Phase 1b/2 Study to Assess the Clinical Effects of Pamiparib, an Investigational PARP Inhibitor, in Combination With Radiation Therapy and/or Temozolomide in Patients With Newly Diagnosed or Recurrent/Refractory Glioblastoma

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Rationale for Combining Pamiparib With Radiation Therapy and/or Temozolomide

DNA damage by TMZ or radiation causes adduct formation and/or SSBs

SSBs are repaired by PARP in the BER process

1. **PARP inhibition impairs BER**
2. **PARP trappers can form cytotoxic DNA–PARP complexes**

Pamiparib is
1. A potent, highly selective PARP inhibitor[1]
2. A potent PARP trapper resulting in cytotoxic DNA-PARP complexes[1]
3. Brain penetrant in preclinical studies

Enhanced PARP-dependent cell killing

Homologous recombination defects
(eg, *BRCA* mutations)

Abbreviations: BER, base excision repair; *BRCA*, breast cancer susceptibility gene; HRD, homologous recombination deficiency; PARP, poly (ADP-ribose) polymerase; SSB, single-strand breaks; TMZ, temozolomide.

1. Tang Z, et al. *Cancer Res*. 2015;75(suppl 15):1653.

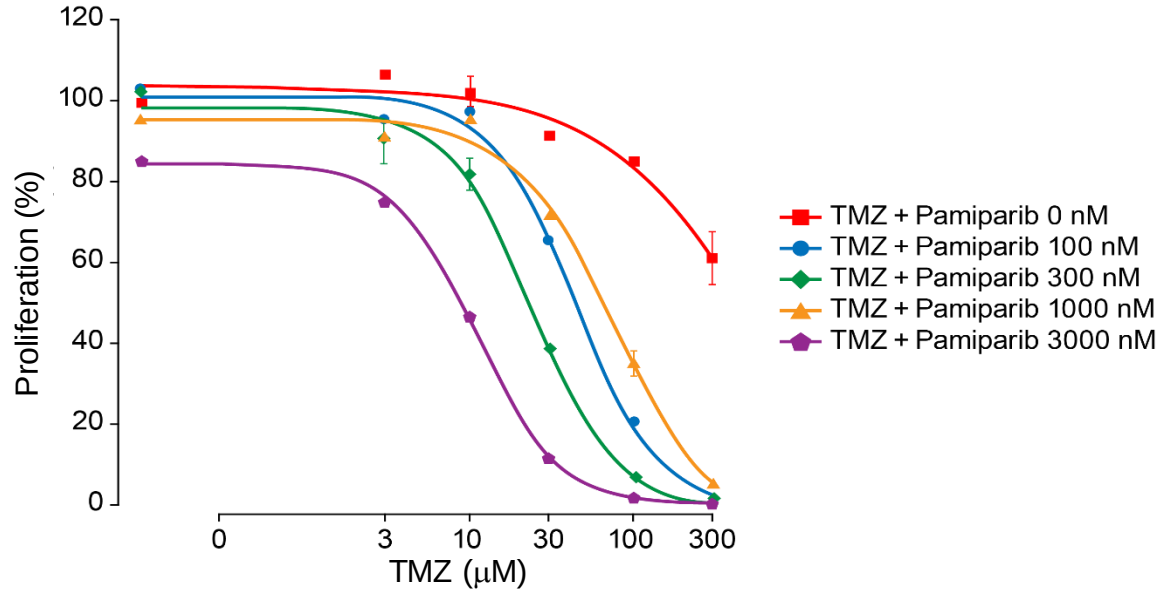
Synergy Between Pamiparib and Temozolomide

- Temozolomide and radiation are each effective DNA damaging agents
- Nonclinical data for pamiparib demonstrate:
  - Synergy in combination with temozolomide in multiple cell lines[1]

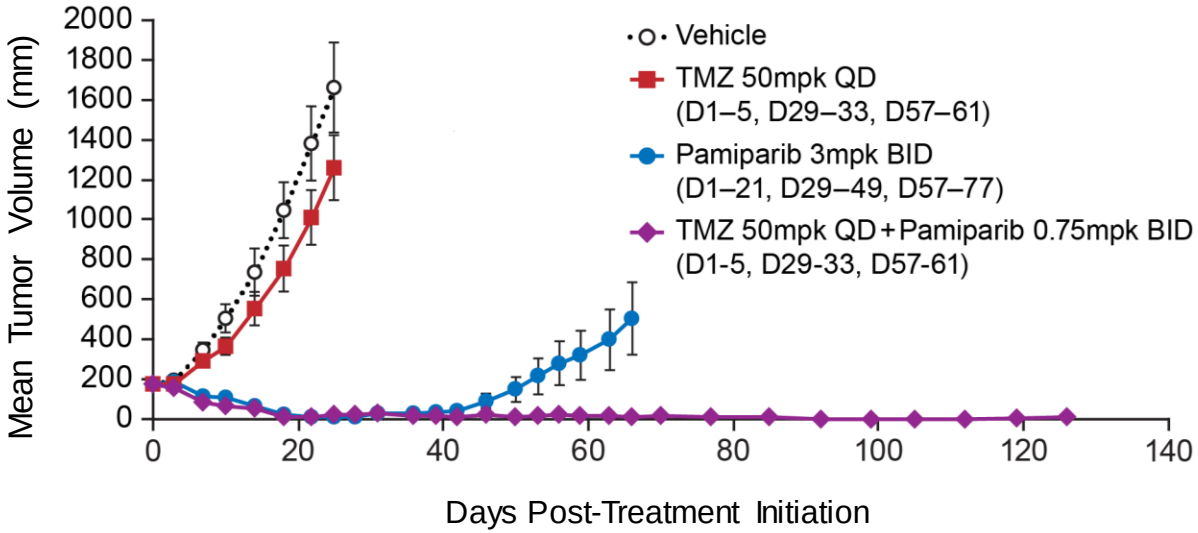
CLINICAL OBJECTIVE:

Evaluate full dose pamiparib in combination with DNA damaging agents, radiation, and/or temozolomide

Synergy With Pamiparib/TMZ in SF295 GBM Cells[1]



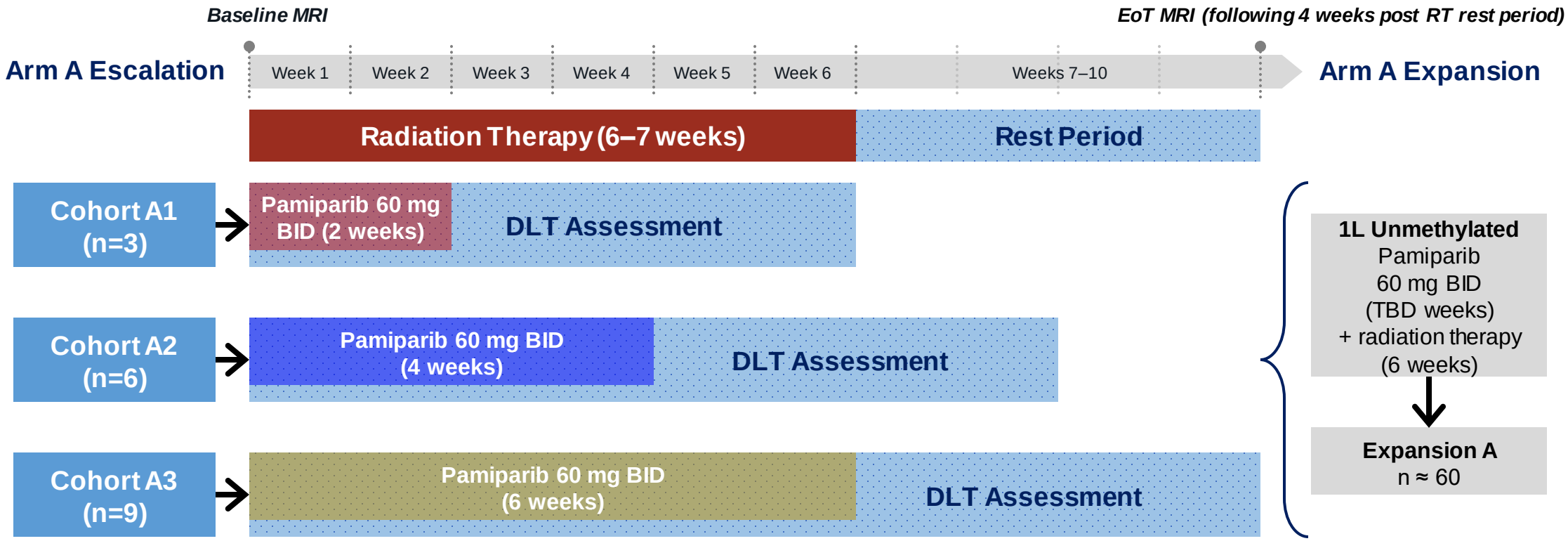
Activity of Pamiparib/TMZ in H209 SCLC Xenograft Model[1]



Abbreviations: GBM, glioblastoma; PARP, poly (ADP-ribose) polymerase; SCLC, small cell lung cancer; TMZ, temozolomide.

1. Tang Z, et al. *Cancer Res*. 2015;75(suppl 15):1651.

Study Design for Arm A (Pamiparib + Radiation in Patients With Newly Diagnosed, Unmethylated GBM)



n=enrolled in cohort.

Arm B: Radiation therapy + pamiparib (60 mg BID PO) + TMZ in 1L unmethylated GBM
(after completion of dose escalation and taking into account safety/tolerability)

Abbreviations: 1L, first line; BID, twice daily; D, day; DLT, dose-limiting toxicity; EoT, end of treatment; GBM, glioblastoma; MRI, magnetic resonance imaging; PD, progressive disease; PO, per oral; QD, daily; RANO, response assessment in neuro-oncology; R/R, recurrent/refractory; RT, radiation therapy; TBD, to be decided; TMZ, temozolomide.

Characteristics and Study Disposition for Patients Enrolled in Arm A

	Total (N=18)
Median age, years (range)	62.0 (42, 71)
Male, n (%)	15 (83.3)
Baseline corticosteroid use, n (%)	12 (66.7)
Median time on pamiparib treatment, weeks (range)	4.0 (0.3, 6.3)
Median time on radiation therapy, weeks (range)	6.0 (0.7, 8.1)
Discontinued early from study treatments, n (%)	4 (22.2)
Reasons for discontinuation of pamiparib	
Adverse events*	3 (16.7)
Withdrawal of consent	1 (5.6)
Reasons for discontinuation of radiation therapy	
Adverse events*	3 (16.7)
Withdrawal of consent	1 (5.6)
Median study follow-up duration, weeks (range)	19 (2, 54)

*Adverse events leading to discontinuation of pamiparib and radiation therapy were grade 3 chills and vertigo (DLT), grade 3 fatigue (DLT), and an SAE of vasogenic edema considered unrelated to treatment.
Abbreviation: SAE, serious adverse event.

Data cut-off: 14 Sep 2018

Safety and Tolerability in Patients Enrolled in Arm A

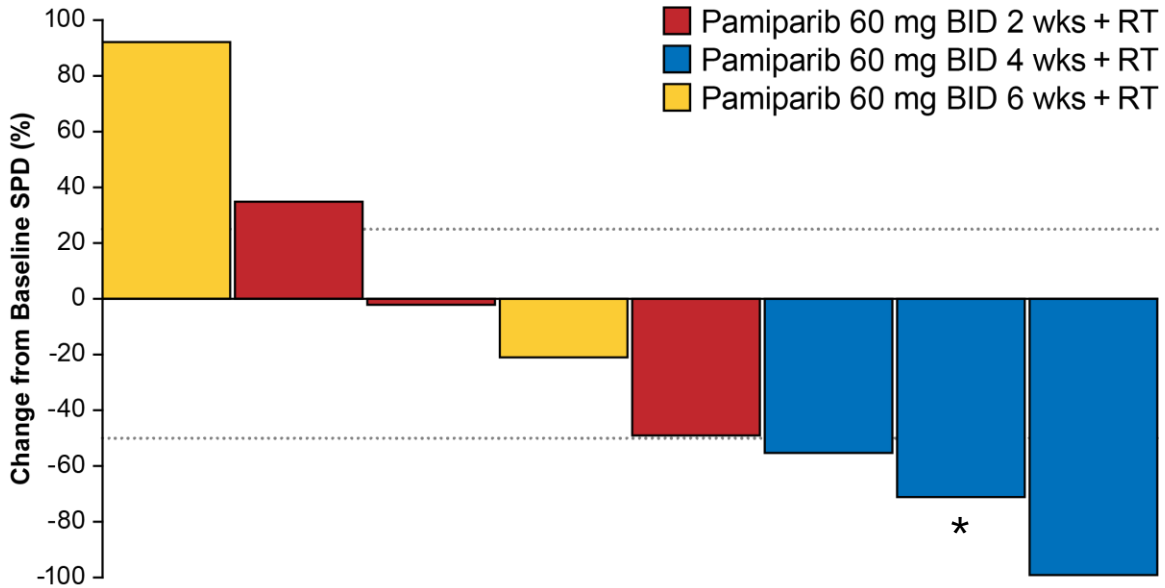
Grade ≥3 TEAEs, n (%)	Pamiparib 2 wk (n=3)	Pamiparib 4 wk (n=6)	Pamiparib 6 wk (n=9)	Total (N=18)	Grade ≥3 TRAEs: Pamiparib or RT (N=18)
Anemia	0	1 (16.7)	0	1 (5.6)	0
Chills	0	0	1 (11.1)	1 (5.6)	1 (5.6)
Deep vein thrombosis	0	1 (16.7)	0	1 (5.6)	0
Diarrhea	0	1 (16.7)	0	1 (5.6)	1 (5.6)
Fatigue	0	0	1 (11.1)	1 (5.6)	1 (5.6)
Gastrointestinal hemorrhage	0	1 (16.7)	0	1 (5.6)	0
Hyperglycemia	1 (33.3)	0	0	1 (5.6)	0
Muscular weakness	0	0	1 (11.1)	1 (5.6)	0
Nausea	0	0	1 (11.1)	1 (5.6)	1 (5.6)
Peripheral motor neuropathy	0	0	1 (11.1)	1 (5.6)	0
Urinary tract infection	0	1 (16.7)	0	1 (5.6)	0
Vasogenic cerebral edema	0	1 (16.7)	0	1 (5.6)	0
Vertigo	0	0	1 (11.1)	1 (5.6)	1 (5.6)

Abbreviations: RT, radiation therapy; TEAE, treatment-emergent adverse event; TRAE, treatment-related adverse event; wk, week.

Data cut-off: 14 Sep 2018

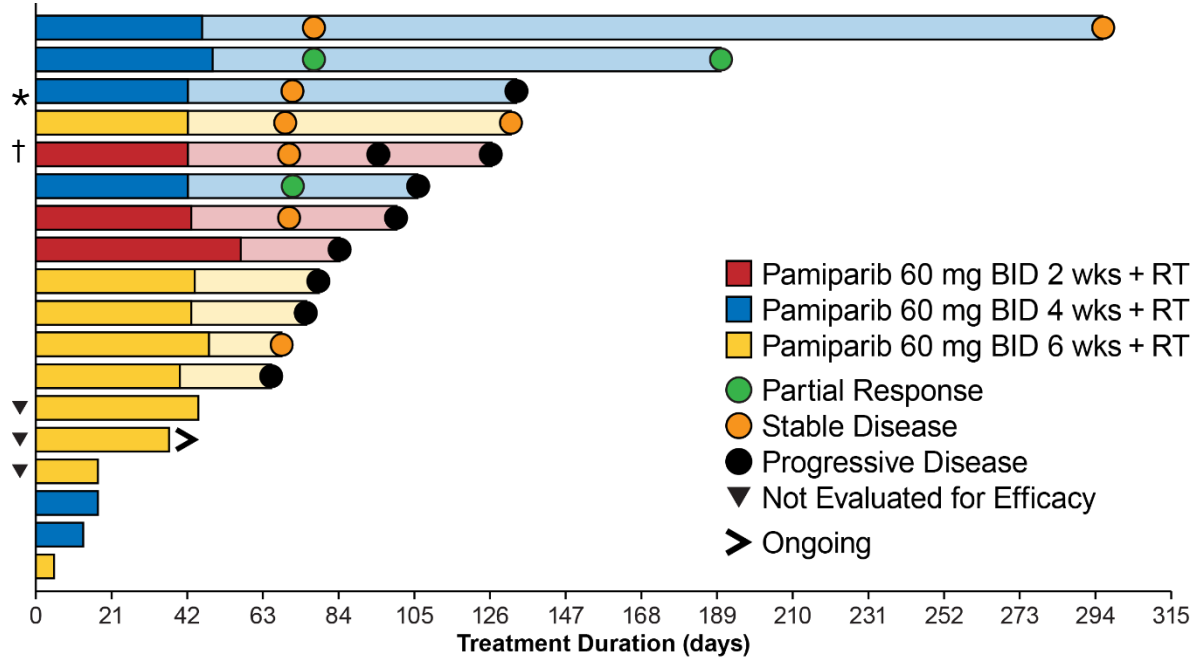
Investigator-Assessed Outcomes in Patients Enrolled in Arm A

Maximum Tumor Reduction in Evaluable Patients



- Eight of 10 patients with measurable disease at baseline had an EoT assessment
  - Two PRs (one cPR) in 10 patients per mRANO overall assessment
  - One PR per tumor measurement was overall SD due to increased enhancement*

Duration of Treatment and Response



Includes all patients in Arm A. EoT tumor assessment is 4 wks post RT completion.
†PD was confirmed per RANO.

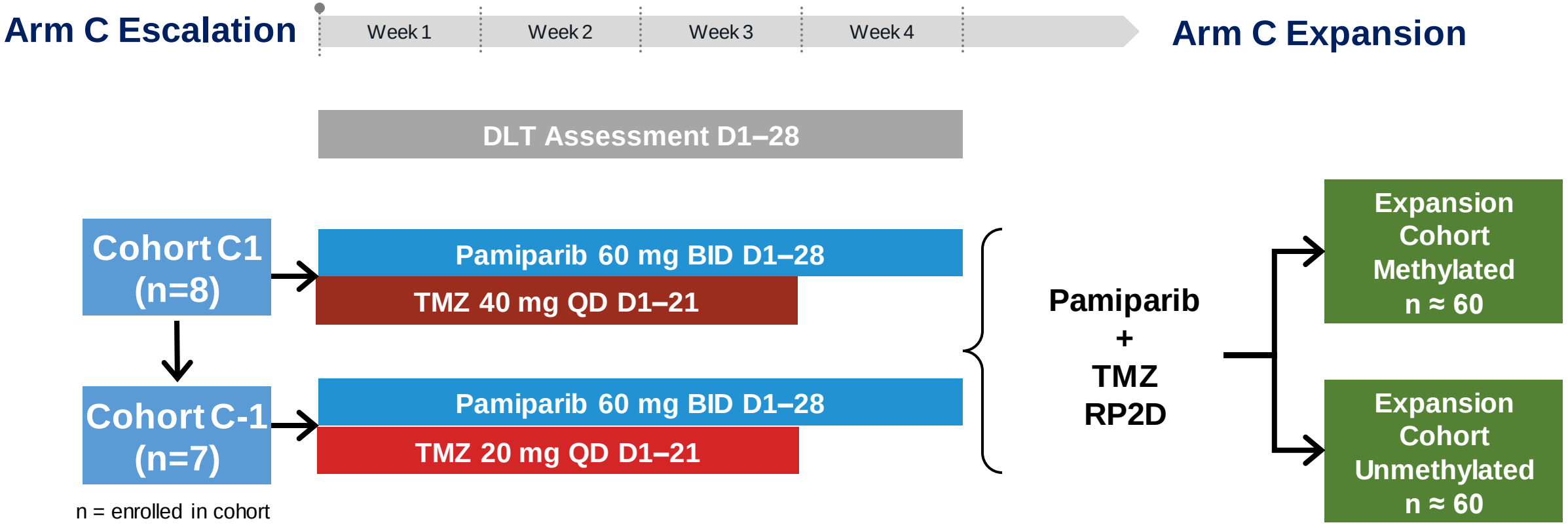
- Evaluable per mRANO criteria: n=15
- Eight of 15 patients achieved PR or SD at the EoT visit
  - DCR[1]=53.3% (95% CI: 26.6–78.7)

Abbreviations: BID, twice daily; CI, confidence interval; cPR, confirmed partial response; CR, complete response; DCR, disease control rate; EoT, end of treatment; mRANO, modified response assessment in neuro-oncology; PR, partial response; RT, radiation therapy; SD, stable disease; SPD, sum of the products of perpendicular dimensions.
DCR includes patients with CR, PR or SD at the EoT Visit.

1. Rivera AL et al. *Neuro Oncol.* 2010;12(2):116-21.

Data cut-off: 14 Sep 2018

Study Design for Arm C (Recurrent/Refractory GBM)



Abbreviations: BID, twice daily; D, day; DLT, dose-limiting toxicity; GBM, glioblastoma; QD, once daily; RP2D, recommended phase 2 dose; TBD, to be decided; TMZ, temozolomide.

Characteristics and Study Disposition for Patients Enrolled in Arm C

	Total (N=15)
Median age, years (range)	55.0 (23, 67)
Male, n (%)	10 (66.7)
Baseline corticosteroid use, n (%)	7 (46.7)
MGMT promoter status, n (%) Methylated Unmethylated Unknown	 4 (26.7) 9 (60.0) 2 (13.3)
Time on study treatment, weeks (range)	4.3 (0.4, 30.4)
Discontinued early from study treatment, n (%)	9 (60.0)
Reasons for discontinuation of pamiparib	
Disease progression	5 (33.3)
Adverse events*	3 (20.0)
Withdrawal of consent	1 (6.7)
Reasons for discontinuation of temozolomide	
Disease progression	5 (33.3)
Adverse events*	3 (20.0)
Withdrawal of consent	1 (6.7)
Median study follow-up duration, weeks (range)	12.9 (0.3, 31.4)

*Adverse events leading to discontinuation of pamiparib and TMZ were grade 3 nausea (DLT), grade 4 neutropenia (DLT), and a serious AE of altered mental status considered unrelated to treatment.
Abbreviations: AE, adverse event; DLT, dose-limiting toxicity; MGMT, O6-methylguanine-DNA methyltransferase.

Data cut-off: 14 Sep 2018

Safety and Tolerability in Patients Enrolled in Arm C

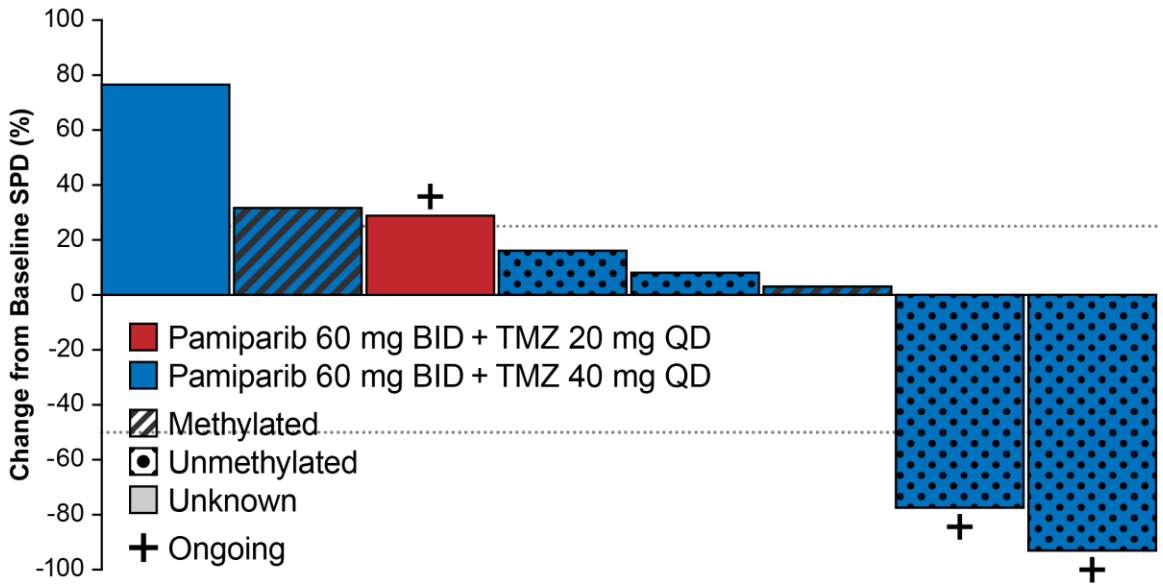
Grade ≥3 TEAEs, n (%)	Pamiparib + TMZ 20 mg (n=7)	Pamiparib + TMZ 40 mg (n=8)	Total (N=15)	Grade ≥3 TRAEs: Pamiparib or TMZ (N=15)
Anemia	0	3 (37.5)	3 (20.0)	3 (20.0)
Fatigue	1 (14.3)	1 (12.5)	2 (13.3)	2 (13.3)
Lymphocyte count decreased	1 (14.3)	1 (12.5)	2 (13.3)	2 (13.3)
Cognitive disorder	1 (14.3)	0	1 (6.7)	0
Hemiparesis	1 (14.3)	0	1 (6.7)	0
Mental status changes	0	1 (12.5)	1 (6.7)	0
Nausea	0	1 (12.5)	1 (6.7)	1 (6.7)
Neutropenia	0	1 (12.5)	1 (6.7)	1 (6.7)
Neutrophil count decreased	0	1 (12.5)	1 (6.7)	1 (6.7)
Platelet count decreased	0	1 (12.5)	1 (6.7)	1 (6.7)
Pulmonary embolism	0	1 (12.5)	1 (6.7)	1 (6.7)
Thrombocytopenia	0	1 (12.5)	1 (6.7)	1 (6.7)
Vasogenic cerebral edema	0	1 (12.5)	1 (6.7)	0
Vomiting	0	1 (12.5)	1 (6.7)	1 (6.7)
White blood cell count decreased	0	1 (12.5)	1 (6.7)	1 (6.7)

Abbreviations: TEAE, treatment-emergent adverse event; TMZ, temozolomide; TRAE, treatment-related adverse event.

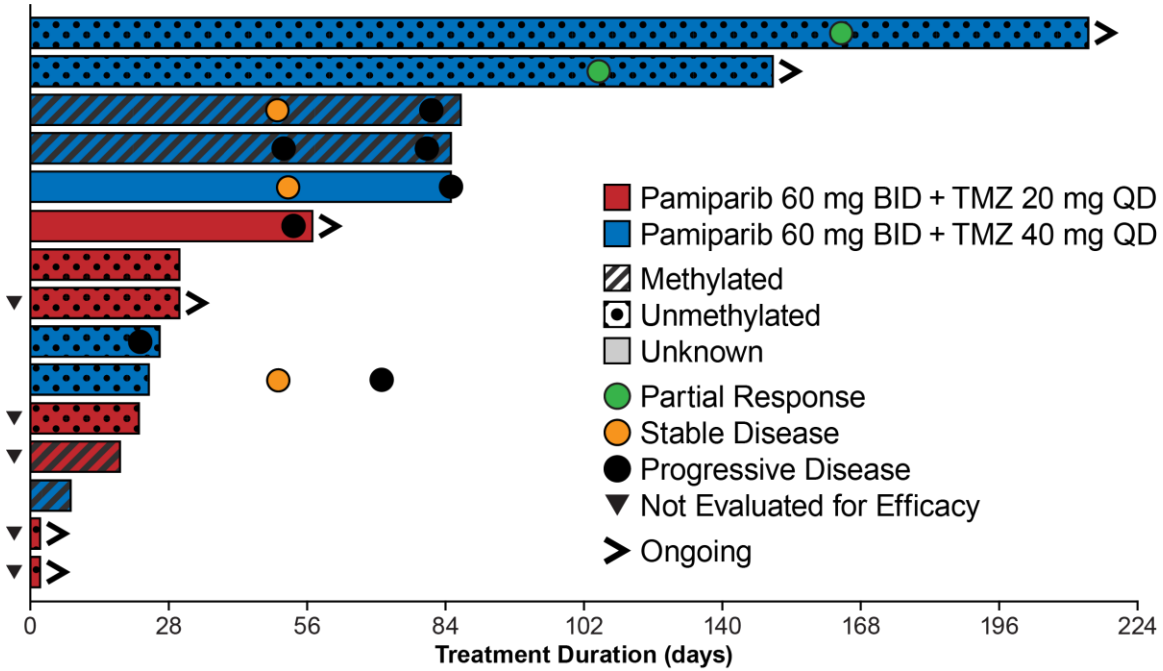
Data cut-off: 14 Sep 2018

Investigator-Assessed Responses in Patients Enrolled in Arm C

Maximum Tumor Reduction in Evaluable Patients



Duration of Treatment and Response



Includes all patients in Arm C.

- Eight of 10 patients with measurable disease at baseline per mRANO criteria had a post-baseline assessment
  - One of the two uPRs was confirmed after data cut off

Abbreviations: BID, twice daily; mRANO, modified response assessment in neuro-oncology; QD, once daily; SPD, sum of the products of perpendicular dimensions; TMZ, temozolomide; uPR, unconfirmed partial response.

Data cut-off: 14 Sep 2018

Summary

- Arm A: 18 patients with untreated, unmethylated MGMT GBM have been enrolled
  - Concurrent treatment with full dose pamiparib in combination with RT was generally well tolerated in all cohorts
  - Preliminary disease control rate at first post-treatment assessment was 53.3% (n=15); 95% CI: 26.6–78.7
  - After data cut off, RP2D was determined to be 6 weeks pamiparib + RT and expansion was initiated
- Arm C: 15 patients with recurrent/refractory GBM ± methylated MGMT have been enrolled
  - Pamiparib in combination with 21 days of 40 mg TMZ was not tolerable; 20 mg TMZ is ongoing
  - Preliminary data suggest that pamiparib in combination with TMZ has antitumor activity
- Collectively, these data support continued investigation of DNA damaging agents in combination with full dose pamiparib