STUPP regimen with or without lenvatinib for newly diagnosed glioblastoma with MGMT promoter methylation: A multicenter, randomized phase II clinical trial

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1. Background

Glioma refers to tumors originating from the brain's glial cells and is one of the most common and aggressive intracranial tumors in adults. The annual incidence of glioma in China is 5/100,000 to 8/100,000, characterized by high recurrence and mortality rates [1]. As the incidence of glioblastoma (GBM) increases with age and China's aging population accelerates, the absolute number of GBM cases will continue to rise, imposing a significant social burden. Currently, the Stupp regimen—maximal safe resection followed by concurrent radiotherapy plus temozolomide (TMZ) and sequential adjuvant TMZ, remains the standard treatment strategy recommended by domestic and international guidelines for newly diagnosed GBM. This regimen yields a median progression-free survival (PFS) of 6.9 months and the median overall survival (OS) of 14.6 months [2]. However, the therapeutic efficacy remains unsatisfactory, with a 5-year OS of less than 10%. The majority of patients still experience recurrence or progression within a relatively short period, and long-term survival benefits are limited. One of the critical biological features of GBM is highly active angiogenesis; tumor growth and invasion are closely related to neovascularization. Various angiogenic receptors and related factors are upregulated in GBM, promoting tumor angiogenesis and microenvironment remodeling by activating multiple signaling pathways, thereby participating in the post-treatment recurrence process. Lenvatinib is an oral multi-targeted tyrosine kinase inhibitor that simultaneously inhibits several key signaling pathways such as VEGFR and FGFR [3]. Its multi-pathway blockade is expected to inhibit the main axis of tumor angiogenesis while reducing bypass compensation and inhibiting vascular regeneration and microenvironment remodeling, thus forming the mechanistic complement to radiotherapy and chemotherapy [4-6].

Regarding molecular stratification, MGMT promoter methylation is a key biomarker for predicting the benefit of TMZ. Methylation-positive patient typically exhibit greater sensitive to TMZ and a relatively better prognosis [7]. Meanwhile, research suggests that MGMT methylation status may be related to the abnormal activation of the VEGF pathway in the tumor microenvironment; methylated tumors may exhibit stronger dependence on angiogenesis [8]. Evaluating the combined with of Lenvatinib with the standard Stupp regimen in the MGMT methylation-positive population aligns with the clinical logic of seeking further gains on an effective foundational therapy.

Based on this background, this study intends to conduct a multicenter, randomized

controlled Phase II trial of Lenvatinib combined with the standard Stupp regimen for newly diagnosed GBM with MGMT promoter methylation positive, systematically evaluating its efficacy and safety to provide higher-level evidence for this molecular subgroup and explore scalable additive treatment paths.

2. Objectives

To compare the efficacy and safety of Lenvatinib combined with the standard Stupp regimen versus the standard Stupp regimen alone in the treatment of newly diagnosed glioblastoma with MGMT promoter methylation positive.

3. Rationale

Temozolomide (TMZ) is an oral alkylating agent that effectively crosses the blood-brain barrier. It exerts anti-tumor effects by alkylating the O6 position of guanine in DNA, thereby affecting DNA replication, and is currently a first-line drug for high-grade gliomas [9]. In 2005, a multi-center, randomized controlled Phase III clinical study published in the New England Journal of Medicine confirmed that TMZ chemotherapy combined with radiotherapy significantly improved OS and PFS compared to radiotherapy alone in newly diagnosed GBM [2]. Consequently, TMZ combined with radiotherapy is recommended as a Level I first-line treatment for newly diagnosed high-grade gliomas by the National Comprehensive Cancer Network (NCCN) guidelines. Although the short-term efficacy of TMZ for GBM is good, its long-term efficacy is poor. Resistance to TMZ chemotherapy is one of the factors leading to treatment failure in glioma. Current research indicates that various mechanisms, including DNA repair and resistant mutations, participate in the formation of TMZ resistance [10]. Some combined therapies, including nitrosoureas [11] and anti-angiogenic drugs [12], have been proven to synergistically enhance anti-tumor effects with TMZ, significantly extending survival in GBM patients. However, combined treatments often bring increased toxicity. A study published in JCO in 2006 showed that postoperative radiotherapy combined with TMZ + lomustine for newly diagnosed GBM resulted in a median OS of 34.3 months, significantly better than historical data. MGMT promoter-methylated patients had a significant PFS benefit (19 months vs. 6 months), but the rate of grade 3-4 hematological toxicity in the combination regimen reached 42% [13]. Therefore, finding a high-efficiency, low-toxicity combined treatment strategy is one of the research directions for improving GBM treatment.

In terms of molecular stratification, MGMT promoter methylation is a key biomarker for predicting the benefits of TMZ [7,14]. MGMT methylation reduces the expression of MGMT repair enzymes, making tumor cells more sensitive to O6-methylguanine damage mediated by TMZ [7,15]. Classic studies based on Stupp trial samples show that MGMT-methylated patients obtain clear survival benefits from TMZ, while unmethylated patients see significantly reduced benefits [7]. Based on this clinical fact, conducting "additive therapy on the basis of Stupp" in MGMT-methylated populations is more logical: it allows for further gains on an established effective treatment and reduces biological heterogeneity, improving the detection of trial effects and the interpretability of conclusions, thereby increasing the probability of success in Phase III studies and clinical guideline transformation value.

However, even in the MGMT-methylated subgroup, relying solely on intensified cytotoxic chemotherapy or new devices has limitations. First, Tumor-Treating Fields (TTFields) is one of the few strategies showing clear additive benefits in randomized trials; the EF-14 study showed TTFields and TMZ significantly improved PFS (6.7 vs. 4.0 months, HR 0.63) and OS (20.9 vs. 16.0 months, HR 0.63) over TMZ alone [16]. However, TTFields requires long-term continuous wear and its efficacy is highly dependent on adherence, which—combined with cost and accessibility issues—limits its widespread promotion. Second, intensified chemotherapy faces toxicity bottlenecks; for example, the CeTeG/NOA-09 study showed that lomustine (CCNU) combined with TMZ significantly improved OS in MGMT-methylated newly diagnosed GBM from 31.4 to 48.1 months compared to standard TMZ [11], but resulted in higher grade 3-4 hematological toxicity, limiting dose intensity and adherence. Thus, there is an urgent clinical need to explore additive strategies that balance efficacy with long-term feasibility, ensuring controllable toxicity and better compliance.

From a tumor biology perspective, a core feature of GBM is high angiogenesis and microenvironment dependence. Randomized controlled studies suggest anti-angiogenic therapy has potential for disease control. A Phase III study in the New England Journal showed bevacizumab combined with chemoradiotherapy extended median PFS from 6.2 to 10.6 months, but OS did not improve (16.7 vs. 16.8 months) [17]. The RTOG0825 study similarly observed a PFS extension (7.3 to 10.7 months) without OS benefit (16.1 vs. 15.7 months) [18]. These results indicate that while the angiogenesis pathway is an important target, single blockade of VEGF-A is insufficient for sustainable OS benefit. Mechanisms suggest that after anti-VEGF treatment, tumors undergo compensatory activation via bypass signals like FGF/FGFR or Ang/Tie,

alongside adaptive microenvironment remodeling, leading to resistance [19]. Therefore, to achieve more durable gains, it is necessary to inhibit the VEGF axis while also inhibiting bypasses like FGF to reduce compensatory angiogenesis and microenvironment "rebound".

Preclinical studies have suggested that multi-target inhibition of VEGFR can suppress vascular regeneration and compensatory bypass mechanisms while improving the microenvironment, thereby enhancing the efficacy of radiotherapy and chemotherapy [20,21]. Furthermore, MGMT methylation can impair DNA repair capabilities, making it difficult to repair DNA damage induced by radiotherapy and TMZ, thereby enhancing tumor sensitivity to these treatments [22]. Additionally, the microenvironmental remodeling caused by radiotherapy provides a favorable biological basis for the synergistic effects of anti-angiogenic therapies [23]. Consistent with this hypothesis, recent clinical evidence suggests that among patients with MGMT promoter methylation, anlotinib, an anti-angiogenesis drug, achieved a significant reduction in the risk of death compared with placebo (HR=0.31, p=0.0093) [24]. Lenvatinib is another oral multi-target receptor tyrosine kinase inhibitor that simultaneously inhibits VEGFR1-3 and FGFR1-4, covering PDGFRα, KIT, RET, and other pathways related to angiogenesis and microenvironment remodeling [3]. Compared to single VEGF blockade, Lenvatinib has the potential to inhibit both VEGF-driven angiogenesis and FGF-mediated bypass compensation [19]. Preclinical studies (including patient-derived xenograft models) indicate Lenvatinib can reduce microvessel density and affect pericyte coverage, thereby inhibiting tumor angiogenesis and vascular dysfunction [3,25]. In GBM, Lenvatinib may also improve abnormal vascular permeability, enhancing radiotherapy-related oxygenation and drug delivery, thus forming a mechanistic complement to radiotherapy and chemotherapy [4-6].

Clinically, Lenvatinib has been studied in recurrent GBM, showing pharmacodynamic effects on tumor vascular function. In a single-arm Phase II study for recurrent GBM progressing after bevacizumab, early changes in imaging perfusion parameters were observed, with a 6-month PFS rate of 8.3%, median PFS of 1.9 months, and median OS of 4.11 months [26]. In the LEAP-005 study's recurrent GBM cohort, Lenvatinib plus pembrolizumab showed clear anti-tumor activity (ORR 20%, median PFS 3.0 months, median OS 8.6 months), with grade ≥ 3 adverse events at 41%, considered manageable [27]. These results provide a basis for moving Lenvatinib to the front-line standard treatment platform. However, current evidence for lenvatinib in the field of GBM remains limited, and there is lack of prospective randomized controlled studies conducted on newly diagnosed GBM patients based on the standard Stupp

regimen to systematically validate its survival benefits. Based on the aforementioned mechanistic insights and previous clinical clues, this study aims to conduct a multicenter, randomized, controlled phase II clinical trial in newly diagnosed, MGMT promoter methylation-positive GBM patients to explore efficacy and safety, providing critical evidence for subsequent large-scale studies in this molecular subgroup.

4. Study Design

4.1 Study Type

This is a prospective, multicenter, randomized controlled Phase II clinical study designed to compare the efficacy of Lenvatinib plus TMZ and radiotherapy versus TMZ and radiotherapy alone in MGMT promoter methylation-positive glioblastoma, with PFS as the primary endpoint. The study aims to explore efficacy and assess safety, providing a basis for subsequent phase III studies. Participants are divided into a control group and an experimental group, with the control group receiving TMZ chemotherapy combined with radiotherapy, while the experimental group receives lenvatinib and TMZ combined with radiotherapy.

4.2 Required Sample Size

The primary efficacy endpoint is assessed PFS. Based on the Stupp trial, the expected median PFS for the control group is 10 months. Assuming the experimental group median PFS is 18 months, with $\alpha = 0.05$ (two-sided), power (1-β) of 80%, a 1:1 allocation ratio, and an 18-month enrollment/18-month follow-up period, the log-rank test was used. Using NCSS PASS 2015 software, the total number of events required is 92, and the total sample size is 124. Accounting for a 10% dropout rate, the planned sample size is 138 (69 per group).

4.3 Study Procedures

1. Subject Enrollment: Subjects sign informed consent, undergo screening, and those meet all inclusion and no exclusion criteria are enrolled.

(1) Record personal information and medical history: enrollment number, gender, age at diagnosis, pathology, smoking/alcohol history, family history, height, weight, and contact info.

(2) Record physical exam and imaging: KPS, neurological exam, cranial nerve exam, pre- and post-operative MRI, and molecular testing results.

2. Treatment:

(1) Radiotherapy: Starts 2–6 weeks post-op; total dose 60 Gy (2.0 Gy/fraction, 30 fractions)

over 6–7 weeks.

(2) Chemotherapy:

1) TMZ Group: During RT, TMZ 75 mg/m² po QD; 4 weeks after RT, 6 cycles of TMZ (150–200 mg/m² po D1–D5, Q4W) maintenance.

2) Lenvatinib-TMZ Group: During RT, TMZ 75 mg/m² po QD and Lenvatinib 20 mg po QD; 4 weeks after RT, 6 cycles of TMZ maintenance; Lenvatinib continues at 20 mg QD post-RT until progression or intolerable toxicity.

3. Recording during Treatment:

(1) Concurrent phase: Record drug timing, dose, cycles, general condition, adverse reactions, weekly labs (CBC, biochemistry, coagulation), and MRI.

(2) Maintenance phase: Record drug timing, dose, cycles, general condition, and adverse reactions; labs checked before each cycle.

(3) Suspension/Termination: Note reasons, treatment for adverse events, and duration for any pause due to severe toxicity.

5. Study Content

5.1 Inclusion Criteria

(1) Newly diagnosed GBM confirmed by post-op pathology/biopsy, MGMT promoter methylation positive, no prior RT or chemo.

(2) Surgery/biopsy ≤ 21 days before enrollment.

(3) Age 18–75 years any gender.

(4) KPS ≥ 70.

(5) Organ function (no blood components or growth factors within 14 days):

a. ANC ≥ 1.5×10^9 /L; PLT ≥ 100×10^9 /L; Hb ≥ 90 g/L.

b. Total bilirubin ≤ 1.5 × ULN.

c. ALT, AST ≤ 3 × ULN.

d. Serum creatinine ≤ 1.5 × ULN or CrCl ≥ 50 mL/min.

(6) Life expectancy ≥ 12 weeks.

(7) Stable or tapering corticosteroid dose for 14 days.

(8) Voluntary participation, signed informed consent, and good compliance.

5.2 Exclusion Criteria

(1) Allergy to Lenvatinib, TMZ, or components.

(2) Other malignancies within 5 years or concurrent, or prior anti-tumor therapy.

(3) Concurrent participation in another clinical trial (except observational).

(4) Comorbidities interfering with treatment:

a. Grade 4 non-hematological toxicity (except hair loss, nausea, vomiting).

b. Conditions interfering with oral drugs (dysphagia, chronic diarrhea, bowel obstruction).

(5) Evidence of increased intracranial pressure (midline shift > 5 mm, papilledema, vomiting, decreased consciousness).

(6) History of drug/alcohol abuse.

(7) Pregnancy or lactation.

(8) Other conditions judged by the investigator (e.g., unstable heart/kidney disease, uncontrolled diabetes, mood disorders).

5.3 Grouping

1:1 randomization to Lenvatinib-TMZ or TMZ group. Stratification: Surgery type (GTR vs. non-GTR). Centralized web-based randomization using block randomization and the Freedman/White minimization method. Treatment must start within 1 week of randomization.

6. Study Treatment/Interventions

6.1 Treatment Regimen

(1) RT: 60 Gy/30 fractions over 6–7 weeks after surgery. (2) Chemo: 1) TMZ group gets 75 mg/m² QD during RT, then 6 cycles of maintenance (150–200 mg/m² D1–D5, Q4W). 2) Lenvatinib-TMZ group adds Lenvatinib (20 mg po QD) from Day 1 of RT through maintenance until progression or intolerable toxicity.

6.2 Chemotherapeutic Agents

(1) TMZ Group Adjustments (Concurrent phase):

TMZ is administered only if the Absolute Neutrophil Count (ANC) is ≥1.5×10^9/L and the platelet count is ≥ 100×10^9/L. During the concurrent phase, the initial dose of TMZ is 75 mg/m^2 daily, starting from the first day of radiotherapy until the last day, for 7 days a week, with a maximum duration of 49 days.

Table 1: TMZ Pause/Discontinuation (Concurrent)

Toxicity	Pause Treatment	Permanently Stop
ANC	**≥ 0.5 × 10^9 /L and < 1.5 × 10^9 /L**	**< 0.5 × 10^9 /L**
PLT	**≥ 10 × 10^9 /L and < 100 × 10^9 /L**	**< 10 × 10^9 /L**
Non-heme (excl. alopecia/nausea/vomit)	**Grade 2**	**Grade 3/4**

Maintenance phase: Starts ~4 weeks post-RT. Cycle 1: 150 mg/m² D1–D5, then 23 days off. Cycle 2: Increase to 200 mg/m² if toxicities are ≤ Grade 2 and labs are stable (ANC ≥ 1.5 × 10^9/L, PLT ≥ 100 × 10^9/L); otherwise stay at 150 mg/m². No re-escalation after reduction.

TMZ-based chemotherapy dose adjustment according to toxicity (refer to Table 2 and Table 3)

Table 2: TMZ Dose Levels

Level	Dose （mg/m²/d）	Remarks
-1	**100**	**Dose reduction due to early toxicity**
0	**150**	**Dose reduction due to Cycle 1**
1	**200**	**Dose at non-toxic levels during cycles 2-6**

Table 3: TMZ Dose Reduction/Termination

Toxicity	Decrease by level 1	Permanently Stop
ANC	**< 1.0 × 10^9 /L**	**a**
PLT	**< 50 × 10^9 /L**	**a**
Non-heme (excl. alopecia/nausea/vomit)	**Grade 3**	**Grade 4**

a: Reduce if ANC < 1.0 × 10^9/L, PLT < 50 × 10^9/L, or Grade 3 non-heme toxicity. Discontinue for Grade 4 non-heme toxicity.

(2) Lenvatinib-TMZ Group Adjustments:

The treatment regimen for the lenvatinib-temozolomide group included: during radiotherapy, patients received daily oral TMZ (75 mg/m², po, QD) and lenvatinib (20 mg po qd). Six cycles of TMZ maintenance therapy (150-200 mg/m², po, D1-D5, Q4W) were initiated 4 weeks after radiotherapy completion. Lenvatinib was administered starting from day 1 of radiotherapy until tumor progression or intolerable toxicity occurred.

1) Lenvatinib: The overall safety profile of lenvatinib is manageable, with hypertension, bleeding, and proteinuria being relatively common. Dosage adjustments should be made based on clinical circumstances, following these principles: 1. Graded management approach: If non-hemorrhagic adverse events (grade 3-4) occur, treatment should be suspended until recovery to grade < 2, after which a dose reduction may be administered. If no improvement is observed within 4 weeks, permanent discontinuation is required. 2. Hemorrhage risk management: In cases of grade 2 hemorrhagic events, treatment should be paused until recovery to grade < 2 within 4 weeks, after which a dose reduction may be considered. If recurrence occurs, permanent discontinuation is mandatory. For grade ≥ 3 hemorrhagic events (e.g., hemoptysis, gastrointestinal bleeding, cerebral hemorrhage), immediate permanent discontinuation and emergency intervention are required. 3. Dose escalation protocol: If a subject is temporarily reduced to a lower dose level due to adverse events, and the investigator confirms stable safety with identified disease progression risks, a single dose escalation (returning to the previous dose

level) may be permitted. Each subject is limited to one dose escalation.

Table 4: Lenvatinib Dose Levels

Starting Dose	**Decrease by level 1**	**Decrease by level 2**	**Decrease by level 3**
20 mg	16 mg	12 mg	8 mg

2) TMZ:

Table 5: TMZ Dose in Combination

Level	Dose (mg/m²/d)	Toxicity[a]
-2	Permanently stop	ANC < 1.0×10^9/L or PLT < 25×10^9/L
-1	50	ANC < 1.5×10^9/L or PLT < 50×10^9/L
0	75	Starting dose
1	100	After the completion of radiotherapy ANC > 2.5×10^9/L or PLT > 100×10^9/L
2	120	After completion of the second cycle of treatment ANC > 2.5×10^9/L or PLT > 100×10^9/L
3	150	After completion of the third cycle of treatment ANC > 2.5×10^9/L or PLT > 100×10^9 /L

a: If the dose is not increased during cycle 2, it should not be increased in subsequent cycles.

b: For patients on the lowest dose level of TMZ (50 mg/m²), if ANC < 1.5×10^9 /L or PLT < 50×10^9 /L occurs for the second time, TMZ will be permanently discontinued.

6.3 Radiotherapy

(1) Position fixation: The patient is placed in supine position with a thermoplastic film head-neck-shoulder cover for fixation.

(2) CT simulation and postoperative MRI fusion localization: The patient is placed in a fixed supine position, with the scanning range extending from the skull apex to the lower border of the C2 vertebral body, and a scan layer thickness of 3 mm.

(3) Target area delineation: Perform target area delineation in the planning system. Delineate the target area according to the EORTC delineation principles.

The EORTC delineation principles are as follows: a target volume receiving 60 Gy of radiation, administered in 2 Gy fractions. The Gross Target Volume (GTV) includes the MRI T1-enhanced region, T2-FLAIR signal abnormality areas, and surgical cavity, excluding peritumoral edema. The Clinical Target Volume (CTV) extends 1.5–2 cm beyond the GTV, with additional expansion of 0–0.5 cm for natural barrier structures such as the skull, ventricles, cerebral falx, tentorium cerebelli, optic apparatus, and brainstem. The Planned Treatment Volume (PTV) is extended 0.3 cm beyond the GTV.

(4) During plan evaluation, the following factors should be prioritized (in order of importance): whether the optic chiasm, optic nerve, brainstem, lens, and temporal lobe exceed dose limits. Referencing RTOG0225, RTOG0615, and QUANTEC standards, the conventional normal tissue limits are as follows: optic nerve and optic chiasm Dmax < 54 Gy, PRV D1 < 60 Gy; brainstem Dmax < 54 Gy, PRV D1 <60 Gy; lens Dmax < 6 Gy; bilateral hippocampus Dmean ≤ 7.3 Gy.

6.4 Concomitant Therapy

(1) Subjects may receive prophylactic treatment for Pneumocystis carinii pneumonia, including but not limited to inhaling pentamidine or taking oral trimethoprim-sulfamethoxazole; such prophylactic treatment is not mandatory.

(2) Prior to administering the initial dose of temozolomide, it is recommended to administer metoclopramide or a serotonin 3 receptor antagonist for antiemetic prophylaxis, on the day of oral adjuvant temozolomide therapy.

(3) The use of corticosteroids is determined by the investigator based on clinical circumstances. However, it is recommended that subjects receiving corticosteroids during radiotherapy should discontinue medication at least 6 weeks after completion of radiotherapy,

with the drug dose being completely and gradually reduced over several weeks. When this approach is not feasible, the subject's hormone dose should be minimized as much as possible.

(4) Prophylactic use of hematopoietic growth factors is not permitted; patients may receive red blood cell transfusions or erythropoietin to maintain hemoglobin levels ≥ 100 g/L.

(5) The metabolism of lenvatinib involves pathways such as CYP3A4. Concomitant use with potent CYP3A4 inducers (e.g., rifampin, phenytoin, carbamazepine, phenobarbital) or potent inhibitors (e.g., ketoconazole, clarithromycin) should be avoided whenever possible to prevent interference with plasma drug concentrations.

(6) Given that GBM patients often require antiepileptic drugs, investigators should refer to Appendix VII: Metabolic Enzymes Associated with Common Antiepileptic Drugs and prioritize medications with minimal impact on CYP enzymes.

6.5 Subsequent Therapy

Upon progression or after 2 years of follow-up, the investigator will independently decide on the treatment for the patient and record the type of second-line therapy. Based on the patient’s clinical condition, treatments include surgery, second-line targeting/chemotherapy, or combinations.

7. Primary and Secondary Endpoints

7.1 Primary Endpoint:

Progression-free survival (PFS), defined as the time from enrollment to the first documented local-regional recurrence, distant metastasis, or death from any cause.

7.2 Secondary Endpoint:

(1) Overall survival (OS), defined as the time from enrollment to death from any cause.

(2) Best Overall Response (BOR), determined by modified RANO criteria for patients with incomplete tumor resection and documented postoperative residual tumor.

(3) Safety, adverse events (AE) and serious adverse events (SAE) graded according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE V5.0).

(4) Function quality of Life, assessed by the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 ((EORTC QLQ-C30) : Scores are converted to 0–100 scale. Higher scores indicate better functioning and quality of life for

functional and global health/QoL domains, while higher symptom scores indicate greater symptom burden.

(5) Brain tumor symptom burden, assessed using the EORTC QLQ-BN20: Scores are converted to 0–100 scale. Higher symptom domain scores indicate more severe disease-related symptoms.

7.3 Exploratory Endpoints (optional)

Evaluate tumor tissue biomarkers: Using tumor tissue specimens provided during the screening period, explore the correlation between TERT promoter mutation, 1p/19q deletion, BRAF V600E gene status, as well as the expression levels of Lenvatinib-related targets (e.g., VEGFR 1-3, FGFR 1-4, PDGFRα/β) with the PFS and OS of the subjects through next-generation sequencing (NGS) or immunohistochemistry (IHC) techniques.

8. Data Processing and Statistical Analysis Plan

8.1 Efficacy Analysis

Cumulative incidence methods will be used to calculate the best overall response and the frequency of chemotherapy delay at the observation endpoints, with 95% confidence intervals (CI) described. Observation endpoints such as PFS and OS will be analyzed using the Kaplan-Meier method and Greenwood's formula, with the median and 95% CI also described. For all efficacy observation endpoints, Intention-to-Treat (ITT) analysis will be utilized, while safety analysis will be performed using the Safety Set (SS).

Changes over time in quality of life assessments (QLQ-C30 and BN20) and neurocognitive function assessments (MMSE) will be evaluated through repeated measures modeling using a mixed effect model. A linear mixed model will be fitted, including treatment, time effect, time-treatment interaction, and other potential baseline covariates as fixed effects, and patient-specific random effects.

The correlations between quality of life assessment, neurocognitive function assessment, progression status based on tumor enhancement, and progression status after integration of FLAIR/T2 will be recorded.

8.2 Safety Assessment

Mainly focusing on treatment-related acute toxicity, descriptive analysis will be the primary method. The number of cases and incidence of adverse events (AEs) and serious adverse events

(SAEs) will be listed and described.

8.3 Analysis Populations

(1) Intention-to-treat (ITT) analysis: Includes all subjects who have been enrolled. Usually, the Full Analysis Set (FAS) is used for analysis. FAS refers to the ideal set of subjects as close as possible to the ITT principle, which is the analysis data set derived after excluding subjects using minimal and reasonable methods.

(2) Safety Set (SS): Includes all subjects who have been screened, grouped, and have received at least one or more treatments.

9. Reference

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