神経膠芽腫に対する　シレンジタイド　の臨床治験

吉田　光一

シレンジタイド

インテグリンαVβ３　および　αVβ５　の　inhibitor

インテグリン

1985年　フィブロネクチンのレセプターとして発見された

細胞膜たんぱく質で細胞接着分子

細胞　⇔　細胞外マトリックス　の細胞接着の主役

構造

α鎖　β鎖　2つのサブユニットからなるヘテロダイマー

多様な組み合わせ　→　インテグリンファミリー

インテグリンの機能は細胞接着が基本であるが、細胞進展、細胞移動、細胞増殖

発生における組織形成、癌の転移、組織修復・血液凝固などの機能に関与

インテグリンαVβ３（ビトロネクチンレセプター）

上皮細胞、メラノーマ、グリオブラストーマ　などで分布する

結合リガンドは、ビトロネクチン、フィブロネクチン、MMP　などなど

創傷治癒、血管新生、骨再生などの生理機能を持つ

増殖性糖尿病性網膜症、手足口病　などで関連が言われている

インテグリンαVβ５

広範な組織に分布

結合リガンドは、ビトロネクチン、TGFβ　など

血管新生や上皮再構築などの生理機能を持つ

増殖性糖尿病性網膜症などで関連が言われている

※細胞外マトリックス分子

フィブロネクチン　ビトロネクチン　ラミニン

コラーゲン　フィブリノーゲン　　など

Neuro-Oncology 15(10):1438–1444, 2013.
doi:10.1093/neuonc/not058
Advance Access publication August 28, 2013

Phase II study of cilengitide in the treatment of refractory or relapsed high-grade gliomas in children: A report from the Children's Oncology Group

Tobey J. MacDonald, Gilbert Vezina, Clinton F. Stewart, David Turner, Christopher R. Pierson, Lu Chen, Ian F. Pollack, Amar Gajjar, and Mark W. Kieran

Department of Pediatric Hematology/Oncology, Aflac Cancer and Blood Disorders Center, Emory University School of Medicine, Atlanta, Georgia (T.J.M.); Department of Radiology, Children's National Medical Center, The George Washington University School of Medicine, Washington, DC (G.V.); Department of Pharmaceutical Sciences, St. Jude Children's Research Hospital, Memphis, Tennessee (C.F.S., D.T.); Department of Laboratory Medicine, Nationwide Children's Hospital, The Ohio State University College of Medicine, Columbus, Ohio (C.R.P.); Statistics, Children's Oncology Group Operations Center, Arcadia, California (L.C.); Department of Neurosurgery, Children's Hospital of Pittsburgh of UPMC, Pittsburgh, Pennsylvania (I.F.P.); Department of Neuro-Oncology, St. Jude Children's Research Hospital, Memphis, Tennessee (A.G.); Department of Pediatric Hematology/Oncology, Dana-Farber Children's Hospital Cancer Center, Boston, Massachusetts (M.W.K.)

Background. Cilengitide, an αv integrin antagonist, has demonstrated activity in recurrent adult glioblastoma (GBM). The Children's Oncology Group ACNS0621 study thus evaluated whether cilengitide is active as a single agent in the treatment of children with refractory high-grade glioma (HGG). Secondary objectives were to investigate the pharmacokinetics and pharmacogenomics of cilengitide in this population.
Methods. Cilengitide (1800 mg/m^2/dose intravenous) was administered twice weekly until evidence of disease progression or unacceptable toxicity. Thirty patients (age range, 1.1–20.3 years) were enrolled, of whom 24 were evaluable for the primary response end point.
Results. Toxicity was infrequent and mild, with the exception of one episode of grade 2 pain possibly related to cilengitide. Two intratumoral hemorrhages were reported, but only one (grade 2) was deemed to be possibly related to cilengitide and was in the context of disease progression. One patient with GBM received cilengitide for 20 months and remains alive with continuous stable disease. There were no other responders, with median time to tumor progression of 28 days (range, 11–114 days). Twenty-one of the 24 evaluable patients died, with a median time from enrollment to death of 172 days (range, 28–325 days). The 3 patients alive at the time of this report had a follow-up time of 37, 223, and 1068 days, respectively.
Conclusions. We conclude that cilengitide is not effective as a single agent for refractory pediatric HGG. However, further study evaluating combination therapy with cilengitide is warranted before a role for cilengitide in the treatment of pediatric HGG can be excluded.

Keywords: childhood, cilengitide, high-grade glioma.

Pediatric high-grade gliomas (pHGGs), including glioblastoma multiforme (GBM) and anaplastic astrocytoma (AA), typically have a dismal prognosis. The 5-year progression-free survival (PFS) rates reported from the Children's Cancer Group (CCG)-945 phase III study, which compared the outcomes in children with

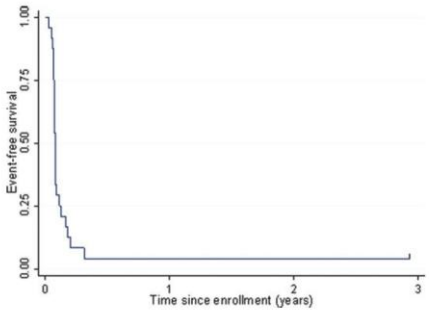


Fig. 1. EFS among patients with pHGG enrolled in ACNS0621.

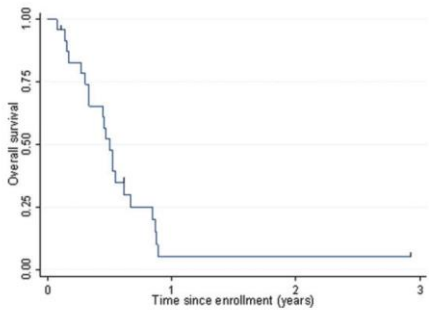


Fig. 2. OS among patients with pHGG enrolled in ACNS0621.

対象は、年齢が 1.13-20.3 歳の再発を繰り返す high grade glioma
cilengitide の monotherapy (週に 2 回　1800mg/m2)therapy
平均生存期間　172 日（28-325 日）

これ論文の他、３-４つの phase II の論文あり
　　いづれも 1800-2000mg/m2 週２回のシレンジタイド投与

Cilengitide combined with standard treatment for patients with newly diagnosed glioblastoma with methylated *MGMT* promoter (CENTRIC EORTC 26071-22072 study): a multicentre, randomised, open-label, phase 3 trial

Roger Stupp, Monika E Hegi, Thierry Gorlia, Sara C Erridge, James Perry, Yong-Kil Hong, Kenneth D Aldape, Benoit Lhermitte, Torsten Pietsch, Danica Grujicic, Joachim Peter Steinbach, Wolfgang Wick, Rafał Tarnawski, Do-Hyun Nam, Peter Hau, Astrid Weyerbrock, Martin J B Taphoorn, Chiung-Chyi Shen, Nalini Rao, László Thurzo, Ulrich Herrlinger, Tejpal Gupta, Rolf-Dieter Kortmann, Krystyna Adamska, Catherine McBain, Alba A Brandes, Joerg Christian Tonn, Oliver Schnell, Thomas Wiegel, Chae-Yong Kim, Louis Burt Nabors, David A Reardon, Martin J van den Bent, Christine Hicking, Andriy Markivskyy, Martin Picard, Michael Weller, for the European Organisation for Research and Treatment of Cancer (EORTC), the Canadian Brain Tumor Consortium, and the CENTRIC study team

Lancet Oncol 2014; 15: 1100–08

Published Online August 20, 2014 http://dx.doi.org/10.1016/S1470-2045(14)70379-1

See Comment page 1044

UniversitätsSpital Zürich, Zurich, Switzerland (Prof R Stupp MD, Prof M Weller MD); **Centre Hospitalier Universitaire Vaudois and University of Lausanne, Lausanne, Switzerland** (Prof R Stupp, M E Hegi PhD, B Lhermitte MD); **EORTC Headquarters, Brussels, Belgium** (T Gorlia PhD); **Edinburgh Cancer Centre, University of Edinburgh, Edinburgh, UK** (S C Erridge MD); **Sunnybrook Health Sciences Centre, Toronto, ON, Canada** (J Perry MD); **The Catholic University of Korea, Seoul St Mary's Hospital, Seoul, South Korea** (Prof Y-K Hong MD); **The University of Texas MD Anderson Cancer Center, Houston, TX, USA** (Prof K D Aldape MD); **Department of Neuropathology, Universität Bonn, Bonn, Germany** (Prof T Pietsch MD, U Herrlinger MD); **Clinic for Neurosurgery, Clinical Center Serbia and Medical Faculty University of Belgrade, Belgrade, Serbia** (Prof D Grujicic MD); **Klinikum**

Summary

Background Cilengitide is a selective αvβ3 and αvβ5 integrin inhibitor. Data from phase 2 trials suggest that it has antitumour activity as a single agent in recurrent glioblastoma and in combination with standard temozolomide chemoradiotherapy in newly diagnosed glioblastoma (particularly in tumours with methylated *MGMT* promoter). We aimed to assess cilengitide combined with temozolomide chemoradiotherapy in patients with newly diagnosed glioblastoma with methylated *MGMT* promoter.

Methods In this multicentre, open-label, phase 3 study, we investigated the efficacy of cilengitide in patients from 146 study sites in 25 countries. Eligible patients (newly diagnosed, histologically proven supratentorial glioblastoma, methylated *MGMT* promoter, and age ≥18 years) were stratified for prognostic Radiation Therapy Oncology Group recursive partitioning analysis class and geographic region and centrally randomised in a 1:1 ratio with interactive voice response system to receive temozolomide chemoradiotherapy with cilengitide 2000 mg intravenously twice weekly (cilengitide group) or temozolomide chemoradiotherapy alone (control group). Patients and investigators were unmasked to treatment allocation. Maintenance temozolomide was given for up to six cycles, and cilengitide was given for up to 18 months or until disease progression or unacceptable toxic effects. The primary endpoint was overall survival. We analysed survival outcomes by intention to treat. This study is registered with ClinicalTrials.gov, number NCT00689221.

Findings Overall, 3471 patients were screened. Of these patients, 3060 had tumour *MGMT* status tested; 926 patients had a methylated *MGMT* promoter, and 545 were randomly assigned to the cilengitide (n=272) or control groups (n=273) between Oct 31, 2008, and May 12, 2011. Median overall survival was 26·3 months (95% CI 23·8–28·8) in the cilengitide group and 26·3 months (23·9–34·7) in the control group (hazard ratio 1·02, 95% CI 0·81–1·29, p=0·86). None of the predefined clinical subgroups showed a benefit from cilengitide. We noted no overall additional toxic effects with cilengitide treatment. The most commonly reported adverse events of grade 3 or worse in the safety population were lymphopenia (31 [12%] in the cilengitide group *vs* 26 [10%] in the control group), thrombocytopenia (28 [11%] *vs* 46 [18%]), neutropenia (19 [7%] *vs* 24 [9%]), leucopenia (18 [7%] *vs* 20 [8%]), and convulsion (14 [5%] *vs* 15 [6%]).

Interpretation The addition of cilengitide to temozolomide chemoradiotherapy did not improve outcomes; cilengitide will not be further developed as an anticancer drug. Nevertheless, integrins remain a potential treatment target for glioblastoma.

Funding Merck KGaA, Darmstadt, Germany.

★ 結果： MGMT メチル化のある新規膠芽腫に対して、現在の標準療法へのシレンジタイドの上乗せ効果は認めない

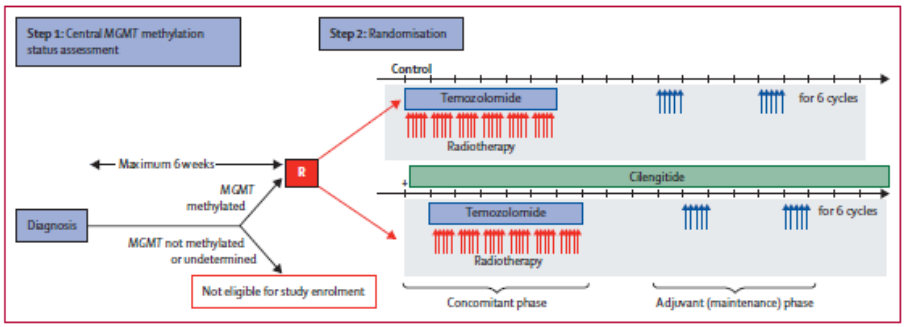
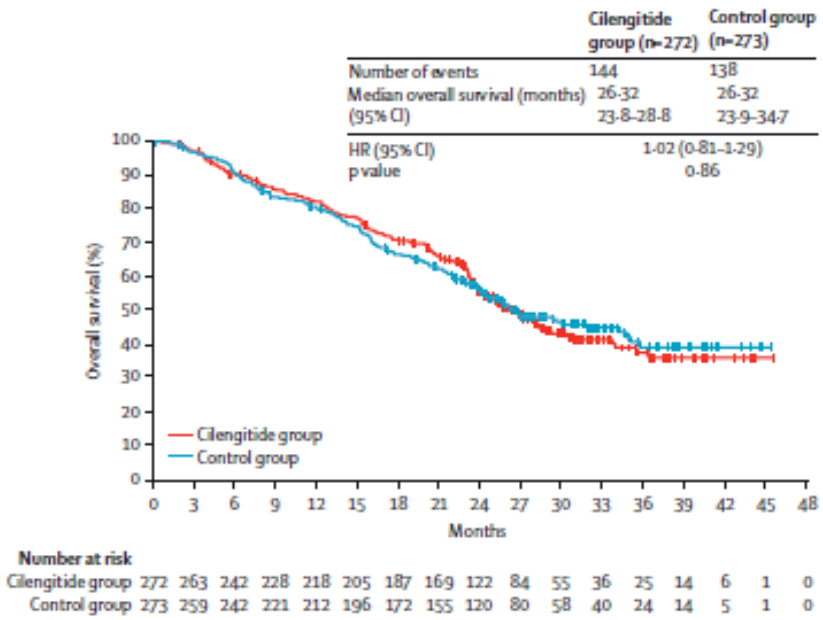


Figure 1: Treatment scheme



2014 年の第 III 相試験の結果　（by Stupp）

25 カ国、146study sites の open-label, phase III study

3471 人の新規 GBM に対する　標準治療（TMZ）への上乗せ効果を検討

＊926 人の metylated MGMT の患者が対象

うち　545 人が study に参加

Cilengitide 群　272 人　controll 群　273 人

週に 2 回　2000mg の dilengitide を静注

mOS はどちらの群も　26.3 ヶ月

side effect は特になし

lymphopenia 31(12%)　vs　26(10%) controll

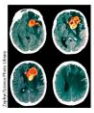
thrombocytopnea 28(11%) vs 46(18%)

neutropenia 19(7%) vs 24(9%)

leucopenia 18(7%) vs 20(8%)

convulsion 14(5%) vs 15(6%)

Cilengitide in glioblastoma: when did it fail?



Published Online
August 20, 2014
http://dx.doi.org/10.1016/
S1470-2045(14)70403-6
See Articles page 1100

Angiogenesis and invasion are both crucial for tumour growth, although more anti-angiogenic drugs have been developed than have drugs with mainly anti-invasive properties. Integrins are a large family of molecules involved in signalling between cells and stromal components, implicated in various processes including tumour angiogenesis and invasion. Many of their receptors are active in both normal and cancerous cells; these molecules are therefore challenging to target. The integrin $\alpha v\beta 3$, involved in angiogenesis in addition to cell migration and proliferation, is expressed at low levels in normal cells and overexpressed in glioblastoma, melanoma, breast, prostate, and pancreatic cancer cells. Cilengitide, one of the few anti-integrin drugs developed to date, selectively inhibits $\alpha v\beta 3$ and $\alpha v\beta 5$. In *The Lancet Oncology*, Roger Stupp and colleagues[1] report the negative results of the CENTRIC phase 3 trial, which assessed the benefit of cilengitide addition to standard care (radiotherapy with concomitant and adjuvant temozolomide chemotherapy) in patients with newly diagnosed glioblastoma. This trial was restricted to patients whose tumour had methylated *MGMT* promoter, an important favourable prognostic factor. Overall survival was similar in both groups (26·3 months [95% CI 23·8–28·8] in the cilengitide group *vs* 26·3 months [23·9–34·7] in the control group; hazard ratio 1·02, 95% CI 0·81–1·29, p=0·86). Additionally, progression-free survival analysis did not detect any activity that could have been diluted in the survival analysis. Although disappointing at this stage of development, these results are in line with the lack of activity of the drug as reported in randomised phase 2 trials in other cancers, leading the drug manufacturer to halt further development of the compound as a cancer treatment.

After such a large effort from all parties, including patients, on a study that benefited from collaboration between industry and academia, how can we interpret these results? First, although the $\alpha v\beta 3$ integrin is present and overexpressed in glioblastoma, targeting of this molecule is complex because of the dose-dependent opposing effects of cilengitide: low doses have been reported to stimulate blood vessel growth and tumour angiogenesis, by contrast with inhibition at higher doses.[2] The two dosing schedules of 500 mg and 2000 mg that have been used in trials of cilengitide in various cancers might not fully reflect the complexity of this dual effect. Second, metabolic imaging and tissue analysis support the suggestion that cilengitide reaches its target; however, little is known about the biological effect of the drug on tumour vasculature or invasiveness in patients. The effects on tumour cell apoptosis and tumour-associated endothelial cell apoptosis seem small and heterogeneous.[2] In preclinical models, the value of adding cilengitide to radiotherapy and temozolomide was inconsistent.[4,5] A recent exploratory analysis of 21 patients with glioblastoma treated with radiotherapy, temozolomide, and cilengitide did not detect a change in pattern of progression compared with historical controls, suggesting a lack of anti-invasive properties of the drug.[6] Whether these findings would be supported by further analysis of the larger dataset of this phase 3 trial is unknown. Moreover, similar to other anti-angiogenic drugs, no reliable biomarker of cilengitide activity has been identified to help isolate the signal of activity. Unfavourable pharmacokinetics of the drug might also partly explain these negative results. Cilengitide has a short half-life of about 2–4 h, which might be suboptimum to fulfil an appropriate anti-angiogenic pressure. Another consequence of the pharmacokinetic properties of cilengitide was that it required intravenous administration twice weekly for patients, hardly suitable for lengthy administration, particularly in the first-line treatment setting.

As stated by Stupp and colleagues, a challenging question that comes from these negative results is why the signal of antitumour activity of cilengitide noted in phase 1 and 2 programmes did not translate into the findings of this phase 3 trial. By contrast with previous trials of cilengitide in pancreatic, prostate, and head and neck cancers, the three phase 2 trials done in glioblastoma did not have a control group without cilengitide.[7–9] In recurrent glioblastoma, the signal of activity came from a modest 6-month progression-free survival of 15% and a radiographic response rate of 13% (both reported with a cilengitide dose of 2000 mg).[7] In patients with newly diagnosed glioblastoma, the signal of activity was interpreted in a small subgroup of patients (n=23) and subsequently compared with a historical non-contemporary control group.[8] In another study, despite a substantially higher signal of activity in recurrent glioblastoma, bevacizumab increased progression-free survival but not overall survival in patients with newly diagnosed tumours, underlining the challenge of improving first-line treatment of patients with glioblastoma.[10]

This trial was restricted to patients with methylated *MGMT* promoter, based mainly on a slightly increased indication of cilengitide activity in this subgroup compared with patients with unmethylated *MGMT* promoter.[8] However, to my knowledge, no biological data have documented an association between *MGMT* status and integrin biology. Moreover, findings from in-vitro studies have suggested that *MGMT* does not change the response of glioma cells to cilengitide, subsequently confirmed in another phase 2 study in which the survival signal of cilengitide activity was noted irrespective of *MGMT* status.[4,6] Tailoring of therapy to patients' individual profiles has generated many achievements (and reached some limits) in oncology in recent years. However, because development of a new agent based on a biomarker needs substantial effort (as reflected, partly, by the fact that only 16% of patients screened were randomly assigned), we should rely on both substantial preclinical research and clinical knowledge for the design of future large registration phase 3 trials based on biomarkers.

Olivier L Chinot
Aix-Marseille University, AP-HM, Department of Neuro-Oncology, CHU Timone, 13005 Marseille, France
olivier.chinot@ap-hm.fr

I have received grants, personal fees, and non-financial support from Roche.

1 Stupp R, Hegi ME, Gorlia T, et al, for the European Organisation for Research and Treatment of Cancer (EORTC), the Canadian Brain Tumor Consortium, and the CENTRIC study team. Cilengitide combined with standard treatment for patients with newly diagnosed glioblastoma with methylated MGMT promoter (CENTRIC EORTC 26071-22072 study): a multicentre, randomised, open-label, phase 3 trial. *Lancet Oncol* 2014; published online Aug 20. http://dx.doi.org/10.1016/S1470-2045(14)70379-1.
2 Reynolds AR, Hart IR, Watson AR, et al. Stimulation of tumour growth and angiogenesis by low concentrations of RGD-mimetic integrininhibitors. *Nat Med* 2009; 15: 392–400.
3 Hariharan S, Gustafson D, Holden S, et al. Assessment of the biological and pharmacological effects of the $\alpha_v\beta_3$ and $\alpha_v\beta_5$ integrin receptor antagonist, cilengitide (EMD 121974), in patients with advanced solid tumors. *Ann Oncol* 2007; 18: 1400–07.
4 Maurer GD, Tritschler I, Adams B, et al. Cilengitide modulates attachment and viability of human glioma cells, but not sensitivity to irradiation or temozolomide in vitro. *Neuro Oncol* 2009; 11: 747–56.
5 Mikkelsen T, Brodie C, Finniss S, et al. Radiation sensitization of glioblastoma by cilengitide has unanticipated schedule-dependency. *Int J Cancer* 2009; 124: 2719–27.
6 Eisele G, Wick A, Eisele AC, et al. Cilengitide treatment of newly diagnosed glioblastoma patients does not alter patterns of progression. *J Neurooncol* 2014; 117: 143–45.
7 Reardon DA, Fink KL, Mikkelsen T, et al. Randomized phase II study of cilengitide, an integrin-targeting arginine-glycine-aspartic acid peptide, in recurrent glioblastoma multiforme. *J Clin Oncol* 2008; 26: 5610–17.
8 Stupp R, Hegi ME, Neyns B, et al. Phase I/IIa study of cilengitide and temozolomide with concomitant radiotherapy followed by cilengitide and temozolomide maintenance therapy in patients with newly diagnosed glioblastoma. *J Clin Oncol* 2010; 28: 2712–18.
9 Nabors LB, Mikkelsen T, Hegi ME, et al. A safety run-in and randomized phase 2 study of cilengitide combined with chemoradiation for newly diagnosed glioblastoma (NABTT 0306). *Cancer* 2012; 118: 5601–07.
10 Chinot OL, Wick W, Mason W, et al. Bevacizumab plus radiotherapy-temozolomide for newly diagnosed glioblastoma. *N Engl J Med* 2014; 370: 709–22.

直後の Lancet-Oncology　2014

Integrin　αVβ３　⇒血管新生　浸潤　増殖　に関与

GBM　melanoma, brest, prostate, pancreatic cancer cell　で発現

★dosedependent opposing effect

low doses：stimulate blood vessel growth and tumor angiogenesis

high doses:contrast with inhibition

little is known about the biological effect of the drug on tumor vasculature or invasiveness

Cilengitide の half-life は　2-4 時間

methyleated MGMT に症例が限られている

⇒slightly increased indication of cilengitide activity in this subgroup

Does cilengitide deserve another chance?

We read with interest the results of the CENTRIC study by Stupp and colleagues[1] which investigated the efficacy of cilengitide in patients with late-stage glioblastoma. Cilengitide is a cyclic RGD-containing peptide that binds cancer cells expressing high concentrations of αVβ3 and αVβ5 integrins. These integrins are also a marker of enhanced invasiveness and metastatic behaviour of the tumour. Clinical trials with cilengitide in patients with either lung cancer or metastatic melanoma or recurrent or metastatic head and neck tumours, showed little effect on overall survival, whereas preliminary data in advanced glioblastoma seemed to suggest an effect on overall survival.[2] The multicentre, randomised, open-label phase 3 CENTRIC trial[1] investigated the potential benefit of the combination of cilengitide with standard treatment in patients newly diagnosed with glioblastoma with methylated *MGMT* promoter.[1] However, results of this study have not shown cilengitide to be better in terms of progression-free survival or overall survival than the standard treatment. Thus, Stupp and colleagues[1] suggested not pursuing the testing of cilengitide in further anticancer clinical trials.

However, the failure of cilengitide in patients with glioblastoma could depend on several factors. First, the short half-life and pharmacokinetic profile of the peptide restricts its anti-angiogenic properties, and thus needs to be given two times a week. Second, the use of cilengitide at low dose apparently stimulates angiogenesis, whereas the best inhibitory effect was achieved by higher drug concentrations. Third, little data has described the role of *MGMT* methylation on the activation of αVβ3, which might explain the negative results of the CENTRIC trial.[1]

On the basis of the ability of αVβ3 to drive the resorbing properties of osteoclasts recruited within the bone metastatic niche in osteotropic tumours—including breast cancer, prostate cancer, and multiple myeloma—we suggest the potential of cilengitide should be further considered in cancer treatment. As previously reported, αVβ3 activation within the tumour microenvironment is crucial for the formation of a so-called viscious cycle that propagates the development of metastatic lesions of the bone. Additionally, Bäuerle and colleagues[3] showed that in-vitro and in-vivo blocking of αVβ3 restrains the propensity of breast cancer cells to colonise the bone as result of the defective resorptive functions of osteoclasts, which reduces angiogenesis and proliferation. In our study,[4] we reported that αVβ3 activation by many myeloma cells induces their differentiation into osteoclast-like bone resorbing cells, leading to the hyperactivation of osteoclastogenesis. Moreover, our preliminary investigation of the role of cilengitide in this multiple myeloma model showed the ability of cilengitide to disable erosive properties of osteoclasts.[5] The main effect of cilengitide is on the inhibition of adhesion without affecting proliferation, as shown by exploring the αVβ3-dependent and αVβ5-dependent intracellular signalling.[5] This mechanism could explain, at least in part, the slight effects of cilengitide in reducing the proliferative extent of glioblastoma cells. These preliminary data suggest the potential role of cilengitide in restraining the development of bone disease in multiple myeloma. Additional future trials could be proposed for treatment or delay of the skeletal complications in patients with haematological and solid tumours.

We declare no competing interests.

Marco Tucci, Stefania Stucci, Franco Silvestris
marco.tucci@uniba.it
Department of Biomedical Sciences and Clinical Oncology, University of Bari 'Aldo Moro', 11-70124 Bari, Italy

1 Stupp R, Hegi ME, Gorlia T, et al, for the European Organisation for Research and Treatment of Cancer (EORTC) the Canadian Brain Tumor Consortium, and the CENTRIC study team. Cilengitide combined with standard treatment for patients with newly diagnosed glioblastoma with methylated MGMT promoter (CENTRIC EORTC 26073-22072 study): a multicentre, randomised, open-label, phase 3 trial. *Lancet Oncol* 2014; 15: 1100–08.
2 Reardon DA, Neyns B, Weller M, Tonn JC, Nabors LB, Stupp R. Cilengitide: an RGD pentapeptide αvβ3 and αvβ5 integrin inhibitor in development for glioblastoma and other malignancies. *Future Oncol* 2011; 7: 339–54.
3 Bäuerle T, Komljenovic D, Merz M, Berger MR, Goodman SL, Semmler W. Cilengitide inhibits progression of experimental breast cancer bone metastasis as imaged non-invasively using VCT, MRI and DCE-MRI in a longitudinal in vivo study. *Int J Cancer* 2011; 128: 2453–62.
4 Tucci M, De Palma R, Lombardi L, et al. β3 integrin subunit mediates the bone-resorbing function exerted by cultured myeloma plasma cells. *Cancer Res* 2009; 69: 6718–26.
5 Stucci LS, Tucci M, Vecchio M, et al. The αvβ3/αvβ5 blockage by Cilengitide disables the osteoclast-like differentiation of malignant plasma cells in multiple myeloma. *Eur J Cancer* 2013; 49 (suppl 2): 5759–5782.

Authors' reply

We thank Marco Tucci and colleagues for their comments about our trial.[1] Results of the 10-year clinical development programme for cilengitide were sobering and raise questions about the prerequisites for a candidate drug to go forward. On the basis of preclinical evidence, tumour types in which angiogenesis, cell adhesion, and migration play an important part were chosen for further clinical development. On one hand and in retrospect, maybe insufficient attention was given to pharmacokinetics. A twice weekly schedule of intravenous administration of a drug with a short half-life of only a few hours might have been suboptimal. A different formulation or a continuous infusion schedule could be more appropriate. On the other hand, preclinical models for orthotopic glioblastoma suggested potential efficacy of combination treatments for intermittent or even single doses of cilengitide with irradiation.[2] Results from clinical exposure data from resected tumour specimens (after previous cilengitide treatment) had suggested a prolonged exposure of the tumour tissue in patients with glioblastoma.[3] In our trial,[1] we used an intermediate-high dose of cilengitide (2000 mg twice weekly), a dose that in two randomised phase 2 trials[4,5] had extended progression-free and overall survival compared with the four times lower, low-intermediate dose (500 mg twice weekly).

The decision to proceed with a phase 3 assessment of cilengitide in glioblastoma still had to be made without the availability of a previous controlled trial,[6] and reference comparisons were made between non-contemporary, non-randomised comparisions and previous experiences or clinical trials. The absence of a sufficient signal of activity in randomised phase 2 trials in pancreas, head and neck, and lung cancer halted further, large-scale investigations.

The reasons for failure of cilengitide in the clinic can only be speculated on; however, this trial[1] emphasises, once again, the limitations of preclinical models and the restriction of their predictive power for efficacy in the clinic. Determination of the correct dose and schedule of a drug is essential, but far from trivial. Targeted drugs are often developed without trying to, or being able to, identify a relevant predictive biomarker. Funding and investment in early clinical phases is insufficient to allow for efficient and successful transition from the laboratory to real-world use. Crucial assessments of tissue distribution of a new drug and its effect on the target are further hampered by false ethical concerns, which prohibit repeat biopsy and additional blood samples, thereby leading to exposure of more patients to ineffective drugs. Although substantial resources are easily attributed to late stages of drug development, funding in the early stages is often too restricted.[7,8]

Tucci and colleagues[9] and Bäuerle and colleagues[10] have shown that lytic bone lesions in myeloma plasma cells and in bone metastases from breast and prostate cancer are associated with the overexpression of αVβ3 integrins, and that this effect can be abrogated by integrin silencing in vitro. Osteoclast activation might in part be mediated by integrin expression, and abrogated by specific inhibition of αVβ3 integrins by cilengitide; whether this can be translated into a clinically meaningful effect is yet to be determined. However, the limitations of the pharmacokinetic properties of cilengitide remain.

Integrin inhibition, per se, should not be discarded as a treatment strategy in glioblastoma or other malignancies; however, drugs other than cilengitide with a longer half-life might be more appropriate for future approaches.

RS declares expenses in relationship with the study from Merck KGaA and has served on advisory boards for Roche, MSD/Merck & Co, and Novartis. MP is employed by Merck KGaA. MW declares consultant or advisory roles for Isarna, Merck Serono, Roche, and Magforce, personal fees from Merck Serono, Roche, MSD, and Magforce, and research funding from Bayer, Merck Serono, Roche, MSD, and Isarna.

Roger Stupp, Martin Picard, Michael Weller
Roger.Stupp@usz.ch
University Hospital Zurich, 8006 Zurich, Switzerland (RS, MW); European Organisation for Research and Treatment of Cancer, Brussels, Belgium (RS, MW); and Merck KGaA, Darmstadt, Germany (MP)

1 Stupp R, Hegi ME, Gorlia T, et al, for the European Organisation for Research and Treatment of Cancer (EORTC); Canadian Brain Tumor Consortium; CENTRIC study team. Cilengitide combined with standard treatment for patients with newly diagnosed glioblastoma with methylated MGMT promoter (CENTRIC EORTC 26073-22072 study): a multicentre, randomised, open-label, phase 3 trial. *Lancet Oncol* 2014; 15: 1100–08.
2 Mikkelsen T, Brodie C, Finniss S, et al. Radiation sensitization of glioblastoma by cilengitide has unanticipated schedule-dependency. *Int J Cancer* 2009; 124: 2719–27.
3 Gilbert MR, Kuhn J, Lamborn KR, et al. Cilengitide in patients with recurrent glioblastoma: the results of NABTC 03-02, a phase II trial with measures of treatment delivery. *J Neurooncol* 2012; 106: 147–53.
4 Reardon DA, Fink KL, Mikkelsen T, et al. Randomized phase II study of cilengitide, an integrin-targeting arginine-glycine-aspartic acid peptide, in recurrent glioblastoma multiforme. *J Clin Oncol* 2008; 26: 5610–17.
5 Nabors LB, Mikkelsen T, Hegi ME, et al. A safety run-in and randomized phase 2 study of cilengitide combined with chemoradiation for newly diagnosed glioblastoma (NABTT 0306). *Cancer* 2012; 118: 5601–07.
6 Stupp R, Hegi ME, Neyns B, et al. Phase I/IIa study of cilengitide and temozolomide with concomitant radiotherapy followed by cilengitide and temozolomide maintenance therapy in patients with newly diagnosed glioblastoma. *J Clin Oncol* 2010; 28: 2712–18.
7 Lacombe D, Burock S, Meunier F. Academia-industry partnerships: are we ready for new models of partnership? the point of view of the EORTC, an academic clinical cancer research organisation. *Eur J Cancer* 2013; 49: 1–07.
8 Lacombe D, Tejpar S, Salgado R, et al. European perspective for effective cancer drug development. *Nat Rev Clin Oncol* 2014; 11: 492–98.
9 Tucci M, De Palma R, Lombardi L, et al. beta(3) Integrin subunit mediates the bone-resorbing function exerted by cultured myeloma plasma cells. *Cancer Res* 2009; 69: 6718–26.
10 Bäuerle T, Komljenovic D, Merz M, Berger MR, Goodman SL, Semmler W. Cilengitide inhibits progression of experimental breast cancer bone metastasis as imaged noninvasively using VCT, MRI and DCE-MRI in a longitudinal in vivo study. *Int J Cancer* 2011; 128: 2453–62.

Lancet Oncology 2014（その 2）

cilengitide: lung cancer/ metastatic melanoma/ recurrent or metastatic head and neck tumor で overall survival に little effect を示した

CENTRIC で negative data が出た原因

- cilengitide の半減期が短すぎて十分な効果を発揮できていない
- low dose では angiogenesis をむしろ stimulate (high dose が必要)
- MGMT methylated の症例に限られている

to their study (multiple myeloma model)

- disable erosive properties of osteoclasts

⇒the main effect of cilengitide is on the inhibition of adhesion without addecting proliferation（増殖抑制に過度に期待されすぎている）

⇒cilengitide の方向は、skeletal complication with haematological and solid tuor へ？

Author's(Stupp) reply

- 半減期や薬物動態に関しては、preclinical model で期待されたものと違った
- 投与量は phase II の結果をもとに
  - (single arm のものしかなかった ⇒検討の余地)
- 新しい biomarker や longer half-life のインテグリン阻害薬が必要

Neuro-Oncology

Neuro-Oncology 17(5), 708–717, 2015
doi:10.1093/neuonc/nou356
Advance Access date 11 March 2015

Two cilengitide regimens in combination with standard treatment for patients with newly diagnosed glioblastoma and unmethylated *MGMT* gene promoter: results of the open-label, controlled, randomized phase II CORE study

L. Burt Nabors, Karen L. Fink, Tom Mikkelsen, Danica Grujicic, Rafal Tarnawski, Do Hyun Nam, Maria Mazurkiewicz, Michael Salacz†, Lynn Ashby, Vittorina Zagonel, Roberta Depenni, James R. Perry, Christine Hicking, Martin Picard, Monika E. Hegi, Benoit Lhermitte, and David A. Reardon

University of Alabama at Birmingham, Birmingham, Alabama (L.B.N.); Baylor University Medical Center, Dallas, Texas (K.L.F.); Henry Ford Hospital, Detroit, Michigan (T.M.); Clinic for Neurosurgery, Clinical Center of Serbia, Medical Faculty University of Belgrade, Belgrade, Serbia (D.G.); Maria Sklodowska-Curie Memorial Cancer Center and Institute of Oncology Gliwice Branch, Radiotherapy and Chemotherapy Clinic, Gliwice, Poland (R.T.); Samsung Medical Center, Seoul, South Korea (D.H.N.); Centrum Onkologii Ziemi Lubelskiej, Lublin, Poland (M.M.); St. Luke's Brain Tumor Center, St. Luke's Hospital, Kansas City, Missouri (M.S.); Barrow Neurological Institute, Phoenix, Arizona (L.A.); Medical Oncology Unit 1, IOV, IRCCS, Padova, Italy (V.Z.); Policlinico di Modena, Modena, Italy (R.D.); Sunnybrook Health Sciences Centre, Toronto, Ontario, Canada (J.R.P.); Merck KGaA, Darmstadt, Germany (C.H., M.P.); Department of Clinical Neurosciences, University Hospital Lausanne, Lausanne, Switzerland (M.E.H.); Institute of Pathology, University Hospital Lausanne, Lausanne, Switzerland (B.L.); Dana-Farber Cancer Institute, Boston, Massachusetts (D.A.R.)

Corresponding Author: Louis Burt Nabors, MD, UAB Department of Neurology, SC 350, 1720 2nd Ave South, Birmingham, AL 35294 (bnabors@uab.edu).

†**Current Institution:** University of Kansas, Kansas City, Kansas.

See the editorial by Mason, on pages 634–635.

Background. Survival outcomes for patients with glioblastoma remain poor, particularly for patients with unmethylated *O*^{6}*-methylguanine-DNA methyltransferase (MGMT)* gene promoter. This phase II, randomized, open-label, multicenter trial investigated the efficacy and safety of 2 dose regimens of the selective integrin inhibitor cilengitide combined with standard chemoradiotherapy in patients with newly diagnosed glioblastoma and an unmethylated *MGMT* promoter.

Methods. Overall, 265 patients were randomized (1:1:1) to standard cilengitide (2000 mg 2×/wk; $n = 88$), intensive cilengitide (2000 mg 5×/wk during wk 1−6, thereafter 2×/wk; $n = 88$), or a control arm (chemoradiotherapy alone; $n = 89$). Cilengitide was administered intravenously in combination with daily temozolomide (TMZ) and concomitant radiotherapy (RT; wk 1−6), followed by TMZ maintenance therapy (TMZ/RT→TMZ). The primary endpoint was overall survival; secondary endpoints included progression-free survival, pharmacokinetics, and safety and tolerability.

Results. Median overall survival was 16.3 months in the standard cilengitide arm (hazard ratio [HR], 0.686; 95% CI: 0.484, 0.972; $P = .032$) and 14.5 months in the intensive cilengitide arm (HR, 0.858; 95% CI: 0.612, 1.204; $P = .3771$) versus 13.4 months in the control arm. Median progression-free survival assessed per independent review committee was 5.6 months (HR, 0.822; 95% CI: 0.595, 1.134) and 5.9 months (HR, 0.794; 95% CI: 0.575, 1.096) in the standard and intensive cilengitide arms, respectively, versus 4.1 months in the control arm. Cilengitide was well tolerated.

Conclusions. Standard and intensive cilengitide dose regimens were well tolerated in combination with TMZ/RT→TMZ. Inconsistent overall survival and progression-free survival outcomes and a limited sample size did not allow firm conclusions regarding clinical efficacy in this exploratory phase II study.

Keywords: cilengitide, newly diagnosed glioblastoma, randomized phase II study, unmethylated *MGMT* promoter.

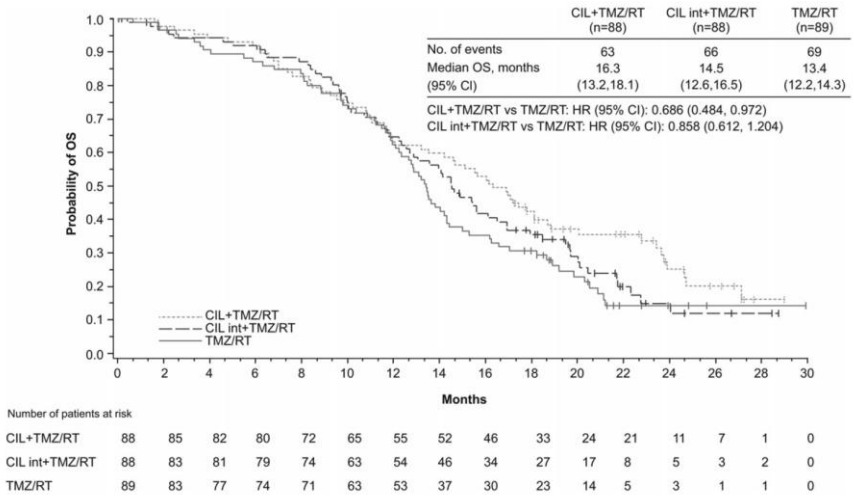


Fig. 2. Kaplan–Meier estimate for OS in the 3 treatment arms of the CORE phase II study. CIL, cilengitide; int, intensive.

Table 2. Treatment-emergent adverse events (safety population)

	Standard Cilengitide Arm ($n = 89$[a])	Intensive Cilengitide Arm ($n = 81$)	Control Arm ($n = 85$)
TEAEs, *n* (%)			
All	88 (98.9)	80 (98.8)	82 (96.5)
Study treatment[b]–related	70 (78.7)	64 (79.0)	56 (65.9)
Serious TEAEs, *n* (%)			
All	47 (52.8)	36 (44.4)	30 (35.3)
Study treatment*–related	13 (14.6)	4 (4.9)	5 (5.9)
NCI-CTCAE grade 3 or 4 TEAEs, *n* (%)			
All	57 (64.0)	47 (58.0)	45 (52.9)
Study treatment[b]–related	25 (28.1)	19 (23.5)	17 (20.0)
TEAEs leading to death, *n* (%)			
All	8 (9.0)	8 (9.9)	5 (5.9)
Study treatment[b]–related	2 (2.2)	2 (2.5)	1 (1.2)

Abbreviation: NCI-CTCAE, National Cancer Institute's Common Terminology Criteria for Adverse Events.
[a]Includes 3 patients who were randomized to cilengitide intensive treatment but actually received cilengitide standard treatment; they were therefore allocated to the cilengitide standard treatment group for the safety population.
[b]Cilengitide, radiotherapy, or temozolomide.

Phase II, randomized, open-label, multicenter trial

新規の MGMT unmetile の症例への efficacy と safety を検討

265 症例を 3 群に

週 2 回 2000mg の cilengitide と 週 5 回 2000mg の cilengitide と controll

	Standard	Intensive	Controll
mOS	16.3m	14.5m	13.4m
PFS	5.6m	5.9m	41m

side effect：well tolerated