Title of Trial: Cilengitide (EMD 121974) and temozolomide with concomitant radiation therapy, followed by cilengitide and temozolomide maintenance therapy in subjects with newly diagnosed glioblastoma - a multicenter, open-label, uncontrolled Phase I/IIa study

Investigational Product: Cilengitide

Trial No.: EMD 121974-010

Study Centers: This study was conducted in 15 centers in Switzerland, Germany and Belgium.

Trial Dates:

Trial Initiation Date: 29 August 2005

Clinical/Survival Cut-off Date: 20 February 2007

Trial Completion Date: 23 January 2012

Development Phase: Phase 1/2a

Publications (references): R. Stupp et al.: Phase I/IIa trial of cilengitide (EMD 121974) and temozolomide with concomitant radiotherapy followed by temozolomide and cilengitide maintenance therapy in patients (pts) with newly diagnosed glioblastoma (GBM). J Clin Oncol 2007; 25: 2000

Study Objectives:

- The primary objective was to estimate the rate of subjects with ≥6-month progression-free survival (PFS) and the target was to reach a 6-month PFS rate of >65%. The analysis was based on the Investigator's assessment of the gadolinium-enhanced magnetic resonance imaging (Gd-MRI) scans.

- Secondary objectives were to estimate overall survival time, rate of 1-year survival, median time to disease progression, and response rate, to investigate safety and tolerability, and to investigate the pharmacokinetics (PK) of cilengitide and temozolomide (TMZ).

Methodology: A multicenter, open-label, uncontrolled, Phase I/IIa study conducted in subjects with newly diagnosed glioblastoma multiforme (GBM) World Health Organisation (WHO) Grade IV. Cilengitide was administered intravenously (i.v.) twice a week at a dose of 500 mg for 35 weeks or until disease progression or the occurrence of unacceptable adverse events (AEs). During the Weeks 2-7 subjects also received an oral daily dose of 75 mg/m^2 TMZ plus focal radiotherapy (RTX) 5 times a week. Four weeks after the end of RTX therapy, subjects continued with concomitant maintenance TMZ at a dose of 150 to 200 mg/m2 daily for 5 days every 4 weeks for the remainder of the study.

Number of Subjects (Planned and Analyzed):

Number (%) of Subjects	Planned	Analyzed
Per-protocol	50	41
Intent-to-treat	-	52
Safety	-	52

Diagnosis and Main Criteria for Inclusion/Exclusion: Diagnosis: newly diagnosed, histologically proven GBM.

Male or female subjects with newly diagnosed GBM and an Eastern Cooperative Oncology Group (ECOG) performance score ≤2 were to be included within 3-5 weeks after diagnostic surgery or biopsy if tumor tissue specimens were available from GBM surgery or biopsy.

Study Treatment:

Test product: EMD 121974 (cilengitide)

Dose	Mode of administration
500 mg twice a week	i.v. infusion over 1 hour

Duration of treatment**:** 35 weeks (with the option to continue therapy with cilengitide alone beyond Week 35 as long as it might have been of benefit to the subject).

Reference therapy: None

Criteria for Evaluation:

- The most important target variable was the 6-month PFS rate in subjects with newly diagnosed GBM after i.v. administration of 500 mg of cilengitide.

- Secondary statistical objectives were to estimate the median survival time, the 1-year survival rate, the response rate (if applicable) and the median time to disease progression, to determine safety and tolerability, and to characterize the PK of cilengitide when given concomitantly with TMZ.

Statistical Methods:

Primary variable: The primary analysis was performed when all subjects had either demonstrated progressive disease (PD) or completed the 35-week treatment phase. Number and percentage of subjects who survived ≥182 days without disease progression were summarized. The 95% confidence interval (CI) for the 6-month PFS rate was calculated using the exact binomial method. Progression status of a subject at the end of 6 months was determined by WHO criteria modified for neurooncology (Macdonald criteria).

Secondary variables: Similar statistical methods as for the primary variable were applied for the 1-year survival rate and the response rate. Responders were defined as subjects with measurable lesions at baseline whose best response during the study was either complete (CR)

or partial (PR). Survival time was defined as the number of days between date of first dose of cilengitide and date of death. Subjects who were alive were censored at the time when the subject was last known to be alive. The survival curve was plotted using the Kaplan-Meier method and median survival time and the corresponding 95% CI were calculated accordingly. The same method was applied for the analysis of the time to disease progression, i.e. the number of days between date of first dose of cilengitide and date of first assessment of PD during the study or until death, whichever occurred first.

Drug safety and tolerability were evaluated by descriptively summarizing AEs, laboratory assessments, physical examinations and vital signs, chest X-rays and 12-lead electrocardiogram (ECG) assessments.

Plasma concentrations and derived PK parameters of cilengitide and TMZ were presented descriptively. The variables were summarized by the number of observations, mean, geometric mean, median, standard deviation (s.d.), standard error of the mean (SEM), minimum, maximum, and coefficient of variation (CV). Concentration values below the lower limit of quantification (LLQ) were taken as zero for descriptive statistics.

Results

Subject Disposition: A total of 52 subjects were treated in the trial. The clinical/survival cut-off for the CTR v1.0 took place after 35 weeks of treatment (on 20 Feb 2007). During the 35 weeks of treatment, 29 subjects discontinued the trial treatment; and 23 subjects completed 35 months of trial treatment as planned and were reported in the CTR v1.0 (2007). Seven of the 23 subjects that completed 35 weeks of treatment received cilengitide monotherapy beyond Week 35.

The safety profiles in the study population showed that treatment with cilengitide 500 mg twice a week was well tolerated. At the safety survival cut-off of 01 Feb 2008, 1 subject was still on treatment. This subject discontinued cilengitide due to progressive disease (PD) on 03 Jan 2012, having tolerated cilengitide treatment well for almost 6 years since 16 Jan 2006.

The median (59.5) number of cilengitide infusions was the same as that reported in the CTR v1.0 (2007). The range of the total number of infusions, 8 to 208, was larger during the addendum period (21 Feb 2007 to 23 Jan 2012) to account for the 7 subjects treated beyond Week 35.

Efficacy Results:

The primary endpoint of 6-month PFS was reached by 36 subjects (69.2%; 95% CI: 54.9, 81.3%) and thus, the target of >65% of subjects with a 6-month PFS was reached. The response rate was 11.4%, with 2 subjects achieving PR and 2 subjects achieving CR. Stable disease (SD) was reported for 36 subjects (70.6%), whereas for 11 subjects (21.6%) PD was reported as the best response during the study. Median time to disease progression was 245.0 days (95% CI: 183.0, 249.0 days) and median overall survival time was not reached (only 33% of events had occurred) at the time of data cut-off.

A subgroup analysis by methylguanine-deoxyribonucleic acid methyltransferase (MGMT) promoter gene methylation status showed markedly increased 6-month PFS in subjects with a methylated MGMT promoter gene (21/23 subjects; 91.3%; 95% CI: 72.0, 98.9%) compared to subjects with a nonmethylated MGMT promoter gene (9/22 subjects; 40.9%; 95% CI: 20.7, 63.6%). Other subgroup analyses by age group, ECOG performance score, or extent of tumor resection did not show clinically relevant differences between respective subgroups.

During the addendum period, partial response (PR) was reported for 2 subjects that initially experienced stable disease (SD) before the clinical/survival cut-off (20 Feb 2007). One subject had methylated O6- methylguanine-DNA methyltransferase (MGMT) gene promoter, was 63 years old, had Eastern Cooperative Oncology Group (ECOG)=0 at screening and 1 at last visit, and tumor subtotal resection. One subject had unknown methylation status, was 61 years old, had ECOG=1 at screening and 0 at last visit, and tumor biopsy.

As it was previously described in the CTR v1.0 (2007), time to disease progression was longer in subjects with the methylated MGMT gene promoter (median 407 days) compared to the non-methylated MGMT gene promoter (median 103.5 days). Death due to PD was reported in 17/23 (73.9%) of the subjects with methylated MGMT gene promoter, and in 21/22 (95.5%) of subjects with non-methylated MGMT gene promoter.

Subjects in the age group of < 50 years had a longer median time to disease progression (365.0 days) than subjects in the age group of ≥ 50 years (227.0 days).

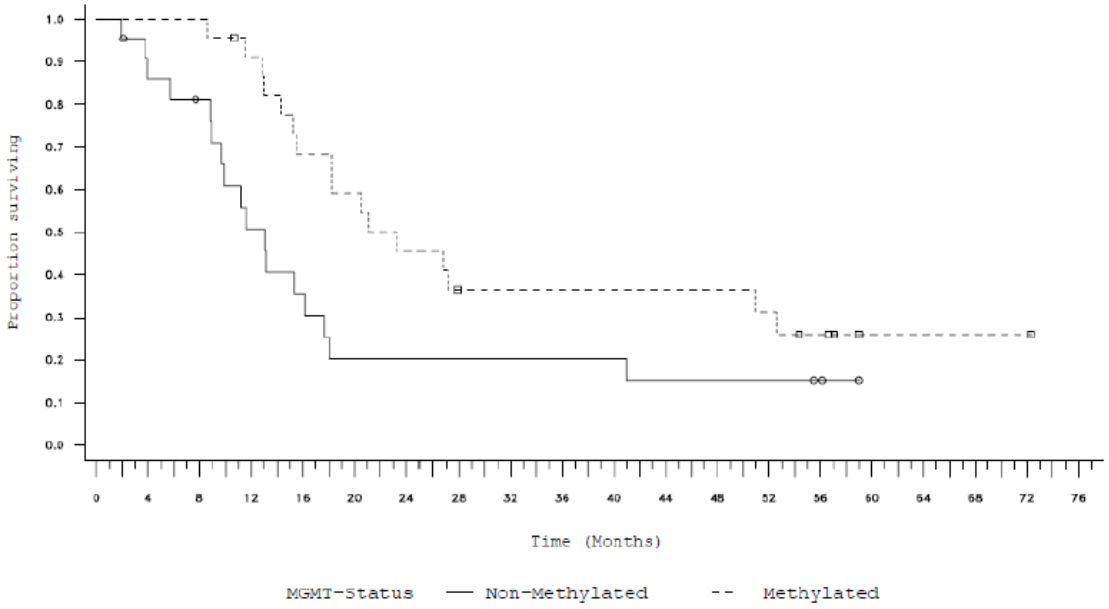
Median time to disease progression decreased from 287.0 days for subjects with baseline ECOG performance score 0 to 203.0 days for subjects with baseline ECOG performance score 1, and to 156.5 days for subjects with baseline ECOG performance score 2. Fewer events of PD or death were observed in subjects with ECOG performance score 0 (80.6%) than in the other 2 groups with higher performance scores (both > 88.0%).

Regarding the extent of tumor resection, median time to disease progression was longest after gross total resection (249.0 days). Time to progression was comparable in the sub total resection and biopsy groups (201.5 days and 203.0 days).

The median overall survival (OS) after end of trial was 16.1 months (95% Confidence Interval [CI]: 13.1, 23.2), and the survival time ranged from 1.9 months to 72.3 months. One subject was alive after 5 years.

Median survival time was longer in subjects with the methylated gene promoter than in subjects with the non-methylated MGMT gene promoter (23.2 months vs. 13.0 months). One subject with the methylated gene promoter was still alive after 5 years.

Figure 1 **Kaplan-Meier Curve: Overall Survival Time by *MGMT* Status (ITT Population)**



Median survival time was higher in the age group < 50 years (19.6 months, 95% CI: 15.2, not calculated) than in the age group ≥ 50 years (14.3 months, 95% CI: 10.9, 26.8).

Median survival time was longer for subjects with ECOG performance score 0 (18.3 months) than for subjects with ECOG performance score 1 (13.2 months) and for subjects with ECOG performance score 2 (8.3 months). Only 1 subject, ECOG performance score 1, was still alive after 5 years.

Median survival time was higher for subjects with gross total resection (18.3 months) than for subjects with biopsy (10.9 months) or for subjects with subtotal resection (13.0 months). Only 1 subject with gross total resection was still alive after 5 years.

Safety Results:

Dropouts: During the course of the study, 29 subjects (55.8%) withdrew. Reasons for study discontinuation were disease progression (19 subjects [36.5%]), AEs (9 subjects [17.3%]), and withdrawal of consent (1 subject [1.9%]).

Adverse Events: All subjects reported at least 1 treatment-emergent adverse event (TEAE), and 28 subjects (54%) reported at least 1 TEAE that the Investigator considered related to study medication. The most frequent TEAEs were nausea (33 subjects [63.5%]), headache (30 [57.7%]), fatigue (22 [42.3%]), constipation (22 [42.3%]), vomiting (20 [38.5%]), alopecia (19 [36.5%]), thrombocytopenia (17 [32.7%]), and anorexia (16 [30.8%]).

A total of 27 subjects (52%) reported NCI-CTCAE Grade 3 or 4 TEAEs, i.e. severe or life-threatening/disabling TEAEs, which were related to study medication in 6 subjects (12%). The

most frequent Grade 3 or 4 TEAEs were thrombocytopenia (6 subjects [11.5%]), leucopenia (4 [7.7%]), lymphopenia, headache, and hemiparesis (3 [5.8%] each). The most frequent related Grade 3 or 4 TEAE was thrombocytopenia (3 [5.8%]).

Serious treatment-emergent adverse events (SAEs) were reported for 32 subjects (62%) and these were considered related to cilengitide by the Investigator for 12 (23%) subjects. The most frequent SAEs were social stay hospitalization (6 subjects [11.5%]), epilepsy (5 [9.6%]), thrombocytopenia, and hemiparesis (4 [7.7%] each). Similarly, most frequent related SAEs were social stay hospitalization (3 [5.8%]) thrombocytopenia, and deep vein thrombosis (2 [3.8%] each).

A total of 15 subjects (28.8%) had a TEAE leading to treatment discontinuation. The most frequent TEAEs leading to treatment discontinuation were headache (3 [5.8%]), thrombocytopenia, general physical health deterioration, aphasia, and deep vein thrombosis (2 [3.8%] each).

Other: There were no findings of concern in analyses of laboratorysafety or vital signs, physical examination, ECG, or chest x-ray assessments.

At the end of trial, the number of subjects who experienced treatment-emergent adverse events (TEAE), related TEAEs, serious AEs (SAE), related SAEs, National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) Grade 3 or 4 AEs, and any TEAEs leading to death were similar to those reported in the main CTR v1.0 (2007) after the clinical/survival cut-off in 2007.

Deaths: At the time of data cut-off for this report, a total of 17 cases of death were observed during this study. Only 2 of these subjects had TEAEs leading to death, and these were not considered related to study medication. The other 15 subjects died due to PD during the survival follow-up, i.e. more than 28 days afterlast dose of cilengitide.

Seventeen deaths were reported during the reporting period covered by the CTR v1.0 (2007), and 23 deaths during the addendum period. PD was the primary cause for all deaths reported during the addendum period. The remaining 12 of the 52 subjects treated were followed up for at least 2 years according to the clinical trial protocol (CTP) Amendment No.2. Five of the 7 subjects treated beyond Week 35 died due to PD. No significant AEs were reported during the addendum period.

During the addendum period, one subject experienced the unrelated SAEs of hemiparesis and somnolence. These events occurred during the 28-day safety follow-up (18 days after the last cilengitide dose), and are known complications and/or symptoms of the underlying disease that could be interpreted as further signs of PD or clinical deterioration. The subject had discontinued trial treatment due to tumor progression before the unrelated SAE occurred.

During the addendum period, one subject experienced abnormal lymphocytes beyond Week 35. Most of the time the abnormality was Grade 2, but sometimes it was Grade 3. The same pattern was observed during the main trial period within the first 35 weeks.

During the addendum period, there were no Grade ≥ 2 clinical chemistry laboratory values reported.

The number of subjects with laboratory values that shifted from Grade ≤ 2 at baseline to NCI-CTCAE Grade ≥ 3 as worst on-treatment, or that shifted from Grade ≤ 2 at baseline to NCI-CTCAE Grade ≥ 3 last on-treatment was the same as those reported in the CTR v1.0 (2007).

Six subjects had significant changes in blood pressure during this period.

Conclusions:

- Taken together, the combination of cilengitide with the recently established standard therapy for newly diagnosed GBM (TMZ combined with RTX, followed by TMZ maintenance treatment) showed clinical activity and was well tolerated. The addition of cilengitide to the standard therapy resulted in an improved 6-month PFS compared with the results from the European Organisation for Research and Treatment of Cancer (EORTC) / National Cancer Institute of Canada (NCIC) study, without substantially altering the safety profile of the standard therapy seen in the EORTC/NCIC study.

- The most promising result of this study, the high 6-month PFS rate in subjects with a methylated MGMT promoter gene, calls for confirmation in a pivotal Phase III study in this subgroup of subjects.

- The combination of cilengitide with temozolomide and radiotherapy, followed by temozolomide maintenance and cilengitide monotherapy, showed long-term clinical activity in terms of prolongation of overall survival time. This effect was more pronounced in subjects with methylated MGMT gene promoter.

- Cilengitide can be safely administered for long periods.