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Concurrent olaparib and radiotherapy in elderly patients with newly diagnosed glioblastoma: the phase I dose escalation PARADIGM trial

Short running title: Olaparib and radiotherapy in elderly glioblastoma

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Conflict of interest

Anthony Chalmers has received research funding from AstraZeneca and has participated in AstraZeneca advisory boards. The other authors report no conflicts of interest.

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Data availability 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 II of the PARADIGM trial, deidentified data will be made publicly available.

Abstract

Background: Patients with glioblastoma who are elderly or have poor performance status (PS) experience particularly poor clinical outcomes. At the time of study initiation, these patients were treated with short-course radiotherapy (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: Phase I of the PARADIGM trial was a 3+3 dose escalation study testing olaparib in combination with radiotherapy (40 Gy 15 fractions) in patients with newly diagnosed glioblastoma who were unsuitable for radical treatment either because they were aged 70 or over (WHO PS 0-1) or aged 18-69 with PS 2. The primary outcome was the recommended phase 2 dose (RP2D) of olaparib. Secondary endpoints included safety and tolerability, overall survival (OS) and progression free survival (PFS). Effects on cognitive function were assessed by mini-mental state examination (MMSE).

Results: Of 16 eligible patients (56.25% male, median age 71.5 [range 44-78 years], 75% PS 0-1), one dose-limiting toxicity was reported (grade 3 agitation). Maximum tolerated dose was not reached and the RP2D was determined as 200 mg twice daily. Median OS and PFS were 10.8 months (80% CI: 7.3-11.4) and 5.5 months (80% CI: 3.9-5.9) respectively. MMSE plots indicated that cognitive function was not adversely affected by the olaparib-radiotherapy combination.

Conclusions: Olaparib can be safely combined with hypofractionated brain radiotherapy and is well tolerated in patients unsuitable for radical chemoradiation. These results enabled initiation of a randomised phase II study and support future trials of PARP inhibitors in combination with radiotherapy for patients with brain tumors.

Introduction

Glioblastoma (GBM) is a cancer of extreme unmet need and is the most commonly occurring malignant primary brain tumour [1]. Disease incidence increases with age and older patients have particularly poor prognosis, with less than half of patients aged over 55 surviving beyond a year [1,2]. Prior to 2017, patients aged 70 or above were generally treated with short course radiotherapy (40 gray (Gy) in 15 fractions over three weeks), with clinical trials having shown no benefit from longer courses of higher radiation doses [3,4]. A randomised phase III clinical trial published in 2017 demonstrated that addition of concomitant and adjuvant temozolomide chemotherapy to short course radiotherapy was associated with improved overall survival (9.3 months vs. 7.6 months) in patients aged 65 and above [5]. Subgroup analysis indicated that this benefit was largely manifested in patients in whose tumours the O^6-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 [6,7].

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 tumours bearing mutations in the *BRCA1* or *BRCA2* genes. It is very well tolerated as a

single agent, including in older women with ovarian cancer [8,9]. The radiosensitising effects of olaparib have been observed across a broad spectrum of cancer models and are not dependent upon BRCA deficiency. In this context olaparib has been tested in combination with radiotherapy in several phase I studies and its tolerability has varied according to anatomical site and radiation dose delivered. In head & neck cancer patients receiving 69.3 Gy in 33 fractions, the maximum tolerated dose (MTD) was limited by oral mucositis to 25 mg twice daily [10], while in lung cancer patients receiving 66 Gy in 24 fractions, oesophagitis limited the MTD to only 25 mg daily [11]. In breast cancer patients, however, olaparib 200 mg twice daily was safely combined with 50.4 Gy and the MTD was not reached [12,13]. Since *in vitro* studies have shown the radiosensitising effects of olaparib to be observed only in proliferating cells, we hypothesised that olaparib could be safely combined with radiotherapy in the context of the brain and that the combination would be well tolerated.

Methods and Materials

Study design and population

The phase I 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 radiosensitiser in combination with short course radiotherapy in older patients with newly diagnosed GBM. Olaparib treatment was given with hypofractionated radiotherapy (details below) 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 or over with World Health Organisation (WHO) performance status (PS) 0-1 *or* aged 18-69 with either PS 2 at initial consultation *or* PS 0-1 but otherwise unsuitable for radical radiotherapy [14]. Patients were not to have received radiotherapy or chemotherapy for a previous central nervous system (CNS) 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 or positive serology for

HIV, Hepatitis B or C. Hematological and biochemical criteria included adequate haemoglobin, platelet, white blood cell and neutrophil counts and adequate liver and renal function (see trial protocol supplement). Adverse events were recorded using the common terminology criteria for adverse events version 4 (CTCAE v4) at each patient visit [15]. The trial opening date was 1st November 2014 with final patient registration on 3rd April 2017 and phase I trial end date 31st July 2018. The subsequent planned phase II study is ongoing with expected completion of recruitment in late 2023. In line with the Declaration of Helsinki the trial was approved by the West of Scotland Research Ethics Committee and registered with the ISRCTN (reference ISRCTN52658296). Written information was provided to all patients in order to obtain informed consent [16].

Procedures

Olaparib was taken orally in tablet form (50 mg, 100 mg and 200 mg tablets) commencing three days prior to, concurrently during and for four weeks following completion of radiotherapy. Radiotherapy dose was 40 Gy in 15 fractions (2.67 Gy per fraction) over 19-21 days. Radiotherapy planning details are described in the PARADIGM radiotherapy planning and delivery guidelines (see supplementary information) which, in brief, included CTV to be extrapolated from gross tumour volume (GTV) at a margin of 2.5 cm with a planning target volume (PTV) margin as per institutional guidance (usually 5 mm). Organs at risk (OARs) delineated were optic chiasm, right and left optic nerves, ocular globes, lenses and brain stem; OAR dose reporting included D5% and mean dose. Radiotherapy Quality Assurance was conducted through the UK RTTQA team (http://www.rttrialsqa.org.uk/) to ensure consistency of radiotherapy planning and delivery across sites [17]. Patients were assessed within 7 days prior to starting radiotherapy including physical and neurological examination, medical review to confirm eligibility, mini mental status examination (MMSE), quality of life questionnaire and olaparib prescription [18]. Patients were then evaluated weekly during radiotherapy and midway through the adjuvant olaparib period. Visits included WHO PS assessment, medication review and adverse event (AE) review using CTCAE v4 criteria. Physical and neurological examination, AE review, MMSE and quality of life questionnaires were undertaken four weeks following radiotherapy and at

return visits thereafter. Radiological imaging included magnetic resonance imaging (MRI) within 28 days of commencing radiotherapy, eight weeks following completion of radiotherapy and at two-month intervals thereafter until progression [19,20]. MRI scans were reported to response assessment in neuro-oncology (RANO) criteria [19,20].

End Points and Statistical Analysis

The primary endpoint was to determine the maximum tolerated dose (MTD) of olaparib given concurrently with radiotherapy in this population. Following 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 12-24 patients would be recruited with 4 cohorts of up to 6 patients. Patients who missed two or more fractions of radiotherapy, two or more days of olaparib during radiotherapy, or seven or more days of adjuvant olaparib for reasons other than DLT or dose interruption due to toxicity were deemed non-evaluable for dose escalation decisions.

Secondary endpoints were identification of dose limiting toxicities (DLTs) of concurrent olaparib and radiotherapy and exploration of the safety and tolerability of this combination. DLTs were defined as failure to complete radiotherapy and any grade ≥3 toxicity that was not present prior to 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 four centres were recruited between July 2015 and April 2017. Of these, two were excluded prior to commencing treatment due to withdrawal of consent and patient fitness, respectively. Of the sixteen patients receiving study treatment, two were excluded due to >2 missed

doses of concurrent olaparib and >2 missed radiotherapy fractions respectively leaving 14 patients in the evaluable population for the primary analysis. Nine (56.25%) patients were male and the median age was 71.5 years (range 44-78 years, Table 1). Eight patients (50%) were recorded as having PS 1, with four patients PS 0 and four PS 2. Ten (62.5%) patients had undergone either gross total or subtotal resection and six (37.5%) had undergone biopsy for tissue diagnosis. Tumour samples from all sixteen patients were demonstrated to be isocitrate dehydrogenase-1 (IDH-1) wild type by immunohistochemistry. MGMT promoter methylation status was available for fifteen patients, of whom seven were MGMT unmethylated and eight methylated.

Safety

Three (18.75%) patients received 50 mg of olaparib once daily, three (18.75%) received 100 mg once daily, seven (43.75%) received 100 mg twice daily and three (18.75%) received 200 mg twice daily. One patient in cohort 2 was subsequently found to be non-evaluable 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 three patients in cohort 4. Regarding radiotherapy 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 radiotherapy off study. Adverse events are summarised in Table 2. Grade 1-2 alopecia was recorded in nine (56.25%) patients, grade 1 dysgeusia in three (18.75%) and grade 1-2 fatigue in thirteen (81.25%). Hematological AEs were rare with one grade 1 thrombocytopenia and no neutropenia recorded. Two grade ≥3 AEs were recorded in cohort 3: one grade 3 agitation (the sole DLT) and one grade 3 hyponatraemia, which was not attributed to study treatment.

PFS and OS

Survival statistics including OS, PFS and confidence intervals (CI) were calculated from time of registration onto the study and included the safety population of sixteen patients. Median OS was

10.8 months (80% CI: 7.3-11.4 months; Figure 1A). All sixteen patients have died, with GBM documented as cause of death in fourteen (87.5%). One (6.25%) cause of death was recorded as pulmonary embolism and cause of death was not available for one 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: cohort 1: 10.3 months, cohort 2: 11.2 months, cohort 3: 7.9 months, cohort 4: 11.2 months. PFS was determined by MRI scans reported to RANO criteria with appropriate clinician judgement. Median PFS was 5.5 months (80% CI: 3.9-5.9 months; Figure 1B), with cohort PFS values as follows: cohort 1: 5.5 months, cohort 2: 3.9 months, cohort 3: 5.8 months, 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.

Cognitive function

Patients were asked to complete MMSE questionnaires at registration and at all visits following completion of treatment. Of the eighteen patients screened, fifteen (83.33%) had MMSE scores of ≥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 post-treatment, 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 post-treatment before falling slightly to 27.4 at week 8 then stabilising at 28 at week 12 and 5 months (Figure 3A). Line plots showing change from baseline for individual patients over time indicate that cognitive function was not adversely affected by treatment with radiotherapy and olaparib (Figure 3B).

Discussion

This phase I 3+3 dose escalation study has demonstrated that olaparib can be safely combined with brain radiotherapy (40 Gy in 15 fractions) at a dose of 200mg 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 one 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 radiotherapy. 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 RP2D for olaparib in combination with hypofractionated radiotherapy to the brain and have demonstrated that this dose is also well tolerated as adjuvant therapy for 4 weeks after radiotherapy. Median OS (10.8 months) and PFS (5.5 months) outcomes compare favourably with other studies undertaken in this population of patients [5,21]. In particular, the randomised phase III study published by Perry and colleagues in the New England Journal of Medicine in 2017 reported median overall survival of 7.6 months for patients receiving radiation therapy alone and 9.3 months for patients receiving radiation concurrently with temozolomide chemotherapy. The Perry study recruited patients aged 65 and over, so the PARADIGM population (predominantly aged 70 and over) 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 [21].

Limitations

Study limitations include those shared with most phase I dose escalation trials: the lack of a control population and the small number of patients evaluated. In addition, four of the 16 patients did not undergo post-treatment MR imaging so have been censored for PFS 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 generalised effects on wellbeing. 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 radiotherapy. We show that olaparib can be combined with hypofractionated brain radiotherapy 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 & neck and lung cancer that have reported exacerbation of acute toxicity by much lower doses of olaparib. There are at least three likely explanations for this discrepancy: (1) our study delivered a lower total radiotherapy dose; (2) olaparib concentrations in GBM were shown in the OPARATIC trial to be approximately 25% of plasma concentrations [22] and it is likely that normal brain penetration is even lower than this; and (3) the radiosensitising effects of olaparib have been shown to occur only in proliferating cells, which are generally absent from the healthy brain.

In summary, phase I of the PARADIGM study has demonstrated olaparib to be safely delivered at 200 mg twice daily in combination with radiotherapy in patients not suitable for radical treatment. This combination was very well tolerated in this patient population and has been taken forward into the ongoing randomized phase II 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 radiosensitising agent in patients with newly diagnosed GBM who are not suitable for radical dose treatment.

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Figure Captions

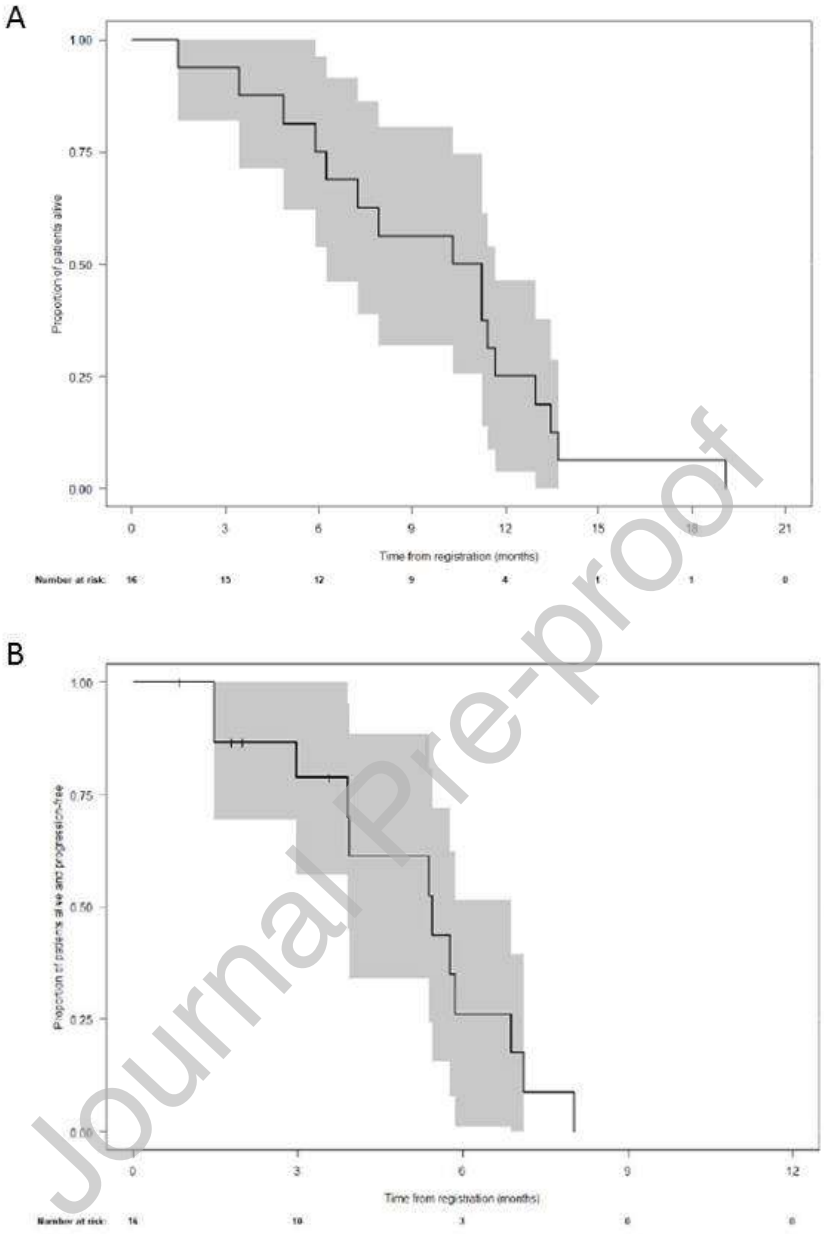

Figure 1

Figure 1: (A) Overall survival and (B) progression-free survival among the 16 patients included in the trial (Kaplan Meier plots with 80% confidence intervals).

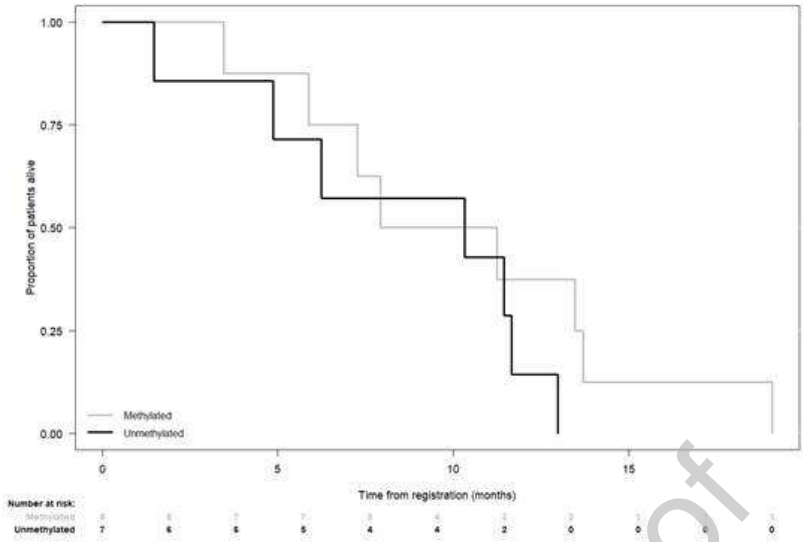

Figure 2

Figure 2: Overall survival of the 15 patients for whom tumor MGMT promoter methylation status was available.

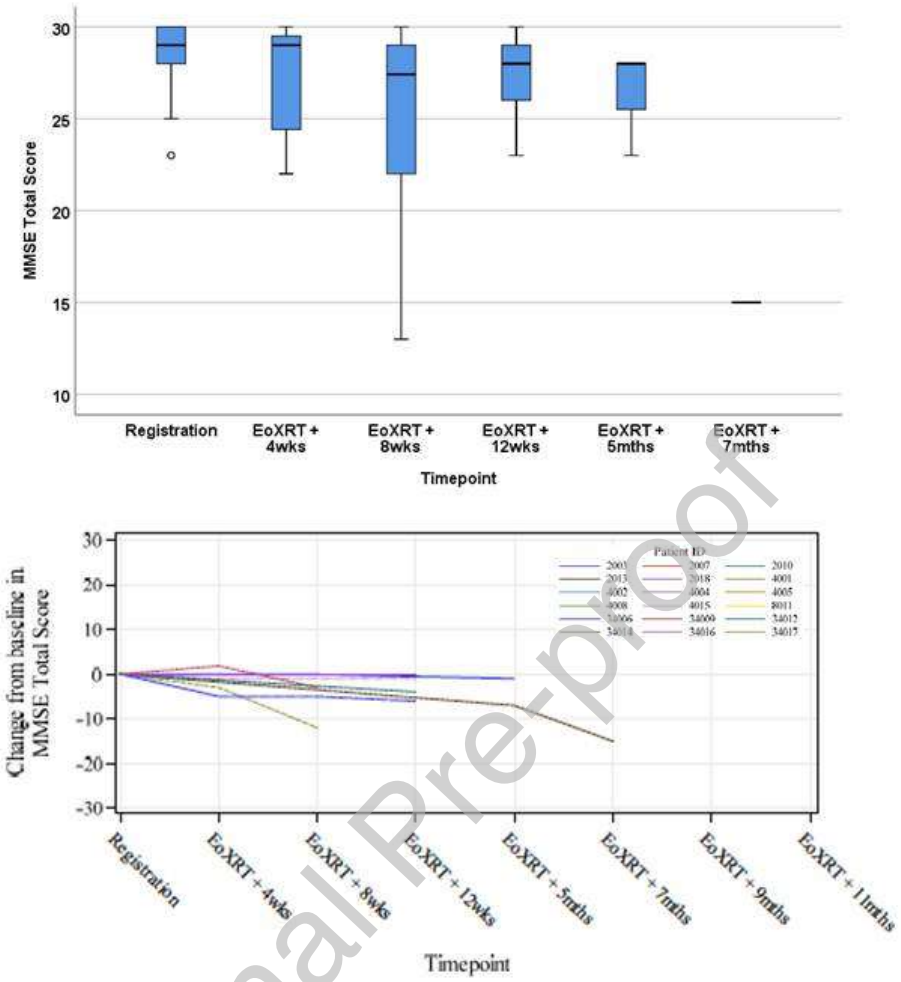

Figure 3

Figure 3: Mini-Mental State Examination scores at each timepoint after the end of radiotherapy. (A) Boxplots of total scores showing median, interquartile range, maximum, minimum and outlier values). (B) Line plots of change from baseline per patient.

Table 1: Patient characteristics at baseline

Patient Characteristics	Patient number (N = 16)
Sex (%)	
Male	9 (56.25)
Female	7 (43.75)
Age median (range)	71.5 (44-78)
WHO* performance status (%)	
0	4 (25)
1	8 (50)
2	4 (25)
Baseline MMSE of ≥25 (of 18 screened patients)	15 (83.33)
Ethnic origin (%)	
White	16 (100)
Resection type (%)	
Gross total resection	7 (43.75)
Sub-total resection	3 (18.75)
Biopsy	6 (6.25)
Tumour location (%)	
Frontal	8 (50)
Parietal	1 (6.25)
Occipital	1 (6.25)
Temporal	5 (31.25)
Pre-existing medical condition (%)	
Cardiac	2 (12.5)
Hypercholesterolaemia	31 (18.75)

Hypertension	0
Diabetes	1 (6.25)
Asthma/COPD	3 (18.75)
*WHO- World Health Organisation	

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

Treatment related adverse effects																
Adverse effect	Cohort 1 50 mg OD				Cohort 2 100 mg OD				Cohort 3 100 mg BD				Cohort 4 200 mg BD			
CTCAE v4 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
Diarrhoea	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
Dyspnoea	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
Hyponatraemia	0	0	0	0	0	0	0	0	2	0	1	0	0	0	0	0
Hypokalaemia	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0
Hypoalbuminaemia	0	1	0	0	1	1	1	0	2	1	0	0	1	0	0	0
Hypercalcaemia	0	0	0	0	1	0	0	0	1	0	0	0	0	0	0	0
Hyperbilirubinaemia	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