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# Tumor Growth Rate (TGR) Analysis Predicts Survival in a Multicenter Phase II Study of the PARP Inhibitor Pamiparib (BGB-290) with Temozolomide in Recurrent IDH-Mutant Gliomas (ABTC-1801)

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## Abstract

**Background and purpose:** Mutations in isocitrate dehydrogenase (IDH) lead to production of the oncometabolite 2-hydroxygluterate (2-HG), which suppresses homologous recombination and induces poly (ADP-ribose) polymerase (PARP) inhibitor sensitivity. Preclinical studies demonstrate that IDH-mutant gliomas are sensitive to PARP inhibition. Tumor growth rate (TGR) assessment offers a novel approach to evaluate treatment effects beyond traditional response criteria. Here, we report the change in TGR in a multicenter phase Ib/II study of the PARP inhibitor pamiparib with low-dose temozolomide in recurrent IDH-mutant gliomas, and evaluate TGR as an independent prognostic biomarker for overall survival.

**Materials and methods:** In this Adult Brain Tumor Consortium multicenter phase Ib/II clinical trial (ABTC-1801; NCT03914742), patients with recurrent IDH-mutant gliomas were enrolled in three cohorts: Arm A (grade 2-3, failed ≥2 alkylators), Arm B (grade 2-3, failed single alkylator ≥12 months prior), and an exploratory cohort of grade 4 IDH-mutant patients. All patients received pamiparib 60mg twice daily with temozolomide 20mg daily. Tumor growth rates were assessed using serial MRI FLAIR measurements before and during treatment. Growth rate inhibition was defined as a decrease in TGR after treatment compared to pre-treatment growth rate.

**Results:** Among evaluable patients in the dose expansion cohorts enrolled between 2020-2022, 45.5% (5/11) in Arm A, 30% (6/20) in Arm B, and 30% (3/10) in the grade 4 arm demonstrated a decrease in TGR during treatment relative to pre-treatment TGRs. Cox regression analysis showed that higher post-treatment TGR (*HR=1.0065 [95%CI:1.0031-1.01], P=0.0002*; Arms A-B, *HR=1.0068 [95%CI:1.0027-1.011], P=0.0012*) and an increase in TGR after treatment were significantly associated with shorter survival for all patients as well as when only including grades 2-3 gliomas in Arms A-B (All patients, *HR=1.007 [95%CI:1.0032-1.0107], P=0.0003*; Arms A-B, *HR=1.008 [95%CI:1.0034-1.0126], P=0.0006*). Patients with TGR change >+25 mL/6 months had significantly worse survival compared to those with TGR <+25 mL/6 months (*HR=4.946, P=0.0044*; Arms A-B, *HR=3.210, P=0.0108*).

**Conclusions:** TGR changes were significantly associated with survival outcomes, suggesting that

growth stabilization may be an important metric for assessing treatment benefit in IDH-mutant gliomas.