

# ENGINE: Phase III randomized study of enzastaurin/R-CHOP versus placebo/R-CHOP in frontline high risk diffuse large B cell lymphoma patients with novel genomic biomarker DGM1

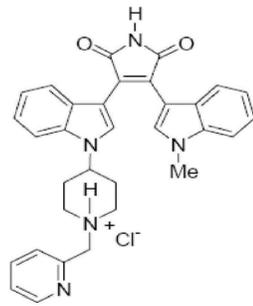
ASCO Abstract  
# TPS7569

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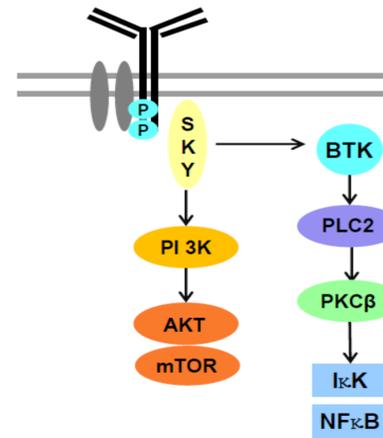
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## INTRODUCTION

- PKC $\beta$  isoforms have been implicated in the progression of many cancer types, including lymphoma, glioblastoma, breast, prostate, and colorectal cancers
- Suppresses signaling via PKC $\beta$  and PI3K/AKT
  - Inhibits phosphorylation of downstream signal proteins, e.g., pGSK3 $\beta$
  - Promote apoptosis and suppresses tumor growth, proliferation and angiogenesis
- Kinase Inhibitor
  - PKC $\beta$ : IC50= 6nM

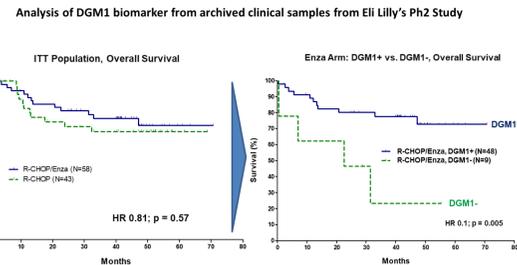
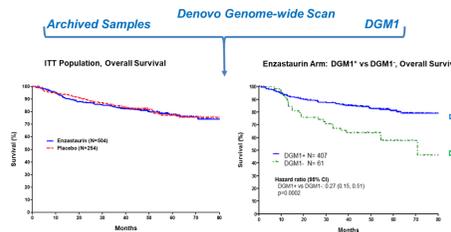


**Enzastaurin**  
A Novel, Acyclic  
Bisindolylmaleimide

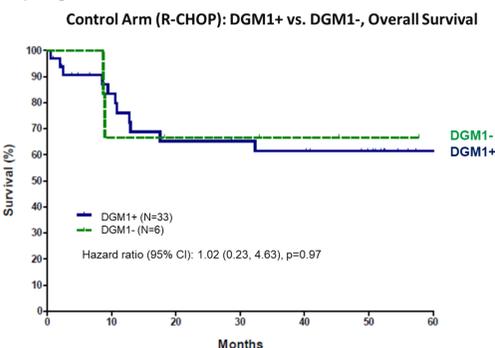


## STUDY RATIONALE

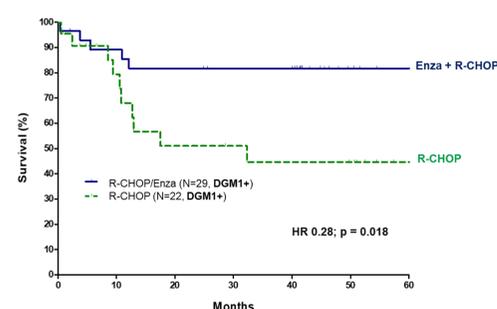
- Using data and patient samples from Eli Lilly's (Lilly) phase 3 maintenance trial in DLBCL patients (PRELUDE), a novel biomarker was identified, Denovo Genomic Marker 1 (DGM1), highly correlated and potentially predictive of enzastaurin benefit
- The predictability of DGM1 was further evaluated in Lilly's DLBCL phase 2 front-line study where there was no statistically significant difference in OS between treatment arms
  - The DGM1 findings from the PRELUDE analysis were replicated: DGM1+ patients receiving R-CHOP plus enzastaurin had significantly improved OS compared to DGM1- patients



- DGM1 biomarker is predictive and not a prognostic marker for survival



Addition of Enza to R-CHOP Improves Survival in DGM1+ High-Risk (IPI  $\geq 3$ ) DLBCL Patients



Current Phase 3 study design replicates this study design with biomarker-guided analysis

- DGM1 and its related SNPs may have potential effects on transcription of its closest gene: TRPS1 (Transcriptional Repressor GATA Binding 1)
- TRPS1 plays a central role in cell cycle and cancer development

- The frequency of DGM1+ in different Ethnic groups

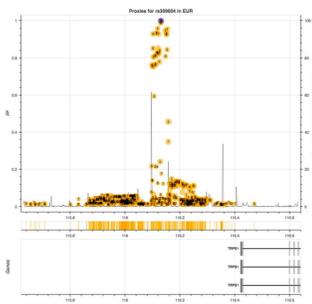
Frequency report:

| Population | DGM1-    |       | DGM1+    |       | Total |    |     |       |    |     |
|------------|----------|-------|----------|-------|-------|----|-----|-------|----|-----|
|            | genotype | count | genotype | count |       |    |     |       |    |     |
| ASW (A)    | C/C      | 0.321 | 17       | C/T   | 0.415 | 22 | T/T | 0.264 | 14 | 53  |
| CEU (C)    | C/C      | 0.116 | 13       | C/T   | 0.491 | 55 | T/T | 0.393 | 44 | 112 |
| CHB (H)    | C/C      | 0.048 | 4        | C/T   | 0.440 | 37 | T/T | 0.512 | 43 | 84  |
| CHD (D)    | C/C      | 0.047 | 4        | C/T   | 0.353 | 30 | T/T | 0.600 | 51 | 85  |
| GIH (G)    | C/C      | 0.261 | 23       | C/T   | 0.420 | 37 | T/T | 0.318 | 28 | 88  |
| JPT (J)    | C/C      | 0.058 | 5        | C/T   | 0.349 | 30 | T/T | 0.593 | 51 | 86  |
| LWK (L)    | C/C      | 0.333 | 30       | C/T   | 0.522 | 47 | T/T | 0.144 | 13 | 90  |
| MEX (M)    | C/C      | 0.040 | 2        | C/T   | 0.540 | 27 | T/T | 0.420 | 21 | 50  |
| MRK (K)    | C/C      | 0.280 | 40       | C/T   | 0.517 | 74 | T/T | 0.203 | 29 | 143 |
| TSI (T)    | C/C      | 0.102 | 9        | C/T   | 0.489 | 43 | T/T | 0.409 | 36 | 88  |
| YRI (Y)    | C/C      | 0.368 | 41       | C/T   | 0.513 | 58 | T/T | 0.124 | 14 | 113 |

Note: the reference allele is the base observed in the reference genome sequence at this position

Population descriptors:  
ASW (A): African ancestry in Southwest USA  
CEU (C): Utah residents with Northern and Western European ancestry from the CEPH  
CHB (H): Han Chinese in Beijing, China  
CHD (D): Chinese in Metropolitan Denver, Colorado  
GIH (G): Gujarati Indians in Houston, Texas  
JPT (J): Japanese in Tokyo, Japan  
LWK (L): Luhya in Webuye, Kenya  
MEX (M): Mexican ancestry in Los Angeles, California  
MRK (K): Maasai in Kinyawa, Kenya  
TSI (T): Tuscan in Italy

C/T and T/T: DGM1+  
C/C: DGM1-

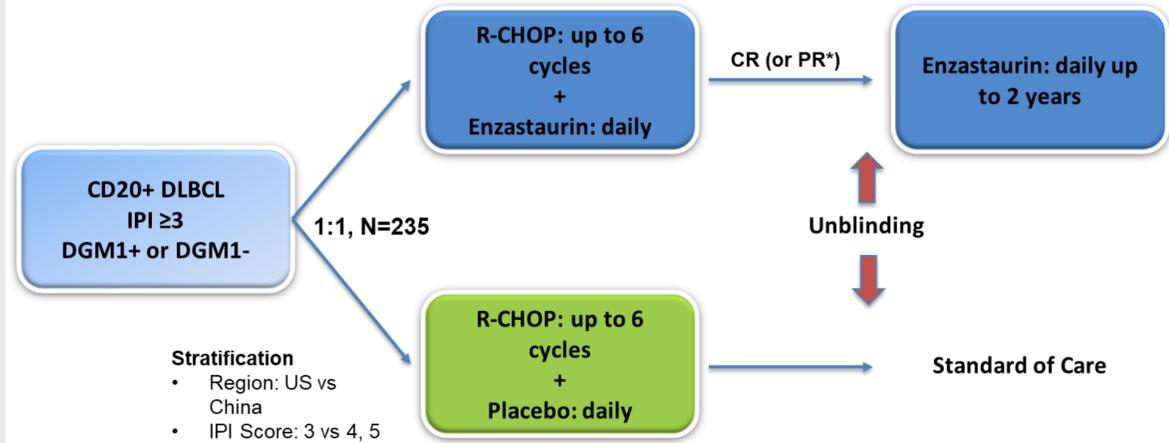


## ENGINE STUDY DESIGN

- Phase 3, randomized (1:1), double-blind, placebo-controlled, multicenter study in patients with treatment naïve 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-naïve 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. Sites and sponsor will remain blinded to biomarker status of each patient
- 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



### Key study design difference - ENGINE trial vs other phase III studies in frontline DLBCL

- Unique Genomic Biomarker
- High risk patient population IPI = 3, 4, 5
- Simplified screening procedures to allow quick treatment initiation, feasible to enroll high-risk patients
- Eligibility based on local pathology diagnosis
- Local safety labs
- Primary endpoint OS with less frequent imaging schedule
- 2 years of single agent phase after induction phase

## 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  $\geq 3$
- DGM1+ or DGM1-
- LVEF  $\geq 50\%$  by echo or MUGA
- Adequate organ function
  - Total bilirubin  $\leq 1.5 \times$  ULN
  - ALT & AST  $\leq 1.5 \times$  ULN ( $< 5 \times$  ULN if liver involvement)
  - Creatinine Clearance  $> 50$  mL/min by Cockcroft- Gault equation
  - Platelet  $\geq 75 \times 10^9/L$  ( $\geq 50 \times 10^9$  if BM involvement)
  - HgB  $\geq 10$  g/dL ( $\geq 8$  g/dL if BM involvement)
  - ANC  $\geq 1.5 \times 10^9/L$  ( $\geq 1.0 \times 10^9$  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+ or
  - HBcAb+ with HBV-DNA(+)

## REFERENCES

- Crump M, et al. Randomized, double-blind, phase III trial of enzastaurin versus placebo in patients achieving remission after first-line therapy for high-risk diffuse large B-cell lymphoma. J Clin Oncol 2016; 34: 2484-92
- Hainsworth JD, et al. A randomized, phase 2 study of R-CHOP plus enzastaurin vs R-CHOP in patients with intermediate- or high-risk diffuse large B-cell lymphoma. Leukemia & Lymphoma 2016; 57(1): 216-8
- 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



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