Activity has potent temozolomide (TMZ)-sensitizing effects and regulates multiple DNA repair pathways and inhibition of PARP. BGB-290, a single agent or combined with TMZ in patient derived GBM xenografts, resulted in enhanced potentiating effects of BGB-290.

Low doses (30-100 nM) of BGB-290 suppressed PARP activity, with an indicated shRNA were treated with DMSO or TMZ ± indicated dose of BGB-290, NS graphs represent NS count relative to the DMSO treated group treated with TMZ alone 80% of mice were moribund.

Analysis of MGMT and MMR status in GBM12TMZ sublines and BGB-290 treatment were assessed by reporter assay in a panel of sublines. Msh2 knockdown in TMZ resistant lines did not result in a marked TMZ resistance in U251 and BGB-290. This study was focused on evaluating efficacy in vivo, in patient derived xenografts of glioblastoma multiforme.

Summary

BGB-290 is a potent and highly specific PARP inhibitor with high potency, cytotoxicity and favorable in vivo efficacy in TMZ sensitive and possibly a subset of recurrent TMZ resistant GBM.

BGB-290 has heterogeneous sensitizing effects in isogenic TMZ resistant lines

Table1: GBM lines selected for TMZ resistance display frequent mutations in DNA repair pathways. Analysis of MGMT and MMR status in GBM12TMZ sublines and by Exome-Seq in TMZ resistant GBM12T sublines and by Exome-Seq in TMZ resistant GBM12T sublines.

Table2: BGB-290 treatment were assessed by reporter assay in a panel of sublines. BGB-290 is a potent inhibitor of PARP activity with high specificity towards PARP1. BGB-290 can significantly enhance the efficacy of TMZ both in vitro and in vivo.

Mutations in DNA repair pathways in TMZ resistant xenograft lines

Analysis of MGMT and MMR status in GBM12TMZ sublines

Disruption of MMR promotes sensitizing effects of PARP inhibition in vitro and in vivo. Analysis of MGMT and MMR status in GBM12TMZ sublines and by Exome-Seq in TMZ resistant GBM12T sublines.

Conclusions

• BGB-290 is a promising PARP inhibitor with favorable in vivo efficacy in TMZ sensitive and possibly a subset of recurrent TMZ resistant GBM.

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