EORTC
European Organisation for Research and Treatment of Cancer
The future of cancer therapy

EORTC
Avenue E. Mounierlaan 83/11
Brussel 1200 Bruxelles
België – Belgique
Tel: +32 2 774 16 11
e-mail: eortc@eortc.org
www.eortc.org

## EORTC Brain Tumor Group

# INTELLANCE 2: ABT-414 alone or ABT-414 plus temozolomide versus lomustine or temozolomide for recurrent glioblastoma: a randomized phase II study of the EORTC Brain Tumor Group

## EORTC protocol 1410-BTG/AbbVie protocol M14-483

(EudraCT 2014-004438-24)

(NCT02343406)

**Study Coordinator:** [redacted]

**Study Co-coordinator:** [redacted]

| Protocol version | Date of PRC approval/notification | Amendment reference | |
|---|---|---|---|
| | | N° | Classification |
| Outline | July 23, 2014 | ---- | ---- |
| 1.0 | October 24, 2014 | ---- | ---- |
| 2.0 | April 15, 2015 | 1 | Scientific |
| 3.0 | July 13, 2015 | 2 | Scientific |
| 4.0 | November 25, 2015 | 3 | Scientific |
| 5.0 | July 01, 2016 | 4 | Scientific |
| 6.0 | January 18, 2017 | 6 | Scientific |
| 7.0 | May 24, 2018 | 8 | Scientific |
| 8.0 | January 04, 2019 | 10 | Scientific |

**Contact addresses**

| | |
|---|---|
| **Writing Committee:** | [redacted] Erasmus MC Cancer Institute - location Daniel den Hoed, Rotterdam, The Netherlands<br>EORTC Headquarters Team, Brussels, Belgium. |
| **Study Coordinator:** | [redacted] |
| **Study Co-coordinator:** | |
| **Clinical Research Physician:** | |
| **Project Manager:** | |
| **Data Manager:** | |
| **Statistician:** | |
| **Safety Management Oncology AbbVie:** | |
| **Study team:** | |
| **Study steering committee:** | Study coordinator<br>Study co-coordinator<br>Study Clinical Research Physician<br>Study statistician |

**Sponsor signatory page**

Protocol 1410

Sponsor:

[redacted] 15/Jan/2019

[redacted] (Date)

AbbVie B.V.
Wegalaan 9
2132 JD Hoofddorp
Netherlands

[redacted]

[redacted] 22/1/2019

(Date)

Erasmus MC Cancer Institute - location Daniel den Hoed
Postbus 5201 (Groene Hilledijk, 3075 EA), 301
3008 AE Rotterdam
The Netherlands

[redacted]

1. I have received and reviewed the Investigator's Brochure for ABT-414

2. I have read this protocol and agree that the study is ethical.

3. I agree to conduct the study as outlined and in accordance with all applicable regulations and guidelines.

4. I agree to maintain the confidentiality of all information received or developed in connection with this protocol.

5. I agree that all electronic signatures will be considered the equivalent of a handwritten signature and will be legally binding.

Protocol EORTC-1410:INTELLANCE 2 : ABT-414 alone or ABT-414 plus temozolomide versus lomustine or temozolomide for recurrent glioblastoma: a randomized phase II study of the EORTC Brain Tumor Group Protocol, version 8.0, January 04, 2019.

Investigator:

_____ _____

Investigator’s full name (in capitals) (Signature) (Date)

# Table of contents:

# Table of appendices:

# Protocol summary

| | |
|---|---|
| **Title of the Study** | INTELLANCE 2: ABT 414 alone or ABT 414 plus temozolomide versus lomustine or temozolomide for recurrent glioblastoma: a randomized phase II study of the EORTC Brain Tumor Group |
| **Objective(s)** | The objectives of the trial are to assess whether ABT-414 alone or in combination with TMZ improves overall survival (OS), PFS, tumor response, quality of life, NDFS and steroid use compared to standard treatment with lomustine single agent or TMZ re-challenge in patients with centrally confirmed recurrent EGFR-amplified glioblastoma.<br><br>Additional exploratory objectives include analyses by stratum of EGFR pathway abnormalities (specifically EGFRvIII mutation), correlation of MGMT methylation status with clinical outcome (PFS/OS), and exploratory clinical and translational research program.<br><br>The objectives will be achieved within a testing strategy, which aims to preserve the global type I error. The objectives will be realized according to the following hierarchical sequence: OS, PFS, response, OS in EGFRVIII mutated. Secondary objectives not included in the testing sequence will be realized for exploratory purpose. |
| **Methodology** | This is a comparative randomized open label multicenter multi-arm phase II trial. A 1:1:1 randomization is used. |
| **Number of patients**<br><br>Number planed (Statistical design)<br><br>Number analyzed | Based on literature review, a median OS of 7 months and PFS of 2.6 months is expected in the mixed control arm (lomustine or TMZ). Based on a one-sided log rank test, at an overall significance level of 2.5% and a power of 91.7% (accounting for the global testing strategy), a total of 170 deaths (118 per comparison, i.e. monotherapy ABT-414 versus control and combination ABT-414 + TMZ versus control) are needed to detect an increase of median OS to 12.9 months in the treatment arms corresponding to a Hazard Ratio (HR) equal to 0.54 (i.e. a reduction in the hazard of death of 46%). Assuming a monthly accrual of 10 patients during month 1 to 12 and 20 patients per month after 12 months, 240 patients can be recruited within 18 months. A duration of follow-up of 13 months after end of accrual is required to observe the 170 deaths.<br><br>At interim analysis one or both of the ABT-414 arms might be discontinued based on lack of efficacy for PFS (Reject H1 in favor of H0) according to RANO criteria assessed by IRC.<br><br>It is assumed that median PFS is 2.6 months in the control arm and 4.8 months in the treatment arms corresponding to HR equal to 0.54. Assuming an accrual rate of 10 patients/month and activation phase of one year, at least 45 PFS events should be observed. Analyses will be performed when at least 31 PFS events are observed in each comparison. Treatment arms which did not show a minimum level of efficacy, defined as a computed treatment PFS HR lower than 0.91 will be dropped. The trial will continue with remaining treatment arm(s) and control. There will be |

| | |
|---|---|
| | no interruption of accrual for the interim analysis.<br><br>An alpha spending of 0.00001 will be allocated to the futility analysis. For the final analyses, efficacy endpoint will be tested at a nominal 1-sided alpha level of 0.02499 Treatment PFS HR will be presented with two-sided 95% CI.<br><br>For each of the two treatment arms the probability of stopping for futility at the interim is 7.4% if the true PFS HR is 0.54 and 60% if the true PFS HR is 1.0 (no benefit).<br><br>Based on the assumed accrual rates and treatment effects stated above, the interim futility analysis is expected to be performed when 90 randomized patients (30 patients per arm) have completed approximately 4 months of follow-up. |
| **Diagnosis and main criteria for inclusion** | **Registration**<br><br>• Histologically confirmed de novo (primary) glioblastoma before or at the time of first progression after RT concurrent/adjuvant TMZ chemotherapy.<br>• In case of testing at the time of first progression: either at least 3 months after the end of radiotherapy or have tumor progression that is clearly outside the radiation field or have tumor progression unequivocally proven by surgery/biopsy<br>• Age ≥ 18 years<br>• Absence of any psychological, familial, sociological or geographical factors potentially hampering compliance with the study protocol and follow-up schedule; such conditions should be assessed with the patient before registration in the trial.<br>• Availability of adequate biological material (formalin-fixed paraffin embedded [FFPE] tumor) for central testing of EGFR amplification<br>• Written informed consent for central *EGFR* screening must be given according to ICH/GCP, and national/local regulations.<br><br>**Randomization**<br><br>• Histologically confirmed *de novo* (primary) glioblastoma with unequivocal first progression after RT concurrent/adjuvant TMZ chemotherapy either at least 3 months after the end of radiotherapy or have tumor progression that is clearly outside the radiation field or have tumor progression unequivocally proven by surgery/biopsy<br>• Presence of EGFR amplification confirmed by central assessment; patients with undetermined EGFR status are excluded<br>• WHO Performance status 0 - 2 (see Appendix C)<br>• No prior treatment with nitrosoureas<br>• No prior treatment with bevacizumab<br>• No previous exposure to EGFR targeted agents, including EGFRvIII targeting agents and participation to placebo controlled trials on EGFR targeted agents |

| | |
|---|---|
| | • No prior discontinuation of temozolomide chemotherapy for toxicity reasons<br>• No more than one line of chemotherapy (concurrent and adjuvant TMZ based chemotherapy including in combination with another investigational agent is considered one line of chemotherapy). Chemotherapy must have been completed at least 4 weeks prior to randomization.<br>• No prior RT with a dose over 65 Gy to the brain, stereotactic radiosurgery or brachytherapy unless the recurrence is histologically proven<br>• No previous other malignancies, except for any previous malignancy which was treated with curative intent more than 5 years prior to randomization, and except for adequately controlled limited basal cell carcinoma of the skin, squamous carcinoma of the skin or carcinoma *in situ* of the cervix<br>• Absence of known hypersensitivity to any part of the ABT-414 compound, TMZ, dacarbazine or lomustine formulations, or to any IgG containing agent<br>• No history of Coeliac disease and wheat allergy<br>• Patient may have been operated for recurrence. If operated:<br>• Residual and measurable disease after surgery is not required but surgery must have confirmed the recurrence<br>• A post-surgery MRI must be available within 48 hours following surgery, however an MRI scan has to be done within 2 weeks prior to randomization<br>• Surgery completed at least 2 weeks before randomization and patients should have fully recovered as assessed by investigators. Criteria for full recovery will include absence of active post-operative infection, recovery from medical complications and capacity for fluid and food intake.<br>• For non-operated patients, recurrent disease must include at least one bi-dimensionally measurable contrast-enhancing lesion with clearly defined margins by MRI scan, with minimal diameters of 10 mm, visible on 2 or more axial slices 5 mm apart, based on an MRI scan done within 2 weeks prior to randomization<br>• Stable or decreasing dosage of steroids for 7 days prior to the baseline MRI scan<br>• No current or recent (within 4 weeks before randomization) treatment with another investigational drug<br>• Patients who require anti-convulsant therapy must be taking non-enzyme inducing antiepileptic drugs (non-EIAED). Patients previously on EIAED must be fully switched to non-EIAED at least 2 weeks prior to randomization<br>• No underlying or previous conditions that could interfere with treatment, including but not limited to:<br>  • No evidence of active infection requiring hospitalization or |

| | |
|---|---|
| | antibiotics, within 2 weeks prior to randomization<br>• No active infectious keratitis<br>• No other diseases interfering with follow up<br>• No planned vaccinations with live vaccines<br>• Adequate hematological function defined as: neutrophils ≥ 1.5 × $10^9$ cells/L and platelets ≥ 100 × $10^9$ cells/L and hemoglobin ≥ 6.2 mmol/L (9.9 g/dl)<br>• Normal liver function: bilirubin < 1.5× upper limit of the normal range (ULN), alkaline phosphatase and transaminases (ASAT) < 2.5× ULN<br>• Renal function: calculated creatinine clearance ≥ 30 mL/min by the Cockcroft-Gault formula (see Appendix E)<br>• Absence of pregnancy. Women of childbearing potential (WOCBP) must be using an adequate method of contraception to avoid pregnancy throughout the study and for 6 months beyond the end of treatment in such a manner that the risk of pregnancy is minimized. In general, the decision for appropriate methods to prevent pregnancy should be determined by discussions between the investigator and the study subject. WOCBP include any female who has experienced menarche and who has not undergone successful surgical sterilization (hysterectomy, bilateral tubal ligation, or bilateral oophorectomy) or is not postmenopausal. Females should not be breastfeeding.<br>• Post menopause is defined as: amenorrhea ≥ 12 consecutive months without another cause or for women with irregular menstrual periods and on hormone replacement therapy (HRT), a documented serum follicle stimulating hormone (FSH) level > 35 mIU/mL<br>• Women who are using oral contraceptives, other hormonal contraceptives (vaginal products, skin patches, or implanted or injectable products), or mechanical products such as an intrauterine device or barrier methods (diaphragm, condoms, spermicide) to prevent pregnancy, or are practicing abstinence or where their partner is sterile (e.g., vasectomy) should be considered to be of childbearing potential.<br>• Women of childbearing potential must have a negative serum or urine pregnancy test (minimum sensitivity 25 IU/L or equivalent units of HCG) within 72 hours prior to randomization.<br>• Female patients within one year of entering the menopause must agree to use an effective non-hormonal method of contraception during the treatment period and for at least 6 months after the last study treatment.<br>• Males must agree to use an effective method of contraception during the treatment period and for at least 6 months after the last study treatment.<br>• Before patient randomization and study related procedures (that |

| | |
|---|---|
| | would not have been performed as part as standard care), written informed consent must be given according to ICH/GCP, and national/local regulations. Informed consent should also be given for biological material to be stored and used for future research on brain tumors.<br>• Patients with a buffer range from the normal values of +/- 5 % for hematology and +/- 10% for biochemistry are acceptable. A maximum of +/- 2 days for timelines are acceptable (with the exception of the pregnancy test). |
| **Treatment**<br><br>Test product, dose and mode of administration | Arm 1: patients will be treated with ABT-414 1.0 mg/kg IV infusion over 30 to 40 minutes once every 2 weeks in combination with TMZ 150 mg/m$^2$ day 1 to 5, for the first 28-day cycle, with dose escalation to 200 mg/m$^2$ in subsequent cycles in case of good tolerance and until one of the treatment withdrawal criteria has been met.<br><br>Arm 2: patients will be treated with ABT-414 monotherapy 1.0 mg/kg IV infusion over 30 to 40 minutes on days 1 and 15 of every 28-day cycle until one of the treatment withdrawal criteria has been met.<br><br>Arm 3: Patients in the control arm will be treated according to the timing of relapse.<br><br>Arm 3A: Patients relapsing during TMZ treatment or within the first 16 weeks after the first day of the last TMZ cycle will be treated with lomustine 110 mg/m$^2$ on day 1 of every 42-day treatment period. Treatment will continue until one of the treatment withdrawal criteria has been met. Lomustine will be given for a maximum of one year.<br><br>Arm 3B: Patients relapsing 16 weeks or more after the first day of the last TMZ cycle will be treated with TMZ 150 mg/m$^2$ on day 1 to 5 for the first 28-day cycle, with dose escalation to 200 mg/m$^2$ in subsequent cycles in case of adequate tolerance. Treatment will continue until one of the treatment withdrawal criteria has been met. |
| Duration of treatment | Whatever the disease status, the treatment will always be discontinued in case of<br><br>• disease progression<br>• patient refusal<br>• excessive toxicity precluding further therapy, according to the treating physician<br>• physician decision, according the best interest of the patient<br>• start of any other anti-cancer agent or modality; surgery at recurrence is allowed<br>• pregnancy<br><br>Patients 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 patient. If, after treatment discontinuation, there is additional clinical information leading the investigator to conclude that the reason for discontinuation is no longer |

| | |
|---|---|
| | valid (except for toxicity), the subject may resume study treatment as long as no other chemotherapy, radiotherapy, immunotherapy, NovoTTF, or other treatment with antineoplastic intent has been received, with the exception of surgical intervention that yields histology not demonstrative of tumor progression.<br><br>After progression, the treatment will be left to the discretion of the treating physician. Any anti-cancer therapy other than the study drug will not be considered as part of the protocol treatment. |
| **Criteria for evaluation and endpoints**<br><br>Efficacy/Safety | The primary endpoint will be OS at final analysis and PFS according to RANO criteria and assessed by IRC at the interim analysis.<br><br>Secondary endpoints will be:<br><br>• PFS according to RANO criteria and assessed by IRC<br>• Objective response rate (ORR) assessed by IRC<br>• OS in the subgroup with EGFRvIII mutation<br>The following are exploratory endpoints:<br>• Best overall response rate (BOR), complete response rate (CRR), duration of response (DR) assessed by IRC will be computed in each arm<br>• PFS in the subgroup with EGFRvIII mutation<br>• Neurological deterioration-free survival (NDFS)<br>• Frequencies and percentages of worst Adverse Events (AEs) or Laboratory Event grades<br>• Quality of life<br>• Steroid use |
| **Statistical methods** | Analysis populations<br><br>• Intention-to-treat population (ITT): All randomized patients will be analyzed in the arm they were allocated by randomization.<br>• Per protocol population (PP): All patients who are eligible and have received at least one dose of the study drug (i.e. one dose of lomustine or TMZ (arm 3), of ABT-414 (arm 2) and of TMZ and ABT-414 (arm 1)). Patients will be classified and analyzed in the arm they were assigned at the time of randomization.<br>• Safety population (SP): All randomized patients who have received at least one dose of the study drug i.e. one dose of lomustine or TMZ (arm 3), of ABT-414 (arm 2) and of TMZ and ABT-414 (arm 1)). Patients will be classified according to treatment received.<br><br>Global testing strategy<br><br>To meet global regulatory requirements, a multiple testing strategy for the following ordered endpoints will be implemented to control the family-wise type I error (alpha) for comparisons of Arm 1 (ABT-414 + TMZ) versus Arm 3 (TMZ/lomustine) and Arm 2 (ABT-414 alone) versus Arm 3 with respect to overall survival (OS) and the pre-defined secondary efficacy endpoints, namely progression-free survival (PFS), objective response rate |

| | |
|---|---|
| | (ORR), and OS for patients with EGFR vIII mutation.<br>The following null hypotheses are considered:<br>H1: Arm 1 is not superior to Arm 3 in OS.<br>H2: Arm 2 is not superior to Arm 3 in OS.<br>H1a: Arm 1 is not superior to Arm 3 in PFS.<br>H2a: Arm 2 is not superior to Arm 3 in PFS.<br>H1b: Arm 1 is not superior to Arm 3 in ORR.<br>H2b: Arm 2 is not superior to Arm 3 in ORR.<br>H1c: Arm 1 is not superior to Arm 3 in OS among EGFR vIII mutated patients.<br>H2c: Arm 2 is not superior to Arm 3 in OS among EGFR vIII mutated patients.<br>To maintain the overall type I error control for the study, the following null hypotheses will be tested in a fixed sequence of {H1, H2, H1a, H2a, H1b, H2b, H1c, H2c} in order at a 1-sided 2.5% level of significance. Hypothesis H1 will be tested first at a 1-sided 2.5% level. No further tests will be performed if H1 is not rejected. Each hypothesis will be tested in order specified above if H1 and all preceding hypotheses show statistically significant results at the 1-sided 2.5% level of significance. Otherwise testing in the fixed sequence will stop.<br>All other endpoints, e.g., PFS in EGFRvIII mutated, global health/QoL status (GHQs), and neurological disease-free survival (NDFS) are considered exploratory and will be tested at a 2-sided 5% level of significance.<br>Chapter 8 details all statistical methods. |

| | |
|---|---|
| **Translational research** | In this study, biological material will be shipped from the study site to a designated CRO according to instructions provided in the study specific laboratory manual. Following the tissue analysis for EGFR amplification and EGFRvIII mutation, all biologic material will be centralized and stored at [redacted]. From here, the biological material will be used or distributed to the other research laboratories involved in the translational research (TR) projects specified in this protocol or defined in the future.<br><br>The following translational research projects are planned for this protocol<br><br>• Testing for MGMT promoter methylation status of the primary tumor<br>• Assessment of EGFR mutations<br>• Targeted next-generation sequencing of relevant cancer genes<br>• Optional future translational research studies according to questions that may arise during the conduct of the study<br><br>The translational research projects are described in detail in chapter 11. |
| **Quality of Life** | Health-related quality of life patient reported outcomes will be collected using questionnaires (EORTC QLQ-C30 and BN-20). These must be completed at baseline; during treatment at weeks 8 and 16; and at 6 months after randomization for all patients. The primary HRQoL endpoint for this study is clinically relevant (i.e. ≥ 10 points) change from baseline in the global health/HRQoL status scale. |
| **PK – PD** | Serum or plasma samples for the translational research, determination of the concentrations of ABT-414, total ABT-806 antibody and unconjugated cys-mcMMAF will be collected during the study. In addition, serum samples for determination of antidrug antibody will be collected throughout the study. Population PK analyses will be performed to identify demographic and/or disease-specific variable(s) that affect the PK of ABT-414, total ABT-806, and cys-mcMMAF. Dose/exposure analyses for relevant safety, efficacy variables will be conducted to understand the contribution of ABT-414, Total ABT-806 antibody and cys-mcMMAF to efficacy and safety. |
| **Pediatric Sub-Study**<br><br>**(see Appendix I)** | Population: Subjects < 18 years old with histologically proven high grade glioma (HGG: WHO grade III glioma [e.g anaplastic astrocytoma, anaplastic oligodendroglioma, anaplastic oligoastrocytoma], grade IV glioma [e.g glioblastoma, gliosarcoma] or diffuse intrinsic pontine glioma [DIPG]).<br><br>Objective: The primary objective will be the evaluation of safety, tolerability and pharmacokinetic of ABT-414 in a pediatric population < 18 years of age. The secondary objective will be to assess the effect of ABT-414 on tumor response per RANO criteria.<br><br>Methodology: This is an uncontrolled, open-label, single-arm global study.<br><br>Number of patients: There will be no maximum enrollment for children with HGG and EGFR amplified; however it is expected that at least 6 subjects will be enrolled. |

Diagnosis and main criteria for inclusion:

Registration Criteria-

- Subjects must have a histologically proven high grade glioma (WHO grade III glioma [e.g anaplastic astrocytoma, anaplastic oligodendroglioma, anaplastic oligoastrocytoma], grade IV glioma [e.g glioblastoma, gliosarcoma] or DIPG).
- Subjects must be <18 years of age.
- The tumor tissue must have been determined to have EGFR amplification (by local or other testing service)
- Availability of adequate biological material (formalin-fixed paraffin embedded [FFPE] tumor) for central testing of EGFR amplification. There must be sufficient tissue to submit for (retrospective) confirmatory EGFR FISH testing at the study-designated central laboratory. If there are less than the requested 30 slides available, it is acceptable to continue the registration process, assuming sufficient material is available for central testing of EGFR amplification.
- Before patient registration or any study-related procedures that would not have been performed as part of standard care, written informed consent/assent by subjects and/or their legal guardians must be given according to ICH/GCP, and national/local regulations.

Enrollment Criteria -

- Subject must either have recurrent/progressive tumor or, if newly diagnosed, have completed any planned radiation therapy at least 4 weeks prior to first dose of ABT-414.
- The investigator must confirm that the subject is able to complete the procedures required in order to assess the primary endpoints, including PK blood draws and safety assessments over the first four weeks of therapy including Day 1 of Week 5.
- The investigator believes that the potential benefit of treating the pediatric subject with ABT-414 outweighs the expected risks and that this treatment is in the best interests of the pediatric subject.
- Subjects and/or their legal guardians must be able to understand the risks and potential benefits, and grant assent/consent to participate by signing the applicable pediatric-specific informed assent and/or consent forms.
- Subject has sufficiently recovered from previous therapy.
- (For recurrent disease) No prior RT with a dose over 65Gy to the brain, sterotactic radiosurgery or brachytherapy unless the recurrence is histologically proven
- No current or recent (within 4 weeks or 5 half-lives (whichever is shorter) before enrollment) treatment with another investigational drug
- Renal function: calculated creatinine clearance ≥ 30 mL/min by the Cockcroft-Gault formula for pediatric patients ≥12 years of age and estimated glomerular filtration rate ≥ 30 mL/min/1.73 $m^2$ by modified

Schwartz equation for pediatric patients < 12 years of age

- Liver function: Total bilirubin ≤ 1.5 times upper limit of normal (ULN), Aspartate Aminotransferase (AST), and Alanine Aminotransferase (ALT) ≤ 3 times ULN. Subjects with Gilbert's syndrome documented in medical history may be enrolled if total bilirubin is < 3 times ULN. Not allowed are subjects with known chronic liver disease and/or cirrhosis documented by the presence of one or more of the following (assessments to be performed per standard of care only if liver disease is suspected):
  - Liver biopsy with histologic findings consistent with cirrhosis
  - CT or US evidence of liver disease with or without portal hypertension
  - Physical examination and clinical and laboratory evidence of chronic liver disease
  - Colloid shift on a liver-spleen scan
  - A Child-Pugh score of 6 or higher (see Appendix M)
- Absence of pregnancy. Female subjects of childbearing potential must be using an adequate method of contraception to avoid pregnancy from Study Day 1 throughout the study and for 6 months beyond the end of treatment in such a manner that the risk of pregnancy is minimized. In general, the decision for appropriate methods to prevent pregnancy should be determined by discussions between the investigator and the study subject. Female subject of childbearing potential includes any female who has experienced menarche and who has not undergone successful surgical sterilization (hysterectomy, bilateral tubal ligation, or bilateral oophorectomy). Female subjects of non-child bearing potential do not need to use birth control.
- Pediatric female patients are not considered to be of child bearing potential if meeting any of the following criteria:
  - Permanently surgically sterile (bilateral oophorectomy, bilateral salpingectomy, or hysterectomy).
  - Females who have not experienced menarche (at least one menstrual period).
- Female subjects of childbearing potential must have a negative serum or urine pregnancy test (minimum sensitivity 25 IU/L or equivalent units of HCG) within 72 hours prior to enrollment.
- Female subjects must not be pregnant, **breastfeeding, or considering becoming pregnant** during the study or for at least 6 months after the last dose of study drug.
- Male subjects that are **sexually active with female partner(s) of childbearing potential** must agree to use an effective method of contraception from Study Day 1, during the treatment period and for at least 6 months after the last study treatment.

| | |
|---|---|
| | • Male subjects must not be considering **fathering a child or donating sperm** during the study or for at least 6 months after the last dose of study drug.<br>• Before patient registration, enrollment and study-related procedures that would not have been performed as part of standard care, written informed consent must be given according to ICH/GCP, and national/local regulations.<br>• Subject must not have a history of a major immunologic reaction to any IgG-containing agent.<br><br>Treatment: All subjects will receive ABT-414 administered at a starting dose of 1.0 mg/kg (age 6-17) or 1.3 mg/kg (age 0-5) IV every other week. Prophylactic steroid eye drops will be administered as described in the adult protocol. It is at the investigator's discretion to use ABT-414 as monotherapy or in combination with temozolomide.<br><br>Duration of treatment: ABT-414 treatment will continue for up to 12 months.<br><br>Criteria of evaluation: Unless otherwise stated, the criteria of evaluation will be the same in children as in adults. QoL will be measured using the PedsQL Cancer module. Performance status will be measured by Karnofsky/Lansky (and WHO status if initially enrolled prior to implementation of Amendment 5 of the protocol). For the primary endpoint of safety, all adverse events will be coded according to MedDRA preferred term, reported and graded using the NCI CTCAE v4. For the safety assessment, a dose limiting toxicity (DLT) will be defined as any grade 3 or 4 adverse event that is attributed to ABT-414, or an ABT-414 toxicity that results in a delay of the second dose of ABT-414 by more than 14 days.<br><br>Statistical Methods: For a sample size of 6 in HGG with EGFR amplification, the probability of observing at least 1 tumor response will be 82.2% if the true response rate is 25%.<br><br>All subjects who receive at least one dose of ABT-414 will be included in the analysis. No interim analysis is planned. Data will be summarized descriptively.<br><br>Translational research: Tumor specimens will be collected where feasible for the same biomarker analyses as planned for the adult population. Central molecular testing will include but not be limited to EGFR, H3.1, H3.3, BRAF, CDKN2A/B, IDH1, INI1, MGMT, PTEN. Insufficient tissue for Translational Research after EGFR amplification analysis will not prevent enrollment of the pediatric patients.<br><br>PK: Serum and plasma samples for the determination of the concentrations of ABT-414 and unconjugated cys-mcMMAF will be collected during the study. In addition, serum samples for determination of antidrug antibody will be collected throughout the study. |

# 1 Background and introduction

## 1.1 Introduction

Gliomas are the most frequent primary brain tumors in adults, with an annual incidence between 4 and 5 per 100.000 inhabitants (Ref. 1, Ref. 2, Ref. 3). According to the CBTRUS registry in the USA, each year over 20.000 patients are diagnosed with a glioma. Low-grade diffusely infiltrating glioma and anaplastic glioma constitute about 30-40% of all glial tumors in adults. Glioblastoma present most of the remaining 60-70% of glial tumors. Glioblastomas are the most aggressive primary brain tumors in adults, with a median survival of 9 to 15 months. Despite aggressive treatment, glioblastomas invariably relapse after combined chemo-irradiation with temozolomide (RT/TMZ) (Ref. 4). Major prognostic factors for survival are age and performance status at the time of diagnosis (Ref. 5, Ref. 6). No curative treatment exists. Standard treatment consists of surgical resection to the extent feasible followed by radiation and concomitant and adjuvant TMZ therapy.

## 1.2 Chemotherapy and outcome in recurring glioblastoma

Once a glioblastoma recurs, the treatment options are usually limited and no uniformly accepted standard of care exists. The most important prognostic factors in this setting are age, performance status, use of steroids and size/number of enhancing lesions (Ref. 7, Ref. 8). Other factors of relevance may include re-resection (tumor burden), promoter methylation status of O6-methyl-guanine-methyl transferase (MGMT). Many patients deteriorate rapidly at the time of recurrence, making further treatment meaningless. Some patients have recurrences that allow re-resection but most patients have lesions inaccessible for surgery (e.g., involvement of the corpus callosum, deeply seated lesions, or lesions in eloquent areas). Re-irradiation is also being used, despite the risk of cumulative neuro-toxicity and this approach is feasible in patients with lesions of limited size (Ref. 9). The efficacy of re-irradiation in glioblastoma is however debated. Chemotherapy is commonly suggested for recurrent disease. Both nitrosoureas (in particular lomustine) and TMZ provide options for selected patients. Studies of retreatment with TMZ at the time of relapse suggest that this approach may be effective in selected patients: especially after a treatment free interval or in the presence of MGMT promoter methylation (Ref. 10). The RESCUE trial, on continuous daily dosing of TMZ in patients having relapsed after RT/TMZ analyzed outcome in relation to the interval between the end of initial chemotherapy and salvage TMZ treatment (Ref. 11). In the entire group, PFS-6 was 23.9% but PFS-6 in the patients relapsing more than two months after the end of TMZ was 35.7%, as opposed to only 7.4% in the patients relapsing after more than 6 cycles of adjuvant TMZ but while still on TMZ treatment. Of note, PFS-6 was 23.9% for patients relapsing during the first 6 cycles of adjuvant TMZ, but here no minimum interval between the end of RT and study entry was specified. The outcome in this last group is quite likely explained by the presence of pseudo-progression and radiation necrosis early after the end of RT, with likely spontaneous improvement over time even in the absence of treatment (Ref. 12, Ref. 13). With respect to OS, only 12 month OS was reported: this was 28% for patients relapsing more than 3 months after the end of TMZ adjuvant treatment and 14% for the patients relapsing within 3 months or during TMZ treatment. Historical data (EORTC 26981) suggest that 60% of randomized patients will relapse before 3 months after the end of adjuvant TMZ treatment, and 40% thereafter (relapses during RT or in the 3 months thereafter are not eligible). The data of EORTC study 26981 also suggest that two-thirds of patients that do not progress until more than three months after the end of TMZ will have a methylated MGMT promoter. There are quite some data available on the outcome of TMZ retreated relapsing glioblastoma patients. The important role of adequate patient selection for retreatment with TMZ is further supported by the initial results reported at ASCO 2014 of the German randomized phase II DIRECTOR trial on ‘week on-week off’ TMZ versus ‘three weeks on-one week off’

TMZ (Tabatabai et al, ASCO 2014, abstract #2015, personal communication). This study did not yield a clinically interesting result in the entire study population. However, the presented analysis based on MGMT promoter methylation is most interesting and shows the same signal as a study by Han et al on dose intensified TMZ retreatment: PFS-6 after dose intensified TMZ was 39.7% in patients with a methylated MGMT promoter gene, vs. 6.9% in patients without MGMT promoter methylation (Ref. 14). Median OS in the MGMT promoter methylated glioblastoma was 55 weeks, and in the unmethylated 34 weeks. This is comparable to the observed OS of 12 and 8 months respectively for the methylated and unmethylated glioblastoma patients in the Dutch BELOB trial; for the lomustine single agent arm the OS figures are 10 and 6 months. Extrapolating from this, it is reasonable to assume that median OS will be in the 10-12 months range for the MGMT promoter methylated and in the 6-8 months range for the unmethylated MGMT promoter glioblastoma and to assume that patients relapsing less than 3 months after completion of TMZ predominantly have a MGMT promoter unmethylated tumor and the patients relapsing more than 3 months after TMZ predominantly have a MGMT promoter methylated tumor.

Nitrosoureas are widely used in relapsed glioblastoma, in particular lomustine (CCNU) but also fotemustine (Ref. 15). A recent randomized study on recurrent glioblastoma that used lomustine noted a 19% PFS probability at 6 months with lomustine, similar to what has previously been observed with TMZ in this indication. Because of these results, lomustine is currently used as comparator in many randomized controlled trials (e.g., the REGAL study, the enzastaurin study, the Dutch BELOB trial, but also the ongoing EORTC study 26101) (Ref. 16, Ref. 17, Ref. 18).
Although bevacizumab, an angiogenesis inhibitor, is widely used for recurrent glioblastoma, in the absence of well-controlled trials its role remains unclear. A first controlled phase II study revealed limited single agent activity of bevacizumab, and preliminary evidence of activity of the combination bevacizumab and lomustine but results of the confirmatory EORTC phase III study are still pending (Ref. 18).

To conclude, with the currently available treatments recurrent glioblastoma remains an unmet clinical need, and to meet that need novel agents must be investigated.

## 1.3 EGFR in glioblastoma

Despite several negative trials of epidermal growth factor receptor (EGFR) inhibitors in glioblastoma, the genetic and molecular analysis of glioblastoma continues to suggest that the EGFR signaling pathway is a compelling target for drug therapy. Fifty to sixty percent of glioblastomas demonstrate abnormalities of the EGFR pathway: 60% show overexpression of the receptor, in 45-50% the EGFR receptor is amplified, and about half of EGFR-amplified tumors harbor a constitutively activated EGFRvIII mutation in parts of the tumor. The EGFRvIII mutation is an intragenic gene rearrangement generated by an in-frame deletion of exons 2-7 that encode part of the extracellular region. If present, this mutation is usually expressed in focal areas of the tumor. In addition to the EGFRvIII mutation, other EGFR mutations are frequently present in EGFR amplified tumors (Ref. 19). However, the exon 19-21 mutations that signify sensitivity to EGFR inhibitors in NSCLC are virtually absent in glioblastoma. Although these EGFR mutations appear to play a pivotal biological role in individual tumors, they do not have a significant prognostic implication for OS in glioblastomas treated with RT/TMZ (Ref. 20). Still both EGFRvIII and EGFR amplifications are key oncogenic events in glioblastoma, and EGFRvIII mutation enhances the tumorigenic potential of glioblastoma by activating and sustaining mitogenic, anti-apoptotic, and pro-invasive signaling pathways (Ref. 21, Ref. 22).

Preliminary research at Erasmus MC on a series of 51 paired glioblastoma samples taken from first diagnosis and at the time of recurrence, shows that in the majority of cases the EGFR status (EGFRvIII/EGFR amplification/EGFR normal) remains the same at the time of relapse. More in detail, of 20

high-level EGFR amplification patients only one lost the amplification, whereas only two of the other cases developed high-level amplification at the time of recurrence. This implies that EGFR amplification status at first diagnosis is a reasonable predictor of EGFR amplification status at the time of progression.

## 1.4 EGFR as a target in glioblastoma

In view of the prominent presence of EGFR signaling abnormalities many trials have explored the activity of EGFR inhibitors in recurrent glioblastoma, either using monoclonal antibodies or Tyrosine Kinase Inhibitors (TKI) (Ref. 23, Ref. 24). Invariably, these trials were negative, including studies on the first generation EGFR TKIs gefitinib and erlotinib, but also studies on second generation TKI's such as afatinib and lapatinib. Other studies evaluated monoclonal antibodies, in particular cetuximab and nimotuzumab (Ref. 25). Notably, these studies did not restrict enrollment to glioblastoma patients with EGFR amplification, and several of these drugs are unlikely to cross an intact blood brain barrier. Currently, clinical testing is underway with dacotinib, an irreversible EGFR inhibitor that has been demonstrated to cross the blood brain barrier in preclinical models. The failure of the anti-EGFR agents to improve outcome are assumed to be related to the limited drug penetration, the absence of exon 19-21 mutations in glioblastoma, and the failure to significantly affect downstream signaling despite target inhibition, because of parallel signaling pathways. These assumptions question the classical targeting with EGFR inhibitors in glioblastoma.

A different approach is to target the EGFR alterations present in 50-60% of glioblastoma as a means to deliver cytotoxic compounds. A variety of constructs has been developed, in which toxins or antineoplastic agents are targeted to EGFR or EGFRvIII (Ref. 26). The absence of EGFRvIII and activated EGFR in normal tissues makes this tumor-specific alteration a potential candidate for such approaches. ABT-414 is an example of this approach which uses an antibody-drug conjugate (ADC) designed for the treatment of tumors expressing EGFR (Ref. 27). Antibody-drug conjugates are a rapidly growing class of cancer drugs that combine the targeting properties of monoclonal antibodies (mAbs) with the anti-tumor effects of very potent cytotoxic drugs. This approach may be successful where tumor cells use redundant signaling pathways to avoid other targeted approaches. A similar ADC (T-DM1) using trastuzumab as the targeting antibody and the microtubule-inhibitory agent DM1 as the cytotoxic was very active in trastuzumab-resistant metastatic breast cancer (Ref. 28). Significant technical advances in linker stability and toxin potency are primarily responsible for the resurgence in ADC development.

The EGFRvIII variant can also elicit an immunogenic response, and currently a vaccine against the EGFRvIII mutations is being investigated in a global phase III trial (Ref. 29). Its clinical significance is still unclear.

## 1.5 ABT-414 and recurrent glioblastoma

ABT-414 is a newer generation ADC consisting of: (1) a veneered "humanized" recombinant IgG1κ antibody (ABT-806) that has binding properties specific to a unique epitope of human EGFR with (2) non-cleavable maleimido-caproyl linkers each attached to (3) a potent antimicrotubule agent, monomethylauristatin F (MMAF). The antibody binds to the activated EGFR epitope (even in the absence of the EGFRvIII mutation), is internalized, and then intracellular enzymes release the toxin leading to inhibition of microtubule function, the disruption of critical cellular processes, and cell death. Importantly, ABT-414 binds to an epitope that is available predominantly on tumor cells with either the EGFRde2-7 (EGFRvIII) deletion mutant or on tumor cells with activated wild-type EGFR (i.e., with EGFR amplification). The epitope is largely inaccessible when EGFR is expressed at normal physiological levels; thus, ABT-414 has limited binding to non-activated, wild-type EGFR expressed on normal tissues. These properties, therefore, favor limited effects of the toxin on normal tissues while maintaining a high degree of activity on EGFR-overexpressing tumor cells. ABT-414 has shown tumor regression in EGFR wild type and mutant EGFRvIII GBM models.

In an ongoing phase I study in glioblastoma, ABT-414 given intravenously (IV) every other week is investigated with radiotherapy and daily temozolomide (RT/TMZ) (Arm A) or with TMZ day 1-5 every four weeks (Arm B). The latter recruited both newly diagnosed and recurrent glioblastoma subjects; in the newly diagnosed setting, ABT-414 was combined with monthly maintenance TMZ after completion of chemo-radiation, whereas in recurrent glioblastoma ABT-414 was administered with TMZ re-challenge. In this phase I project, responses have been observed. Preliminary efficacy results to date showed that 4 out of 15 recurrent glioblastoma subjects in Arm B had objective responses, including 1 of 3 patients treated at 0.5 mg/kg, 2 of 5 subjects at 1.0 mg/kg, 0 of 3 subjects at 1.0 mg/kg and 1 of 4 subjects at 1.5 mg/kg (ASCO abstract 2014 and personal communication from AbbVie). Three of these responses occurred in patients with EGFRvIII mutation or amplification. The remaining responding patient who relapsed one year after combined chemo-irradiation, had a methylated MGMT promoter and had low EGFR expression level; therefore, the response may have been due to TMZ. Of 6 tumors that were EGFR amplified in recurrent glioblastoma, 3 objective responses were observed. Their responses were durable, as these 3 patients were on study for between 5.5 to 12.5 months (personal communication AbbVie), and 2 of the 3 patients are still receiving ABT-414 to date. Moreover, in the first-in-man-phase I study, a response to ABT-414 monotherapy was observed in a non-CNS metastatic tumor (triple negative breast cancer) with EGFR amplification. These data warrant further exploration of ABT-414 in recurrent glioblastoma, alone and in combination with TMZ. Both the current data on responding patients and the mechanism of action of the compound warrant conducting the trial in an enriched recurrent glioblastoma population characterized by EGFR amplification.

## 1.6 Pharmacokinetics of ABT-414

In preclinical studies, ABT-414 pharmacokinetics was characterized following a single bolus intravenous (IV) dose in CD-1 mice, Sprague-Dawley rats, and cynomolgus monkeys. Additional studies characterized ABT-414 pharmacokinetics following once-weekly dosing in CD-1 mice and cynomolgus monkeys (4 doses). In all studies, the ABT-414 pharmacokinetic profiles were characteristic of a monoclonal antibody, with low serum clearance (0.27 to 0.34 mL/hr/kg), small volumes of distribution (79.0 to 85.7 mL/kg) and a terminal half-life (t1/2) of 8.0 to 9.5 days. The area under the concentration-time curve (AUC) values for ABT-414 were approximately 40% to 50% lower than those of total ABT-806 (unconjugated ABT-806 and ABT-806-mcMMAF combined). Plasma concentrations of unconjugated cys-mcMMAF were very low following dosing with ABT-414, with both maximum observed plasma concentration (Cmax) and AUC values more than 3 to 5 orders of magnitude lower than Cmax and AUC of ABT-414. Following repeated once-weekly dosing in mice and monkeys, ABT-414 pharmacokinetics were characterized by dose proportional increases in AUC, with values after the third dose being approximately 1.2- to 2.4-fold higher than those obtained after the first dose.

Cys-mcMMAF, identified as a metabolite of ABT-414, is eliminated through the hepatic-biliary pathway and is a substrate of human P-glycoprotein (P-gp, MDR-1). At concentration up to 1 µM, cys-mcMMAF was not a direct, time-or metabolism-dependent inhibitor of CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, or CYP3A4/5, nor an inducer of CYP1A2, 2B6, or 3A/4/5 enzyme activity or gene expression and thus, is unlikely to have drug-drug interaction in combination studies.

The human pharmacokinetics of ABT-414 are under investigation in two ongoing clinical studies. Study M12-356 is a Phase 1 study of ABT-414 in combination with RT plus TMZ, with TMZ, or as single-agent ABT-414 in subjects with glioblastoma multiforme. Study M13-379 is a first-in-human (FIH) Phase 1/2 study in subjects with advanced solid tumors likely to overexpress EGFR. The dose range studied was 0.5 to 3.2 mg/kg in M12-356 and 1 to 4 mg/kg in M13-379 study. The pharmacokinetic data from both studies indicate that the systemic exposures (AUC and Cmax) of ABT-414, total ABT-806, and cys-mcMMAF achieved after administration of ABT-414 via IV infusion were approximately dose-

proportional. ABT-414 serum exposure was moderately lower than that of total ABT-806. In M13-379, for dose-normalized Cmax, cys-mcMMAF was approximately 400 -fold lower than that of ABT-414 in molar concentration. The observed harmonic mean terminal phase elimination half-life ranged approximately from 7.5 to 12 days and 9 to 15 days for ABT-414 and total ABT-806, respectively. The observed mean clearance of ABT-414 ranged approximately from 0.19 to 0.37 mL/h/kg. The observed harmonic mean terminal phase elimination half-life of cys-mcMMAF was approximately 4 days.

## 1.7 Safety profile of ABT-414

Subjects in ABT-414 ongoing studies have reported frequent ophthalmologic toxicities, more commonly at the 1.0 mg/kg dose level and above. ABT-414 is composed of an EGFR targeted antibody bound to a microtubule toxin, MMAF. MMAF has been described to cause a unique and specific toxicity to the cornea; the formation of corneal epithelial microcysts. These microcysts are thought to be in reaction to damage caused by MMAF to the rapidly dividing transient amplifying cells that give rise to the cornea. When this damage occurs, these cells become necrotic and produce very small microcysts that become lodged in the early corneal layer. As the cornea regenerates, the microcysts traverse across the cornea, causing a variety of symptoms, and ultimately are sloughed off when a completely new cornea re-generates. It should be noted that this process can take 3-4 weeks and thus symptoms that arise may take at least a month or more before they start to improve. These adverse events have included dry eyes, blurry vision, eye pain, photophobia and watery eyes. Similar ophthalmologic toxicities have been previously reported with another MMAF compound, SGN-75 (Ref. 30). The ophthalmology examination findings with SGN-75 as well as with ABT-414 are similar to the findings noted with high dose cytarabine administration. Dexamethasone eye drops are commonly used with high dose cytarabine administration to prevent the formation of epithelial microcysts. The steroid ophthalmic solution is thought to reduce the cellular turnover in the epithelium and thus make the cells more resistant to the effects of chemotherapy damage. Dexamethasone, or an equivalent steroid ophthalmologic solution, will be recommended around the time of each ABT-414 infusion for all ABT-414 trials.

At the current recommended phase II dose of 1.25 mg/kg via IV infusion every 2 weeks for ABT-414 in combination with TMZ in Arm B, 1 of 10 subjects had a severe adverse event of the eye attributable to ABT-414. In Arm C, which tested ABT-414 at 1.25 mg/kg as monotherapy in recurrent GBM, 2 of the 8 patients enrolled had adverse eye events attributable to ABT-414.

In the ongoing phase I study, as of April 29 2015, 40 subjects have been treated in Arm B and 42 in Arm C. Common treatment emergent AEs in at least 30% of subjects in Arm B included photophobia (15/37.5%), blurred vision (23/57.5%), nausea (19/47.5%), fatigue (17/42.5%) and headache (12/30%); in Arm C, they were blurred vision (25/59.5%) and fatigue (24/57.1%). Grade 3/4 AEs found in > 10% of subjects in Arm B included keratitis (5/12.5%), gamma GT elevation (4/10%) and decreased platelet (4/10%); in Arm C, the only grade 3/4 AEs of > 10% was keratitis (6/14.3%). Overall, in the 1.25 mg/kg dose cohort the grade 3/4 ocular toxicity rate was 27%. ABT-414 administration was suspended in those who developed grade 3/4 eye toxicity until symptoms recovered to grade 1, which took a median of 40 days.

Because of the high rate of significant eye toxicity and the need for drug interruption, the starting dose of ABT-414 for the present study for both Arm 1 and 2 will be 1.00 mg/kg.

**Additional Safety Information:**

Preliminary safety data were available for 488 subjects who received at least 1 dose of ABT-414 in 4 open-label studies at the most recent IB update (version 7.0). This Phase 2 Study M14-483 (INTELLANCE-2) in recurrent GBM is the only trial for which safety data from a control arm (TMZ or lomustine monotherapy) is available. Adverse events reported for more than 20% of subjects receiving ABT-414

were fatigue (34.9%), vision blurred (27.3%), headache and keratitis (25.0% for each), dry eye (24.4%) and corneal epithelial microcysts (22.1%). The majority of subjects who received ABT-414 (77.3%) experienced at least 1 Treatment Emergent Adverse Event coded to the Standard Organ Class of Eye Disorders. In addition to ocular side effects related to corneal epitheliopathy, treatment-emergent adverse events reported by ≥ 10% of subjects in the ABT-414 treatment groups and ≥ 5% more frequently than the lomustine/TMZ control group included headache, fatigue, constipation, and liver transaminase elevations (alanine aminotransferase and aspartate aminotransferase). The rate of constipation was mainly accounted for by the ABT-414/TMZ combination arm, for which the rate was similar to that of subjects receiving TMZ monotherapy.

In an ongoing blinded study in newly diagnosed GBM (M13-813 (RTOG 3508)), one subject receiving ABT-414 (unblinded) with radiation and TMZ in the chemoradiation phase and with TMZ in the adjuvant phase experienced Grade 5 (fatal) events of acute liver injury and cerebral edema after approximately 5 months of treatment. The subject had grade 4 GGT (>33x ULN) and grade 1 fatty liver at Screening. The investigator considered the event of fatal acute liver injury to be reasonably possibly related to ABT-414. The sponsor also assessed that there was a reasonable possibility that ABT-414 caused or contributed to the liver injury and subsequent death. The above-described case is the only event of fatal liver injury that has been reported in ABT-414 open-label or blinded studies, in which approximately 809 people have received ABT-414 to date.

Taken together, the efficacy and safety data available to date demonstrate an acceptable benefit/risk profile of ABT-414 in patients with EGFR-amplified GBM and support continued clinical research of this investigational agent in the current trial.

## 1.8 Potential combination effect of ABT-414 with temozolomide and the choice for the control arm

In a U87 model expressing EGFRvIII, the activity of RT/TMZ was significantly increased when ABT-414 was co-administered, whereas ABT-414 plus TMZ was more effective compared to ABT-414 with RT. The responses observed in the ongoing phase I study were on patients receiving both TMZ and ABT-414. This leaves the possibility open that TMZ may add to the activity of ABT-414. In case of favorable results in the combination arm ABT-414/TMZ it will be possible that this is in part caused by activity of TMZ. This brings the need to design phase II studies in a way this can be addressed. It is however not justifiable to have a control arm with TMZ in a phase II study on recurrent glioblastoma, as many glioblastoma patients are relapsing during or shortly after TMZ chemotherapy. In these patients, retreatment with temozolomide is not rational, and another comparator is needed. Still, having TMZ treated patients in the control arm will allow some further analysis of a potential TMZ contribution to the outcome. As illustrated above, for selected glioblastoma patients (in particular those relapsing more than three months after the end of adjuvant TMZ adjuvant chemotherapy) TMZ re-treatment is an option. Therefore, the treatment in the control arm will depend on the timing of relapse in relation to the end of adjuvant TMZ treatment (as part of the initial treatment with chemo-irradiation). Thus, this study will be developed as a three-arm study with the control arm being treated by either lomustine or TMZ depending on the timing of the relapse: (A) patients relapsing within 3 months from the end of adjuvant TMZ cycles (16 weeks from the first day of the last TMZ cycle) will receive lomustine; (B) patients relapsing three months or more after the end of TMZ chemotherapy (16 weeks from the first day of the last TMZ cycle) will receive TMZ standard dosing day 1-5 every 4 weeks.

## 1.9 Evaluation of ABT-414 in Children with High Grade Gliomas

Appendix I provides information related to the evaluation of ABT-414 in children (M14-483 pediatric sub-study). Unless specifically addressed in Appendix I, all of the adult protocol elements will apply to the pediatric population.

Background: Pediatric high grade gliomas [HGG] (WHO grade III and IV glioma and diffuse intrinsic pontine glioma [DIPG]) have no adequate therapy and are almost universally fatal. Unlike in adult GBM, EGFR amplification is rare (3% or lower) in pediatric HGG and screening for EGFR amplification is not routinely part of standard care for pediatric tumors, which makes it profoundly difficult to identify children with EGFR amplified HGG. Consequently, it is not feasible to conduct a stand-alone study in this population. It is most important that a pediatric study in EGFR-amplified HGG addresses whether a proposed dose of ABT-414 can be used safely in the pediatric population, with recognition that assessment of efficacy beyond a description of outcomes in a very small number of subjects is likely infeasible.

# 2 Objectives of the trial

## 2.1 General objectives

The objectives of the trial are to assess whether ABT-414 alone or in combination with TMZ improves overall survival (OS), PFS, tumor response, quality of life, NDFS and steroid use compared to standard treatment with lomustine single agent or TMZ re-challenge in patients with centrally confirmed recurrent EGFR-amplified glioblastoma.

Additional exploratory objectives include analyses by stratum of EGFR pathway abnormalities (specifically EGFRvIII mutation), correlation of MGMT methylation status with clinical outcome (PFS/OS), and exploratory clinical and translational research program.

The objectives will be achieved within a testing strategy, which aims to preserve the global type I error. The objectives will be realized according to the following hierarchical sequence: OS, PFS, response, OS in EGFRVIII mutated. Secondary objectives not included in the testing sequence will be realized for exploratory purpose.

## 2.2 End-points

### 2.2.1 Primary endpoint

The primary endpoint will be OS at final analysis and Progression Free Survival (PFS) according to RANO criteria and assessed by IRC at the interim analysis.

### 2.2.2 Secondary endpoints

Secondary endpoints will be:

- PFS according to RANO criteria and assessed by IRC
- Objective response rate (ORR) assessed by IRC
- OS in the subgroup with EGFRvIII mutation

The following are exploratory endpoints:

- Best overall response rate (BOR), complete response rate (CRR), duration of response (DR) assessed by IRC will be computed in each arm
- PFS in the subgroup with EGFRvIII mutation
- Neurological deterioration-free survival (NDFS)

- Steroid use
- Frequencies and percentages of worst Adverse Events (AEs) or Laboratory Event grades
- Quality of life

# 3 Patient selection criteria

Patients with histologically confirmed de novo (primary) glioblastoma may register and have their tumor tissue screened after diagnose and before tumor progression. Eligibility at the time of tumor progression will depend on the confirmation of EGFR amplification during the screening, the fulfillment of all other patient selection criteria and the trial status (whether the study is still open for accrual).

**For patients < 18 years old, please refer to the inclusion criteria listed in Appendix I**

## 3.1 Registration

- Histologically confirmed de novo (primary) glioblastoma before or at the time of first progression after RT concurrent/adjuvant TMZ chemotherapy.
    - In case of testing at the time of first progression: either at least 3 months after the end of radiotherapy or have tumor progression that is clearly outside the radiation field or have tumor progression unequivocally proven by surgery/biopsy
- Age ≥ 18 years
- Absence of any psychological, familial, sociological or geographical factors potentially hampering compliance with the study protocol and follow-up schedule; such conditions should be assessed with the patient before registration in the trial.
- Availability of adequate biological material (formalin-fixed paraffin embedded [FFPE] tumor) for central testing of EGFR amplification
- Written informed consent for central EGFR screening must be given according to ICH/GCP, and national/local regulations.

## 3.2 Randomization

The following criteria should be assessed within 2 weeks prior to randomization.

- Histologically confirmed *de novo* (primary) glioblastoma with unequivocal first progression after RT concurrent/adjuvant TMZ chemotherapy either at least 3 months after the end of radiotherapy or have tumor progression that is clearly outside the radiation field or have tumor progression unequivocally proven by surgery/biopsy
- Presence of EGFR amplification confirmed by central assessment; patients with undetermined EGFR status are excluded
- WHO Performance status 0 - 2 (see Appendix C)
- No prior treatment with nitrosoureas
- No prior treatment with bevacizumab
- No previous exposure to EGFR targeted agents, including EGFRvIII targeting agents and participation to placebo controlled trials on EGFR targeted agents
- No prior discontinuation of temozolomide chemotherapy for toxicity reasons
- No more than one line of chemotherapy for GBM (concurrent and adjuvant TMZ based chemotherapy including in combination with another investigational agent is considered one line of chemotherapy). Chemotherapy must have been completed at least 4 weeks prior to randomization.
- No prior RT with a dose over 65 Gy to the brain, stereotactic radiosurgery or brachytherapy unless the recurrence is histologically proven

- No previous other malignancies, except for any previous malignancy which was treated with curative intent more than 5 years prior to randomization, 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 known hypersensitivity
    - to any part of the ABT-414 compound, TMZ, dacarbazine or lomustine formulations
    - to any IgG containing agent
- No history of Coeliac disease and wheat allergy
- Patient may have been operated for recurrence. If operated:
    - residual and measurable disease after surgery is not required but surgery must have confirmed the recurrence
    - a post-surgery MRI must be available within 48 hours following surgery, however an MRI scan has to be done within 2 weeks prior to randomization
    - surgery completed at least 2 weeks before randomization and patients should have fully recovered as assessed by investigators. Criteria for full recovery will include absence of active post-operative infection, recovery from medical complications and capacity for fluid and food intake.
- For non-operated patients, recurrent disease must include at least one bi-dimensionally measurable contrast-enhancing lesion with clearly defined margins by MRI scan, with minimal diameters of 10 mm, visible on 2 or more axial slices 5 mm apart, based on an MRI scan done within 2 weeks prior to randomization
- Stable or decreasing dosage of steroids for 7 days prior to the baseline MRI scan
- No current or recent (within 4 weeks before randomization) treatment with another investigational drug
- Patients who require anti-convulsant therapy must be taking non-enzyme inducing antiepileptic drugs (non-EIAED). Patients previously on EIAED must be fully switched to non-EIAED at least 2 weeks prior to randomization
- No underlying or previous conditions that could interfere with treatment, including but not limited to:
    - no evidence of active infection requiring hospitalization or antibiotics, within 2 weeks prior to randomization
    - no active infectious keratitis
    - no other diseases interfering with follow up
- No planned vaccinations with live vaccines
- Adequate hematological function defined as: neutrophils ≥ $1.5 \times 10^9$ cells/L and platelets ≥ $100 \times 10^9$ cells/L and hemoglobin ≥ 6.2 mmol/L (9.9 g/dl)
- Normal liver function: bilirubin < 1.5× upper limit of the normal range (ULN), alkaline phosphatase and transaminases (ASAT) < 2.5× ULN
- Renal function: calculated creatinine clearance ≥ 30 mL/min by the Cockcroft-Gault formula (see Appendix E)
- Absence of pregnancy. Women of childbearing potential (WOCBP) must be using an adequate method of contraception to avoid pregnancy throughout the study and for 6 months beyond the end of treatment in such a manner that the risk of pregnancy is minimized. In general, the decision for appropriate methods to prevent pregnancy should be determined by discussions between the investigator and the study subject. WOCBP include any female who has experienced menarche and

who has not undergone successful surgical sterilization (hysterectomy, bilateral tubal ligation, or bilateral oophorectomy) or is not postmenopausal. Females should not be breastfeeding.

- Post menopause is defined as: amenorrhea ≥ 12 consecutive months without another cause or for women with irregular menstrual periods and on hormone replacement therapy (HRT), a documented serum follicle stimulating hormone (FSH) level > 35 mIU/mL
- Women who are using oral contraceptives, other hormonal contraceptives (vaginal products, skin patches, or implanted or injectable products), or mechanical products such as an intrauterine device or barrier methods (diaphragm, condoms, spermicide) to prevent pregnancy, or are practicing abstinence or where their partner is sterile (e.g., vasectomy) should be considered to be of childbearing potential.
- Women of childbearing potential must have a negative serum or urine pregnancy test (minimum sensitivity 25 IU/L or equivalent units of HCG) within 72 hours prior to randomization.
- Female patients within one year of entering the menopause must agree to use an effective non-hormonal method of contraception during the treatment period and for at least 6 months after the last study treatment.

- Males must agree to use an effective method of contraception during the treatment period and for at least 6 months after the last study treatment.
- Before patient randomization and study related procedures (that would not have been performed as part as standard care), written informed consent must be given according to ICH/GCP, and national/local regulations.
- Patients with a buffer range from the normal values of +/- 5 % for hematology and +/- 10% for biochemistry are acceptable. A maximum of +/- 2 days for timelines are acceptable (with the exception of the pregnancy test).

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

# 4 Study Procedures

This is a randomized open label multicenter phase II trial (see objectives in chapter 2).

For detailed statistical considerations, see chapter 8.

Patients will be randomized at the EORTC headquarters **after verification of the eligibility criteria (see chapter3)** to receive one of the following:

Arm 1: patients will be treated with ABT-414 1.0 mg/kg IV infusion over 30 to 40 minutes once every 2 weeks in combination with TMZ 150 mg/m$^2$ day 1 to 5, for the first 28-day cycle, with dose escalation to 200 mg/m$^2$ in subsequent cycles in case of adequate tolerance and until one of the treatment withdrawal criteria has been met. In this Arm 1 the schedule of clinical and lab assessments follows the cycle of TMZ (a delay of TMZ delays the assessment schedule, withholding ABT-414 does not affect the assessment schedule).

Arm 2: patients will be treated with ABT-414 monotherapy 1.0 mg/kg IV infusion over 30 to 40 minutes once every 2 weeks until one of the treatment withdrawal criteria has been met.

Arm 3: Patients in the control arm will be treated according to the timing of relapse.

Arm 3A: Patients relapsing during TMZ treatment or within the first 16 weeks after the first day of the last TMZ cycle will be treated with lomustine 110 mg/m$^2$ on day 1 of every 42-day treatment period.

Treatment will continue until one of the treatment withdrawal criteria has been met. Lomustine will be given for a maximum of one year.

Arm 3B: Patients relapsing 16 weeks or more after the first day of the last TMZ cycle will be treated with TMZ 150 mg/m$^2$ on day 1 to 5 for the first 28-day cycle, with dose escalation to 200 mg/m$^2$ in subsequent cycles in case of adequate tolerance. Treatment will continue until one of the treatment withdrawal criteria has been met.

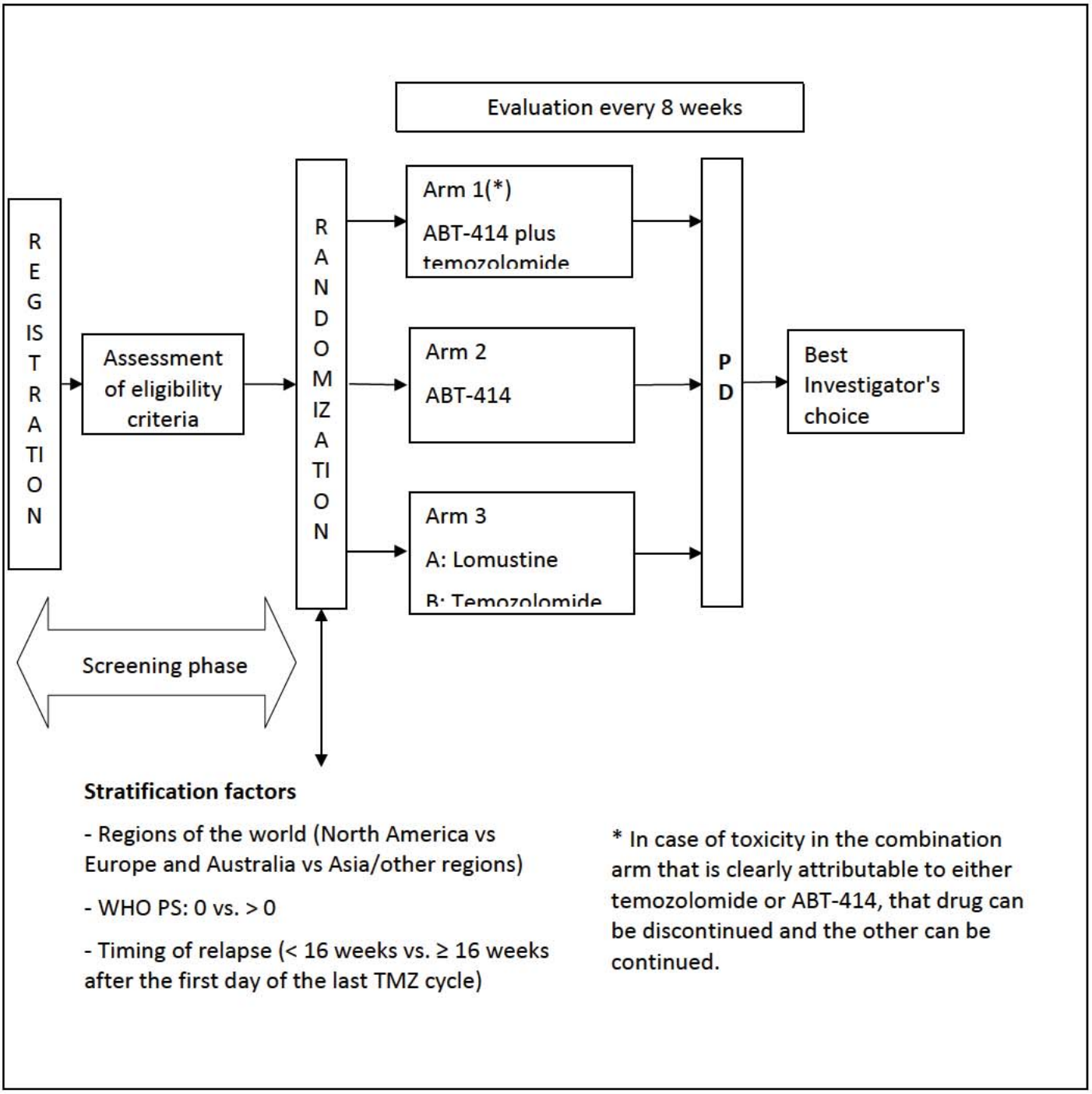
Treatment should start within 96 hours from randomization.

Treatment at further progression will be according to investigators discretion. Day 1 of the first cycle will be the first day when the study medication is taken.

There will be an interim futility analysis organized. At interim analysis one or both of the ABT-414 arms might be discontinued based on lack of efficacy for PFS (Reject H1 in favor of H0) according to RANO criteria assessed by IRC (see section 8.3).

Disease will be assessed by study-specific MRI according to the study specific imaging protocol every 8 weeks. Response and progression will be assessed by the RANO criteria (see section 7.1).

The safety profile will be assessed separately for each cycle of therapy with CTCAE v4 (see section 7.2).




**Stratification factors**

- Regions of the world (North America vs Europe and Australia vs Asia/other regions)
- WHO PS: 0 vs. > 0
- Timing of relapse (< 16 weeks vs. ≥ 16 weeks after the first day of the last TMZ cycle)

* In case of toxicity in the combination arm that is clearly attributable to either temozolomide or ABT-414, that drug can be discontinued and the other can be continued.

# 5 Therapeutic regimens, expected toxicity, dose modifications

## 5.1 General information

### 5.1.1 ABT-414

Guidelines for ABT-414 dose preparation, volume, and rate of infusion will be supplied by AbbVie to the site staff, within the study manual.

#### 5.1.1.1 Drug supplies

Drug supplies and re-supplies will be provided free of charge by AbbVie as long as patients are on protocol treatment (for procedures: see study manual that will be provided at the time of activation).

The investigator should ensure that the investigational product is stored in accordance with the environmental conditions (temperature, light, and humidity) as determined by AbbVie. If concerns regarding the quality or appearance of the investigational product arise, do not dispense the investigational product and contact AbbVie immediately. Pharmacy and clinic personnel should wear disposable chemotherapy gloves. Pregnant personnel should avoid exposure to the medication.

#### 5.1.1.2 Packaging, dispensing and storage

Medication labels will comply with the legal requirements as applicable and will be printed in the local language. The storage conditions for study drug will be described on the medication label.

#### 5.1.1.3 Drug reconciliation procedures

Accountability of the investigational study drug(s) is under the responsibility of the investigator and can be delegated to an appropriately qualified person.

The Investigator or representative will verify that study drug supplies are received intact, at the appropriate temperature and in the correct amounts. This will be documented by signing and dating the Proof of Receipt or similar document or via direct recording in the Interactive response technology (IRT)

An overall accountability of the study drug will be performed and verified by the AbbVie monitor throughout the study and at the study site closeout visit. An accurate running inventory of study drug will be maintained utilizing the IRT drug accountability module and, if required, according to your institutional policy, which should include the lot number, POR number(s), the bottle/kit numbers, and the date study drug was dispensed for each subject.

In the event that the IRT is not operable, the above information will be documented on forms provided by the Sponsor.

After verification of drug accountability, used/empty vials may be destroyed at the site according to local regulations governing biohazardous waste. Destruction of used study supplies must be documented. All unused study drug unit doses must be inventoried, accounted for, and returned to AbbVie or destroyed per instructions from AbbVie and according to local regulations. A copy of the Return Shipment Form, in accordance with instructions provided by the AbbVie monitor, will also be included in the shipment.

Labels must remain attached to the containers. If pre-arranged between AbbVie and the site, destruction of the study drug may be performed at the site.

In addition to internal accountability documentation on site, EORTC/AbbVie study-specific accountability and drug destruction forms will be supplied for this purpose, if site-specific forms are deemed not

sufficiently detailed or do not provide enough information, according to EORTC Quality Assurance criteria.

The medication provided for this trial is to be used only as indicated in this protocol and only for the patients entered in this study.

### 5.1.2 Lomustine

Lomustine is considered as a standard treatment in many countries for this indication and commercial sources will be used. The exception will be in countries where Lomustine is not available commercially or in countries which mandate sponsor to supply drugs within the context of clinical trials. For those countries, AbbVie may provide or reimburse for Lomustine to participating sites as required based upon availability or local regulations.

### 5.1.3 Temozolomide (TMZ)

TMZ is considered as a standard treatment for this indication and commercial sources will be used, except in countries which mandate Temozolomide be supplied by the sponsor in the context of clinical trials. For those countries, AbbVie may provide or reimburse for TMZ to participating sites as required based upon availability or local regulations.

## 5.2 Initial dose and administration

### 5.2.1 ABT-414

ABT-414 will be given at dose level of 1.0 mg/kg by IV infusion over 30 to 40 minutes once every 2 weeks. The dose of ABT-414 does not have to be adjusted unless there has been at least a 10% change in body weight; recalculation of ABT-414 dose for < 10% weight changes is allowed at the discretion of the Investigator. Each configuration of ABT-414 drug product (Type A and/or Type L) that a subject receives during the study will be recorded.

Subjects will be closely monitored for treatment-related adverse events, especially allergic reactions, during the infusion. For the initial ABT-414 infusion, pre-infusion vital signs should be taken, direct observation is required for the first 15 minutes of the infusion, and subjects should be monitored for 1 hour post-infusion. For subsequent infusions, direct observation and monitoring post-infusion are not required; however, pre-infusion vital signs should still be taken.

Due to the risk of eye toxicity, each administration of ABT-414 should be given with steroid ophthalmic solution. The recommended type, dose, and schedule of eye drops is as follows: dexamethasone 0.1% solution (or equivalent corticosteroid solution), 2 drops (GTTS) in each eye (OU) every 8 hours to start 48 hours prior to ABT-414 dosing and continue for a total of 7 days (or 21 doses total). The type of ophthalmic solution used may vary depending on the availability of the solution at each location. A modification to the eye drop dosing or schedule based on ongoing clinical experience may be suggested.

Allergic reactions of any grade require interruption of ABT-414 treatment and management as described in section 5.5.1.1.

Subjects will not be treated at doses less than 0.5 mg/kg. If a subject requires a dose modification below 0.5 mg/kg, the subject will be discontinued from the study treatment.

### 5.2.2 Lomustine

Arm 3A: Patients relapsing during TMZ treatment or within the first 16 weeks after the first day of the last TMZ cycle will be treated with lomustine 110 mg/m$^2$ on day 1 of every 42-day treatment period. However, similar to subjects who are randomized to ABT-414 plus TMZ (Arm 1), ABT-414 (Arm 2) or TMZ control (Arm 3B), scans (MRI) should be performed as per the schedule outlined for all other arms (see section 6.3.5). Treatment will continue until one of the treatment withdrawal criteria has been met. Lomustine will be given for a maximum of one year.

The doses may be rounded to the nearest 40 mg to accommodate tablet strengths. The dose of lomustine does not have to be adjusted unless there has been at least a 10% change in body weight; recalculation of lomustine dose for < 10% weight changes is allowed at the discretion of the Investigator.

### 5.2.3 Temozolomide

Arm 1: patients will be treated with ABT-414 1.0 mg/kg IV infusion over 30 to 40 minutes once every 2 weeks in combination with TMZ 150 mg/m$^2$ day 1 to 5, for the first 28-day cycle, with dose escalation to 200 mg/m$^2$ in subsequent cycles in case of adequate tolerance (CTCAE v.4 toxicity grade less than 2) and until one of the treatment withdrawal criteria has been met.

Arm 3B: Patients relapsing 16 weeks or more after the first day of the last TMZ cycle will be treated with TMZ 150 mg/m$^2$ on day 1 to 5 for the first 28-day cycle, with dose escalation to 200 mg/m$^2$ in subsequent cycles in case of adequate tolerance (CTCAE v.4 toxicity grade less than 2). Treatment will continue until one of the treatment withdrawal criteria has been met.

The dose of TMZ does not have to be adjusted unless there has been at least a 10% change in body weight; recalculation of TMZ dose for < 10% weight changes is allowed at the discretion of the Investigator.

## 5.3 Treatment duration

Treatment will be administered until one of the withdrawal criteria (section 5.4) has been met. Lomustine will be given for a maximum of one year. Administration of TMZ with ABT-414 will continue if tolerated, and patients receiving treatment for more than 12 months will be evaluated and assess the risk of prolonged treatment.

## 5.4 Withdrawal criteria

Whatever the disease status, study treatment will be discontinued in case of:

- disease progression
- patient refusal
- intolerable toxicity precluding further protocol therapy
- patient's best interest
- start of any other anti-cancer agent/modality (surgery at recurrence is allowed)
- pregnancy

Patients discontinuing therapy in the absence of progression should not receive other cancer treatment before their disease progresses, unless this is clearly not in the interest of the patient. If, after treatment discontinuation, there is additional clinical information leading the investigator to conclude that the reason for discontinuation is no longer valid (except for toxicity), the subject may resume study treatment as long as no other chemotherapy, radiotherapy, immunotherapy, NovoTTF, or other treatment with antineoplastic intent has been received, with the exception of surgical intervention that yields histology not demonstrative of tumor progression. In case of toxicity in the combination arm that is

clearly attributable to either TMZ or ABT-414, that drug can be discontinued and the other can be continued. Patients that discontinue study treatment for toxicity, patient refusal and other reasons remain 'on study' and must be followed according to the follow-up schedule for progression, survival etc unless patient specifically withdraws consent from all further data collection for the study (this decision should be clearly documented e.g in the medical notes).

## 5.5 Dose and schedule modifications

In the combination arm, dose reductions or delays should be made for the likely causative agent. If in the combination arm one of the agents should be stopped for any reason other than PD, the patient can continue on the other single agent alone.

### 5.5.1 ABT-414

ABT-414 will be given by IV infusion over 30 to 40 minutes, on Days 1 (±2 days) and 15 (±2 days) of every 28-day cycle. Information about the ABT-414 formulation to be used in this study are presented below:

| | ABT-414[a] |
|---|---|
| Dosage Form | Lyophilized powder for reconstitution and intravenous admixture |
| Formulation | Vial |
| Strength (mg) | 20 or 100 |

a. Information applicable to both ABT-414 and ABT-414 manufactured under two separate manufacturing processes (A and L).

Based upon results from the first clinical and preclinical safety pharmacology evaluation of ABT-414, experience with other inhibitors of EGFR, and experience with MMAF ADCs, potential toxicities may include fatigue, vomiting, thrombocytopenia, allergic reactions, rash, eye complaints, and liver function test abnormalities.

For all observed toxicities, except those listed below, subjects should be assessed for inter-current illness or other causes and treated as appropriate. For severe toxicities (Grade 3 or higher), dosing should be withheld until toxicity resolves to Grade 1 or less (unless otherwise indicated). Dose reduction of ABT-414 for Grade 3 toxicity will be at the discretion of the investigator and the study team. Re-initiation of ABT-414 may be considered at a reduced dose (to 1.0 mg/kg, 0.75 mg/kg, or 0.5 mg/kg) for grade 4 toxicities provided full recovery to grade 1 or less has occurred (unless otherwise indicated).

All dose reductions are permanent, except as listed below (hepatic laboratory abnormalities, section 5.5.1.4).

ABT-414 Dose Modification Table

| Toxicity | Starting Dose | First Occurrence | Second Occurrence | Third Occurrence |
|---|---|---|---|---|
| Grade 1 or 2 | 1.0 mg/kg | No requirement for dose reduction | No requirement for dose reduction | No requirement for ABT-414 discontinuation |
| Grade 3 | 1.0 mg/kg | Can continue at 1.0 mg/kg or reduce to 0.75 mg/kg once the toxicity has resolved to grade 1 or baseline | Can continue at 0.75 mg/kg or reduce to 0.5 mg/kg once the toxicity has resolved to grade 1 or baseline | Can continue at 0.5 mg/kg once the toxicity has resolved to grade 1 or baseline or permanently stop ABT-414 |
| Grade 4 | 1.0 mg/kg | Reinitiate treatment at 0.75 mg/kg once the toxicity has resolved to grade 1 or baseline | Reinitiate treatment at 0.5 mg/kg, once the toxicity has resolved to grade 1 or baseline | Permanently stop ABT-414 |

More aggressive dose reductions are always allowed if the investigator believes that it is in the best interests of the subject. While investigator discretion should be used for subject management with regards to toxicities, some suggested guidelines are included in the following sections.

#### 5.5.1.1 Allergic reactions

Subjects will be closely monitored for treatment-related adverse events, especially allergic reactions during all infusions. For the initial ABT-414 infusion, pre infusion vital signs should be taken and direct observation is required for the first 15 minutes of the infusion. Also for the initial ABT-414 infusion, subjects must remain at the site for monitoring for 60 minutes post infusion. For subsequent infusions, post-infusion monitoring is not required; however, pre-infusion vital signs should still be taken. Longer observation periods and more frequent vital sign checks may be required in subjects who experience infusion reactions.

Institutional standards should be used to treat all allergic reactions.

##### 5.5.1.1.1 Severe allergic reactions (grade 3 or grade 4)

These require the immediate interruption of ABT-414 treatment and discontinuation from the study. Appropriate medical therapy including epinephrine, corticosteroids, intravenous antihistamines, bronchodilators, and oxygen should be available for use in the treatment of such reactions. Subjects should be carefully observed until the complete resolution of all signs and symptoms.

#### 5.5.1.1.2 Moderate allergic reactions (grade 1 or grade 2)

These will also require the immediate interruption of ABT-414 treatment. Once symptoms have resolved, retreatment is allowed with an infusion over 60 to 70 minutes. All subsequent infusions will also be administered over 60 to 70 minutes.

### 5.5.1.2 Dermatologic toxicities

Subjects developing dermatologic toxicities while receiving ABT-414 should be monitored for the development of inflammatory or infectious sequelae, and appropriate treatment of these symptoms initiated. In subjects with mild and moderate (grade 1 or grade 2) skin toxicity, treatment should continue without dose delay or modification. Treatment with topical and/or oral antibiotics should be considered.

If a subject experiences severe (grade 3 or grade 4) acneiform rash, ABT-414 treatment adjustments should be made based on a discussion between the investigator, the AbbVie medical monitor and the EORTC HQ team.

Subjects who experience a grade 3 or higher dermatological toxicity will be treated as following: The subject will require a dose interruption and ABT-414 may be reintroduced at a reduced dose (per the guidance previously stated above) if the toxicity returns to ≤ grade 1 within 4 weeks.

### 5.5.1.3 Ophthalmologic toxicities

All subjects should receive prophylactic administration of steroid ophthalmic solution for each administration of ABT-414. The recommended type, dose, and schedule of eye drops is as follows: dexamethasone 0.1% solution, 2 drops (GTTS) in each eye (OU) every 8 (q8) hours to start 48 hours prior to ABT-414 dosing and continue for a total of 7 days (or 21 doses total). Subjects developing ophthalmologic toxicities despite the use of prophylactic steroids must have an examination by an ophthalmologist, including a thorough slit-lamp exam, to evaluate for the presence of epithelial microcysts. If ocular toxicity is grade 1 or 2, subjects may continue on ABT-414 without dose delay, reduction or suspension, but they must receive treatment from an ophthalmologist and will need to have repeated eye examinations. For grade 3 or 4 toxicity, ABT-414 must be suspended until resolution of ocular symptoms to grade 1. Afterward, patient may re-initiate treatment at a lower dose upon discussion with the medical monitor. No dose modification below a total dose of 0.5 mg/kg is allowed. Re-treatment at a lower dose of ABT-414 has generally resulted in no reported eye event or less severe toxicities.

#### 5.5.1.3.1 Prophylaxis

In efforts to prevent the formation of some of these microcysts, dexamethasone and other steroids may be used to slow down the turn-over of the transient amplifying cells, thereby protecting them from the damage caused by a toxin that targets cells in rapid division. Although early use has shown that steroid eye drops may help reduce the severity of symptoms by preventing the formation of microcysts, they generally do not get rid of them completely. Given that the steroid eye drops are to be used to protect the transient amplifying cells during exposure to MMAF, the best time to administer them is around the time of infusion when the levels of MMAF are at their peak. The prolonged use of steroid eye drops outside of the time when there is MMAF exposure is not recommended as they may cause other side effects and prevent the healing process.

Intra-ocular pressure (IOP) should be monitored as appropriate during ophthalmologic examination. If increase in IOP occurs, it should be controlled with IOP-lowering medication according to the investigator discretion.

#### 5.5.1.3.2 Treatment once symptoms occur

Once corneal microcysts have formed, there are no known therapies that can remove them from the cornea. Thus, only therapies that can control symptoms and promote healing are indicated. Thus, steroid eye drops may not be the best strategy as they may inhibit the healing process. Rather, lubricating drops and gels, corneal bandages, and antibiotic drops (if an infectious process is evident) are the best strategy for the promotion of healing and control of symptoms. Frequent monitoring by an ophthalmologist is also recommended at this time to make sure that the appropriate bandaging and antibiotics are prescribed for the promotion of healing and adequate alleviation of symptoms.

#### 5.5.1.3.3 Discussions with patients

It is important that patients understand this toxicity and the importance of following the recommendations for the eye drops as well as the rapid reporting of their symptoms. It is also important to let them know that at this time, in all of the patients, symptoms have improved over time and there is no evidence to suggest that there is any permanent damage done to the cornea. It does take some time, however, for symptoms to resolve and thus an immediate reversible of symptoms should not be promised. At least 3-4 weeks must take place for the regeneration of the cornea; this is an approximate timeline for when symptoms should improve and corneal healing should take place.

#### 5.5.1.3.4 Ophthalmological photography

Sites that agree will be asked to provide ophthalmologic photography (e.g slit lamp, confocal microscopy, Heidelberg Retinal Tomography [HRT3] etc.) of corneal abnormalities.

Patients treated with ABT-414 and experiencing ocular side effects may be presented with an approved optional consent form asking them for the release of these photographs of their eyes. If patients agree and sign and date the form, copies of new or already taken photographs will be sent to AbbVie. Included are the trial number, patient number and the date the photograph was taken (either written on the photograph or within the file name) and the date of patient consent confirmed by the (sub)-investigator or delegate. Consent forms and photographs should be filed in patient notes and site file. No other patient identifiers should be present on the data provided to AbbVie. Photographs collected during scheduled visits should be of the eye or part of the eye only and not including the full face, nose, ear, or mouth. If two eyes are affected these should be submitted as two separate photographs.

### 5.5.1.4 Hepatic Laboratory Abnormalities (ABT-414)

ABT-414 Dose Modification Guidelines for Hepatic Laboratory Abnormalities:

| Hepatic Laboratory Abnormality | ABT-414 |
|---|---|
| ALT or AST >5x ULN* but ≤ 20x ULN (and TBL ≤ 2x ULN) | [redacted] |
| ALT or AST > 20x ULN<br><br>or<br><br>ALT or AST >3x ULN **and** TBL >2x ULN | [redacted] |

* If elevated at baseline, either 5x the baseline value or 8x ULN, whichever is lower

For guidelines for pediatric patients, see Appendix I.

### 5.5.2 Lomustine

Patients requiring more than two consecutive lomustine dose reduction (i.e. only two dose reductions are allowed based on product labeling) will discontinue lomustine treatment. Study efficacy evaluations will not be modified because of dose delays. Dose modifications are based on toxicity during the prior treatment cycle. If multiple toxicities are seen, the dose administered should be based on the dose reduction required for the most severe grade of any single toxicity.

#### 5.5.2.1 Dose levels of lomustine

The lomustine dose will be rounded to the closest multiple available; the dosage is calculated based on BSA but a maximum dose (cap) is used. Two dose levels of lomustine will be used.

| Dose | Dose mg/m² q6 weeks |
|---|---|
| 0 | 110 mg/m$^2$ (cap 200 mg) |
| -1 | 90 mg/m$^2$ (cap 160 mg) |
| -2 | 70 mg/m$^2$ (cap 120 mg) |

##### 5.5.2.1.1 Hematological toxicity

In general, the nadirs for hematological toxicity with lomustine are expected between days 28 and 35. In case of hematological toxicity grade 3 or 4 (according to CTCAE v. 4.0), the dosage of the next cycle will be reduced with one level. If the hematological toxicity does not recover within 4 weeks or if after recovery the hematological toxicity recurs at a subsequent cycle to grade ≥ 2, lomustine treatment should be discontinued. No more than two dose reductions are allowed.

Administration of next cycle: If blood examination on day 42 or 43 (which may have been obtained in the prior 48 hours) show recovery of platelets above $100\times10^9$ and granulocytes counts above $1.5\times10^9$, the next dose may be administered on day 43. If this is not possible, hematologic parameters will be repeated weekly and the next cycle will be given upon recovery of granulocytes and platelets. If after 4 weeks the patient has still not recovered, they should discontinue study treatment and stay on study until progression.

##### 5.5.2.1.2 Non hematological toxicity

- Liver toxicity grade >2: the dose of the next cycles will be reduced by 1 dose level
- In case of pulmonary toxicity grade 1-2, or appearance of symptoms, DLCO will be performed.
  - If DLCO ≥ 60% of the predicted value: patient will receive the next cycle at the same dose
  - If DLCO < 60% of the predicted value: patient should discontinue study treatment and stay on study until progression
- In case of pulmonary toxicity grade 3 or higher, patient should discontinue study treatment and stay on study until progression
- Any grade 4 non hematological toxicity: the patient should discontinue study treatment and stay on study until progression
- If the non-hematological toxicity does not recover within two weeks or if non hematological toxicity recurs at the next cycle to a grade ≥ 2 the patient should discontinue study treatment and stay on study until progression

### 5.5.3 Temozolomide

The following dose levels of TMZ will be used: 1000 mg/m$^2$ per cycle (5 days 200 mg/m$^2$); 750 mg/m$^2$ per cycle (5 days 150 mg/m$^2$); 500 mg/m$^2$ per cycle (5 days 100 mg/m$^2$).

| Dose | Dose mg/m² q4 weeks |
|---|---|
| +1 | 200 mg/m$^2$ |
| 0 | 150 mg/m$^2$ |
| -1 | 100 mg/m$^2$ |

- The starting dose in cycle 1 is 150 mg/m$^2$ temozolomide on day 1-5, to be taken at least 2 hours after a meal, on empty stomach.
- Patients with no or only grade 1 toxicities in cycle 1 are allowed to dose escalate in any subsequent cycles to 200 mg/m$^2$ day 1-5.
- In case of nadir (usually ± day 21) CTCAE hematological toxicity grade 3 or 4, the dosage of the next cycles will be reduced by one dose level.
- In case of CTCAE grade 3 non-hematological toxicity, the dosage of TMZ of the next cycles will be reduced by one dose level.
- In case of CTCAE grade 4 non-hematological toxicity, the patient should discontinue treatment.
- In case of grade 3 cardiac toxicity, the patient should discontinue treatment.
- In case of toxicity requiring dose reductions in patients treated at the 100 mg/m$^2$ daily level (500 mg/m$^2$ per cycle) the patient goes off treatment.
- In case of dose reductions, dose re-escalation is not allowed.
- In case of hepatic laboratory abnormalities, see Appendix L for guidelines on repeat testing and evaluation (regardless of the assessed relationship to study treatments).

| Nadir granulocytes | Nadir thrombocytes | Temozolomide modification |
|---|---|---|
| ≥ 1.0×10$^9$ | ≥ 50×10$^9$ | Dose unchanged |
| < 1.0×10$^9$ | <50×10$^9$ | Decrease dose by 1 dose level |

Administration of next cycle: If blood examination on day 28 or 29 (which may have been obtained in the prior 48 hours) show recovery of platelets above 100×10$^9$ and granulocytes counts above 1.5×10$^9$, the next dose may be administered on day 29. If this is not possible, hematologic parameters will be repeated weekly and the next cycle will be given upon recovery of granulocytes and platelets. If after 2 weeks the patient has still not recovered, they should discontinue study treatment and stay on study until progression.

### 5.5.4 Concomitant treatments

#### 5.5.4.1 Prophylactic treatments

Anti-emetic prophylaxis should be given to lomustine treated patients on day 1 and to TMZ treated patients on day 1-3 or day 1-5 of every treatment cycle per local practice, and thereafter as clinically necessary. The use of 5HT-3 antagonists is recommended, and it is recognized they may cause constipation.

Hematopoietic growth factors: The prophylactic use of growth factors is not permitted during the screening period as a low hematologic lab value could be masked. Patients may receive red cell transfusions or erythropoietin to maintain hemoglobin > 9.9 mg/dL or 6.2 mmol/L.

### 5.5.5 Other concomitant medication

Corticosteroids should be used in the smallest dose possible to control symptoms of cerebral edema and mass effect, and should be reduced and/or discontinued if possible.

No other anticancer agents or investigational drugs are allowed during the study or within 28 days before the inclusion into the trial, nor the participation into another study on investigational agents.

The use of live attenuated vaccines is prohibited during the study and for a period of 49 days after the end of ABT-414 administration.

The uses of concomitant medications that are contraindicated per the national prescribing information are prohibited during the conduct of the study

All concomitant medication will be collected on the CRFs.

# 6 Clinical evaluation, laboratory tests and follow-up

Patients with histologically confirmed glioblastoma may register and have their tumor tissue screened after diagnose and before tumor progression. Eligibility at the time of tumor progression will depend on the confirmation of EGFR amplification during the screening, the fulfillment of all other in- and exclusion criteria and the trial status (whether the study is still open for accrual).

Tumor tissue for EGFR assessment should be prepared and sent to central lab as described in the study specific study manual.

## 6.1 Registration

- Histologically confirmed de novo (primary) glioblastoma before or at the time of first progression after RT concurrent/adjuvant TMZ chemotherapy
  - In case of testing at the time of first progression: either at least 3 months after the end of radiotherapy or have tumor progression that is clearly outside the radiation field or have tumor progression unequivocally proven by surgery/biopsy
- Confirmation that biological material (at least from initial diagnosis and if further resection had been performed at recurrence) to determine diagnosis is available for central review
- Written informed consent for central EGFR screening must be given according to ICH/GCP, and national/local regulations

## 6.2 Before randomization

All pretreatment evaluations should be performed within 2 weeks before randomization.

The baseline evaluations include:

- Histologically confirmed *de novo* (primary) glioblastoma with unequivocal first progression after RT concurrent/adjuvant TMZ chemotherapy either at least 3 months after the end of radiotherapy or have tumor progression that is clearly outside the radiation field or have tumor progression unequivocally proven by surgery/biopsy
- Informed consent and consent for future studies
- Demographics (height, weight, race, ethnicity)
- Complete medical history, including documentation of any clinically significant medical condition
- Prior anti-cancer therapy (including start and end dates for prior TMZ chemotherapy and RT)
- Physical examination including, but not limited to, WHO performance status and neurological evaluation
- Ocular examination by an ophthalmologist
- Vital signs (blood pressure, pulse rate and body temperature)
- Quality of life assessment, including EORTC QLQ-C30 and EORTC-BN20 (see section 10.1)
- 12-lead ECG
- ♦ Concomitant medications
- ♦ Steroid intake
- Assessment of all adverse events according to CTCAE 4.0
- Hematology (WBC, absolute neutrophil count, lymphocytes, hematocrit, hemoglobin and platelet count)
- Biochemistry (serum creatinine, total bilirubin, ASAT, ALAT, alkaline phosphatase, phosphate, total protein, albumin, sodium, potassium, calcium and chloride)
- Serum or urine pregnancy test for WOCBP within 72 hours prior to randomization.
- Gadolinium-enhanced MRI of the brain within 2 weeks prior to randomization. For operated patients, the post-surgery MRI within 48 hours is mandatory and can be used as baseline. However, if a subject is not randomized within 2 weeks from the post-surgery MRI, then a new MRI scan is required and will be used as baseline.
- Demonstrated EGFR gene amplification by centralized testing using EGFR FISH developed by Abbott Molecular.
- Although not considered necessary activities prior to randomization, the following samples are optional and all subjects randomized may consent to participate in future translational research:
    - Tumor tissue remaining following EGFR amplification testing for future TR projects (optional samples, see section 11.8)
    - Whole blood for germline DNA and TR projects (optional samples, see section 11.8)

## 6.3 From treatment start until end of protocol treatment

### 6.3.1 Day 1 of each cycle

All day 1 evaluations should be performed and laboratory results reviewed within 3 days before or at day 1 of the cycle, and prior to dosing. For day 1 of cycle 1, if the evaluations listed below have been already performed during the screening phase and within 2 weeks prior to this day 1, the same results can be used for cycle 1 and tests do not need to be repeated.

- Physical examination including, but not limited to, WHO performance status and neurological evaluation
- Ocular examination if clinically indicated (Arms 1 and 2 only)
- Hematology and biochemistry (as section 6.2)
- Vital signs (as section 6.2)
- Weight
- 12-lead ECG immediately after ABT-414 dosing on day 1 of cycle 1 and cycle 3, for subjects assigned to ABT-414 (Arm 1 or 2)
- Assessment of all adverse events according to CTCAE 4.0
- Concomitant medications, including steroid intake (maximal intake (mg per day)).

For patients in Arm 3A, lomustine, the above physical examination, hematology, vital signs and adverse event assessments need to be repeated at day 28 (+/- 3 days).

### 6.3.2 Day 1 and day 5 for cycles 1 and 2; day 1 for cycle 3 and every 2 cycles thereafter (day 1 of C5, C7 etc.)

- Pharmacogenetic (PG) sample: optional sample collection for all subjects that consent. If the PG sample is not collected at the Day 1 visit, it may be collected anytime during the study.
- For subjects assigned to ABT-414 (Arm 2) or ABT-414 in combination with TMZ (Arm 1): Pharmacokinetic (PK) and pharmacodynamic (PD) sample collection according to the following schedule. Refer to the study specific laboratory manual for detailed instructions on sample collection, volumes, processing and shipment.

| | Cycle 1<br>Day 1 of ABT-414 | Cycle 1<br>Day 5 (Day 4 up to day 7 is acceptable) of ABT-414 | Cycle 2<br>Day 1 of ABT-414 | Cycle 2<br>Day 5 (Day 4 up to day 7 is acceptable) of ABT-414 | Cycle 3<br>Day 1 of ABT-414 | Cycle 5, Cycle 7 etc. Every two cycles starting from ABT-414 cycle 5 | 35 Day Safety Follow-up |
|---|---|---|---|---|---|---|---|
| PK – ABT-414, and Total ABT-806 Assays | X[a] | X[e] | X[a] | X[e] | X[a] | X[b] | X[c] |
| PK - Cys-mcMMAF assay | X[a] | X[e] | X[a] | X[e] | X[a] | X[b] | |
| PK Antidrug Antibody Assay (ADA/nADA) | X[b] | | X[b] | | X[b] | X[b] | X[c] |
| PD Plasma Markers | X[b] | | X[b] | | X[b] | | |
| PD serum markers | X[b] | | X[b] | | X[b] | | |
| PG Sample (Optional) | X[d] | | | | | | |

a. Samples will be collected before infusion (0 hour, pre-dose) and immediately after ABT-414 infusion

b. Samples will be collected before infusion (0 hour, pre-dose).

c. Samples will be collected 35 days (within a two-day window) after last ABT-414 infusion for subjects able to return to the clinic for the follow-up visit.

d. If the pharmacogenetic sample is not collect at this visit, it may be collected anytime during the study.

e. Samples will be collected 96 hrs post ABT-414 infusion, but may be collected from 4 up to 7 days post infusion.

The date/time of collection of each PK/ADA/PD/PG sample will be recorded. The date, start and end time of each ABT-414 infusion will be recorded on the appropriate eCRF.

Dose administration information will be collected for subjects receiving TMZ and lomustine and will be recorded on the appropriate eCRF.

### 6.3.3 Day 14 of each cycle - Arm 1 and 2 patients only

All day 14 evaluations should be performed and laboratory results reviewed within 3 days before or at day of dosing of ABT-414.

- Physical examination including, but not limited to, WHO performance status and neurological evaluation
- Ocular examination if clinically indicated
- Vital signs (as section 6.2)
- Hematology (as section 6.2)
- Assessment of all adverse events according to CTCAE 4.

### 6.3.4 Day 21 of each cycle - Arm 1 and 3B patients only

All day 21 evaluations should be performed within 3 days before or 3 days after day 21 of the cycle.

- Hematology (as 6.2 - this can be omitted once treatment at the present dose level was shown to cause only grade 1 or less hematological toxicity at day 21 and only grade 2 or less at day 28).

### 6.3.5 Day 28 of each cycle - Arm 3A patients only

All day 28 evaluations should be performed within 3 days before or 3 days after day 28 of the cycle.

- Physical examination including, but not limited to, WHO performance status and neurological evaluation
- Hematology (see section 6.2)
- Vital signs (see section 6.2)
- Assessment of all adverse events according to CTCAE 4.0

### 6.3.6 Every 8 weeks (+/- 7 days)

- Gadolinium-enhanced MRI. If PR, CR, an additional scan after 4 weeks should be done to confirm the response (as per chapter 4)
- Quality of life assessment, including EORTC QLQ-C30 and EORTC-BN20 at week 8 (+/- 7 days) and 16 (+/- 7 days) only (see section 10.1)

### 6.3.7 At end of treatment (35 days after last administration/infusion)

- Concomitant medications
- Assessment of all adverse events according to CTCAE 4.0
- For subjects assigned to ABT-414: Pharmacokinetic sample collection 35 days (± 2 day window) after last infusion for subjects able to return to the clinic (see table in section 6.3.2)
- Steroid intake

### 6.3.8 At end of treatment (49 days after last administration/infusion)

- Concomitant medications
- Assessment of all adverse events according to CTCAE 4.0
- Steroid intake

### 6.3.9 At 6 months after randomization (+/- 1 month)

- Quality of life assessment, including EORTC QLQ-C30 and EORTC-BN20 (see section 10.1)

## 6.4 After end of treatment

Every 12 weeks (+/- 14 days) since last protocol treatment administration until death or loss to follow up:

- Survival follow up
- Further anti-cancer treatments/modalities
- Physical examination including WHO performance status and neurological examination
- Ocular examination if clinically indicated
- Vital signs if clinically relevant
- Steroid intake
- Concomitant medication collection if clinically relevant
- Assessment of all adverse events according to CTCAE 4.0 (i.e. for events not resolved after the end of treatment and new events related to study treatment)
  If a subject is unable to return to the clinic for this visit, survival follow up and other assessments as appropriate may be completed via phone.

### 6.4.1 From end of study treatment until progressive disease

Every 8 weeks (+/- 7 days)

- Gadolinium-enhanced MRI. If PR, CR, an additional scan after 4 weeks should be done to confirm the response (as per chapter 4)

## 6.5 Summary table

| | Before registration | Registration | Baseline 2 wks prior to randomization | Randomization | During protocol treatment, each cycle | | | | Every 8 weeks | EoT[9] | 6 months after randomization | Follow-up |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | Day 1[0] | Day 14 Arm 1 & 2 | Day 21 Arm 1 and 3B | Day 28 Arm 3A[14] | | | | every 12 weeks |
| PIS/IC for registration (EGFR) | x | | | | | | | | | | | |
| Histology | x | | x | | | | | | | | | |
| WHO Performance Status | | | x | | x | x | | x | | | | x |
| Biological samples for central EGFR assessment | x | | | | | | | | | | | |
| EGFR gene amplification | | | x | | | | | | | | | |
| Biological samples for TR projects (optional) | | | x | | | | | | | | | |
| PIS/IC for study | | | x | | | | | | | | | |
| Weight | | | x | | x | | | | | | | |
| Medical his. & Demographic | | | x | | | | | | | | | |
| Whole blood for germline DNA and TR projects (optional) | | | x | | | | | | | | | |
| Prior anti-cancer therapies | | | x | | | | | | | | | |
| Physical examination[1] | | | x | | x | x | | x | | | | x |
| Vital signs | | | x | | x | x | | x | | | | x[10] |

| | Before registration | **Registration** | Baseline 2 wks prior to randomization | **Randomization** | During protocol treatment, each cycle | | | | Every 8 weeks | EoT[9] | 6 months after randomization | Follow-up |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | Day 1[0] | Day 14 Arm 1 & 2 | Day 21 Arm 1 and 3B | Day 28 Arm 3A[14] | | | | every 12 weeks |
| Quality of life assessment | | | x | | | | | | x[8] | | x | |
| ECG | | | x | | x[5] | | | | | | | |
| Concomitant medication collection | | | x | | x | | | | | x | | x[10] |
| Steroid intake | | | x | | x | | | | | x | | x |
| Prophylactic eye drops[15] | | | | | x | x | | | | | | |
| Adverse events (CTCAE v.4.0) | | | x | | x | x | | x | | x | | x[11] |
| Hematology[2] | | | x | | x | x | x[7] | x | | | | |
| Biochemistry[3] | | | x | | x | | | | | | | |
| Serum/urine pregnancy test | | | x[4] | | | | | | | | | |
| Pk samples | | | | | x[6] | | | | | x[9] | | |
| PD samples | | | | | x[12] | | | | | | | |
| PG samples (optional) | | | | | x[13] | | | | | | | |
| Gd-MRI | | | x | | | | | | x | | | |
| Survival and further anti-cancer treatments | | | | | | | | | | | | x |

0 For day 1 of cycle 1, if the evaluations listed here have been already performed during the screening phase and within 2 weeks prior to this day 1, the same results can be used for cycle 1 and tests do not need to be repeated: physical examination including, but not limited to, WHO performance status and neurological evaluation; ocular examination if clinically indicated; hematology and biochemistry; vital signs; weight.

1 Physical examination including neurological evaluation, and ocular examination at baseline and if clinically indicated

2 Including WBC, absolute neutrophil count, lymphocytes, hematocrit, hemoglobin and platelet count

3 Including serum creatinine, total bilirubin, ASAT, ALAT, alkaline phosphatase, phosphate, total protein, albumin, sodium, potassium, calcium and chloride

4 Pregnancy test must be done within 72 hours prior to randomization

5 ECG only day 1 of cycle 1 and 3, immediately after the ABT-414 infusion and only for patient treated with ABT-414 (Arm 1 or 2)

6 PK samples to be collected at day 1 of ABT-414 cycles 1, 2, 3 and then every 2 ABT-414 cycles (Day 5 samples will only be collected during cycles 1 and 2)

7 Hematology at day 21 can be omitted once treatment at the present dose level caused only grade 1 or less hem. toxicity at day 21 and only grade 2 or less at day 28

8 QoL only at week 8 and week 16 while on treatment

9 End of Treatment visits 35 days and 49 days after last protocol drug administration. PK samples to be drawn at 35 days after last protocol drug administration only.

10 If clinically indicated / if clinically relevant

11 Assessment of AEs not resolved after EOT or AEs related to study treatment

12 PD samples to be collected at day 1 of cycles 1, 2 and 3 and only for patient in an ABT-414 arm (Arm 1 or 2)

13 PG sample optional, to be collected at day 1 of cycle 1or it may be collected anytime during the study

14 Repeat physical examination including WHO performance status and neurological evaluation, hematology, vital signs and adverse event assessments at day 28 for patients in the lomustine arm (Arm 3A)

15 Prophylactic steroid ophthalmic solution prior to each infusion of ABT-414; 2 drops in each eye every 8 hours to start 48 hours prior to ABT-414 dosing and continue for a total of 7 days

# 7 Criteria of evaluation

## 7.1 Evaluation of activity

### 7.1.1 General method of response assessment

Response to treatment is assessed on the basis of a set of target lesion(s) chosen before the first treatment administration (the complete list of target lesions must be reported on the initial measurement form before the start of treatment). These lesions must initially be measured in their two perpendicular dimensions, and these measurements must be repeated at each evaluation of the disease by the same method. Response evaluation is based on neuro-radiological imaging (MRI). For this protocol objective response (complete, partial response) and progression will be assessed by MRI (see section 7.1.1.4). Objective response will only be assessed in patients not having undergone second surgery with complete removal of contrast enhancing lesions prior to study entry. For these patients measurable disease is required, which is defined as a clearly enhancing tumor with at two perpendicular diameters at entry equal or superior to 1 cm.

The contrast enhancing area will be considered as the basis for the tumor size assessment. Tumor size is defined as the product of the two largest perpendicular diameters. For evaluating partial and complete response, the baseline scan must be used for initial comparison. In initially responding (≥ 50% reductions in cross-sectional areas) or stabilized (< 50% reduction and < 25% increase in cross-sectional areas) patients, new scans must be compared to the nadir, this is the scan showing the maximum response (i.e. minimum tumor size) during or after treatment. In assessing response, changes on T2 weighted images must be taken into consideration.

#### 7.1.1.1 Definition of target lesions

Only the following lesions are eligible as target lesions:

- MRI contrast enhancing lesions with two perpendicular diameters of 10 mm or more visible on 2 or more axial slices which are 5 mm apart.
- Target lesion(s) must be measurable in two perpendicular diameters

In most patients, only one lesion will be present. In case of multifocal disease, a minimum of 2 lesions and maximum of 3 largest enlarging lesions will be chosen as target lesions and the sum of the products of the perpendicular diameters will be determined. All other lesions than target lesions, if applicable, are assessed according to the same schedule. They are only taken into account in two situations:

- if one of them clearly progresses, the overall response to therapy will be evaluated as "progression", independent of the response of target lesions
- all lesions must have completely disappeared to report a "complete response".

Adequate investigations must be carried out at each evaluation of the disease to detect eventual new lesions. If any new lesion is found, the response will be evaluated as "progression". Regardless of the status of enhancing lesions, if progressive lesions are observed on T2 weighted images or FLAIR images, the patient will be considered radiologically progressive, but treatment may continue if this is considered to be in the best interest of the patient and there are no signs or symptoms of clinical progression.

By definition, non-target lesions are those that do not meet the criteria for target lesion.

#### 7.1.1.2 Evaluation of patient treated after re-operation

Postoperative changes on contrast enhanced neuro-imaging may interfere with disease evaluation. Within the first three days after surgery on MR imaging a thin linear enhancement may develop around the resection cavity, thereafter this enhancement may become thick and nodular. Enhancement of dura and meninges may be more pronounced, even within the first days. The postoperative linear enhancement may persist for up to 3-6 months, dural and meningeal enhancement may last much longer. If MRI made within 48 hours after surgery shows enhancing lesions with a nodular or mass like appearance in areas showing tumor on the pre-operative scans this is highly suggestive of residual tumor. The use of diffusion-weighted MR imaging in the immediate postoperative MRI may help with the identification of ischemic areas around the surgical cavity that may show enhancement with further follow-up.

#### 7.1.1.3 Schedule of disease evaluation

The initial assessment of disease (including measurement of all target lesions) must be performed in the two weeks preceding randomization. Follow-up assessments will be performed every 8 weeks (or earlier if clinically indicated) until disease progression.

#### 7.1.1.4 Definition of response

For this trial, the primary measure of response and progression will be determined by central review according to the RANO criteria. All treatment decisions should be based on the RANO criteria as assessed by the local investigator. However, local investigators assessments will be confirmed by central radiographic review. The independent central radiologist will give feedback on investigator reads shortly after MRI submissions for the first 15 PFS events. In addition, top recruiting sites will receive more frequent feedback from the independent central radiologist. Otherwise, local MRIs will be assessed by central review in batches.

Although ORR, PFS endpoints will be mainly based upon central radiographic review, these endpoints based on investigator reviews will also be presented for comparisons.

Target lesions are measured in their two largest perpendicular diameters. Their area is conventionally calculated as the product of these diameters. In case of multifocal disease with more than one target lesion, the total tumor size is calculated as the sum of the area of all target lesions.

Response is defined as follows according to the RANO criteria, which also consider T2 weighted and FLAIR images:

- Complete response (CR) requires all of the following: 1) Complete disappearance of all enhancing measurable and non-measurable disease; 2) No new lesions; 3) Stable or improved non-enhancing abnormalities on FLAIR/T2 images as compared to baseline; 4) Patients must be off corticosteroids (or on physiologic replacement doses only) and stable or improved clinically.
- Partial response (PR) requires all of the following: 1) Only reductions of cross-sectional areas of 50% or more in the sum of product of perpendicular diameters of target lesions will be considered a response; when calculating the response, the baseline MRI must be used for comparison ; 2) No progression of non-target lesions; 3) No new lesions; 4) Stable or improved non-enhancing abnormalities on FLAIR/T2 images as compared to baseline; 5) Patients should be on a corticosteroid dose that should not be greater than the dose at time of baseline scan, and should be stable or improved clinically.

- Progressive disease (PD):
  - Progression is defined by any of the following: 1) 25% increase in sum of the products of perpendicular diameters of enhancing lesions (compared with baseline if no decrease) on stable or increasing doses of corticosteroids; 2) a significant increase in T2/FLAIR non-enhancing lesions on stable or increasing doses of corticosteroids compared with baseline scan or best response after initiation of therapy, not due to comorbid events; 3) the appearance of any new lesions; 4) clear progression of non-measurable lesions; or 5) definite clinical deterioration not attributable to other causes apart from the tumor, or to decrease in corticosteroid dose. Failure to return for evaluation as a result of death or deteriorating condition should also be considered as progression.
  - If the evidence of PD is equivocal (target or non-target), treatment may continue until the next assessment, but if PD is confirmed at the next follow-up, the earlier date must be used as the date of progression
  - For patients operated at recurrence and without measurable or non-measurable disease after surgery, any new appearance of tumor will qualify for PD. In case non measurable tumor is left after surgery i.e. tumor less than 10 mm, unequivocal progression of non-target disease may be accepted as evidence of disease progression, where the overall tumor burden has increased sufficiently to merit discontinuation of treatment. Modest increase in the size of a non-target lesion is not considered unequivocal progression. If the evidence of PD is equivocal (target or non-target), treatment may continue until the next assessment, but if confirmed, the earlier date must be used as the date of progression. This implies that in case of gross total resection of the enhancing lesion, if at follow up minimal enhancement of unclear significance arises, treatment may continue until further follow-up gives unequivocal evidence of tumor progression.
- Stable Disease: This occurs if the patients did not qualify for complete response, partial response, or progression (see below) and requires: 1) No meaningful change in the appearance of the FLAIR/T2 images compared to baseline or to the nadir (point with the smallest FLAIR/T2 abnormalities) if a decrease occurred. 2) The patient should be stable clinically. In the event the steroid dosage has been increased for new signs and symptoms without confirmation of disease progression on imaging, and further follow-up imaging shows that with hindsight this increase in steroids was indeed unequivocally needed due to disease progression, the date of progression will be the date steroids were increased.
- In this protocol, although the primary endpoint is OS, in view of the relevance of objective responses, PR, CR, and equivocal PD need to be confirmed with an extra MRI made 4 weeks later.

| Criterion | CR | PR | SD | PD |
|---|---|---|---|---|
| T1 gadolinium enhancing disease | None | ≥ 50% ↓ | <50% ↓ but <25% ↑ | ≥ 25% ↑ |
| T2/FLAIR | Stable or ↓ | Stable or ↓ | Stable or ↓ | ↑ |
| New lesion | None | None | None | Present |
| Corticosteroids | None | Stable or ↓ | Stable or ↓ | Not applicable* |
| Clinical status | Stable or ↑ | Stable or ↑ | Stable or ↑ | ↓ |
| Requirements for response | All | All | All | Any |

*increase in steroids alone does not qualify for PD

### 7.1.2 Overall Survival

Overall Survival (OS) is calculated from the date of randomization up to the date of death (any cause). For patients still alive or lost to follow-up at the time of analysis, survival will be censored at last follow-up visit date.

### 7.1.3 Overall response

The overall response is evaluated at each assessment of the disease according to RANO criteria.

#### 7.1.3.1 Best overall response

Best overall response is the best response designation recorded from the date of randomization until disease progression.

#### 7.1.3.2 Objective response

Objective response includes best overall responses CR and PR. All responses must be confirmed by repeat MRI 4 weeks later.

#### 7.1.3.3 Response duration

For responders, duration of objective response (CR/PR) and complete response (CR) will be measured similarly to PFS (see section 7.1.4) but starting from the time measurement criteria for CR/PR or CR (whichever is recorded first) is met.

#### 7.1.3.4 Clinical /neurological progression

Clinical/neurological progression is defined as the presence of the following conditions:

- decrease in WHO performance status:
  - for patients with baseline WHO performance status 0 or 1: deterioration to WHO performance status 2 or worse for which no other explanation is present
  - for patients with baseline WHO performance status 2: deterioration to WHO performance status 3 or worse for which no other explanation is present
- deterioration of neurological functions
- appearance of signs/symptoms of increased intracranial pressure (headache, nausea and vomiting without other explanations)

- and/or start of corticosteroid or increase of corticosteroid dosage by 50% for control of neurological signs and symptoms, unless the increase is of short duration to control for transient clinical deterioration, lasting one week or less.

### 7.1.4 Progression Free Survival

Progression Free Survival (PFS) will be measured from the date of randomization until the date of first objective progression or the date of patient's death whichever occurs first. Patients without evidence of progression will be censored at the last date of adequate imaging assessment. A patient receiving a second anti-tumoral therapy without prior documentation of disease progression, the patient will not be censored at the date of starting new anti-tumoral therapy.

### 7.1.5 Neurological deterioration-free survival

This study will assess neurological deterioration-free survival (NDFS) as a secondary endpoint to correlate with MRI and clinical findings. Neurological deterioration (ND) is defined as a decrease in WHO performance status:

- for patients with baseline WHO performance status 0 or 1: deterioration to WHO performance status 2 or worse for which no other explanation is present, and which is maintained for at least 3 weeks
- for patients with baseline WHO performance status 2: deterioration to WHO performance status 3 or worse for which no other explanation is present and which is maintained for at least 3 weeks

NDFS will be measured from the date of randomization until the date of first neurological deterioration or the date of patient's death whichever occurs first, regardless of whether radiological progression has occurred or not. Patients without evidence of ND will be censored at the last WHO performance status assessment. If a patient received a second anti-tumoral therapy without prior documentation of disease progression, the patient will not be censored at the date of starting new anti-tumoral therapy. The assessment of neurological deterioration requires continuation of WHO performance status assessment after discontinuation of therapy.

## 7.2 Evaluation of safety

Safety information will be collected for all randomized subjects and reported in the safety population (see chapter 8).

### 7.2.1 Adverse events and side effects

The Investigator will monitor each subject for clinical and laboratory evidence of adverse events on a routine basis throughout the study. Any laboratory value outside the reference range that is considered clinically significant by the Investigator will be followed as appropriate. Clinically significant laboratory values will be recorded as adverse events if they meet the criteria specified below. The Investigator will assess and record any adverse event in detail including the date of onset, event diagnosis (if known) or sign/symptom, severity, time course (end date, ongoing, intermittent), relationship of the adverse event to study drug, and any action(s) taken. For serious adverse events considered as having "no reasonable possibility" of being associated with study drug, the Investigator will provide an Other cause of the event. For adverse events to be considered intermittent, the events must be of similar nature and severity. Adverse events, whether in response to a query, observed by site personnel, or reported spontaneously by the subject will be recorded.

All adverse events will be followed to a satisfactory conclusion.

### 7.2.1.1 Definitions

These definitions reflect the minimal regulatory obligations; specific protocol requirements apply in addition (see following chapters).

**AE:** An **Adverse Event** (please refer to section 7.2.1.2)

**AR**: An **Adverse Reaction of an investigational medicinal product** is defined as “any noxious and unintended response to a medicinal product related to any dose administered”.

**UAR**: An **Unexpected Adverse Reaction** is “any adverse reaction, the nature, or severity of which is not consistent with the applicable product information" (e.g. investigator's brochure for an unapproved investigational product or summary of product characteristics (SmPC) for a marketed product).

When the outcome of the adverse reaction is not consistent with the applicable product information this adverse reaction should be considered as unexpected.

**SAE:** A **Serious Adverse Event** (please refer to section 7.2.1.3)

**SAR**: A **Serious Adverse Reaction** is defined as any SAE which is considered related to the protocol treatment.

**Second primary malignancy** is one unrelated to the treatment of a previous malignancy (and is NOT a metastasis from the previous malignancy).

**Secondary malignancy** is a cancer caused by treatment for a previous malignancy (e.g., treatment with investigational agent/intervention, radiation or chemotherapy). A secondary malignancy is not considered a metastasis of the previous malignancy.

**Any secondary malignancy should also be reported in expedited way on a SAE form with the appropriate seriousness criteria.**

### 7.2.1.2 Adverse Event

An adverse event is defined as any untoward medical occurrence or clinical investigation in a subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not the event is considered causally related to the use of the product.

Such an event can result from use of the drug as stipulated in the protocol or labeling, as well as from accidental or intentional overdose, drug abuse, or drug withdrawal. Any worsening of pre-existing condition or illness is considered an adverse event. Worsening in severity of a reported adverse event should be reported as a new adverse event. Laboratory abnormalities and changes in vital signs are considered to be adverse events only if they result in discontinuation from the study, necessitate therapeutic medical intervention, meet protocol specific criteria (regarding toxicity management, refer to section 5.5) and/or if the Investigator considers them to be adverse events.

An elective surgery/procedure scheduled to occur during a study will not be considered an adverse event if the surgery/procedure has been pre-planned prior to study entry. However, if the pre-existing condition deteriorates unexpectedly during the study (e.g., surgery performed earlier than planned), then the deterioration of the condition for which the elective surgery/procedure is being done will be considered an adverse event.

The following situations do not need to be reported as SAEs:

- Elective hospitalization for pre-existing conditions that have not been exacerbated by trial treatment.
- Hospitalization which was planned before the patient consented for study participation and where admission did not take longer than anticipated and no worsening of condition for which the hospitalization was planned.
- Hospitalization planned for protocol related treatment or protocol related procedure as per institutional standard timelines.
- Social and/or convenience admission to a hospital
- A medical or surgical procedure (e.g. endoscopy, appendectomy) is not a correct event term for an (S)AE; instead the condition that leads to the procedure should be reported as an (S)AE
- Situations where an untoward medical occurrence did not occur (palliative care, rehabilitation, overdose without occurrence of an adverse event).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

#### 7.2.1.3 Serious Adverse Events

If an adverse event meets any of the following criteria, it is to be reported to AbbVie as a serious adverse event (SAE) within 24 hours of the site being made aware of the serious adverse event:

- Death of Subject: An event that results in the death of a subject.
- Life-Threatening: An event that, in the opinion of the Investigator, would have resulted in immediate fatality if medical intervention had not been taken. This does not include an event that would have been fatal if it had occurred in a more severe form.
- Hospitalization or prolongation of hospitalization: An event that results in an admission to the hospital for any length of time or prolongs the subject's hospital stay. This does not include an emergency room visit or admission to an outpatient facility or hospitalization for respite care, or hospitalization due solely to progression of the underlying cancer.
- Congenital Anomaly: An anomaly detected at or after birth, or any anomaly that results in fetal loss.
- Persistent or Significant Disability/Incapacity: An event that results in a condition that substantially interferes with the activities of daily living of a study subject. Disability is not intended to include experiences of relatively minor medical significance such as headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g, sprained ankle).
- Important Medical Event Requiring Medical or Surgical Intervention to Prevent Serious Outcome: An important medical event that may not be immediately life-threatening or result in death or hospitalization, but based on medical judgment may jeopardize the subject and may require medical or surgical intervention to prevent any of the outcomes listed above (i.e., death of subject, life-threatening, hospitalization, prolongation of hospitalization, congenital anomaly, or persistent or significant disability/incapacity). Additionally, any elective or spontaneous abortion or stillbirth is considered an important medical event. Examples of such events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

For serious adverse events with the outcome of death, the date and cause of death will be recorded on the appropriate case report form.

#### 7.2.1.4 Deaths

For this protocol, mortality is an efficacy endpoint. Deaths that occur during the protocol specified adverse event collection period (section 7.2.1.8) that are more likely related to disease progression will therefore be an expected adverse event and will not be an expedited report to the regulatory agencies or IRB/EC.

Death should be considered an outcome and not a distinct event. The event or condition that caused or contributed to the fatal outcome should be recorded as the single medical concept on the adverse event eCRF/Paper 500AE CRF. Generally, only one such event should be reported. The term "sudden death" should only be used for the occurrence of an abrupt and unexpected death due to presumed cardiac causes in a patient with or without pre-existing heart disease, within 1 hour of the onset of acute symptoms or, in the case of an unwitnessed death, within 24 hours after the patient was last seen alive and stable. If the cause of death is unknown and cannot be ascertained at the time of reporting, "unexplained death" should be recorded on the adverse event eCRF/Paper 500AE CRF. If the cause of death later becomes available (e.g., after autopsy), "unexplained death" should be replaced by the established cause of death.

#### 7.2.1.5 Lack of Efficacy or Worsening of Disease

Events that are clearly consistent with the expected pattern the disease or of progression of the underlying disease are considered an expected outcome for this study and will not be subject to expedited reporting. These data will be captured as efficacy assessment data only. Appendix H contains a list of expected adverse events related to GBM or progression of GBM. These events may occur alone or in various combinations and are considered expected for reporting purposes for this protocol. If there is any uncertainty as to whether an event is due to disease progression, it should be reported as an adverse event.

Although exempted from expedited reporting to Health Authorities and ethics committees as individual cases, if an event commonly associated with GBM or progression of GBM meets seriousness criteria (as defined in Section 7.2.1.3), it must be reported to AbbVie within 24 hours of the site being made aware of the serious adverse event.

#### 7.2.1.6 Adverse Event Severity

The Investigator will rate the severity of each adverse event according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE Version 4.0). A copy of the CTCAE can be accessed from the CTEP home page (**Error! Hyperlink reference not valid.**https://ctep.cancer.gov/). NYHA criteria will be used for reporting congestive heart failure.

If a reported adverse event increases in severity, the initial adverse event should be given an outcome date and a new adverse event should be reported to reflect the change in severity.

The term “severe” is often used to describe the intensity (severity) of a specific event (as in mild, moderate or severe, or as described in CTC grades); the event itself, however, may be of relative minor medical significance (such as severe headache). This is not the same as “serious,” which is based on patient/event outcome or action criteria usually associated with events that pose a threat to patient’s life or functioning. Seriousness (not severity) serves as a guide for defining regulatory reporting obligations.

### 7.2.1.7 Relationship to Study Drug

The Investigator will use the following definitions to assess the relationship of the adverse event to the use of study drug (ABT-414, Temozolomide or Lomustine):

**Reasonable Possibility:** An adverse event where there is evidence to suggest a causal relationship between the study drug and the adverse event.

**No Reasonable Possibility:** An adverse event where there is no evidence to suggest a causal relationship between the study drug and the adverse event.

For causality assessments, events assessed as having a reasonable possibility of being related to the study drug will be considered "associated". Events assessed as having no reasonable possibility of being related to study drug will be considered "not associated". In addition, when the Investigator has not reported a causality or deemed it not assessable, AbbVie will consider the event associated.

If an Investigator's opinion of no reasonable possibility of being related to study drug is given, an Other cause of event must be provided by the Investigator for the serious adverse event.

### 7.2.1.8 Adverse Event Collection Period

All adverse events reported from the time of study drug administration until 49 days following discontinuation of study drug administration have elapsed will be collected, whether solicited or spontaneously reported by the subject.

In addition, serious and non-serious adverse events occurring after the subject signed the study-specific informed consent and prior to the initial dose of study drug will be collected only if they are considered by the Investigator to be causally related to required study procedures.

Adverse event information will be collected as shown below.

Adverse Event Collection

| Protocol Related SAEs and Nonserious Adverse Events* | Serious and Nonserious Adverse Events Elicited and/or Spontaneously Reported | | |
|---|---|---|---|
| Consent Signed | Study Drug Start | Study Drug Stopped | 49 Days After Study Drug Stopped** |

* Only if considered by the Investigator to be casually related to study-required procedures.

**If an AE/SAE occurs more than 49 days after study drug was stopped, it only needs to be reported it is considered to have a reasonable possibility to be related to the protocol treatment or study participation.

### 7.2.1.9 Serious Adverse Event Reporting

In the event of a serious adverse event, whether associated with study drug or not, the Investigator will notify the AbbVie Oncology Clinical Safety Management Team within 24 hours of the site being made aware of the serious adverse event. Notification to AbbVie will be done by submitting the paper SAE forms to the email or fax specified below.

**FAX to:** [redacted]

**Email:** [redacted]

In order to be compliant with regulatory reporting requirements, all initial SAE reports should always include the following minimal information:

- Name of person sending the report (i.e., name, address of Investigator)
- Patient identification (screening/randomization number, NOT patient name or initials)
- Protocol number
- Description of SAE
- Causality assessment

All applicable forms need to be dated and signed by the principal investigator (PI) or designated sub-investigator (Sub-I).

For serious adverse event concerns, contact the Oncology Safety Team at:

Safety Management Oncology
AbbVie
1 North Waukegan Road
[redacted]
North Chicago, IL 60064

Contact Information:

[redacted]

EORTC Clinical Research Physician:

[redacted]

For any subject safety concerns, please contact the listed below:

In case of subject safety concerns or medical emergencies the individuals noted above are unavailable, please call the following central back-up number:

Phone: [redacted]

The Sponsor will be responsible for Suspected Unexpected Serious Adverse Reactions (SUSAR) reporting for the Investigational Medicinal Products (IMP) ABT-414, Lomustine and Temozolomide in accordance with Directive 2001/20/EC. The reference documents used for SUSAR reporting in the EU countries will be the most current version of the Investigator's Brochure for ABT-414 and Summary of Product Characteristics (SmPC) for Lomustine and Temozolomide.

#### 7.2.1.10 Pregnancy

Pregnancy in a study must be reported to AbbVie within 1 working day of the site becoming aware of the pregnancy. This applies to subjects who become pregnant during the study while on study drug or within 49 days post study drug discontinuation.

Subjects who become pregnant during the study must be discontinued (section 5.4).

Information regarding a pregnancy occurrence in a study subject and the outcome of the pregnancy will be collected.

Male subjects should be informed that contraceptive measures should be taken by their female partners. If the subject's partner should become pregnant during the study, this should also be reported and data may be collected. In the event of pregnancy occurring in the partner of an enrolled subject, written informed consent for release of medical information from the partner must be obtained prior to the collection of any pregnancy-specific information and the pregnancy will be followed to outcome.

Pregnancy in a study is not considered an adverse event. However, the medical outcome of an elective or spontaneous abortion, stillbirth or congenital anomaly is considered a serious adverse event and must be reported to AbbVie within 24 hours of the site becoming aware of the event.

#### 7.2.1.11 Toxicity Management

For the purpose of medical management, all adverse events and laboratory abnormalities that occur during the study must be evaluated by the Investigator. The table of clinical toxicity grades modified from the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) Version 4.0 is to be used in the grading of adverse events and laboratory abnormalities that are reported as adverse events, each of which will be followed to satisfactory clinical resolution.

## 7.3 Evaluation of Quality of Life

Quality of life assessment is described in detail in chapter 10.

# 8 Statistical considerations

## 8.1 Statistical design

### 8.1.1 Sample size

This is a comparative randomized open label multicenter/multiarm phase II trial. Overall Survival (OS) is the primary endpoint.

Based on literature review, a median OS of 7 months is expected in the mixed control arm (lomustine or TMZ). Based on a one-sided logrank test, at an overall significance level of 2.5% and a power of 91.7% (accounting for the global testing strategy), a total of 170 deaths (118 per comparison, i.e. monotherapy ABT-414 versus control and combination ABT-414 + TMZ versus control) are needed to detect an increase of median OS to 12.9 months in the treatment arms corresponding to a Hazard Ratio (HR) equal to 0.54 (i.e. a reduction in the hazard of death of 46%). Assuming a monthly accrual of 10 patients during month 1 to 12 and 20 patients per month after 12 months, 240 patients can be recruited within 18 months. A follow-up duration of 13 months after end of accrual is required to observe the 170 deaths.

There will be an interim futility analysis organized after observation of 45 PFS events (see section 8.3).

Provided that PFS and OS effects are independent, the overall power of the study is estimated to be approximately 85%. However, treatment effect on PFS and on OS may reasonably be assumed to be positively correlated, and hence the overall power of the study accounting for the interim analysis is expected to exceed 85%.

### 8.1.2 Randomization and stratifications

All patients entered in this trial will be centrally randomized at the EORTC Headquarters (for practical details, see section 13.3 on randomization procedure). The minimization technique (Ref. 37) used by the EORTC for random treatment allocation is based on the variance method with semi-random assignment dependent on a preset threshold as implemented by Freedman and White (Ref. 38). However, per suggestion of the ICH E9 statistical guidelines, the algorithm has been modified to incorporate a random allocation component in order to ensure an additional 15% of completely random assignments.

In this trial, the threshold is set to 3, the total number of stratification factors.

Stratification factors are:

- Regions of the world (North America (USA, Puerto Rico & Canada) vs Europe and Australia vs Asia/other regions)
- WHO Performance Status (0 vs >0)
- Timing of relapse (< 16 weeks vs ≥ 16 weeks after the first day of the last TMZ cycle)

## 8.2 Statistical analysis plan

### 8.2.1 Primary and secondary endpoints

#### 8.2.1.1 Primary endpoint

The primary endpoint is OS at the final analysis and Progression Free Survival (PFS) according to RANO criteria and assessed by IRC at the interim analysis. In addition to the OS Hazard Ratio, the following parameters will be assessed: median OS, probability of survival at 1 year (OS12), probability of survival at 2 years (OS24). See chapter 1 for the definition of endpoints.

#### 8.2.1.2 Secondary and exploratory endpoints

##### 8.2.1.2.1 Secondary Endpoints

- PFS assessed according to RANO criteria and assessed by IRC. In addition to the Hazard Ratio, the following parameters will be computed in each arm: median PFS, probability of progression or death at 6 months (PFS6), probability of progression or death at 1 year (PFS12).
- The OS analysis will be performed in the subgroup with EGFRvIII mutation.
- Objective response rate (ORR) assessed by IRC will be computed in each arm.

##### 8.2.1.2.2 Exploratory Endpoints

- The PFS analysis will be performed in the subgroup with EGFRvIII mutation.
- Best overall response rate (BOR), complete response rate (CRR), duration of response (DR) assessed by IRC will be computed in each arm.
- Neurological Deterioration Free Survival (NDFS), in addition to the Hazard Ratio, the following parameters will be computed in each arm: median NDFS, probability of NDFS at 6 months (NDFS6), probability of survival at 1 year (NDFS12).
- Frequencies and percentages of worst Adverse Event (AEs) or Laboratory Event grades and grade 3/4 per AE term and category as measured by CTCAEs Version 4.0 criteria.
- Quality of Life will be assessed and analyzed according to the methodology described in chapter 10.
- Use of steroids will be analyzed (but not exclusively) with the methodology developed by Vredenburgh et al. (Ref. 39). Schedule of collection of steroids data is detailed in chapter 6.

### 8.2.2 Analysis populations

- Intention-to-treat population (ITT): All randomized patients will be analyzed in the arm they were allocated by randomization.
- Per protocol population (PP): All patients who are eligible and have received at least one dose of the study drug (i.e. one dose of lomustine or TMZ (arm 3), of ABT-414 (arm 2) and of TMZ and ABT-414 (arm 1)). Patients will be classified and analyzed in the arm they were assigned at the time of randomization.
- Safety population (SP): All randomized patients who have received at least one dose of the study drug (i.e. one dose of lomustine or TMZ (arm 3), of ABT-414 (arm 2) and of TMZ and ABT-414 (arm 1)). Patients will be classified according to treatment received.

A patient will be considered to be eligible if he/she did not have any deviation from the patient entry criteria listed in chapter 3 of the protocol. Potential eligibility problems will be assessed by the Clinical Research Physician at time of medical review.

### 8.2.3 Statistical methods

#### 8.2.3.1 Overall Survival

In the ITT:

OS will be compared between arm 1 versus arm 3 and/or arm 2 versus arm 3 when 170 deaths (118 per comparison) are observed.

Differences between the treatment groups in OS will be assessed by a Logrank test stratified by the randomization stratification factors, testing the null hypotheses (H1: Arm 1 is not superior to Arm 3 in OS; H2: Arm 2 is not superior to Arm 3 in OS, respectively). The hazard ratios of the two treatment arms over the control arm will be calculated by Cox's proportional hazards model (score test) stratified by randomization stratification factors.

The OS probability at 12 months (OS12), at 2 years (OS24) and the median OS (mOS) will be estimated from the Kaplan-Meyer OS curve. Two-sided 95% CI will be computed based on the Greenwood's formula. For the median the Reflected Method will provide two-sided 95% CI.

#### 8.2.3.2 Progression Free Survival

In the ITT (RANO criteria assessed by IRC):

Differences between the treatment groups in PFS will be assessed by a Logrank test stratified by the randomization stratification factors, testing the null hypotheses (H1a: Arm 1 is not superior to Arm 3 in PFS; H2a: Arm 2 is not superior to Arm 3 in PFS, respectively). The hazard ratios of the two treatment arms over the control arm will be calculated by Cox's proportional hazards model (score test) stratified by randomization stratification factors.

The PFS probability at 6 months (PFS6), at 12 months (PFS12) and the median PFS (mPFS) will be estimated from the Kaplan-Meyer PFS curves. Two-sided 95% CI will be computed based on the Greenwood's formula. For the median the Reflected Method will provide two-sided 95% CI.

#### 8.2.3.3 Radiological response

In the ITT (RANO criteria assessed by IRC):

The best overall response will be presented in contingency table with frequencies and percentages. The objective response (ORR: CR/PR) and complete response rates will be reported with exact (binomial) two-sided 95% CI. The medians of objective (PR/CR) and complete (CR) response duration will be estimated from the Kaplan-Meier curves. The Reflected Method will provide two-sided 95% CI.

#### 8.2.3.4 OS and PFS in patients with EGFRvIII mutation

In the ITT (for PFS, RANO criteria assessed by IRC):

OS and PFS analyses will be performed in the subgroup of patients with EGFRvIII mutation at final analysis. The same methodology as for analyses in the whole cohort will be applied (see sections 8.2.3.1, 8.2.3.2).

#### 8.2.3.5 Neurological Deterioration Free Survival

In the ITT:

Differences between the treatment groups in NDFS will be assessed by a Logrank test stratified by the randomization stratification factors, testing the null hypotheses (H0: NDFS of the 2 treatment arms equal to that of control arm; Arm 1 vs. Arm 3 and Arm 2 vs. Arm 3, respectively). The hazard ratios of the two treatment arms over the control arm will be calculated by Cox's proportional hazards model (score test) stratified by randomization stratification factors.

The NDFS probability at 6 months (NDFS6), at 12 months (NDFS12) and the median NDFS (mNDFS) will be estimated from the Kaplan-Meyer NDFS curve. Two-sided 95% CI will be computed based on the Greenwood's formula. For the median the Reflected Method will provide two-sided 95% CI.

#### 8.2.3.6 Global strategy to control type I error for efficacy endpoints

To meet global regulatory requirements, a multiple testing strategy for the following ordered endpoints will be implemented to control the family-wise type I error (alpha) for comparisons of Arm 1 (ABT-414 + TMZ) versus Arm 3 (TMZ/lomustine) and Arm 2 (ABT-414 alone) versus Arm 3 with respect to overall survival (OS) and the pre-defined secondary efficacy endpoints, namely progression-free survival (PFS), objective response rate (ORR), and OS for patients with EGFR vIII mutation.

The following null hypotheses are considered:

H1: Arm 1 is not superior to Arm 3 in OS.

H2: Arm 2 is not superior to Arm 3 in OS.

H1a: Arm 1 is not superior to Arm 3 in PFS.

H2a: Arm 2 is not superior to Arm 3 in PFS.

H1b: Arm 1 is not superior to Arm 3 in ORR.

H2b: Arm 2 is not superior to Arm 3 in ORR.

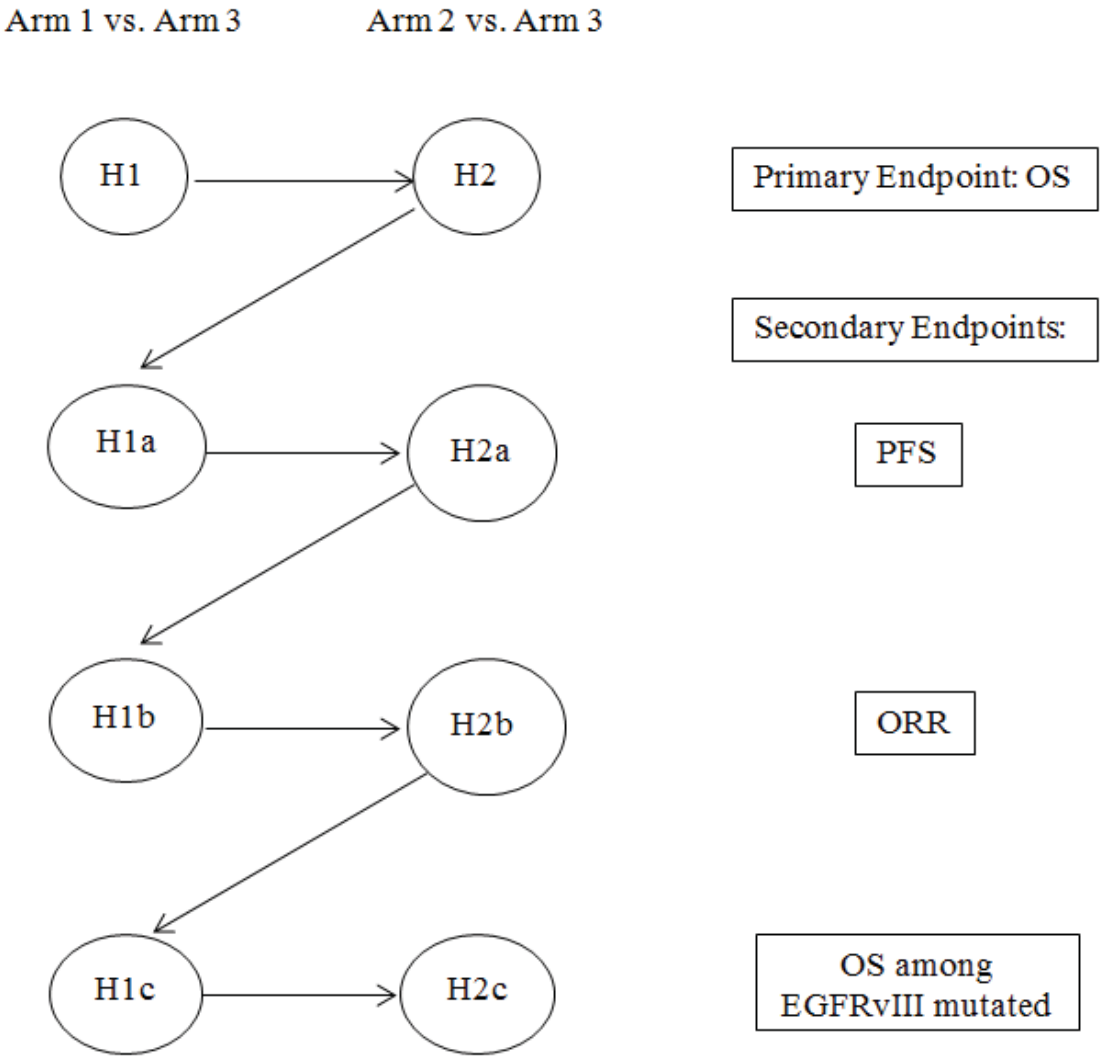
H1c: Arm 1 is not superior to Arm 3 in OS among EGFR vIII mutated patients.

H2c: Arm 2 is not superior to Arm 3 in OS among EGFR vIII mutated patients.

To maintain the overall type I error control for the study, the following null hypotheses will be tested in a fixed sequence of {H1, H2, H1a, H2a, H1b, H2b, H1c, H2c} in order at a 1-sided 2.5% level of significance. Hypothesis H1 will be tested first at a 1-sided 2.5% level. No further tests will be performed if H1 is not

rejected. Each hypothesis will be tested in order specified above if H1 and all preceding hypotheses show statistically significant results at the 1-sided 2.5% level of significance. Otherwise testing in the fixed sequence will stop.

All other endpoints, e.g., PFS in EGFRvIII mutated, global health/QoL status (GHQs), and neurological disease-free survival (NDFS) are considered exploratory and will be tested at a 2-sided 5% level of significance.



#### 8.2.3.7 Safety and tolerability

In the SP:

The safety and tolerability analyses will be presented for the whole study duration. Severe grades (3/4) which did not resolve after treatment discontinuation or emerged during follow-up will be identified and listed. All forms up to the last safety assessment before progression or start of further anti-tumoral therapy will be used. There will be no formal comparison of safety endpoints. No p-value and confidence intervals will be carried out. Baseline laboratory and AE grades will not be accounted for in whole study duration safety analyses.

Laboratory and AE events occurring in patients who did not start their allocated treatment (ie excluded from SP) will be reported separately.

##### 8.2.3.7.1 Hematological parameters

The worst value of each hematological category will be identified and graded for each patient. Frequencies and percentages of each category will be tabulated per arm. A table with grade 3/4 frequencies and percentages will be provided.

##### 8.2.3.7.2 Biochemical parameters

The worst value of each biochemical category will be identified and graded for each patient. Frequencies and percentages of each category will be tabulated. A table with grade 3/4 frequencies and percentages will be provided.

##### 8.2.3.7.3 All AEs

The worst grade of each AE item will be identified for each patient. Frequencies and percentages of each CTCAE term will be tabulated grouped by System Organ Class (SOC). Tables with all grades and grade 3/4 frequencies and percentages will be provided.

##### 8.2.3.7.4 SAEs

After reconciliation with the SAEs listing extracted from the pharmacovigilance database, the worst grade of each SAE item will be identified for each patient and will be considered for the analysis. Frequencies and percentages of each CTCAE term will be tabulated grouped by SOC. Tables with all grades and grade 3/4 frequencies and percentages will be provided.

##### 8.2.3.7.5 Related AEs

The worst grade of each related AE item will be identified for each patient. Frequencies and percentages of each CTCAE term will be tabulated grouped by SOC. Tables with all grades and grade 3/4 frequencies and percentages will be provided.

### 8.2.4 Pre-planned sensitivity or exploratory analyses

In case more than 10% are excluded from the PP, OS analysis (both comparisons) will be performed in the PP population at two-sided alpha 5%.

In the ITT, for OS, PFS, tumor response, NDFS treatment effect will be assessed in the following subgroups:

- Timing of relapse: < 16 weeks and ≥ 16 weeks after the first day of the last TMZ cycle;
- MGMT promoter methylation status: methylated and unmethylated;
- EGFR pathway abnormalities: abnormal and normal.

To assess the predictive value of the above three factors for OS, PFS, NDFS, the score interaction test will be computed by fitting a Cox regression model including treatment, factor and interaction term (treatment X factor). Forest plots will be displayed. KM curves comparing treatments will be presented in each subgroup.

To assess factor univariate prognostic value, the score test will be computed by fitting a Cox model including the factor in each arm (control and treatments). KM curves by factor stratum will be displayed.

For treatment comparison and prognostic value assessment, an exploratory two-sided significance of 5% will apply. For each interaction test, a significance of 10% will apply.

Treatment comparisons in the ITT population and above mentioned other sensitivity analyses will also be performed with PFS assessed by local investigators with the same calculation methods than for PFS assessed by IRC. Other exploratory analyses may be performed based on other subsets of patients. The results of these exploratory analyses may not serve as a basis for drawing conclusions concerning protocol efficacy, but rather as hypothesis generating and the rationale for additional subset analyses should be clearly documented.

### 8.2.5 Prognostic factor analyses

Data of this trial will be added to the EORTC Recurrent GBM data warehouse for further pooled analyses of prognostic factors and other research objectives.

### 8.2.6 Data re-coding and display

Frequency tables will be tabulated (by treatment group or otherwise) for all categorical variables by the levels of the variables as they appear on the CRF (with %). Categories with a text field specification will be tabulated as categories and then supplemented by a listing with the following information for the patients fulfilling the condition for the specification (patient id, institution, treatment group, value of the item and text field contents).

Dates relating to events prior to entry will be presented as the delay in days (or weeks, months, or years) between the past event and the date of entry (date of randomization – date of past event + 1) and presented using the median and range. For example, on the randomization checklist, the date of last administration of prior treatment (or the date of first diagnosis of the cancer) will be presented as the time elapsed (in days, weeks, months or years, as appropriate) since the day of the last administration and the date of entry on study (date of randomization – last administration/diagnosis +1).

Other delays (eg. re-treatment delays) are presented as continuous variables using the median and range.

Continuous variables for which a coding system exists (such as for laboratory data) will be recoded into categories (for adverse events, the grading scale specified in the protocol will be used). Whenever no specific scale exists, lab data will be categorized based on the normal range: for example, below the lower normal limit (when appropriate), within the normal range, above the upper normal limit (ULN) and the degree to which it is above the ULN (for example > 2.5 x ULN, > 5 x ULN, > 10 x ULN). For laboratory data, the nadir is generally displayed. The nadir in a given cycle is the lowest laboratory value in that cycle; the overall nadir for a patient is the lowest laboratory value among all cycles.

Other continuous variables (for example age, dose …) are presented using the median and range (minimum, maximum).

If appropriate, continuous data may also be presented in categories (for example, age may also be grouped in decades).

## 8.3 Interim futility analyses

At interim analysis one or both of the ABT-414 arms might be discontinued based on lack of efficacy for PFS (Reject H1 in favor of H0) according to RANO criteria assessed by IRC.

It is assumed that median PFS is 2.6 months in the control arm and 4.8 months in the treatment arms corresponding to HR equal to 0.54. Assuming an accrual rate of 10 patients/month and activation phase of one year, at least 45 PFS events should be observed. Analyses will be performed when at least 31 PFS events are observed in each comparison. Treatment arms which did not show a minimum level of efficacy, defined as a computed treatment PFS HR lower than 0.91 will be discontinued. The trial will continue with remaining treatment arm(s) and control. There will be no interruption of accrual for the interim analysis.

Treatment PFS HR will be presented with two-sided 95% CI. However, since efficacy data will be analyzed for futility purpose, an alpha spending of 0.00001will be allocated to the futility analysis. For the final analyses, efficacy endpoint will be tested at a nominal 1-sided alpha level of 0.02499.

For each of the two treatment arms the probability of stopping for futility at the interim is 7.4% if the true PFS HR is 0.54 and 60% if the true PFS HR is 1.0 (no benefit).

Based on the assumed accrual rates and treatment effects stated above, the interim futility analysis is expected to be performed when 90 randomized patients (30 patients per arm) have completed approximately 4 months of follow-up.

## 8.4 Re-randomization Test

The robustness of the results to the use of the minimization randomization algorithm will be evaluated by performing a re-randomization test on the primary efficacy analysis, the stratified log-rank test and Cox's proportional hazards model (score test) stratified by randomization stratification factors, to compare the duration of overall survival between the treatment arm(s) and the control.

The re-randomization test will be performed as follows:

- The procedure will use 50,000 replications of the ITT population (all randomized patients).
- Based on the value of their randomization stratification factors, for each replicate, patients will be (virtually) re-assigned to treatments using the original minimization randomization algorithm in the order in which they were randomized into the trial.
- For each replicate the stratified log-rank test statistic and Cox's proportional hazards model (score test) stratified by randomization stratification factors comparing the duration of overall survival will be computed.
- The re-randomization test p-values will be the fraction of replications where the log-rank and Cox' model-based p-values from the replicates are less than or equal to the corresponding p-values from the original analysis.

Robustness of the results will be established if the re-randomization test p-values are then found to be comparable to the corresponding p-values from the original analysis.

## 8.5 End of study

End of study occurs when all of the following criteria have been satisfied:

1. The trial is mature for the analysis of the primary endpoint as defined in the protocol (i.e. at least when 170 deaths will be observed for two comparisons and 118 deaths for one comparison).
2. The database has been fully cleaned and frozen for this analysis.
3. Forty nine days after all patients have stopped protocol treatment.

# 9 Trial Governance and Data Monitoring

## 9.1 Study committees

### 9.1.1 Study Management Group (SMG)

The Study Management Group is set up for this study. It consists of the EORTC Headquarters team in charge of running the study (clinical research physician, statistician, clinical scientist, clinical operations manager and data managers) and the principal study coordinator.

The EORTC Headquarter team, in collaboration with AbbVie, is responsible for the day -to-day conduct of the trial. The Study Coordinator will assist the team in case of problems with patient evaluation (eligibility, treatment compliance, safety).

The Study management Group also performs the medical review as indicated below.

### 9.1.2 Study Steering committee (SSC)

The Study Steering Committee for this study is composed of the study coordinators, the representatives of Academic Groups collaborating to the study, at least one representative of the EORTC Headquarters (Study Clinical Research Physician or Clinical Scientist) and one representative of the Sponsor, if the sponsor is not the EORTC.

This committee provides the general oversight of the study and has the executive power. The SSC monitors study progress and conduct and advises on its scientific credibility. The SSC will consider and act, as appropriate, upon the recommendations of the independent data monitoring committee.

### 9.1.3 Independent data monitoring committee (IDMC)

The independent data monitoring committee for EORTC studies (IDMC) is in charge of the independent oversight of this study. The composition of the IDMC is described in EORTC Policy "Independent Data Monitoring Committees for EORTC studies" (ref. EORTC POL004) and its functioning is ruled by the charter annexed to the Policy.

The study-specific experts on the IDMC performing this review will be selected for their relevant expertise with the disease and/or treatments assessed in the study.

The IDMC reports its recommendations in writing to the Study Management Group through the clinical operations manager to the Study Steering Committee and other relevant parties (supporting bodies, collaborative groups…).

## 9.2 Data Monitoring

### 9.2.1 Monitoring during medical review meetings

The medical review will be performed on a regular basis by the clinical research physician assisted as needed by the study management group. The main study coordinator will, in particular, support the Study Clinical Research Physician during the medical review process and will assist the team in case of problems with patient evaluation (safety, eligibility, treatment compliance). The main study coordinator is also responsible for the review and approval of the medical review plan and medical review reports.

For blinded trials, the medical review is conducted blinded to treatment allocation.

If at any time during the course of the study, the medical review identifies safety signals or other elements that could affect the potential risks and benefits to the study participants. These will be reported to the Study Steering Committee and may trigger a review by the EORTC Independent Data Monitoring Committee (IDMC) as well as the collaborative partner (AbbVie).

### 9.2.2 Monitoring by the IDMC

The IDMC will be asked to give advice on whether the accumulating data from the trial justifies continuing recruitment of further patients or further follow-up.

The IDMC will review the trial whenever safety problems or other elements are identified during the medical review or by the SMG and/or SSC that could affect the potential risks and benefits for study participants.

The IDMC will also review the intermediate reports of accumulating data according to the study interim monitoring plan described in the statistical section of this protocol. If a decision is made to continue without change, the IDMC may advise on the frequency of future reviews of the data on the basis of accrual and event rates.

While the trial is ongoing the accumulating data will generally remain confidential, unless the SSC and IDMC agree that the data should be made public.

# 10 Quality of Life assessment

## 10.1 Rationale

Health related quality of life (HRQoL) is a multidimensional construct, which can be defined as a state of general wellbeing reflecting physical, psychological, and social wellbeing and the impact of the disease and/or treatment related symptoms on daily-life functioning. The patient's subjective perspective is an inherent component of HRQoL and is therefore best assessed via self-administration.
Reducing mortality and morbidity is still the most important factor in cancer clinical research. Nevertheless, issues such as reducing side effects, symptom relief and improving patients' satisfaction have also become relevant parameters in the evaluation of medical strategies. Cancer treatments may produce adverse effects and diminish a patient's quality of life even when survival is extended. Progress in the acceptance of new cancer therapies is sometimes critically dependent on their HRQoL consequences.

## 10.2 Objective

The current experience with angiogenesis inhibiting agents in recurrent GBM has demonstrated considerable difficulties with assessing response and progression in previously treated patients. So, we hypothesize that measures of clinical functioning will yield information (HRQoL, need for steroids, cognitive functioning) that is critical for the patient perception of clinical benefit.

The study hypothesis is that ABT-414 alone or in combination with TMZ improves overall survival compared to lomustine or TMZ single agent. In the present study, HRQOL is an exploratory endpoint. The main objective of HRQOL assessment within this trial is to determine the impact of ABT-414 on **overall global health and HRQoL.** A secondary objective is to evaluate the effect of the treatment on the remaining symptoms and functioning scales as treatment-related side effects may have a (temporary) negative influence on the health related domains of HRQOL of these patients.

## 10.3 HRQoL instrument

Quality of life will be assessed with the EORTC Quality of Life Questionnaire (QLQ-C30) version 3. This is composed of multi-item and single scales. These include five functional scales (physical, role, emotional, social, and cognitive), three symptoms (fatigue, nausea and vomiting and pain) and a global health status/HRQoL scale and six single items (dyspnea, insomnia, appetite loss, constipation, diarrhea and financial difficulties). All scales and single items meet the standards for reliability. The reliability and validity of the questionnaire is highly consistent across different language-cultural groups (Ref. 32). While this standard is used in EORTC studies, it lacks some dimensions that pertain to the QL issues in certain brain cancer. Therefore, we will use the EORTC Brain Cancer module (QLQ-BN20), designed for use in patients undergoing protocol treatment or radiotherapy. It includes 20 items assessing visual disorders, motor dysfunction, communication deficit, future uncertainty, as well as other specific symptoms, such as headaches, seizures or drowsiness. A retrospective validation study has been performed confirming the psychometric validity of this questionnaire (Ref. 33).

## 10.4 Study design

Patients are eligible for the quality of life assessment in this study if they fulfill the eligibility criteria (Chapter3). Should the HRQoL forms not be available in the required language or should the patient refuse to fill out the form, then this should not exclude the patient from further participation in the study. Patients will be informed in the patient informed consent form that they will have their quality of life assessed regularly while involved in this trial. In this phase II trial, HRQoL will be an exploratory outcome and evaluated in a longitudinal design in all patients entered in this study.

HRQoL questionnaires must be filled out at the hospital when patients come for a scheduled visit according to the EORTC “Guidelines for administration of questionnaires” (see Appendix G). The pre-treatment questionnaires must be filled within 2 weeks before randomization. Subsequent questionnaires are administered at week 8 and 16 on-treatment, coinciding with the imaging visits. All patients are requested to complete a HRQoL assessment 6 months after randomization.

Master copies of the HRQoL questionnaires will be sent to the institutions. Additional copies or translations can be provided upon request via the EORTC contact person. The clinical report forms will include a question whether the HRQoL forms have been filled in, and if not, the reason why. The questionnaire will be handed out to the patients by the investigator or a study nurse prior to seeing the doctor for clinical evaluations. The patient should complete the questionnaires by her/himself in her/his own language during the visit as completely and accurately as possible. It is recommended that a key person (e.g. research nurse) at each center should be responsible for questionnaire data collection in order to optimize the compliance of the patient and to ensure the completeness of the data.

The time windows for eligible HRQoL assessments will be as follows:

| Assessment | Time window |
|---|---|
| Baseline | **For all patients.**<br>Can be completed before or on the day of randomization itself but no earlier than 2 weeks before. |
| Week 8<br>(on-treatment) | To be completed at the week 8 MRI visit **while on protocol treatment**. |
| Week 16<br>(on-treatment) | To be completed at the week 16 MRI visit **while on protocol treatment**. |
| At 6 months | **For all patients.**<br>Can be completed at any time during the sixth and seventh month after date of randomization regardless of treatment or progression status. |

## 10.5 Statistical considerations

The primary HRQoL endpoint that is considered relevant for this study is the Global health/QoL status (GHQs) scale of the QLQ-C30 instrument. Other scales will be analyzed on an exploratory basis as secondary HRQoL endpoints, such as fatigue, communication deficit etc. The financial difficulties scale will not be analyzed.

The GHQs scale will be used as primary outcome of interest for this study. A change of 10 points on the 100-point QLQ-C30 scale will be considered as clinically relevant. The standard deviation of this scale is approximately 20 points. With the 2-sided alpha set at 5% and a power of 80% to detect a difference of 10 points (effect size of 0.5), a minimum of 128 patients (64 per treatment arm) is required. For an effect size of 0.75 (difference of 15 points), 56 patients (28 per treatment arm) are required. Therefore, this study is sufficiently powered to detect differences in HRQoL, although the emphasis is on establishing the magnitude and relevance of HRQoL differences rather than comparative tests.

Data will be scored according to the algorithm described in the EORTC scoring manual. All scales and single items are scored on categorical scales and linearly converted to 0-100 scales.

Changes in HRQoL scores per time point will be evaluated by classifying them according to the 10 point change threshold into 3 categories: improved, stable and deteriorated. Patients without a valid HRQoL outcome will be considered as having deteriorated. In case of discrete numbers (N<10), categories may be combined. The subsequent proportions will be compared between treatment arms using a chi-square test in the intent-to-treat population. In order to assess the robustness of the results, the following sensitivity analyses will be performed: a clinical relevant threshold of 5 and 15 points will be used and patients without a valid HRQoL score will be classified according to the reported reason for non-compliance.

### 10.5.1 Missing data

Missing data is a potential major source of bias in HRQoL assessment.

In order to check the potential impact in the study, the compliance mechanism will be investigated prior to initiating the HRQoL analysis. Characteristics of patients with and without valid HRQoL data will be compared and trends over time per dropout pattern will be investigated. Model building will be used in order to investigate whether the compliance mechanism is linked to selected prognostic variables.

Once the main analysis is completed, sensitivity analyses will be undertaken to verify the robustness of the results vis-à-vis the missing data.

In case overall compliance is deemed too low (<50%), only an exploratory analysis will be performed in lieu of the main analysis.

# 11 Translational research

## 11.1 General principles for human biological material (HBM) collection

In this study, biological material (tumor tissue) will be shipped from the study site to a designated CRO according to instructions provided in the study specific laboratory manual. Following the tissue analysis for EGFR amplification and EGFRvIII mutation, all biologic material will be centralized and stored at [redacted]. From here, the biological material will be used or distributed to the other research laboratories involved in the translational research (TR) projects specified in this protocol or defined in the future.

To allow confirmatory studies for EGFR and other mutations in glioblastoma DNA will be collected as part of the study protocol for confirmatory studies. In addition, the biobank will distribute HBM to the other research laboratories involved in the translational research (TR) projects specified in this protocol or defined in the future.

The following principles apply to storage of HBM:

- The biobank will have a designated manager responsible for collection and will act as a communication point with the EORTC
- The collected HBM should be documented, i.e. the amount remaining and its location.
- The 1410-BTG study steering committee (SSC) will be responsible for TR project review and prioritization, including the consideration of newly proposed TR projects not specified in the protocol. In the absence of a SSC, responsibilities of the SSC are transferred to the Group and/ or EORTC HQ as applicable.

Final decisions on the use of HBM will be determined by a majority vote of the SSC/BTG committee. Additional expertise may be sought through advisory non-SSC/BTG committee members.

**Access to HBM** (see EORTC Biobanking Policy POL020): HBM may be used for another purpose for which it was originally collected, subject to meeting ethical principles/and is covered by informed consent/ethics approval. In the case of secondary use of HBM, (i.e. for new TR projects that are not specified in the clinical study protocol and that were not foreseen at the time of protocol writing) interested parties may apply for the use of HBM and will follow the next steps:

A short description of the new TR projects will be written and submitted to EORTC HQ for coordination with the SSC/BTG committee.

- The SSC/BTG committee will prioritize the TR projects. Access procedures defined by the SSC/BTG committee will build on the following key points:
    - Project prioritization
        - should be strongly based on scientific merit,
        - should consider the contribution of the different investigators to the trial and TR project,

    - will take into consideration if the applicant is an EORTC member or not (whilst maintaining the principle of access to the wider scientific community and commitments owed to study participants and ethical committees).
    - Protection of confidentiality must be respected.
- An EORTC HQ feasibility check, including recommendations for regulatory and ethical matters and other restrictions on the use of the HBM, will take place. If in the event the HBM collections are still retained at individual clinical sites, the TR project leader and the involved EORTC Group are responsible for collecting and providing information on availability of HBM for the feasibility assessment.
- Prioritized TR projects will then be reviewed by the Translational Research Advisory Committee (TRAC).

Once SSC/BTG committee prioritization, the EORTC HQ feasibility assessment, and TRAC review are complete and when all applicable competent Ethics Committees approvals are in place and ethical principles are met, the TR project can be activated and HBM release and analysis can commence.

The EORTC Board will mediate any disagreements of opinion between TRAC, the EORTC HQ feasibility assessment, the SSC/BTG committee and the TR project leader(s), as needed.

## 11.2 Pharmacokinetic Analysis of Blood Samples for ABT-414, Total ABT-806, Unconjugated Cys-mcMMAF, and ADA (nADA)

In this study, pharmacokinectic blood and/or serum samples collected from subjects in Arms 1 and 2 will be shipped from the study site to a designated CRO according to instructions provided in the study specific laboratory manual. Serum or plasma concentrations of ABT-414, Total ABT-806, ADA/nADA, and unconjugated cyc-mcMMAF will be determined using validated methods under the supervision of the Drug Analysis Department at AbbVie.

Peak and trough concentrations (Cmax and Ctrough) of ABT-414 and total ABT-806 antibody will be summarized from the observed concentration data. A nonlinear mixed effect modeling analysis will be conducted to estimate the population pharmacokinetic parameters of ABT-414, total ABT-806 and cys-mcMMAF such as clearance and volume of distribution. Effect of demographic and/or disease-specific variable(s) on the PK parameters of ABT-414, total ABT-806, and cys-mcMMAF will be examined.

Exposure-response analyses for relevant safety and/or efficacy variables may be conducted to understand the contribution of ABT-414, total ABT-806 antibody, and cys-mcMMAF to efficacy and safety.

## 11.3 Pharmacodynamic Analysis of Plasma Markers and Serum Markers

Pharmacodynamic plasma and serum samples collected from subjects randomized to Arm 1 and 2 will be shipped from the study site to a designated CRO according to instructions provided in the study specific laboratory manual and will be analyzed by AbbVie. Examination of the plasma and serum components of blood in subjects may reveal patterns of metabolites, cell-free nucleic acids or protein/peptide concentrations that may be further evaluated in future clinical studies to determine any prognostic value and any correlation with clinical response. Serum and plasma samples may be analyzed for predictive or drug-responsive proteomic or nucleic acid markers

## 11.4 Pharmacogenetic Analysis of Blood Samples - optional

All subjects enrolled in the study may consent to provide samples for the optional pharmacogenetic analysis. These samples will be shipped from the study site to a designated CRO according to instructions provided in the study specific laboratory manual. The PG samples may be analyzed by Abbvie or companies working with AbbVie. DNA samples may be sequenced and data analyzed for genetic factors contributing to the disease or subject's response to ABT-414, or other study treatment, in terms of pharmacokinetics, efficacy, tolerability and safety. Such genetic factors may include genes for drug metabolizing enzymes, drug transport proteins, genes within the target pathway, or other genes believed to be related to drug response or disease. Some genes currently insufficiently characterized or unknown may be understood to be important at the time of analysis. The samples may be analyzed as part of a multi-study assessment of genetic factors involved in the response to ABT-414, drugs of this class, or the disease state. The samples may also be used for the development of diagnostic tests related to the disease or ABT-414 (or drugs of this class). The results of pharmacogenetic analyses may not be reported with the study summary.

## 11.5 Methylation status of the primary tumor

It is increasingly clear that the methylation status of the MGMT promoter gene plays a primary role in the resistance of glioma against alkylating agents. In newly diagnosed GBM, MGMT promoter gene methylation was correlated with clinical benefit from combined chemo-irradiation with temozolomide (Ref. 34). Several studies have now given evidence of the impact of MGMT promoter methylation at the time of primary diagnosis for the outcome of treatment at the time of recurrence, with an impact on both PFS and OS in lomustine and TMZ treated patients (Ref. 14, Ref. 18). It is however unclear if MGMT status is only predictive for response to alkylating agents or whether it is also prognostic in recurrent GBM. In view of the improved outcome of MGMT promoter methylated patients after combined chemo-irradiation with TMZ, it is anticipated that with longer time to first progression the percentage of patients with a MGMT promoter methylated tumor will increase. For exploratory analysis of the correlation between outcome and MGMT promoter methylation MGMT promoter status will therefore be assessed, using methylation specific PCR (MS-PCR). Analysis will explore whether MGMT status is balanced between the groups, and will correlate OS and PFS with MGMT status in each of the treatment arms (see section 8.2.4).

Although IDH mutations have prognostic significance in glioblastoma and are associated with MGMT promoter methylation, the presence of IDH mutations is mutually exclusive with the presence of EGFR amplification and IDH mutational status assessment in this study is not required.

Tissue samples submitted for EGFR amplification from subjects that have been enrolled in the study will be analyzed for methylation status.

## 11.6 RNA expression profiling

Due to the pivotal relevance of EGFRvIII mutations for this study, EGFRvIII status will also be determined retrospectively by PCR on tumor tissue samples.

ABT-414 is an ADC composed of the anti-EGFR antibody ABT-806 conjugated to the potent tubulin inhibitor monomethylauristatin F (MMAF). ABT-806 is a humanized gamma 1 antibody with kappa light chain (IgG1κ) specific for a unique epitope of the EGFR which is largely inaccessible when EGFR is expressed at physiological levels. The targeted epitope is however accessible in tumors that express EGFR with deletion of exons 2 through 7 (EGFRde2-7, also referred to as EGFRvIII) and in tumors with wild-type amplified EGFR or excessive EGFR activation. Although one of the inclusion criteria in this trial is EGFR amplification (which results in receptor activation), many other mutations in the EGFR receptor gene are

often present in EGFR amplified tumors and often 3-4 different mutations are detected within a single tumor. For example, a single EGFR-amplified GBM may harbor several different intrachromosomal deletions (EGFRvIII ex12-13, ex14-15), point mutations (A289V, G598V) and/or 3'deletions (Ref. 19, Ref. 35). When different mutations also show differential sensitivity to EGFR inhibitors, this may impact the efficacy of treatments targeting the activated EGF receptor (Ref. 36). Therefore, any treatment that specifically targets EGFR should determine which genetic alterations are present and at what frequency in the EGFR locus. As most mutations are present only in a minority of alleles, the sensitivity of targeted re-sequencing on the DNA level will be insufficient. RNA-sequencing can identify such changes and at present this technique appears the most sensitive and cost effective method to detect somatic alterations of the EGFR locus. RNA sequencing may also allow exploratory analysis of mechanisms of resistance of the tumor involved in resistance to the active portion of ABT414, MMAC.

See section 8.2.4 for statistical considerations.

Tissue samples submitted for EGFR amplification from subjects that have been enrolled in the study will be further assessed for additional EGFR mutations.

## 11.7 Targeted next-generation sequencing of relevant cancer genes

Samples submitted for EGFR amplification testing from subjects that have been randomized will also be assessed for other DNA mutations, including but not limited to, mutations in the EGFR signaling pathway, such as PTEN, TP53, Rb, CDKN2A, and PI3K. All analysis of outcome related to these mutations will be exploratory.

## 11.8 Future translational studies - optional

During the conduct of the study and thereafter new questions may arise regarding the biological behavior of glioblastoma and/or treatment of glioblastoma with ABT-414, TMZ, lomustine or other agents. For these new research questions, analysis of tumor samples collected within the present studies may prove useful. Therefore, all patients will be asked for consent for future translational research on remaining tumor and all other remaining material from patients treated within this study, including the optional translational research blood sample. Details on handling and shipment of the human biological material can be found in the study manual.

Translational research projects will be coordinated by:

[redacted]
Erasmus MC Hospital
Dept. of Neurology - Erasmus MC Hospital
Postbus 2040 ('s-Gravendijkwal 230)
3000 CA Rotterdam
Netherlands

## 11.9 Data storage, transfer and development of technical appendices

The translational projects will be the result of the work of collaborating institutions and EORTC HQ. Bioinformatics and statistical analysis plan will be jointly developed for each project. These documents will be developed and approved before starting any analysis. They will specify the analytical and methodological details. Clinical data will be stored in the EORTC clinical database and biological investigational data will be stored in respective collaborating institutions. Transfer of data will be performed according to applicable policies in each organization (e.g. EORTC POL008) or according to jointly approved data transfer charters.

# 12 Investigator authorization procedure

Investigators will be authorized to register and/or randomize/enroll patients in this trial only once they have returned the following documents to AbbVie:

- The updated signed and dated curriculum vitae of the Principal Investigator in English with a GCP training proof.
- The Study Agreement between Abbvie and investigator's institution.
- A copy of the favorable opinion of the local or national (whichever is applicable) ethics committee mentioning the documents that were reviewed (including the version numbers and version dates of all documents). A list of all members of the ethics committee is also requested.
- A copy of the translated and adapted (according to all national requirements) Patient Information / Informed Consent sheet. Version numbers and dates must be clearly stated on each page.
- The full name, address, phone numbers and e-mail address of the local pharmacist who will be responsible for the trial medication (for any trial where the drug will be provided).

Also should be provided prior to use of local labs:

- The current list of normal ranges for the investigator's institution to include all lab tests required by the protocol.
- An accreditation, a certification, an established quality control / external quality assessment or another validation should be provided for the own laboratory.

The new investigator will be added to the "authorization list", and will be allowed to register/randomize/enroll patients in the trial as soon as

- Investigational Product release approval received from AbbVie.
- All applicable national legal and regulatory requirements are fulfilled.

Patient registration/randomization from centers not (yet) included on the authorization list will not be accepted.

Additional documents may be requested by AbbVie to initiate release of study drug and activation of the centers in the IRT system.

# 13 Patient registration and randomization procedure

Patient registration will only be accepted from authorized investigators (see chapter on "investigator authorization procedure").

Patients should be registered immediately after signing the informed consent for registration, directly on the **EORTC online randomization system** (ORTA = online randomized trials access), accessible 24 hours a day, 7 days a week, through the internet. To access the interactive randomization program, the investigator needs a username and a password (which can be requested at http://orta.eortc.be/).

In case of problems investigators can phone the EORTC Headquarters from 9.00 am to 5.00 pm (Belgian local time) from Monday through Friday in order to randomize patients via the EORTC call center. Randomization via the phone is not available on Belgian holidays. A list of these holidays is available on the EORTC web site (http://orta.eortc.be/) and it is updated annually.

| | |
|---|---|
| Through internet: | http://orta.eortc.be/ |
| *In case of problems randomization by phone:* | [redacted] |

**A patient can only be registered/randomized after verification of eligibility. Both the eligibility check and randomization must be done before the start of the protocol treatment.**

## 13.1 Registration (step 1)

A list of questions to be answered during the registration procedure is included in the registration checklist, which is part of the case report forms.

STANDARD INFORMATION REQUESTED:

- institution number
- protocol number (1410)
- step number: (1 - New patient)
- name of the responsible investigator
- patient's code (*maximum 4 alphanumerics*)
- patient's birth date (year only) in the *day/month/year* format, to be captured as 01/01/year; for pediatric patients the month and year of birth (01/month/year) will be captured.
- PROTOCOL SPECIFIC QUESTIONS:
- all registration criteria will be checked one by one
- date of written informed consent for registration (*day/month/year*)

Once registration criteria have been verified, a **sequential patient identification number ("seqID")** will be allocated. This number will allow the identification of the patients in the VISTA/Remote Data Capture system (VISTA/RDC) that will be used to complete the Case Report Forms.

**All SAMPLE SHIPMENTS and REPORTS must be identified with the EORTC Id (seqID) attributed at registration**

## 13.2 Central lab review procedure (step 2)

After registration and shipment of the sample, the central laboratories will assess the patient's EGFR status. Details of the testing procedure are specified in the laboratory manual. The assessment results of the central lab will be entered in the ORTA system (step 2).

A patient who has not been registered before the EGFR assessment will not be accepted for the study at a later date and cannot be entered for the second step of the study. Patients who have tissue screening prior to tumor progression will have their information registered and EGFR assessment recorded in the ORTA system but will not proceed further until tumor progression. At the time of tumor progression, all eligibility criteria must be met before proceeding to step 3 (below).

At the end of step 2, once the test results have been verified, the site will be informed by a notification email if, following the EGFR assessment, the patient is eligible to start the randomization procedure (step 3).

The central lab review procedure is not applicable for the pediatric sub-study.

## 13.3 Randomization procedure (step 3)

A patient who has not been registered and had the EGFR assessment done by the central lab will not be accepted for the study at a later date and cannot be checked for eligibility by the third step of the study.

An exhaustive list of questions to be answered during the randomization procedure is included in the eligibility checklist, which is part of the case report forms.

STANDARD INFORMATION REQUESTED:

- institution number
- protocol number (1410)
- step number: (3 – Existing patient)
- name of the responsible investigator

The patient will have to be selected in the list of patients that have already been registered in the first step. Once the patient has been identified in the list, select the corresponding patient's code. The patient's code and date of birth will automatically be inserted in the identification screen.

PROTOCOL SPECIFIC QUESTIONS:

- all eligibility criteria will be checked one by one
- actual values of the eligibility parameters will be requested when applicable
- stratification factors
- date of written informed consent for the main study (*day/month/year*)

Once eligibility and stratification factors have been checked, the treatment will be randomly allocated to the patient (minimization technique) and the site will be informed of it by an automatic notification email if the patient is eligible.

Pediatric patients will have Enrollment in ORTA as Step 2. There is no requirement to wait for central lab EGFR amplification result. Enrollment in ORTA follows a similar procedure although patients will not be randomized.

## 13.4 Confirmation of treatment arm and drug dispensation

Once a subject's eligibility has been confirmed and randomization has been completed, sites will access the Interactive response technology (IRT) system and confirm the treatment arm the subject was randomized to. This will initiate drug dispensation and allocation of the proper study drug (ABT-414 and TMZ and lomustine for the countries where these will be provided by the sponsor).

STANDARD INFORMATION REQUESTED:

- patient's SeqID
- treatment arm

## 13.5 Interactive Response Technology (IRT)

Before the study is initiated, the telephone log-in/call-in directions for the IRT will be provided to each site. Study drug will be dispensed at the study visits summarized in chapter 6. Unused study drug should not be redispensed to the subject.

# 14 Forms and procedures for collecting data

## 14.1 Case report forms and schedule for completion

Data will be reported on the forms specifically designed by the EORTC Headquarters for this study. Forms should be electronically sent to the EORTC Headquarters through the VISTA/RDC (Remote Data Capture) system, with the exception of the Quality of Life form, the SAE form and the Pregnancy notification form which are paper CRFs.

Copies of the Quality of Life forms should be sent directly to the EORTC Headquarters by one of the following means:

- By fax, to the attention of BTG Data manager: + [redacted]
- By scanning and e-mailing the forms (see Guidelines for completion of Case Report Forms) to [redacted]
- By post to the EORTC Headquarters:

(BTG Data Manager)

EORTC Headquarters
Avenue E. Mounierlaan 83/11
Brussel 1200 Bruxelles
België - Belgique

**SERIOUS ADVERSE EVENTS AND PREGNANCY NOTIFICATION FORMS SHOULD BE IMMEDIATELY REPORTED ACCORDING TO THE PROCEDURE DETAILED IN THIS PROTOCOL** (see chapter on Reporting Serious Adverse Events).

**A. Before the treatment starts:**

♦ The patient must be registered/randomized in the trial by INTERNET or in case of problems by phone.

The electronic CRFs to be completed for a patient are available on the VISTA/RDC website one day after the registration on http://rdc.eortc.be/ or on http://www.eortc.org in the section for "Research Tools".

The paper CRF(s) will be made available to the institution at the time the institution is authorized.

**B. During/after treatment**

The list of forms to be completed for this study and their submission schedule are available on the VISTA/RDC website and are also described in the "guidelines for completion of case report forms" that are provided to each participating investigator.

**ALL Forms must be electronically approved and sent by the responsible investigator or one of his/ her authorized staff members with the exception of the paper Quality of Life form (no signature needed).**

## 14.2 Data flow

The case report forms must be completed electronically, with the exception of the paper forms (SAE form, Pregnancy Notification form if applicable, and the Quality of Life forms), dated and signed by the investigator or one of his/her authorized staff members as soon as the requested information is available.

The list of staff members authorized to sign case report forms (with a sample of their signature) must be sent to the EORTC Headquarters by the responsible investigator before the start of the study. To enter the RDC system, the investigator or authorized staff member needs to use the same username and password that are used to access the interactive randomization program (ORTA).

In all cases, it remains the responsibility of the principal investigator to check that data are entered as soon as possible and that the (electronic) forms are filled out completely and correctly. The EORTC data manager will subsequently apply the corrections into the database.

The EORTC Headquarters will perform extensive consistency checks on the CRFs and issue queries in case of inconsistent data. The queries for the electronic forms will appear in the VISTA/RDC system and must be answered there directly.

If an investigator (or an authorized staff member) or monitor needs to modify a CRF after the form has been electronically sent to the EORTC Headquarters, he/she should create a request for data correction in the VISTA/RDC system.

The data corrections will appear in the VISTA/RDC system and the EORTC data manager will subsequently apply the corrections into the database.

When satellite institutions are involved all contacts are done exclusively with the primary institution, for purposes of data collection and all other study related issues.

More details on the data flow and related monitoring activities can be found in the Guidelines for completion of Case Report Forms.

# 15 Quality assurance

## 15.1 Control of data consistency

Data forms will be electronically sent to the EORTC Headquarters database by the VISTA/RDC (Remote Data Capture) system. Computerized and manual consistency checks will be performed on newly received forms; queries will be issued in case of inconsistencies. Consistent forms will be validated by the data manager. Inconsistent forms will be kept "pending" until resolution of inconsistencies.

## 15.2 Routine Monitoring Visits

AbbVie will perform on-site monitoring visits, as follows:

The initial site monitoring visit will be conducted within approximately 2-6 weeks following first subject enrolled. The frequency of the routine monitoring visits will be approximately every 10-14 weeks, but may be adjusted as appropriate based on enrollment, visit schedule or subject status at the investigative site.

The aim of these site visits will be:

- to verify that the site facilities remain adequate for performing the trial
- to verify that the principal investigator and site staff involved in the trial are working in compliance with GCP and protocol requirements
- to assess the consistency of data reported on the case report forms with the source data
- to check that Serious Adverse Events have been properly reported and that follow-up information or queries are correctly fulfilled
- to assist the site in resolving any outstanding queries
- to control the drug accountability process

## 15.3 Audits

AbbVie, any third party (e.g. a CRO) acting on behalf of the EORTC, or any domestic or foreign regulatory agency, may come at any time to audit or inspect their site and all subsites, if applicable.

This audit consists of interviews with the principal investigator and study team, review of documentation and practices, review of facilities, equipment and source data verification.

The investigator will grant direct access to paper and/or electronic documentation pertaining to the clinical study (e.g. CRFs, source documents such as hospital patient charts and investigator study files) to these authorized individuals. All site facilities related to the study conduct could be visited during an audit (e.g. pharmacy, laboratory, archives …). The investigator agrees to co-operate and provide assistance at reasonable times and places with respect to any auditing activity.

If applicable, the company(ies) supplying the study drug(s), if different from the sponsor, may have access to anonymized data but will not have access to source documents.

If a regulatory authority inspection is announced, the investigator must inform the EORTC Headquarters QA&C Unit immediately (contact at: [redacted]

In this way EORTC can provide support in preparing and/or facilitating the inspection. EORTC representatives/delegates may also attend the inspection.

## 15.4 Central review of histology

Central pathology review will be performed retrospectively at the end of the study for all patients included.

Human biological material needed for the review is:

- A paraffin embedded tumor sample (tumor material at initial diagnosis and/or recurrence if available) (preferably a tumor block, otherwise 30 unstained slides)
- The anonymized local pathology report

For further operational procedure refer to the study manual.

The review will be done by:

[redacted]
Josephine Nefkens Institute - Dept of Pathology
Doctor Molewaterplein 50-60
3000DR Rotterdam
The Netherlands
E-mail: [redacted]
Phone: [redacted]
Fax: [redacted]

## 15.5 External review of responses

All MRI scans of all patients will be centrally reviewed using the RANO criteria during the conduct of the study. The radiology reviewer will be kept blinded to the study treatment. Centers will be requested to submit anonymized imaging data of all patients meeting this criterion, for external independent review (IRC) of responses (as described in the study manual). Reviews will be done independently without knowledge of the local assessment, with emphasis on T2 weighted and T2-FLAIR MR images. Central radiologist will give feedback on investigator reads shortly after MRI submissions for the first 15 PFS events. In additional, top recruiting sites will receive more frequent feedback from the central radiologist. Otherwise, local MRIs will be assessed by central review in batches.

The outcome of the review and the local response evaluation will be captured in the database. Central radiographic review will be used for all endpoints and reporting to regulatory agencies. Details on MRI shipment/uploading are provided in the study manual.

## 15.6 Scan submission Quality Assurance and Quality Control in imaging

The designated central imaging vendor will track all scans of all patients received from the sites and will request/query missing/incomplete scans. Furthermore, if the scans arrive in unacceptable quality or in a non-acceptable format, the site will be informed to provide substitute scans.

Scans will be uploaded by the participating centers via a central imaging platform. Please refer to the imaging guidelines/manual for more details regarding submission of images, qualification of sites, and imaging QA/QC level description.

# 16 Ethical considerations

## 16.1 Patient protection

The responsible investigator will ensure that this study is conducted in agreement with either the Declaration of Helsinki (available on the World Medical Association web site (http://www.wma.net)) and/or the laws and regulations of the country, whichever provides the greatest protection of the patient.

The protocol has been written, and the study will be conducted according to the ICH Harmonized Tripartite Guideline on Good Clinical Practice (ICH-GCP, available online at https://www.ema.europa.eu/documents/scientific-guideline/ich-e6-r1-guideline-good-clinical-practice_en.pdf).

The protocol must be approved by the competent ethics committee(s) as required by the applicable national legislation.

## 16.2 Subject identification

The name of the patient will neither be asked for nor recorded at the EORTC Headquarters. A sequential identification number will be automatically allocated to each patient registered in the trial. This number will identify the patient and will be included on all case report forms. In order to avoid identification errors, the patient's code (maximum of 4 alphanumerics) and date of birth (year only) will also be reported on the case report forms (for pediatric patients the month and year of birth).

## 16.3 Informed consent

All patients will be informed about

- the aims of the study
- the possible adverse events
- the procedures and possible hazards to which the patient will be exposed
- the mechanism of treatment allocation
- strict confidentiality of any patient data
- medical records possibly being reviewed for trial purposes by authorized individuals other than their treating physician

The template of the patient's informed consent statement is given as a separate document dated and version controlled to this protocol.

An adapted translation of the PIS/PIC will be provided by EORTC Headquarters and it is the responsibility of the Coordinating investigators for this trial (sometimes called National Coordinators) to adapt it to national/local requirements where necessary.

The translated informed consent documents are to be submitted to ethics committees for approval. The competent ethics committee for each institution must approve the informed consent documents before the center can join the study. It is the responsibility of the competent ethics committee to ensure that the translated informed documents comply with ICH-GCP guidelines and all applicable national legislation.

It is emphasized in the patient information sheet that participation is voluntary and that the patient is free to refuse further participation in the protocol whenever he/she wants to. This will not have any impact on the patient's subsequent care. Documented informed consent must be obtained for all patients included in the study before they are registered and/or randomized at the EORTC Headquarters. The written informed consent form must be signed and personally dated by the patient or by the patient's legally acceptable representative.

All of the above must be done in accordance with the applicable national legislation and local regulatory requirements.

# 17 Administrative responsibilities

## 17.1 The study coordinator

The Study Coordinator works closely with the study team to develop the outline and full protocol and discusses the contents of the reports with the study team. The Study coordinator is responsible for publishing the study results. He/she will assist the Clinical Research Physician for answering some clinical questions concerning eligibility, treatment, and contributes to the medical review of the patients.

**Study coordinator:**

[redacted]
Erasmus MC - Daniel den Hoed Cancer Center
(Postbus 5201) Groene Hilledijk 301,
3075 EA Rotterdam
The Netherlands
Phone: [redacted]
Fax:
E-mail: [redacted]

**Study co-coordinator:**

[redacted]
Ospedale Bellaria
Via Altura, 3
Bologna
Italy
Phone: [redacted]
Fax:
E-mail: [redacted]

## 17.2 The EORTC Headquarters

The EORTC Headquarters will be responsible for writing the protocol and PIS/IC, reviewing the protocol, setting up the trial, collecting case report forms, controlling the quality of the reported data, organizing the medical review and generating reports and analyses in cooperation with the Study Coordinator. All methodological questions should be addressed to the EORTC Headquarters.

**EORTC HEADQUARTERS**

Avenue E. Mounierlaan 83/11
Brussel 1200 Bruxelles
België - Belgique
Fax: [redacted]

## 17.3 The EORTC group

All questions concerning ongoing membership in the group should be addressed to the chairman and/or secretary of the group.

For new membership contact Membership Committee at [redacted]

EORTC Brain Tumor group

**Chairman:**

[redacted]
UniversitaetsSpital Zurich
Raemistrasse 100
8091 Zurich
Switzerland
Phone: [redacted]
Fax: [redacted]
E-mail: [redacted]

**Secretary:**

[redacted]
Vrije Universiteit Medisch Centrum
P.O. Box 7057 - (De Boelelaan 1117)
1007MB Amsterdam
Netherlands
Phone: [redacted]
Fax: [redacted]
E-mail: [redacted]

## 17.4 AbbVie (Study Sponsor)

AbbVie Study Designated Physician:

[redacted]
Senior Medical Director AbbVie B.V.
Oncology Development, Global Pharmaceutical R & D
Wegalaan 9
2132 JD Hoofddorp
NETHERLANDS
OFFICE: [redacted]
CELL:
E-MAIL:

# 18 Trial insurance

Clinical trial insurance has been taken out according to the laws of the countries where the study will be conducted. An insurance certificate will be made available to the participating sites at the time of study initiation, as required per local requirements.

# 19 Publication policy

All publications must comply with the terms specified in the EORTC Policy 009 “Release of Results and Publication Policy” version 4.02 dated 19/03/2012.

The final publication of the main trial results will be written by the EORTC Study Coordinator on the basis of the final analysis performed at the EORTC Headquarters and published in a major scientific journal.

The final publication of associated translational research studies will be written by the Coordinator of the corresponding translational research study.

Authors of the manuscript(s) will include the Study Coordinators, the investigators who have included more than 5% of the eligible patients in the trial (by order of inclusion), the central review pathologist, neuro-radiologists, the statistician and clinical research physician in charge of the trial at the EORTC Headquarters. For publication of translational research results, co-authors will also include scientific collaborators who made substantial contribution to the research.

The title of all manuscripts will include “EORTC”, and all manuscripts will include an appropriate acknowledgment section, mentioning all investigators who have contributed to the trial, the EORTC Headquarters staff involved in the study, as well as AbbVie.

Prior to submission, all publications (papers, abstracts, presentations, etc.) including data pertaining to patients from the present trial will be submitted for review to the EORTC Headquarters, to all co-authors, and to AbbVie.

The above rules are applicable to publications involving any individual patient registered/randomized in the trial.

The data collected during this study are confidential. Any publications or abstracts arising from this study require approval by EORTC and AbbVie prior to publication or presentation and must adhere to EORTC's publication requirements as set forth in the approved clinical trial agreement (CTA). All draft publications, or detailed summaries of any proposed presentations, must be submitted to the EORTC and AbbVie at the earliest practicable time for review, not less than 30 days (14 days for abstracts) before submission or presentation unless otherwise set forth in the CTA.

# Appendix A: References


Ref. 1 Schwartzbaum JA, Fisher JL, Aldape KD, Wrensch M. Epidemiology and molecular pathology of glioma. Nat.Clin Pract.Neurol 2006 Sep;2(9):494-503

Ref. 2 Ohgaki H, Kleihues P. Epidemiology and etiology of gliomas. Acta Neuropathol 2005;109:93-108

Ref. 3 Hess KR, Broglio KR, Bondy ML. Adult glioma incidence trends in the United States, 1977-2000. Cancer 2004;101:2293-9

Ref. 4 Stupp R, Mason WP, van den Bent MJ, Weller M, Fisher B, Taphoorn MJ, Belanger K, Brandes AA, Marosi C, Bogdahn U, et al. Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma. N Engl J Med 2005;352:987-96

Ref. 5 Curran WJ, Scott CB, Horton J, Nelson JS, Weinstein AS, Fischbach J, Chang CH, Rotman M, Asbell SO, Krisch RE, et al. Recursive partitioning analysis of prognostic factors in three radiation therapy oncology group malignant glioma trials. J Natl Canc Inst 1993;85:704-10

Ref. 6 Simpsom JR, Horton J, Scott C, Curran W, Rubin P, Fischbach J, Isaacson S, Rotman M, Asbell SO, Nelson JS, et al. Influence of location and extent of surgical resection on survival of patients with glioblastoma multiforme: results of three consecutive radiation therapy oncology group (RTOG) clinical trials. Int J Radiation Oncol Biol Phys 1993;26:239-44

Ref. 7 Gorlia T, Stupp R, Brandes AA, Rampling RR, Fumoleau P, Dittrich C, Campone MM, Twelves CC, Raymond E, Hegi ME, et al. New prognostic factors and calculators for outcome prediction in patients with recurrent glioblastoma: a pooled analysis of EORTC Brain Tumour Group phase I and II clinical trials. Eur.J.Cancer 2012 May;48(8):1176-84

Ref. 8 Carson KA, Grossman SA, Fisher JD, Shaw EG. Prognostic factors for survival in adult patients with recurrent glioma enrolled onto the new approaches to brain tumor therapy CNS consortium phase I and II clinical trials. J Clin Oncol 2007 Jun 20;25(18):2601-6

Ref. 9 Veninga T, Langendijk HA, Slotman BJ, Rutten EHJM, van der Kogel AJ, Prick MJJ, Keyser A, van der Maazen RWM. Reirradiation of primary brain tumors: survival, clinical response and prognostic factors. Radioth Oncol 2001;59:127-37

Ref. 10 van den Bent MJ, Taal W. Are we done with dose-intense temozolomide in recurrent glioblastoma? Neuro.Oncol. 2014 Sep;16(9):1161-3

Ref. 11 Perry JR, Belanger K, Mason WP, Fulton D, Kavan P, Easaw J, Shields C, Kirby S, Macdonald DR, Eisenstat DD, et al. Phase II trial of continuous dose-intense temozolomide in recurrent malignant glioma: RESCUE study. J Clin Oncol 2010 Apr 20;28(12):2051-7

Ref. 12 Chamberlain MC, Glantz MJ, Chalmers L, Van HA, Sloan AE. Early necrosis following concurrent Temodar and radiotherapy in patients with glioblastoma. J Neurooncol. 2007 Mar;82(1):81-3

Ref. 13 Taal W, Brandsma D, de Bruin HG, Bromberg JE, Swaak-Kragten AT, Sillevis Smitt PA, van Es CA, van den Bent MJ. Incidence of early pseudo-progression in a cohort of malignant glioma patients treated with chemoirradiation with temozolomide. Cancer 2008 May 16;113:405-10

Ref. 14 Han SJ, Rolston JD, Molinaro AM, Clarke JL, Prados MD, Chang SM, Berger MS, Desilva A, Butowski NA. Phase II Trial of 7days on/7 days off temozolmide for recurrent high-grade glioma. Neuro.Oncol 2014 Mar 26

Ref. 15 Brandes AA, Tosoni A, Franceschi E, Blatt V, Santoro A, Faedi M, Amista P, Gardiman M, Labianca R, Bianchini C, et al. Fotemustine as second-line treatment for recurrent or progressive glioblastoma after concomitant and/or adjuvant temozolomide: a phase II trial of Gruppo Italiano Cooperativo di Neuro-Oncologia (GICNO). Cancer Chemother.Pharmacol. 2009 Jan 24

Ref. 16 Wick W, Puduvalli VK, Chamberlain MC, van den Bent MJ, Carpentier AF, Cher LM, Mason W, Weller M, Hong S, Musib L, et al. Phase III study of enzastaurin compared with lomustine in the treatment of recurrent intracranial glioblastoma. J.Clin.Oncol 2010 Mar 1;28(7):1168-74

Ref. 17 Batchelor TT, Mulholland P, Neyns B, Nabors LB, Campone M, Wick A, Mason W, Mikkelsen T, Phuphanich S, Ashby LS, et al. Phase III randomized trial comparing the efficacy of cediranib as monotherapy, and in combination with lomustine, versus lomustine alone in patients with recurrent glioblastoma. J.Clin.Oncol. 2013 Sep 10;31(26):3212-8

Ref. 18 Taal W, Oosterkamp HM, Walenkamp AM, Dubbink HJ, Beerepoot LV, Hanse MC, Buter J, Honkoop AH, Boerman D, de Vos FY, et al. Single-agent bevacizumab or lomustine versus a combination of bevacizumab plus lomustine in patients with recurrent glioblastoma (BELOB trial): a randomised controlled phase 2 trial. Lancet Oncol. 2014 Aug;15(9):943-53

Ref. 19 Brennan CW, Verhaak RG, McKenna A, Campos B, Noushmehr H, Salama SR, Zheng S, Chakravarty D, Sanborn JZ, Berman SH, et al. The somatic genomic landscape of glioblastoma. Cell 2013 Oct 10;155(2):462-77

Ref. 20 Weller M, Kaulich K, Hentschel B, Felsberg J, Gramatzki D, Pietsch T, Simon M, Westphal M, Schackert G, Tonn JC, et al. Assessment and prognostic significance of the epidermal growth factor receptor vIII mutation in glioblastoma patients treated with concurrent and adjuvant temozolomide radiochemotherapy. Int.J.Cancer 2014 May 15;134(10):2437-47

Ref. 21 Prigent SA, Nagane M, Lin H, Huvar I, Boss GR, Feramisco JR, Cavenee WK, Huang HS. Enhanced tumorigenic behavior of glioblastoma cells expressing a truncated epidermal growth factor receptor is mediated through the Ras-Shc-Grb2 pathway. J.Biol.Chem. 1996 Oct 11;271(41):25639-45

Ref. 22 Huang HS, Nagane M, Klingbeil CK, Lin H, Nishikawa R, Ji XD, Huang CM, Gill GN, Wiley HS, Cavenee WK. The enhanced tumorigenic activity of a mutant epidermal growth factor receptor common in human cancers is mediated by threshold levels of constitutive tyrosine phosphorylation and unattenuated signaling. J.Biol.Chem. 1997 Jan 31;272(5):2927-35

Ref. 23 van den Bent MJ, Brandes AA, Rampling R, Kouwenhoven MC, Kros JM, Carpentier A, Clement PMJ, Frenay M, Campone M, Baurain J-F, et al. Randomized phase II trial of erlotinib versus temozolomide or carmustine in recurrent glioblastoma: report from EORTC Brain Tumor Group study 26034. J Clin Oncol 2008

Ref. 24 Rich JN, Reardon DA, Peery T, Dowell JM, Quinn JA, Penne KL, Wikstrand CJ, Van Duyn LB, Dancey JE, McLendon RE, et al. Phase II trial of gefitinib in recurrent glioblastoma. J.Clin.Oncol. 2004 Jan 1;22(1):133-42

Ref. 25 Neyns B, Sadones J, Joosens E, Bouttens F, Verbeke L, Baurain JF, D'Hondt L, Strauven T, Chaskis C, In't VP, et al. Stratified phase II trial of cetuximab in patients with recurrent high-grade glioma. Ann.Oncol. 2009 Sep;20(9):1596-603

Ref. 26 Sampson JH, Akabani G, Archer GE, Berger MS, Coleman RE, Friedman AH, Friedman HS, Greer K, Herndon JE, Kunwar S, et al. Intracerebral infusion of an EGFR-targeted toxin in recurrent malignant brain tumors. Neuro.Oncol. 2008 Jun;10(3):320-9

Ref. 27 Leal M, Sapra P, Hurvitz SA, Senter P, Wahl A, Schutten M, Shah DK, Haddish-Berhane N, Kabbarah O. Antibody-drug conjugates: an emerging modality for the treatment of cancer. Ann.N.Y.Acad.Sci. 2014 Aug;1321(1):41-54

Ref. 28 Verma S, Miles D, Gianni L, Krop IE, Welslau M, Baselga J, Pegram M, Oh DY, Dieras V, Guardino E, et al. Trastuzumab emtansine for HER2-positive advanced breast cancer. N.Engl.J.Med. 2012 Nov 8;367(19):1783-91

Ref. 29 Gan HK, Kaye AH, Luwor RB. The EGFRvIII variant in glioblastoma multiforme. J.Clin.Neurosci. 2009 Jun;16(6):748-54

Ref. 30 Tannir NM, Forero-Torres A, Ramchandren R, Pal SK, Ansell SM, Infante JR, de VS, Hamlin PA, Kim SK, Whiting NC, et al. Phase I dose-escalation study of SGN-75 in patients with CD70-positive relapsed/refractory non-Hodgkin lymphoma or metastatic renal cell carcinoma. Invest New Drugs 2014 Aug 22

Ref. 31 Wen PY, Macdonald DR, Reardon DA, Cloughesy TF, Sorensen AG, Galanis E, Degroot J, Wick W, Gilbert MR, Lassman AB, et al. Updated response assessment criteria for high-grade gliomas: response assessment in neuro-oncology working group. J Clin Oncol 2010 Apr 10;28(11):1963-72

Ref. 32 Aaronson NK, Ahmedzai S, Bergman B, Bullinger M, Cull A, Duez NJ, Filiberti A, Flechtner H, Fleishman SB, de Haes JC, et al. The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. J Natl Cancer Inst 1993 Mar 3;85(5):365-76

Ref. 33 Taphoorn MJ, Claassens L, Aaronson NK, Coens C, Mauer M, Osoba D, Stupp R, Mirimanoff RO, van den Bent MJ, Bottomley A. An international validation study of the EORTC brain cancer module (EORTC QLQ-BN20) for assessing health-related quality of life and symptoms in brain cancer patients. Eur.J Cancer 2010 Apr;46(6):1033-40

Ref. 34 Hegi ME, Diserens A-C, Gorlia T, Hamou M-F, de Tribolet N, Weller M, Kros JM, Hainfellner JA, Mason W, Mariani L, et al. MGMT gene silencing and benefit from temozolomide in glioblastoma. N Engl J Med 2005;352:997-1003

Ref. 35 Kastenhuber ER, Huse JT, Berman SH, Pedraza A, Zhang J, Suehara Y, Viale A, Cavatore M, Heguy A, Szerlip N, et al. Quantitative assessment of intragenic receptor tyrosine kinase deletions in primary glioblastomas: their prevalence and molecular correlates. Acta Neuropathol. 2014 May;127(5):747-59

Ref. 36 Vivanco I, Robins HI, Rohle D, Campos C, Grommes C, Nghiemphu PL, Kubek S, Oldrini B, Chheda MG, Yannuzzi N, et al. Differential sensitivity of glioma- versus lung cancer-specific EGFR mutations to EGFR kinase inhibitors. Cancer Discov. 2012 May;2(5):458-71

Ref. 37 Pocock SJ, Simon R. Sequential treatment assignment with balancing for prognostic factors in the controlled clinical trial. Biometrics 1975; 31: 103-115.

Ref. 38 Freedman LS, White SJ. On the use of Pocock and Simon's method for balancing treatment numbers over prognostic factors in the controlled clinical trial. Biometrics 1976; 32: 691-694.

Ref. 39 Vredenburgh JJ, Cloughesy T, Samant M, Prados M, Wen PY, Mikkelsen T, Schiff D, Abrey LE, Yung WK, Paleologos N, Nicholas MK, Jensen R, Das A, Friedman HS. Corticosteroid use in patients with glioblastoma at first or second relapse treated with bevacizumab in the BRAIN study. Oncologist. 2010;15(12):1329-34.

Ref. 40 Korshunov A1, Ryzhova M, Hovestadt V, Bender S, Sturm D, Capper D, Meyer J, Schrimpf D, Kool M, Northcott PA, Zheludkova O, Milde T, Witt O, Kulozik AE, Reifenberger G, Jabado N, Perry A, Lichter P, von Deimling A, Pfister SM, Jones DT. Integrated analysis of pediatric glioblastoma reveals a subset of biologically favorable tumors with associated molecular prognostic markers. Acta Neuropathol. 2015 May;129(5):669-78

# Appendix B: Abbreviations

Abbreviations

| | |
|---|---|
| ADA | Antidrug Antibody |
| ADC | Antibody-Drug Conjugate |
| AE | Adverse Event |
| ALP | Alkaline Phosphatase |
| ALT | Alanine Aminotransferase |
| AST | Aspartate Aminotransferase |
| BOR | Best Overall Response |
| CNS | Central Nervous System |
| CR | Complete Response |
| CRR | Complete Response Rate |
| CTCAE | Common Terminology Criteria for Adverse Events |
| DILI | Drug Induced Liver Injury |
| DLCO | Diffusing capacity of the lung for carbon monoxide |
| DNA | Deoxyribonucleic acid |
| DR | Duration of Response |
| ECG | Electrocardiogram |
| eCRF | Electronic Case Report Forms |
| EGFR | Epidermal Growth Factor Receptor |
| EGFRde2-7 (EGFRvIII) | EGFR variant III containing deletion of exons 2-7 |
| EORTC | European Organization for Research and Treatment of Cancer |
| FDA | US Food and Drug Administration |
| FFPE | Formalin Fixed Paraffin Embedded |
| FIH | First in Human |
| GBM | Glioblastoma Multiforme |
| GCP | Good Clinical Practice |
| GGT | Gamma–Glutamyl Transferase |
| GLP | Good Laboratory Practice |

| | |
|---|---|
| Gtts | Drops |
| ICH | International Conference on Harmonization |
| IDMC | Independent Data Monitoring Committee |
| IEC | Independent Ethics Committee |
| IgG | Immunoglobulin G |
| INR | International normalized ratio |
| IRB | Institutional Review Board |
| IRC | Independent Review Committee |
| IV | Intravenous |
| mAbs | monoclonal Antibodies |
| MMAF | Monomethyl auristatin F |
| MRI | Magnetic Resonance Imaging |
| NASH | Non-Alcoholic Steatohepatitis |
| NCI | National Cancer Institute |
| NCI CTCAE | National Cancer Institute Common Terminology Criteria for Adverse Events |
| NDFS | Neurological Deterioration Free Survival |
| OE | Each Eye |
| ORR | Objective Response Rate |
| OS | Overall Survival |
| PD | Progressive Disease |
| PE | Physical Exam |
| PG | Pharmacogenetic |
| PK | Pharmacokinetic |
| PR | Partial Response |
| RANO | Response Assessment in Neuro-Oncology |
| RT | Radiation Therapy |
| SAE | Serious Adverse Event |
| SD | Stable Disease |
| SMG | Study Management Group |

| | |
|---|---|
| SmPC | Summary of Product Characteristics |
| TBL | Total Bilirubin |
| TMZ | Temozolomide |
| TRAC | Translational Research Advisory Committee |
| TTP | Time to Progression |
| ULN | Upper limit of normal range |
| WBC | White Blood Cell |

Pharmacokinetic and Statistical Abbreviations

| | |
|---|---|
| AUC | Area under the plasma concentration-time curve |
| AUCt | Area under the plasma concentration-time curve from time zero to time of last measurable concentration |
| AUC∞ | Area under the plasma concentration-time curve from time zero to infinity |
| CL/F | Apparent oral clearance |
| Cmax | Maximum observed plasma concentration |
| t1/2 | Terminal phase elimination half-life |
| Tmax | Time to maximum observed plasma concentration |

# Appendix C: WHO performance status scale

| Grade | Performance scale |
|---|---|
| 0 | Able to carry out all normal activity without restriction |
| 1 | Restricted in physically strenuous activity but ambulatory and able to carry out light work. |
| 2 | Ambulatory and capable of all self-care but unable to carry out any work; up and about more than 50% of waking hours. |
| 3 | Capable of only limited self-care; confined to bed or chair more than 50% of waking hours |
| 4 | Completely disabled; cannot carry on any self-care; totally confined to bed or chair. |

# Appendix D: New York Heart Association (NYHA) classification of heart failure

| | |
|---|---|
| Class I | Patients with cardiac disease but without resulting limitations of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnoea or anginal pain. |
| Class II | Patients with cardiac disease resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnoea or anginal pain. |
| Class III | Patients with cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary physical activity causes fatigue, palpitation, dyspnoea or anginal pain. |
| Class IV | Patients with cardiac disease resulting in inability to carry on physical activity without discomfort. Symptoms of cardiac insufficiency or of the anginal syndrome may be present even at rest. If any physical activity is undertaken, discomfort is increased. |

(The Criteria Committee of the New York Heart Association: Diseases of the Heart and Blood Vessels; Nomenclature and Criteria for Diagnosis, 6th ed Boston, Little, Brown 1964).

# Appendix E: Calculation of the glomerular filtration rate (GFR)

COCKCROFT AND GAULT FORMULA

**For the calculation of GFR age is measured in years and weight is measured in kilograms.**

**If serum creatinine is measured in µmol/l, the following formula applies:**

**In males**: $GFR[ml/min] = \frac{1.23 \times (140 - age) \times weight}{serum\ creatinine}$

**In females**: $GFR[ml/min] = \frac{1.05 \times (140 - age) \times weight}{serum\ creatinine}$

**If serum creatinine is measured in mg/dl, the following formula applies:**

**In males**: $GFR[ml/min] = \frac{(140 - age) \times weight}{72 \times serum\ creatinine}$

**In females**: $GFR[ml/min] = \frac{0.85 \times (140 - age) \times weight}{72 \times serum\ creatinine}$

# Appendix F: Common Terminology Criteria for Adverse Events

In the present study, adverse events and/or adverse drug reactions will be recorded according to the

**Common Terminology Criteria for Adverse Events (CTCAE), version 4.0.**

At the time this protocol was issued, the full CTC document was available on the NCI web site, at the following address: https://ctep.cancer.gov/protocoldevelopment/electronic_applications/ctc.htm#ctc_40 .

The EORTC Headquarters web site https://www.eortc.be/services/doc/ctc/ provides a link to the appropriate CTC web site. This link will be updated if the CTC address is changed.

# Appendix G: EORTC Quality of Life evaluation: guidelines for administration of questionnaires

**EORTC Quality of Life evaluation: guidelines for administration of questionnaires**

The instructions given below are intended to provide some general guidelines for collecting quality of life (QOL) data in EORTC studies. These instructions apply for all types of questionnaires.

**1. Who is the responsible person (RP) for QOL data collection?**

In each institution, the principal investigator is the responsible for the local organization of QoL data collection. This can be delegated to a physician, data manager, (research) nurse or a psychologist. Such a person should have the full protocol at his/her disposal as well as the questionnaire(s). This person would also be the intermediate contact point in case of any necessary clarification asked by the EORTC Headquarters.

**2. Who should fill out the questionnaire?**

In principle it is the patient who has to complete the QOL forms and preferably without help from others. In the case where a patient is too sick to fill out the questionnaire by him/herself or if the patient is not able to complete the questionnaire for such reasons as forgetting his/her glasses, another person could read the questions without making any suggestions and report the answers on the forms. It is not allowed for another person to fill in the questionnaire as if (s)he was the patient (proxy assessment) unless specifically allowed by the protocol.

**3. What instructions should be given to the patient?**

At entry in a study, the RP should give the patient an explanation of the objective of the study and instructions for completing the questionnaires.

The patient should be informed that participation in the QOL protocol is voluntary and that the information provided is confidential (identification is only for administrative purposes and includes date of birth and today's date (completion date)).

The following issues should be explained to the patient:

- The schedule of assessments.
- The questionnaire is a self administered questionnaire that should be completed by the patient him(her)self. The patient can ask for aid in reading or writing but should not let another person provide the answers.
- The patient should circle the choice that best corresponds to his/her situation.
- There is no right or wrong answer to any of these questions. The answers will not influence any medical decision making.
- All questions should be answered.
- The patient will be given a questionnaire in the default language(s) of the hospital. If desired, the patient may request another language. The RP will then contact the EORTC Headquarters for the appropriate translation.

The RP should make sure that the patient understands the instructions.

At each subsequent assessment as defined by the protocol, the patient should receive the questionnaire from the RP or from other appropriate staff if the RP is unavailable.

**4. Where should the patient complete the questionnaire?**

The patient should complete the questionnaire at the clinic, and, ideally in a quiet, private room. If this is not possible, the waiting room is an acceptable alternative. In general it does not take long to complete the questionnaire, but patients should be given the time they need to answer all questions.

**5. When should they complete the questionnaire?**

The timing of the planned QoL assessments is detailed in the protocol. When a QOL assessment is planned, the questionnaire should be given to the patient preferably before the meeting with the physician, ensuring that the patient has enough time to complete the questionnaire. If the patient is to receive a therapy, the questionnaire should be filled out before administration of the treatment (unless indicated otherwise in the protocol). The questionnaire should not be taken home and/or mailed (unless indicated otherwise in the protocol).

**6. Review of the completed questionnaire**

After the patient has completed the questionnaire, the person handling the questionnaire should:

- Complete the “Hospital Staff” specific data box.
- Check that the completion date is correctly filled in by the patient.
- Screen the questionnaire for omissions.

*If this is the case:*

- Please ask the patient the reason for omissions. It may be that patient forgot to flip a page or did not understand a question. The patient should not be forced to provide an answer if (s)he does not wish to do so.
- Additional explanation may be provided, but the questions should not be rephrased.

**7. Missing forms**

If for some reason the patient is unable or does not wish to complete a quality of life questionnaire the reason and the date of visit should be documented on the corresponding CRF (case report form).

**8. Mailing to EORTC Headquarters**

A copy of the questionnaires should be sent to EORTC Headquarters as soon as possible, while the original source document should be kept on site. As it is impossible to retrospectively collect missing quality of life data, please make sure the patient completes the questionnaire at the time-point when he/she is supposed to complete it.

Thank you very much for your cooperation.

**E-mail:** [redacted]

# Appendix H: Adverse Events expected due to GBM or progression of GBM

- Tinnitus
- Diplopia
- Dysphagia
- Hypoaesthesia oral
- Paraesthesia oral
- Facial pain
- Disease progression
- Pyrexia
- Subdural haematoma
- Subdural haemorrhage
- Abnormal loss of weight
- Decreased appetite
- Dehydration
- Anaplastic astrocytoma
- Glioblastoma
- Glioblastoma multiforme
- Malignant glioma
- Malignant neoplasm progression
- Neoplasm progression
- VIIth nerve paralysis
- Oculofacial paralysis
- Facial nerve disorder
- Facial paresis
- Facial neuralgia
- Hypoaesthesia
- Burning sensation
- Paralysis
- Dementia
- Dysarthria
- Agnosia
- Prosopagnosia
- Apraxia
- Hemiapraxia
- Gait apraxia
- Dyspraxia
- Agraphia
- Alexia
- Cerebral haemorrhage
- Cerebral haematoma
- Hyperaesthesia
- Ataxia
- Cerebellar ataxia

- Cerebral ataxia
- Myoclonus
- Post-anoxic myoclonus
- Amnesia
- Ataxia
- Atonic seizures
- Balance disorder
- Brain compression
- Brain oedema
- Cerebrospinal fluid retention
- Cerebrospinal thrombotic tamponade
- Cervicogenic headache
- Clonic convulsion
- Clumsiness
- Cluster headache
- Convulsion
- Convulsions local
- Coordination abnormal
- Cranial nerve disorder
- Cranial nerve palsies multiple
- Cranial nerve paralysis
- Epilepsy
- Epileptic aura
- Exertional headache
- Fumbling
- Headache
- Hemianopia
- Hemiparesis
- Hemiplegia
- IIIrd nerve paralysis
- IIIrd nerve paresis
- Incoherent
- Intracranial pressure increased
- IVth nerve paresis
- Language disorder
- Lethargy
- Loss of consciousness
- Memory impairment
- Movement disorder
- Myoclonic epilepsy
- Paraesthesia
- Paresis cranial nerve
- Partial seizures
- Partial seizures with secondary generalisation
- Postictal headache

- Postictal state
- Preictal state
- Quadranopia
- Sedation
- Seizure like phenomena
- Slow speech
- Somnolence
- Speech disorder
- Status epilepticus
- Stupor
- Tension headache
- Tonic clonic movements
- Tonic convulsion
- Tonic posturing
- Tunnel vision
- Typical aura without headache
- Vascular headache
- Vertigo CNS origin
- VIIIth nerve lesion
- Visual field defect
- Affect lability
- Agitation
- Anxiety
- Anxiety disorder
- Anxiety disorder due to a general medical condition
- Depressed mood
- Distractibility
- Elevated mood
- Executive dysfunction
- Hyposomnia
- Impaired reasoning
- Inappropriate affect
- Initial insomnia
- Insomnia
- Mood altered
- Mood swings
- Incontinence
- Urinary incontinence
- Intracerebral haematoma evacuation
- Subdural haematoma evacuation
- Drain of cerebral subdural space
- Deep vein thrombosis
- Thrombosis

# Appendix I: Evaluation of ABT-414 in Children with High Grade Gliomas

This appendix provides information related to the evaluation of ABT-414 in children (M14-483 pediatric sub-study). Unless specifically addressed below, all of the adult protocol elements will apply to the pediatric population.

**Background**

Pediatric high grade gliomas [HGG] (WHO grade III and IV glioma and diffuse intrinsic pontine glioma [DIPG]) have no adequate therapy and are almost universally fatal. Unlike in adult GBM, EGFR amplification is rare (3% or lower) in pediatric HGG and screening for EGFR amplification is not routinely part of standard care for pediatric tumors, which makes it profoundly difficult to identify children with EGFR amplified HGG. Consequently, it is not feasible to conduct a stand-alone study in this population. It is most important that a pediatric study in EGFR-amplified HGG address whether a proposed dose of ABT-414 can be used safely in the pediatric population, with recognition that assessment of efficacy beyond a description of outcomes in a very small number of subjects is likely infeasible.

Molecular marker panels for subjects with HGG are increasingly including EGFR amplification assessment. Potentially eligible subjects for the pediatric sub-study may be identified by investigators from the results of locally arranged diagnostic testing. EGFR amplification will then be confirmed retrospectively by central FISH (Fluorescent In-Situ Hybridization) assay once subjects are enrolled on the study.

To ensure that enough subjects can be enrolled to address pharmacokinetic and safety objectives, both eligibility criteria and subject treatment options need to be as flexible as possible. Data from adults receiving ABT-414 as monotherapy or in combination with temozolomide suggest that the toxicities of ABT-414 and temozolomide (predominantly ocular and hematologic, respectively) are independent of each other, with no evidence that one agent exacerbates the toxicity of the other, and there is no evidence of pharmacokinetic interactions between the two agents.

To assess if there would be any additional toxicity of ABT-414 on patients aged under 3 years (compared to what is already known from the adult toxicity profile), Juvenile Crl:CD1(ICR) mice were administered 5, 25, or 50 mg/kg/dose ABT-414 once every two weeks from Postnatal Day (PND) 7 to 70, followed by a 98 day non-dosing recovery phase. ABT-414 administered to juvenile mice once every 2 weeks from Post Natal Day (PND) 7 to 70 was associated with adverse histological effects in the testes, lung, ovaries and heart at ≥5 mg/kg. Therefore, a no-observed-adverse-effect-level (NOAEL) for ABT-414 in juvenile mice was not established, and was determined to be <5 mg/kg (PND 63 Conjugated Antibody AUC of 15400 µg*hr/mL). In addition, the overall systemic exposure to ABT-414 and its toxicity profile in this repeat dose juvenile mouse toxicity study was comparable to the toxicity profile observed in repeat dose adult mouse toxicity studies, and no new or unexpected toxicities were observed. Therefore, following the completion of the mouse study, the pediatric sub-study was opened to include patients aged under 3 years.

Allowing investigator discretion to use ABT-414 as monotherapy or in combination with temozolomide (informed by factors such as patient preference and prior exposure to temozolomide) minimizes barriers to subject inclusion, and it is reasonable to extrapolate from adult data that variable temozolomide use in children receiving ABT-414 will not affect the ability to assess pharmacokinetic or safety objectives of this sub-study. The use of TMZ in combination with ABT-414 for a pediatric patient must be reviewed by the EORTC/AbbVie medical monitor prior to the initiation of therapy. The safety profile of ABT-414 in combination with other anti-neoplastic agents has not been assessed to date.

This appendix will describe the evaluation of pharmacokinetics, safety and efficacy of ABT-414 in the pediatric HGG population, allowing access to a novel therapy for those who are in great need of better treatment options. Subjects < 18 years of age with pediatric HGG whose tumors demonstrate EGFR amplification will be assigned to this pediatric sub-study. Pediatric subjects will receive open-label ABT-414 at a dose of 1.0 mg/kg for subjects who are 6 to 17 years old (at the date of first ABT-414 dose), or 1.3 mg/kg for subjects who are 0 to 5 years old. These dosages are expected to produce pharmacokinetic drug exposures comparable to a 1.0 mg/kg dose in adults, the recommended starting dose for the adult portion of the study.

**Objectives of the sub-study**

The primary objectives will be the evaluation of safety, tolerability and pharmacokinetics of ABT-414 in a pediatric population < 18 years of age. The secondary objective will be to assess the effect of ABT-414 on tumor response per RANO (Response Assessment in Neuro-Oncology) criteria.

**Primary Endpoints of the pediatric sub-study:**

Safety including toxicities according to CTCAE criteria (Percentage of subjects with adverse events from subject's first visit until 49 days after the subject's last dose of study drug)

Pharmacokinetic parameters for ABT-414 and cys-mcMMAF (Maximum observed serum concentration (Cmax) for ABT-414 and Cys-mcMMAF (toxin), half-life for ABT-414 and Cys-mcMMAF (toxin), and total drug exposure over time (AUC: Area Under the Curve) for ABT-414 and Cys-mcMMAF (toxin)

**Secondary Endpoints of the pediatric sub-study:**

Objective response rate, best response rate, and duration of response based on RANO criteria

Overall survival, Time to Progression, and Time to progression-free survival

Changes in neurological status and functioning (including PedsQL cancer module)

**Exploratory Endpoints of the pediatric sub-study:**

Assessment for tumor aberrations of H3.1, H3.3, BRAF, CDKN2A/B, IDH1, INI1, MGMT, PTEN.

Anti-drug antibodies

**Methodology:**

This is an uncontrolled, open-label, single-arm global study.

Patient selection criteria: Registration and enrollment of pediatric subjects is projected to take up to 3 years and the study will remain open after the adult portion of the study has completed. Given the rarity of the eligible population, the pediatric registration and enrollment criteria are written to be as inclusive as possible. Registration and Enrollment criteria for pediatric subjects are noted below.

**Registration criteria**

- Subjects must have a histologically proven high grade glioma (WHO grade III glioma [e.g anaplastic astrocytoma, anaplastic oligodendroglioma, anaplastic oligoastrocytoma], grade IV glioma [e.g glioblastoma, gliosarcoma] or DIPG).
- Subjects must be <18 years of age
- The tumor tissue must have been determined to have EGFR amplification, (by local or other testing service).
- Availability of adequate biological material (formalin-fixed paraffin embedded [FFPE] tumor) for central testing of EGFR amplification. There must be sufficient tissue to submit for (retrospective) confirmatory EGFR FISH testing at the study-designated central laboratory. If there are less than the requested 30 slides available, it is acceptable to continue the registration process, assuming sufficient material is available for central testing of EGFR amplification.
- Before patient registration and study-related procedures that would not have been performed as part as standard care, written informed consent/assent by subjects and/or their legal guardians must be given according to ICH/GCP, and national/local regulations.

**Enrollment criteria**

- Subject must either have recurrent/progressive tumor or, if newly diagnosed, have completed radiation therapy at least 4 weeks prior to first dose of ABT-414.
- The investigator must confirm that the subject is able to complete the procedures required in order to assess the primary endpoints, including PK blood draws and safety assessments over the first four weeks of therapy including Day 1 of Week 5.
- The investigator believes that the potential benefit of treating the pediatric subject with ABT-414 outweighs the expected risks and that this treatment is in the best interests of the pediatric subject.
- Subjects and/or their legal guardians must be able to understand the risks and potential benefits, and grant assent/consent to participate by signing the applicable pediatric-specific informed assent and/or consent forms.
- Subject has sufficiently recovered from previous therapy.
- (For recurrent disease) No prior RT with a dose over 65Gy to the brain, stereotactic radiosurgery or brachytherapy unless the recurrence is histologically proven
- No current or recent (within 4 weeks or 5 half-lives (whichever is shorter) before enrollment) treatment with another investigational drug
- Renal function: calculated creatinine clearance ≥ 30 mL/min by the Cockcroft-Gault formula (Appendix E) for pediatric patients ≥12 years of age and estimated glomerular filtration rate ≥ 30 mL/min/1.73 $m^2$ by modified Schwartz equation for pediatric patients < 12 years of age

Modified Schwartz equation (pediatric patients < 12 years of age)a:

CrCl (ml/min/1.73 $m^2$) = (K * Ht) / Scr

height (Ht) in cm; serum creatinine (Scr) in mg/dl

K (proportionality constant):

Female Child (< 12 years): K=0.55

Male Child (< 12 years): K=0.70

a. From FDA guidance on "General Clinical Pharmacology Considerations for Pediatric Studies for Drugs and Biological Products", December 2014

- Liver function: Total bilirubin ≤ 1.5 times upper limit of normal (ULN), Aspartate Aminotransferase (AST), and Alanine Aminotransferase (ALT) ≤ 3 times ULN. Subjects with Gilbert's syndrome documented in medical history may be enrolled if total bilirubin is < 3 times ULN.
  Not allowed are subjects with known chronic liver disease and/or cirrhosis documented by the presence of one or more of the following (assessments to be performed per standard of care only if liver disease is suspected):
  - Liver biopsy with histologic findings consistent with cirrhosis
  - CT or US evidence of liver disease with or without portal hypertension
  - Physical examination and clinical and laboratory evidence of chronic liver disease
  - Colloid shift on a liver-spleen scan
  - A Child-Pugh score of 6 or higher (see Appendix M)
- Absence of pregnancy. Female subjects of childbearing potential must be using an adequate method of contraception to avoid pregnancy from Study Day 1 throughout the study and for 6 months beyond the end of treatment in such a manner that the risk of pregnancy is minimized. In general, the decision for appropriate methods to prevent pregnancy should be determined by discussions between the investigator and the study subject. Female subject of childbearing potential includes any female who has experienced menarche and who has not undergone successful surgical sterilization (hysterectomy, bilateral tubal ligation, or bilateral oophorectomy) or is not postmenopausal. Female subjects of non-childbearing potential do not need to use birth control.
  Pediatric female patients are not considered to be of child bearing potential if meeting any of the following criteria:
- Permanently surgically sterile (bilateral oophorectomy, bilateral salpingectomy, or hysterectomy).
- Females who have not experienced menarche (at least one menstrual period).
- Female subjects of childbearing potential must have a negative serum or urine pregnancy test (minimum sensitivity 25 IU/L or equivalent units of HCG) within 72 hours prior to enrollment.
- Female subjects must not be **pregnant, breastfeeding, or considering becoming pregnant** during the study or for at least 6 months(5 × the half-life of AbbVie product or 30 days, whichever is longer, plus an additional 30 days to the 5 half-lives, if genotoxic) after the last dose of study drug.

- Male subjects that are **sexually active with female partner(s) of childbearing potential** must agree to use an effective method of contraception from Study Day 1, during the treatment period and for at least 6 months after the last study treatment.
- Male subjects must not be considering **fathering a child or donating sperm** during the study or for at least 6 months after the last dose of study drug.
- Before patient registration, enrollment and study-related procedures that would not have been performed as part as standard care, written informed consent must be given according to ICH/GCP, and national/local regulations.
- Subject must not have a history of a major immunologic reaction to any IgG-containing agent.

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

**Pre-Enrollment Recommendations to Support Efficacy Evaluation**:

Although not required for study eligibility, the following guidelines should be followed whenever possible to maximize the likelihood that tumor assessments yield data interpretable for tumor response assessment:

If the subject has been operated upon for recurrence:

Residual and measurable disease after surgery is not required, but surgery must have confirmed recurrence

A post-surgery MRI should be available following surgery and an additional MRI scan (baseline scan) has to be done within 2 weeks prior to the first dose of ABT-414.

Surgery completed at least 2 weeks before the first dose of ABT-414 and subjects should have fully recovered as assessed by investigators. Criteria for full recovery will include absence of active post-operative infection, recovery from medical complications and capacity for fluid and food intake.

Dosage of steroids is stable or decreasing for 7 days prior to the baseline MRI scan.

Randomization: Subjects will not be randomized. All subjects will receive ABT-414 at a starting dose of 1.0 mg/kg (age 6-17) or 1.3 mg/kg (age 0 - 5). Treatment should start within 96 hours from enrollment. No stratification will be used.

**Study Procedures**:

The subjects will follow the same study procedure table as described in the adult protocol (refer to Chapter 6), with the exception of research blood samples, ocular assessments, and long term follow up as described in this appendix.

The PK schedule for 3 to 17 year olds will be as follows:

| | Cycle 1 Day 1 | Cycle 1 Day 2 | Cycle 1 Day 3 | Cycle 1 Day 5 | Cycle 1 Day 8 | Cycle 1 Day 15 | Cycle 2 Day1 | Cycle 3 Day 1 | Cycle 5, Cycle 7 etc. Every two cycles starting from Cycle 5 | 35 Day Safety Follow-up |
|---|---|---|---|---|---|---|---|---|---|---|
| PK – ABT-414 Assay | X[a] | Xb | X[c] | Xd | X[e] | X[f] | X[f] | Xf | X[g] | X[h] |
| PK – Cys-mc MMAF Assay | X[a] | Xb | X[c] | Xd | X[e] | | | | | |
| PK Antidrug Antibody Assay (ADA/nADA) | X[g] | | | | | | X[g] | X[g] | X[g] | X[h] |

The PK schedule for < 3year old will be as follows:

| | Cycle 1 Day 1 | Cycle 1 Day 8 | Cycle 1 Day 15 | Cycle 2 Day1 | Cycle 3 Day 1 | Every four cycles starting from Cycle 5 | 35 Day Safety Follow-up |
|---|---|---|---|---|---|---|---|
| PK – ABT-414 Assay | X[i] | X[e] | X[f] | X[g] | X[g] | X[g] | X[h] |
| PK Antidrug Antibody Assay (ADA/nADA) | X[g] | | | X[g] | X[g] | X[g] | X[h] |

a. Samples will be collected before infusion (0 hour, pre-dose), immediately after ABT-414 infusion, and 4 hr after the start of infusion.

b. One sample at the 24-hour time point only

c. One sample at the 48-hour time point only (within ± 4 hours)

d. One sample at the 96-hour time point only (within ± 24 hours)

e. One sample at the 168-hour time point only (within ± 4 hours)

f. Samples will be collected before infusion (0 hour, pre-dose) and immediately after ABT-414 infusion

g. Samples will be collected before infusion (0 hour, pre-dose)

h. Samples will be collected 35 days (within a two-day window) after last ABT-414 infusion for subjects able to return to the clinic for the follow-up visit.

i. Samples will be collected immediately after ABT-414 infusion

NOTE:

For 0 - 5 year-old population 1mL of blood for each analyte (ABT-414, cys-mcMMAF) will be collected. For ABT-414, the resulting serum of ~0.5mL will be put into one split and labeled accordingly. For cys-mcMMAF, the resulting ~0.45mL plasma will be equally distributed into two splits. For ADA and nADA 1ml of blood will be drawn and the resulting serum volume of approximately 0.5mL will be split into two tubes and labeled accordingly.

For 6 – 17 year-old population 2 mL of blood will be collected for ABT-414 and the resulting ~1 mL serum will be split into two tubes and labeled accordingly.

1 mL of blood will be collected for cys-mcMMAF and the resulting ~0.45mL plasma will be equally distributed into two splits. For ADA and nADA, 1ml of blood will be drawn and the resulting serum volume of approximately 0.5mL will be split into two tubes and labeled accordingly.

Pharmacogenetic (PG) sample: optional 3mL blood sample collection for all pediatric subjects that consent. If the PG sample is not collected at the Day 1 visit, it may be collected anytime during the study.

MRI scanning frequency will be as described in the adult protocol, but may be less frequent if deemed to be appropriate by the investigator (e.g. subject is unable to tolerate the scanning frequency).

**Therapeutic regimens, expected toxicity, dose modifications**:

ABT-414 will be administered at a starting dose of 1.0 mg/kg or 1.3 mg/kg IV (depending on the age) over 30 – 40 minutes or as directed by the administration guidelines every 2 weeks. ABT-414 treatment will continue for up to 12 months. Prophylactic steroid eye drops will be administered as described in the adult protocol. Each subject enrolled will have PK sampling to assess the exposure of ABT-414 in the pediatric population. Pediatric PK data will be assessed on an ongoing basis throughout the study, and the ABT-414 dosage or frequency of dosing may be adjusted for individual pediatric subjects or for all pediatric subjects subsequently enrolled if exposures are substantially outside the range predicted from the adult experience. If the dose is revised for all newly enrolling pediatric subjects, the Sponsor will notify the sites of this new dose as a written communication, and the change in dose will be described in a later amendment to the protocol. ABT-414 has not been studied in children; therefore the expected toxicities are unknown but expected to be similar to the adult experience. Dose modifications from toxicities will follow the recommendations in the adult protocol, with successive dose reductions from 1.0 mg/kg to 0.75 mg/kg to 0.5 mg/kg in 6 – 17 year-olds, and from 1.3 mg/kg to 1.0 mg/kg to 0.67 mg/kg in 0 - 5 year-olds. More aggressive dose reductions are allowed if the investigator believes that it is in the best interest of the subject.

If ABT-414 is used in combination with temozolomide, ABT-414 will be dosed on Day 1 and Day 15 of the temozolomide cycle (assuming a standard regimen of 200 mg/m$^2$/day for 5 days of each 28-day cycle; for other temozolomide schedules, timing of the ABT-414 dosing schedule should be discussed with the medical monitor). Temozolomide will be allowed only if its use is in accordance with local clinical practice. Temozolomide will not be considered an investigational product for the study (unless this is a local requirement). Anti-neoplastic agents other than temozolomide are specifically prohibited during study treatment unless allowed after discussion with the EORTC study chair. Live attenuated vaccines are not allowed during the study treatment period and for a period of 49 days after last ABT-414 administration.

**Clinical evaluation, laboratory tests, and follow-up**:

The clinical evaluation, laboratory tests and follow up will follow the adult protocol, except as noted below.

Pediatric subjects will have an ophthalmology examination during screening (baseline); prior to dosing (within 7 days) on Day 1 of cycles 2, 3, 4 and all even-numbered cycles thereafter while ABT-414 treatment is being received; at the 49-Day Safety Follow-Up visit; and at any other time as clinically indicated. The schedule of eye examinations may be altered as appropriate to synchronize with ABT-414 dosing if the frequency of ABT-414 dosing is altered as described above.

Physical exams will include regular height assessment (at a minimum height should be collected once every 3 months whilst on treatment). The performance status collected will be Karnofsky (age ≥ 16 years) or Lansky (age < 16 years), and WHO status if initially enrolled prior to implementation of Amendment 5 of the protocol. See Appendix J.

The PedsQL Cancer Module will be administered as a QoL measure, in place of the EORTC QLQ C30 and BN20. See Appendix K.

Long-term follow up: All subjects will be followed up every 6 months for 5 years following the study and annually thereafter until death or loss to follow up. Subjects will be evaluated in long-term follow-up care clinics for:

- visual functioning
- neurocognitive adverse events
- possible treatment related AEs (see section 7.2.1.8)
- serious AEs (see section 7.2.1.8)
- growth and developmental delays
- progression/relapse and survival

Accurate information on the age (years and months) at the time of the adverse reaction, weight, height, dose (including individual and total daily dose of study drugs), relevant medical history, other drugs, and onset of reaction will be collected.

In case hepatic laboratory abnormalities are observed, follow guidance below in place of section 5.5.1.4; Appendix L should also be followed.

ABT-414 Dose Modification Guidelines for Hepatic Laboratory Abnormalities in Pediatric patients:

| Hepatic Laboratory Abnormality | ABT-414 |
|---|---|
| ALT or AST > 3x but ≤5x ULN*<br>(and TBL ≤ 2x ULN) | May proceed with dosing.<br>Perform testing (ALT, AST, ALP, TBL) within 3 days prior to next dose. |
| ALT or AST >5x ULN* but ≤ 20x ULN (and TBL ≤ 2x ULN) | **Hold drug regardless of assessed relationship to drug**. See Appendix L for guidelines on repeat testing (ALT, AST, ALP, TBL) and evaluation.<br>**Dosing may not be resumed until ALT and AST have recovered to ≤ 5x ULN***<br>Dosing may be resumed at the **same dose** if ALT or AST was elevated >5x ULN* for less than 2 weeks. Additionally, dosing may be resumed at the same dose if another likely cause has been identified.<br>Dosing must be resumed at a reduced dose (see section 5.5.1 ABT-414 Dose Modification Table) if ALT or AST was elevated >5x ULN* for more than 2 weeks and no other likely cause has been identified.<br>Following dose reduction, if ALT and AST remain ≤5x ULN* after 2 doses at the reduced dose level, then **re-escalation** to the previous dose is allowed at the investigator's discretion.<br>If a subsequent dose reduction is required due to hepatic laboratory abnormalities, then re-escalation is not allowed. |

| Hepatic Laboratory Abnormality | ABT-414 |
|---|---|
| ALT or AST > 20x ULN<br><br>or<br><br>ALT or AST >3x ULN **and** TBL >2x ULN | **Hold drug regardless of assessed relationship to drug.** See Appendix L for guidelines on repeat testing (ALT, AST, ALP, TBL) and evaluation.<br><br>If another clear cause has been identified, drug may be resumed when ALT and AST ≤ 5x ULN and TBL ≤ 2x ULN<br><br>In general, if no other cause has been identified, drug should be permanently discontinued, and rechallenge not attempted. Rechallenge can be considered after consultation with the sponsor if **all** the following are met:<br>• the subject has shown important benefit from the drug and other options are not available,<br>• ALT and AST have recovered to ≤ 5x ULN and TBL has recovered to ≤ 2x ULN,<br>• the subject and/or subjects legal guardians have been informed of the potential risk and have assented/consented to the rechallenge (as appropriate)<br>• close follow-up of the subject is feasible. |

* If elevated at baseline, either 5x the baseline value or 8x ULN, whichever is lower

**Criteria of evaluation**:

Unless otherwise stated, the criteria of evaluation will be the same in children as in adults. QoL will be reported descriptively. For the primary endpoint of safety, all adverse events will be coded according to MedDRA preferred term and reported and graded using the NCI CTCAE v4. For the safety assessment, a dose limiting toxicity (DLT) will be defined as any grade 3 or 4 adverse event that is attributed to ABT-414, or an ABT-414 toxicity that results in a delay of the second dose of ABT-414 by more than 14 days.

**Statistical considerations**:

There will be no maximum enrollment for children with HGG and EGFR amplification; however it is expected that at least 6 subjects will be enrolled. A dose in children where there are 1 or fewer dose limiting toxicities (DLTs) is expected to be determined. Given the small expected sample size, the pharmacokinetic profile, safety assessments, and efficacy evaluations, including neurological status and PedsQL™ Cancer Module Questionnaires will be summarized descriptively.

Kaplan-Meier survival curve will be estimated for overall survival. Joint Kaplan-Meier survival plots with matched historical patients at least from Korshunov (2015) (Ref. 40) will also be presented.

Pharmacokinetic parameters of ABT-414 and Cys-mcMMAF will be determined by noncompartmental methods. Individual pharmacokinetic parameters will be listed and summarized. The pediatric pharmacokinetic data may be analysed with adult pharmacokinetic data from other studies in a non-linear mixed effects modelling to estimate population pharmacokinetic parameters of ABT-414 and csy-mcMMAF, such as clearance and volume of distribution. The effect of demographic and/or disease-specific variable(s) on the pharmacokinetic parameters of ABT-414 and csy-mcMMAF will also be examined.

Assuming the same PK variability as in adults, ≥ 6 pediatric subjects will yield a two-sided 95% confidence interval within 60% and 140% of the geometric mean estimate for the area under the concentration-time curve (AUC) with greater than 90% probability. This criteria follows FDA draft guidance on the General Clinical Pharmacology Considerations for Pediatric Studies (released Dec 2014).

For a sample size of 6 in HGG with EGFR amplification, the probability of observing at least 1 tumor response will be 82.2% if the true response rate is 25%.

| Response rate | Probability of observing 1 or more tumor responses | | |
|---|---|---|---|
| | Sample size N = 6 | Sample size N = 9 | Sample size N = 12 |
| 15% | 62.3% | 76.8% | 85.8% |
| 20% | 73.8% | 86.6% | 93.1% |
| 25% | 82.2% | 92.5% | 96.8% |

All subjects who receive at least one dose of ABT-414 will be included in analyses. No interim analysis is planned.

**Data Monitoring**:

The EORTC and sponsor study teams will have open access to pediatric data throughout the study to inform the ongoing conduct of this open-label sub-study. EORTC will identify at least three individuals (a statistician, the PI, and a clinician from headquarters) that will review the safety events from the pediatric patients at the following timepoints: 4 weeks after each subject is enrolled and again at q4-6 month intervals while there are subjects that remain on therapy. If there are no subjects on active therapy, then the EORTC will not hold pediatric safety reviews.

Otherwise, data monitoring will be the same as specified for the adult population (refer to Chapter 9). Pediatric data will be analyzed separately from the adult study, but findings will be compared to those from the adult study. Pediatric data will not be included in the efficacy and safety analyses of the adult main study.

**Translational research**:

Tumor specimens will be collected where feasible for the same biomarker analyses that are planned for the adult population. Central molecular testing will include but not be limited to EGFR, H3.1, H3.3, BRAF, CDKN2A/B, IDH1, INI1, MGMT, PTEN. Insufficient tissue for Translational Research after EGFR amplification analysis will not prevent enrollment of the pediatric patients.

**Forms and procedures for collecting data**:

Data will be reported on the forms specifically designed by the EORTC Headquarters for this pediatric sub-study. Forms will be sent electronically to the EORTC Headquarters through the VISTA/RDC (Remote Data Capture System) as outlined in Chapter 14 of the adult protocol.

**Informed consent**:

Subjects and/or their legal guardians must be able to understand the risks and potential benefits and grant assent/consent to participate by signing a pediatric-specific informed assent/consent form(s) as per local and country specific laws and regulations.

# Appendix J: Karnofsky and Lansky Performance Status

Karnofsky Performance status, for assessment in Pediatric patients aged 16 or older.

| Performance status % | Comments |
|---|---|
| 100 | Normal. No complaints. No evidence of disease. |
| 90 | Able to carry on normal activity. Minor signs or symptoms of disease. |
| 80 | Normal activity with effort. Some signs or symptoms of disease. |
| 70 | Cares for self. Unable to carry on normal activity or to do active work. |
| 60 | Requires occasional assistance, but is able to care for most of personal needs. |
| 50 | Requires considerable assistance and frequent medical care. |
| 40 | Disabled. Requires special care and assistance. |
| 30 | Severely disabled. Hospital admission is indicated although death is not imminent. |
| 20 | Hospitalization necessary. Very sick, active supportive treatment necessary. |
| 10 | Moribund; fatal processes progressing rapidly. |
| 0 | Dead. |

(Karnofsky DA, Burchenal JH. The clinical evaluation of chemotherapeutics in cancer. In: MacLoed CM, ed. Evaluation of Chemotherapeutic Agents. New York: Columbia University Press, 1949; page 196.)

Lansky Performance status for patients aged under 16 years.

| Performance status % | Comments |
|---|---|
| 100 | Fully active, normal |
| 90 | Minor restrictions in physically strenuous activity |
| 80 | Active, but tires more quickly |
| 70 | Both greater restriction of, and less time spent in, active play |
| 60 | Up and around, but minimal active play; keeps busy with quieter activities |
| 50 | Gets dressed, but lies around much of the day; no active play; able to participate in all quiet play and activities |
| 40 | Mostly in bed; participates in quiet activities |
| 30 | In bed; needs assistance even for quiet play |
| 20 | Often sleeping; play entirely limited to very passive activities |
| 10 | No play: does not get out of bed |
| 0 | Unresponsive |

(Lansky SB, List MA, Lansky LL, et al. The measurement of performance in childhood cancer patients. Cancer 1987; 60:1651–1656)

# Appendix K: PedsQL Guidelines for Administration

The following guidelines are intended for use by individuals trained in the administration of standardized questionnaires. The PedsQL™ administrator is crucial in developing rapport with the respondents, emphasizing the importance of the questionnaire, addressing concerns, and ensuring that the PedsQL™ is completed accurately and confidentially.

General Protocol

If feasible, the PedsQL™ should be completed before the respondents complete any other health data forms and before they see their physician or healthcare provider.

PedsQL™ Cancer Module Questionnaires should be completed at the visit as below:

| | |
|---|---|
| Age 0-1 | No questionnaire |
| Age 2-4 | Parent questionnaire (2-4) |
| Age 5-7 | Interview administered young child (5-7) AND parent questionnaire (5-7) |
| Age 8-12 | Child self-report (8-12) AND parent questionnaire (8-12) |
| Age 13-18 | Adolescent self-report (13-18) AND parent questionnaire (13-18) |

Parents, Children (8-12 years) and Teens (13-18 years) may self-administer the PedsQL™ after introductory instructions from the administrator. If the administrator determines that the child or teen is unable to self-administer the PedsQL™ (e.g., due to illness, fatigue, reading difficulties), the PedsQL™ should be read aloud to the child or teen. For the Young Child (5-7 years), the PedsQL™ should be administered by reading the instructions and each item to the young child word for word. At the beginning of each subscale repeat the recall interval instructions (one month) to remind the young child to respond only for that specific recall interval. Use the separate page with the three faces response choices to help the young child understand how to answer. When reading items aloud to a child, intonation should be kept neutral to avoid suggesting an answer.

If a child has difficulty understanding the age-appropriate PedsQL™, the preceding age group version may be administered to the child (e.g., administering the Young Child (5-7 years) Self-Report version with the three faces response choices to an 8 year old). However, if a child presents with severe cognitive impairments (as determined by the administrator), the PedsQL™ may not be appropriate for that child. In such cases, only the Parent-Proxy Report should be administered to the child's parent.

The parent and child must complete the questionnaires independently of one another. Discourage the parent, child, or other family members from consulting with one another during the completion of the questionnaire. Let them know that they can feel free to discuss their answers following completion of the questionnaires, but that it is important to get both the parent's and the child's individual perspectives. If you are administering the questionnaire to the child, the child should be facing away from the parent.

If the child or parent has a question about what an item means or how they should answer it, do not interpret the question for them. Repeat the item to them verbatim. Ask them to answer the item according to what they think the question means. If they have trouble deciding on an answer, ask them to choose the response that comes closest to how they feel. The child and/or the parent has the option of not answering a question if they truly do not understand the question.

If a parent/child asks you to interpret the responses, tell her/him that you are not trained to interpret or provide a score for the answers given. If the PedsQL™ is being used for a clinical study, let the parent/child know that their answers will be combined with other participants' answers and analyzed as a group rather than as individual respondents.

Document all reasons for refusals and non-completions of the PedsQL™.

Administering the PedsQL™

The following scripts have been developed as a guide to introduce the PedsQL™ to the child and his/her parent(s). Modify the language to a style that is most appropriate for you and the respondent.

For the child:

"The PedsQL™ asks you questions about how you feel and what you think about your health. It is not a test, and there are no right or wrong answers. It takes about 5 minutes to complete. If you have any questions, please let me know."

For the parent:

"The PedsQL™ is a questionnaire that assesses health-related quality of life in children and adolescents. It contains questions about your child's physical, emotional, social, and school functioning in the past one month.

The PedsQL™ is brief and typically takes less than 5 minutes to complete. It is not a test, and there are no right or wrong answers. Please be sure to read the instructions carefully and choose the response that is the closest to how you truly feel. Please do not compare your answers with your child's responses. We are interested in your and your child's individual perspectives. However, feel free to discuss the questionnaire with your child after you have both completed it and returned it to me. If you have any questions, please let me know."

Provide the respondent with a pen or pencil and a solid writing surface. If a table is not available, the participant should be provided with an item such as a clipboard. Remain nearby should questions or concerns arise.

When the parent/child returns the PedsQL™, look it over and check to see that all answers have been completed. Verify that no item has more than one response. If any responses are incomplete, illegible, or there are multiple responses for an item, please ask the parent or child to indicate their response.

Ask the participants if they had any difficulties completing the questionnaire or if they have any other comments regarding the questionnaire. Document any important feedback.

Thank the parent and child for taking the time to complete the questionnaire. If the study design involves following up with these respondents, let them know that they may be asked to complete the PedsQL™ again at another time. Indicate when they can expect to be contacted again if known.

**Review of the completed questionnaire**

After the patient or parent has completed the questionnaire, the person handling the questionnaire should:

- Complete the “Hospital Staff” specific data box.
- Check that the completion date is correctly filled in by the patient.
- Screen the questionnaire for omissions.

*If this is the case:*

- Please ask the patient or parent the reason for omissions. It may be that patient forgot to flip a page or did not understand a question. The patient or parent should not be forced to provide an answer if (s)he does not wish to do so.
- Additional explanation may be provided, but the questions should not be rephrased.

**Missing forms**

If for some reason the patient or parent is unable or does not wish to complete a quality of life questionnaire the reason and the date of visit should be documented on the corresponding CRF (case report form).

**Mailing to EORTC Headquarters**

A copy of the questionnaires should be sent to EORTC Headquarters as soon as possible, while the original source document should be kept on site. As it is impossible to retrospectively collect missing quality of life data, please make sure the patient or parent completes the questionnaire at the time-point when he/she is supposed to complete it.

Thank you very much for your cooperation. If you have any remarks about this leaflet or if you need further information, please contact:

**Quality of Life Department - EORTC Headquarters:**

**Phone:** [redacted]

**Fax:** [redacted]

**E-mail:** [redacted]

# Appendix L: Hepatic Laboratory Abnormalities (safety monitoring and observation guidelines)

This section provides information on safety monitoring, evaluation of potential causes, and appropriate documentation for subjects with hepatic laboratory abnormalities suggesting potential drug-induced liver injury (DILI). It was adapted with modifications from the FDA Guidance for Industry, Drug-Induced Liver Injury: Premarketing Clinical Evaluation (https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM174090.pdf) in consultation with a hepatologist with expertise in DILI.

Information derived from the scientific literature and public databases on liver injury attributable to prescription and nonprescription medications, herbals and dietary supplements can be found at the LiverTox database (https://livertox.nlm.nih.gov).

If a subject develops one of the following laboratory abnormalities, hepatic laboratory abnormalities should be confirmed by repeat testing, and the subject should be monitored and evaluated as described in this section, **regardless of the assessed relationship to the study treatments:**

- ALT or AST > 3× ULN **and** TBL > 2× ULN, or
- ALT or AST > 5x ULN (or >5x the baseline value if elevated or >8x ULN, whichever is lower)

**Confirmation of Liver Test Abnormalities**

For subjects meeting either of the criteria above, confirmation of hepatic laboratory abnormalities should be done as follows:

- **Repeat testing of all four of the usual measures (ALT, AST, alkaline phosphatase, and TBL) should be performed within 3 days of the initial abnormality** to confirm the abnormalities and to determine if they are increasing or decreasing.
    - Serum transaminases may rise and fall quite rapidly, and waiting a week or two before obtaining confirmation of elevations may lead to a false conclusion that the initially observed abnormality was spurious.
    - The need for prompt repeat testing is especially great if AST or ALT is >3x ULN **and** TBL > 2x ULN.
    - If the subject is unable to return to the trial site promptly, the subject should be retested locally, with results and normal laboratory ranges recorded in the CRFs.
- **Inquire about concurrent new or escalating symptoms** (e.g., right upper quadrant pain or tenderness, fever, rash). Although non-specific in the setting of GBM treatment, fatigue nausea, and vomiting should also be assessed as clinical symptoms potentially associated with liver injury.

**Close Observation**

*It is appropriate to initiate close observation to determine whether the abnormalities are improving or worsening and to consider whether the subject meets criteria for stopping study drug if symptoms suggestive of liver injury (as described above) persist or if repeat testing shows:*

- ALT or AST > 5x ULN (or 5x baseline if elevated or >8x ULN, whichever is lower) or
- ALT/AST > 3x ULN **and** total bilirubin > 2x ULN.

It is critical to initiate this close observation immediately upon detection and confirmation of early signals of possible DILI, and not to wait until the next scheduled visit or monitoring interval. The primary goal of close observation is to determine as quickly as possible whether observed abnormal findings are transient and will resolve spontaneously or will progress to marked serum aminotransferase elevation or evidence of functional impairment, as indicated by rising bilirubin or INR (international normalized ratio), which represent substantial liver injury.

Close observation includes:

- **Repeating liver enzyme (AST, ALT, ALP) and serum bilirubin tests two or three times weekly. If total bilirubin is elevated, obtain direct bilirubin.** Frequency of retesting can decrease to once a week or less if abnormalities stabilize or drug has been discontinued and the subject is asymptomatic.
- **Obtaining additional tests, as appropriate, to evaluate liver function, (e.g. INR); diagnostic measures (e.g. ultrasound of the liver), serum ammonia, etc.**
- Obtaining a more detailed history of symptoms and prior or concurrent diseases. Update the appropriate eCRFs (if applicable).
- Obtaining a history of concomitant drug use (including nonprescription medications and herbal and dietary supplement preparations), alcohol use, recreational drug use, and special diets. Update the appropriate eCRFs (if applicable).
- Ruling out other immediately apparent possible causes of aminotransferase (ALT or AST) elevation and hyperbilirubinemia, as described below.
- Obtaining a history of exposure to environmental chemical agents.
- Considering gastroenterology or hepatology consultations.

Relevant supplemental information must be collected and entered in the appropriate eCRF(s) for instances observed after the implementation of protocol version 7.

**Evaluating Data for Alternative Causes**

An important purpose of close observation is to gather additional clinical information to seek other possible causes of the observed liver test abnormalities, such as one of the following common causes:

- **Acute viral hepatitis**. The usual onset of hepatocellular DILI is indistinguishable from acute viral hepatitis A or B. Hepatitis C is much less often acute in its onset and tends to be insidious, but it sometimes can resemble acute DILI. The presence of acute viral hepatitis A, B, and C should be evaluated by serological markers. Viral hepatitis D (requires concomitant hepatitis B infection) and E are relatively rare in the United States. Hepatitis E is more common in developing countries, including Southeast Asia, and should be considered in recent travelers to those countries and in patients in trials conducted in those countries. Also rare are hepatocellular liver injuries caused by Epstein-Barr virus, cytomegalovirus, herpes simplex virus, toxoplasmosis, varicella, and parvovirus, although these infections are seen more typically in immuno-suppressed individuals.

Adolescent and young adult patients with possible DILI should be tested for Epstein-Barr virus. Hepatitis is common among transplant patients with cytomegalovirus disease.

- **Alcoholic and autoimmune hepatitis**. Acute alcoholic hepatitis usually is recurrent, with a history of binging exposure to alcohol preceding episodes, and it has some characteristic features, such as associated fever, leukocytosis, right upper quadrant pain and tenderness, hepatomegaly, and AST >ALT, that may help distinguish it from other causes of liver injury. Other features of the physical examination may include the presence of stigmata of cirrhosis, such as spider nevi, palmar erythema, estrogenic changes in males, and Dupuytren's contractures. Alcoholic and autoimmune hepatitis should be assessed by history, physical examination, and laboratory testing, including serologic testing (e.g., antinuclear or other antibodies).
- **Hepatobiliary disorders**. Biliary tract disease, such as migration of gallstones or intrahepatic lesions, more often causes cholestatic injury initially and should be investigated with gall bladder and ductal imaging studies, especially if alkaline phosphatase is increased. Malignant interruption of the biliary tract also should be considered.
- **NASH (non-alcoholic steatohepatitis).** NASH may be seen in obese, hyperlipoproteinemic, and/or diabetic patients and may be associated with fluctuating aminotransferase levels, and hepatic and sometimes splenic enlargement. It is sometimes associated with cirrhosis and portal hypertension.
- **Cardiovascular causes.** Cardiovascular disease, especially right heart failure and hypotension or any cause of impaired oxygenation of the liver, may cause acute centrilobular hypoxic cell necrosis (ischemic hepatitis) with rapid and sometimes spectacular increases of serum transaminases (e.g., ALT or AST >10,000 U/L). Cardiovascular dysfunction or impaired liver oxygenation, including hypotension or right heart failure, should be assessed by physical examination and history.
- **Concomitant treatments.** It is critical to discover concomitant treatments, including exposure to nonprescription and dietary supplement products that might be responsible for injury. The possible exposure to potentially toxic herbal or dietary supplement mixtures (sometimes of unknown composition), nonprescription medications such as acetaminophen, or to occupational chemical agents may not be volunteered unless subjects are specifically questioned.

**Follow-Up to Resolution**

For all subjects showing hepatic laboratory abnormalities suggestive of possible DILI, an attempt should be made to follow the subject until satisfactory resolution of the laboratory abnormalities. DILI may develop or progress even after the causative drug has been stopped. Local lab results should be recorded on appropriate eCRFs.

**Dose Modifications for Study Drugs**

See the dose modification guidelines for each respective drug (protocol section 5.5).

# Appendix M: Child-Pugh score

| | Points Assigned for Observed Findings | | |
|---|---|---|---|
| Parameter | 1 | 2 | 3 |
| Total bilirubin, µmol/L (mg/dL) | < 34.2 (< 2) | 34.2 – 51.3 (2 – 3) | > 51.3 (> 3) |
| Serum albumin, g/L (g/dL) | > 35 (> 3.5) | 28 – 35 (2.8 – 3.5) | < 28 (< 2.8) |
| INR | < 1.7 | 1.7 – 2.3 | > 2.3 |
| Ascites | None | Slight | Moderate to severe |
| Hepatic encephalopathy* | None | Grade 1 or 2 (or suppressed with medication) | Grade 3 or 4 (or refractory) |

* Grade 0: normal consciousness, personality, neurological examination, electroencephalogram.

Grade 1: restless, sleep disturbed, irritable/agitated, tremor, impaired handwriting, 5 cps waves.

Grade 2: lethargic, time-disoriented, inappropriate behavior, asterixis, ataxia, slow triphasic waves.

Grade 3: somnolent, stuporous, place-disoriented, hyperactive reflexes, rigidity, slower waves.

Grade 4: unarousable coma, no personality/behavior, decerebrate, slow 2 to 3 cps delta activity.

The Child-Pugh classification is defined in terms of the sum of the scores for the five parameters.

- A score of 5 or 6 indicates Child-Pugh Category A (mild hepatic impairment).
- A score of 7, 8, or 9 indicates Child-Pugh Category B (moderate hepatic impairment).