

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

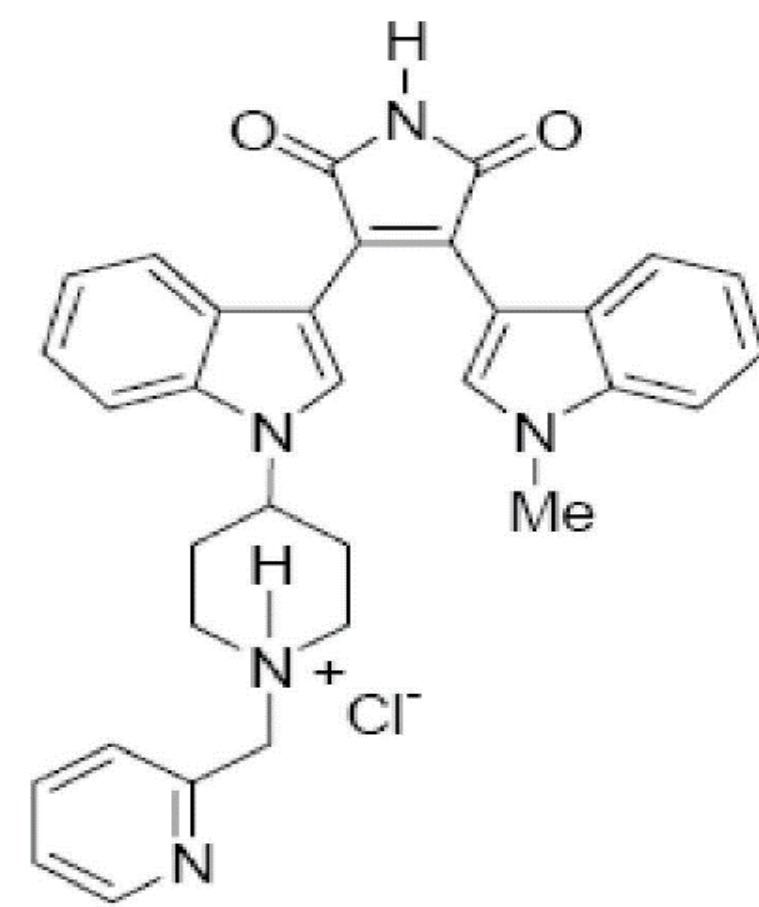
ASCO Abstract
TPS7569

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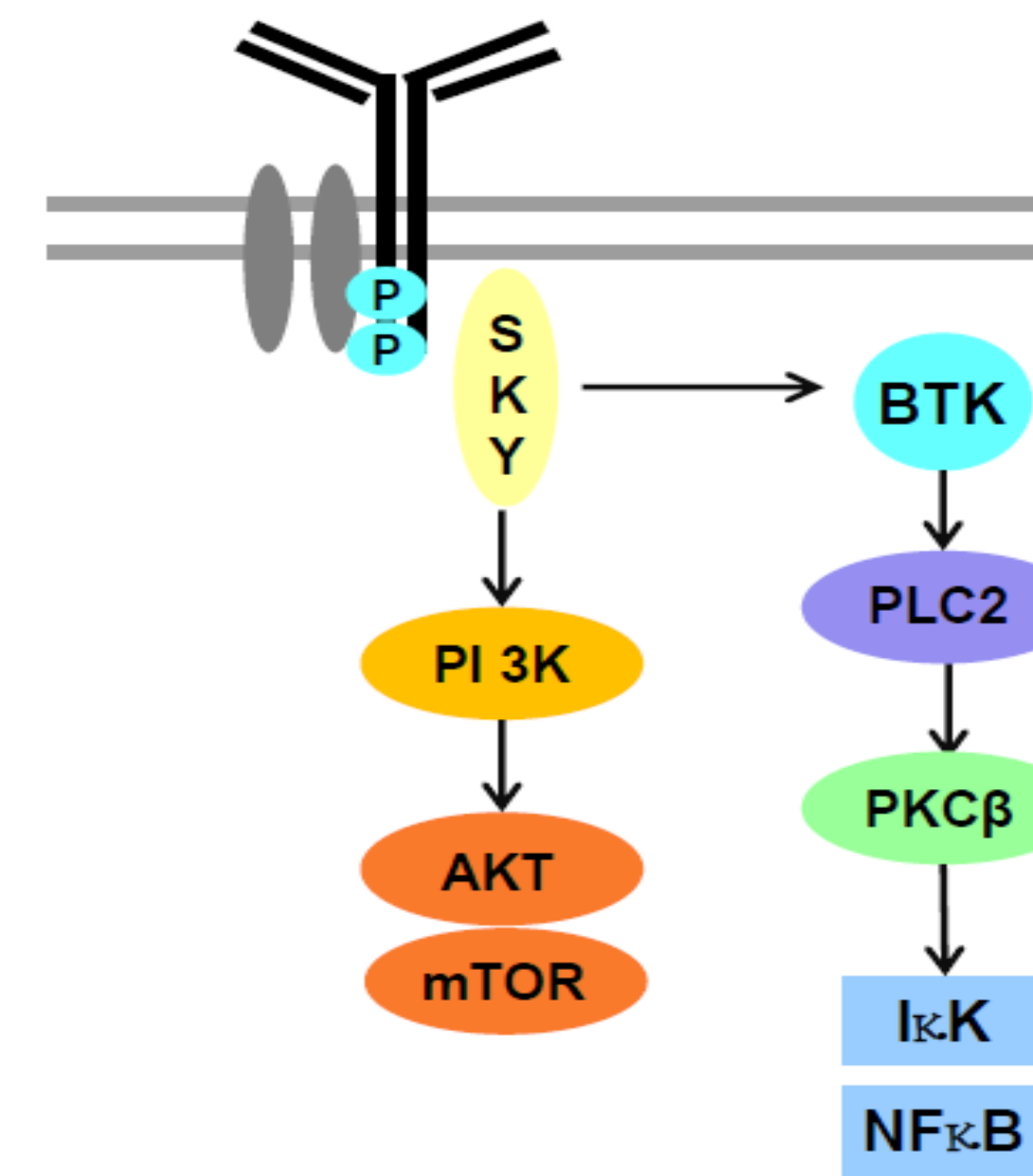
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INTRODUCTION

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

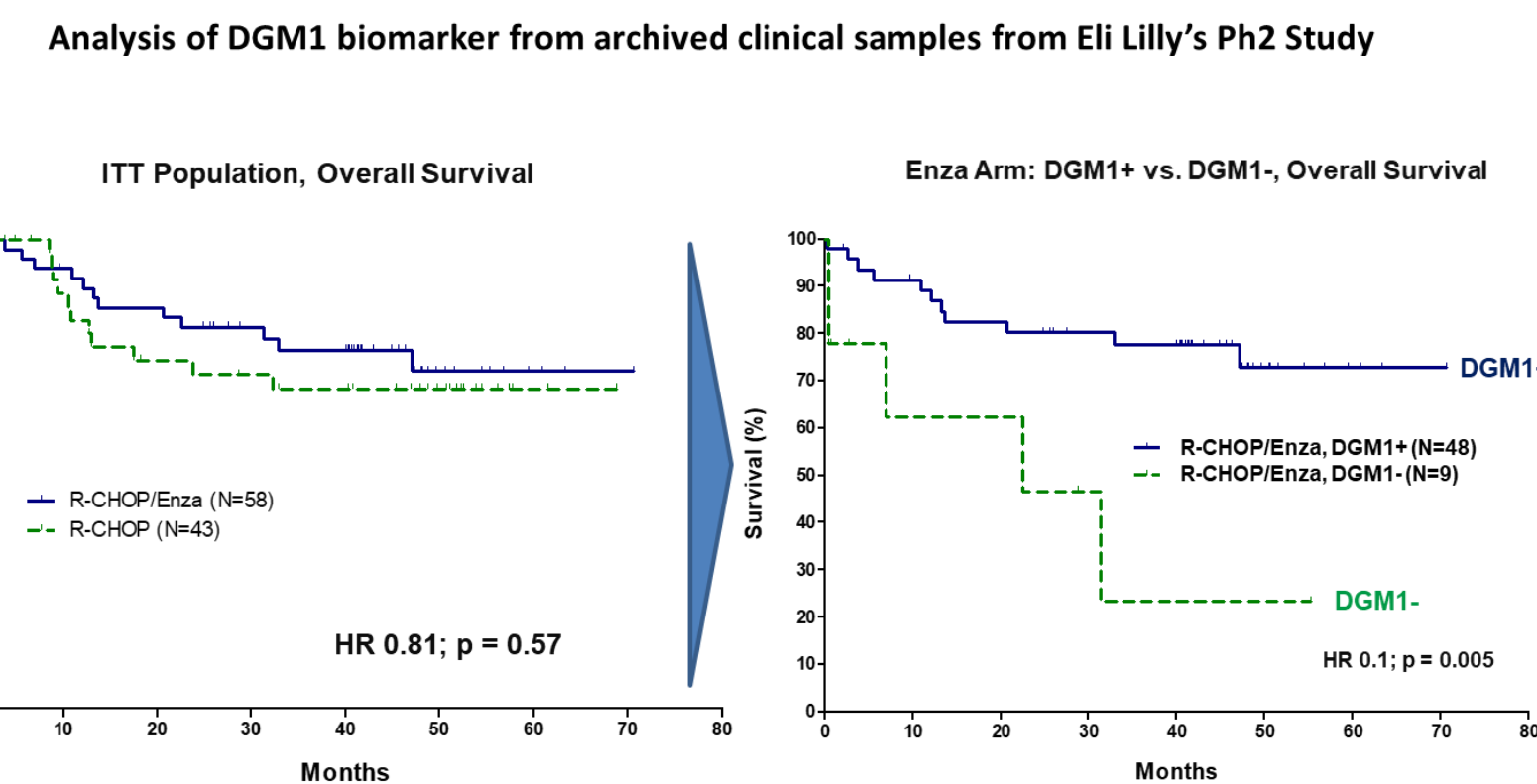
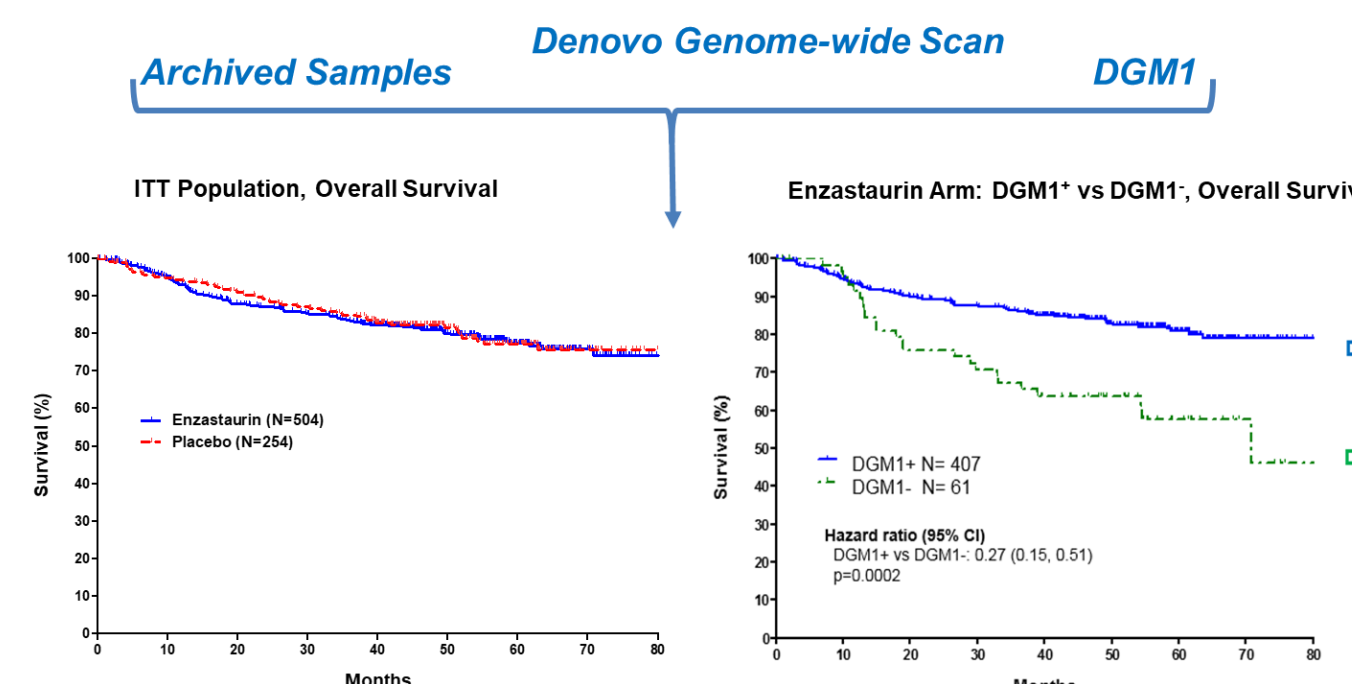


Enzastaurin
A Novel, Acyclic
Bisindolymaleimide

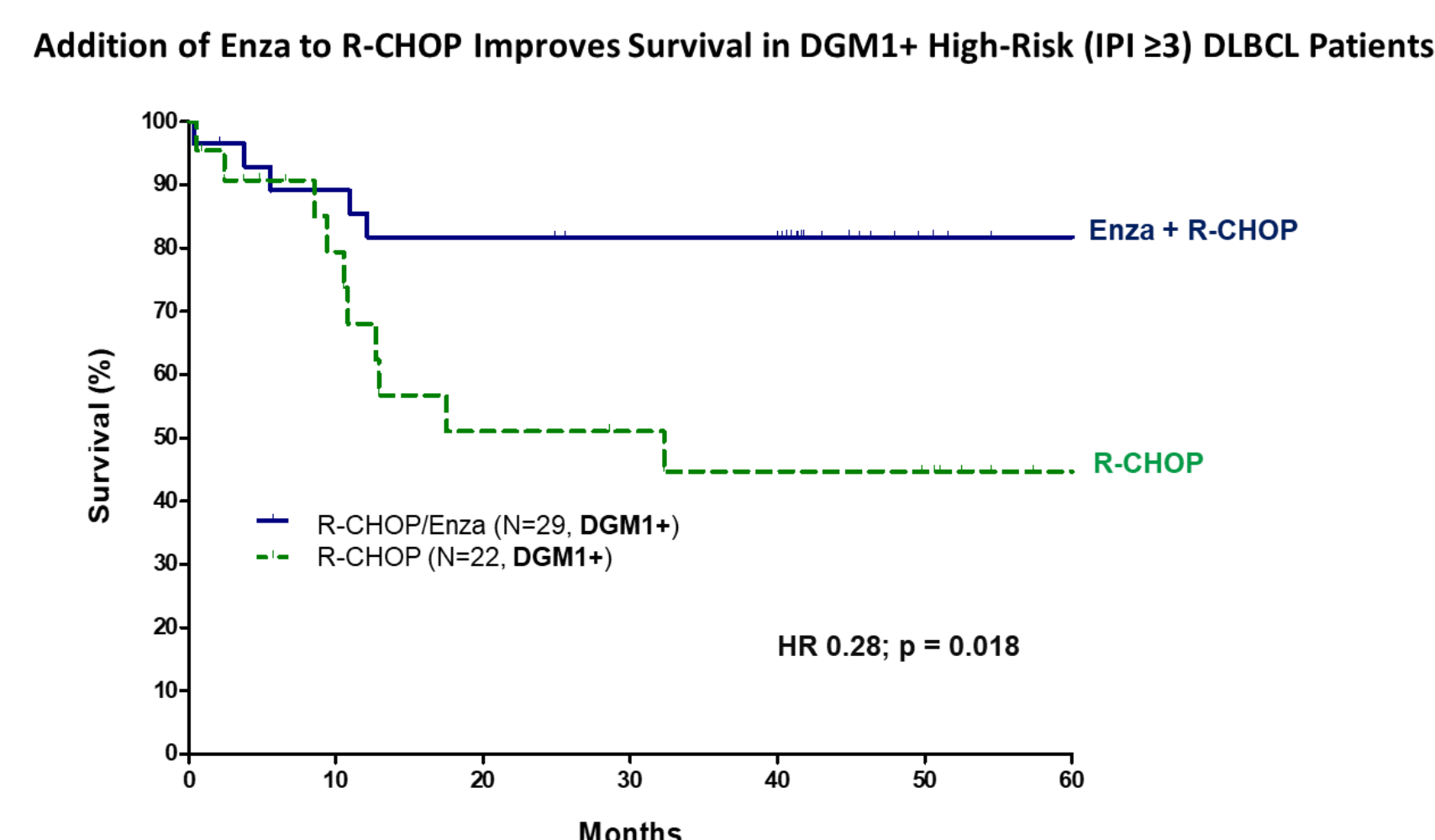
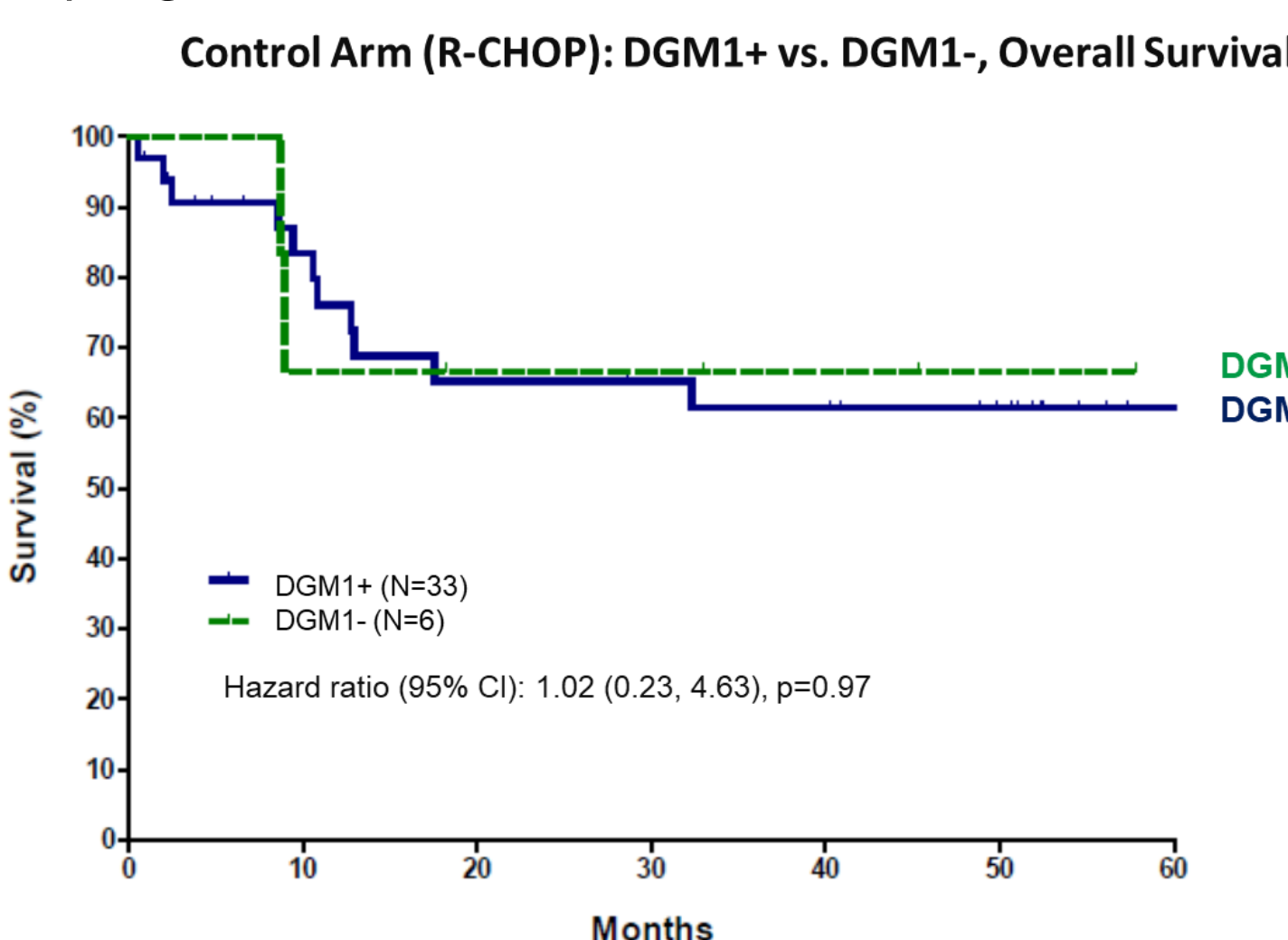


STUDY RATIONALE

- 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



- 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

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

- The frequency of DGM1+ in different Ethnic groups

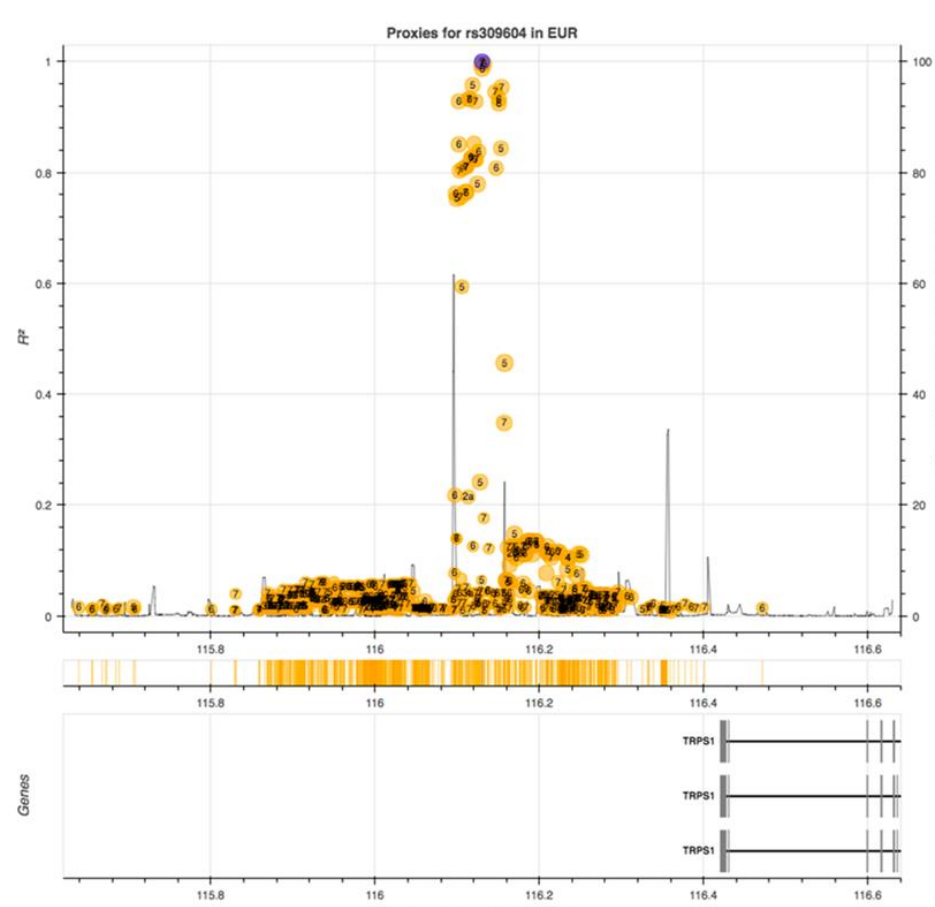
Frequency report:

| Population | DGM1- | | DGM1+ | | Total DGM1+ | |
|------------|----------|-------|----------|-------|-------------|-------|
| | genotype | count | genotype | count | genotype | count |
| ASW (A) | C/C | 0.321 | C/T | 0.415 | T/T | 0.264 |
| CEU (C) | C/C | 0.116 | C/T | 0.491 | T/T | 0.393 |
| CHB (H) | C/C | 0.048 | C/T | 0.440 | T/T | 0.512 |
| CHD (D) | C/C | 0.047 | C/T | 0.353 | T/T | 0.600 |
| GIH (G) | C/C | 0.261 | C/T | 0.420 | T/T | 0.318 |
| JPT (J) | C/C | 0.058 | C/T | 0.349 | T/T | 0.593 |
| LWK (L) | C/C | 0.333 | C/T | 0.522 | T/T | 0.144 |
| MEX (M) | C/C | 0.040 | C/T | 0.540 | T/T | 0.420 |
| MRK (K) | C/C | 0.280 | C/T | 0.517 | T/T | 0.203 |
| TSI (T) | C/C | 0.102 | C/T | 0.489 | T/T | 0.409 |
| YRI (Y) | C/C | 0.368 | C/T | 0.513 | T/T | 0.124 |

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

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

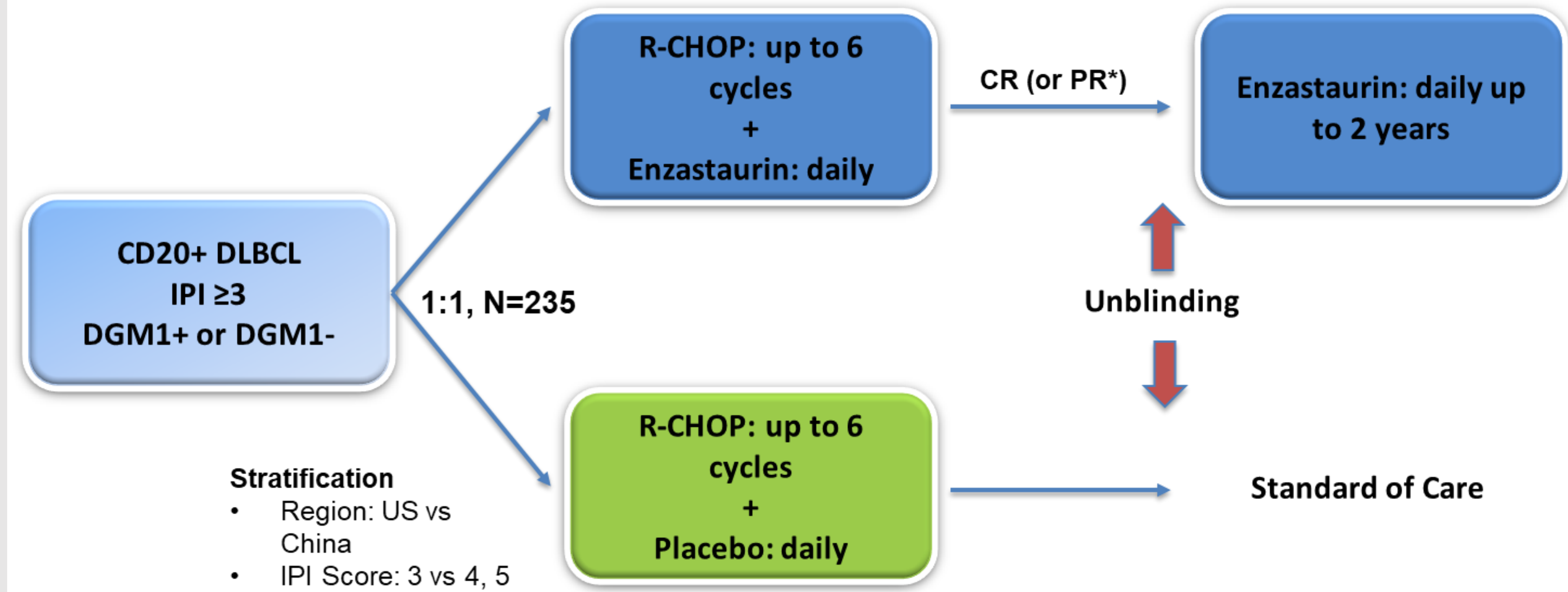


ENGINE STUDY DESIGN

- 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 ≥ 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 ≥ 10 g/dL (≥ 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(+)

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- 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
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