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

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Title: Angiotensin II Receptor Blockers, steroids and radiotherapy in glioblastoma - A randomized multicenter trial (ASTER Trial). An ANOCEF Study.

Running title: ARB s (Losartan) in de novo glioblastoma.

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Abstract

Background

Glioblastomas (GBM), induce a peritumoral vasogenic edema impairing functional status and quality of life. Steroids reduce brain tumor-related edema, but are associated with numerous side effects. It was reported in a retrospective series that angiotensin receptor blockers might be associated with reduced peritumoral edema. The ASTER study is a randomized, 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 randomized 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 edema 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 edema on MRI, 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 edema 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 OS 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](https://clinicaltrials.gov).

Key words: Glioblastoma (GBM), Angiotensin receptor blockers (ARBs), Losartan, steroids, peritumoral edema.

INTRODUCTION

Glioblastoma (GBM) is the most common malignant primary brain tumor 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 of about 15 months [2]. The tumor-treating fields device represents an additional treatment option for glioblastoma [3].

Malignant brain tumor patients develop peritumoral vasogenic edema, which further increases neurological deficits and intracranial pressure [4]. Steroids reduce brain tumor-related edema 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 can also become life-threatening [6-7]. Because of these side effects, steroid-sparing drugs represent an unmet medical need. Peritumoral edema 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, can be associated with significant side effects and approval in this clinical setting is lacking [8-9]. Corticorelin acetate, a synthetic analog of human corticotropin-releasing factor, reduced dexamethasone requirement when compared to control-treated patients but this reduction did not reach statistical significance [10]. In a randomized study, although *Boswellia serrata* slightly reduced cerebral edema on 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 radiotherapy [12]. This observation was further extended in MRI analysis of newly diagnosed GBM patients, treated or not with ARBs. The volumes of peritumoral hyper T2-Fluid Attenuated Inversion Recovery (FLAIR) signal were significantly lower in patients treated with ARBs when compared to the non ARB-treated group, suggesting that ARBs might be associated with reduced peritumoral edema [13]. These observations were supported by studies reporting local expression of angiotensinogen and angiotensin receptors in human glioblastoma [14-15], and reduction of angiogenesis and VEGF expression by ARBs in several tumor models [16-18], including glioma [19].

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

PATIENTS AND METHODS

Trial design

ASTER was a multi-center (7 academic centers in France), prospective, double-blinded, placebo-controlled, randomized (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.

Patient Eligibility criteria

The study was open to patients aged 18 years and older, with newly diagnosed GBM (World Health Organization (WHO) 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 radiotherapy starting within 10 weeks after surgery.

Exclusion criteria were the absence of residual tumor left on the screening MRI (complete surgical resection), any prior treatment of glioblastoma 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 contra-indication to Losartan, pregnant or breast feeding women and MRI contra-indication.

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

Treatment and drug administration

After biopsy or partial surgical resection, patients with histologically confirmed glioblastoma and planned for standard of care (SOC) with RT and TMZ were randomized between Losartan or placebo. Randomization was stratified by center and by type of intervention (biopsy vs 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, then, twice a day (100mg/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 one month after completion of RT. Treatment with any other approved or investigational chemotherapeutic agents was not allowed until tumor recurrence. If a patient experienced tumor progression, second-line chemotherapy was offered per local practice.

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. Magnetic resonance imaging (MRI) were performed at the end of RT, one 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.

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 edema. The indicative recommendation was to taper steroids by 2-10mg/day every week (eq prednisone) if the patient was clinically stable. In case of clinical worsening, the recommendation was to increase dosage by 30mg/day (eq prednisone) if the patient experienced headaches and nausea/vomiting, and by 10-20mg/day (eq prednisone) in other cases.

Peritumoral edema assessment

Evolution of cerebral edema 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 done retrospectively by 2 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.).

MGMT methylation status

The MGMT status of glioblastoma patients was determined using pyrosequencing (PSQ). A 10 µm FFPE section of tumoral tissue with histologically estimated tumor 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 5 CpGs tested was considered and a cut-off of 8% was used to classify the patients [20].

IDH1R132H expression status

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

Statistical considerations and outcomes

The primary objective was the median steroid dosage required to control brain edema on the last day of radiotherapy in each arm. The secondary outcomes were: steroids dosage 1 month after the end of RT, assessment of cerebral edema 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, glycemia, 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 endpoint as well as quantitative secondary criteria were carried out by mixed model of ANOVA (random factor patient, fixed factor treatment). A Log transformation was used when distribution was not Gaussian. Incidence of steroids side-effects were analyzed by Chi-2 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 Man-Whitney test. All tests will be two-sided with a significance level at 5%.

RESULTS

Patient characteristics

Eighty patients (80) were included and randomized between March 2013 and August 2014. Five (5) patients, who did not even start radiotherapy because of fast clinical deterioration (n=4), or treatment with placebo/Losartan because of low blood pressure (n=1), were not considered in the intent-to treat analysis (Figure 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; 3 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.

Steroids and performance status (KPS)

Within the ITT population, the steroid dosage required to control brain edema either on the last day of radiotherapy (primary endpoint), or one month after completion of RT, was not impacted by Losartan (table 2). At the time of the enrollment, 9 patients (25%) were free of steroids in losartan arm and 7 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).

Peritumoral edema

In 60 patients, the MRI 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 peritumoral edema was seen (Figure 2).

Tolerance

At the end of radiotherapy, mean blood pressure decrease from baseline was significantly higher in Losartan arm, compared to placebo; sitting systolic blood pressure (-9,9 mmHg vs -1,3 mmHg, $p = 0,009$), sitting diastolic blood pressure (-5,5 mmHg vs -0,9 mmHg, $p = 0,036$), in Losartan arm and placebo arm respectively.

The incidence of adverse events (AE) was similar in both arms (84,2% in control arm vs 83,8% in Losartan arm). In addition, 27 patients reported at least one serious adverse event (SAE), 17 (44,7%) in control arm vs 10 (27,0%) in Losartan arm ($p = 0,11$). Among them, 6 SAEs were considered as possibly related to the protocol: 1 in the Losartan arm (grade 4 thrombopenia) and 5 (2 grade 4

thrombopenia, 1 hypertemia, 1 headaches and 1 venous thrombosis) in the control arm. In addition five (5) SAEs were considered as possibly related to the treatment received: 1 in the Losartan arm (grade 4 thrombopenia) and 4 (1 grade 4 thrombopenia, 1 fever and 2 grade 4 alanine aminotransferase increased) in the control arm.

Survival and patient follow-up

At time of analysis, 64 pts 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) 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]) (Figure 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 overall survival: median OS was 23,8 months [19,4-32,8] for methylated patients and 9,5 months [6,7-13,3] 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.

DISCUSSION

Management of cerebral edema for glioblastoma patients remains a major challenge in neuro-oncology. Chronic steroid administration reduces vasogenic cerebral edema 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 peritumoral edema in GBM [12,13,24], this randomized trial was designed to assess the impact of ARB (Losartan) in patients with newly-diagnosed GBM. The steroid dosage required to control brain edema on the last day of radiotherapy in losartan arm was the primary objective of our trial. No significant differences were observed between the study groups. This endpoint 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 radiotherapy. Studies of peritumoral edema on MRI might be more accurate, although modifications of steroid dosages over time and inherent difficulty to measure edema on MRI raise other issues. On MRI, GBM are classically described as heterogeneously contrast enhancement surrounded by peritumoral hyper T2-FLAIR signal that reflects a combination of edema and tumor infiltration. In this trial, the evolution of cerebral edema 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 peritumoral edema was seen in patients taking ARBs, one month after RT. These disappointing results are in sharp contrast with previous studies made in series of glioblastoma patients showing reductions of both steroid dosage and peritumoral 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 endpoint was focused on steroid requirement during the period of radiotherapy.

Over the recent years, a considerable interest was raised about the potential antitumor 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) signaling promotes VEGF-mediated angiogenesis [26], and that tumor growth is inhibited by angiotensin-II inhibitors in several tumor models [16 - 18]. In addition, Losartan can improve tumor perfusion, hence exposure to chemotherapy, through vascular decompression, doing so by reducing matrix components (CAFs, hyaluronan and collagen) synthesis, responsible for high intra-tumoral pressure [27]. Finally, several 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 glioblastomas [33-34]. One recent retrospective analysis did not support this hypothesis [35]. In our prospective randomized 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% vs 61% of methylated MGMT in patients with available MGMT status in the Losartan and placebo-treated groups, respectively). Tumor expression of MGMT is a major prognosis factor in GBM patients [36] and in our trial, MGMT methylation was indeed associated with median overall survival (23.8 vs 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 radiotherapy in this trial.

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Conflict of Interest Statement: OC is consultant for Hoffman - La Roche, Ipsen and Abbvie. ELR has received research grants from Mundipharma and Amgen and honoraria for lectures or advisory boards from Abbvie, Daiichi-Sankyo, Mundipharma, Novartis. FD has received honoraria from Hoffman - La Roche, UCB Pharma, GSK, BMS, Abbvie. Other authors have nothing to declare.

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TABLE CAPTIONS

Table 1: Patients characteristics.

Table 2: Steroid dosage required to control brain edema and the performance status (KPS) at inclusions, on the last day of RT and one month after completion of RT.

FIGURE CAPTIONS

Figure 1: Flow chart

Figure 2: Estimation of the peritumoral edema [T2-FLAIR volume] – [gadolinium-enhanced volume] variations from baseline, (median [Q1-Q3] min max in cm³).

Figure 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).

Patient disposition

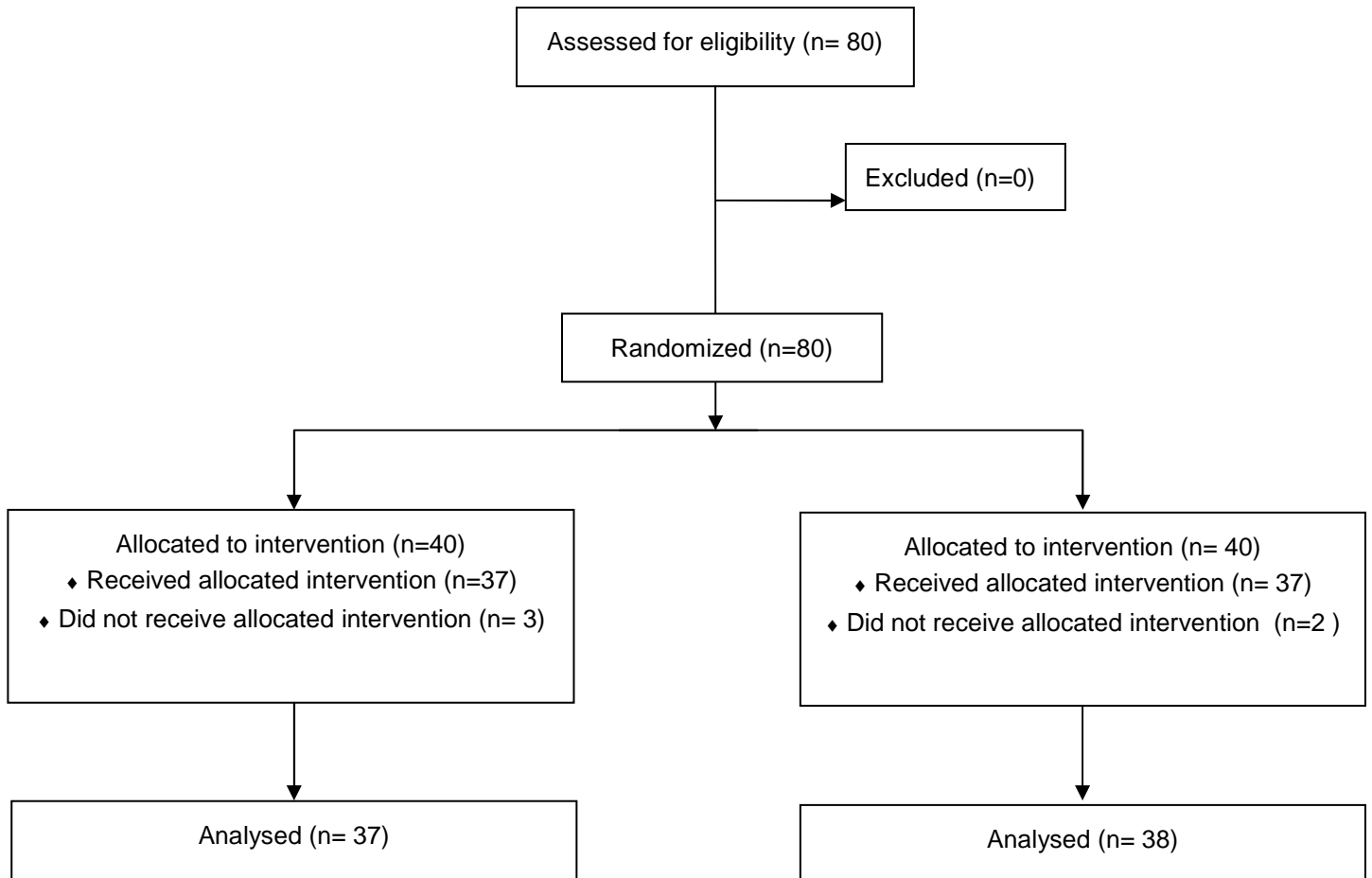


Fig 2: Estimation of the peritumoral edema [T2-FLAIR volume] – [gadolinium-enhanced volume] variations from baseline, (median [Q1-Q3] min max in cm3).

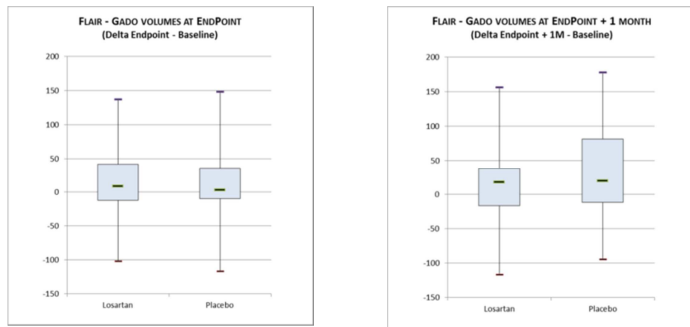


Figure 3; Kaplan Meier survival curve of patients treated within the protocol. Overall survival (upper left) and Progression free survival (upper right) in the ITT population. Overall survival in MGMT-unmethylated patients (lower left) and in methylated MGMT patients (lower right)

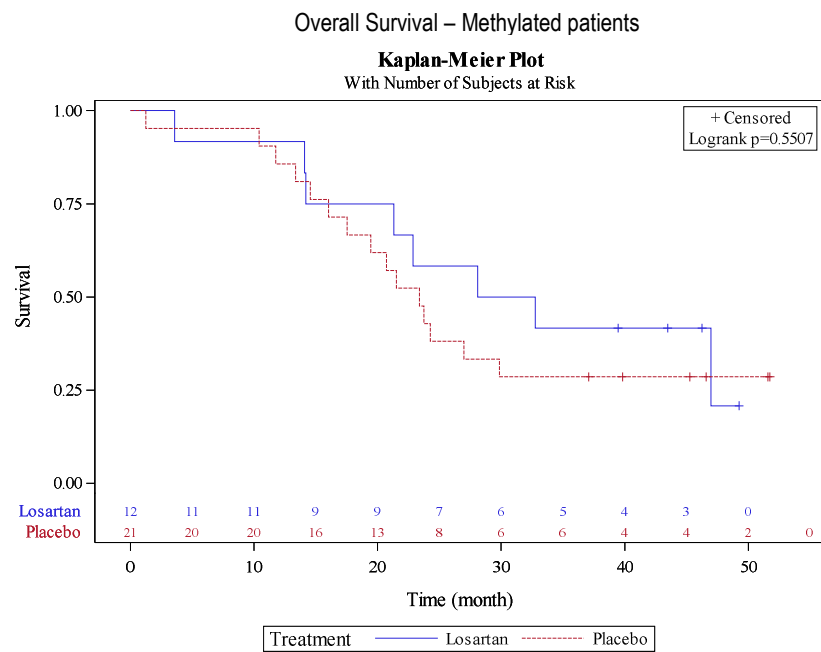
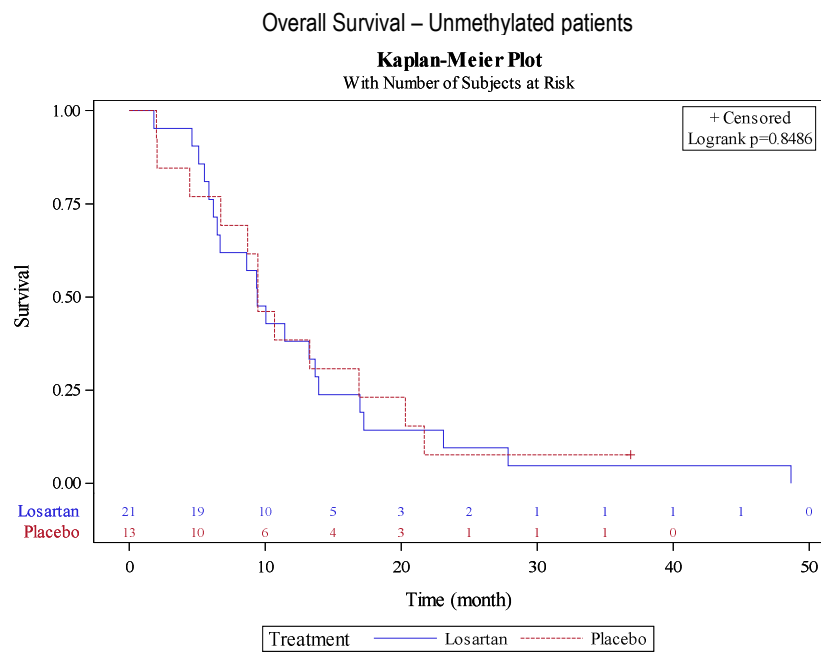
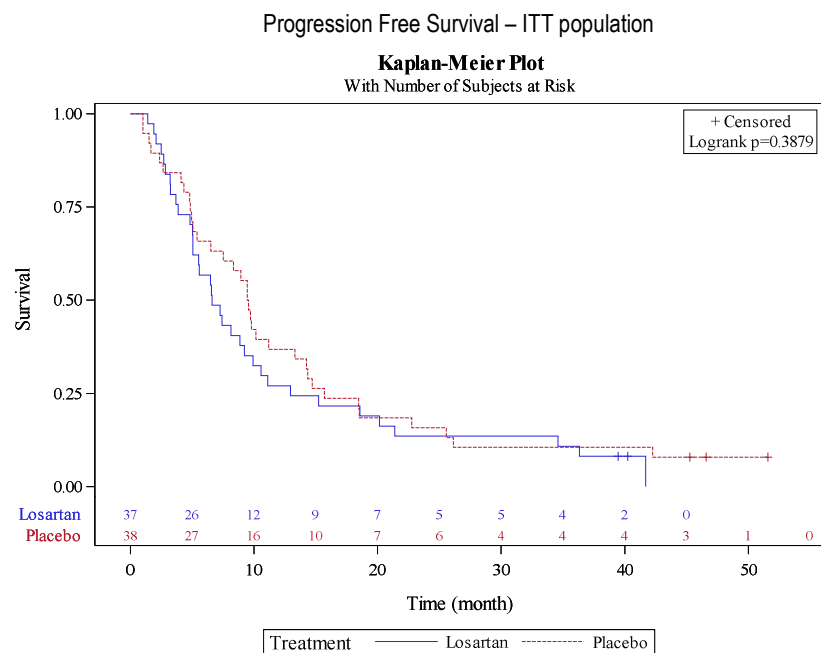
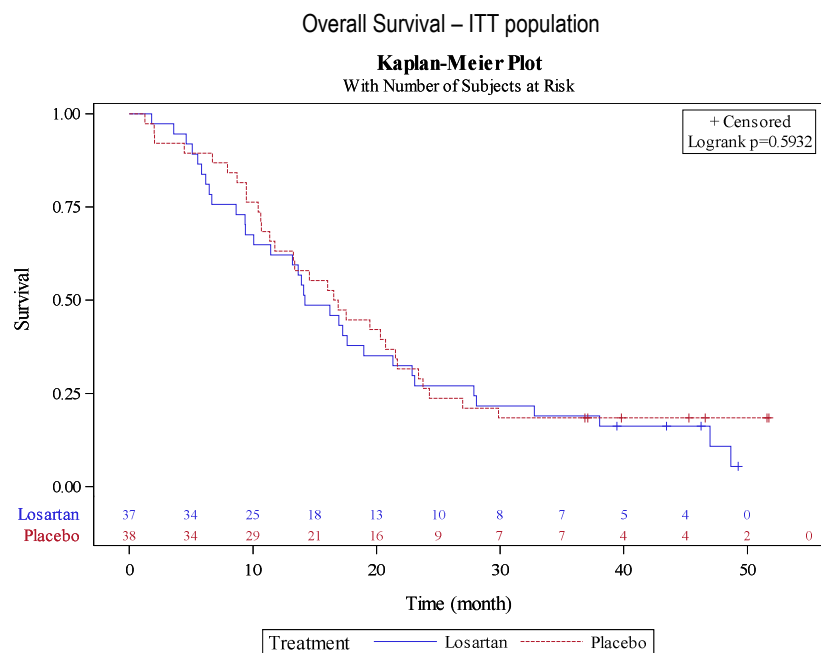


Table 1: Patients characteristics :

	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 (KPS)		
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 edema and the performance status (KPS) at inclusions, on the last day of RT and one month 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