

**BACKGROUND**

**Enzastaurin**

Enzastaurin is a potent and selective inhibitor of protein kinase C (PKC), has been shown to have antiangiogenic and antitumor effects, and demonstrated cytostatic activity against glioma cells, in preclinical studies.

- It 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.

**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 1 maintenance study (PRELUDE) of enzastaurin 500 mg/dy in patients with newly diagnosed GBM.
- Replication of the findings was observed in a randomized phase 2 study of enzastaurin 500 mg/dy 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 TCGA project.
- The prevalence of DGM1 varies by ethnicity, and different ethnic groups are readily accessible through the TCGA project.

**RESULTS**

- **DGM1 in Glioblastoma**: Consistent with the findings from the TCGA, DGM1+ patients demonstrated improved survival compared to DGM1- patients regardless of methylstatus.

**METHODS**

**Primary Objective**

- To assess whether there is superiority of OS when enzastaurin rather than placebo is added to TMZ with follow-up by TMZ.

**Key Eligibility**

- Newly diagnosed supratentorial glioblastoma (2016 WHO)
- Partial or complete resection (biopsy only patients excluded)
- ECOG ≤ 2
- No contraindications to temozolomide

**REFERENCES**

- Rampil R, Sanson M, Gorlia T, et al. Primary Objective: To assess whether there is superiority of OS when enzastaurin rather than placebo is added to TMZ with follow-up by TMZ.
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**CONCLUSION**

- DGM1+ biomarker was correlated with improved survival for patients receiving enzastaurin in two different malignancies across three trials.
- These data support DGM1 as a potential 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/dy.
- Administering enzastaurin at 500 mg/dy during the adjuvant phase of the phase 1/2 trial may improve enzastaurin response.
- Based on these data, a randomized phase 3 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/dy supported by a separate phase 1 study reporting enzastaurin 500 mg/dy plus TMZ 200 mg/m2 did not exceed the MTD.

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

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