of indolent lymphoma or follicular Grade 3b lymphoma
- Primary mediastinal (thymic) large B-cell lymphoma; B-cell lymphoma unclassifiable
- Known CNS involvement or SPM
- Use of a strong inducer or moderate/strong inhibitor of CYP3A4
- History of long QT syndrome, QTcF > 450 msec (males) or > 470 msec (females)
- Use of medication that can prolong QT/QTc
- Ongoing > G2 peripheral neuropathy
- Evidence of chronic hepatitis C by antibody to HCV with HCV-RNA(+)
- Evidence of chronic hepatitis B as by either
  - HBSAg(+)
  - HBCAb+ with HBV-DNA(+)

REFERENCES

- Sehn LH, et al. The revised International Prognostic Index (R-IPI) is a better predictor of outcome than the standard IPI for patients with diffuse large B-cell lymphoma treated with R-CHOP. Blood 2007; 109(5): 1857-61