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

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BACKGROUND

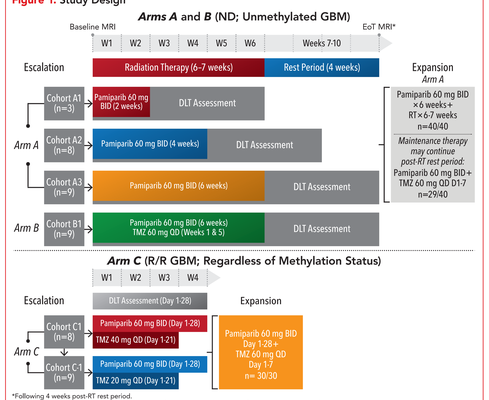
- Poly(ADP-ribose) polymerase (PARP) proteins play a key role in the repair of single-strand and double-strand DNA breaks[1-3]
- Normal cells repair DNA breaks using base-excision repair and homologous recombination pathways; cancer cells that are homologous recombination–deficient lack the ability to competently repair double-strand DNA breaks[1]
- Pamiparib is an investigational PARP1/2 inhibitor that has demonstrated brain penetration and PARP-DNA complex–trapping capabilities in preclinical studies[4]
- Temozolomide (TMZ) given in combination with radiation therapy (RT) following tumor debulking surgery is the standard treatment regimen for patients with glioblastoma (GBM)
- We hypothesize that the addition of TMZ to a PARP regimen may further sensitize tumors to PARP inhibition due to the DNA damage caused by TMZ[4,5] allowing an increase of areas for PARP trapping
- We previously reported data from our clinical trial (BGB-290-104; NCT03150862), which showed that pamiparib 60 mg twice daily (BID) was generally well tolerated by patients when administered for 6 weeks concurrently with RT for newly diagnosed (ND) unmethylated GBM;[6] we also reported clinical trial data (BGB-290-103; NCT03150810), which showed pamiparib + low dose TMZ was generally well tolerated in patients with solid tumors (non GBM)[7]
  - Recommended phase 2 doses (RP2Ds) were established for *Arm A* (pamiparib 60 mg BID × 6 weeks plus 6-7 weeks RT) in the current study and for *Arm C* (pamiparib 60 mg BID Days 1-28 plus TMZ 60 mg Days 1-7 of each 28-day cycle) and maintenance treatment (pamiparib 60 mg BID + TMZ 60 mg Days 1-7) in the BGB-290-103 study that assessed pamiparib + low dose TMZ in patients with solid tumors[7]
  - The maintenance dose and schedule for *Arms A* and *B* was defined as the RP2D in *Arm C*
- In this final analysis, we report updated data on the clinical activity and safety of pamiparib plus RT with or without intermittent low-dose TMZ in patients with ND GBM or recurrent/refractory (R/R) GBM

METHODS

Study Design

- This dose-escalation/expansion study has three arms (**Figure 1**)
  - *Arm A:* Pamiparib 60 mg BID (2, 4, or 6 weeks) plus RT in ND GBM patients with unmethylated O^6-methylguanine-DNA methyltransferase (MGMT) promoter (unmethylated GBM)
  - *Arm B:* Pamiparib 60 mg BID (6 weeks) plus RT and TMZ 60 mg dosed in Weeks 1 and 5 of RT in ND, unmethylated GBM patients
  - *Arm C:* Pamiparib 60 mg BID (4 weeks) plus TMZ 20 or 40 mg Day 1-21 in methylated/unmethylated R/R GBM patients
- *Arm A* and *Arm B* expansion: Maintenance treatment (pamiparib 60 mg BID + TMZ 60 mg Days 1-7) post-RT rest period was optional for *Arm A* patients but required for *Arm B* patients

Figure 1: Study Design



*Following 4 weeks post-RT rest period.
Abbreviations: BID, twice daily; D, day; DLT, dose-limiting toxicity; EoT, end of treatment; GBM, glioblastoma; MRI, magnetic resonance imaging; ND, newly diagnosed; QD, once daily; R/R, recurrent/refractory; RT, radiation therapy; TMZ, temozolomide; W, week.

Assessments

- Clinical activity was assessed in all patients with measurable disease at baseline and every 8 weeks thereafter, or as clinically indicated, based on RANO v1.1 criteria
  - Modified disease control rate (DCR) was defined as the proportion of patients who achieve complete response, partial response (PR), or stable disease (SD) as the response assessment at the end of treatment visit, as scheduled per protocol
- Safety and tolerability were evaluated in all patients who received at least one dose of pamiparib + RT, pamiparib + RT and TMZ, or pamiparib + TMZ
- Safety and tolerability assessments were based on monitoring of adverse events (AEs), as well as of vital signs, electrocardiograms, physical examinations, and clinical laboratory results

RESULTS

- At the time of database lock (August 11, 2020), 116 patients (n=60, *Arm A;* n=9, *Arm B;* n=47, *Arm C*) had been enrolled (**Table 1**)
- A total of 72.5% of patients in *Arm A* (expansion, n=29/40) and 66.7% of patients in *Arm B* (n=6/9) received maintenance pamiparib plus TMZ after a post-RT rest period
- Median study follow-up was 12 months (range, 0-22) in *Arms A/B* and 7 months (range, 1-25) in *Arm C*

Table 1: Patient Demographics and Baseline Characteristics

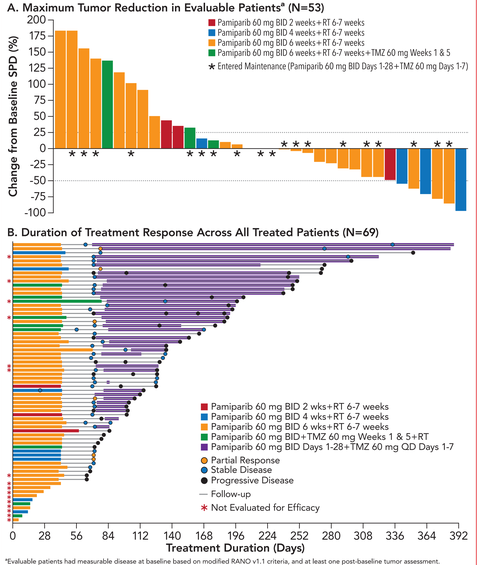
		Arms A/B (n=69)	*Arm C* (n=47)
Median age (range), years		61 (31-79)	55 (24-87)
Male, n (%)		45 (65.2)	32 (68.1)
Baseline corticosteroid use, n (%)		36 (52.2)	25 (53.2)
MGMT promoter status, n (%)	Methylated	0	16 (34.0)
	Unmethylated	69 (100)	29 (61.7)
	Indeterminate	0	1 (2.1)
	Unavailable	0	1 (2.1)
Median treatment duration, weeks (range)	Pamiparib + RT + TMZ	6 (1-11)	NA
	Pamiparib + RT	6 (1-10)	NA
	Pamiparib + TMZ (MP)	14 (0-46)	NA
	Pamiparib + TMZ	NA	7 (0-78)

Abbreviations: MGMT, O^6-methylguanine-DNA methyltransferase; MP, maintenance phase; NA, not applicable; RT, radiation therapy; TMZ, temozolomide.

Clinical Efficacy

- At the time of database lock (August 11, 2020), 53 patients with unmethylated ND GBM in *Arms A/B* had a tumor assessment at end of treatment and at least one postbaseline assessment
- Within these 53 patients, the confirmed modified DCR was 67.9% (95% confidence interval [CI], 53.7-80.1)
- In patients with measurable disease at baseline (n=53, eight patients did not have measurable disease at baseline due to lack of residual disease post resection), two patients had confirmed PR, six patients had unconfirmed PR, and 35 patients experienced SD (**Figure 2A**)
  - Median duration of response was 8.4 months (95% CI, 6.4-10.3) (**Figure 2B**)

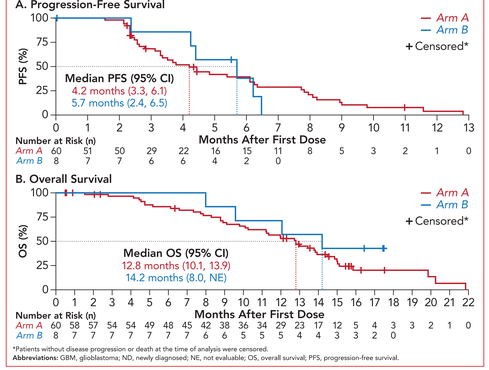
Figure 2: Investigator-Assessed Clinical Activity in Patients With ND Unmethylated GBM



[a]Evaluable patients had measurable disease at baseline based on modified RANO v1.1 criteria, and at least one post-baseline tumor assessment.
Abbreviations: BID, twice daily; GBM, glioblastoma; ND, newly diagnosed; QD, once daily; RT, radiation therapy; SPD, sum of the products of the perpendicular diameter; TMZ, temozolomide.

- Median progression-free survival (PFS) (**Figure 3A**) and overall survival (OS) (**Figure 3B**) were estimated as 4.4 months (95% CI, 3.4-6.1) and 12.8 months (95% CI, 10.3-14.2), respectively

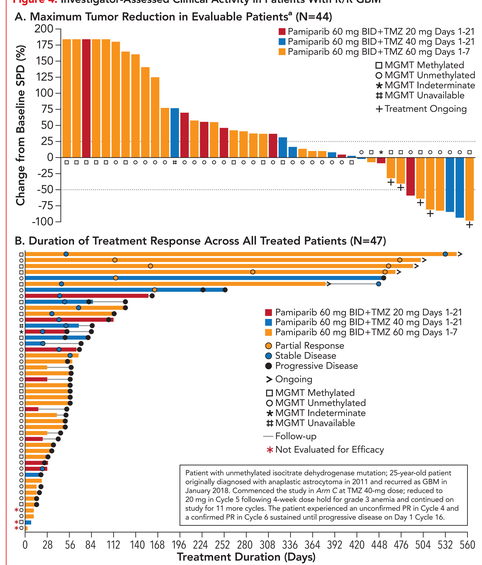
Figure 3: Survival Estimates in Patients With Unmethylated ND GBM



*Patients without disease progression or death at the time of analysis were censored.
Abbreviations: GBM, glioblastoma; ND, newly diagnosed; NE, not evaluable; OS, overall survival; PFS, progression-free survival.

- At the time of database lock (August 11, 2020), 44 patients with R/R GBM in *Arm C* had at least one postbaseline assessment
- Among these 44 patients, 17 achieved PR (n=4, confirmed; n=5, unconfirmed) and 14 achieved SD (**Figure 4A**)
  - Confirmed DCR was 40.9% (95% CI: 26.3-56.8), the objective response rate was 9.1% (95% CI: 2.5-21.7), and the median duration of response was not evaluable (NE) (95% CI: 11.2 months-NE) (**Figure 4B**)

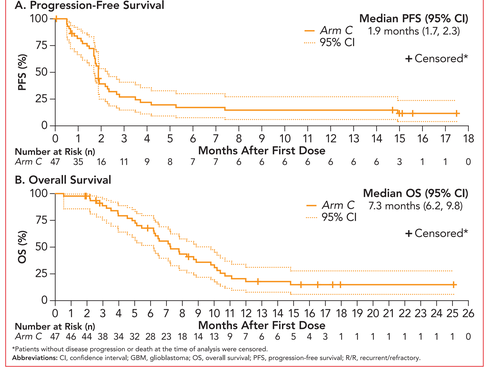
Figure 4: Investigator-Assessed Clinical Activity in Patients With R/R GBM



[a]Evaluable patients had measurable disease at baseline based on RANO v1.1 criteria, and at least one post-baseline tumor assessment.
Abbreviations: BID, twice daily; GBM, glioblastoma; MGMT, O^6-methylguanine-DNA methyltransferase; PR, partial response; R/R, recurrent/refractory; SPD, sum of the products of the perpendicular diameter; TMZ, temozolomide.

- Median PFS (**Figure 5A**) and OS (**Figure 5B**) were estimated as 1.9 months (95% CI, 1.7-2.3) and 7.3 months (95% CI, 6.2-9.8), respectively

Figure 5: Survival Estimates in Patients With R/R GBM



*Patients without disease progression or death at the time of analysis were censored.
Abbreviations: CI, confidence interval; GBM, glioblastoma; OS, overall survival; PFS, progression-free survival; R/R, recurrent/refractory.

Safety/Tolerability Profile

- Fatigue (*Arm A*, 72.5%; *Arm B*, 66.7%; *Arm C*, 48.9%) and nausea (*Arm A*, 72.5%; *Arm B*, 77.8%; *Arm C*, 48.9%) were the most common AEs (**Table 2** and **Table 3**)
- Most common grade ≥3 AEs included anemia (8.3% [*Arm A*]) and decreased neutrophil and white blood cell count (22.2% each [*Arm B*]) in unmethylated ND GBM patients, and fatigue and decreased lymphocyte count (10.6% each) in patients with R/R GBM
- Grade 4 treatment-related AEs were neutropenia related to pamiparib and TMZ in *Arm A* (n=2); decreased neutrophil count and decreased white blood cell count related to pamiparib and TMZ in *Arm B* (n=1 each); and decreased neutrophil count, decreased white blood cell count, decreased lymphocyte count, neutropenia, thrombocytopenia, and lymphopenia related to pamiparib and TMZ in *Arm C* (n=1 each)
- No grade 5 treatment-related AEs were reported; two grade 5 AEs (vasogenic edema, *Arm A*; pneumonia, *Arm C*) were reported, neither of which were considered related to treatment
- In *Arm A*, four patients had at least one AE that led to pamiparib plus RT discontinuation
- In *Arm B*, there were no AEs that led to the discontinuation of pamiparib plus RT plus TMZ; however, an AE in one patient (decreased white blood cell count) led to pamiparib plus TMZ treatment discontinuation (maintenance phase)
- In *Arm C*, six patients had at least one AE that led to discontinuation of pamiparib and TMZ

Table 2: Most Commonly Reported Treatment-Emergent AEs (All Grades) Occurring in Patients With Unmethylated ND GBM

	Arm A				*Arm B*
	Dose Escalation			Dose Expansion	
	Pamiparib 2 weeks + RT 6 weeks (n=3)	Pamiparib 4 weeks + RT 6 weeks (n=8)	Pamiparib 6 weeks + RT 6 weeks (n=9)	Pamiparib 6 weeks + RT 6 weeks (n=40)	Pamiparib 6 weeks + RT 6 weeks + TMZ 60 mg Weeks 1 & 5 (n=9)
Fatigue	3 (100.0)	2 (25.0)	6 (66.7)	29 (72.5)	6 (66.7)
Nausea	1 (33.3)	3 (37.5)	5 (55.6)	29 (72.5)	7 (77.8)
Headache	1 (33.3)	1 (12.5)	4 (44.4)	18 (45.0)	2 (22.2)
Alopecia	2 (66.7)	2 (25.0)	2 (22.2)	14 (35.0)	4 (44.4)
Decreased appetite	1 (33.3)	1 (12.5)	3 (33.3)	14 (35.0)	4 (44.4)
Constipation	0 (0.0)	1 (12.5)	3 (33.3)	14 (35.0)	3 (33.3)
Vomiting	1 (33.3)	0 (0.0)	3 (33.3)	13 (32.5)	2 (22.2)
Anemia	0 (0.0)	1 (12.5)	0 (0.0)	13 (32.5)	4 (44.4)
Diarrhea	0 (0.0)	2 (25.0)	0 (0.0)	12 (30.0)	2 (22.2)
Dizziness	0 (0.0)	1 (12.5)	0 (0.0)	11 (27.5)	2 (22.2)
Aphasia	0 (0.0)	1 (12.5)	3 (33.3)	6 (15.0)	1 (11.1)
Dysgeusia	0 (0.0)	0 (0.0)	0 (0.0)	10 (25.0)	2 (22.2)
Hemiparesis	0 (0.0)	0 (0.0)	1 (11.1)	9 (22.5)	3 (33.3)
Decreased weight	0 (0.0)	0 (0.0)	1 (11.1)	9 (22.5)	0 (0.0)
Seizure	0 (0.0)	0 (0.0)	1 (11.1)	8 (20.0)	1 (11.1)

Data are presented as n (%).
Abbreviations: AE, adverse event; GBM, glioblastoma; ND, newly diagnosed; RT, radiation therapy; TMZ, temozolomide.

CONCLUSIONS

- Results of this phase 1b/2 study of pamiparib plus RT and/or TMZ in patients with ND GBM or pamiparib plus TMZ in patients with R/R GBM showed that:
  - In *Arm A* (N=60) and *Arm B* (N=9), the modified DCR was 67.9% (95% CI, 53.7-80.1), median PFS was 4.4 months, and median OS was 12.8 months
  - In *Arm C* (N=47), pamiparib plus TMZ in methylated/unmethylated R/R GBM patients showed limited clinical activity, with an objective response rate of 9.1% (95% CI, 2.5-21.7); median PFS was 1.9 months and median OS was 7.3 months
- These results showed a manageable safety profile for pamiparib 60 mg BID plus RT and/or TMZ in patients with ND GBM or R/R GBM
  - In *Arm A*, in the escalation phase, the addition of pamiparib to standard RT was found to be safe and tolerable when dosed over the full 6 weeks of RT
  - In *Arm B*, the addition of TMZ to pamiparib plus RT was generally well tolerated, although cytopenias were observed
  - In *Arm C*, the most frequent grade 4 AEs related to pamiparib plus TMZ were cytopenias
- These results support further evaluation of pamiparib plus RT and/or TMZ in ND GBM patients
- An investigator-sponsored research clinical brain penetrance study is ongoing at the Ivy Brain Tumor Center, Barrow Neurological Institute

Table 3: Most Commonly Reported Treatment-Emergent AEs (All Grades) Occurring in Patients With R/R GBM

	Dose Escalation		Dose Expansion	
	Pamiparib + TMZ 20 mg Days 1-21 (n=9)	Pamiparib + TMZ 40 mg Days 1-21 (n=8)	Pamiparib + TMZ 60 mg Days 1-7 (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)	13 (43.3)	22 (48.9)
Constipation	2 (22.2)	2 (25.0)	12 (40.0)	16 (34.0)
Vomiting	1 (11.1)	5 (62.5)	7 (23.3)	13 (27.7)
Anemia	3 (33.3)	3 (37.5)	6 (20.0)	12 (25.5)
Decreased platelet count	3 (33.3)	1 (12.5)	8 (26.7)	12 (25.5)
Decreased appetite	2 (22.2)	1 (12.5)	7 (23.3)	10 (21.3)
Dizziness	1 (11.1)	1 (12.5)	8 (26.7)	10 (21.3)
Fall	0 (0.0)	3 (37.5)	6 (20.0)	9 (19.1)
Headache	1 (11.1)	0 (0.0)	8 (26.7)	9 (19.1)
Hemiparesis	4 (44.4)	1 (12.5)	4 (13.3)	9 (19.1)
Decreased neutrophil count	2 (22.2)	2 (25.0)	5 (16.7)	9 (19.1)
Decreased white blood 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)
Muscular weakness	2 (22.2)	1 (12.5)	5 (16.7)	8 (17.0)
Diarrhea	2 (22.2)	1 (12.5)	4 (13.3)	7 (14.9)

Data are presented as n (%).
Abbreviations: AE, adverse event; GBM, glioblastoma; R/R, recurrent/refractory; TMZ, temozolomide.

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