UniversitätsKlinikum Heidelberg

Name of Sponsor/Company: Universitätsklinikum Heidelberg		**Sponsor-Code of Study:** DIRECTOR	*(For National Authority Use only)*
Name of (Finished) Product: Temodal		**Name of Active Ingredient:** Temozolomide	
EudraCT-Nr.: 2008-006871-60	**BfArM Vorlage-Nr.:** 4035040	**Ethik Antrags-Nr.:** AFmu-050/2009	

SYNOPSIS

Title of Study:

Dose-intensified Rechallenge with Temozolomide, One Week on One Week Off versus Three Weeks on One Week Off in Patients with Progressive or Recurrent Glioblastoma (DIRECTOR)

Protocol version 04, 2010-07-30

One amendment was implemented in protocol version 04, 2010-07-30:
According to Tonn et al [J Clin Oncol 28:15s, 2010 (suppl; abstr 2076)] the MGMT promoter methylation status in the recurrent tumors is typically the same as in the primary tumor. Therefore, either tissue available from the recurrent or the primary tumor could be used for the determination of MGMT promoter methylation (change of inclusion criterion No. 3). In addition, several administrative changes (e.g. wording) were implemented in protocol version 04, 2010-07-30.

Investigators:

01	Prof. Dr. P. Vajkoczy
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Study Centre(s):

01 Charite, Department of Neurosurgery, Berlin, Germany
02 Knappschaftskrankenhaus, Department of Neurology, Bochum, Germany
03 University Hospital Bonn, Department of Neurology, Bonn, Germany
04 Klinikum der Johann-Wolfgang von Goethe-Universität, Dr. Senckenbergisches Institut für Neuroonkologie, Zentrum für Neurologie und Neurochirurgie, Frankfurt am Main, Germany
05 University Hospital Heidelberg, Department of Neurooncology, Heidelberg, Germany
06 Saarland University, Department of Neurosurgery, Homburg/Saar, Germany
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Publication (reference):
Pending

Study period: **(date of first enrolment)** **(date of last completed)**	23.09.2009 – 30.06.2013	**Study Phase:** II

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Objectives:

Primary Objective

Median time to treatment failure. Treatment failure is reached

(i) upon tumor progression
(ii) if treatment has to be terminated due to toxicity or
(iii) if the patient dies for any reason.

Secondary Objectives

- Progression-free survival (PFS)
- Overall survival
- Objective responses (complete response, CR, and partial responses, PR)
- Outcome (PFS-6, PFS, survival, best response) relative to O6-methylguanine DNA methyltransferase (MGMT) promoter methylation
- Outcome relative to duration of prior treatment (e.g. number of completed 5/28 cycles after radiation therapy)
- Outcome relative to interval from completion of prior TMZ chemotherapy treatment (< 3 months versus > 3 months)
- Toxicity including lymphocytes, CD4 T cell and regulatory T cell counts
- Expression of the mismatch repair genes MLH-1, MSH-2, MSH-6 und PMS2 in tumor tissue determined by immunohistochemistry
- Changes in MGMT status in recurrent disease relative to initial tumor tissue if applicable
- Changes in MGMT activity in peripheral blood during ongoing therapy will be assessed during the first cycle at days 1, 8, 15, 22, then MGMT activity will be investigated every 8 weeks
- Quality of life determined by EORTC QoL-Brain 20 Neurotoxicity determined by MRI
- Neurotoxicity determined by MMSE, MRI and NeuroCogFx neuropsychological examination
- Outome relative to extent of resection (gross total resection versus resection with residual contrast-enhancing tumor versus biopsy)
- Screening for aberrant MGMT promoter methylation in peripheral blood

Methodology:

Prospective, open, randomized, 2 parallel groups

Number of patients (planned and analysed):

Planned: 166
Recruited: 105
Analysed: 105

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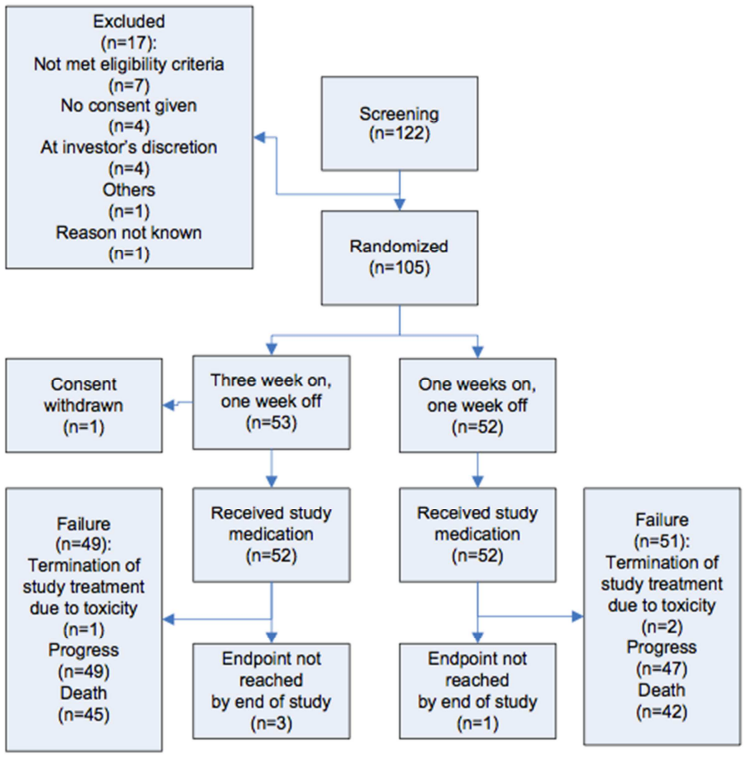

Fig. 1, CONSORT diagram

In total, 166 patients were necessary for a comparison of two dose-dense regimens. Due to withdrawal of financial support, the study was prematurely closed for recruitment after enrollment of 105 patients.

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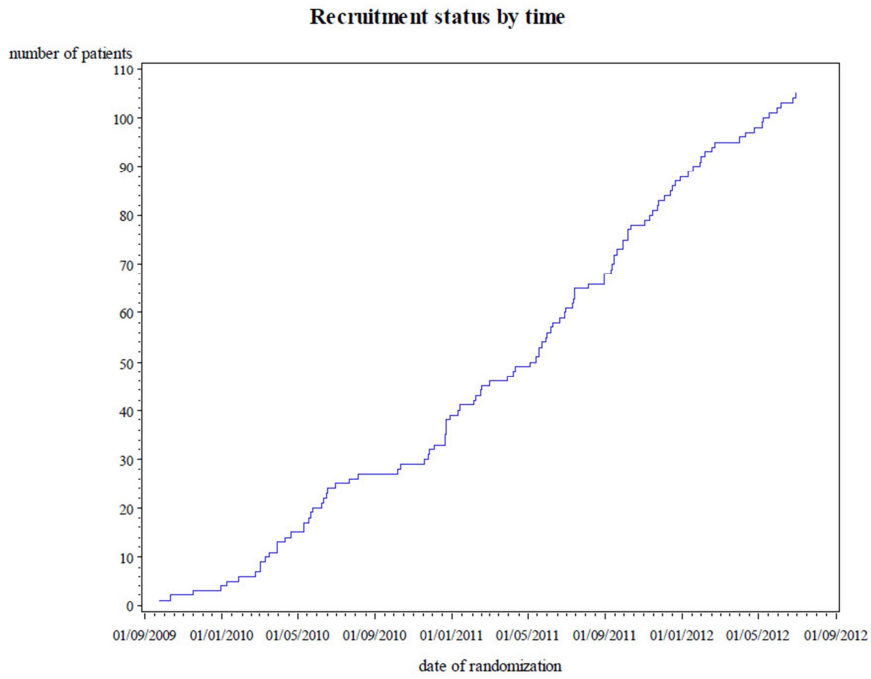

Fig. 2: Overall recruitment over time

Overall, the study recruited well with two phases with stagnation in the beginning and from June through November 2010. The recruitment over time is outlined above (Fig. 2).

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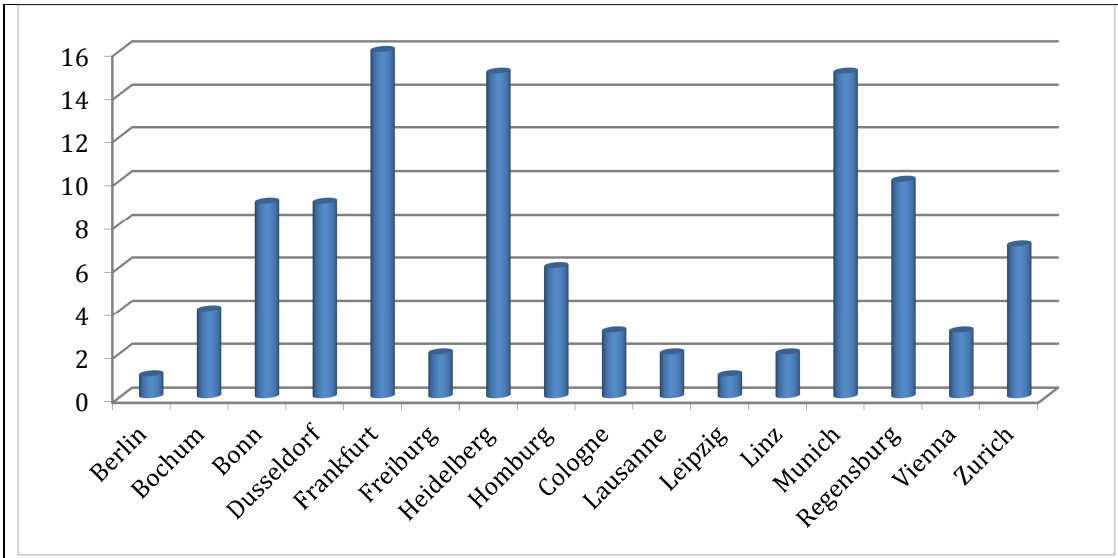

Fig. 3: Recruitment per study site

Recruitment was stopped on 30 June 2013 after inclusion of 105 patients. The last patient stopped study medication on 25.3.2013. As of 22 May 2013, no more patients were on study treatment. The study database was closed for data entry on 30 June 2013. Then, queries were sent to the site to clarify discrepancies. Most discrepancies concerned units for laboratory values. All queries were clarified and, wherever necessary, assessed in addition by the study coordinator. The final database closure occurred on 29 November 2013.

Diagnosis and main criteria for inclusion:

Diagnosis

First progression or relapse of glioblastoma after radiation therapy and concomitant temozolomide and at least 2 completed cycles of maintenance temozolomide

Criteria for inclusion

- Progressive or recurrent glioblastoma documented by MRI no earlier than 180 days after first surgery for glioblastoma and no earlier than 90 days after completion of radiotherapy.
- Histological diagnosis of glioblastoma
- Tissue available for the determination of MGMT promoter methylation in the primary tumor or from the recurrent tumor if a patient undergoes a surgical procedure at recurrence prior to study entry.
- Prior treatment with temozolomide administered concomitantly with radiotherapy and at least for two cycles (5/28) as an adjuvant treatment
- Informed consent
- Age 18-80 years
- Karnofsky performance score > 50%
- Neutrophil counts > 1 500/µl
- Platelet counts > 100 000/µl

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- Hemoglobin > 10 g/dl
- Serum creatinin < 1.5-fold upper normal range
- ASAT or ALAT < 3-fold upper normal range unless attributed to anticonvulsants
- Alkaline phosphatase < 3-fold upper normal range
- Women with childbearing potential must have a negative serum pregnancy test ≤14 days prior to study enrollment
- Willingness to apply contraception according to local requirements (as stated in patient information)

Criteria for exclusion

- Progressive or recurrent glioblastoma documented by MRI earlier than 180 days after first surgery for glioblastoma and earlier than 90 days after completion of radiotherapy.
- Treatment with any chemotherapy other than temozolomide according to the schedule of the EORTC NCIC trial (Stupp et al. N Engl J Med 2005;352:987-996) except that an adjuvant starting dose of 200 mg/m2 and more than 6 cycles of adjuvant temozolomide are allowed
- Prior systemic or local treatment with DNA-damaging agents, tyrosine kinase inhibitors or anti-angiogenic agents for any cancer
- Allergy to or other intolerability of temozolomide
- Unable to undergo MRI
- Past medical history of diseases with poor prognosis, e.g. severe coronary heart disease, severe diabetes, immune deficiency, residual deficits after stroke, severe mental retardation
- HIV infection
- Pregnancy
- Breast feeding

Test product, dose and mode of administration, batch number:

Test product: Temozolomide

Dose-intensified temozolomide was applied either according to the one week on / one week off regimen or according to the three weeks on / one week off regimen.

Arm A: patients were treated with an initial dose of 120 mg/m2 unless there was grade III or IV myelotoxicity with conventional temozolomide (5/28) previously. These patients started at 90 mg/m2. Temozolomide was given orally on days 1-7 and 15-21. The dose was modified according to haematological parameters as outlined below.

Arm B: patients were treated with an initial dose of 80 mg/m2 unless there was significant myelotoxicity with conventional temozolomide (5/28) previously. These patients started at 60 mg/m2. Temozolomide was given orally on days 1-21. The dose was modified according to haematological parameters as outlined below.

A treatment cycle was defined as two completed weeks of TMZ within four weeks in Arm A and as three weeks of continuous TMZ within four weeks in Arm B.

Dose adjustments according to hematological parameters
The criteria were solely based on hematological toxicities that were observed while the patients were on treatment. To continue TMZ after a drug-free week, the following conditions had to be met:

ANC	Lymphocytes	Platelets	Hb

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[counts/µl]	[counts/µl]	[counts/µl]	[g/dl]
≥ 1.5 x 10^3	≥ 500	≥ 1 x 10^5	≥ 9

Dose adjustments were performed in dose levels. A dose level was defined as a step of 30 mg/m2 in Arm A and as a step of 20 mg/m2 in Arm B.
Patients in Arm A started with a initial dose of 120 mg/m2. Patients in Arm B started with an initial dose of 80 mg/m2. If the following conditions were met throughout the first cycle, the dose was escalated in each arm as follows:

ANC [counts/µl]	Lymphocytes [counts/µl]	Platelets [counts/µl]	Hb [g/dl]	Dosage for second cycle
≥ 2 x 10^3	≥ 800	≥ 1 x 10^5	≥ 11	Arm A: 150 mg/m^2 Arm B: 100 mg/m^2

Further dose escalations beyond 150 mg/m2 in Arm A and beyond 100 mg/m2 in Arm B were not allowed.
Temozolomide administration should be interrupted if any of the following toxicities oc-cured during a treatment week:

ANC [counts/µl]	Lymphocytes [counts/µl]	Platelets [counts/µl]
< 1.0 x 10^3	< 250	< 5 x 10^4

Temozolomide administration should also be interrupted if non-haematological toxicities of CTC grade IV occur or if non-haematological toxicities of CTC grade III persist longer than 14 days.
The occurrence of two of the following toxicities in line I or one the following toxicities in line II either in a treatment week or in a drug free week necessitates a dose reduction in the following cycle.

	ANC [counts/µl]	Lymphocytes (L) [counts/µl]	Platelets (P) [counts/µl]	Reduction of dose levels
Line I	1.0 x 10^3 < ANC < 1.5 x 10^3	400< L <500	$4x10^4$ < P < $8x10^4$	-1
Line II	0.5 x 10^3 < ANC < 1.0 x 10^3	250< L < 400	$1x10^4$ < P <$4x10^4$	-2

Treatment could be withheld up to 8 weeks after the last intake of TMZ. Interruption for more than 8 weeks due to hematologic toxicity was defined as treatment failure due to hematological toxicity, leading to withdrawal of the patient from the study.
Antiemetics were applied to prevent nausea and vomiting during study treatment. The following drugs were recommended: Ondansetron (e.g. Zofran®) 4 mg, Tropisetron (e.g. Navoban®) 5 mg, 20 drops Metoclopramid (e.g. Gastrosil®, Paspertin®), Domperidon (e.g. Motilium®) 10 mg. If toxicities occured (as outlined above), prophylactic treatment with aciclovir (e.g. Zovirax) as well as trimethoprim and sulfamethoxazol (e.g Cotrim) should be started depending on the lymphocyte counts and concomitant steroid medication:

Lymphocytes	Concomitant steroid medication (e.g. dexamethasone)	Prophylactic treatment
≤ 500 / µl	Yes	Aciclovir (e.g. Zovirax®) 5mg/kg: t.i.d. Sulfamethoxazol 800 mg & Trimethoprim 160 mg (e.g. Cotrim

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		forte®): b.i.d. once a week
≤ 500 / µl	No	Sulfamethoxazol 800 mg & Trimethoprim 160 mg (e.g. Cotrim forte®): b.i.d. once a week
> 500/µl	Yes	Sulfamethoxazol 800 mg & Trimethoprim 160 mg (e.g. Cotrim forte®): b.i.d. once a week
> 500/µl	No	*Optional*

Duration of treatment:

Study treatment was continued until treatment failure (progression, toxicity or death) or up to 12 months. A continuation of study treatment beyond 12 months was discussed on an individual basis. Three patients had been given TMZ for more than one year, two of them by less than two weeks more, one by half a year more. One treatment failure was diagnosed because of toxicity, all other treatment failures were diagnosed because of progression or death.

Reference therapy, dose and mode of administration, batch number:

Not applicable (test product was given in both arms; comparison of two regimens of dose-intensified temozolomide)

Criteria for evaluation: (efficacy, safety)

Criteria for the evaluation of efficacy

Response and progression were evaluated using the response criteria of MacDonald et al. (J Clin Oncol, 1990,8:1277-1280) as outlined below. The measure of "size" was according to the study protocol the largest cross sectional area (largest cross-sectional diameter x largest diameter perpendicular to it).

Complete Response: Disappearance of all contrast-enhancing lesions on MRI at least 1 month apart, without steroids and neurologically stable or improved.

Partial Response: At least 50% reduction in the size of all contrast-enhancing lesions on MRI at least 1 month apart, steroids stable or reduced, and neurologically stable or improved.

Stable disease: Less than 50% reduction or less than 25% increase in the size of a solid mass or all contrast-enhancing lesions on MRI, with no escalation of steroid treatment and no neurological deterioration.

Progression: At least 25% increase in the size of a solid mass or contrast-enhancing lesions on MRI or the appearance of a new lesion or neurologically worse, and steroids stable or increased.

Progression-free survival: The progression free survival is defined as the time from the first study drug administration to the first documented evidence of progression of disease.

Time to Treatment Failure: Time to treatment failure is defined as the duration from the date of first study drug administration to any of the following: Progressive disease, death for any reason, toxicity leading to end of study or discontinuation of study treatment for any reason

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Survival is defined as the duration from the date of the first study drug administration to the date of death due to any cause before the end of study.

Evaluation of safety
All Adverse events were categorized by system organ class.

The following conditions were not considered as SAEs: hospitalization in the absence of an adverse event, hospitalization due to epileptic seizures, hospitalization due to progression of disease, death due to progression of disease.

All SAEs were reported and assessed as regulated by law.

Statistical methods:

The statistical planning as outlined in the study protocol was as follows:

The statistical analysis will also focus on the predictive impact of *MGMT* gene promoter methylation, prior treatment and time interval from last tumor-specific treatment on outcome to both temozolomide regimens tested here and its duration. A number of 83 patients per treatment arm is likely to provide conclusive answers to these questions. An interim analysis is not planned.
This study is designed as a prospective, open-label, randomized, 2-arm trial of two competing dose regimens with temozolomide for patients with glioblastoma at first relapse or progression. All patients will be treated with temozolomide. The primary objective of this study is to show the superiority of Arm A (one week on one week off) versus Arm B (three weeks on one week off) in terms of time to treatment failure.
The full analysis set (FAS) according to intention to treat (ITT) consists of all consenting patients randomized into the study. The Per Protocol population comprises only patients meeting all eligibility criteria and receiving treatment according to this protocol. However, due to the complex dose-reduction and –escalation as well as re-escalation scheme, 30% erroneous dose modification in each patient will be allowed to qualify for the per protocol population. Treatment modifications are counted as planned dose and per protocol treatment. The safety population comprises all patients who received at least one dose of study medication. The primary efficacy analysis will be based on the full analysis set. The primary efficacy analysis will be repeated using the Per Protocol population to confirm the overall study results. All safety analyses will be based on the safety population.

Assuming the distribution of PFS events is exponential, a total of 166 patients recruited in 24 months will result in approximately 147 events during a total trial period of 48 months (24 months of accrual, 12 months of treatment and 12 months of additional follow-up). This will allow for a detection of an improvement in median time-to-treatment failure from 18.2 weeks for Arm B to 29.2 weeks for Arm A (hazard ratio = 0.63). Based on these assumptions, there is approximately 80% power to detect the stated difference in time to treatment failure between the two treatment arms for a two-sided level of 0.05.

Primary Efficacy Endpoint
Time to treatment failure will be summarized by Kaplan-Meier curves. Median time estimates as well as associated 95% confidence intervals will be reported for each treatment arm. The hazard ratio in time to treatment failure between the two treatment arms (Arm B versus Arm A) will be tested with a re-randomization test at the 5% alpha level, which takes into account the minimization allocation procedure. In addition Cox regression analyses adjusted (if feasible, considering the degrees of freedom needed) and unadjusted for stratification factors will be performed in an exploratory manner. The analysis will be based on the full analysis set and repeated for the per-protocol population.
Differences in PFS will be tested with a re-randomization test at the 5% alpha level. Kaplan-Meier curves will be displayed, and median survival estimates will be provided.

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Similarly, differences in overall survival will be tested with a re-randomization test at the 5% alpha level. Kaplan-Meier curves will be displayed, with median survival estimates provided.
Differences in duration of response will be tested with a re-randomization test at the 5% alpha level. Kaplan-Meier curves will be displayed, with median survival estimates provided.
The overall response rate will be reported descriptively based on the full analysis set as well as the per-protocol population. This will include the response rates, the confirmed complete and confirmed partial responders and the estimated difference in response rates.
Patients who did not receive at least one dose of any study medication will be excluded from the analysis of safety.

Adverse events data
Tables of adverse event incidence (preferred term classification) and individual incidence will be produced. A complementary analysis of adverse events by severity of event and by relationship to trial treatment will also be performed.
Dose reductions and premature withdrawals will also be described. A standard safety analysis with tables and shift tables for laboratory data will be provided.Vital signs will be presented in listings as well as in summaries by time windows. Quality of Life Analysis Quality of life will be assessed using the validated quality of life scale (QLQ-C30 and QLQ-BN20) by the European Organization for Research and Treatment of Cancer (EORTC), the Mini Mental Status Examination (MMSE), Brain 20 and NeuroCogFX test. The global score as well as the functional scales and the symptom scales will be analyzed descriptively. Changes from baseline will be calculated and summarized by mean, standard deviation, minimum, median and maximum.

Summary – Conclusions:

Efficacy Results:

All results are listed in the enclosed tables. We include here the most relevant results. There was no difference between both arms for the primary endpoint – median time to treatment failure- (Fig. 4), for overall survival (Fig. 5) and progression-free survival (Fig. 6). The parametric estimates of relative risks with 95 per cent confidence interval for one week on/one week off vs. three weeks on/one week off were 1.16 [0.76; 1.76] for treatment failure as well as for progression-free survival, and 1.02 [0.66; 1.57] for overall survival.

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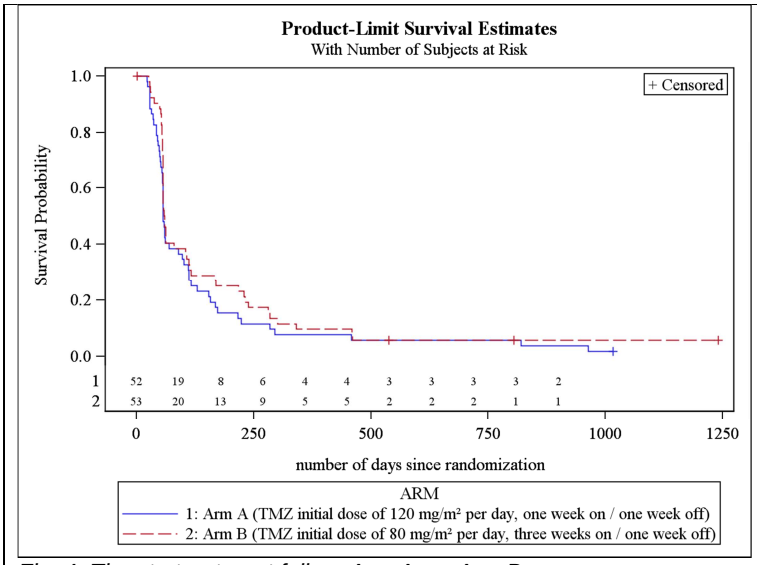

Fig. 4: Time to treatment failure Arm A vs. Arm B

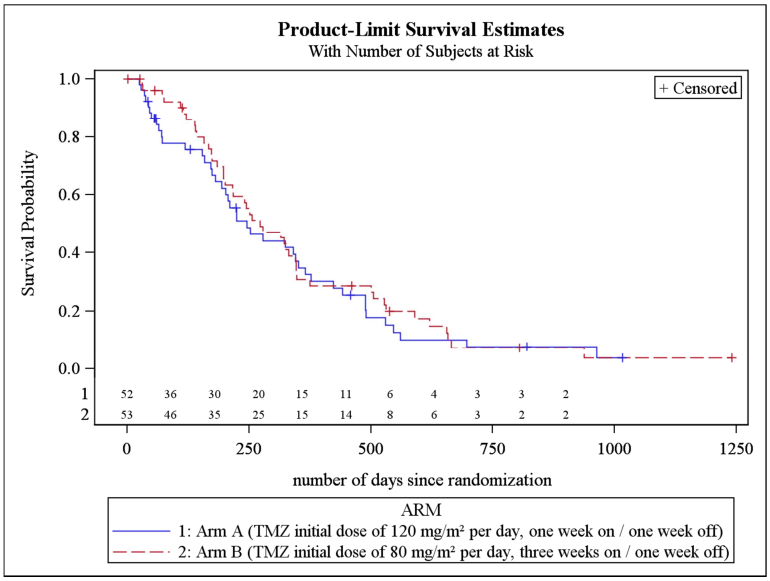

Fig. 5: Overall survival Arm A vs. Arm B

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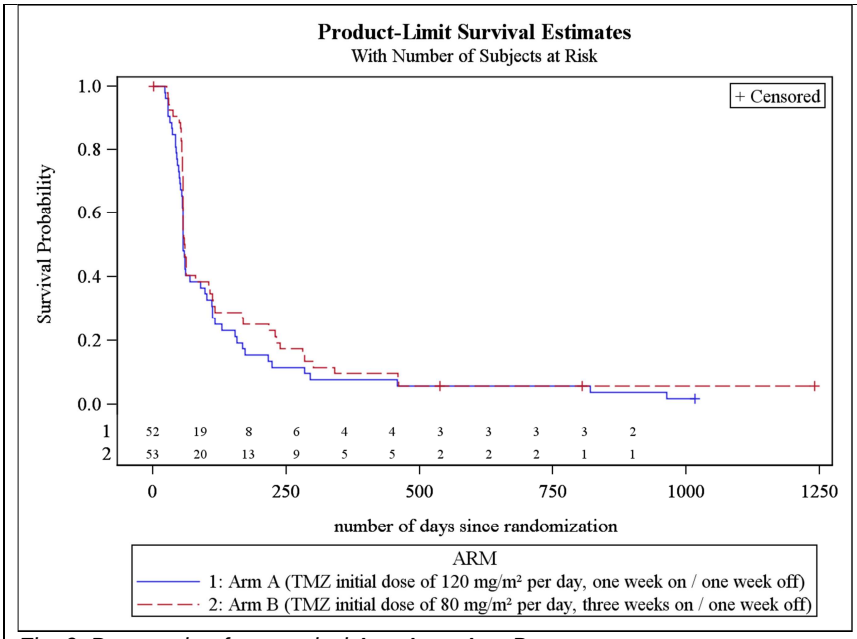

Fig. 6: Progression-free survival Arm A vs. Arm B

The methylation of the MGMT promoter was assessed in all 105 patients. Consequently, we assessed whether median time to treatment failure, overall survival and pro-gression-free survival are different in patients with MGMT promoter-methylated versus MGMT promoter-unmethylated tumors.
Patients with MGMT promoter-methylated tumors had a better outcome with dose-dense te-mozolomide than patients with MGMT promoter-unmethylated tumors. Median time to treatment failure, overall survival and progression-free survival were superior in patients with MGMT promoter-methylated versus -unmethylated tumors. Specifically, the relative risk estimates for no methylation vs methylation along with their 95 per cent confidence intervals are 1.92 [1.19; 3.14] for treatment failure, 2.02 [1.25; 3.31] for overall survival and 1.93 [1.20; 3.15] for progression-free survival. The visual representation of the Kaplan-Meier estimates suggest that methylation does not affect the risk of early tumour progressions.
The progression-free survival at 6 months was 7% in unmethylated patients vs. 39% in methylated patients.

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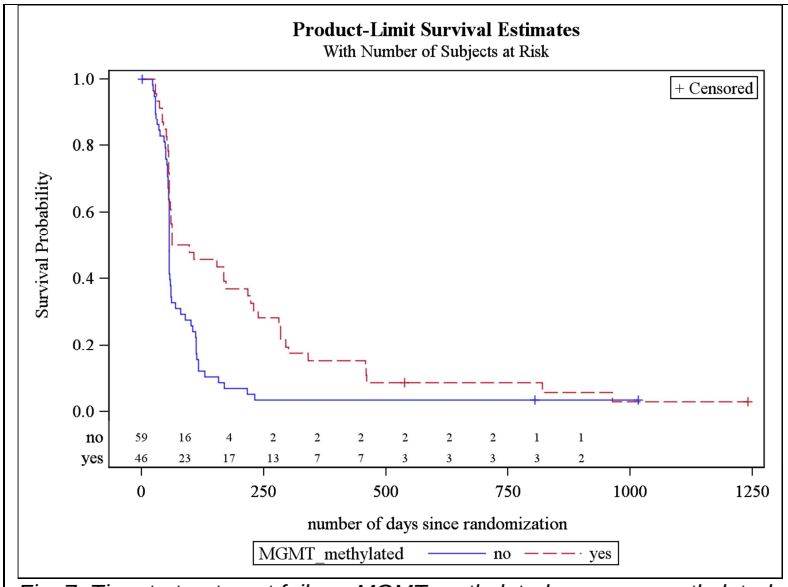

Fig. 7: Time to treatment failure: MGMT-methylated versus unmethylated

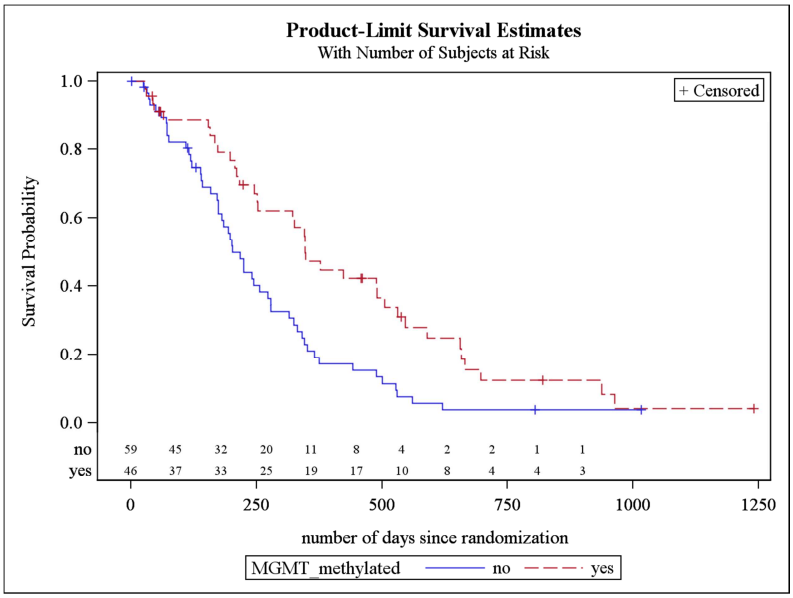

Fig. 8: Overall survival: MGMT-methylated versus unmethylated

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EudraCT-Nr.: 2008-006871-60	**BfArM Vorlage-Nr.:** 4035040	**Ethik Antrags-Nr.:** AFmu-050/2009	

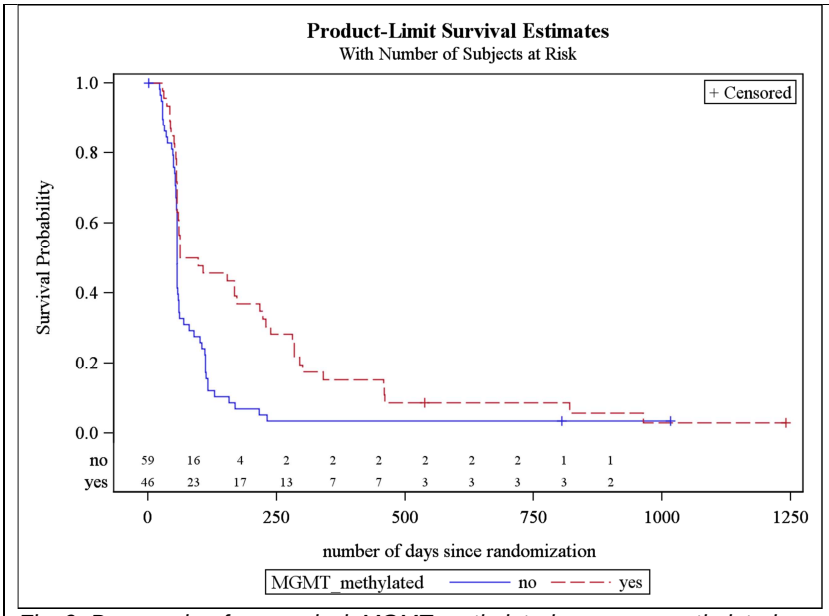

Fig. 9: Progression-free survival: MGMT-methylated versus unmethylated

Safety Results:

Non-hematological adverse events e.g. disorders of the gastrointestinal system, nervous system, metabolism, respiratory system, skin, cardiovascular system or musculoskeletal system occurred at similar rates in both treatment arms.
Hematological adverse events in total occurred more often in patients receiving the three weeks on / one week off regimen in Arm B (36.5% in Arm A versus 44.2% in Arm B). The rate of adverse events that were considered as “not related” were similar in both arms but adverse events that were rated as “possible”, “probable” and “very likely” occurred more often in Arm B.
There was no significant difference between both arms regarding the severity of adverse events in the hematological system (Grade I, Arm A: 3.8% vs Arm B 7.7%; grade II, 5.8% in both arms; grade III, Arm A: 21.2% vs Arm B: 26.9%; grade IV: Arm A: 5.8% vs Arm B: 3.8%).
A comparison of adverse events in the hematological system by preferred terms leukopenia, lymphopenia, neutropenia and thrombocytopenia revealed that lymphopenia occurred significantly more often in Arm B (38.5%) as compared with Arm A (26.9%). There was no significant difference for the other preferred terms in the hematological system.

In total, 87 deaths were documented at the timepoint of database closure, 84 because of documented disease progression and 3 deaths with unknown reason (Center 003, patient 007; center 006, patient 003; center 007, patient 002).
SAR and SUSAR did not occur.

The study treatment was overall well tolerated with expected toxicity, predominantly in the hematological system. It should be taken into account that temozolomide is a registered drug and that clinicians had already gained experience in the toxicity profile and the management of hemtological toxicity, not only with standard dosing but also with dose-

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dense regimens.
Within the DIRECTOR study population, we did not identify a population that was at higher risk for developing serious adverse events. Taken together, the safety profile of both dose-dense temozolomide regimens that were applied here is acceptable.

Conclusion:

Based on the data outlined above, we conclude that for patients with tumors with MGMT promoter methylation, dose-dense temozolomide can be considered as a valuable treatment option in the recurrent setting. Dose-dense rechallenge with temozolomide should not be considered for patients with tumors with an unmethylated MGMT gene promoter. The regimen of choice, either one week on/off or three weeks on/one week off, still needs to be identified. Importantly, the administration of dose-dense temozolomide at first glioblastoma progression was overall safe and tolerated well without the occurrence of any SAR or SUSAR.

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