Clinical benefit in biomarker-positive patients (pts) with locally advanced or metastatic solid tumours treated with the PARP1/2 inhibitor pamiparib in combination with low-dose (LD) temozolomide (TMZ)


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Background

DNA damage caused by the alkylator TMZ can sensitize tumors to PARP inhibitors. Pamiparib, an investigational oral PARP1/2 inhibitor, has shown PARP-DNA complex trapping activity, brain penetration, and synergistic cytotoxicity with LD TMZ in nonclinical studies and preliminary antitumor activity in pts with solid tumors.

Methods

This ongoing phase Ib study consists of a dose-escalation (3+3 design) and dose-expansion phase. In dose escalation, pts received pamiparib 60 mg PO BID on Days 1-28 and LD TMZ at escalating doses PO QD on Days 1-7, 1-14, or 1-28 of each 28-day cycle. Dose-expansion pts, including pts with gastric cancer and SCLC with 1-2 prior lines of chemotherapy, were treated at the recommended phase II dose of pamiparib 60 mg PO BID on Days 1-28 and LD TMZ 60 mg PO QD on Days 1-7. Tumor assessments occurred every 8 weeks. Endpoints were safety/tolerability (CTCAE v4.03) and antitumor activity (RECIST v1.1). Biomarker assessments included determination of DDR mutational status (SNV/CNV homozygous loss) of 16 core DDR genes in circulating tumor DNA and genomic instability score (GIS) by the Myriad myChoice® HRD test. Herein, we present data from the biomarker analysis.

Results

As of 10 April 2020, 114 pts were enrolled (n=66, dose escalation; n=48, dose expansion). Median follow-up was 8.5 mo (range: 0.3, 26.5). Of 36 pts analyzed for GIS, 11 (31%) were GIS positive (GIS+ ≥33), with an ORR of 82% and disease control rate (DCR) of 91% across multiple tumor types. Antitumor activity was observed in BRCA+/GIS+ (n=5; ORR and DCR, 100%) and BRCA+/GIS+ pts (n=6; ORR, 67%; DCR, 83%). Responses were observed in 3 GIS+ pts with pancreatic cancer, pheochromocytoma, and nonsquamous NSCLC (ORR=12%; DCR, 52%). Of 104 pts analyzed for DDR mutational status, 27 (26%) were DDR+, with an ORR of 26% and DCR of 52%. In DDR+ pts, ORR was 14% and DCR was 67%. Five pts were both GIS+ and DDR+.

Conclusions

In this limited subset of pts analyzed for GIS status, GIS+ pts derived superior benefit from pamiparib + LD TMZ, irrespective of BRCA status. GIS status appears to be the most robust biomarker to predict response to pamiparib + LD TMZ.

Clinical trial identification

NCT03150810.