Patupilone (Epothilone B) for recurrent glioblastoma: Clinical outcome and translational analysis of a single-institution phase I/II trial

Oehler, C; Frei, K; Rushin, E J; McSheehy, P M J; Weber, D; Allegrini, P R; Weniger, D; Lütolf, U M; Knuth, A; Yonekawa, Y; Barath, K; Broggini-Tenzer, A; Pruschy, M; Hofer, S

Abstract: Background: Patients with glioblastoma (GBM) inevitably develop recurrent or progressive disease after initial multimodal treatment and have a median survival of 6-9 months from time of progression. To date, there is no accepted standard treatment for GBM relapse or progression. Patupilone (EPO906) is a novel natural microtubule-stabilizing cytotoxic agent that crosses the blood-brain barrier and has been found to have preclinical activity in glioma models. Methods: This is a single-institution, early-phase I/II trial of GBM patients with tumor progression who qualified for second surgery with the goal of evaluating efficacy and safety of the single-agent patupilone (10 mg/m², every 3 weeks). Patients received patupilone 1 week prior to second surgery and every 3 weeks thereafter until tumor progression or toxicity. Primary end points were progression-free survival (PFS) and overall survival (OS) at 6 months as well as patupilone concentration in tumor tissue. Secondary end points were toxicity, patupilone concentration in plasma and translational analyses for predictive biomarkers. Results: Nine patients with a mean age of 54.6 ± 8.6 years were recruited between June 2008 and April 2010. Median survival and 1-year OS after second surgery were 11 months (95% CI, 5-17 months) and 45% (95% CI, 14-76), respectively. Median PFS was 1.5 months (95% CI, 1.3-1.7 months) and PFS6 was 22% (95% CI, 0-46), with 2 patients remaining recurrence-free at 9.75 and 22 months. At the time of surgery, the concentration of patupilone in tumor tissue was 30 times higher than in the plasma. Tumor response was not predictable by the tested biomarkers. Treatment was generally well tolerated with no hematological, but cumulative, though reversible sensory neuropathy grade 3 was seen in 2 patients (22%) at 8 months and grade 4 diarrhea in the 2nd patient (11%). Non-patupilone-related peri-operative complications occurred in 2 patients resulting in discontinuation of patupilone therapy. There were no neurocognitive changes 3 months after surgery compared to baseline. Conclusions: In recurrent GBM, patupilone can be given safely pre- and postoperatively. The drug accumulates in the tumor tissue. The treatment results in long-term PFS in some patients. Patupilone represents a valuable novel compound which deserves further evaluation in combination with radiation therapy in patients with GBM.

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Patupilone (Epothilone B) for Recurrent Glioblastoma: Clinical Outcome and Translational Analysis of a Single-Institution Phase I/II Trial

Christoph Oehler a, Karl Frei b, Elisabeth J. Rushing c, Paul M.J. McSheehy g, Dirk Weber g, Peter R. Allegrini g, Dorothea Weniger d, Urs M. Lütolf a, Alexander Knuth e, Yasuhiro Yonekawa b, Krisztina Barath f, Angela Brogini-Tenzer a, Martin Pruschy a, Silvia Hofer e

Departments of a Radiation Oncology, b Neurosurgery, c Neuropathology, d Neurology, e Oncology and f Neuroradiology, University Hospital Zürich, Zürich, and g Department of Clinical Development Oncology, Novartis Pharma AG, Basel, Switzerland

Abstract

Background: Patients with glioblastoma (GBM) inevitably develop recurrent or progressive disease after initial multimodal treatment and have a median survival of 6–9 months from time of progression. To date, there is no accepted standard treatment for GBM relapse or progression. Patupilone (EPO906) is a novel natural microtubule-stabilizing cytotoxic agent that crosses the blood-brain barrier and has been found to have preclinical activity in glioma models.

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Results: Nine patients with a mean age of 54.6 ± 8.6 years were recruited between June 2008 and April 2010. Median survival and 1-year OS after second surgery were 11 months (95% CI, 5–17 months) and 45% (95% CI, 14–76), respectively. Median PFS was 1.5 months (95% CI, 1.3–1.7 months) and PFS6 was 22% (95% CI, 0–46), with 2 patients remaining recurrence-free at 9.75 and 22 months. At the time of surgery, the concentration of patupilone in tumor tissue was 30 times higher than in the plasma. Tumor response was not predictable by the tested biomarkers. Treatment was generally well tolerated with no hematological, but cumulative, though reversible sensory neuropathy grade ≥3 was seen in 2 patients (22%) at 8 months and grade 4 diarrhea in the 2nd patient (11%). Non-patupilone-related peri-operative complications occurred in 2 patients resulting in discontinuation of patupilone therapy. There were no neurocognitive changes 3 months after surgery compared to baseline.

Conclusions: In recurrent GBM, patupilone can be given safely pre- and postoperatively. The drug accumulates in the tumor tissue. The treatment results in long-term PFS in some patients. Patupilone represents a valuable novel compound which deserves further evaluation in combination with radiation therapy in patients with GBM.
Introduction

Patients with glioblastoma (GBM) inevitably develop recurrent or progressive disease after initial treatment, which comprises gross tumor resection followed by radiation therapy (RT), and concomitant and adjuvant temozolomide (TMZ) [1]. At recurrence, median overall survival (OS) is approximately 6–9 months [2–5]. To date, there is no standard treatment for recurrent disease.

A variety of treatment modalities have been investigated for recurrent GBM. Most commonly, systemic therapy is used, while some institutions apply a second round of local treatment, including second surgery, second RT or experimental local treatment options [6]. Second surgery alone results in very limited survival prolongation requiring additional postoperative systemic therapy [7, 8]. Treatments offered are TMZ, nitrosoureas, PCV (procarbazine, CCNU and vincristine), cyclophosphamide, platinum-based regimens or, more recently, bevacizumab, an antibody against VEGF [9]. Following single-agent therapy, progression-free survival (PFS) at 6 months results range from 20 to 30% without bevacizumab and up to 45% with bevacizumab [4].

Patupilone is a novel, well-tolerated microtubule-stabilizing agent belonging to the group of epothilones, which are not cross-resistant with taxanes. They are currently being tested in phase I–III trials [10, 11]. Patupilone has a higher affinity for the βIII-tubulin subunit of microtubules than the taxanes and has been shown to be active in βIII-tubulin-overexpressing cell lines [12]. It has a long half-life (89 h) in tumor tissue and is known to cross the blood-brain barrier in mice, rats and dogs [13]. Preclinical studies have demonstrated activity against glioma/medulloblastoma cell lines as well as multidrug-resistant cell lines due to the independency of patupilone of the efflux pump P-glycoprotein, which is abundant in glioma cells and the blood-brain barrier [13–15]. Patupilone is cytotoxic to ex vivo GBM cell cultures [K. Frei, pers. commun.] and murine intracranial tumors [16, 17].

Furthermore, patupilone is known to have anti-angiogenic effects via paracrine activity at the level of VEGF secretion and other factors [18, 19]. This anti-angiogenic activity can be detected by magnetic resonance imaging (MRI) [20–22]. Of note, the effect of patupilone is independent of tumor hypoxia [18]. Combination therapy of patupilone with other agents such as imatinib or ionizing radiation results in synergistically enhanced effects against subcutaneous experimental tumor xenografts, e.g. rat C6 gliomas and medulloblastomas [15, 23]. In a phase I trial in patients with central nervous system malignancies, combined treatment with ionizing radiation was well tolerated and safe, which supports further study of this regimen in the upfront setting in GBM [24].

Patients and Methods

Study Design and Patient Selection

The study was designed as a single-institution (University Hospital Zürich), open-label, early-phase I–II study of patupilone to explore single-agent activity, toxicity, pharmacokinetics and correlative translational biomarkers in GBM patients at first recurrence/progression after standard surgery and chemoradiation according to the EORTC 22981/26981 protocol [1]. Eligible patients were adults (>18 years) with a histologically proven GBM according to World Health Organization (WHO) criteria (2007), radiologically (MRI) measurable tumor ≥ 2 cm and eligibility for second surgery. Patients requiring enzyme-inducing anti-epileptic therapy were switched to a non-enzyme-inducing compound. Other eligibility criteria included a WHO performance status of 0–1, normal hematological function (leukocytes ≥ 3 × 10^9 cells/l, platelets ≥ 100 × 10^9 cells/l, hemoglobin ≥ 9 g/dl) and adequate hepatic (bilirubin <1.5 × upper limit of the normal (ULN) range, alkaline phosphatase and transaminases (ASAT-ALAT) <2.5 × ULN) and renal function (serum creatinine <1.5 × ULN; fig. 1). All patients gave written informed consent and the study was approved by the local ethics committee. The study was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice Guidelines. The trial was registered at clinicaltrials.gov (NCT00715013). The protocol was amended for more rigorous dose adjustments following grade 4 diarrhea in patient 2.

End Points

Primary end points were patupilone concentration in glioma tissue with respect to its level in the blood, and PFS and OS at 4 and 6 months. Secondary end points included pharmacokinetics of patupilone in plasma, toxicity/safety, neurocognitive changes, predictive biomarkers and MRI-based evaluation of blood volume parameters before and after the first patupilone dose. Adverse events were recorded according to the National Cancer Institute-Common Toxicity Criteria (version 3.0).

Statistical Analysis

Initially, the study was intended as a two-sided, two-stage trial: 16 patients in the first step and another 16 patients in the second step, resulting in a total of 32 patients. The number of patients was calculated for P1 = 25% as the lowest response probability (which if true implied that therapeutic activity warranted further investigation) and P0 = 5% as the largest response probability (which if true implied that the therapeutic activity does not warrant further investigation). α and β errors chosen were 5 and 10%, respectively. The study was terminated prematurely and only descriptive statistics were used due to the small number of patients. PFS and OS were calculated from the time of second surgery to disease progression or death (last update November 2011) according to the Kaplan-Meier method using SPSS (IBM SPSS statistics 19).
Patupilone (EPO906) was administered in a ready-made solution of PEG-300 (10 mg/4 ml) during a 20-min infusion at a total dose of 10 mg/m² i.v. every 3 weeks. No specific premedication (e.g. antihistamines or anti-emetics) was recommended. Patients received patupilone at least 5 days prior to the second surgery. Patupilone was provided by Novartis, Basel, Switzerland. Baseline tumor imaging with MRI was carried out within 14 days before treatment start and every 2 months thereafter. Treatment was continued every 3 weeks until tumor progression, toxicity or patient refusal. In the event of any toxic manifestation (e.g. diarrhea or neuropathy), patupilone was reduced according to the protocol. The protocol was amended after the 2nd patient developed grade 4 diarrhea by prolonging the interval between surgery and the next patupilone dose from 3 to 4 weeks, a more rigorous medical history of stool habits was obtained and loperamide prophylaxis was prescribed for loose stools.

Salvage treatment after patupilone consisted of bevacizumab, CCNU, a second RT round or surgery.

Evaluation
Clinical evaluation before each patupilone cycle included physical and neurological examination. Neuropsychological assessment was carried out before and 3 months after surgery during ongoing patupilone treatment. The 3-month time point was scheduled early to minimize overlapping neurocognitive dysfunction due to tumor progression. This assessment comprised the examination of expressive and receptive language functions with an abridged version of the Aachen Aphasia Test [25], an evaluation of verbal and visual memory functions with the Rey Auditory-Verbal Learning Test and the Rey Visual Design Learning Test, and an appraisal of executive functioning with a set of tests that tap sustained and selective attention and conceptual flexibility. Visual-spatial abilities were evaluated with the Rey-Osterrieth Complex Figure Test, a visual search test (Bells Test) and a simple line bisection task.

Complete blood count and blood chemistry were assessed before each chemotherapy cycle. For pharmacokinetic analysis, plasma concentrations of patupilone were determined on cycle 1 and 2 prior to infusion, at the end of infusion, and at 1, 2, 120, 168 and 504 h. Patupilone concentration in frozen tumor tissue, which was obtained during the second surgery, was analyzed using a high-performance liquid chromatography tandem mass spectrometry, as described by Blum et al. [26].

Relative tumor blood volume (rTBV) was measured using a dynamic contrast-enhanced MRI (1.5-tesla GE scanner) prior to

**Fig. 1.** Study design. DCE = Dynamic contrast enhancement; KPS = Karnofsky performance status.
and at least 120 h after the first patupilone dose. Dynamic multislice, T₁*-weighted echoplanar imaging was performed using the following acquisition parameters: TE: 55 ms, temporal resolution TR: 1.5–7.5 s, number of repetitions: 40 or 50, field of view: 241 × 241 mm² and slice thickness: 3–5 mm. The number of slices was chosen so as to capture the entire brain, i.e. 28–52 slices. Images were obtained before contrast enhancement and after intravenous injection of 20 ml Gd chelate (Dotarem, 0.5 mmol/ml) as a single bolus at an infusion rate of 20 ml/5 s with an injector (Medrad). rTBV was assessed by analyzing the first passage of the contrast agent [27]. The signal decay induced by the contrast bolus was converted into relative contrast agent concentrations in a pixel-by-pixel manner. The resulting time courses were then modeled by a γ-variate fit to eliminate the contribution of tracer recirculation. The change in rTBV was expressed as fractional change of the integral of the γ-variate curve as a result of patupilone treatment (rTBV after treatment/rTBV at baseline).

In each case, tumor tissue collected during first and second surgery was evaluated. Immunohistochemistry was performed on 3-μm sections of formalin-fixed, paraffin-embedded tissue. Briefly, tissue sections were mounted on glass slides (SuperFrost Plus; Menzel, Braunschweig, Germany) and deparaffinized. For staining with the proliferation marker Ki-67, CC1 (antigen retrieval solution; Ventana)-pretreated sections were incubated with monoclonal rabbit Ki-67 antibody (clone SP6; Epitomics Plus; Menzel, Braunschweig, Germany) and deparaffinized. For IDH1 R132H staining, antiYIDH1-R132H antibody clone DIA-H09 was obtained from Dianova (Hamburg, Germany) and the antibody concentration of 1:200 was used. Briefly, formalin-fixed, paraffin-embedded sections were placed in a Bond Max Autostainer (Leica Microsystems, Wetzlar, Germany) and RNA was extracted according to the manufacturer’s instructions [ApopTag peroxidase in situ oligo ligation (ISOL) kit; Chemicon, Millipore AG, Zug, Switzerland]. The percentage of TUNEL- and Ki-67-positive cells was determined by counting 10 randomly chosen high-power fields. BIII-Tubulin staining was performed with a polyclonal rabbit IgG (Abcam, Cambridge, UK) and visualized using an anti-rabbit IgG secondary antibody (Vectostain kit; Vector Laboratories, Burlingame, Calif., USA) and peroxidase detected by 3,3-diaminobenzidine tetrahydrochloride (DAB; Dako, Carpinteria, Calif., USA). DNA fragmentation (apoptosis) was visualized by the deoxynucleotidyl transferase-mediated dUTP-biotin nick-end labelling (TUNEL) reaction according to the manufacturer’s instructions [ApopTag® peroxidase in situ oligo ligation (ISOL) kit; Chemicon, Millipore AG, Zug, Switzerland]. The percentage of TUNEL- and Ki-67-positive cells was determined by counting 10 randomly chosen high-power fields. BIII-Tubulin staining was performed with a polyclonal rabbit IgG (Abcam, Cambridge, UK) and visualized using an anti-rabbit IgG secondary antibody (Vectostain kit; Vector Laboratories, Burlingame, Calif., USA) and peroxidase as detected by DAB (Dako, Glostrup, Denmark).

A semiquantitative analysis was performed based on the following criteria: + = <10% positive cells; ++ = 10–50% positive cells, and +++ >50% positive cells. Negative controls were performed using isotype antibodies followed by the appropriate secondary IgG HRP antibody.

For IDH1 [R132H] staining, antiYIDH1-R132H antibody clone DIA-H09 was obtained from Dianova (Hamburg, Germany) and the antibody concentration of 1:200 was used. Briefly, formalin-fixed, paraffin-embedded sections were placed in a Bond Max Autostainer (Leica Microsystems, Wetzlar, Germany) according to the standard protocol. Briefly, sections were heated at 95°C using EDTA buffer (pH 8.8) for 20 min. After washing, peroxidase blocking was carried out for 10 min using the Bond Polymer Refine Detection Kit DC9800 (Leica Microsystems). Tissues were again washed and then incubated with the primary antibody for 30 min. Subsequently, tissues were incubated with polymer for 10 min and developed with DAB (Dako) for 10 min. We defined cases with at least 10% cells as positive.

For class I β-tubulin sequencing, frozen tumor material was homogenized in TRI Reagent® solution (Ambion, Austin, Tex., USA) and RNA was extracted according to the manufacturer’s protocol. cDNA preparation, PCR and sequencing were performed by Microsynth (Balgach, Switzerland) using primers specific for human class I β-tubulin (GenBank accession No. J00314): forward primer TCGTGCACATCCAGGCTGGTC and reverse primer AGGCCTCCTCTTCGGCCTCC.

### Results

#### Patient and Tumor Characteristics

A total of 9 patients with histologically proven, recurrent GBM were recruited at the University Hospital Zürich from June 2008 to April 2010. Patient characteristics at study entry are summarized in table 1. All patients were male, with a mean and median age of 54.6 ± 8.6 and 54 years, respectively, and WHO performance status was 0 or 1. All patients had received standard upfront treatment for their GBM prior to study enrolment, including gross total resection, concurrent RT and chemotherapy (TMZ) followed by TMZ for 1–6 cycles. Two of 9 patients had received TMZ on a 1-week-on, 1-week-off regimen for recurrent disease and 6 of 9 patients (66%) were on steroids before being enrolled in the study. All GBM cases were negative for the IDH-1 (isocitrate dehydrogenase-1) mutation and those tested for MGMT gene promoter methylation (patients 4–9) were unmethylated, indicating a cohort of patients with a poor prognosis.

#### Patupilone Distribution

A total of 54 cycles of patupilone (range 1–30/patient) were administered. Patupilone concentrations in plasma and tumor tissue were determined in 2 patients at the time of surgery, revealing a 30-fold patupilone accumulation in the tumor tissue. In the 1st patient, patupilone concentrations were 1.58 ng/ml in the plasma and 43.4 ng/g in the tumor tissue, and in the 2nd patient they were 3.29 ng/ml and 208 ng/g, respectively. Pharmacokinetic findings were comparable to previous results (data not shown) [11]. The maximum plasma patupilone concentration was measured at the end of the 20-min infusion (1.6–3.3 ng/ml) followed by a steady decline.

#### Response and Survival

Median survival after second surgery was 11 months (95% CI, 5–17 months) and 1-year OS was 45% (95% CI, 14–76; online suppl. fig. 1a; for all online suppl. material, see www.karger.com/doi/10.1159/000339152). Median PFS was 1.5 months (95% CI, 1.3–1.7 months). PFS at 4
and 6 months was 22% (PPF6 95% CI, 0–46), and 2 of 9 patients were free of disease for 9.75 and 22 months on study treatment (online suppl. fig. 1b). Of note, 3 patients were excluded from further patupilone treatment due to peri-operative complications (2 patients) or toxicity (1 patient). Median OS from the time of the initial diagnosis was 21.5 months (95% CI, 17–25 months) and 1-year survival was 100% (95% CI, 80–100).

Safety and Toxicity
Treatment with patupilone was generally well tolerated at a dose of 10 mg/m², with no patients developing hematological toxicity (table 2). Cumulative but reversible sensory neuropathy grade 3 occurred in 2 of 9 patients (22%) after 8 months of treatment. The 2nd patient developed grade 4 diarrhea following his second patupilone application 3 weeks after second surgery. With a longer interval after second surgery and proactive loperamide prescription, only mild diarrhea occurred (grade ≤2) in subsequently treated patients. Two patients experienced peri-operative complications (meningitis) not considered to be adverse events of the study drug.
Neurocognitive Evaluation
Complete neuropsychological assessment before and 3 months after surgery was performed in 6 of 9 patients (66%). Comparable levels of performance were achieved in the two assessments. Difficulties in word finding, memory impairment or visual-constructive problems corresponded with the tumor site. Deficiencies in executive functioning were observed irrespective of the tumor site and hemisphere. All patients showed reduced performance in tests of selective attention and conceptual flexibility before and 3 months after surgery.

Biomarkers
Dynamic Contrast-Enhanced MRI
rTBV was measured prior and >5 days after the first patupilone application using MRI in 8 of 9 patients. The median fractional change was 1.0 (95% CI 0.62–0.92) and the mean rTBV change was 0.94. However, the rTBV change ranged from strong (max. 2.05) to substantial decreases (max. 0.04). Interestingly, rTBV was clearly reduced after treatment with patupilone in patient 8, which is seen by an 86% reduction in rTBV (fig. 2).

IHC of Apoptosis and βIII-Tubulin, Class I β-Tubulin Sequencing and Ki-67 at Second Surgery
Immunohistochemical assessment of apoptosis as an indicator of cell death induction ≥5 days following patupilone administration demonstrated rather low apoptotic activity ranging from <1% (4 cases) to a maximum of 6.2%. βIII-Tubulin, which is often overexpressed and thereby co-determines treatment resistance, was detectable in all 9 patients. There was strong βIII-tubulin expression (>50%) in 6 of 9 patients, intermediate expression (10–50%) in 2 patients and weak expression (<10%) in only 1 patient (fig. 3). In order to determine possible epothilone resistance mechanisms related to mutated class I β-tubulin, defining patupilone binding, the entire coding region of class I β-tubulin was sequenced in the
tumor biopsies of each patient. No deviations from the wild-type amino acid sequence could be identified, indicating that other resistance mechanisms at the molecular-cellular level contributed to the differential treatment responses. The tumor proliferation marker Ki-67 was between 9 and 28% (mean 18%) at first surgery and between 12 and 43% (mean 26%) at second surgery (p = 0.045), indicating a more aggressive behavior at the time of tumor progression. In all but 2 patients, the difference factor ΔF Ki-67 was positive (table 2).

In summary, there was no significant correlation between OS or PFS6 and the rate of apoptosis, βIII-tubulin expression, Ki-67 rate or change in rTBV.

**Discussion**

In the treatment of recurrent or progressive GBM, there is no standard of care, and therefore a major need for novel therapeutic options exists. In this phase I/II single-institution trial, we found that patupilone monotherapy was well tolerated with a low toxicity profile and stable neurocognition, which allows for peri-operative and long-term application. Patupilone achieved high drug concentrations within the tumor tissue, with a high plasma/tumor tissue ratio (>30), most probably due to an impaired and pathological blood-tumor barrier and diminished drug clearance [28, 29]. Although PFS6 was only 22%, there were 2 long-lasting responses of 9.75 and 22 months, and OS was noteworthy (median 11 months,
45% at 1 year), which indicates that patupilone shows activity in patients with GBM.

The rate of patients being alive and progression free at 6 months (PFS6) has been established as a reproducible surrogate end point in phase II trials for recurrent gliomas [2]. In our study, PFS6 was 22%, which is in line with results from phase II trials reporting a PFS6 of 20–30% after therapy with single agents for recurrent GBM [2]. Other studies with newer agents demonstrated lower or similar PFS6: 6.7% (sagopilone), 7.7% (afibercept), 9.4% (sorafenib/TMZ), 10.6% (imatinib/hydroxyurea), 12% (cilengitide), 25.8% (cediranib) and 30% (cetuximab/bevacizumab/irinotecan) [30–35].

There were 2 long-term responders to patupilone in our trial (patients 7 and 8). BIII-Tubulin expression was <50% in patient 8 but >50% in patient 7. High BIII-tubulin expression has been associated with resistance to microtubule-binding agents in the literature [12]. An intermediate BIII-tubulin expression (<50%) could indicate patupilone sensitivity at least in patient 8 with reduced rTBV after patupilone and a remarkable PFS of 22 months.

Overall, there was no correlation between OS or PFS6 and tested biomarkers as BIII-tubulin expression, rate of apoptosis, class I β-tubulin mutation or change in rTBV. As expected, the proliferation marker Ki-67 was significantly higher at second surgery compared to the first one, indicating a transition to a more aggressive disease.

Patupilone with its favorable safety profile represents a potential drug for further investigations in combination with RT or other therapy. There is evidence from a phase I trial showing that combining patupilone with a variety of radiation doses and fractionation schedules is well tolerated and safe in patients with central nervous system malignancies [24].

However, there are limitations to the current study. The number of patients included was low, a fact that was aggravated by drug-independent discontinuation of patupilone in 2 patients. Furthermore, there was a selection bias inherent to the inclusion criteria (Karnofsky performance status and operability). It is unclear whether the time points chosen for biomarker evaluation were appropriate.

Conclusions

Patupilone represents a treatment option in recurrent GBM with efficacy, manageable toxicity and convenience of administration. Its radiosensitizing potential renders patupilone a promising agent for upfront combination treatment with RT in patients with GBM, particularly in tumors with an unmethylated MGMT gene promoter.

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Disclosure Statement

P.R. Allegrini, D. Weber and P.M.J. McSheehy are employees of the Novartis Institute of Biomedical Research. P.R. Allegrini and D. Weber also hold stock options in Novartis Pharma AG. The other co-authors declare no conflict of interest.

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