UPDATED RESULTS OF THE PARP1/2 INHIBITOR PAMIPARIB IN COMBINATION WITH LOW-DOSE TEMOZOLOMIDE IN PATIENTS WITH LOCALLY ADVANCED OR METASTATIC SOLID TUMORS

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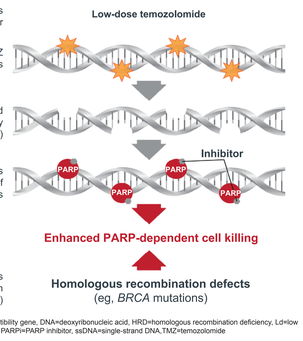
BACKGROUND

- Poly (ADP-ribose) polymerase (PARP) proteins play a key role in the repair of single strand (ss) and double strand (ds) DNA breaks[1-2]
- Normal cells repair DNA 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 PARP1/2 inhibitor that has demonstrated brain penetration and PARP-DNA complex–trapping capabilities in preclinical studies and promising antitumor activity in ovarian cancer[10]
- 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**)
- Low-dose (ld) TMZ (11.5 mg/m^2 to 69 mg/m^2) 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 ld TMZ may synergize with PARP inhibition, and that this synergy will result in increased antitumor activity
- This phase 1b study (NCT03150810) evaluates the safety and preliminary antitumor activity of pamiparib in combination with ld TMZ in patients with locally advanced and metastatic tumors. We have previously shown that pamiparib in combination with ld TMZ was generally well-tolerated and has antitumor activity.[12] Here, we present updated results that include the recommended dose (RP2D) and schedule as well as data from patients enrolled in the gastric/gastroesophageal junction (G/GEJ) cancer and the extensive-stage small cell lung cancer (ES SCLC) expansion cohorts

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



Abbreviations: *BRCA*=breast cancer susceptibility gene, DNA=deoxyribonucleic acid, HRD=homologous recombination deficiency, Ld=low dose, PARP=poly(ADP-ribose) polymerase, PARPi=PARP inhibitor, ssDNA=single-strand DNA, TMZ=temozolomide

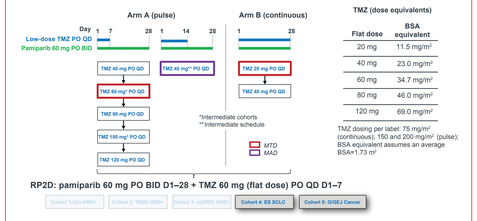
METHODS

- The study design is detailed in **Figure 2**
  - The design allowed for exploration of intermediate doses and alternate administration schedules based on emerging safety and pharmacokinetic data
- Radiographic assessments are being conducted every 8 weeks; efficacy set was defined as patients with ≥1 post-baseline tumor assessments

Key Eligibility

- Adult patients (≥18 years old) with a confirmed malignancy that has progressed to advanced or metastatic stage with no option for effective standard therapy
- ECOG PS ≤1
- Disease that is measurable or evaluable per RECIST v1.1; prostate cancer patients were evaluated using Prostate Cancer Working Group 2 (PCWG2) criteria
- Patients were excluded if they had hypersensitivity to TMZ or dacarbazine, or had prior treatment with a PARP inhibitor
- ≤2 prior lines of chemotherapy in the advanced setting (for patients enrolled in the ES SCLC and G/GEJ cancer expansion cohorts only)

Figure 2: Study Design



TMZ (dose equivalents)

Flat dose	BSA equivalent
20 mg	11.5 mg/m^2
40 mg	23.0 mg/m^2
60 mg	34.7 mg/m^2
80 mg	46.0 mg/m^2
120 mg	69.0 mg/m^2

TMZ dosing per label: 75 mg/m^2 (continuous); 150 and 200 mg/m^2 (pulse); BSA equivalent assumes an average BSA=1.73 m^2

Abbreviations: BID=twice daily, BSA=body surface area, D=day, ES SCLC=extensive-stage small cell lung cancer, G/GEJ=gastric/gastroesophageal junction, HRD=homologous recombination deficiency, MAD=maximum administered dose, mCRPC=metastatic castration-resistant prostate cancer, MTD=maximum tolerated dose, OvCa=ovarian cancer, PO=per orem, QD=once daily, RP2D=recommended phase 2 dose, TMZ=temozolomide, TNBC=triple-negative breast cancer

RESULTS

Patient Disposition

- As of 29 July 2019, 113 patients with solid tumors have been enrolled in the study (**Table 1**); median treatment duration was 2.4 months (range: 0.2–18.1)
- A total of 17 patients (15%) remain on pamiparib and ld TMZ treatment

Table 1: Patient Demographics

		Dose escalation (n=66)	Dose expansion (n=47)	Overall (N=113)
Median age, years (range)		66 (38–85)	61.0 (26–77)	64.0 (26–85)
Sex, n (%)	Male	33 (50.0)	26 (55.3)	59 (52.2)
	Female	33 (50.0)	21 (44.7)	54 (47.8)
Race, n (%)	Caucasian	46 (69.7)	38 (80.9)	84 (74.3)
	Black/African American	9 (13.6)	1 (2.1)	10 (8.8)
	Asian	1 (1.5)	1 (2.1)	2 (1.8)
	Other	5 (7.6)	5 (10.6)	10 (8.8)
	Unknown	5 (7.6)	2 (4.3)	7 (6.2)
ECOG PS, n (%)	0	16 (24.2)	14 (29.8)	30 (26.5)
	1	50 (75.8)	33 (70.2)	83 (73.5)
Median prior cancer therapies, n (range)		3.0 (1–10)	2.0 (1–5)	3.0 (1–10)
Prior anticancer therapies, n (%)	≤3	34 (51.5)	44 (93.6)	78 (69.0)
	4–6	22 (33.3)	2 (4.3)	24 (21.2)
	≥7	10 (15.2)	0 (0)	10 (8.8)
	Missing	0	1 (2)	1 (0.9)

Abbreviations: ECOG PS=Eastern Cooperative Oncology Group performance status

Recommended Phase 2 Dose and Schedule

- Enrollment in the dose-escalation phase was completed in September 2018; the RP2D was determined to be pamiparib 60 mg PO BID D1–28 in combination with TMZ 60 mg PO QD D1–7, based on tolerability

Pharmacokinetics

- Pamiparib plasma exposure in patients treated with the combination regimen (**Table 2**) was similar to that of single-agent pamiparib

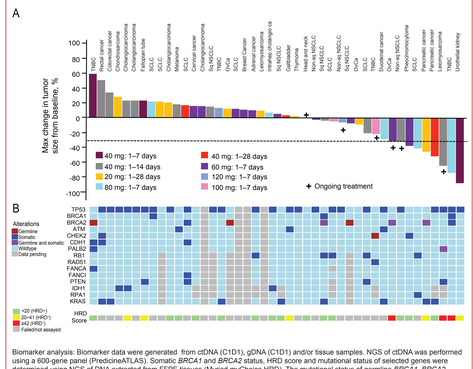
Table 2: Pamiparib Pharmacokinetics

Time point	Geometric Mean Pamiparib Concentration (%CV)			
	Pamiparib + ld TMZ (N=51)		Pamiparib monotherapy (N=11)	
	Single dose	Steady state	Single dose	Steady state
Predose	0 ng/mL (0)	2005 ng/mL (69)	0 ng/mL (0)	2327 ng/mL (35)
2h postdose	1744 ng/mL (32)	3450 ng/mL (40)	1881 ng/mL (27)	3891 ng/mL (47)

Abbreviations: CV=coefficient of variation, ld=low dose, TMZ=temozolomide

Dose Escalation: Preliminary Antitumor Activity

Figure 3: Maximum Tumor Reduction in Evaluable Patients (A) and Biomarker Assessment (B)



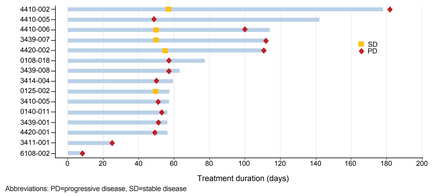
Biomarker analysis: Biomarker data were generated from ctDNA (C1D1), gDNA (C1D1) and/or tissue samples. NGS of ctDNA was performed using a 600-gene panel (PredicineATLAS). Somatic *BRCA1* and *BRCA2* status, HRD score and mutational status of selected genes were determined using NGS of DNA extracted from FFPE tissues (Myriad myChoice HRD). The mutational status of germline *BRCA1*, *BRCA2* status, and selected genes were determined using NGS of gDNA (Color Genomics). Only pathogenic mutations are shown (ClinVar) annotated as germline, somatic, or both.

Abbreviations: *BRCA*=breast cancer susceptibility gene, ctDNA=circulating tumor DNA, DNA=deoxyribonucleic acid, FFPE=formalin-fixed/parafin embedded, gDNA=genomic DNA, HRD=homologous recombination deficiency, NGS=next-generation sequencing, Non-sq NSCLC=non-squamous non-small cell lung cancer, OvCa=ovarian cancer, PCWG2=Prostate Cancer Working Group 2, PSA=prostate-specific antigen, SCLC=small cell lung cancer, Sq NSCLC=squamous non-small cell lung cancer, TNBC=triple-negative breast cancer

- As of 29 July 2019, 57/66 patients enrolled in the dose-escalation phase were evaluable for response; 52/66 patients had measurable disease and were evaluated by either RECIST (**Figure 3**) or PCWG2 (prostate cancer)
  - Overall response rate (ORR) was 19.3% (11 PR); 8/11 responses were confirmed. In addition, an unconfirmed PSA response was observed in 1 prostate cancer patient
  - Disease control rate (DCR) was 64.9% (95% CI, 51.1–77.1)
  - Median duration of response was 6.4 months (95% CI, 2.1–7.7)
  - Median treatment duration was 3.7 months (range 0.2–18.1)
- Biomarker analyses showed an HRD$^+$ score rate of 32.2% (N=22; HRD$^+$=8/22)
  - 62.5% of patients (5/8) with HRD$^+$ scores showed a response
- Not all HRD$^+$ patients harbored mutations in *BRCA1*, *BRCA2*, or *PALB2*

G/GEJ Cancer Expansion Cohort: Preliminary Antitumor Activity (≤2 Prior Lines of Chemotherapy)

Figure 4: Treatment Duration in Evaluable Patients

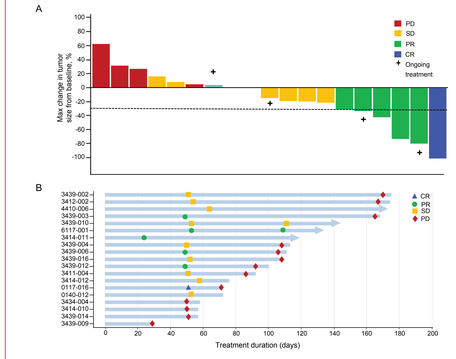


Abbreviations: PD=progressive disease, SD=stable disease

- At the time of data cut off, 20 G/GEJ cancer patients had been enrolled in the dose-expansion phase, and 15 were evaluable for response. The median follow-up time was 4 months (range 0.4–7.4)
  - 70% of patients had an ECOG PS of 1
  - ORR was 0%; DCR was 33.3% (95% CI, 11.8–61.6)
  - Median treatment duration was 1.94 months (range 0.3–5.8); 2 patients are still ongoing (**Figure 4**)

ES SCLC Expansion Cohort: Preliminary Antitumor Activity (≤2 Prior Lines of Chemotherapy)

Figure 5: Maximum Tumor Reduction in Evaluable Patients (A) and Treatment Duration (B)



Abbreviations: CR=complete response, PD=progressive disease, PR=partial response, SD=stable disease

- As of 29 July 2019, 22 ES SCLC patients had been enrolled in the dose-expansion phase and 19 were evaluable for response (**Figure 5**). The median follow-up time was 4 months (range 0.5–6.4)
  - 50% of patients had a chemotherapy-free interval ≥90 days from their last platinum regimen and 86.4% of patients had an ECOG PS of 1
  - ORR was 31.6% (5 PR and 1 CR); DCR was 78.9% (95% CI, 54.4–93.9) (**Figure 5A**)
  - Median treatment duration was 3.6 months (range 1.0–5.7); 5 patients are still ongoing (**Figure 4**)

Safety and Tolerability

- 112 patients had ≥1 treatment-emergent adverse event (TEAE); the most common TEAEs (all grades) were anemia, nausea, fatigue, decreased appetite, neutropenia, thrombocytopenia, and vomiting (**Table 3**)
- 63 (55.8%) patients experienced Grade ≥3 TEAEs related to the study drug (**Table 4**)
  - The most common Grade ≥3 adverse events (AEs) were cytopenias (anemia, neutropenia, and thrombocytopenia), all of which were manageable and reversible
  - Related Grade 4 AEs included neutropenia (9.7%), decreased neutrophil counts (8.8%), thrombocytopenia (11.5%), decreased platelet counts (7.1%), decreased WBC (2.7%); and anemia, aspartate aminotransferase (AST) elevation and alanine aminotransferase (ALT) elevation (0.9% each)
  - No related Grade 5 AEs were reported
- 3 (2.7%) patients experienced AEs related to the study drug that resulted in treatment discontinuation
- Serious AEs related to study treatment were reported in 11 (9.7%) patients
- 4 (3.5%) patients experienced AEs with fatal outcome, all of which were deemed unrelated to the study drug

Table 3: TEAEs Occurring in ≥9% of Patients Regardless of Relationship (All Grades)

TEAEs	Dose escalation (n=66)	Dose expansion (n=47)	All patients (N=113)
Anemia	36 (54.5)	29 (61.7)	65 (57.5)
Nausea	35 (53.0)	26 (55.3)	61 (54.0)
Fatigue	30 (45.5)	25 (53.2)	55 (48.7)
Decreased appetite	20 (30.3)	19 (40.4)	39 (34.5)
Neutropenia	22 (33.3)	15 (31.9)	37 (32.7)
Thrombocytopenia	23 (34.8)	13 (27.7)	36 (31.9)
Vomiting	15 (22.7)	18 (38.3)	33 (29.2)
Platelet count decrease	12 (18.2)	14 (29.8)	26 (23.0)
Constipation	7 (10.6)	15 (31.9)	22 (19.5)
Diarrhea	14 (21.2)	8 (17.0)	22 (19.5)
Neutrophil count decrease	12 (18.2)	10 (21.3)	22 (19.5)
Abdominal pain	11 (16.7)	7 (14.9)	18 (15.9)
Cough	9 (13.6)	6 (12.8)	15 (13.3)
Dyspnea	12 (18.2)	3 (6.4)	15 (13.3)
Dizziness	10 (15.2)	4 (8.5)	14 (12.4)
Aspartate aminotransferase increase	9 (13.6)	4 (8.5)	13 (11.5)
Headache	7 (10.6)	5 (10.6)	12 (10.6)
White blood cell count decrease	8 (12.1)	4 (8.5)	12 (10.6)
Blood bilirubin increase	7 (10.6)	3 (6.4)	10 (8.8)
Hypokalemia	8 (12.1)	2 (4.3)	10 (8.8)

Abbreviation: TEAE=treatment-emergent adverse event

CONCLUSIONS

- The RP2D and schedule of the combination was determined to be pamiparib 60 mg PO BID D1–28 and TMZ 60 mg PO QD D1–7
- The combination of pamiparib and ld TMZ shows:
  - a manageable safety profile, with cytopenias being the most frequent Grade ≥3 events
  - promising preliminary efficacy in patients with ES SCLC and various other tumor types
- Dose-escalation patients with HRD$^+$ tumors, irrespective of *BRCA* mutational status, showed a high response rate
  - HRD status may be a promising biomarker for sensitivity to the pamiparib + ld TMZ combination, regardless of tumor type
- Further biomarker exploration is underway

Table 4: TEAEs Grade ≥3 Reported as Related to Pamiparib and/or Temozolomide Occurring in More Than 2 Patients

TEAEs	Dose escalation (n=66)	Dose expansion (n=47)	All patients (N=113)
Anemia	21 (31.8)	16 (34.0)	37 (32.7)
Neutropenia	18 (27.3)	11 (23.4)	29 (25.7)
Thrombocytopenia	13 (19.7)	9 (19.1)	22 (19.5)
Neutrophil count decrease	11 (16.7)	9 (19.1)	20 (17.7)
Platelet count decreased	7 (10.6)	8 (17.0)	15 (13.3)
WBC count decreased	7 (10.6)	4 (8.5)	11 (9.7)
Asthenia	0 (0)	3 (6.4)	3 (2.7)

Abbreviations: TEAE=treatment-emergent adverse event, WBC=white blood cell

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