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Abstract # 2023

# DGM1 may serve as a novel genetic biomarker of response to enzastaurin in glioblastoma

Nicolas Butowski[1], Ronald L. Shazer[2], Lei Zhang[2], Hong Sun[2], Isabel Han[2], Manoj A. Jivani[2], Wen Luo[2]

[1]University of California, San Francisco, San Francisco, CA; [2]Denovo Biopharma LLC, San Diego, CA

## BACKGROUND

### Enzastaurin

- Enzastaurin, a potent and selective inhibitor of protein kinase C-beta (PKCβ), has been shown to have antiangiogenic and antitumor effects, including direct cytotoxic activity against glioma cells, in preclinical studies.
- Enzastaurin has been evaluated in clinical trials across multiple malignancies.
- Signs of enzastaurin efficacy were observed in subsets of patients in various tumor types, including malignant glioma.
- The clinically recommend dose is 500 mg/day to achieve targeted steady-state average plasma concentrations of 1400 nM for clinically efficacy based on $IC_{90}$ of 70 nM and 95% protein binding of enzastaurin.

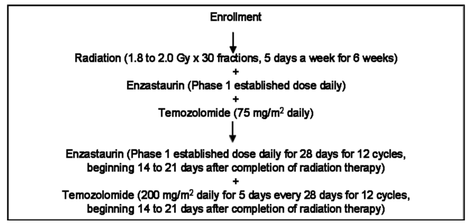
### Denovo Genomic Marker 1 (DGM1)

- DGM1 is a germline polymorphism comprised of a specific configuration of two single nucleotide polymorphisms located on chromosome 8.
- DGM1 was discovered by a genome-wide screen on DNA from patients participating in a randomized phase 3 maintenance study (PRELUDE) of enzastaurin 500 mg/day vs placebo in diffuse large B-cell lymphoma (DLBCL).
- Replication of the findings were observed in a randomized phase 2 study of enzastaurin 500 mg/day or placebo added to R-CHOP in patients with newly diagnosed DLBCL.
- DGM1 is potentially predictive of enzastaurin benefit: the DGM1+ biomarker was correlated with improved survival with enzastaurin treatment in two DLBCL trials.
- The DGM1+ biomarker is tumor type agnostic and prevalence is based on ethnicity.
- The prevalence of the DGM1+ biomarker among different ethnic groups is readily accessible through the HapMap project: approximately 68%, 90%, and 95% of African ancestry, European ancestry, and Chinese, respectively, are expected to be DGM1+

### Phase 1/2 Study of Enzastaurin in Newly Diagnosed Glioblastoma

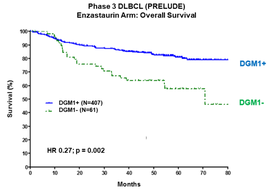
- A previous single arm, phase 1/2 study of enzastaurin added to radiotherapy (RT) plus temozolomide (TMZ) followed by TMZ was conducted in patients with newly diagnosed glioblastoma.
- N=72 (12 Phase 1, 60 Phase 2)
- MTD of enzastaurin in combination with RT and TMZ was 250 mg/day.
- MTD of enzastaurin and TMZ without RT was not evaluated in this study.
- Median overall survival (mOS) of 17.1 months was favorable to the stated historical mOS of 15 months.
- Analysis of the DGM1 biomarker was performed on this study.

**Phase 1/2 of Enzastaurin in Newly Diagnosed Glioblastoma**

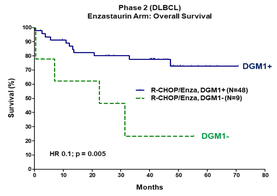



## METHODS

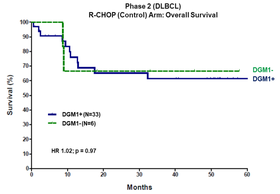
- **Discovery:** Patients with DGM1+ biomarker in the enzastaurin arm of a large randomized phase 3 trial in DLBCL patients (PRELUDE) demonstrated improved mOS compared to patients that were DGM1-.




- **Replication:** Confirmation of the biomarker was performed in a randomized phase 2 study of enzastaurin added to R-CHOP vs R-CHOP plus placebo in patients with newly diagnosed DLBCL.




- **Biomarker Type:** DGM1+ patients did not demonstrate improved survival compared to DGM1- patients in the control arm arguing against DGM1+ as a prognostic biomarker.



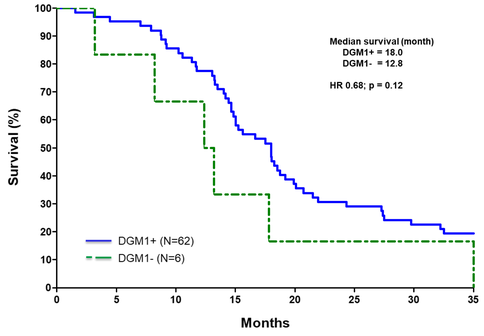

- **DGM1 in Glioblastoma:** DNA was extracted from archive samples from patients that participated in a phase 1/2 trial of enzastaurin added to RT+TMZ followed by TMZ in newly diagnosed glioblastoma and analyzed for DGM1 status.
- DGM1 results were then evaluated for correlation to survival.
- **Enzastaurin Dose:** The enzastaurin dose of 250 mg daily administered in phase 2 and to most patients in phase 1 was below the dose needed to achieve recommended steady-state concentrations for efficacy.
- Data were evaluated by mean daily dose of enzastaurin administered to evaluate potential impact of dose level to overall survival, if any.

## RESULTS

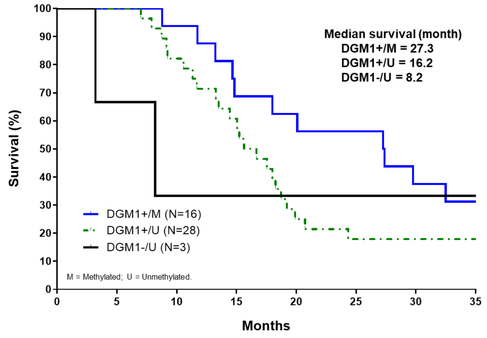
### Phase 1/2 Trial of Enzastaurin in Newly Diagnosed Glioblastoma

- **DGM1 in Glioblastoma**: Consistent with the findings in DLBCL, DGM1+ patients demonstrated improved survival compared to DGM1- patients regardless of methylation status.
- **MGMT Promotor Methylation**: DGM1+ patients with unmethylated MGMT had nearly double the mOS of DGM1- patients with unmethylated MGMT (16.2 vs 8.2 months).
- Comparison of methylated MGMT and DGM1 status was not feasible; there was only one DGM1- patient with methylated MGMT.
- **Enzastaruin Mean Daily Dose**: DGM1+ patients receiving a mean daily dose ≥ 245 mg demonstrated improved mOS compared to DGM1+ patients receiving a mean daily dose < 245 mg (19.6 vs 15.0 months).
- Median OS for patients receiving a mean daily dose < 245 mg was greater for DGM1+ patients compared to DGM1- patients (15.0 vs 12.4 months).
- There was only one DGM1- patient that received a mean daily dose ≥ 245 mg.

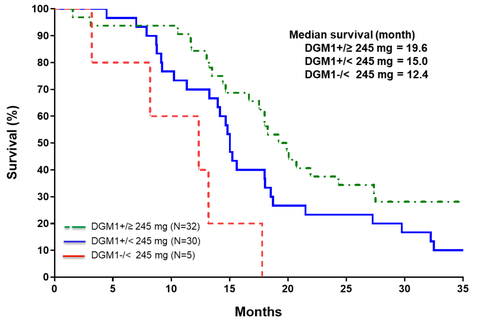
***Phase 1/2 Glioblastoma***
***Overall Survival by DGM1 Status***




***Phase 1/2 Glioblastoma***
***OS by DGM1 and MGMT Methylation Status***



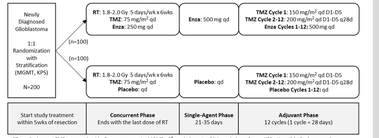

***Phase 1/2 Glioblastoma***
***OS by Mean Daily Dose and DGM1 Status***




## CONCLUSION

- The DGM1+ biomarker was correlated with improved survival for patients receiving enzastaurin in two different malignancies across three trials.
- These data are supportive of the DGM1+ biomarker as potentially predictive of enzastaurin benefit.
- Notably, in the trial that DGM1 was discovered and the trial that replicated the discovery findings, the enzastaurin dose was 500 mg/day.
- Administering enzastaurin at 500 mg/day during the adjuvant phase of the phase 1/2 glioblastoma trial may have improved enzastaurin response.
- Based on these data, a randomized, placebo-controlled, phase 2b study of enzastaurin or placebo added to RT/TMZ followed by TMZ is planned.
- The planned dose of enzastaurin during the adjuvant phase is 500 mg/day; this dose is supported by a separate phase 1 study reporting enzastaurin 500 mg/day plus TMZ 200 mg/m² did not exceed the MTD.

## PHASE 2 GLIOBLASTOMA STUDY




RT = radiotherapy; TMZ = temozolomide; Enza = enzastaurin; MGMT = O⁶-methylguanine-DNA-methyltransferase; KPS = Karnofsky Performance Score

### Primary Objective

- To assess whether there is superiority of OS when enzastaurin rather than placebo is added to TMZ with RT followed by TMZ

### Key Eligibility

- Newly diagnosed supratentorial glioblastoma (2016 WHO)
- Partial or complete resection (biopsy only patients excluded)
- KPS ≥60
- No contraindications to temozolomide

## REFERENCES

- Butowski N, Chang SM, Lamborn Kr, et al. Enzastaurin plus temozolomide with radiation therapy in glioblastoma multiforme: A phase I study. Neuro-Oncol 2010; 12(6): 608-13
- Butowski N, Chang SM, Lamborn KR, et al. Phase II and pharmacogenomics study of enzastaurin plus temozolomide during and following radiation therapy in patients with newly diagnosed glioblastoma multiforme and gliosarcoma. Neuro-Oncol 2011; 13(12): 1331-38
- Rampling R, Sanson M, Gorlia T, et al. A phase I study of LY317615 (enzastaurin) and temozolomide in patients with gliomas (EORTC trial 26054). Neuro-Oncol 2012; 14(3): 344-50