



Clinical Trial

Angiotensin II receptor blockers, steroids and radiotherapy in glioblastoma—a randomised multicentre trial (ASTER trial). An ANOCEF study



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KEYWORDS

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Abstract Background: Glioblastomas (GBMs) induce a peritumoural vasogenic oedema impairing functional status and quality of life. Steroids reduce brain tumour-related oedema but are associated with numerous side-effects. It was reported in a retrospective series that angiotensin receptor blockers might be associated with reduced peritumoural oedema. The ASTER study is a randomised, placebo-controlled trial to assess whether or not the addition of Losartan to standard of care (SOC) can reduce steroid requirement during radiotherapy (RT) in patients with newly diagnosed GBM.

Patients and methods: Patients with a histologically confirmed GBM after biopsy or partial surgical resection were randomised between Losartan or placebo in addition to SOC with RT and temozolomide (TMZ). The primary objective was to investigate the steroid dosage required to control brain oedema on the last day of RT in each arm. The secondary outcomes were steroids dosage 1 month after the end of RT, assessment of cerebral oedema on magnetic resonance imaging, tolerance and survival.

Results: Seventy-five patients were randomly assigned to receive Losartan (37 patients) or placebo (38 patients). No difference in the steroid dosage required to control brain oedema on the last day of RT, or one month after completion of RT, was seen between both arms. The incidence of adverse events was similar in both arms. Median overall survival was similar in both arms.

Conclusions: Losartan, although well tolerated, does not reduce the steroid requirement in newly diagnosed GBM patients treated with concomitant RT and TMZ.

Trial registration number NCT01805453 with ClinicalTrials.gov.

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1. Introduction

Glioblastoma (GBM) is the most common malignant primary brain tumour in adults, with an incidence over three per 100 000 people [1]. The standard of care (SOC), with surgical resection followed by radiotherapy (RT) with concomitant and maintenance temozolomide (TMZ) chemotherapy, generally leads to a median overall survival (OS) of about 15 months [2]. The tumour-treating fields device represents an additional treatment option for GBM [3].

Malignant brain tumour patients develop peritumoural vasogenic oedema, which further increases neurological deficits and intracranial pressure [4]. Steroids reduce brain tumour-related oedema and are thus required in almost all patients [5]. However, steroids are associated with numerous side-effects that not only impact the quality of life but also can become life-threatening [6,7]. Because of these side-effects, steroid-sparing drugs represent an unmet medical need. Peritumoural oedema results from blood-brain barrier alterations and leakage of plasma fluid and proteins into the surrounding tissue, a process in which vascular endothelial growth factor (VEGF) is reported to play a key role [7]. Bevacizumab, a monoclonal antibody targeting VEGF, has thus shown a striking steroid-sparing effect. However, this drug requires intravenous infusions and can be associated with significant side-effects, and approval in this clinical setting is lacking [8,9]. Corticorelin acetate, a synthetic analogue of human

corticotropin-releasing factor, reduced dexamethasone requirement when compared with control-treated patients, but this reduction did not reach statistical significance [10]. In a randomised study, although *Boswellia serrata* slightly reduced cerebral oedema on magnetic resonance imaging (MRI), no reduction of dexamethasone dosage was seen in these patients [11].

In 2012, a reduced steroid requirement in patients taking angiotensin-converting enzyme inhibitors or angiotensin receptor blockers (ARBs) for high blood pressure was reported in a retrospective series of patients undergoing cerebral RT [12]. This observation was further extended in MRI analysis of newly diagnosed GBM patients, treated or not with ARBs. The volumes of peritumoural hyper T2-Fluid Attenuated Inversion Recovery (FLAIR) signal were significantly lower in patients treated with ARBs when compared with the non-ARB-treated group, suggesting that ARBs might be associated with reduced peritumoural oedema [13]. These observations were supported by studies reporting local expression of angiotensinogen and angiotensin receptors in human GBM [14,15] and reduction of angiogenesis and VEGF expression by ARBs in several tumour models [16–18], including glioma [19].

The ASTER study was thus designed as a randomised, placebo-controlled, clinical trial to assess whether or not the addition of Losartan, an ARBs that cross the blood-brain barrier [18,19], to SOC can reduce steroid requirement during RT in patients with newly diagnosed GBM.

2. Patients and methods

2.1. Trial design

ASTER was a multicentre (7 academic centres in France), prospective, double-blinded, placebo-controlled, randomised (1:1), phase III trial. The study was compliant with the Declaration of Helsinki and Good Clinical Practice guidelines. The full trial protocol can be found in Appendix 1. The trial was registered with ClinicalTrials.gov, number NCT01805453.

2.2. Patient eligibility criteria

The study was open to patients aged 18 years and older, with newly diagnosed GBM (World Health Organisation grade IV GBM) and with a Karnofsky performance status (KPS) score of 50% or higher. Patients had to be eligible for standard RT with concomitant TMZ [2], with RT starting within 10 weeks after surgery.

Exclusion criteria were the absence of residual tumour left on the screening MRI (complete surgical resection), any prior treatment of GBM including any local therapy during surgical resection, any treatment for high blood pressure (whatever the therapeutic class of drugs), systolic blood pressure <110 mmHg, relative or definite contraindication to Losartan, pregnant or breast feeding women and MRI contraindication.

Before being included in the study, patients signed an informed consent form, which was approved by the institutional review board.

2.3. Treatment and drug administration

After biopsy or partial surgical resection, patients with histologically confirmed GBM and planned for SOC with RT and TMZ were randomised between Losartan or placebo. Randomisation was stratified by centre and by type of intervention (biopsy versus surgical resection). The treatment (Losartan/placebo) was started 7–10 days before the beginning of concomitant RT and TMZ and was maintained during the total study duration.

A progressive escalation in Losartan 50mg/placebo treatment was done, starting with 1 tablet/day during the first 7–10 days and then, twice a day (100 mg/day) until halting for any reason (end of the study period, unacceptable toxicity, withdrawal of patient consent or death). The treatment by Losartan/placebo was stopped 1 month after completion of RT. Treatment with any other approved or investigational chemotherapeutic agents was not allowed until tumour recurrence. If a patient experienced tumour progression, second-line chemotherapy was offered per local practice.

2.4. Patient surveillance and follow-up

A complete physical examination with collection of laboratory parameters was performed within 1 week before treatment initiation. At baseline, end of RT and each follow-up visits, neurological and general examinations, complete blood count, serum biochemistry, liver function tests and steroid dosage adaptation were performed.

The KPS was assessed by the treating clinician at baseline, at the end of RT and at each follow-up visits. MRIs were performed at the end of RT, 1 month after completion of RT and then every other month until radiological progression.

Toxicity was graded according to the NCI expanded common toxicity criteria (NCI CTC 3.0). Radiologic progressions were assessed by the local investigators, following RANO criteria.

2.5. Steroids dosage management

The steroid dosage (always converted to equivalent prednisone) was assessed by the clinician on charge of the patient on a weekly basis. The corticosteroids had to be prescribed at the minimal dose required to control the mass effect or symptoms of cerebral oedema. The indicative recommendation was to taper steroids by 2–10 mg/day every week (eq prednisone) if the patient was clinically stable. In case of clinical worsening, the recommendation was to increase dosage by 30 mg/day (eq prednisone) if the patient experienced headaches and nausea/vomiting and by 10–20 mg/day (eq prednisone) in other cases.

2.6. Peritumoural oedema assessment

Evolution of cerebral oedema on MRI (based on MRI at the beginning, at the end and 1 month after the end of RT), by the extraction of [T2-FLAIR volume] – [gadolinium-enhanced volume] from MRI images, was carried out retrospectively by two investigators. The T2-FLAIR and T1 gadolinium-enhanced volumes were calculated from MRI using the Philips' Pinnacle treatment planning system (TPS) with the Pinnacle version P16.02 (C. L-P; AF.C.).

2.7. MGMT methylation status

The MGMT status of GBM patients was determined using pyrosequencing (PSQ). A 10 µm FFPE section of tumoural tissue with histologically estimated tumour cell content above 50% was first processed with the EpiTect Fast FFPE Bisulfite Kit (Qiagen, France), following manufacturer's recommendation. PSQ was then performed on this bisulfite-treated DNA as

previously described [20,21] using the PyroMark Q24 MGMT kit on a PyroMark Q24 system (Qiagen, France). All assays were performed in duplicate, and each sample was averaged together. The average percentage of the five CpGs tested was considered, and a cut-off of 8% was used to classify the patients [20].

2.8. IDH1 R132H expression status

Immunohistochemistry staining for IDH1 R132H mutant protein was carried out on 4- μ m paraffin sections of formalin-fixed tumour samples using mouse monoclonal anti-R132H-IDH1 antibody culture supernatant, as previously described [22].

2.9. Statistical considerations and outcomes

The primary objective was the median steroid dosage required to control brain oedema on the last day of RT in each arm. The secondary outcomes were steroids dosage 1 month after the end of RT, assessment of cerebral oedema on MRI (MRI at the beginning, at the end and 1 month after the end of RT), tolerance (NCI-CTCAE v3.0), blood pressure, HbA1C, glycaemia, body weight and side-effects of steroids, progression-free survival (PFS) and OS.

According to the database of our previous patients corresponding to those to be included in the trial [12], the standard deviation of the dose (corresponding to our primary criterion) was around 46 mg/day (eq prednisone), thus a sample size of $N = 39$ patients/group will allow a 80% power to detect a difference between groups around 30 mg/day (eq prednisone) corresponding to an effect size $(\Delta/\delta) = 0.65$. We considered a two-sided 5% significance level. To consider the possibility of one patient lost for follow-up in each arm, we plan to include 40 patients in each arm.

The intent-to-treat (ITT) population was limited to patients that received at least one day of concomitant treatment. The ITT analysis on the primary end-point as well as quantitative secondary criteria were carried out by mixed model of analysis of variance (random factor patient, fixed factor treatment). A log transformation was used when distribution was not Gaussian. Incidence of steroids side-effects was analysed by Chi-square or Fisher's exact probability test. Tolerance (NCI-CTCAE v3.0) at the beginning, at the end and 1 month after the end of RT were compared by Mann-Whitney test. All tests will be two-sided with a significance level at 5%.

3. Results

3.1. Patient characteristics

Eighty patients (80) were included and randomised between March 2013 and August 2014. Five (5) patients, who did not even start RT because of fast clinical

deterioration ($n = 4$) or treatment with placebo/Losartan because of low blood pressure ($n = 1$), were not considered in the ITT analysis (Fig. 1). The characteristics of the 75 remaining patients are shown in Table 1. The two groups were well balanced at baseline except for the MGMT status (Table 1).

The compliance to the treatment was good in 68/75 patients (91%). Two (2) patients had a reduced RT regimen (3 weeks) due to poor clinical conditions; three patients died before completion of RT; one patient stopped losartan/placebo after 4 weeks due to low blood pressure and one patient stopped Losartan/placebo after 6 days because of a Lyell syndrome, probably related to lamotrigine.

3.2. Steroids and performance status (KPS)

Within the ITT population, the steroid dosage required to control brain oedema either on the last day of RT (primary end-point) or 1 month after completion of RT was not impacted by Losartan (Table 2). At the time of the enrolment, nine patients (25%) were free of steroids in Losartan arm and seven patients (19%) in placebo arm. When steroids were required, patients were treated with methylprednisolone, prednisolone or prednisone (dexamethasone was not given to any patients).

Similarly, the performance status (KPS), either on the last day of RT or one month after completion of RT, was not different between both arms (Table 2).

3.3. Peritumoural oedema

In 60 patients, the MRIs were available and centrally reviewed. Two (2) of these patients died before completion of RT, leaving 58 patients (32 in the placebo arm; 26 in the Losartan arm) for this analysis. No reduction of peritumoural oedema was seen (Fig. 2).

3.4. Tolerance

At the end of RT, mean blood pressure decrease from baseline was significantly higher in Losartan arm compared with placebo; sitting systolic blood pressure (-9.9 mmHg versus -1.3 mmHg, $p = 0.009$), sitting diastolic blood pressure (-5.5 mmHg versus -0.9 mmHg, $p = 0.036$) in Losartan arm and placebo arm, respectively.

The incidence of adverse events was similar in both arms (84.2% in control arm versus 83.8% in Losartan arm). In addition, 27 patients reported at least one serious adverse event (SAE), 17 (44.7%) in control arm versus 10 (27.0%) in Losartan arm ($p = 0.11$). Among them, six SAEs were considered as possibly related to the protocol: one in the Losartan arm (grade 4 thrombopenia) and five (2 grade 4 thrombopenia, 1 hypertension, 1 headaches and 1 venous thrombosis) in the control arm. In addition, five (5) SAEs were considered

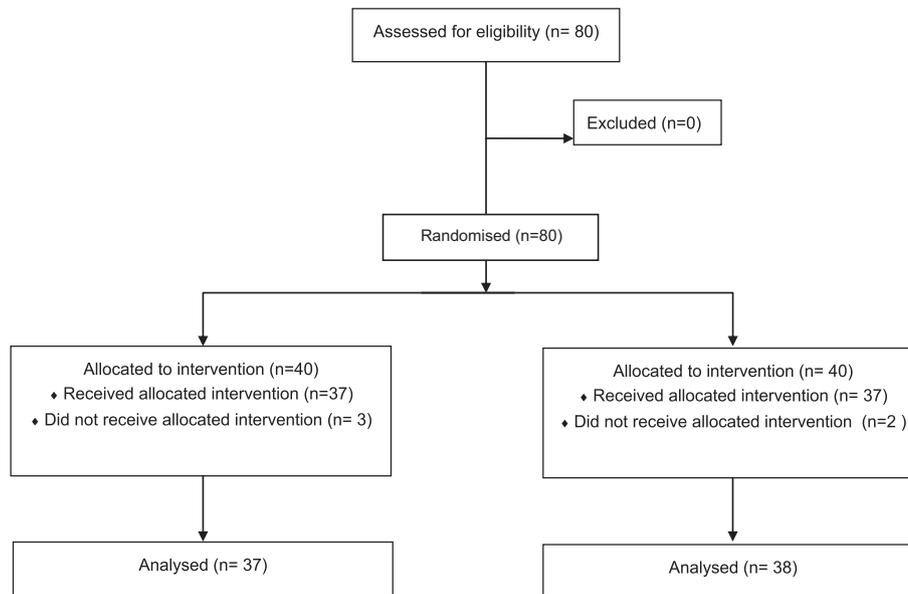


Fig. 1. Flow chart.

as possibly related to the treatment received: one in the Losartan arm (grade 4 thrombopenia) and four (1 grade 4 thrombopenia, 1 fever and 2 grade 4 alanine aminotransferase increased) in the control arm.

3.5. Survival and patient follow-up

At time of analysis, 64 patients had died, and 70 had progressed after the initial treatment. When disease progression occurred, further treatments were left at the

investigator's choice. A few patients underwent a second surgery ($n = 4$) or a second course of RT ($n = 2$), but most of them had one or several lines of chemotherapy. Chemotherapy consisted of TMZ ($n = 10$), nitrosoureas ($n = 31$), platinum-based chemotherapy ($n = 10$), bevacizumab ($n = 38$) and metronomic cyclophosphamide ($n = 2$).

Median OS was 14.2 months [10,1–21,3] in the Losartan arm and 16.7 months [11,4–21,5] in the placebo arm (hazard ratio [HR] = 1.14 [0.70–1.87]) (Fig. 3). The median PFS was 6.6 months [5,1–9,9] in the Losartan arm and 9.5 months [5,4–13,3] in the placebo arm (log rank test, $p = 0,3879$).

MGMT methylation status was obtained in 67 patients. Thirty-three (33) patients (49%) were MGMT-methylated, and 34 (51%) were not. MGMT methylation was significantly associated with OS: median OS was 23.8 months [19,4–32,8] for methylated patients and 9.5 months [6–13,3] for unmethylated patients (HR = 0.28 [0.16–0.49], p -value < 0,0001). Treatment by Losartan had no impact on survival within each MGMT status subgroups of patients.

4. Discussion

Management of cerebral oedema for GBM patients remains a major challenge in neuro-oncology. Chronic steroid administration reduces vasogenic cerebral oedema but results in many adverse effects that impairs quality of life, underscoring the need for corticoid-sparing drugs [6,7,23]. Because several studies have suggested that ARBs might reduce VEGF secretion [24,25] and vasogenic peritumoural oedema in GBM [12,13,24], this randomised trial was designed to assess the impact of ARB (Losartan) in patients with newly

Table 1
Patients characteristics.

	Treatment group	
	Losartan arm (n= 37)	Placebo arm (n= 38)
Age		
Median (Q1–Q3)	58.0 (50.0–64.0)	59.0 (52.0–66.0)
Gender		
Male/female, n (%)	21 (56.8%)/16 (43.2%)	23 (60.5%)/15 (39.5%)
Surgery, n (%)		
Resection	21 (56.8%)	21 (55.3%)
Biopsy	16 (43.2%)	17 (44.7%)
Histology, n (%)		
Glioblastoma	37 (100%)	38 (100%)
MGMT methylation status, n (%)		
Methylated patients	12 (32.4%)	21 (55.3%)
Unmethylated patients	21 (56.8%)	13 (34.2%)
Missing data	4 (10.8%)	4 (10.5%)
IDH1 R132H mutation status, n (%)		
IDH1 mutated patients	1 (2.7%)	1 (2.6%)
Missing data	1 (2.7%)	0
Karnofsky performance score		
Median (Q1–Q3)	80.0 (70.0–90.0)	80.0 (70.0–90.0)
Steroid dosage at inclusion, (mg/day) (eq prednisone)		
Median (Q1–Q3)	40.0 (0.0–60.0)	40.0 (20.0–60.0)

Table 2

Steroid dosage required to control brain oedema and the performance status (KPS) at inclusions, on the last day of RT (radiotherapy) and 1month after completion of RT.

	Treatment group		
	Losartan arm (n = 37)	Placebo arm (n = 38)	
Steroid dosage (eq prednisone in mg/day)			
At inclusion, Median (Q1–Q3)	40 (0–60)	40 (20–60)	
On the last day of RT, median (Q1–Q3)	30 (10–70)	30 (5–40)	p = 0.49
1-month post RT, median (Q1–Q3)	25 (5–70)	20 (10–50)	p = 0.79
Karnofsky performance score (KPS)			
At inclusion, median (Q1–Q3)	80% (70–90)	80% (70–90)	
On the last day of RT, median (Q1–Q3)	70% (60–90)	80% (70–90)	p = 0.31
1-month post RT, median (Q1–Q3)	80% (60–90)	80% (70–90)	p = 0.20

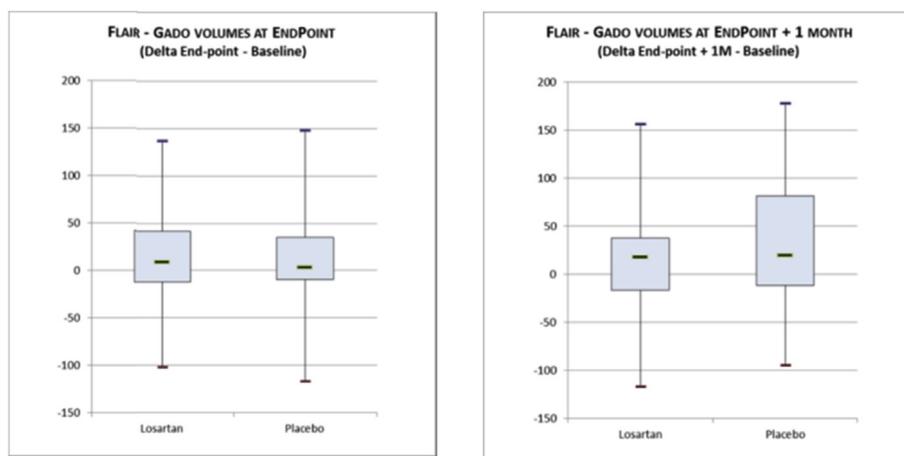


Fig. 2. Estimation of the peritumoural oedema [T2-FLAIR volume] – [gadolinium-enhanced volume] variations from baseline, (median [Q1-Q3] min max in cm3).

T2-FLAIR, T2-Fluid Attenuated Inversion Recovery.

diagnosed GBM. The steroid dosage required to control brain oedema on the last day of RT in Losartan arm was the primary objective of our trial. No significant differences were observed between the study groups. This end-point was probably not an optimal one, because tapering steroids in a given patient closely depends on subjective and repeated assessments by the physicians, who might leave the steroid dosage unchanged during RT. Studies of peritumoural oedema on MRI might be more accurate, although modifications of steroid dosages over time and inherent difficulty to measure oedema on MRI raise other issues. On MRI, GBM are classically described as heterogeneously contrast enhancement surrounded by peritumoural hyper T2-FLAIR signal that reflects a combination of oedema and tumour infiltration. In this trial, the evolution of cerebral oedema on MRI at the end and 1 month after the end of RT was arbitrary evaluated by the formula [T2-FLAIR volume] – [gadolinium-enhanced volume]. No significant reduction of peritumoural oedema was seen in patients taking ARBs, one month after RT. These disappointing results are in sharp contrast with previous studies conducted in series of GBM patients showing

reductions of both steroid dosage and peritumoural FLAIR images on MRI [12,13]. These discrepancies might be explained by the retrospective nature of these studies and/or association with other drugs taken by ARBs-treated patients in these series. However, we cannot exclude that the time exposure to Losartan in this trial (<3 months) was too short to mediate significant biological effects. A limited time exposure to Losartan/placebo was selected for this trial because the primary end-point was focused on steroid requirement during the period of RT.

Over the recent years, a considerable interest was raised about the potential antitumour properties of angiotensin-II inhibitors. The scientific basis behind this interest relies on the fact that angiotensin II/angiotensin II receptor type 1 (AngII/AT1R) signalling promotes VEGF-mediated angiogenesis [26] and that tumour growth is inhibited by angiotensin-II inhibitors in several tumour models [16–18]. In addition, Losartan can improve tumour perfusion, hence exposure to chemotherapy, through vascular decompression, doing so by reducing matrix components (CAFs, hyaluronan and collagen) synthesis, responsible for high intratumoural pressure [27]. Finally, several

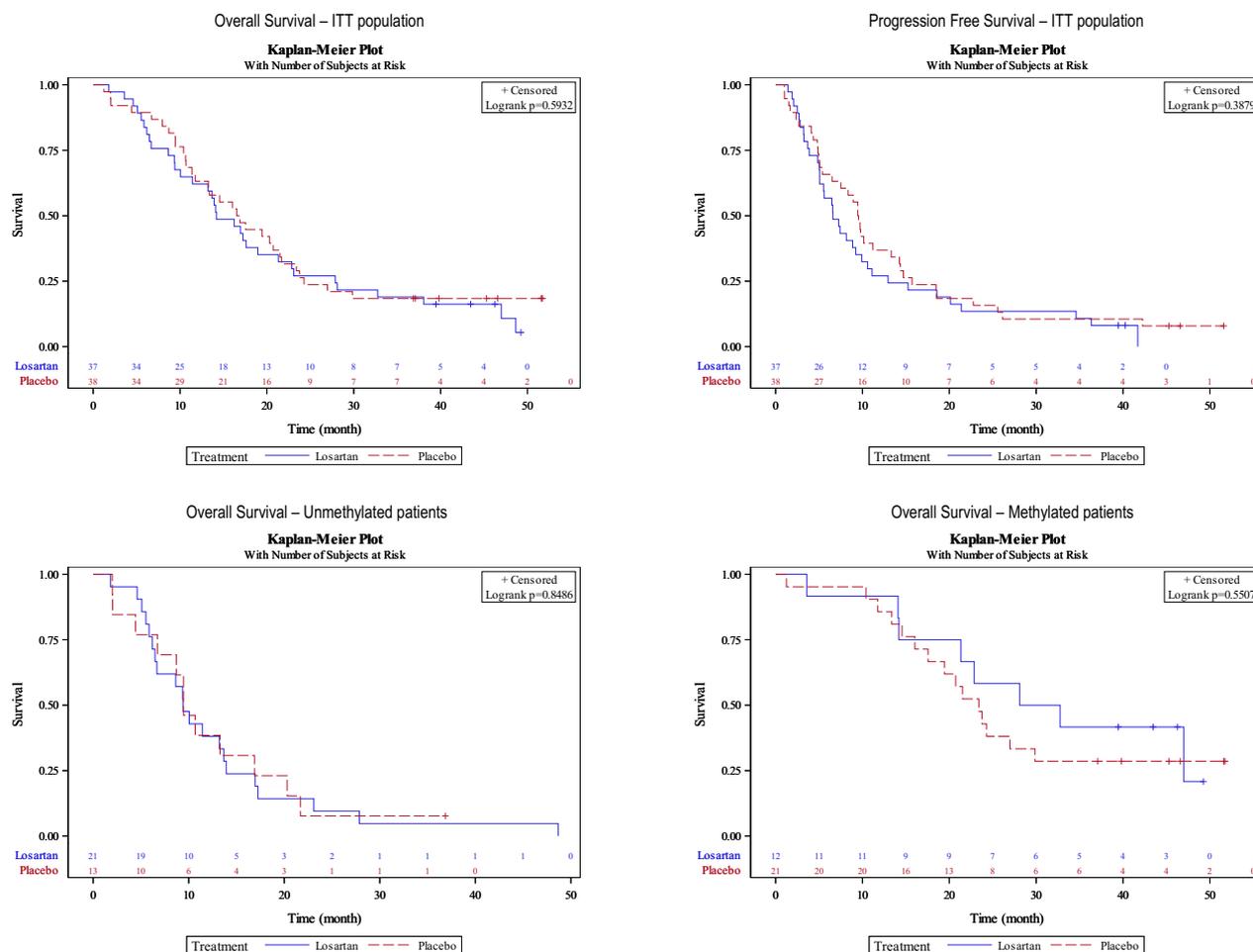


Fig. 3. Kaplan-Meier survival curve of patients treated within the protocol. Overall survival (upper left) and progression-free survival (upper right) in the ITT population. Overall survival in MGMT-unmethylated patients (lower left) and in methylated MGMT patients (lower right).

retrospective studies have shown improved survival in patients taking angiotensin system inhibitors, in several cancers such as pancreatic cancer [28], lung cancer [29,30], renal cancer [31,32] and even GBMs [33,34]. One recent retrospective analysis did not support this hypothesis [35]. In our prospective randomised trial, no significant difference in survival between Losartan- and placebo-treated patients was seen. Yet, no definite conclusion can be drawn because patients were exposed to Losartan for less than 3 months, over a 15-month median survival time. In addition, even though the patients were randomly assigned, the treatment groups were misbalanced on MGMT status (36% versus 61% of methylated MGMT in patients with available MGMT status in the Losartan- and placebo-treated groups, respectively). Tumour expression of MGMT is a major prognosis factor in GBM patients [36], and in our trial, MGMT methylation was indeed associated with median OS (23.8 versus 9.5 months for methylated and unmethylated MGMT status, respectively, $p < 0.0001$).

In conclusion, despite the documented role of the AngII/ATR1 axis in VEGF-mediated angiogenesis,

angiotensin-II inhibitors did not show any impact on steroid requirements during RT in this trial.

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Conflict of interest statement

O.C. is consultant for Hoffman - La Roche, Ipsen and Abbvie. E.L.R. has received research grants from Mundipharma and Amgen and honoraria for lectures or advisory boards from Abbvie, Daiichi-Sankyo, Mundipharma and Novartis. F.D. has received honoraria from Hoffman-la Roche, UCB Pharma, GSK, BMS and Abbvie. Other authors have nothing to declare.

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