PAMIPARIB IN COMBINATION WITH RADIATION THERAPY AND/OR TEMOZOLOMIDE IN PATIENTS WITH NEWLY DIAGNOSED OR RECURRENT/REFRACTORY GLIOBLASTOMA: PHASE 1B/2 STUDY UPDATE

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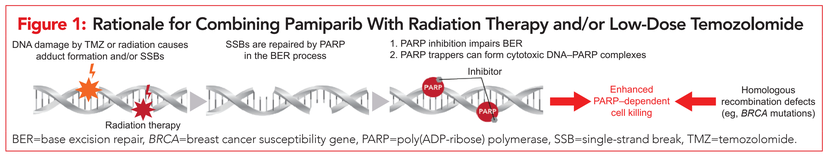
POSTER ACTR-39
SNO 24th Annual Meeting
Nov 20–24, 2019 | Phoenix, Arizona

BACKGROUND

- Poly(ADP-ribose) polymerase (PARP) proteins play a key role in the repair of single-strand and double-strand (ds) DNA breaks[1,2]
- Normal cells repair DNA breaks using base-excision repair (BER) and homologous recombination (HR) pathways; cancer cells that are HR deficient lack the ability to competently repair dsDNA breaks
- Pamiparib is an investigational PARP1/2 inhibitor that has demonstrated brain penetration and PARP-DNA complex–trapping capabilities in preclinical studies[3]
- Temozolomide (TMZ) methylates DNA bases, creating adducts that are repaired by the BER pathway in a PARP-dependent fashion; PARP inhibition results in the accumulation of highly cytotoxic adducts, leading to cell death (**Figure 1**)
- TMZ has been shown to cause DNA damage in tissues and peripheral blood cells in preclinical *in vivo* studies[4]
- We hypothesize that DNA damage caused by low-dose TMZ with or without radiation therapy may synergize with PARP inhibition, and that this synergy will result in increased antitumor activity
- We previously reported preliminary data (NCT03150862) that pamiparib 60 mg twice daily (BID) was generally well tolerated by patients when administered 6 weeks concurrently with radiation therapy (RT) for newly diagnosed unmethylated glioblastoma (GBM) and when combined with intermittent low-dose TMZ for recurrent/refractory (R/R) GBM[5]
- In the current analysis with fully accrued dose-escalation/expansion phase data, we report updated safety and antitumor effects of pamiparib + RT ± intermittent low-dose TMZ in patients with newly diagnosed or R/R GBM

Figure 1: Rationale for Combining Pamiparib With Radiation Therapy and/or Low-Dose Temozolomide



BER=base excision repair, *BRCA*=breast cancer susceptibility gene, PARP=poly(ADP-ribose) polymerase, SSB=single-strand break, TMZ=temozolomide.

METHODS

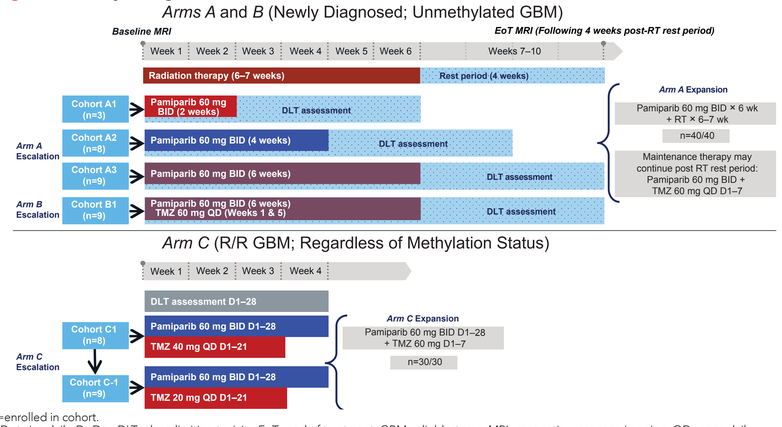
Study Design

- This dose-escalation/expansion study has 3 arms (**Figure 2**)
  - *Arm A*, pamiparib (2, 4, or 6 weeks) + RT in newly diagnosed GBM patients with unmethylated O^6-methylguanine-DNA methyltransferase (*MGMT*) promoter (unmethylated GBM)
  - *Arm B*, pamiparib (6 weeks) + RT and TMZ 60 mg dosed in Weeks 1 and 5 of RT in newly diagnosed, unmethylated GBM patients
  - *Arm C*, pamiparib + TMZ in methylated/unmethylated R/R-GBM patients
- Maintenance treatment post-RT rest period was optional for *Arm A* patients but required for *Arm B* patients

Study Assessments and Analyses

- Antitumor activity was assessed in all patients with measurable disease at baseline based on modified RANO v1.1 criteria
- Safety and tolerability were evaluated in all patients who received ≥1 dose of pamiparib and/or RT/TMZ
- Safety and tolerability assessments were based on monitoring of treatment-emergent adverse events (TEAEs), as well as on vital signs, electrocardiogram, physical examinations, and clinical laboratory results

Figure 2: Study Design



n=enrolled in cohort.
BID=twice daily, D=Day, DLT=dose-limiting toxicity, EoT=end of treatment, GBM=glioblastoma, MRI=magnetic resonance imaging, QD=once daily, R/R=recurrent/refractory, RT=radiation therapy, TMZ=temozolomide.

RESULTS

- As of 25 September 2019, accrual was completed for *Arms A (n=20), B (n=9),* and *C (n=17)* dose-escalation phase and for *Arms A (n=40)* and *C (n=30)* dose-expansion phase (**Table 1**)
- Recommended phase 2 doses (RP2Ds) were established for *Arms A* (pamiparib 60 mg BID × 6 weeks + 6–7 weeks RT) and C (pamiparib 60 mg BID D1–28 + TMZ 60 mg D1–7/28-day cycle)
- The maintenance dose for *Arms A* and *B* was defined as the *Arm C* RP2D

Table 1: Patient Demographics and Baseline Characteristics

	Arm A (N=60)	*Arm B* (N=9)	*Arm C* (N=47)
Median age (range), y	60.5 (31–79)	62.0 (45–77)	55 (24–87)
Male, n (%)	40 (66.7)	5 (55.6)	32 (68.1)
Baseline corticosteroid use, n (%)	32 (53.3)	5 (55.6)	25 (53.2)
MGMT promoter status, n (%)			
Methylated	–	–	16 (34.0)
Unmethylated	60 (100)	9 (100)	29 (61.7)
Unknown	–	–	1 (2.1)
Not done	–	–	1 (2.1)
Treatment exposure duration, median (range)	Pami + RT: 6.1 (1–10) wk M Pami + TMZ: 2.1 (0–6) mo	Pami + RT + TMZ: 6.1 (1–7) wk M Pami + TMZ: 3.7 (2–6) mo	1.7 (0–15) mo
Median study follow-up duration (range), mo	6.5 (1–22)	8.5 (0–9)	6.5 (1–17)

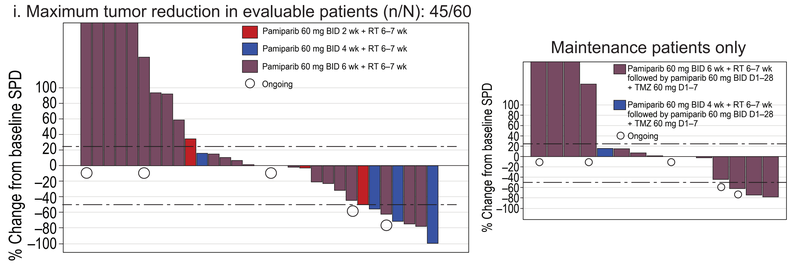
M=maintenance, *MGMT*=O^6-methylguanine-DNA methyltransferase, Pami=pamiparib, RT=radiation therapy, TMZ=temozolomide.

Efficacy

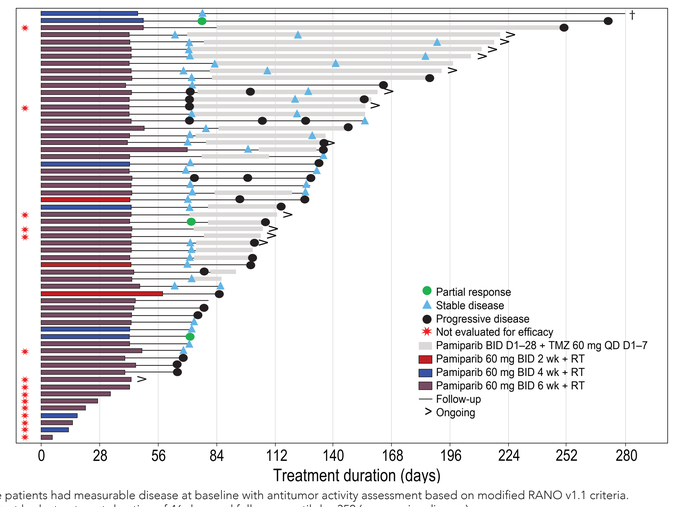
- As of 25 September 2019, 45 patients in *Arm A* and 6 patients in *Arm B* had a tumor assessment at end of treatment, and 43 in *Arm C* had at least 1 post-baseline assessment
- *Arm A*
  - Modified disease control rate (DCR) (complete response, partial response [PR], and stable disease [SD] as best response without confirmation) was 66.7% (95% confidence interval [CI], 51.0%–80.0%)
  - In patients with measurable disease at baseline (n=45), 1 patient had a confirmed PR (cPR), 2 patients had unconfirmed PR (uPR), and 33 patients had SD (**Figure 3i**)
  - Median treatment duration was 6.1 (range, 1–10) weeks for pamiparib + RT and 2.1 (range, 0–6) months, for pamiparib + TMZ (maintenance) (**Figure 3ii**)
  - Median overall survival (OS) was 11.24 (interquartile range [IQR], 8.28–20.24) months
  - Median progression-free survival (PFS) was 4.44 (IQR, 2.56–7.72) months

Figure 3: Investigator-Assessed Outcomes in Patients Enrolled in *Arm A*

i. Maximum tumor reduction in evaluable patients (n/N): 45/60



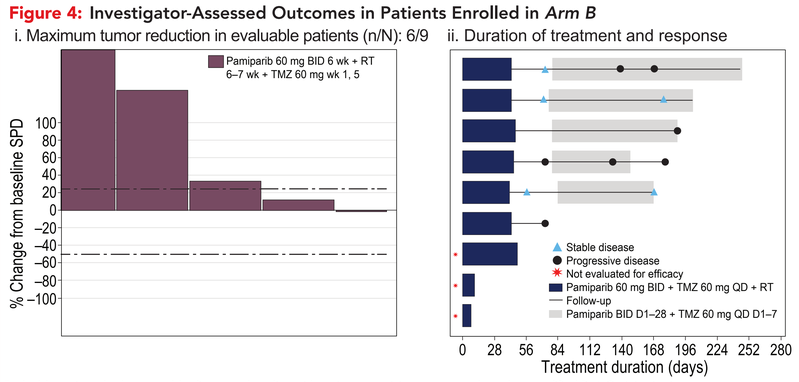
ii. Duration of treatment and response



Evaluable patients had measurable disease at baseline with antitumor activity assessment based on modified RANO v1.1 criteria.
[1]One patient had a treatment duration of 46 days and follow-up until day 352 (progressive disease).
28 days=1 cycle of maintenance treatment
BID=twice daily, D=Day, QD=once daily, RT=radiation therapy, SPD=sum of perpendicular diameter, TMZ=temozolomide.

- *Arm B*
  - Modified DCR was 50% (95% CI, 11.8%–88.2%) (**Figure 4i**)
  - Median treatment duration was 6.1 (range, 1–7) weeks for pamiparib + RT + TMZ and 3.7 (range, 2–6) months for pamiparib + TMZ (maintenance) (**Figure 4ii**)
  - Median OS and IQR were not reached
  - Median PFS was 5.31 (IQR, 2.37–6.21) months

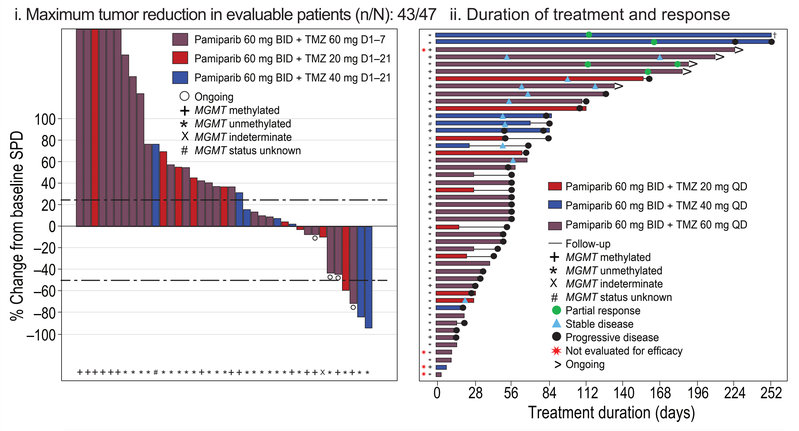
Figure 4: Investigator-Assessed Outcomes in Patients Enrolled in *Arm B*



Evaluable patients had measurable disease at baseline with antitumor activity assessment based on modified RANO v1.1 criteria.
28 days=1 cycle of maintenance treatment.
BID=twice daily, D=Day, QD=once daily, RT=radiation therapy, SPD=sum of perpendicular diameter, TMZ=temozolomide.

- *Arm C*
  - DCR was 30.2% (95% CI, 17.2%–46.1%)
  - Objective response rate (ORR) in patients with measurable disease at baseline (n=43) was 9.3% (2 cPR and 2 uPR); 9 patients had SD (**Figure 5i**)
  - Median duration of response was 11.2 (range, 0.03–11.17) months (**Figure 5ii**)
  - Median OS was 7.79 (IQR, 4.53–10.02) months
  - Median PFS was 1.87 (IQR, 1.48–3.71) months
  - Six-month PFS was 0.14 (95% CI, 0.05%–0.27%)

Figure 5: Investigator-Assessed Outcomes in Patients Enrolled in *Arm C*



Patient **0140-002** – Unmethylated *IDH* mutant 25-year-old patient originally diagnosed with anaplastic astrocytoma in 2011 and recurred as GBM in January 2018. Commenced the study in *Arm C* at TMZ 40-mg dose. Reduced to 20 mg in Cycle 5 following 4-week dose hold for G3 anemia and continued on study for 11 more cycles. uPR in Cycle 4 and cPR in Cycle 6 sustained until PD on Cycle 16 Day 1.

Evaluable patients had measurable disease at baseline with antitumor activity assessment based on modified RANO v1.1 criteria.
[1]One patient (0140-002) continued treatment to 452 days; patient course described in the above text box.
28 days=1 cycle.
Abbreviations: BID=twice daily, cPR=confirmed partial response, GBM=glioblastoma, *IDH*=isocitrate dehydrogenase; *MGMT*=O^6-methylguanine-DNA methyltransferase, PD=progressive disease, QD=once daily, SPD=sum of perpendicular diameter, TMZ=temozolomide, uPR=unconfirmed partial response.

CONCLUSIONS

- As of 25 September 2019, accrual is complete in this phase 1b/2 study of pamiparib + RT and/or TMZ in patients with newly diagnosed GBM or pamiparib + TMZ in R/R GBM
  - In *Arm A* (N=60), pamiparib (2, 4, or 6 weeks) + RT in patients with newly diagnosed GBM with unmethylated *MGMT* promoter
    - The addition of pamiparib to standard RT was found to be safe and tolerable when dosed over the full 6 weeks of RT
    - Antitumor activity was observed with a modified DCR of 66.7% (95% CI, 51.0%–80.0%)
  - In *Arm B* (N=9), dose escalation with pamiparib (6 weeks) + RT and increasing TMZ dosed in Weeks 1 and 5 of RT in patients with newly diagnosed unmethylated GBM
    - The addition of TMZ to pamiparib + RT was generally well tolerated, although cytopenias were observed
  - In *Arm C* (N=47), pamiparib + increasing TMZ doses in methylated/unmethylated R/R-GBM patients
    - Most frequent Grade ≥3 TRAEs related to pamiparib + TMZ were cytopenias
    - Limited antitumor activity was observed with an ORR of 9.3%
- RP2Ds established were as follows: *Arm A*, pamiparib 60 mg BID × 6 weeks + 6–7 weeks RT followed by maintenance treatment with pamiparib + TMZ; *Arm C*, pamiparib 60 mg BID D1–28 + TMZ 60 mg D1–7/28-day cycle
- Collectively, pamiparib 60 mg BID + RT and/or TMZ was generally well tolerated in patients with newly diagnosed or R/R GBM
- Pamiparib + TMZ showed limited activity in R/R GBM. Analysis of efficacy data in the newly diagnosed population is ongoing

Safety

- The most common TEAEs (all grades) were fatigue and nausea in *Arms A, B,* and *C* (**Table 2**)
- Grade 4 treatment-related adverse events (TRAEs) included neutropenia related to pamiparib in *Arm A* maintenance phase (n=2) and thrombocytopenia related to pamiparib and TMZ in *Arm C* (n=1). There were no Grade 5 TRAEs across all arms
- Dose-limiting toxicities (DLTs) from *Arms A* and *C* were previously reported. One DLT (Grade 3 febrile neutropenia) was reported in *Arm B*
- In *Arm A*, 4 patients had ≥1 TEAE that led to pamiparib + RT treatment discontinuation
- In *Arm B*, there were no TEAEs that led to discontinuation of pamiparib + RT + TMZ; a TEAE in one patient (white blood cell count decreased) led to pamiparib + TMZ treatment discontinuation (maintenance phase)
- In *Arm C*, 7 patients had ≥1 TEAE that led to pamiparib + TMZ treatment discontinuation
  - One patient in *Arm C* had an unrelated TEAE of pneumonia that led to death

Table 2: Treatment-Emergent Adverse Events (All Grades)

TEAEs, n (%)	Dose Escalation		Dose Expansion		
Arm A (≥15% of patients)	Pami 2 wk + RT 6 wk (n=3)	Pami 4 wk + RT 6 wk (n=8)	Pami 6 wk + RT 6 wk (n=9)	Pami 6 wk + RT 6 wk (n=40)	All patients (N=60)
Fatigue	3 (100)	1 (12.5)	5 (55.6)	29 (72.5)	38 (63.3)
Nausea	1 (33.3)	3 (37.5)	5 (55.6)	28 (70.0)	37 (61.7)
Headache	1 (33.3)	0	4 (44.4)	17 (42.5)	22 (36.7)
Alopecia	2 (66.7)	2 (25.0)	3 (33.3)	14 (35.0)	21 (35.0)
Anorexia	1 (33.3)	1 (12.5)	3 (33.3)	13 (32.5)	18 (30.0)
Constipation	0	1 (12.5)	3 (33.3)	13 (32.5)	17 (28.3)
Vomiting	1 (33.3)	0	3 (33.3)	12 (30.0)	16 (26.7)
Diarrhea	0	2 (25.0)	0	12 (30.0)	14 (23.3)
Anemia	0	1 (12.5)	0	10 (25.0)	11 (18.3)
Dizziness	0	1 (12.5)	0	10 (25.0)	11 (18.3)
Dysgeusia	0	0	0	10 (25.0)	10 (16.7)
Weight loss	0	0	1 (11.1)	9 (22.5)	10 (16.7)
Aphasia	0	1 (12.5)	3 (33.3)	5 (12.5)	9 (15.0)
Decreased platelet count	0	0	1 (11.1)	8 (20.0)	9 (15.0)

Arm B (≥2 of patients)*	Dose Escalation Pami 6 wk + RT 6 wk + TMZ 60 mg (N=9)
Fatigue, nausea	6 (66.7) each
Alopecia, anemia, anorexia, decreased white blood cell count	4 (44.4) each
Constipation, hemiparesis, decreased neutrophil count, rash maculo-papular	3 (33.3) each
Anxiety, diarrhea, dizziness, dysgeusia, gait disturbance, edema peripheral, headache, hypertension, insomnia, hypokalemia, decreased lymphocyte count, urinary incontinence, vomiting	2 (22.2) each

	Dose Escalation		Dose Expansion	
Arm C (≥15% of patients)	Pami + TMZ 20 mg (n=9)	Pami + TMZ 40 mg (n=8)	Pami + TMZ 60 mg (n=30)	All patients (N=47)
Fatigue	1 (11.1)	5 (62.5)	17 (56.7)	23 (48.9)
Nausea	4 (44.4)	5 (62.5)	12 (40.0)	21 (44.7)
Constipation	2 (22.2)	2 (25.0)	11 (36.7)	15 (31.9)
Anemia	3 (33.3)	3 (37.5)	6 (20.0)	12 (25.5)
Decreased platelet count	3 (33.3)	1 (12.5)	7 (23.3)	11 (23.4)
Vomiting	1 (11.1)	5 (62.5)	5 (16.7)	11 (23.4)
Anorexia	2 (22.2)	1 (12.5)	6 (20.0)	9 (19.1)
Dizziness	1 (11.1)	1 (12.5)	7 (23.3)	9 (19.1)
Headache	1 (11.1)	0	8 (26.8)	9 (19.1)
Hemiparesis	4 (44.4)	1 (12.5)	4 (13.3)	9 (19.1)
Decreased white cell count	2 (22.2)	1 (12.5)	6 (20.0)	9 (19.1)
Decreased lymphocyte count	3 (33.3)	1 (12.5)	4 (13.3)	8 (17.0)
Decreased neutrophil count	2 (22.2)	2 (25.0)	4 (13.3)	8 (17.0)
Muscular weakness	2 (22.2)	1 (12.5)	5 (16.7)	8 (17.0)

*Cutoff of ≥2 patients chosen due to small n in cohort.
Pami=pamiparib, TEAE=treatment-emergent adverse event, TMZ=temozolomide.

ACKNOWLEDGMENTS

We would like to thank the investigators, site support staff, and especially the patients for participating in this study. This study was sponsored by BeiGene. Editorial support funded by BeiGene was provided by Ira Mills, PhD, Erin Spohr, and Joshua Safran of Ashfield Healthcare Communications.

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