RTOG 5308/AbbVie M13-813

A Randomized, Placebo Controlled Phase 2b/3 Study of ABT-414 with Concurrent Chemoradiation and Adjuvant Temozolomide in Subjects with Newly Diagnosed Glioblastoma (GBM) with Epidermal Growth Factor Receptor (*EGFR*) Amplification (Intellance 1)

Primary Objective

Phase 2b: To determine whether the addition of ABT-414 to concomitant radiotherapy and temozolomide plus adjuvant temozolomide prolongs Progression Free Survival (PFS) among subjects with newly diagnosed GBM harboring *EGFR* amplification.

Phase 3: To determine whether the addition of ABT-414 to concomitant radiotherapy and temozolomide plus adjuvant temozolomide prolongs Overall Survival (OS) among subjects with newly diagnosed GBM harboring *EGFR* amplification.

SCHEMA

STEP 1 REGISTRATION

Central Pathology Review for confirmation of histology and adequacy of tissue for *MGMT* and *EGFR* analysis. Testing for *EGFR* amplification, *MGMT* promoter methylation, and *EGFRvIII* must be complete before Step 2 of Registration. Only subjects with *EGFR* amplified tumors and sufficient tissue for *MGMT* analysis will be eligible.
NOTE: Tumor tissue must be received and central review confirmation completed before STEP 2 registration can occur.

↓

STEP 2 REGISTRATION

Da protocollo se investigator ravvede benefit, si può andare fino a 12 cicli (anziché 6) di TMZ adiuvante (vedi slide 5)

STRATIFY

MGMT methylation status: methylated vs. Unmethylated*
RPA class: III vs. IV vs. V
Region of the world: US/Canada vs. Other
EGFRvIII mutation status: mutated vs. Other

Da protocollo se investigator ravvede benefit, si può andare oltre i 12 cicli di ABT-412 (vedi slide 21) fino a PD

RANDOMIZE

↓ ↓

Arm A

RT: ~60 Gy in 30 fractions over 42 days (d) (up to 49 d)**
+
Temozolomide: Daily for 42 d (up to 49 d)**
+
Blinded ABT-414: D1 of Weeks 1, 3 and 5

28 d (+/– 3 d) after completion of chemoradiation
Temozolomide: D1-5 of 28-d cycle x 6 cycles**
+
Blinded ABT-414: D1 and D15 of q 28-d cycle x 12 cycles

Arm B

RT: ~ 60 Gy in 30 fractions over 42 d (up to 49 d)**
+
Temozolomide: Daily for 42 d (up to 49 d)**
+
Blinded Placebo: D1 of Weeks 1, 3 and 5

28 d (+/– 3 d) after completion of chemoradiation
Temozolomide: D1-5 of 28-d cycle x 6 cycles**
+
Blinded Placebo: D1 and D15 of q 28-d cycle x 12 cycles

Non è concessa RT ipofrazionata!

* A test result of "insufficient tissue" or indeterminate for *MGMT* is exclusionary and the subject will not be able to be continue to Step 2 registration for stratification and randomization.

** Per local prescribing information or local institutional guidelines.

SUBJECT SELECTION, ELIGIBILITY, AND INELIGIBILITY CRITERIA

Screening Requirements (Step 1)

- Tumor tissue from surgery submitted for histological confirmation of GBM diagnosis by a central pathologist and for central biomarker testing for *EGFR* amplification, *EGFR*vIII mutation, and *MGMT* promoter methylation status. Results for each of these tests are required for study eligibility.
- Post-operative contrast-enhanced Magnetic Resonance Imaging (MRI) scan must be done within 72 hours after surgery.

Separate informed consent documents will also be required for the optional substudies in this protocol: for the collection of pharmacogenetic samples and the collection of tumor tissue post-treatment after disease progression, Section 15.3.

Operativamente:

Step 1 (Screening 1) : far firmare il **consenso informato prima di tutto (Consent for Tumor Tissue Testing!**), poi inviare il tessuto neuropatologico (**2 blocchetti, minimo 1**) ed aspettare la revisione centralizzata. Eseguire **MRI entro 72 ore dall'intervento (bisogna inviare alla revisione centralizzata sia quella prima pre-intervento che la post-intervento!)**

Inclusion Criteria

1. Histologically confirmed de novo Grade IV glioma (GBM, gliosarcoma or other subvariants) confirmed by central pathology tissue screening.
2. *EGFR* amplification in tumor tissue confirmed by central assessment.
3. Supratentorial tumor.
4. The subject must have recovered from the effects of surgery, postoperative infection, and other complications before enrollment including suture/staple removal from brain surgery and sufficient wound healing before step 2 registration. Post-operative contrast-enhanced MRI scan must be done within 72 hours after surgery.
5. ≥ 18 years of age.
6. Karnofsky performance status ≥ 70 at assessment ≤ 14 days prior to randomization (Step 2).
7. Results for required stratification factors (*EGFRvIII* status, *MGMT* methylation status, Recursive Partitioning Analysis (RPA) class, and region of world) available prior to randomization (Step 2).
8. Subject has adequate bone marrow, renal, and hepatic function ≤ 21 days prior to randomization (Step 2) as follows:
   a) Absolute neutrophil count (ANC) ≥1,500/mm^3;
   b) Platelets ≥ 100,000/mm^3;
   c) Hemoglobin (Hgb) ≥ 9.0 g/dL (Note: The use of transfusion or other intervention to achieve Hgb ≥ 9.0 g/dL is acceptable.);
   d) Renal function: calculated creatinine clearance ≥ 30 mL/min by the Cockcroft-Gault formula;
   e) Hepatic function: Total bilirubin, Aspartate Aminotransferase (AST), and Alanine Aminotransferase (ALT) ≤ 1.5 times upper limit of normal (ULN). Subjects with Gilbert's syndrome documented in medical history may be enrolled if bilirubin is < 3 times ULN.

- Solo tumori sopratentoriali
- GBM unica lesione (non multifocali)
- Non includibili gliomatosi cerebri (vedi criteri esclusione)

- Calcolare RPA

9. Electrocardiogram (ECG) without evidence of acute cardiac ischemia ≤ 21 days prior to randomization (Step 2).
10. Female subjects of childbearing potential (i.e., those who are not postmenopausal for at least 1 year or surgically sterile by bilateral tubal ligation, bilateral oophorectomy or hysterectomy) and their male partners should practice at least one of the methods of birth control listed below during study entry, for the entire duration of the study and for at least 6 months after treatment with ABT-414 and TMZ. In addition to the use of a condom, male subjects and their female partners of childbearing potential should practice at least one of the methods of birth control listed below during the study and for at least 6 months after ABT-414 and TMZ:
11. Women of child-bearing potential must have a negative pregnancy test (urine or serum) within 7 days prior to randomization (Step 2).
12. Must voluntarily sign and date informed consent form, for tumor tissue biomarker testing and for study participation, approved by an Independent Ethics Committee (IEC)/ Institutional Review Board (IRB), prior to the initiation of any screening or study-specific procedures.

- Leggere regole anticoncenzionali pag 20-21 protocollo

Exclusion Criteria

Randomization Criteria (Step 2)

1. Subject has multifocal GBM.
2. Gliomatosis cerebri (a diffuse glioma [usually astrocytic] growth pattern consisting of exceptionally extensive infiltration of a large region of the central nervous system [CNS], with involvement of at least 3 cerebral lobes, usually with bilateral involvement of the cerebral hemispheres and/or deep grey matter, and frequent extension to the brain stem, cerebellum, and even the spinal cord.)
3. Subject has recurrent GBM.
4. Subject has infratentorial tumor.
5. Subject has metastatic GBM.
6. Prior chemotherapy or radiosensitizers for cancers of the head and neck region; note that prior chemotherapy for a different cancer is allowable, except prior temozolomide.
7. Prior radiotherapy to the head or neck (except for T1 glottic cancer), resulting in overlap of radiation fields.
8. Any prior therapy for glioblastoma (intra-operative techniques to guide resection are allowed as are experimental imaging techniques).
9. Prior invasive malignancy (except for non-melanomatous skin cancer; carcinoma in situ of the breast, oral cavity, or cervix) unless disease free for ≥ 2 years.
10. Prior, concomitant, or planned concomitant treatment with NovoTumor Treatment Fields (Novo TTF), *EGFR*-targeted therapy (including *EGFRvIII*-directed therapy), bevacizumab, Gliadel wafers or other intratumoral or intracavitary anti-neoplastic therapy, or other experimental therapeutics intended to treat the tumor; the exceptions are diagnostic or imaging studies, quality of life, biomarker or epidemiological studies; and operative guides to improve extent of resection.

11. Subject has had major immunologic reaction to an IgG-containing agent.
12. Subject has had LASIK (laser-assisted in situ keratomileusis) procedure within the last 1 year.
13. Subject has a history of hypersensitivity to TMZ or excipients, ABT-414 components or excipients, and dacarbazine (contraindication for TMZ).
14. Subject is unsuitable for receiving ocular steroids:
    - Subject has any active viral disease of the cornea or conjunctiva, including epithelial herpes simplex keratitis (dendritic keratitis), vaccinia, and varicella; mycobacterial infection of the eye; fungal diseases of ocular structures; or any other contraindication for ocular steroid use.
    - Subject has a known or suspected hypersensitivity to any ocular steroid.
    - Subject has primary open angle glaucoma or a history of steroid-induced intraocular pressure elevation.
15. Subject is a lactating or pregnant female.
16. Severe, active co-morbidity, defined as follows:
    - Moderate or severe hepatic impairment (Child-Pugh category B or higher [score of 7 or higher (Appendix VII)]);
    - Unstable angina and/or congestive heart failure within the last 6 months;
    - Transmural myocardial infarction within the last 6 months;
    - Evidence of recent myocardial infarction or ischemia by the findings of S-T elevations of ≥ 2 mm using the analysis of an EKG performed within 14 days prior to enrollment;

Chiedere in anamnesi!!

- New York Heart Association grade II or greater congestive heart failure requiring hospitalization within 12 months prior to enrollment (Appendix IV);
- History of stroke, cerebral vascular accident (CVA) or transient ischemic attack within 6 months;
- Serious and inadequately controlled cardiac arrhythmia;
- Acute bacterial or fungal infection requiring intravenous antibiotics at the time of enrollment;
- Chronic obstructive pulmonary disease exacerbation or other respiratory illness requiring hospitalization or precluding study therapy at the time of enrollment;
- Subjects with clinically defined Acquired Immune-Deficiency Syndrome (AIDS)-defining illness. This is necessary to ensure subjects are likely to be able to receive the full TMZ regimen;
- Active connective tissue disorders, such as lupus or scleroderma, that in the opinion of the Investigator may put the subject at high risk for radiation toxicity;
- Any other major medical illnesses or psychiatric impairments that in the Investigator's opinion will prevent administration or completion of protocol therapy;

17. Subjects treated on any other therapeutic clinical protocols within 30 days prior to study entry or during participation in the study except intra-operative therapy to guide resection or experimental imaging without therapeutic intent.
18. Inability to undergo contrast-enhanced MRI scans.

Screening requirements (Step 2) → **entro 14 -3 giorni dall'inizio del trattamento (quando ricevuta revisione centralizzata EGFR)**

Medical and Oncologic History

The following will be collected during the Screening Visit:

- Demographic information, including age, sex, and ethnicity. Ethnicity will include whether a subject is first generation Han Chinese.
- Complete medical history, including documentation of any clinically significant medical condition. **Problemi oculistici da indagare!!!**
- History of tobacco and alcohol use.
- Detailed oncologic history including:
  - Date of primary cancer diagnosis;
  - Histology at the time of study entry;
  - Date and extent of surgical resection;
  - Neurologic deficits, if any, at the time of enrollment;

(EQ-5D-5L) EQ-5D-VAS
Health-Related Quality of Life (HRQoL)
MD Anderson Symptom Inventory – Brain Tumor

Physical Examination compreso peso e altezza **Karnofsky Performance Status**

Vital Signs **Systemic Corticosteroid Use** nei 7 giorni precedenti l'inizio del trattamento

12-Lead Electrocardiogram (ECG) **Pregnancy Test** entro 21 giorni dall'inizio del trattamento

Clinical Laboratory Tests entro 21 giorni dall'inizio del trattamento

MRI and Clinical Assessment for Disease Progression entro **7 giorni** dall'inizio del trattamento (baseline)

ABT-414-Targeted Ophthalmologic Examinations (ABT-414-TOE) baseline

Raccomandare inizio di profilassi con steroide 48 ore prima dell'inizio di RT + ABT-414

Neurocognitive Functioning – Clinical Trial Battery (**Alice Malabaila**, durata 20 minuti)

5.6 Duration of Therapy

In the absence of treatment delays due to adverse event(s), treatment may continue as specified in the treatment plan overview, Section 5.1, or until one of the following criteria applies:

- Subject experiences disease progression
- Subject experiences intercurrent illness that prevents further administration of treatment
- Subject experiences excessive toxicity precluding further therapy with either ABT-414 or temozolomide, according to the Investigator
- Subject decides to withdraw consent for participation in the study
- General or specific changes in the subject's condition render the subject unacceptable for further treatment in the judgment of the Investigator
- Subject become pregnant while on study

Subjects unable to continue either temozolomide or ABT-414/placebo due to excessive drug-specific toxicity will be allowed to continue therapy with the other, tolerated therapy components until one of the other criteria above is met.

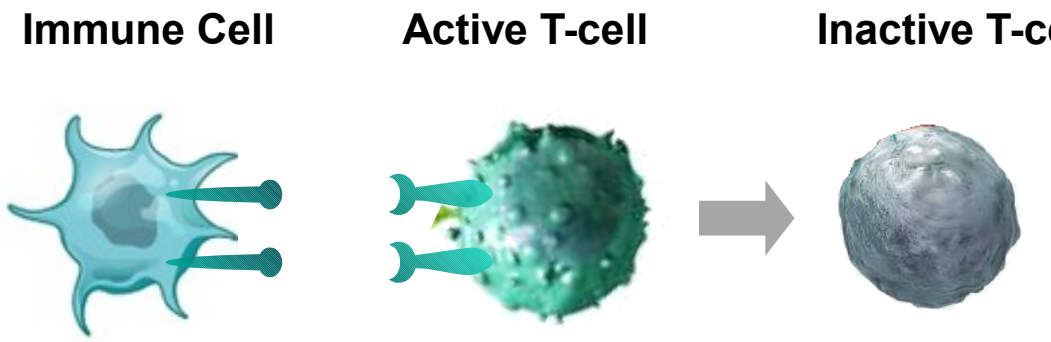
Subjects discontinuing therapy in the absence of progression should not receive any other cancer treatment before their disease progresses, unless this is clearly not in the interest of the subject.

After progression, the treatment will be left to the discretion of the Investigator. Any anti-cancer therapy other than the study drug will not be considered as part of the protocol treatment. However, treatments will be recorded.

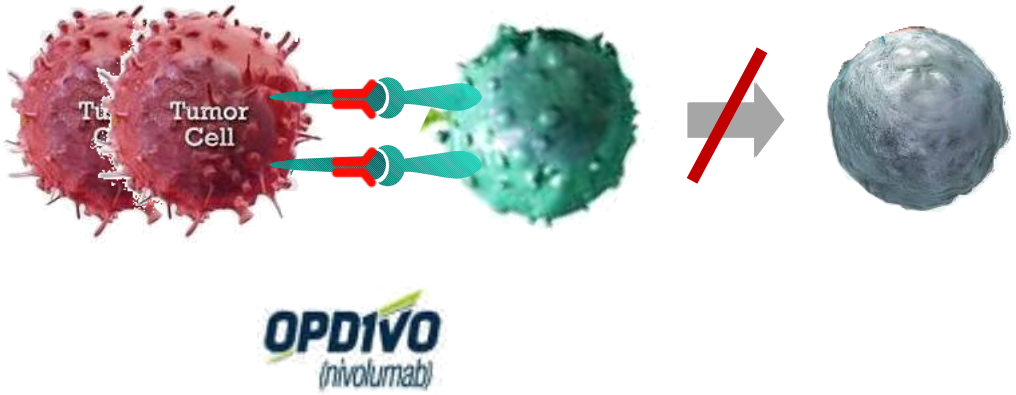
CA209-498 and CA209-548 clinical protocols

Programmed Death Pathway and Nivolumab

Normal Homeostatic Mechanism



Tumor Microenvironment



- **Normal function of PD-1 pathway is to attenuate immune response to avoid immune system attack of "self"**
- **A "brake" to prevent overreaction & overproliferation**

- **Tumor cells "co-opt" the PD-1 pathway to evade T-cell immune responses**

- **Nivolumab occupies the PD-1 receptor of T-cells → prevents inhibitory ligand binding & T-cell inactivation**

Clinical Protocol CA209498

A Randomized Phase 3 Open Label Study of Nivolumab vs Temozolomide Each in Combination with Radiation Therapy in Newly Diagnosed Adult Subjects with Unmethylated MGMT (tumor O-6-methylguanine DNA methyltransferase) Glioblastoma

CheckMate498: CHECKpoint pathway and nivoluMAb Trial Evaluation: 498

1.3.1 Primary Objective

To compare overall survival (OS) of nivolumab plus radiation therapy (RT + nivolumab) versus temozolomide plus radiation therapy (RT + TMZ) in subjects with newly-diagnosed GBM and unmethylated MGMT tumors after surgical resection.

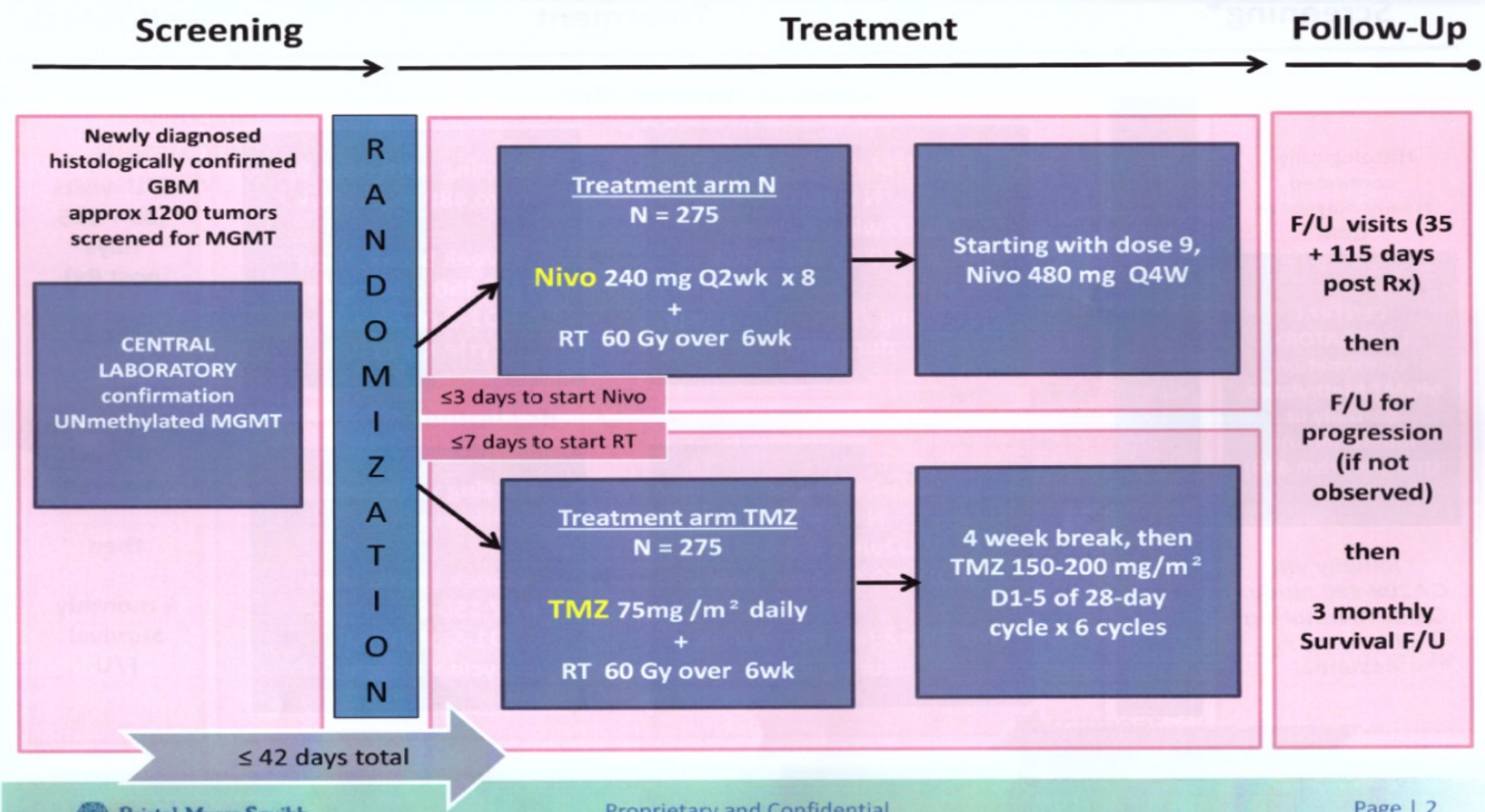
1.3.2 Secondary Objectives

- To compare investigator-assessed progression-free survival (PFS) of RT + nivolumab versus RT + TMZ;
- To estimate the overall survival rate at 24 months (OS[24]) of RT + nivolumab versus RT + TMZ (final analysis only);

Enrollment and randomization of 550 subjects is expected to require approximately 10 months.
Interim and final analyses are planned after at least 298 and 397 deaths have been reported, these analyses are anticipated to occur at approximately 24 and 35 months after first subject is randomized.
At discretion of the Sponsor, survival data may continue to be collected for up to 5 years.
This is a survival study, therefore subjects discontinuing study treatment will **remain on study** for documentation of progression and death.

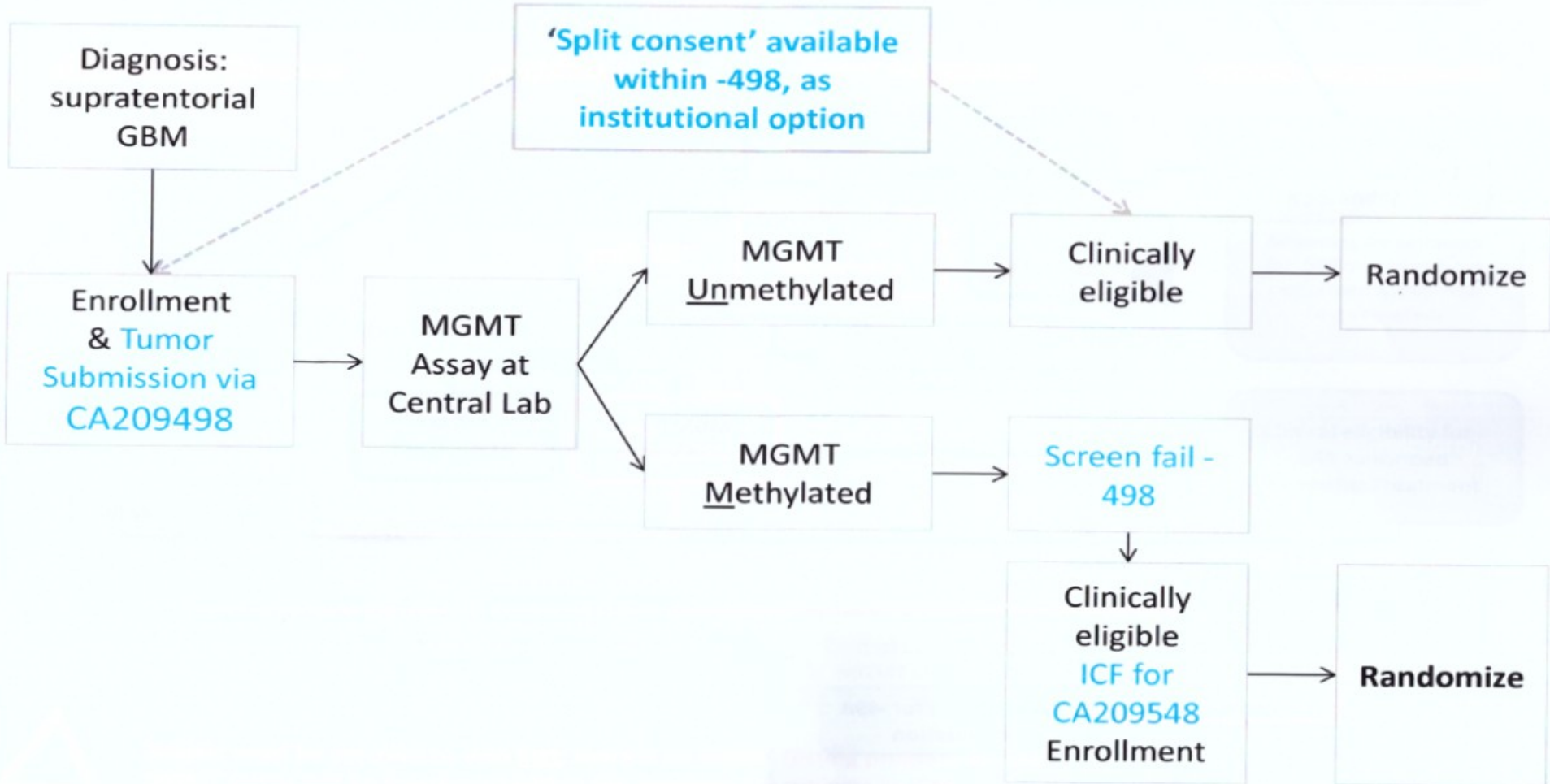
CheckMate
CHECKpoint pathway and nivoluMAb clinical Trial Evaluation

CA209-498 Study Design



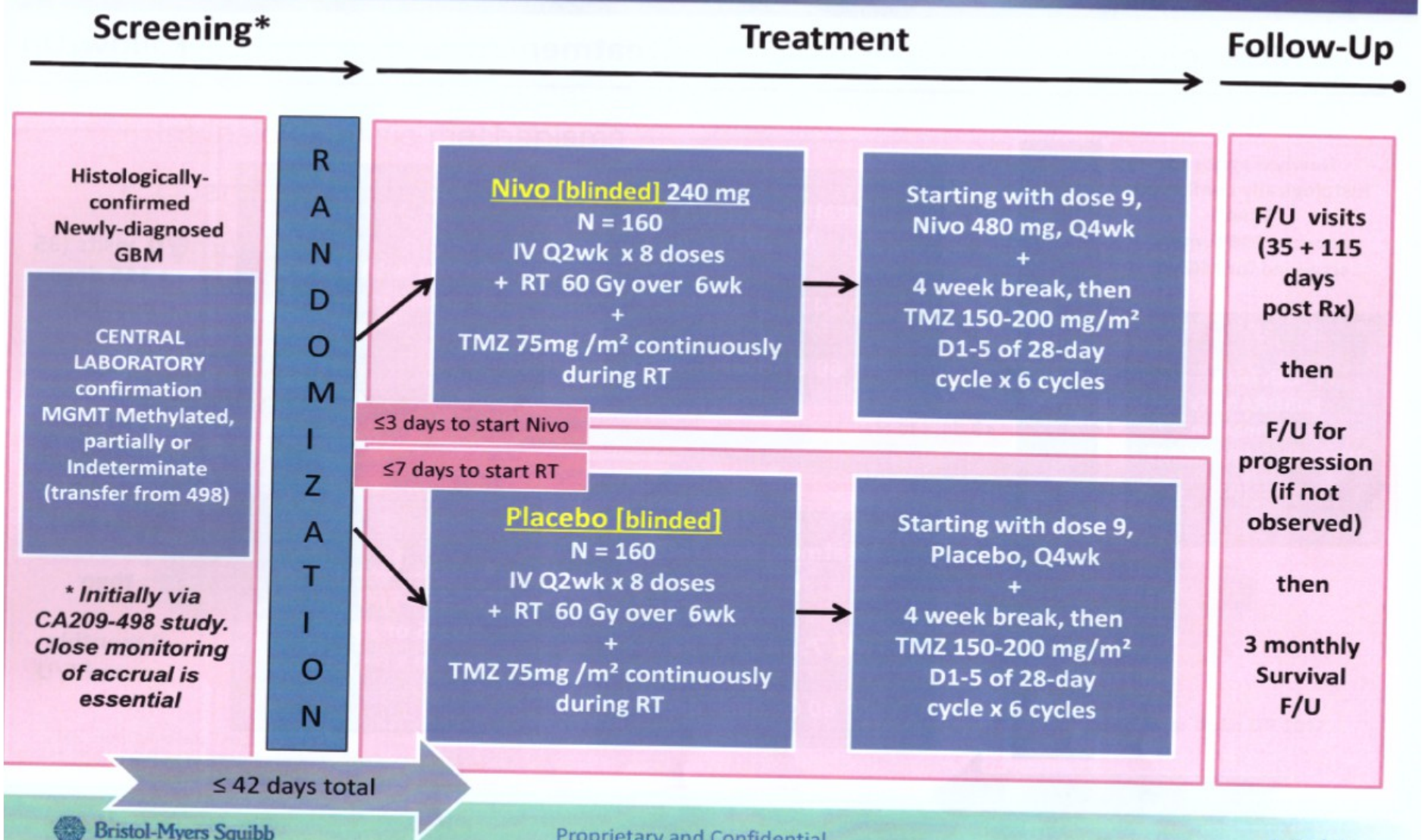
MGMT Screening and Consent Process: Split-consent in -498, Re-consent for -548

CheckMate
CHECKpoint pathway and nivoluMAb clinical Trial Evaluation



CheckMate
CHECKpoint pathway and nivoluMAb clinical Trial Evaluation

CA209-548 Study Design



Inclusion Criteria

1. **Signed Written Informed Consent**
2. **Target Population**
   a) Newly-diagnosed histologically-confirmed supratentorial glioblastoma (Grade IV malignant glioma by World Health Organization, including gliosarcoma)[49]
      i) No treatment for GBM other than surgery;
      ii) Post-operative baseline MRI within 48 hours (preferably 24 hours) of surgical resection
   b) Full recovery from surgical resection
      i) No major ongoing safety issues following surgery;
      ii) ≤ 20 mg prednisone or ≤ 3 mg dexamethasone daily (or equivalent);
   c) Centrally confirmed (ie, third-party vendor) unmethylated MGMT;
   d) Karnofsky performance status of ≥ 70 (Appendix 2)
   e) Eligible for radiation therapy based on NCCN guidelines[49]
   f) Subject Re-enrollment: This study permits the re-enrollment of a subject that has discontinued the study as a pre-treatment failure (ie, subject has not been randomized/has not been treated) is permitted. If re-enrolled, the subject must be re-consented.

Le biopsie cerebrali non sono consentite

RM encefalo con Gad deve essere fatta entro 24 ore, massimo 48 ore dall'intervento!!!

Limite dello steroide

Uso di acido valproico nel braccio RT + TMZ E' PROIBITO!

Exclusion Criteria

1. **Target Disease Exceptions**
   a) Prior treatment for GBM (other than surgical resection)
   b) Recurrent GBM
   c) MGMT methylated, partially methylated, or indeterminate GBM
   d) Biopsy-only of GBM at surgery, defined as <20% resection
   e) Ongoing requirement for supraphysiologic steroid, defined as > 20 mg prednisone or > 3 mg dexamethasone daily (or equivalent), due to intracranial mass effect
   f) CNS hemorrhage of Grade > 1 on baseline MRI scan, unless subsequently documented to have resolved;
   g) Any known metastatic extracranial or leptomeningeal disease
   h) Secondary GBM (ie, progression from prior low-grade or anaplastic glioma)
   i) Known IDH-mutated tumor (if available; test not required)

2. Medical History and Concurrent Diseases

a) Any serious or uncontrolled medical disorder that, in the opinion of the investigator, may increase the risk associated with study participation or study drug administration, impair the ability of the subject to receive protocol therapy, or interfere with the interpretation of study results;

b) Prior treatment with an anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CTLA-4 antibody or any other antibody or drug specifically targeting T-cell co-stimulation or immune checkpoint pathways;

c) Subjects with an active, known or suspected autoimmune disease. Subjects with type I diabetes mellitus, hypothyroidism only requiring hormone replacement, skin disorders (such as vitiligo, psoriasis or alopecia) not requiring systemic treatment, or conditions not expected to recur in the absence of an external trigger are permitted to enroll;

d) Subjects with a condition requiring systemic treatment with either corticosteroids (> 20 mg daily prednisone or > 3 mg dexamethasone or equivalent) or other immunosuppressive medications within 14 days of randomization. Inhaled or topical steroids, and adrenal replacement steroid doses > 20 mg daily prednisone or > 3 mg dexamethasone or equivalent, are permitted in the absence of active autoimmune disease.

e) Subjects with interstitial lung disease that is symptomatic or may interfere with the detection or management of suspected drug-related pulmonary toxicity

f) Subjects with history of life-threatening toxicity, including hypersensitivity reaction, related to prior immunoglobulin treatment for another condition (except those considered unlikely to re-occur, with written approval of BMS medical monitor) or any other study drug component.

g) History or evidence upon physical/neurological examination of other central nervous system condition (eg, seizures, abscess) unrelated to cancer, unless adequately controlled by medication or considered not potentially interfering with protocol treatment;

h) Surgical procedure < 7 days prior to study treatment, vascular access device no restriction;

i) Subjects unable (eg, due to pacemaker or ICD device) or unwilling to have a contrast-enhanced MRI of the head;

j) History of allergy or hypersensitivity to study drug components;

k) Unable to swallow oral medication or any gastrointestinal disease or surgical procedure that may impact the absorption of study drug;

3. Physical and Laboratory Test Findings

a) Any positive test for hepatitis B virus or hepatitis C virus

b) Known history of positive test for human immunodeficiency virus (HIV) or known acquired immunodeficiency syndrome (AIDS). NOTE: Testing for HIV must be performed at sites where mandated by local regulation.

4. Allergies and Adverse Drug Reaction

a) History of allergy or hypersensitivity to study drug components

Concomitant Treatments

Concurrent anti-neoplastic therapy, including other chemotherapy, immunotherapy, additional radiation therapy or investigational agents for treatment of GBM are prohibited during the treatment phase. Use of any additional noninvasive medical device treatment of GBM (eg, novoTTF, Optune©) is prohibited.

Use of valproic acid is prohibited on the RT + TMZ arm; the subject must be transitioned to an alternative anticonvulsant.

Permitted Therapy

Subjects are permitted the use of topical, ocular, intra-articular, intranasal, and inhalational corticosteroids (with minimal systemic absorption). Adrenal replacement steroid doses < 20 mg daily prednisone are permitted. A brief (less than 3 weeks) course of corticosteroids for prophylaxis (eg, contrast dye allergy) or for treatment of non-autoimmune conditions (eg, delayed-type hypersensitivity reaction caused by a contact allergen) is permitted.

Steroid use should be minimized prior to randomization. Systemic corticosteroid use or physiologic replacement doses of steroids are permitted, even if > 20 mg/day prednisone equivalents, for: a) treatment-related AEs b) symptoms related to GBM, including suspected tumor flare or pseudoprogression, or c) treatment of non-autoimmune conditions (eg, prophylaxis for contrast dye allergy, contact hypersensitivity).

Regorafenib alla prima recidiva di glioblastoma.
Studio clinico di fase II, randomizzato, in aperto

End points

Primary end-point :

- Overall survival, assessed from the date of randomization to the date of death from any cause

Secondary end-points :

- Progression free survival, assessed from the date of randomization to the date of disease progression or to the date of death, whichever occurs first
- Objective response rate, as percentage of patients achieving a complete response plus partial response
- Disease control rate, as percentage of patients achieving a complete response plus partial response plus stable disease
- Toxicity during the treatment, graded according to the NCI-Common Terminology Criteria for Adverse Events (CTCAE) v.4
- Quality of Life assessed by EORTC QLQ-C30 and QLQ-BN20

Exploratory end-points:

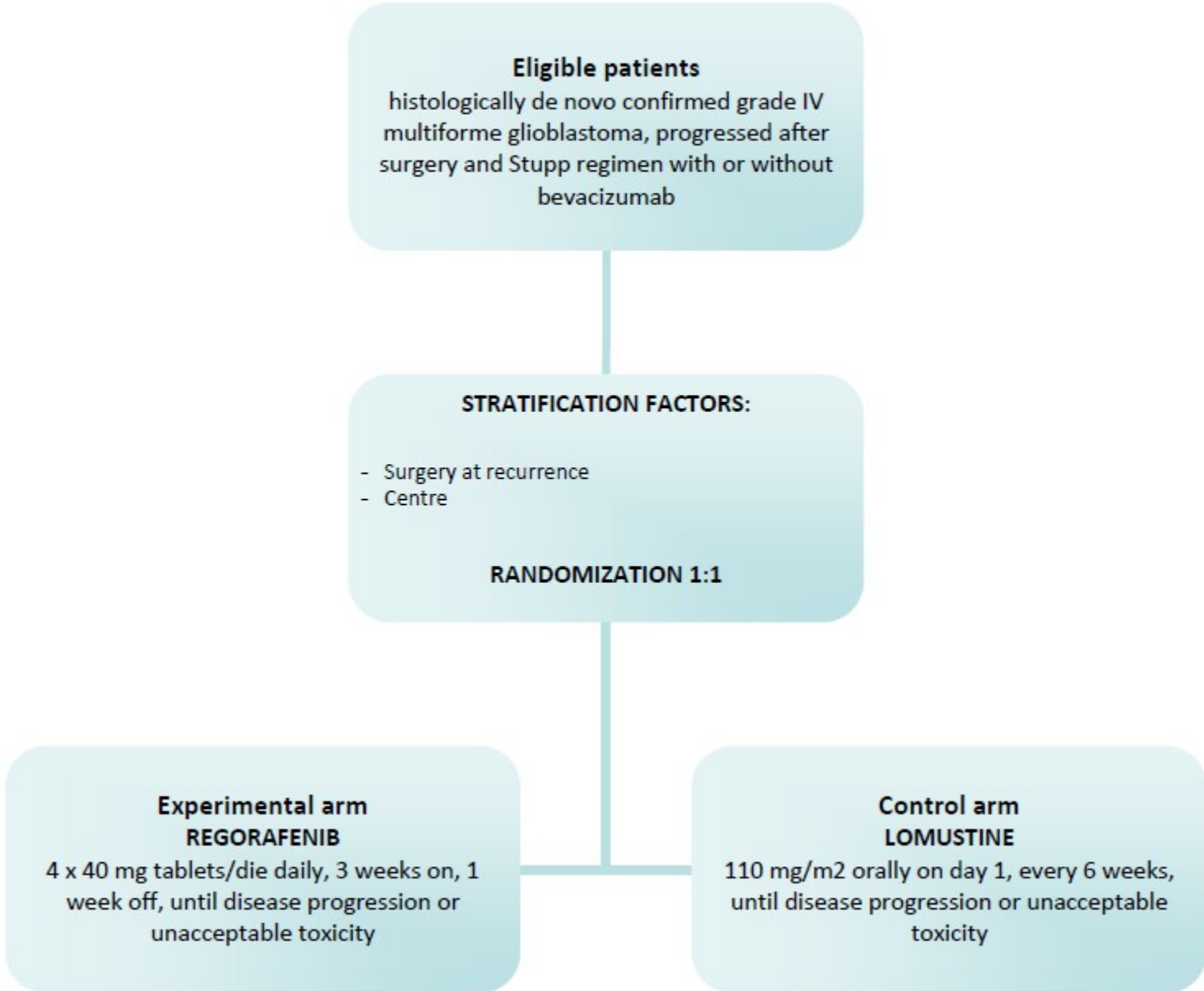
- Protein expression of VEGFR2, TIE2, PDFGRbeta, FGFR1, MCT1, MCT4, pAMPK, pACC
- Transcript expression of VEGF-A, FGF, PDGF, IL-8 mRNAs
- MicroRNA expression by miR profiling array analysis testing the expression of 1,210 candidate miRs in clustered groups of patients according to their clinical outcome

Biological mechanism and use of regorafenib

Regorafenib deactivates tumors across three dimensions (angiogenesis, oncogenesis and stromagenesis) by inhibition of angiogenic receptor tyrosine kinases (RTK) (e.g., VEGFR1-3, TIE2), oncogenic (e.g., KIT, RET) and stromal RTKs (e.g., platelet derived growth factor receptor [PDGFR], fibroblast growth factor receptor [FGFR]). The

RAS/RAF signaling pathway is an important mediator of responses to growth signals and angiogenic factors (Herrera & Sebolt-Leopold, 2002)

The novel drug regorafenib, a new oral multikinase inhibitor of angiogenic, stromal and oncogenic receptor tyrosine kinases, demonstrated efficacy in various solid tumours and some studies demonstrated activity in glioblastoma (in vitro). Regorafenib being a multikinase inhibitor could have a greater antiangiogenic activity than bevacizumab limiting the activation of VEGF-independent angiogenesis.


Eligible patients
histologically de novo confirmed grade IV multiforme glioblastoma, progressed after surgery and Stupp regimen with or without bevacizumab
STRATIFICATION FACTORS:
- Surgery at recurrence
- Centre
RANDOMIZATION 1:1
Experimental arm
REGORAFENIB
4 x 40 mg tablets/die daily, 3 weeks on, 1 week off, until disease progression or unacceptable toxicity
Control arm
LOMUSTINE
110 mg/m2 orally on day 1, every 6 weeks, until disease progression or unacceptable toxicity

Criteri di esclusione

- Concomitant medications:

CYP 3A4 Inhibitors	CYP 3A4 Inducers
Amiodarone	Barbiturates
Aprepitant [a]	Carbamazepine [d]
Boceprevir	Efavirenz
Chloramphenicol	Glucocorticoids
Cimetidine [b]	Modafinil
Ciprofloxacin	Nevirapine
Clarithromycin [c]	Oxcarbazepine
Delaviridine	Phenobarbital [d]
Diethyl-Dithiocarbamate	Phenytoin [d]
Diltiazem [a]	Pioglitazone
Erythromycin [a]	Rifabutin
Fluconazole [a]	Rifampin [d]
Fluvoxamine	St. John's Wort [d]
Gestodene	Troglitazone
Grapefruit Juice [c]	
Imatinib	
Indinavir [c]	
Itraconazole [c]	
Ketoconazole [c]	
Mibefradil	
Mifepristone	
Nefazodone [c]	
Nelfinavir [c]	
Norfloxacin	
Norfluoxetine	
Posaconazole [c]	
Ritonavir [c]	
Saquinavir [c]	
Starfruit	
Telaprevir	
Telithromycin [c]	
Verapamil [a]	
Voriconazole [c]	

A. A moderate inhibitor is one that causes a > 2-fold increase in the plasma AUC values or 50-80% decrease in clearance.
B. A weak inhibitor is one that causes a > 1.25-fold but < 2-fold increase in the plasma AUC values or 20-50% decrease in clearance.
C. A strong inhibitor is one that causes a > 5-fold increase in the plasma AUC values or more than 80% decrease in clearance, and are NOT allowed during this clinical trial.
D. Strong inducers are not allowed during this clinical trial.

Source: Prescribing Information for Regorafenib (SEP 2012) and Indiana University School of Medicine, Division of Clinical Pharmacology (Update: 25 JAN 2012): http://medicne.iupui.edu/clinpharm/ddis/table.aspx