

## CLINICAL INVESTIGATION

# Concurrent Olaparib and Radiation Therapy in Older Patients With Newly Diagnosed Glioblastoma: The Phase 1 Dose-Escalation PARADIGM Trial

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Received Oct 18, 2023; Accepted for publication Jan 4, 2024

**Purpose:** Patients with glioblastoma who are older or have poor performance status (PS) experience particularly poor clinical outcomes. At the time of study initiation, these patients were treated with short-course radiation therapy (40 Gy in 15 fractions). Olaparib is an oral inhibitor of the DNA repair enzyme poly (ADP-ribose) polymerase (PARP) that is well tolerated as a single agent but exacerbates acute radiation toxicity in extracranial sites. Preclinical data predicted that PARP inhibitors would enhance radiosensitivity in glioblastoma without exacerbating adverse effects on the normal brain.

**Methods and Materials:** Phase 1 of the PARADIGM trial was a 3+3 dose-escalation study testing olaparib in combination with radiation therapy (40 Gy 15 fractions) in patients with newly diagnosed glioblastoma who were unsuitable for radical treatment either because they were aged 70 years or older (World Health Organization PS 0-1) or aged 18 to 69 years with PS 2. The primary outcome was the recommended phase 2 dose of olaparib. Secondary endpoints included safety and tolerability, overall survival, and progression-free survival. Effects on cognitive function were assessed via the Mini Mental State Examination.

**Results:** Of 16 eligible patients (56.25% male; median age, 71.5 years [range, 44-78]; 75% PS 0-1), 1 dose-limiting toxicity was reported (grade 3 agitation). Maximum tolerated dose was not reached and the recommended phase 2 dose was determined as 200 mg twice daily. Median overall survival and progression-free survival were 10.8 months (80% CI, 7.3-11.4) and 5.5 months (80% CI, 3.9-5.9), respectively. Mini Mental State Examination plots indicated that cognitive function was not adversely affected by the olaparib–radiation therapy combination.

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Disclosures: A.J.C. has received research funding from AstraZeneca and has participated in AstraZeneca advisory boards. The other authors report no conflicts of interest. This work was supported by an externally sponsored scientific research grant from AstraZeneca and by 2 Cancer Research UK Clinical Trials Unit Programme Awards (C1348/A15960 and C1348/A25355).

Data Sharing Statement: Initially, deidentified trial data will be made available to researchers whose proposed use of the data has been approved by the PARADIGM Trial Management Group. Upon completion and publication of phase 2 of the PARADIGM trial, deidentified data will be made publicly available.

Supplementary material associated with this article can be found in the online version at [doi:10.1016/j.ijrobp.2024.01.011](https://doi.org/10.1016/j.ijrobp.2024.01.011).

**Conclusions:** Olaparib can be safely combined with hypofractionated brain radiation therapy and is well tolerated in patients unsuitable for radical chemoradiation. These results enabled initiation of a randomized phase 2 study and support future trials of PARP inhibitors in combination with radiation therapy for patients with brain tumors. © 2024 The Authors. Published by Elsevier Inc. This is an open access article under the CC BY license (<http://creativecommons.org/licenses/by/4.0/>)

## Introduction

Glioblastoma (GBM) is a cancer of extreme unmet need and is the most commonly occurring malignant primary brain tumor.<sup>1</sup> Disease incidence increases with age and older patients have particularly poor prognosis, with less than half of patients aged older than 55 years surviving beyond a year.<sup>1,2</sup> Before 2017, patients aged 70 years or older were generally treated with short-course radiation therapy (40 Gy in 15 fractions over 3 weeks), with clinical trials having shown no benefit from longer courses of higher radiation doses.<sup>3,4</sup> A randomized phase 3 clinical trial published in 2017 demonstrated that addition of concomitant and adjuvant temozolomide chemotherapy to short-course radiation therapy was associated with improved overall survival (9.3 vs 7.6 months) in patients aged 65 years and older.<sup>5</sup> Subgroup analysis indicated that this benefit was largely manifested in patients in whose tumors the O<sup>6</sup>-methylguanine-DNA methyltransferase (MGMT) gene promoter region was methylated. Outcomes in this patient population remain dismal, however, and there is an urgent need for more effective treatments that can be tolerated by these vulnerable patients.<sup>6,7</sup>

Olaparib is an orally bioavailable inhibitor of the poly (ADP-ribose) polymerase (PARP) enzyme family, which plays an important role in DNA repair. It is licensed for the treatment of breast, ovarian and other solid tumors bearing mutations in the *BRCA1* or *BRCA2* genes. It is very well tolerated as a single agent, including in older women with ovarian cancer.<sup>8,9</sup> The radiosensitizing effects of olaparib have been observed across a broad spectrum of cancer models and are not dependent on BRCA deficiency. In this context olaparib has been tested in combination with radiation therapy in several phase 1 studies and its tolerability has varied according to anatomic site and radiation dose delivered. In patients with head and neck cancer receiving 69.3 Gy in 33 fractions, the maximum tolerated dose (MTD) was limited by oral mucositis to 25 mg twice daily,<sup>10</sup> and in patients with lung cancer receiving 66 Gy in 24 fractions, esophagitis limited the MTD to only 25 mg daily.<sup>11</sup> In patients with breast cancer, however, olaparib 200 mg twice daily was safely combined with 50.4 Gy and the MTD was not reached.<sup>12,13</sup> Because in vitro studies have shown the radiosensitizing effects of olaparib to be observed only in proliferating cells, we hypothesized that olaparib could be safely combined with radiation therapy in the context of the brain and that the combination would be well tolerated.

## Methods and Materials

### Study design and population

The phase 1 component of PARADIGM (OlaPARib and RADiotherapy In newly diagnosed GlioblastoMa) was a single-arm dose-escalation study to determine the safety and tolerability of olaparib as a radiosensitizer in combination with short-course radiation therapy in older patients with newly diagnosed GBM. Olaparib treatment was given with hypofractionated radiation therapy (see details in the following section) and dose escalation was performed following a 3+3 cohort design with 4 planned cohorts: 50 mg once daily, 100 mg once daily, 100 mg twice daily, and 200 mg twice daily. Eligible patients were aged 70 years or older with World Health Organization (WHO) performance status (PS) 0 to 1 or aged 18 to 69 years with either PS 2 at initial consultation or PS 0 to 1 but otherwise unsuitable for radical radiation therapy.<sup>14</sup> Patients were not to have received radiation therapy or chemotherapy for a previous central nervous system malignancy. Exclusion criteria were PS >2, active concurrent malignancy or within 5 years of malignancy (except non-melanoma skin cancer or carcinoma in situ of the cervix), previous PARP inhibitor treatment, olaparib hypersensitivity, uncontrolled seizures, and positive serology for HIV, hepatitis B, or hepatitis C. Hematological and biochemical criteria included adequate hemoglobin, platelet, white blood cell and neutrophil counts, and adequate liver and renal function (see trial protocol in [Appendix E1](#)). Adverse events were recorded using Common Terminology Criteria for Adverse Events version 4 at each patient visit.<sup>15</sup> The trial opening date was November 1, 2014, with final patient registration on April 3, 2017, and phase 1 trial end date of July 31, 2018. The subsequent planned phase 2 study is ongoing with expected completion of recruitment in Q2 2024. In line with the Declaration of Helsinki, the trial was approved by the West of Scotland Research Ethics Committee and registered with the International Standard Randomised Controlled Trial Number (reference ISRCTN52658296). Written information was provided to all patients to obtain informed consent.<sup>16</sup>

### Procedures

Olaparib was taken orally in tablet form (50, 100, and 200 mg tablets) commencing 3 days before, concurrently during, and for 4 weeks after completion of radiation

therapy. Radiation therapy dose was 40 Gy in 15 fractions (2.67 Gy per fraction) over 19 to 21 days. Radiation therapy planning details are described in the PARADIGM radiation therapy planning and delivery guidelines (Appendix E1), which, in brief, included clinical target volume to be extrapolated from gross tumor volume at a margin of 2.5 cm with a planning target volume margin as per institutional guidance (usually 5 mm). Organs at risk delineated were optic chiasm, right and left optic nerves, ocular globes, lenses, and brain stem; organ-at-risk dose reporting included D5% and mean dose. Radiation therapy quality assurance was conducted through the UK Radiotherapy Trials Quality Assurance team (<http://www.rtrialsqa.org.uk/>) to ensure consistency of radiation therapy planning and delivery across sites.<sup>17</sup> Patients were assessed within 7 days before starting radiation therapy, including physical and neurologic examination, medical review to confirm eligibility, Mini Mental Status Examination (MMSE), quality-of-life questionnaire, and olaparib prescription.<sup>18</sup> Patients were then evaluated weekly during radiation therapy and midway through the adjuvant olaparib period. Visits included WHO PS assessment, medication review, and adverse event (AE) review using Common Terminology Criteria for Adverse Events version 4 criteria. Physical and neurologic examination, AE review, MMSE, and quality-of-life questionnaires were undertaken 4 weeks after radiation therapy and at return visits thereafter. Radiologic imaging included magnetic resonance imaging (MRI) within 28 days of commencing radiation therapy, 8 weeks after completion of radiation therapy, and at 2-month intervals thereafter until progression.<sup>19,20</sup> MRI scans were reported to response assessment in neuro-oncology (RANO) criteria.<sup>19,20</sup>

## Endpoints and statistical analysis

The primary endpoint was to determine the MTD of olaparib given concurrently with radiation therapy in this population. After completion of each cohort of patients, data were reviewed by the safety review committee to determine ongoing safety for patient cohorts. With a 3+3 dose-escalation design, it was estimated that between 12 and 24 patients would be recruited with 4 cohorts of up to 6 patients. Patients who missed 2 or more fractions of radiation therapy, 2 or more days of olaparib during radiation therapy, or 7 or more days of adjuvant olaparib for reasons other than dose limiting toxicities (DLTs) or dose interruption due to toxicity were deemed nonevaluable for dose-escalation decisions.

Secondary endpoints were identification of DLTs of concurrent olaparib and radiation therapy and exploration of the safety and tolerability of this combination. DLTs were defined as failure to complete radiation therapy and any grade  $\geq 3$  toxicity that was not present before commencing olaparib. Dates of tumor progression and death were recorded for all patients, and overall survival (OS) and progression-free survival (PFS) probabilities were calculated using the Kaplan-Meier method. Cognitive function was

evaluated by MMSE as an exploratory endpoint and descriptive statistics were used for analysis.

## Results

### Patients

Eighteen patients from 4 centers were recruited between July 2015 and April 2017. Of these, 2 were excluded before commencing treatment due to withdrawal of consent and patient fitness, respectively. Of the 16 patients receiving study treatment, 2 were excluded due to  $>2$  missed doses of concurrent olaparib and  $>2$  missed radiation therapy fractions, respectively, leaving 14 patients in the evaluable population for the

**Table 1 Patient characteristics at baseline (N = 16)**

Patient characteristic	Value
Sex (%)	
Male	9 (56.25)
Female	7 (43.75)
Age, median (range), y	71.5 (44-78)
WHO performance status (%)	
0	4 (25)
1	8 (50)
2	4 (25)
Baseline MMSE of $\geq 25$ (of 18 screened patients) (%)	15 (83.33)
Ethnic origin (%)	
White	16 (100)
Resection type (%)	
Gross total resection	7 (43.75)
Subtotal resection	3 (18.75)
Biopsy	6 (6.25)
Tumor location (%)	
Frontal	8 (50)
Parietal	1 (6.25)
Occipital	1 (6.25)
Temporal	5 (31.25)
Pre-existing medical condition (%)	
Cardiac	2 (12.5)
Hypercholesterolemia	31 (18.75)
Hypertension	0
Diabetes	1 (6.25)
Asthma/COPD	3 (18.75)

*Abbreviations:* COPD = chronic obstructive pulmonary disease; MMSE = Mini Mental State Examination; WHO = World Health Organization.

**Table 2 Treatment-related adverse events reported during follow-up**

Adverse effect	Cohort 1 50 mg OD				Cohort 2 100 mg OD				Cohort 3 100 mg BD				Cohort 4 200 mg BD			
	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4
CTCAE version 4 grade	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4
Fatigue	2	1	0	0	2	0	0	0	3	2	0	0	3	0	0	0
Alopecia	1	1	0	0	1	0	0	0	1	3	0	0	1	1	0	0
Agitation	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0
Anorexia	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0
Depressed conscious level	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0
Diarrhea	0	0	0	0	1	0	0	0	1	0	0	0	0	0	0	0
Dizziness	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0
Dysgeusia	1	0	0	0	1	0	0	0	1	0	0	0	0	0	0	0
Dyspnea	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0
Headache	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Nausea	0	0	0	0	0	0	0	0	2	0	0	0	1	0	0	0
Scalp erythema	0	1	0	0	1	0	0	0	2	0	0	0	0	0	0	0
Thrombocytopenia	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0
Hyponatremia	0	0	0	0	0	0	0	0	2	0	1	0	0	0	0	0
Hypokalemia	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0
Hypoalbuminemia	0	1	0	0	1	1	1	0	2	1	0	0	1	0	0	0
Hypercalcemia	0	0	0	0	1	0	0	0	1	0	0	0	0	0	0	0
Hyperbilirubinemia	0	0	0	0	0	0	0	0	1	1	0	0	0	0	0	0
ALT	1	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0
Creatinine	0	0	0	0	0	0	0	0	2	0	0	0	0	0	0	0

*Abbreviations:* ALT = alanine aminotransferase; BD = twice a day; CTCAE = Common Terminology Criteria for Adverse Events; OD = once a day.

primary analysis. Nine (56.25%) patients were male, and the median age was 71.5 years (range, 44-78; [Table 1](#)). Eight patients (50%) were recorded as having PS 1, with 4 patients PS 0 and 4 PS 2. Ten (62.5%) patients had undergone either gross total or subtotal resection and 6 (37.5%) had undergone biopsy for tissue diagnosis. Tumor samples from all 16 patients were demonstrated to be isocitrate dehydrogenase-1 wild type by immunohistochemistry. MGMT promoter methylation status was available for 15 patients, of whom 7 were MGMT unmethylated and 8 methylated.

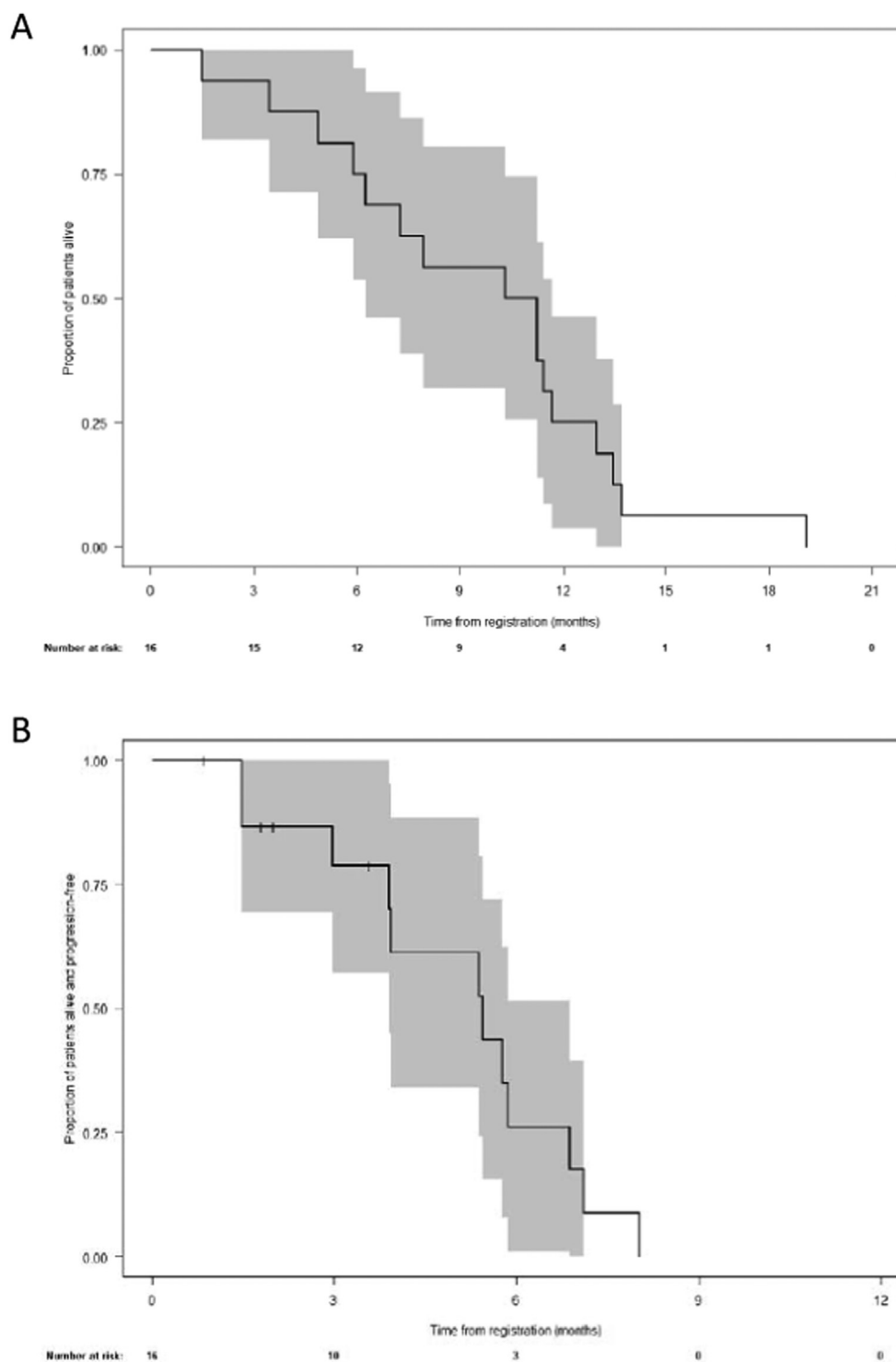
## Safety

Three (18.75%) patients received 50 mg of olaparib once daily, 3 (18.75%) received 100 mg once daily, 7 (43.75%) received 100 mg twice daily, and 3 (18.75%) received 200 mg twice daily. One patient in cohort 2 was subsequently found to be nonevaluable, but this was noted during analysis after completion of cohort 4, meaning the patient was not replaced. One patient in cohort 3 experienced a DLT with grade 3 agitation that was attributed to olaparib. Another cohort 3 patient died suddenly after the mid olaparib visit, unrelated to study treatment, and was therefore

replaced. The MTD of olaparib was not reached, with the maximum planned dose of 200 mg twice daily being tolerated by all 3 patients in cohort 4. Regarding radiation therapy delivery, all patients received between 39.9 and 40.1 Gy in 15 fractions. The patient who experienced the DLT came off study after 5 fractions and completed radiation therapy off study. Adverse events are summarized in [Table 2](#). Grade 1 to 2 alopecia was recorded in 9 (56.25%) patients, grade 1 dysgeusia in 3 (18.75%), and grade 1 to 2 fatigue in 13 (81.25%). Hematological AEs were rare with 1 grade 1 thrombocytopenia and no neutropenia recorded. Two grade  $\geq 3$  AEs were recorded in cohort 3: 1 grade 3 agitation (the sole DLT) and 1 grade 3 hyponatremia, which was not attributed to study treatment.

## PFS and OS

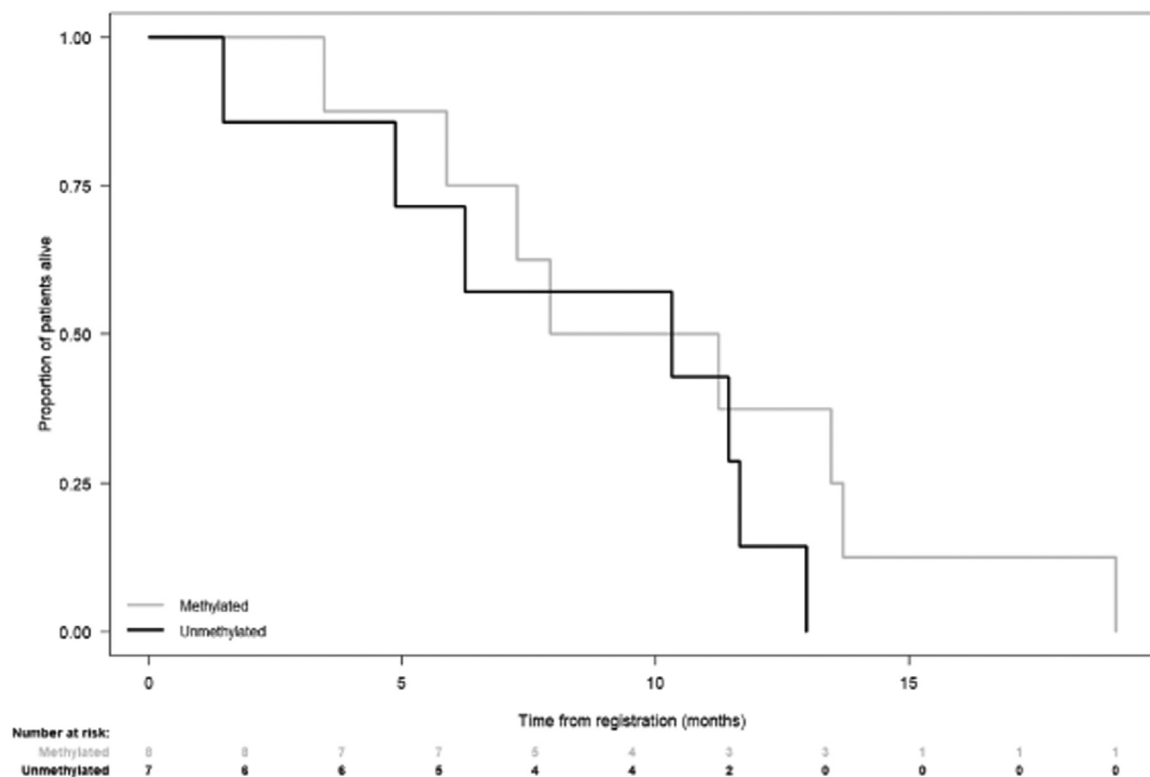
Survival statistics including OS, PFS, and CIs were calculated from time of registration for the study and included the safety population of 16 patients. Median OS was 10.8 months (80% CI, 7.3-11.4 months; [Fig. 1A](#)). All 16 patients have died, with GBM documented as cause of death in 14 (87.5%). One (6.25%) cause of death was recorded as pulmonary embolism



**Fig. 1.** (A) Overall survival and (B) progression-free survival among the 16 patients included in the trial (Kaplan-Meier plots with 80% CIs).

and cause of death was not available for 1 patient. However, this patient was documented to have progressive disease and had been discharged from oncology follow-up to receive supportive care. Median OS by cohort was as follows: cohort 1: 10.3 months, cohort 2: 11.2 months, cohort 3: 7.9 months, and cohort 4: 11.2 months. PFS was determined by MRI scans reported to RANO criteria with appropriate clinician

judgment. Median PFS was 5.5 months (80% CI, 3.9-5.9 months; Fig. 1B), with cohort PFS values as follows: cohort 1: 5.5 months, cohort 2: 3.9 months, cohort 3: 5.8 months, and cohort 4: 5.9 months. Median OS for MGMT methylated and unmethylated patients was 9.6 months (80% CI, 5.9-13.5 months) and 10.3 months (80% CI, 4.9-11.7 months), respectively; survival curves are shown in Figure 2.



**Fig. 2.** Overall survival of the 15 patients for whom tumor O<sup>6</sup>-methylguanine-DNA methyltransferase promoter methylation status was available.

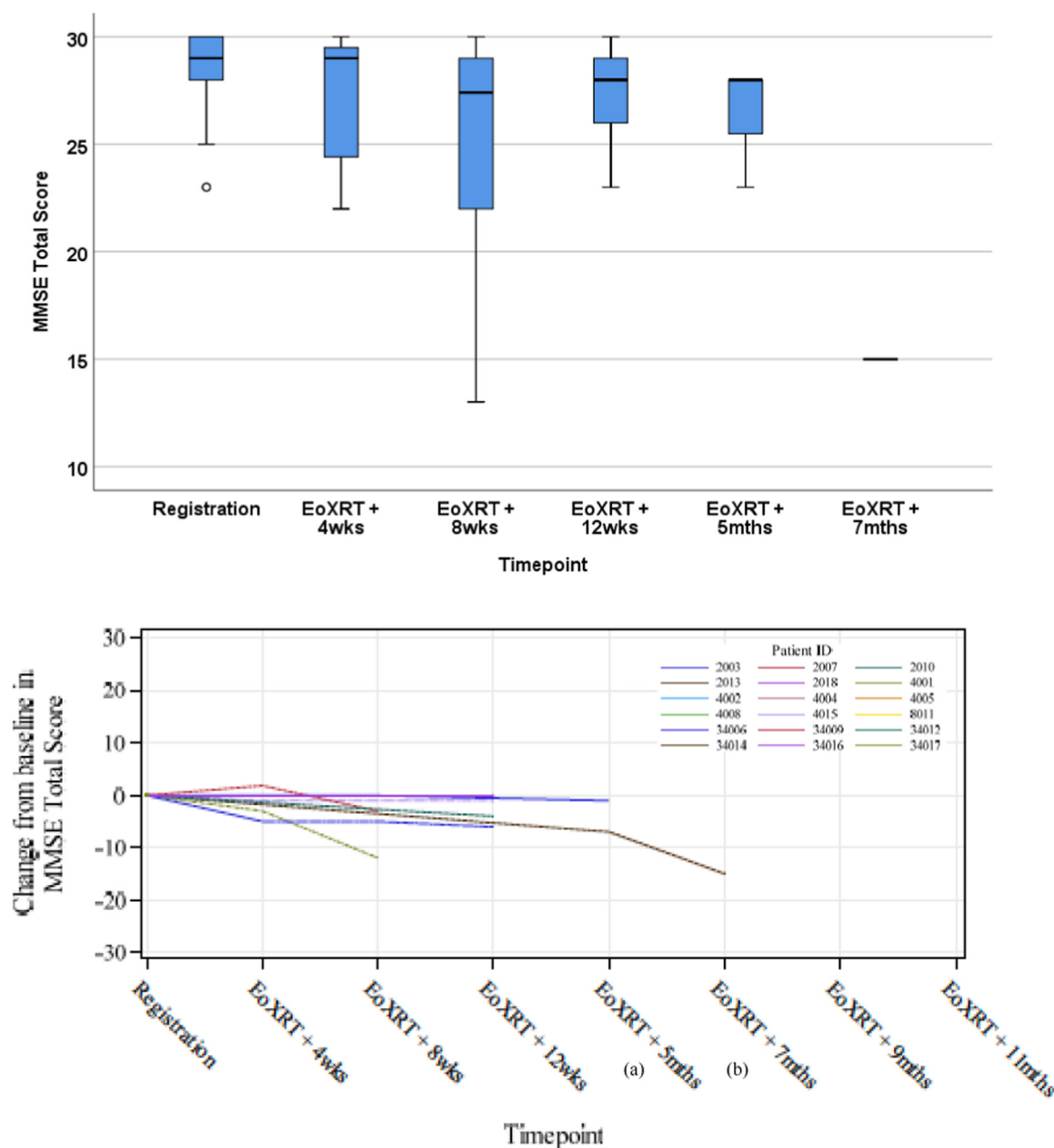
## Cognitive function

Patients were asked to complete MMSE questionnaires at registration and at all visits after completion of treatment. Of the 18 patients screened, 15 (83.33%) had MMSE scores of  $\geq 25$  at baseline. In total there were 78 possible MMSE opportunities, 42 (54%) of which produced completed questionnaires for analysis. Completion rates were 94.4% at baseline, 50% at 4 weeks posttreatment, 57.1% at 8 weeks, 46.2% at 12 weeks, and 33% at 5 months. Median MMSE score was 29 at baseline; this was maintained 4 weeks posttreatment before falling slightly to 27.4 at week 8 then stabilizing at 28 at week 12 and 5 months (Fig. 3A). Line plots showing change from baseline for individual patients over time indicate that cognitive function was not adversely affected by treatment with radiation therapy and olaparib (Fig. 3B).

## Discussion

This phase 1 3+3 dose-escalation study has demonstrated that olaparib can be safely combined with brain radiation therapy (40 Gy in 15 fractions) at a dose of 200 mg twice daily, in a population of patients with GBM who were not suitable for radical treatment because of age  $>70$  or WHO PS  $>1$ . The MTD was not reached and only 1 DLT (G3

agitation) was recorded. Adverse event rates and severities were low, with the majority of grade 2 AEs being alopecia and fatigue, both of which are expected in patients receiving brain radiation therapy. The absence of hematological toxicities indicates that combining olaparib with both temozolomide chemotherapy and radiation may be feasible in this population. We recommend 200 mg twice daily throughout treatment as the recommended phase 2 dose for olaparib in combination with hypofractionated radiation therapy to the brain and have demonstrated that this dose is also well tolerated as adjuvant therapy for 4 weeks after radiation therapy. Median OS (10.8 months) and PFS (5.5 months) outcomes compare favorably with other studies undertaken in this population of patients.<sup>5,21</sup> In particular, the randomized phase 3 study published by Perry et al<sup>5</sup> in the *New England Journal of Medicine* in 2017 reported median OS of 7.6 months for patients receiving radiation therapy alone and 9.3 months for patients receiving radiation concurrently with temozolomide chemotherapy. The Perry et al study recruited patients aged 65 years and older, so the PARADIGM population (predominantly aged 70 and older) might have been expected to have worse survival outcomes. There was no measurable difference in survival between MGMT methylated and unmethylated patients, consistent with other studies of older GBM patients who did not receive temozolomide.<sup>21</sup>



**Fig. 3.** Mini Mental State Examination scores at each time point after the end of radiation therapy. (A) Boxplots of total scores showing median, IQR, maximum, minimum, and outlier values. (B) Line plots of change from baseline per patient.

## Limitations

Study limitations include those shared with most phase 1 dose-escalation trials: the lack of a control population and the small number of patients evaluated. In addition, 4 of the 16 patients did not undergo posttreatment MRI, resulting in PFS censoring at their end-of-treatment date. Avoiding excess toxicity is of crucial importance in this population of patients, and documenting AEs might not always capture more generalized effects on well-being. In the absence of a comprehensive quality-of-life study, we undertook serial MMSE evaluations as a convenient marker of cognitive functioning. As expected, completion rates decreased over

time, making it difficult to draw robust conclusions. It is probable that MMSE scores during follow-up were skewed because the tests were more likely to be completed by patients in better general health.

## Scientific relevance

Our findings add to the growing body of literature describing the opportunities and challenges of combining PARP inhibitors with radiation therapy. We show that olaparib can be combined with hypofractionated brain radiation therapy at a dose similar to the single agent dose (usually

300 mg twice daily) without any measurable increase in toxicity, in contrast to previous studies in head and neck and lung cancer that have reported exacerbation of acute toxicity by much lower doses of olaparib. There are at least 3 likely explanations for this discrepancy: (1) our study delivered a lower total radiation therapy dose; (2) olaparib concentrations in GBM were shown in the OPARATIC trial to be approximately 25% of plasma concentrations,<sup>22</sup> and it is likely that normal brain penetration is even lower than this; and (3) the radiosensitizing effects of olaparib have been shown to occur only in proliferating cells, which are generally absent from the healthy brain.

## Conclusion

In summary, phase 1 of the PARADIGM study has demonstrated olaparib to be safely delivered at 200 mg twice daily in combination with radiation therapy in patients not suitable for radical treatment. This combination was very well tolerated in this patient population and has been applied in the ongoing randomized phase 2 component of PARADIGM. The MTD was not reached, and an OS of 10.8 months was reported. We therefore recommend 200 mg twice-daily olaparib as a safe radiosensitizing agent in patients with newly diagnosed GBM who are not suitable for radical dose treatment.

## References

- Ostrom QT, Gittleman H, Liao P, et al. CBTUS statistical report: Primary brain and other central nervous system tumors diagnosed in the United States in 2010-2014. *Neuro Oncol* 2017;19(suppl 5):v1-v88.
- Ahmadloo N, Kani AA, Mohammadianpanah M, et al. Treatment outcome and prognostic factors of adult glioblastoma multiforme. *J Egypt Natl Canc Inst* 2013;25:21-30.
- Roa W, Brasher PM, Bauman G, et al. Abbreviated course of radiation therapy in older patients with glioblastoma multiforme: A prospective randomized clinical trial. *J Clin Oncol* 2004;22:1583-1588.
- Malmström A, Grønberg BH, Marosi C, et al. Temozolomide versus standard 6-week radiotherapy versus hypofractionated radiotherapy in patients older than 60 years with glioblastoma: The Nordic randomised, phase 3 trial. *Lancet Oncol* 2012;13:916-926.
- Perry JR, Laperriere N, O'Callaghan CJ, et al. Short-course radiation plus temozolomide in elderly patients with glioblastoma. *New Engl J Med* 2017;376:1027-1037.
- Cao JQ, Fisher BJ, Bauman GS, Megyesi JF, Watling CJ, Macdonald DR. Hypofractionated radiotherapy with or without concurrent temozolomide in elderly patients with glioblastoma multiforme: A review of 10-year single institutional experience. *J Neurooncol* 2012;107:395-405.
- Asmaa A, Dixit S, Rowland-Hill C, et al. Management of elderly patients with glioblastoma-multiforme-a systematic review. *Br J Radiol* 2018;91 20170271.
- Dockery LE, Tew WP, Ding K, Moore KN. Tolerance and toxicity of the PARP inhibitor olaparib in older women with epithelial ovarian cancer. *Gynecol Oncol* 2017;147:509-513.
- Maiorano BA, Maiorano MFP, Lorusso D, Di Maio M, Maiello E. Efficacy and safety of PARP inhibitors in elderly patients with advanced ovarian cancer: A systematic review and meta-analysis. *Int J Gynecol Cancer* 2022;32:1410-1418.
- Karam SD, Reddy K, Blatchford P, et al. Final report of a phase I trial of olaparib with cetuximab and radiation for heavy smoker patients with locally advanced head and neck cancer. *Clin Cancer Res* 2018;24:4949-4959.
- de Haan R, van den Heuvel MM, van Diessen J, et al. Phase I and pharmacologic study of olaparib in combination with high-dose radiotherapy with and without concurrent cisplatin for non-small cell lung cancer. *Clin Cancer Res* 2021;27:1256-1266.
- Loap P, Loirat D, Berger F, et al. Combination of olaparib and radiation therapy for triple negative breast cancer: Preliminary results of the RADIOPARP phase 1 trial. *Int J Radiat Oncol Biol Phys* 2021;109:436-440.
- Derby SJ, Chalmers AJ, Carruthers RD. Radiotherapy-poly(ADP-ribose) polymerase inhibitor combinations: Progress to date. *Semin Radiat Oncol* 2022;32:15-28.
- Oken MM, Creech RH, Tormey DC, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. *Am J Clin Oncol* 1982;5:649-655.
- National Cancer Institute. Common Terminology Criteria for Adverse Events (CTCAE). Version 4.0. Accessed January 17, 2023. [https://evs.nci.nih.gov/ftp1/CTCAE/CTCAE\\_4.03/Archive/CTCAE\\_4.0\\_2009-05-29\\_QuickReference\\_8.5x11.pdf](https://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03/Archive/CTCAE_4.0_2009-05-29_QuickReference_8.5x11.pdf).
- Olaparib and radiotherapy In newly-diagnosed glioblastoma. ISRCTN identifier: ISRCTN52658296. Updated March 29, 2016. Accessed January 17, 2023. <https://www.isrctn.com/ISRCTN52658296>.
- Ishikura S. Quality assurance of radiotherapy in cancer treatment: Toward improvement of patient safety and quality of care. *Jpn J Clin Oncol* 2008;38:723-729.
- O'Neill D. The Mini-Mental Status Examination. *J Am Geriatr Soc* 1991;39:733.
- Chang SM, Wen PY, Vogelbaum MA, Macdonald DR, van den Bent MJ. Response Assessment in Neuro-Oncology (RANO): More than imaging criteria for malignant glioma. *Neurooncol Pract* 2015;2:205-209.
- Wen PY, Macdonald DR, Reardon DA, et al. Updated response assessment criteria for high-grade gliomas: Response assessment in Neuro-Oncology Working Group. *J Clin Oncol* 2010;28:1963-1972.
- Wick W, Platten M, Meisner C, et al. Temozolomide chemotherapy alone versus radiotherapy alone for malignant astrocytoma in the elderly: The NOA-08 randomised, phase 3 trial. *Lancet Oncol* 2012;13:707-715.
- Hanna C, Kurian KM, Williams K, et al. Pharmacokinetics, safety and tolerability of olaparib and temozolomide for recurrent glioblastoma: Results of the phase I OPARATIC trial. *Neuro Oncol* 2020;22:1840-1850.