Final Study Report

Cilengitide and Metronomic Temozolomide for Relapsed or Refractory High Grade Gliomas or Diffuse Intrinsic Pontine Gliomas in Children and Adolescents - A Phase II Study

(Prospective, non-randomized, single-arm multicenter phase II trial)

HIT-HGG-CilMetro

Investigational Medicinal Products:
Cilengitide®+ Temodal®

Indication: Relapsed or refractory high grade gliomas or diffuse intrinsic pontine gliomas

Phase of the clinical trial: Phase II

EudraCT-Number: 2009-011898-33

HIT-HGG-CilMetro

Version Date: 06.03.2020
Version: V01

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Study Start (FPI): 08.02.2012
End of Study (LPO): 07.03.2014

Signature

I agree with the content of the final study report in its final version. The reported clinical trial was conducted in accordance with the current version of the Declaration of Helsinki, ICH-GCP Guideline (International Conference on Harmonization – Good Clinical Practice) and applicable national laws and regulatory requirements.

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Abt. Pädiatrische
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Göttingen, March 9, 2020
Place, Date

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1. Name of the Sponsor

Martin-Luther-University Halle-Wittenberg, represented by the chancellor, represented by the Dean of the Faculty of Medicine.

2 Finished Products	3 Active Substances
Cilengitide®	cyclo-(Asp-D-Phe_N-MeVal-Arg-Gly)
Temodal®	Temozolomide

4 Individual Study Chart

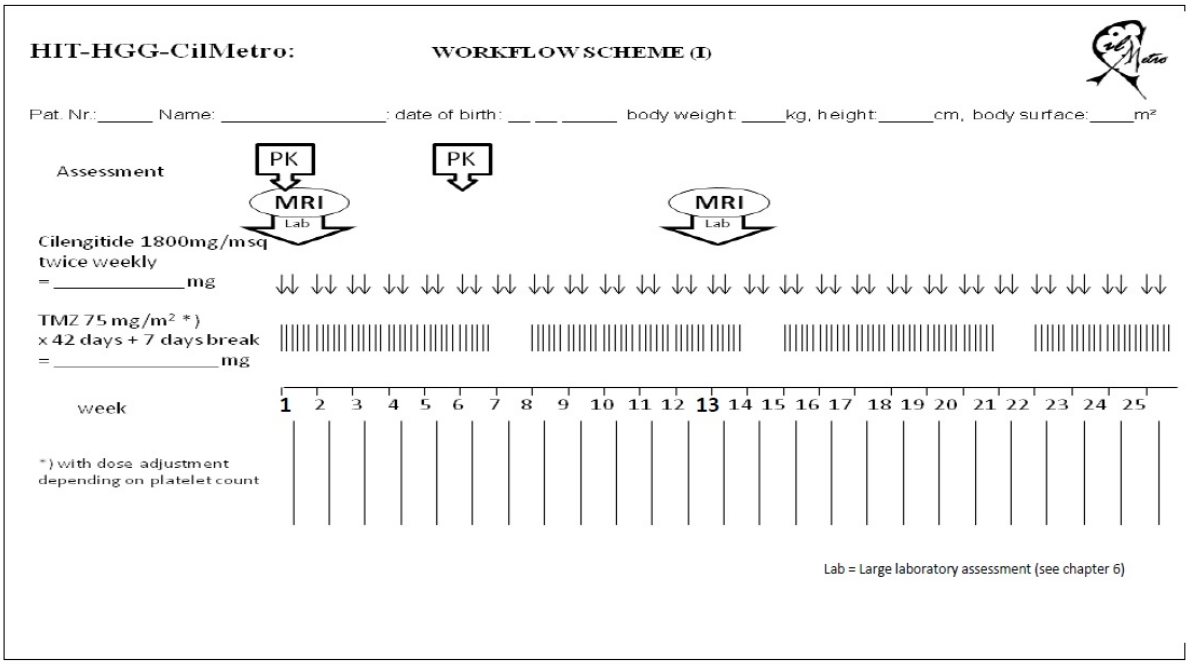

Figure 1: Flow-chart on study design and proceedings I (PK: Blood sampling time points for analysis of pharmacokinetics)

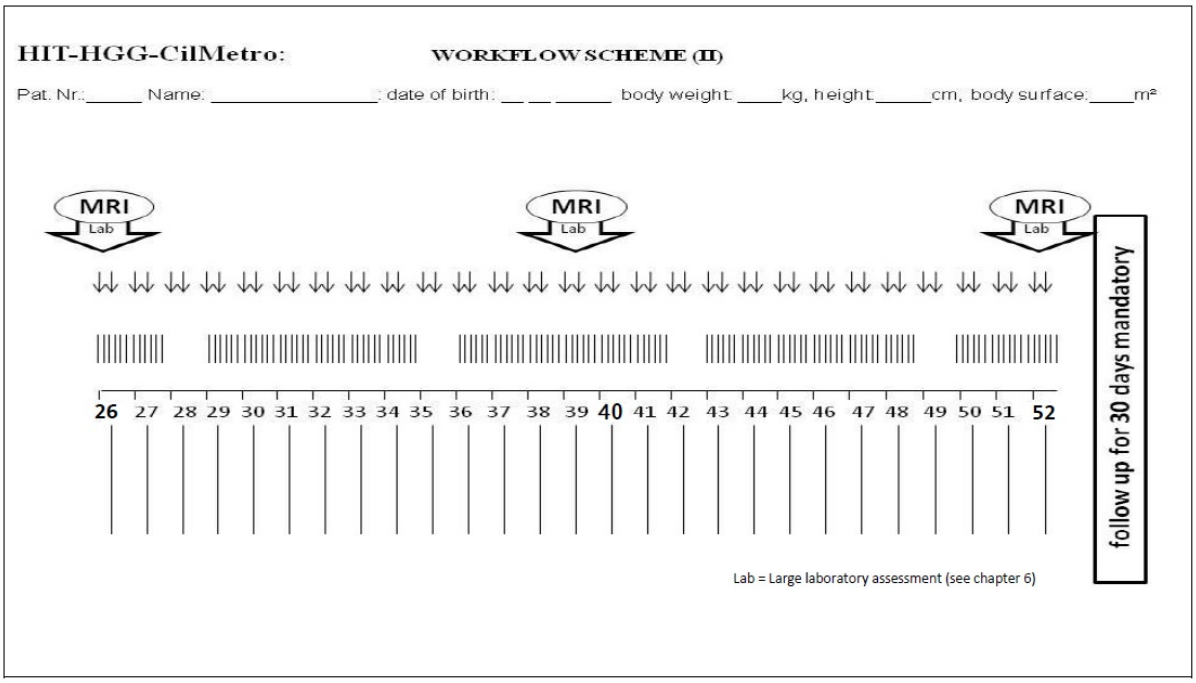

Figure 2: Flow-chart on study design and proceedings (II)

5 Study Title

Cilengitide and Metronomic Temozolomide for Relapsed or Refractory High Grade Gliomas or Diffuse Intrinsic Pontine Gliomas in Children and Adolescents - A Phase II Study

- Protocol-Versions:
    - Version 1.1 (September 29, 2011) was the first version, Version 1 (March 7, 2011) was not approved neither by the EC nor by the CA.
    - Version 2 (February 1, 2013) was the last valid version of the protocol (approved by the EC on 21.03.2013 and by the CA on 17.04.2013)

- Amendment 01:
  Change of 2 co-ordinating investigators, change of several investigators at 10 sites, approved by the EC on 13.03.2012, 16.03.2012, 19.03.2012, 20.03.2012, 21.03.2012, 26.03.2012, 29.03.2012 and 16.05.2012.

- Amendment 02:
  Change of 2 co-ordinating investigators, change of several investigators at 3 sites, approved by the EC on 29.03.2012, 04.04.2012 and 20.04.2012

- Submission of a cross-reference letter for Cilengitide IMPD (Merck), receipt from CA on 26.04.2012

- Amendment 04:
  Submission of new protocol version, approved by the EC on 21.03.2013, receipt from CA on 17.04.2013

- Amendment 07:
  Submission of new IB version, approved by CA on 19.03.2013.

- Amendment 09:
  Permanent stop of patient recruitment approved by the EC on 30.05.2013, approved by CA on 27.06.2013.

- Amendment 10:
  New version of IMPD; approved by CA on 20.08.2013.

- Amendment 11:
  Removal of 33 sites approved by the EC on 11.12.2013, receipt from CA on 28.11.2013.

Trial sites which enrolled patients are highlighted in grey.

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8 Publications

Not applicable

9 Study Period (years)

Date of first enrolment: 08.02.2012
Date of last patient last visit: 05.02.2014

Patient recruitment was shortly interrupted at March 5, 2013 because of two SAEs with intratumoral/intracranial haemorrhage and a current publication of negative trial results in adult glioblastoma patients. The topic was discussed with the data safety and monitoring committee (DSMC). In agreement with the members of the DSMC, recruitment was restarted at March 12, 2013 as benefit for HIT-HGG-CilMetro patients was still expected.

Before achieving the required sample size, recruitment of new patients was permanently stopped at April 30, 2013 because of decreased benefit/risk ratio after altogether four SAEs with intratumoral/intracranial haemorrhage together with the publication of negative trial results in adult glioblastoma patients. At time of recruitment stop three patients still received treatment. The last patient completed study therapy at 05.02.2014. End of study was reached 30 days later (07.03.2014).

10 Phase of Development

HIT-HGG-CilMetro is a Phase II trial.

- Cilengitide is an integrin inhibitor without marketing authorization in the member state concerned.
- Temodal is an alkylating antineoplastic agent with a marketing authorization in the member state concerned. It is licensed as single agent for treatment of high grade gliomas in adults in the newly diagnosed and relapsed setting, for children it is licensed only for recurrent high grade glioma.

11 Objectives

To date, most paediatric patients with recurrent high grade gliomas (HGG) are treated on the basis of individual considerations and recommendations outside of clinical trials. As no relevant published data on second line treatment strategies in paediatric HGG patients are available, findings from adult trials may help to identify potential candidate strategies for paediatric relapse trials. Unfortunately, these data cannot simply be extrapolated to children and adolescents, since paediatric relapsed high grade gliomas are biologically different and must be evaluated in separate paediatric trials. In particular, this is true for targeted therapies aiming at tumour specific signal cascades and/ or pathogenetic mechanisms. One of the promising candidate treatment strategies for paediatric patients with relapsed high grade gliomas is represented by the combination of the integrin inhibitor cilengitide and an intensified application regimen of the chemotherapeutic agent temozolomide.

Besides the potential antiangiogenetic effect of cilengitide, its mode of action may also include direct effects on tumour cells by affecting their attachment, migration, invasion, and viability. Application of metronomic temozolomide showed a significant therapeutic efficiency in (adult) relapsed glioblastomas. This might be due to a higher total dose of the drug in comparison to conventional dosage schemes and might induce depletion of the MGMT gene, which encodes a DNA repair enzyme that can abrogate the effects of alkylating agents like temozolomide. Cilengitide and metronomic temozolomide both act on tumors via antiangiogenetic mechanisms and their combination may imply some potential for a synergistic antitumour efficacy. Furthermore, both agents displayed a favourable toxicity profile in paediatric phase I brain tumour trials.

Thus, the HIT-HGG-CilMetro trial was designed as a clinical phase II trial to evaluate whether the combination of cilengitide and metronomic temozolomide is safe and suggests a clinical

benefit for paediatric patients with relapsed high grade gliomas including diffuse intrinsic pontine gliomas.

Primary objectives:

Evaluation of the efficacy of a combined treatment with cilengitide and metronomic oral temozolomide as measured by 6 months overall survival (OS) after diagnosis of relapse or tumour progression in children and adolescents with relapsed or refractory high-grade malignant glioma and diffuse intrinsic pontine glioma, as compared to a historical control.

Secondary objectives:

1. Evaluation of the safety and toxicity of the study treatment by common toxicity criteria (CTC; version 4.0).

2. Assessment of

- the response rates at 6 months (continuous complete response = CCR, complete response = CR, partial response = PR, stable disease = SD, progressive disease = PD) and

- progression-free survival (PFS) at 6 months, and

- response rates, OS, and PFS at 12 months after relapse diagnosis or diagnosis of tumour progression.

Response is presented including histopathological variants.

3. Assessment of the pharmacokinetics of cilengitide administered as part of the study treatment.

12 Methodology

This trial was designed as prospective, non-randomized, single-arm phase II trial.

Study treatment:

Patients included in the study received…

- Cilengitide 1800 mg/m² i.v. twice weekly

- Temozolomide 75 mg/m²/d p.o. for six weeks, followed by one week rest with a mandatory dose adaptation rule in regards to haematatological and non-haematological toxicities

Treatment schedule:

Week 1-6 / 8-13 / 15-20 / 22-27 / 29-34 / 36-41 / 43-48 / 50-52:

Temozolomide: (75 mg/m^2 p.o., platelet-dependent dose adjustment!), day 1 till day 7

Cilengitide: (1800 mg/m^2 i.v.), day 1 & day 4

Week 7 / 14 / 21 / 28 / 35 / 42 / 49:

Temozolomide: pause

Cilengitide: (1800 mg/m^2 i.v.), day 1 & day 4

After Week 52:

Follow up for 30 days after the end of protocol treatment is mandatory. Further follow up including 3monthly MRI imaging is strongly recommended for at least one more year.

Every relevant modification of trial design (temporary stop of patient recruitment, permanent stop of patient recruitment due to decreased benefit/risk ratio) was conducted in accordance with the trial Data and Safety Monitoring Committee (DSMC).

55 trial sites took part in this study, 21 enrolled patients.

13 Number of Patients

Between February 2012 and March 2013, 28 patients were enrolled at 23 trial sites (2 patients were dropped out). Before achieving the required sample size of 33, recruitment was terminated early on April 30, 2013, because of decreased risk/benefit ratio. The last patient completed study therapy in February 2014.

Discontinuation / Drop-out / Protocol Violators

One patient (guardians) gave no informed consent and met the exclusion criterion "Laboratory test results outside the defined ranges". Thus, he did not receive the study medication. Another patient (guardians) withdrew informed consent before start of study treatment.

Thus, 26 patients received at least one cycle cilengitide and temozolomide. In median [minimum, maximum], at least 80% of 1800 mg/m² cilengitide was administered twice weekly for 6.5 [0, 56] weeks, and at least 80% of 75 mg/m²/d temozolomide for 39 [7, 343] days (Table 3.2). 10 of these 26 patients did not receive at least these doses of study medication for at least 4 weeks.

24 patients terminated study therapy prematurely, 17 of them due to progressive disease. 12 of the included 27 patients did not reach the regular end of study. The main reason was death (in 11 patients).

13.1 Demographic and Other Baseline Characteristics

Patients 3 years and < 18 years of age with high grade glioma or diffuse intrinsic pontine glioma relapsed after or refractory to standard therapy recruited by approved trial sites.

The safety/ intention-to-treat analysis set included 26 children and adolescents aged 5-17 years in a 1:1 gender ratio. 23 of them had the current diagnosis of local progression.

Histological/ radiological type of primary tumour according to reference diagnostic finding was diffuse intrinsic pontine glioma in 13 patients, glioblastoma multiforme (WHO IV) in 9, anaplastic astrocytoma (WHO III) in 2, anaplastic oligoastrocytoma (WHO III) and giant cell glioblastoma (WHO IV) in one patient each.

Data sets analyzed:

All 26 patients who received at least one dose of cilengitide or temozolomide were included in the safety/ intention-to-treat (ITT) analysis set. Per-protocol patients were those remaining 16 patients without inclusion/ exclusion exceptions who received at least 4 weeks of treatment according to the present protocol HIT-HGG-CilMetro, i.e., cilengitide with a dose of at least 1440 (80% of 1800) mg/m² twice weekly for at least 4 weeks and temozolomide with a dose of at least 60 (80% of 75) mg/m²/d for at least 4 weeks.

Analyses were performed in the safety/ITT analysis set, efficacy analyses additionally in the per-protocol (PP) analysis set.

14 Diagnosis and main inclusion criteria

Inclusion criteria:

- Diagnosis of high-grade malignant glioma confirmed by central neuropathological review (last MRI diagnosis not older than 4 weeks) - including glioblastoma multiforme (WHO IV), anaplastic astrocytoma (WHO III), anaplastic oligodendroglioma (WHO III), anaplastic oligoastrocytoma (WHO III), anaplastic pilocytic astrocytoma (WHO III), anaplastic ganglioglioma (WHO III), anaplastic pleomorphic xanthoastrocytoma (analogous to WHO III), giant cell glioblastoma (WHO IV), and gliosarcoma (WHO IV) - or diagnosis of diffuse intrinsic pontine glioma confirmed by central neuroradiological review - refractory to standard treatment, or relapsed or progressive after first-line therapy.

- Patient aged 3 years and older but under 18 years at time of relapse diagnosis

- Written informed consent of the patient (mandatory from 15 years of age) or the parents/ guardians (mandatory till 18 years of age).

Exclusion criteria:

- Known hypersensitivity or contraindication to any study drugs
- Other (simultaneous) malignancies
- Pregnancy and / or lactation
- Patients who are sexually active refusing to use effective contraception (oral contraception, intrauterine devices, barrier method of contraception in conjunction with spermicidal jelly or surgical sterile)
- Current or recent (within 30 days prior to start of trial treatment) treatment with another investigational drug or participation in another investigational trial
- Severe concomitant diseases (e.g. immune deficiency syndrome) or HIV infection
- Severe psychological disease or neurological damage without possibility to communicate
- Clinical signs of intracranial pressure
- Intracerebral hemorrhage or history of intracerebral hemorrhage
- Following laboratory test results (not older than 2 weeks before patient´s inclusion):
- Platelets < 100 000/µl (< 100 Gpt/l)
- PT, INR and PTT above normal range
- Absolute neutrophil count < 1 500/µl (< 1,5 Gpt/l)
- Hemoglobin < 10g/dl (< 6,4 mmol/L)

- Serum creatinine ≥ 1,5 x upper limit of normal range or creatinine clearance rate < 60 ml/min/m^2 (corrected for body surface area)
- Total bilirubin ≥ 1,5 x upper limit of normal range
- SGOT (ASAT) and SGPT (ALAT) ≥ 2,5 x upper limit of normal range
- Alkaline phosphatase ≥ 2,5 x upper limit of normal range
- Hereditary Intrinsic Platelet Disorders
- Ongoing irradiation or chemotherapy (within the last 4 weeks)
- Estimated life expectancy of less than 2 months

15 Investigational medicinal products, dose, mode of administration

Trade name: **Cilengitide®**

Active substance: Cilengitide, cyclo-(Asp-D-Phe_N-MeVal-Arg-Gly)

Dose: 1800 mg/m^2 per day

Mode of administration: intravenous

Duration of treatment: 52 weeks

Formulation: solution for infusion (Cilengitide, sodium chloride, water)

Dose strength: 8 mg/ml

Batch Numbers: A 083 14875

M 248 14164

U 028 14875

Storage: Cilengitide Vials have to be stored in a refrigerator

(5 °C ± 3 °C) without any specific precautions against light exposure

Mode of action: Antagonist of the avß3 and avß5 integrin receptors, inhibitor of angiogenesis and tumour cell migration

Trade name: **Temodal®**

Active substance: Temozolomide

Dose: 75 mg/m^2 per day

Mode of administration: oral use, enteral use (noncurrent) or nasogastric use

Duration of treatment: 52 weeks

Formulation: Temozolomide, anhydrous lactose

Dose strength: 5 mg, 20 mg, 100 mg, 140 mg, 180 mg, 250 mg

Batch Number: Not applicable since Temodal® is already licensed for the indication of the present study, and, thus, freely available.

Storage: Do not store over 30 °C

Mode of action: antineoplastic, alkylating agent

16 Duration of treatment

Please see 12 Methodology

17 Test product, dose, mode of administration

Not applicable

18 Criteria for evaluation

18.1 Efficacy

The efficacy analysis was done according to the intention-to-treat (ITT) principle in the safety/ ITT analysis set including 26 patients. Additionally, a per-protocol (PP) analysis was performed in the PP analysis set of 16 patients.

Analysis of primary endpoint:

In the ITT analysis set, 6 of 26 patients were still alive at 6 months. The 6-month overall survival rate estimated by Kaplan-Meier method was 0.231 with 95% CI [0.094,0.403]. This survival rate was lower than that of 0.44 of the historical control. The null hypothesis H0: $p \leq 0.44$ could not be rejected at the 5% level of significance (one sample $\chi 2$-test, 1-sided, $p=0.984$).

The additional PP analysis resulted in a 6-month overall survival rate of 0.313 with 95% CI [0.114,0.536] and no rejection of the null hypothesis neither when comparing with the historical control (H0: $p \leq 0.44$, one sample $\chi 2$-test, 1-sided, $p=0.848$).

Analysis of secondary endpoints:

In the ITT analysis set, response was death in 20 of 26 patients, PD in 3, SD in 2 and CCR in one of 26 patients at 6 months, and death in 22 of 26 patients, PD, SD, PR and CCR in one patient each at 12 months after diagnosis of relapse or tumour progression.

Progression-free survival rates were 0.154 with 95% CI [0.048,0.315] at 6 months and 0.077 with 95% CI [0.013,0.217] at 12 months after diagnosis of relapse or tumour progression in the ITT analysis set. The 12-month overall survival rate was 0.154 with 95% CI [0.048,0.315]. Median event times with 95% CI were 67 [39,80] days of PFS and 101 [80,174] days of OS.

Overall response (OR) showed one and 2 of 26 patients within 6 and 12 months after the reference date, respectively. Best response within 6/12 months was CCR in 1/1 of 26 patients, PR in 0/1, SD in 5/4, PD in 18/18 and death in 2/2 of 26 patients in the ITT analysis set.

18.2 Safety

Adverse Events (AE):

25 of 26 patients experienced adverse events. Overall, 356 AEs were documented, most of them among aberrant laboratory investigations, gastrointestinal disorders and nervous system disorders.

No multiply occurring AE on preferred term (PT) level was counted more than once per patient. The most frequently observed AEs were vomiting (17 patients), increased alanine aminotransferase (13), nausea (12), decreased white blood cell count (12), constipation (10), increased aspartate aminotransferase (9), decreased haemoglobin (8), headache (7) and pyrexia (6). 5 of 26 patients suffered CTC grade 5 and 10 patients CTC grade 4 AEs.

CTC grade 5 AEs were neoplasm progression in 2 patients, pneumonia aspiration, disturbance in attention and dysphagia in one and the same patient, convulsion and tumour haemorrhage in one patient each. CTC grade 4 AEs were somnolence, increased intracranial pressure and abasia in one and the same patient, headache and vomiting in one and the same patient, neoplasm progression, cerebral haemorrhage, convulsion, status epilepticus, hypernatraemia, thrombocytopenia, decreased lymphocyte count and decreased white blood cell count in one patient each.

112/217 of 356 AEs were possibly (79/90), probably (32/126) or definitely (1/1) related to cilengitide (a)/temozolomide (b). Solely one AE was evaluated as definitely related to cilengitide and temozolomide: increased aspartate aminotransferase with common toxicity criteria (CTC) grade 1 in one patient. 5/7 of 26 patients had probably related AEs to cilengitide/ temozolomide. Regarding cilengitide, these were increased alanine aminotransferase (3 patients), nausea (2 patients), constipation, diarrhoea, stomatitis, vomiting, increased aspartate aminotransferase, decreased neutrophil count, decreased white blood cell count and cerebral haemorrhage (one patient each), and regarding temozolomide, decreased white blood cell count (6 patients), decreased neutrophil count (4 patients), increased alanine aminotransferase and decreased haemoglobin (3 patients each), nausea (2 patients), neutropenia, thrombocytopenia, constipation, diarrhea, stomatitis, vomiting, pyrexia, infection, increased aspartate aminotransferase, decreased granulocyte count, decreased platelet count and pruritus (one patient each). Of these AEs with probable relationship to cilengitide/ temozolomide had 1 (cerebral haemorrhage)/ 2 (thrombocytopenia and decreased white blood cell count) CTC grade 4 in one patient each. One patient had CTC grade 5 tumour haemorrhage with possible relationship to cilengitide and temozolomide and CTC grade 4 hypernatraemia with possible relationship to temozolomide. The other CTC grade 4 AEs possibly related to cilengitide and temozolomide were decreased lymphocyte count and headache, possibly related to cilengitide convulsion (one patient each).

5 of the CTC grade 4 and 5 AEs were defined as toxic events because of probable or possible relationship to study medication. For definition of the secondary safety endpoint toxic event, see section 2.2. 4 of 26 patients had at least one toxic event, i.e. tumour haemorrhage and hypernatraemia in one and the same patient, cerebral haemorrhage, convulsion and headache in one patient each. The probability of a toxic event was 0.154 with 95% CI [0.015,0.293]. Thus, the null hypothesis H0: $p1>0.15$ could not be rejected at the 5% level of significance (binomial test, 1-sided, $p=0.522$.

Severe Adverse Events (SAE):

In total, 38 SAEs were reported in 16 of 26 patients. The most frequently occurring SAEs were neoplasm progression and convulsion (3 patients each), tumour haemorrhage, pyrexia, infection and somnolence (2 patients each). 7 patients suffered more than one SAE (up to 8 SAEs). 7 SAEs were evaluated as probably or possibly related to study medication (cilengitide and/or temozolomide), i.e. tumour haemorrhage and convulsion (2 patients each), cerebral haemorrhage, infection and oedema (one patient each).

Deaths:

22 of 26 patients died within one year after study entry, all of them due to primary tumour/ local progression and/or due to relapse/metastases. Further causes of death were

consequence of treatment (chemotherapy, cerebral haemorrhage) in one patient and aspiration pneumonia in another patient.

Premature study termination due to a decreased risk/benefit ratio:

After three subsequent SAEs reporting intratumoural/ intracranial haemorrhages the risk for these bleeding events appeared increased. Since there was also in parallel a reported lack of efficacy within two other Cilengitide trials the risk/ benefit ratio of the HIT-HGG-CilMetro trial was reassessed by the trial Data Monitoring and Safety Committee (DMSC) suggesting less benefit and more risk than initially assumed for trial patients.

As a consequence of this altered risk/ benefit assessment, the patient recruitment was stopped on April 30, 2013. Patients who had been already enrolled in HIT-HGG-CilMetro were asked if they want to continue on the trial. All active patients and their parents wanted indeed to continue and signed a renewed informed consent with the new additional information on the changed risk/ benefit assessment.

To note: Since no further intratumoral/ intracranial haemorrhages were reported during the further course of the trial and there is anyway an increased therapy-independent risk for intratumoural/ intracranial haemorrhage in paediatric brain tumour patients, the final conclusion is that there is no proof for an increased intracranial bleeding risk within the present trial.

19 Statistical methods

Primary Analysis:

Main question of the trial was whether the probability for being alive 6 months after diagnosis of refractory or relapsed disease with cilengitide and metronomic temozolomide was higher than 0.44 as found in a historical study population with relapsed high grade gliomas (including diffuse intrinsic pontine gliomas) from the HIT-GBM data base. The 6-month overall survival rate was estimated by Kaplan-Meier estimates and presented with the corresponding 2-sided 95% CI.

The comparison with the historical control (0.44) was performed with the one sample $\chi 2$-test (1-sided, $\alpha=5\%$, H0: $p \leq 0.44$, H1: $p > 0.44$).

Secondary Analyses:

Efficacy:

ORR (overall response rate) was defined as the number of subjects whose best overall response was either CCR, CR or PR divided by the number of subjects belonging to the analysis set. The ORR, CCR, and the response rates (CR, PR, SD or PD) were presented together with two-sided 95% confidence intervals (CIs) at 6 and 12 months after relapse diagnosis or diagnosis of tumour progression. For the analysis of overall survival time and progression-free survival time Kaplan-Meier estimates (product-limit estimates) were presented together with a summary of associated statistics (median, 6- and 12-monthly rates) including the corresponding 2-sided 95% CIs.

Safety:

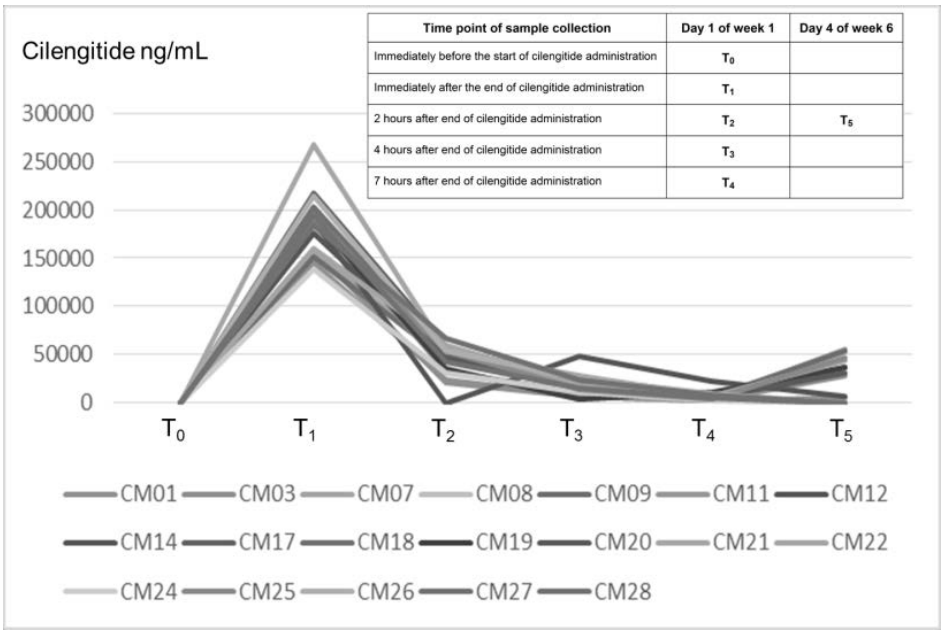
Adverse events (AE) were coded using the Medical Dictionary for Regulatory Activities (MedDRA), version 15.0, English. AEs were summarized by System Organ Class (SOC) and Preferred Term (PT), CTC grade (NCI-CTCAE v. 4.0) and relationship to study treatment. Absolute frequencies of AEs and the number of patients experiencing an AE were given. In the summary by CTC grade, only the worst case per PT for each patient was counted, if a patient experienced more than one AE within a PT. All AEs were included in the summary by relationship to study treatment.

To assess the applicability of cilengitide at a dose of 1800 mg/m^2 in paediatric patients cotreated with metronomic temozolomide with tolerable toxicity, it was analysed if the probability of a toxic event as defined above was lower than or equal to p1=0.15 by means of a binomial instead of the planned one sample χ2-test (1-sided, α=5%, H0: p1>0.15, H1: p1≤0.15).

Pharmacokinetic analysis:

For the pharmacokinetic analysis, patient plasma levels were analysed in 20 patients at 6 different time points each, i.e. T0 (immediately before the start of first Cilengitide administration), T1 (immediately after the end of first Cilengitide administration), T2 (2 hours after end of first Cilengitide administration), T3 (4 hours after end of first Cilengitide administration), T4 (7 hours after end of first Cilengitide administration), and T5 (2 hours after end of Cilengitide administration at day 4 of week 6 of therapy).

After reliably being negative at T0, Cilengitide levels rose to values between 139,000 and 267,000 ng/ml at T1, falling down to 21,400 - 66,200 ng/ml at T2; declining in most patients further down to minimal levels at T4 (1810-23,100 ng/ml). The T5 levels were extremely low in two patients (5080 and 6260 ng/ml), possibly indicating induction of inactivating mechanisms, but in the others similar to those at T2 (28,700 to 55,900 ng/ml). No unexpected pharmacokinetic course was observed.



Time point of sample collection	Day 1 of week 1	Day 4 of week 6
Immediately before the start of cilengitide administration	T_0	
Immediately after the end of cilengitide administration	T_1	
2 hours after end of cilengitide administration	T_2	T_5
4 hours after end of cilengitide administration	T_3	
7 hours after end of cilengitide administration	T_4	

Figure 3: Pharmacokinetics of Cilengitide

20 Summary / Conclusions

The aim of the clinical trial covered by this report was to investigate the combination of Cilengitide and metronomic Temozolomide as a new treatment strategy in the above-named paediatric patient population. For that purpose, the efficacy of this combined treatment was evaluated as measured by 6-months overall survival (OS) after diagnosis of relapse or tumour progression in children and adolescents with high-grade malignant glioma or diffuse intrinsic pontine glioma. Moreover, safety and toxicity of the study treatment were evaluated as secondary objectives.

In regards to therapeutic efficacy, 6-months overall survival rate as primary measure of efficacy could not be shown to be higher than the 0.44 of the historical control group. Indeed, in the present study population, 6-month overall survival rate was with 0.23 lower and far away from 0.59 considered to be of clinical relevance. Secondary efficacy analyses of overall survival, progression-free survival and overall response rate gave no promising results neither.

The overall safety profile of the combined treatment with Cilengitide and Temozolomide did not appear unfavourable for paediatric patients with recurrent or progressive high grade gliomas or pontine gliomas.

However, after three subsequent SAEs reporting intratumoural/ intracranial haemorrhages and a lack of efficacy within two other Cilengitide trials an altered risk/ benefit ratio was assessed by the DMSC of HIT-HGG-CilMetro. As a consequence, the patient recruitment was prematurely stopped after 28 of planned 33 patients. Since no further intratumoral/ intracranial haemorrhages were reported during the further course of the trial, the final conclusion regarding intratumoural/ intracranial haemorrhages is that there was no proof of an increased bleeding risk within the present trial. This is in line with fact that there is an increased therapy-independent risk for intratumoural/intracranial haemorrhage in paediatric brain tumour patients.

Summarized in short, we conclude that the present study showed that despite the premature termination of patient recruitment due to an altered risk/benefit ratio the overall toxicity profile does not seem to be unusual in comparison to other trials in the same patient group. Especially, the suspected higher risk for intratumoural/intracranial haemorrhage which led to the premature termination of patient recruitment could not be sustained during the further course of the trial. The overall haemorrhage incidence of 3 in 26 treated patients (=11.5%) did not exceed the incidence of intratumoural/ intracranial haemorrhage reported in other studies in relapsed paediatric high grade glioma/DIPG. Regarding therapeutic efficacy it must be stated that the trial was not able to show therapeutic superiority in comparison to a historical control. In fact, the overall survival at 6 months was markedly lower than in the historical control. This might be due to an imbalance of better and poor prognostic tumours in both groups but subgroup analysis was not part of the present study. However, we observed 3 out of 9 glioblastoma patients with an extraordinarily long survival given the overall palliative situation in these patients. This was completely unexpected and warrants further exploration in a larger patient series to see if certain subgroups of paediatric glioblastoma might benefit from a treatment strategy like in HIT-HGG-CilMetro.