# PRELIMINARY RESULTS OF PAMIPARIB, A PARP1/2 INHIBITOR, IN COMBINATION WITH TEMOZOLOMIDE IN PATIENTS WITH LOCALLY ADVANCED OR METASTATIC SOLID TUMORS


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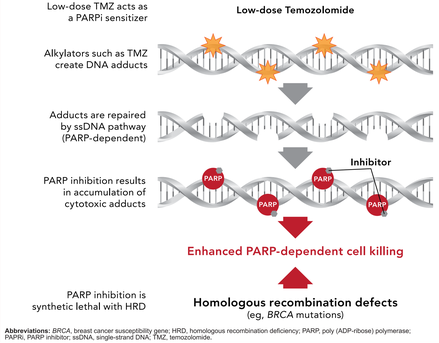
## BACKGROUND

- Poly (ADP-ribose) polymerase (PARP) proteins are a family of proteins involved in DNA repair, genome stability, and programmed cell death that play a key role in the repair of single strand (ss) and double strand (ds) DNA breaks[1,2]
- Normal cells repair ssDNA and dsDNA breaks using the base excision repair (BER) and the homologous recombination (HR) pathways; cancer cells that are HR deficient (HRD+) are unable to repair dsDNA breaks
- PARP inhibition impairs DNA repair and traps PARP proteins on damaged DNA, resulting in cytotoxicity that is exacerbated in HRD+ cells (synthetic lethality)[3–9]
- Pamiparib is an investigational PARP1 and PARP2 inhibitor that has demonstrated brain penetration and PARP–DNA complex trapping capabilities
- Results from an ongoing phase 1 study (NCT02361723) in patients with advanced solid tumors suggested that pamiparib was generally well tolerated and had promising antitumor activity in ovarian cancer[10]
- The alkylator, temozolomide (TMZ), methylates DNA bases, creating DNA 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, at doses equivalent to 11.5 mg/m$^2$ to 69 mg/m$^2$ (low-dose), has been shown to cause DNA damage in tissues and peripheral blood cells in preclinical in vivo studies[11]
- We hypothesize that DNA damage caused by low doses of TMZ may synergize with PARP inhibition, and that this synergy, in the context of HRD, will result in increased antitumor activity
- This phase 1b study (NCT03150810) evaluates the safety and preliminary antitumor activity of pamiparib in combination with low doses of TMZ in patients with locally advanced and metastatic tumors

**Figure 1: Rationale for Combining Pamiparib With Low-Dose Temozolomide**




**Abbreviations:** *BRCA*, breast cancer susceptibility gene; HRD, homologous recombination deficiency; PARP, poly (ADP-ribose) polymerase; PARPi, PARP inhibitor; ssDNA, single-strand DNA; TMZ, temozolomide.

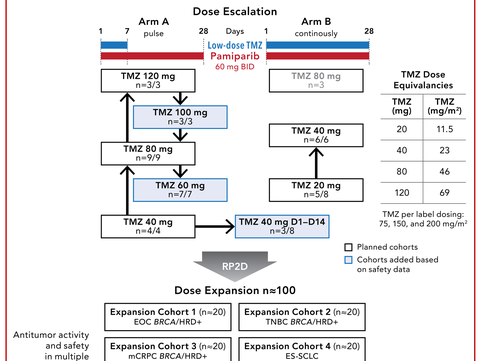
## METHODS

- The study design is detailed in **Figure 2** (white cohorts)
  - The design allows for exploration of intermediate doses and alternate administration schedules based on emerging safety and pharmacokinetic data; modifications made are shown in **Figure 2** (blue cohorts)
  - Radiographic assessments are being conducted every 8 weeks

### Key Eligibility Dose Escalation

- Adult patients (≥18 years old) with a confirmed malignancy that has progressed to advanced or metastatic stage with no option for effective standard therapy
- Disease that is measurable or evaluable per RECIST v1.1; prostate cancer patients will be evaluated using Prostate Cancer Working Group 2 (PCWG2) criteria
- Patients are excluded if they had hypersensitivity to TMZ or dacarbazine, or had prior treatment with a PARP inhibitor (except for iniparib)

**Figure 2: Study Design**




| TMZ Dose Equivalancies | |
|---|---|
| TMZ (mg) | TMZ (mg/m$^2$) |
| 20 | 11.5 |
| 40 | 23 |
| 80 | 46 |
| 120 | 69 |

TMZ per label dosing: 75, 150, and 200 mg/m$^2$

**Abbreviations:** BID, twice daily; *BRCA*, breast cancer susceptibility gene; D, day; EOC, epithelial ovarian carcinoma; ES-SCLC, extensive-stage small cell lung cancer; GEJ, gastroesophageal junction; HRD, homologous recombination deficiency; mCRPC, metastatic castration-resistant prostate cancer; RP2D, recommended phase 2 dose; TMZ, temozolomide; TNBC, triple-negative breast cancer.

## RESULTS

### Patient Disposition

- As of 24 August 2018, a total of 40 patients with solid tumors have been enrolled in the study (**Table 1**); median treatment duration was 1.6 months (range: 0–9)
  - A total of 18 patients (45%) remain on pamiparib and low-dose TMZ treatment
  - The most frequent tumor types were prostate (n=7), small cell lung cancer (n=6), breast (n=4), epithelial ovarian cancer (n=4), and pancreatic cancer (n=3)

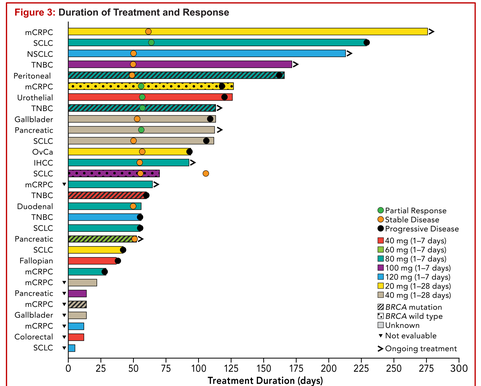
**Table 1: Patient Demographics and Disease Characteristics**

| | | Overall (N=40) |
|---|---|---|
| Median age, years (range) | | 66 (38-85) |
| Sex, n (%) | Male | 21 (52.5) |
| | Female | 19 (47.5) |
| Race, n (%) | Caucasian | 28 (70.0) |
| | Black/African American | 6 (15.0) |
| | Other | 2 (5.0) |
| | Unknown | 2 (5.0) |
| | Asian | 1 (2.5) |
| | Not reported | 1 (2.5) |
| Median prior cancer therapies, n (range) | | 4 (1-10) |
| Prior anticancer therapies, n (%) | ≤3 | 13 (32.5) |
| | 4-6 | 20 (50.0) |
| | ≥7 | 7 (17.5) |
| *BRCA* status, n (%) | Wild type | 4 (10.0) |
| | Mutated | 8 (20.0) |
| | Unknown | 28 (70.0) |

**Abbreviation:** *BRCA*, breast cancer susceptibility gene.

### Preliminary Antitumor Activity

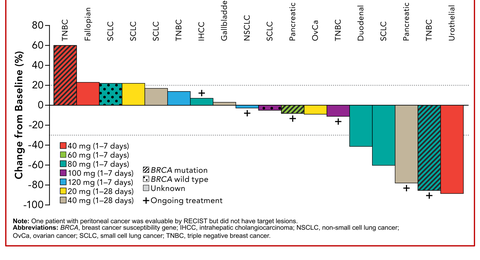
**Figure 3: Duration of Treatment and Response**




**Abbreviations:** *BRCA*, breast cancer susceptibility gene; IHCC, intrahepatic cholangiocarcinoma; mCRPC, metastatic castration resistant prostate cancer; NSCLC, non-small cell lung cancer; OvCa, ovarian cancer; SCLC, small cell lung cancer; TNBC, triple negative breast cancer.

- As of 24 August 2018, 23 patients (excluding those with prostate cancer) were evaluable for response, by RECIST defined as being enrolled by 22 June, 2018 (≥1 post-baseline tumor assessments or at least 9 weeks follow-up; **Figures 3 and 4**)
  - Confirmed partial response (PR) was achieved by two patients (pancreatic cancer and small cell lung cancer (40 mg TMZ Days 1–28 and 80 mg TMZ Days 1–7, respectively). Ten patients achieved stable disease (SD) and four patients were not evaluable due to a lack of a post-baseline tumor assessment
  - Unconfirmed PR was achieved by two patients (triple-negative breast cancer, 80 mg TMZ Days 1–7 and urothelial cancer, 40 mg TMZ Days 1–7) (**Figure 3**)
- Seven prostate cancer patients were evaluated using the PCWG2 criteria
  - A visceral PR and prostate-specific antigen (PSA) response was achieved by one patient at the first post-baseline tumor assessment. PR and PSA response were reported at the second tumor assessment, but a new lesion was also observed. The patient was discontinued from therapy before confirmation of disease progression (**Figure 3**)

**Figure 4: Maximum Tumor Reduction in Evaluable Patients (Excluding Prostate Cancer Patients)**




**Note:** One patient with peritoneal cancer was evaluable by RECIST but did not have target lesions.
**Abbreviations:** *BRCA*, breast cancer susceptibility gene; IHCC, intrahepatic cholangiocarcinoma; NSCLC, non-small cell lung cancer; OvCa, ovarian cancer; SCLC, small cell lung cancer; TNBC, triple negative breast cancer.

### Safety and Tolerability

- Dose limiting events: neutropenia grade 4 lasting more than 7 days observed in two patients in each cohort dosed at 120 mg TMZ Days 1–7 and 100 mg TMZ Days 1–7
- Thirty-eight patients had ≥1treatment-emergent adverse event (TEAE); the most common TEAEs (all grades) were nausea, anemia, neutropenia, thrombocytopenia, and fatigue (**Table 2**)
- Eighteen patients experienced grade ≥3 related TEAEs (**Table 3**)
  - The most common grade ≥3 AEs were neutropenia, anemia, and thrombocytopenia
  - Cytopenias were manageable and reversible
- Two patients experienced AEs that resulted in discontinuation of pamiparib and low-dose TMZ: decreased platelet counts (related, n=1) and dyspnea (unrelated, n=1)
- Serious AEs related to study treatment occurred in four patients (neutropenia, abdominal abscess, thrombocytopenia + leukopenia, and dehydration)
- There were no AEs with fatal outcome

**Table 2: Treatment-Emergent Adverse Events Occurring in More Than 2 Patients (All Grades)**

| | Arm A (D1–7) | | | | | Arm A (D1–14) | | Arm B (D1–28) | | Overall |
|---|---|---|---|---|---|---|---|---|---|---|
| TMZ dose | 40 mg | 60 mg | 80 mg | 100 mg | 120 mg | 40 mg | 20 mg | 40 mg | | |
| Number of patients | (n=4) | (n=7) | (n=9) | (n=3) | (n=3) | (n=3) | (n=5) | (n=6) | | N=(40) |
| Nausea | 3 (75.0) | 5 (71.4) | 4 (44.4) | 1 (33.3) | 2 (66.7) | 1 (33.3) | 1 (20.0) | 4 (66.7) | | 21 (52.5) |
| Anemia | 0 | 1 (14.3) | 5 (55.6) | 2 (66.7) | 3 (100.0) | 0 | 1 (20.0) | 3 (50.0) | | 15 (37.5) |
| Neutropenia | 1 (25.0) | 1 (14.3) | 3 (33.3) | 2 (66.7) | 3 (100.0) | 0 | 1 (20.0) | 1 (16.7) | | 12 (30.0) |
| Fatigue | 2 (50.0) | 3 (42.9) | 4 (44.4) | 0 | 1 (33.3) | 0 | 0 | 1 (16.7) | | 11 (27.5) |
| Thrombocytopenia | 1 (25.0) | 1 (14.3) | 4 (44.4) | 1 (33.3) | 3 (100.0) | 0 | 0 | 1 (16.7) | | 11 (27.5) |
| Platelet count decreased | 1 (25.0) | 0 | 3 (33.3) | 1 (33.3) | 0 | 0 | 1 (20.0) | 2 (33.3) | | 8 (20.0) |
| Decreased appetite | 1 (25.0) | 1 (14.3) | 3 (33.3) | 1 (33.3) | 0 | 0 | 0 | 1 (16.7) | | 7 (17.5) |
| Vomiting | 1 (25.0) | 1 (14.3) | 1 (11.1) | 0 | 2 (66.7) | 1 (33.3) | 0 | 1 (16.7) | | 7 (17.5) |
| Abdominal pain | 0 | 1 (14.3) | 2 (22.2) | 0 | 2 (66.7) | 0 | 0 | 1 (16.7) | | 6 (15.0) |
| Diarrhea | 0 | 0 | 3 (33.3) | 0 | 0 | 0 | 1 (20.0) | 1 (16.7) | | 5 (12.5) |
| Neutrophil count decreased | 0 | 0 | 2 (22.2) | 1 (33.3) | 0 | 0 | 0 | 2 (33.3) | | 5 (12.5) |
| White blood cell decreased | 0 | 0 | 2 (22.2) | 0 | 0 | 0 | 1 (20.0) | 2 (33.3) | | 5 (12.5) |
| Constipation | 0 | 1 (14.3) | 0 | 0 | 0 | 0 | 2 (40.0) | 1 (16.7) | | 4 (10.0) |
| Dyspnea | 1 (25.0) | 1 (14.3) | 1 (11.1) | 0 | 0 | 0 | 0 | 1 (16.7) | | 4 (10.0) |
| Hypophosphatemia | 1 (25.0) | 0 | 1 (11.1) | 0 | 0 | 0 | 1 (20.0) | 1 (16.7) | | 4 (10.0) |
| Insomnia | 0 | 1 (14.3) | 1 (11.1) | 0 | 0 | 0 | 0 | 2 (33.3) | | 4 (10.0) |
| Peripheral edema | 0 | 0 | 2 (22.2) | 1 (33.3) | 0 | 0 | 0 | 1 (16.7) | | 4 (10.0) |
| Pyrexia | 1 (25.0) | 0 | 1 (11.1) | 0 | 1 (33.3) | 1 (33.3) | 0 | 0 | | 4 (10.0) |
| Blood bilirubin increased | 0 | 1 (14.3) | 0 | 0 | 0 | 0 | 0 | 2 (33.3) | | 3 (7.5) |
| Cough | 2 (50.0) | 0 | 1 (11.1) | 0 | 0 | 0 | 0 | 0 | | 3 (7.5) |
| Dizziness | 1 (25.0) | 0 | 1 (11.1) | 0 | 0 | 0 | 1 (20.0) | 0 | | 3 (7.5) |
| Dysgeusia | 1 (25.0) | 1 (14.3) | 1 (11.1) | 0 | 0 | 0 | 0 | 0 | | 3 (7.5) |
| Hypokalemia | 0 | 1 (14.3) | 0 | 1 (33.3) | 1 (33.3) | 0 | 0 | 0 | | 3 (7.5) |
| Weight decreased | 0 | 0 | 2 (22.2) | 1 (33.3) | 0 | 0 | 0 | 0 | | 3 (7.5) |

Data presented as n (%).
**Abbreviations**: D, day; TMZ, temozolomide.

**Table 3: Treatment-Emergent Adverse Events of Grade ≥3 Reported as Related to Either Pamiparib or Temozolomide Occurring in More Than 2 Patients**

| | Arm A (D1–7) | | | | | Arm A (D1–14) | | Arm B (D1 –28) | | Overall |
|---|---|---|---|---|---|---|---|---|---|---|
| TMZ dose | 40 mg | 60 mg | 80 mg | 100 mg | 120 mg | 40 mg | 20 mg | 40 mg | | |
| Number of patients | (n=4) | (n=7) | (n=9) | (n=3) | (n=3) | (n=3) | (n=5) | (n=6) | | N=40 |
| Neutropenia | 0 | 1 (14.3) | 3 (33.3) | 2 (66.7) | 3 (100.0) | 0 | 1 (20.0) | 1 (16.7) | | 11 (27.5) |
| Anemia | 0 | 0 | 2 (22.2) | 1 (33.3) | 2 (66.7) | 0 | 1 (20.0) | 3 (50.0) | | 9 (22.5) |
| Thrombocytopenia | 1 (25.0) | 1 (14.3) | 1 (11.1) | 1 (33.3) | 3 (100.0) | 0 | 0 | 1 (16.7) | | 8 (20.0) |
| Neutrophil count decreased | 0 | 0 | 2 (22.2) | 1 (33.3) | 0 | 0 | 0 | 2 (33.3) | | 5 (12.5) |
| White blood cell count decreased | 0 | 0 | 2 (22.2) | 0 | 0 | 0 | 1 (20.0) | 2 (33.3) | | 5 (12.5) |
| Platelet count decreased | 0 | 0 | 2 (22.2) | 1 (33.3) | 0 | 0 | 0 | 1 (16.7) | | 4 (10.0) |

Data presented as n(%).
**Abbreviations**: D, day; TMZ, temozolomide.

## CONCLUSIONS

- Treatment with pamiparib and low-dose TMZ up to 60 mg administered Days 1-7 and up to 20 mg administered continuously was generally well tolerated
- No new safety events were identified with the combination of pamiparib and low-dose TMZ
  - Consistent with the hypothesis of combining a potent DNA-damaging agent with full dose PARP inhibition, cytopenias were frequently observed and their severity correlated with the TMZ dose
  - Cytopenias were manageable and reversible
- Median treatment duration for all patients was 1.6 months (range: 0–9)
- Pamiparib in combination with low doses of TMZ demonstrated antitumor activity, including disease control, in 14 out of 23 evaluable patients regardless of known *BRCA* mutation status
- Additional analyses are being conducted to determine the best TMZ dose and schedule for combination therapy with pamiparib to advance into the expansion cohorts

### REFERENCES


1. Thomas C, Tulin AV. Poly-ADP-ribose polymerase: machinery for nuclear processes. *Mol Aspects Med.* 2013;34(6):1124–1137.
2. Coleman RL, Sill MW, Bell-McGuinn K, et al. A phase II evaluation of the potent, highly selective PARP inhibitor veliparib in the treatment of persistent or recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer in patients who carry a germline *BRCA1* or *BRCA2* mutation - An NRG Oncology/Gynecologic Oncology Group study. *Gynecol Oncol.* 2015;137(3):386–391.
3. Pommier Y, O'Connor MJ, de Bono J. Laying a trap to kill cancer cells: PARP inhibitors and their mechanisms of action. *Sci Transl Med.* 2016;8(362):362ps317.
4. Kubota E, Williamson CT, Ye R, et al. Low ATM protein expression and depletion of p53 correlates with olaparib sensitivity in gastric cancer cell lines. *Cell Cycle.* 2014;13(13):2129–2137.
5. Ledermann J, Harter P, Gourley C, et al. Olaparib maintenance therapy in platinum-sensitive relapsed ovarian cancer. *N Engl J Med.* 2012;366(15):1382–1392.
6. Owonikoko TK, Dahlberg SE, Khan SA, et al. A phase 1 safety study of veliparib combined with cisplatin and etoposide in extensive stage small cell lung cancer: a trial of the ECOG-ACRIN Cancer Research Group (E2511). *Lung Cancer.* 2015;89(1):66–70.
7. Robinson D, Van Allen EM, Wu YM, et al. Integrative clinical genomics of advanced prostate cancer. *Cell.* 2015;161(5):1215–1228.
8. Tutt A, Robson M, Garber JE, et al. Oral poly(ADP-ribose) polymerase inhibitor olaparib in patients with *BRCA1* or *BRCA2* mutations and advanced breast cancer: a proof-of concept trial. *Lancet.* 2010;376(9737):235–244.
9. Murai J, Huang S-Y, Das B et al. Trapping of PARP1 and PARP2 by clinical PARP inhibitors. Cancer Res 2012; 72(21) : 5588-5599
10. Lickliter J, Mileshkin L, Voskoboynikm M et al. Dose escalation/expansion study to investigate the safety, pharmacokinetics, food effect, and antitumor activity of BGB-290 in patients with advanced solid tumors. *Ann Oncol.* 2017; 28 (suppl 5): v122–v141.
11. Guerard M, Johnson G, Dertinger S et al. Dose-response relationship of temozolomide, determined by the Pig-a, comet, and micronucleous assay. *Arch Toxicol* 2017; 91:2443–2453.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