Patients with a buffer range from the normal values of +/- 5% for hematology and +/- 10% for biochemistry are acceptable.

Important note: All eligibility criteria must be adhered to, in case of deviation discussion with Headquarters and study coordinator is mandatory.

4 Trial Design

This randomized phase III study investigates the optimal treatment in patients with newly diagnosed anaplastic glioma without combined 1p/19q loss. Patients will be randomized after surgery to one of the four following therapeutic options:

Arm 1: Radiotherapy and further treatment including chemotherapy if indicated at progression
Arm 2: Radiotherapy & concurrent temozolomide
Arm 3: Radiotherapy + adjuvant temozolomide for 12 cycles
Arm 4: Radiotherapy & concurrent temozolomide + adjuvant temozolomide for 12 cycles

For patients randomized to receive adjuvant temozolomide, twelve months of adjuvant treatment is foreseen. Patients will be included based on the 1p/19q status of the tumor. Centers with known expertise in 1p/19q testing will be allowed to include patients based on their local diagnosis, with central review for both the histological diagnosis and 1p/19q testing. For sites without access to 1p/19q testing a central facility is available. Methylation status of the MGMT promoter gene will be a stratification factor. Clinical follow-up must be continued after the diagnosis of first progression to allow assessment of time to neurological deterioration and to assess Quality of Life.

† Institution must choose to evaluate 1p/19q LOH locally or use central facility.
† After registration, all material is centrally reviewed for MGMT methylation status.
* Investigators can’t randomize a patient:
  - If the central facility is used: before the histological diagnosis, diagnosis of no combined 1p/19q LOH has been centrally confirmed and the MGMT methylation status (methylated/ unmethylated or indeterminate) has been communicated by the EORTC Data Centre. The randomization is based on the central histological and 1p/19q LOH evaluation.
  - If the local assessment is used: before the MGMT methylation status (methylated/unmethylated or indeterminate) has been communicated by the EORTC Data Centre. The randomization is based on the local histological and 1p/19q LOH evaluation.
2.3.2 **Secondary endpoints**

Secondary endpoints of the study are progression free survival, neurological deterioration free survival, quality of life, toxicity, and development of cognitive deterioration.

3 **Patient selection criteria**

All patients are initially registered into the trial as soon as possible after surgery. After this point, material must be sent for 1p/19q analysis and MGMT promoter methylation assay. This should again be done as soon as possible. Patients can only be randomized into the trial within 8 days from the start of radiotherapy; at this time, all baseline requirements for the study must have been fulfilled.

3.1 **At the time of registration**

- Histologically confirmed newly diagnosed anaplastic oligodendroglioma, anaplastic oligoastrocytoma or anaplastic astrocytoma by local diagnosis
- Availability of tumor material for central 1p/19q assessment, central MGMT promoter methylation assessment and central pathology review.
- Previous surgery for a low grade tumor is allowed, provided histological confirmation of an anaplastic tumor is present at the time of progression
- WHO performance status 0-2
- Age ≥ 18 years
- All patients must use effective contraception if of reproductive potential. Females must not be pregnant or breast feeding
- Absence of known HIV infection, chronic hepatitis B or hepatitis C infection
- Absence of any other serious medical condition that can interfere with follow-up
- Absence of any medical condition which could interfere with oral medication intake (e.g., frequent vomiting, partial bowel obstruction)
- No previous other malignancies, except for any previous malignancy which was treated with curative intent more than 5 years prior to registration, and except for adequately controlled limited basal cell carcinoma of the skin, squamous carcinoma of the skin or carcinoma in situ of the cervix.
- Absence of any psychological, familial, sociological or geographical condition potentially hampering compliance with the study protocol and follow-up schedule; those conditions should be discussed with the patient before registration in the trial
- No prior chemotherapy (including no treatment with BCNU containing wafers (Gliadel®))
- No prior radiotherapy to the brain
- Before patient registration, written informed consent must be obtained, according to ICH/GCP, and national/local regulations.
3.2 Randomization step

- The combination of:
  - Histologically confirmed newly diagnosed anaplastic oligodendroglioma, anaplastic oligoastrocytoma or anaplastic astrocytoma by local diagnosis
  AND
  - Absence of combined 1p/19q loss
both of which must have been determined by either local testing or central review
- Availability of tumor material for central 1p/19q assessment, central MGMT promoter methylation assessment and central pathology review
- WHO performance status 0-2
- Age ≥ 18 years
- Previous surgery for a low grade tumor is allowed, provided histological confirmation of an anaplastic tumor is present at the time of progression
- Start of radiotherapy within 8 days from randomization
- Start of radiotherapy within 7 weeks (49 days) from surgery (extra 2 days could be allowed)
- Patients must be on a stable or decreasing dose of steroids for at least two weeks
- No prior chemotherapy (including no treatment with BCNU containing wafers (Gliadel®)
- No prior radiotherapy to the brain
- No concomitant treatment with other anti-cancer agents or with any other experimental agent
- Adequate hematological, renal and hepatic function according to all of the following laboratory values (to be performed within 28 days prior to randomization):
  - neutrophils greater or equal to 1.5*10^9 cells/l
  - platelets greater or equal to 100*10^9 cells/l
  - bilirubin < 1.5 times upper limit of laboratory normal
  - alkaline phosphatase, ASAT and ALAT <2.5 times upper limit of laboratory normal
  - serum creatinine lower than 1.5 times upper limit of laboratory normal
- All patients must use effective contraception if of reproductive potential. Females must not be pregnant or breast feeding
- Absence of known HIV infection, chronic hepatitis B or hepatitis C infection
- Absence of any other serious medical condition that could interfere with follow-up
- Absence of any medical condition which could interfere with oral medication intake (e.g., frequent vomiting, partial bowel obstruction)
- Absence of any psychological, familial, sociological or geographical condition potentially hampering compliance with the study protocol and follow-up schedule.
- Before patient randomization, written informed consent must be given according to ICH/GCP, and national/local regulations.