Improved Survival with Enzastaurin Treatment in Diffuse Large B-Cell Lymphoma (DLBCL) Patients with the Novel Genetic Biomarker, DGM1

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Abstract # 4207

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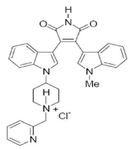
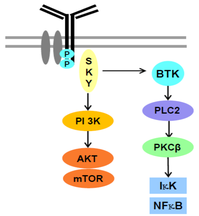
BACKGROUND

Drugs that have benefited a subset of patients but discontinued for development may be rescued through identification of a biomarker predictive of response

- Enzastaurin, a potent and selective inhibitor of protein kinase C-β (PKCβ), also inhibits signaling through the PI3K/AKT pathway promoting apoptosis and suppressing tumor growth, proliferation, and angiogenesis
- PKCβ is the major isoform expressed in normal and malignant B cells and is required for B cell receptor signaling, activation of NFκB, and VEGF-mediated angiogenesis

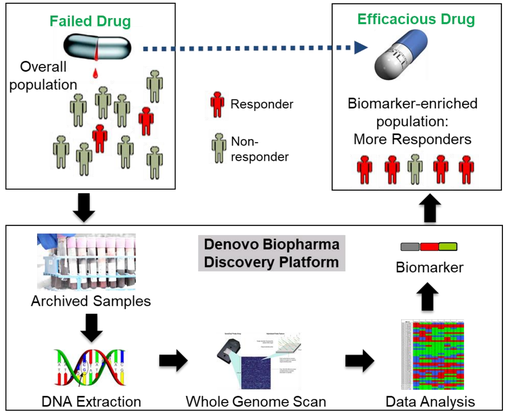


Enzastaurin
A Novel, Acyclic
Bisindolylmaleimide



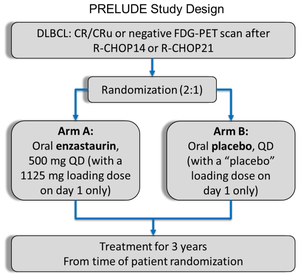
- Enzastaurin improved PFS in newly diagnosed DLBCL patients in a randomized phase 2 trial when combined with R-CHOP, but not in a randomized phase 3 trial when administered as maintenance therapy in DLBCL patients achieving CR/CRu after R-CHOP

Using data and patient samples from previous trials, we identified a biomarker potentially predictive of enzastaurin benefit

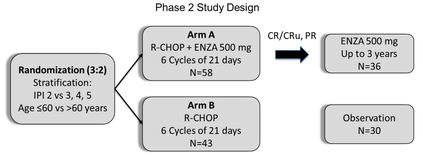


METHODS

- Biomarker discovery was conducted on Eli Lilly's (Lilly) PRELUDE study, a phase 3 maintenance trial that enrolled approximately 750 DLBCL patients who achieved CR/CRu or negative FDG-PET scan after R-CHOP front-line therapy and were randomized to enzastaurin or placebo maintenance for up to three years
- A genome-wide screen was performed on DNA from patients participating in this study and results were evaluated for correlation to efficacy endpoints through bioinformatic analysis

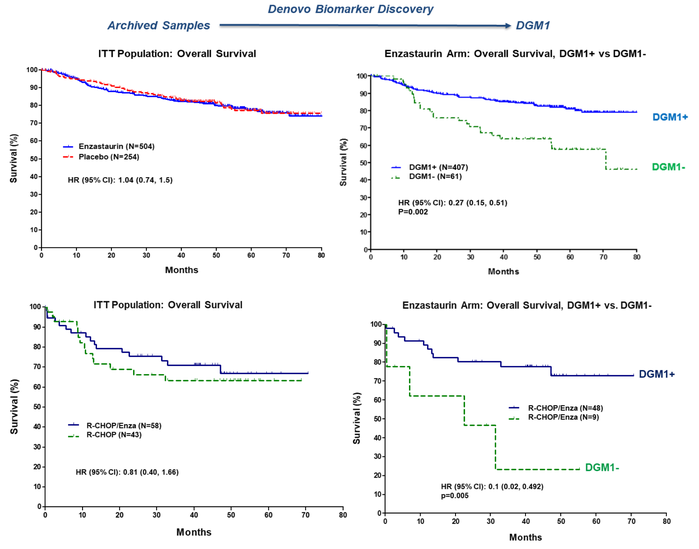


- Confirmation of the biomarker identified in the phase 3 study was performed by independent analysis of the biomarker in a separate completed Lilly enzastaurin study in patients with DLBCL
- The study was a phase 2 trial in 101 newly diagnosed DLBCL patients randomized to treatment with R-CHOP plus enzastaurin or R-CHOP
- Patients receiving R-CHOP plus enzastaurin and achieving a CR/CRu or PR after induction were eligible to continue with single agent enzastaurin for up to 3 years



RESULTS

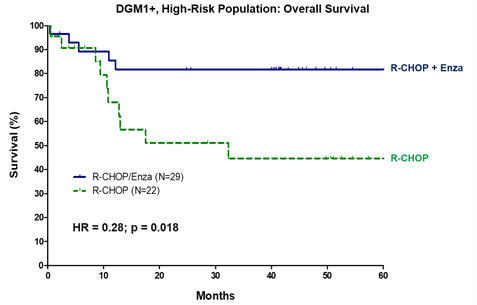
- There was no difference in overall survival (OS) in the ITT population in the original study analysis of the PRELUDE study
- Analysis of patient samples from the PRELUDE study identified a biomarker highly correlated and potentially predictive of enzastaurin response: Denovo Genomic Marker 1 (DGM1), a polymorphism on chromosome 8
- Biomarker analysis of the PRELUDE study found that DGM1+ patients receiving enzastaurin had significantly improved overall survival (OS) compared to DGM1- patients receiving enzastaurin (HR 0.27, p=0.002)



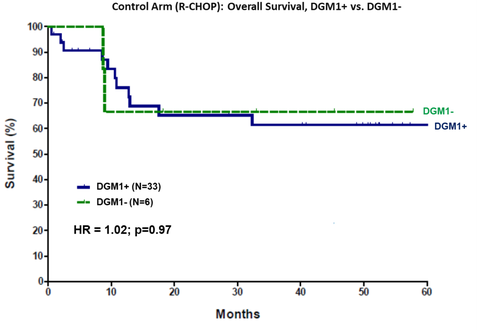
- To further evaluate DGM1, the predictability of the biomarker was assessed in the DLBCL phase 2 front-line study
- There was no statistically significant OS difference between the treatment arms in the ITT population of the phase 2 study
- The DGM1 findings from the PRELUDE analysis were replicated in the phase 2 study: DGM1+ patients receiving R-CHOP plus enzastaurin had significantly improved OS (HR 0.1, p=0.005) compared to DGM1- patients

RESULTS

- The original analysis of the phase 2 study found a trend toward improved, but not statistically significant, OS in patients with high-risk (IPI≥3) DLBCL receiving R-CHOP plus enzastaurin, an area of significant unmet need
- Biomarker analysis of this population demonstrated significant improvement in OS (HR 0.28, p=0.018) for high-risk DLBCL DGM1+ patients receiving R-CHOP plus enzastaurin compared to high-risk DLBCL DGM1+ patients receiving R-CHOP alone.



- DGM1 was evaluated for utility as a prognostic biomarker in DLBCL
- DGM1+ status was not predictive of efficacy in the control (R-CHOP only) arm arguing against DGM1 as a prognostic biomarker



CONCLUSION

- These data are supportive of DGM1 as a potentially predictive biomarker for enzastaurin response
- The mechanism of DGM1 impact in DLBCL is under study
- Based on these data, a biomarker driven phase 3 study (ENGINE Study) of R-CHOP plus enzastaurin versus R-CHOP in DGM1+ and DGM1- patients with newly diagnosed high-risk DLBCL was initiated and is currently enrolling patients (NCT03263026)

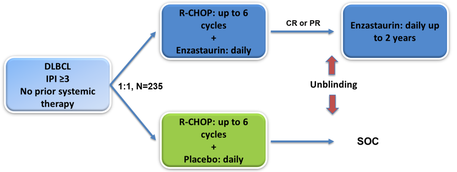
ENGINE STUDY DESIGN

- 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
- Primary Objective is to compare the effect of R-CHOP plus enzastaurin versus R-CHOP on overall survival (OS) in treatment-naïve subjects with high-risk DLBCL who possess the DGM1 biomarker

ENGINE STUDY KEY ELGIBILITY

- CD20-positive DLBCL
- Treatment naïve
- IPI ≥3
- ECOG PS ≤2
- DGM1+ or DGM1-

ENGINE STUDY



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