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CLINICAL STUDY

Cost-effectiveness of the long-term use of temozolomide for treating newly diagnosed glioblastoma in Germany

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Abstract

Concomitant radiochemotherapy followed by six cycles of temozolomide (=short term) is considered as standard therapy for adults with newly diagnosed glioblastoma. In contrast, open-end administration of temozolomide until progression (=long-term) is proposed by some authors as a viable alternative. We aimed to determine the cost-effectiveness of long-term temozolomide therapy for patients newly diagnosed with glioblastoma compared to standard therapy. A Markov model was constructed to compare medical costs and clinical outcomes for both therapy types over a time horizon of 60 months. Transition probabilities for standard therapy were calculated from randomized controlled trial data by Stupp et al. The data for long-term temozolomide therapy was collected by matching a cohort treated in the Department of Neurosurgery at Jena University Hospital. Health utilities were obtained from a previous cost utility study. The cost perspective was based on health insurance. The base case analysis showed a median overall survival of 17.1 months and a median progression-free survival of 7.4 months for patients in the long-term temozolomide therapy arm. The cost-effectiveness analysis using all base case parameters in a time-dependent Markov model resulted in an incremental effectiveness of 0.022 quality-adjusted life-years (QALYs). The incremental cost-effectiveness ratio (ICER) was €351,909/QALY. Sensitivity analyses showed that parameters with the most influence on ICER were the health state utility of progression in both therapy arms. Although open-ended temozolomide therapy is very expensive, the ICER of this therapy is comparable to that of the standard temozolomide therapy for patients newly diagnosed with glioblastoma.

Keywords Brain tumor · Glioblastoma · Temozolomide · Cost-effectiveness analysis · Markov model

Abbreviations

TMZ	Temozolomide
RT	Radiotherapy
FDA	Food and Drug Administration
OS	Overall survival
PFS	Progression-free survival
ICER	Incremental cost-effectiveness ratio
QALY	Quality-adjusted life-year
QALM	Quality-adjusted life-month
LYG	Life-year gained
WHO	World Health Organization
G-DRG	German Diagnosis-Related Group
GDP	Gross domestic product
MRI	Magnetic resonance imaging

Introduction

Approximately 7000 new cases of malignant brain tumors arise annually in Germany [1] with glioblastoma being the most common malignant brain tumor [2]. The current standard treatment for newly diagnosed glioblastoma begins with surgical resection to the extent feasible, followed by radiation therapy with concomitant and adjuvant temozolomide (TMZ) maintenance therapy. Temozolomide is an oral alkylating agent with a chemical structure similar to nitrosourea derivatives [3]. Based on the Stupp trial [4], the

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Food and Drug Administration (FDA) approved TMZ for treating adults newly diagnosed with glioblastoma in 2005. The study established a median overall survival (OS) of 14.6 months and a median progression-free survival (PFS) of 6.9 months associated with the use of radiotherapy followed by 6 cycles of adjuvant TMZ [3]. In contrast to that, the Department of Neurosurgery at the Jena University Hospital routinely administers a long-term TMZ treatment in the sense of an open-ended application over the entire treatment period. TMZ is only stopped, when progression or serious side effects occur. The long-term use of TMZ is currently controversial. Long-term administration of adjuvant TMZ is common practice in many institutions, mainly due to safety and tolerability of the treatment. There is some evidence that long term use of TMZ correlates with PFS and OS [5]. Other authors found that median survival correlates with the number of TMZ cycles administered [6]. On the other hand, there is class-3-evidence that prolonged TMZ does not affect PFS and OS and therefore should not be used beyond 6 months [7–9].

The treatment of glioblastoma, similar to other types of cancer treatment, is expensive and represents a significant burden on health care system's financial resources. The cost of Temodar® (Temozolomid brand names in the US) is between $1600 and $4600 per month in the USA. The total cost of adjuvant treatment is up to US$9000 per month, although surgery costs are not yet included [10].

The Markov model is a stochastic model particularly used to modeling chronic disease in healthcare concept [11]. Markov model are based on a chain of 'states' that a patient can occupy at a given point in time and transition probabilities are allocated for movement between these states over a discrete time period, called cycles. The duration of these cycles will depend on the disease and interventions that are being evaluated, but might be a month or a year [11, 12]. Two different types of Markov models can be characterized by the form of the transition probabilities. For chains in basic Markov model, all transition probabilities are assumed to be constant over time. In another form of Markov model, the transition probabilities can vary over time, known as time-dependent Markov model. Because of the assumption of constant transition probabilities, the basic Markov model may be too restrictive for many potential applications in health field. In contrast, time-dependent Markov processes are much more flexible with regard to the modeling of chronic diseases [11]. Each state in the model usually has a cost related to it and, when QALYs are used as outcome measure, a health-related quality of life (i.e., utility values) weight [12].

The quality-adjusted life-year (QALY) is routinely used in most economic evaluations as a summary measure of health outcome, which incorporates the impact on both the quantity and quality of life [13]. A review of the health economic studies relevant to glioblastoma therapy showed that most cost-effectiveness studies reported the incremental cost-effectiveness ratios (ICERs) as the cost per QALY [14].

A widely used indicator of health quality of life is self-rated health. Like perceptions of disability, this is a rather subjective indicator. However, there is some evidence that self-related health could be a better indicator of morbidity than more "objective" indicators including physician's ratings of their patient's health [15]. Interestingly, there is no relationship between self-reported functional limitations and perceived disability [16]. Indeed, for glioblastoma patients there are some reports dealing with health related quality of life (HRQoL), but data on utility values that would represent the preferences of the general public in relation to health states associated with high-grade glioma is limited. Regarding this, the work of Garside et al. provides data from 36 members of a panel rating the glioma health state scenarios [17].

The objective of this study is to determine the cost-effectiveness of open-ended long-term therapy of temozolomide plus radiotherapy for patients newly diagnosed with glioblastoma. Cost-utility analysis evaluates the ICER, expected to be the monetary costs per QALY gained from the incorporation of long-term TMZ into the standard therapy. The cost perspective was based on a health care payer (health insurance) system.

Methods

Model, population, and treatment

A Markov model was constructed using Tree Age Pro Healthcare (Tree Age Software, Inc., One Bank Street, Williamstown, MA, USA). Markov models are increasingly used for health economic analyses and are particularly suited for modeling chronic disease such as glioblastoma [10, 18, 19]. We used this Markov model to measure and compare the medical costs and health outcomes for both therapy types (long-term TMZ therapy vs. standard therapy) in a time horizon of 5 years (60 months). The model contained three health states: stable, progressive disease and death. The patient population considered for the standard treatment (therapy arm 1) is characterized by the inclusion criteria of Stupp et al.'s study [3]. The main inclusion and exclusion criteria are presented in Table 1. Patients under corticosteroid treatment must be treated with a stable or decreasing dose. Patients in therapy arm 2 (n = 57, long-term TMZ) were selected as a "matched" cohort from the Department of Neurosurgery at Jena University Hospital. All selected cases were operated from November 2008 to April 2014 and were subsequently treated with concomitant radiochemotherapy. Additional information concerning patient characteristics is

Table 1 Inclusion and exclusion criteria

Parameter	Inclusion criteria	Exclusion criteria
Age	18 ≤ adults ≤ 70 years of age	Children and elderly patients
Tumor entity	Newly diagnosed and histologically confirmed glioblastoma (WHO grade IV)	All other gliomatous brain tumors
General condition	WHO performance status 0–2	WHO performance status 3–5
Hematologic function	> 1500 neutrophil granulocytes/mm^3 > 100,000 thrombocytes/mm^3	< 1500 neutrophil granulocytes/mm^3 < 100,000 thrombocytes/mm^3
Renal function	Serum creatinine < 1.5 times the upper limit value	Serum creatinine > 1.5 times the upper limit
Liver function	Values < three times the upper limit value	Liver function values > three times the upper limit

Table 2 Patient characteristics in both treatment arms

Characteristic	Therapy arm 1/ standard therapy	Therapy arm 2/long term temozolomide
Age		
< 50	172 (30.0%)	15 (26.3%)
> 50	401 (70.0%)	42 (73.7%)
Gender		
Male	360 (62.8%)	36 (63.2%)
Female	213 (37.2%)	21 (36.8%)
WHO performance status		
0	223 (38.9%)	22 (38.6%)
1	277 (48.3%)	29 (50.9%)
2	73 (12.7%)	6 (10.5%)
Surgery		
Biopsy only	93 (16.2%)	8 (14.0%)
Resection	480 (83.8%)	49 (86.0%)

None of the presented parameters reached significance regarding difference between groups

presented in Table 2. PFS and OS were acquired through the local tumor center.

All patients began the simulation in the stable disease state. A cycle length of 1 month and a lifetime horizon were selected. At the end of each month, patients could stay in only one health state at a time and had a defined probability of staying in the same health state or moving to progression or death. No backward transitions were permitted; i.e., a transition from "progression" to "stable" corresponding to an improvement was not possible (see Supplementary Fig. S1). Stable disease was divided into three different phases of treatment: month 1, month 2–6 and subsequent months. The maximum number of cycles was limited to 60.

Model 1: markov model with variable transition probabilities

A time-dependent Markov model was developed to simulate the disease process over 60 months (model horizon) and recalculate variable transition probabilities to the next state for each cycle (time-dependent transition probabilities). For the standard therapy, we extrapolated the monthly OS and PFS from the Kaplan–Meier curve of Stupp et al.'s study. For the long-term TMZ therapy, the respective data was acquired from the local tumor center at the Jena University Hospital. From these monthly OS and PFS data, we calculated the monthly probability of each allowable transition within the model according to the formula

$$P = 1 - e^{\frac{\ln y}{t}} \quad (1)$$

where P is the transition probability and y represents OS or PFS at time t [20]. The transition probability of death is the probability of changing to the health state of death in the next Markov cycle; these probabilities differ in each cycle and depend on the progression of the Kaplan–Meier curve. We used the Weibull function and method of least squares as it has been done in similar analyses [21, 22] to extrapolate the probabilities from the Kaplan–Meier curve of Stupp et al.'s study up to 60 months.

Model 2: markov model with constant transition probabilities

We also developed a Markov model with constant probabilities for both standard therapy and long-term TMZ therapy. We calculated monthly transition probabilities from median OS and median PFS using Eq. 1 (Table 3). This model assumes that patients have a constant risk of death during the period.

Direct costs

For the economic evaluation, the direct costs of the entire treatment were identified for both the standard and the long-term TMZ therapies. The costs of irradiation and concomitant chemotherapy have not been considered, since these are assumed to be the same for all patients in both therapy arms. Medical and nonmedical costs included

Table 3 Transition probabilities from median OS and PFS for the traditional Markov model

State transition	Monthly transition probabilities	
	Standard TMZ therapy	Long-term TMZ therapy
Stable disease to progression	0.0956	0.0894
Stable disease to death	0.0464	0.0397
Progression to death	0.0861	0.0689

TMZ temozolomide

hospitalization [based on the German Diagnosis-Related Group (G-DRG) system], ambulant diagnostics (imaging, laboratory), medical consultations (neurooncological consultation) and medical transport. Costs of ambulant treatment and diagnostic were calculated based on the Uniform Value Scale ("Einheitlicher Bewertungsmaßstab"—EBM) system [23]. The dosage for TMZ was calculated based on the prescribing information for TMZ in Germany. During the first month of adjuvant TMZ treatment, the dose was 150 mg/m^2. In the following months, the dose was increased to 200 mg/m^2 if no side effects occurred. Based on the average body surface area of 1.73 m^2 for adults, TMZ doses of 260 and 350 mg/day are obtained for 5 days/cycle (month). In this study, costs were estimated based on the health care payer (health insurance) system and calculated using the 2015 rates (Table 4). Indirect costs were not included.

Health state utilities

In our analysis, we used health state utilities from Garside et al.'s study [17], which evaluated the clinical benefit of TMZ and carmustine wafers in the adjuvant treatment for newly diagnosed glioblastoma. However, only 36 individuals in total were recorded in this analysis. This number is certainly not representative, but these are the only available estimates of utility value to date and previous studies have referred to these data [10, 24, 25]. Supplementary Table S1 shows these utility values that were used in our base case analysis and that were varied in sensitivity analyses. While debatable, we assumed that patients with longer lengths of time in a progression state were associated with proportional decrements in health utility values. This should reflect the natural course of the disease in a lot of patients and was applied by other authors, too [17, 24, 25]. We used a decrease of 0.02 QALYs per consecutive month of progression up to 24 months.

Analysis

The ICERs, expressed as monetary costs per additional quality-adjusted life-month (QALM) and QALY, were calculated for both Markov models based on constant and time-dependent transition probabilities. Additionally, a one-way sensitivity analysis with variable transition probabilities for costs and utility parameters was performed. In one-way sensitivity analysis, the impact of each variable is examined systematically by varying it across a plausible range of values while all other variables are constant [26]. We used

Table 4 Monthly input costs for both strategies

	Stable disease [€]			Progression [€]	Death [€]
	Month 1	Month 2–6	Subsequent months		
Standard TMZ therapy					
Adjuvant TMZ	1755	2332	0		
Prophylaxis	69	69	0		
Imaging	57	57	57		
Medical visits	22	22	22		
Transport	134	134	45		
Total	1944	2453	350	2720	0
Long-term TMZ therapy					
Adjuvant TMZ	1755	2332	2332		
Prophylaxis	69	69	69		
Imaging	57	57	57		
Medical visits	22	22	22		
Transport	134	134	134		
Total	1944	2453	2453	2720	0

TMZ temozolomide

All costs are reported as 2015 Euros per month

this form of sensitivity analysis because it is a quick way to understand the quantitative relationship between changes in inputs and outputs [12]. We changed ± 20% of the cost parameters and ± 5% of the utilities separately. In addition, we applied a one-way sensitivity analysis of the Markov model with constant transition probabilities of all parameters. We applied ± 20% on costs, ± 5% on utilities, and ± 2 weeks on the median OS and median PFS.

Results

The base case analysis showed a median OS of 17.1 months and median PFS of 7.4 months for the patients in the long-term TMZ therapy arm (see Supplementary Figs. S2, S3).

Cost-effectiveness analysis (model 1)

The results of the cost-effectiveness analysis show that the long-term use of TMZ, based on all base case parameters in the time-dependent Markov model, was effective for 10.85 months compared with 10.59 months for standard TMZ therapy. This results in an incremental effectiveness of 0.26 QALMs or 0.022 QALYs leading to an ICER of €351,909/QALY.

One-way sensitivity analyses shows that the parameters with the greatest influence on ICER were the health state utility of progression in both the standard and the long-term TMZ therapies. Other parameters demonstrated a similarly strong influence on the ICER, such as the cost of progression in both therapy arms. Two parameters in our sensitivity analysis, namely the health state utility of the stable state in both therapy arms, showed negative lower-bound ICERs. A negative ICER indicates dominance in this study (an option is said to be dominated, if it both costs more and is less effective than a comparator). The results of the one-way sensitivity analysis are presented in Table 5.

Cost-effectiveness analysis (model 2)

On the other hand, the cost-effectiveness analysis using all base case parameters in a Markov model with constant transition probabilities demonstrated effectiveness for 8.77 months in standard TMZ therapy and 9.94 months in long-term TMZ therapy (incremental effectiveness: an additional 1.17 QALMs or 0.098 QALYs). The total costs were €31,591 for standard TMZ therapy and €43,858 for long-term TMZ therapy (incremental cost: €12,267). We calculated the base case ICER to be €10,445 per QALM or €125,340 per QALY.

The results of one-way sensitivity analyses of all the parameters in model 2 demonstrated that the costs of progression in both therapy arms were the most powerful parameter affecting the ICER. Other variables with strong influence on the ICER were the costs of the stable state in long-term TMZ therapy and the health state utility of the stable state in both arms. The results of sensitivity analyses in this model are presented in Table 6, the resulting tornado diagrams are displayed in Fig. 1.

Table 5 One-way sensitivity analysis (model 1)

Parameter	Range (%)	ICER (Costs/QALY)	Change in ICER (%)
Stable costs (long-term TMZ)	− 20	117,818	− 66.5
	+ 20	585,955	66.5
Stable costs (standard TMZ)	− 20	482,727	− 37.2
	+ 20	221,045	37.2
Progression costs (long-term TMZ)	− 20	201,545	− 42.7
	+ 20	502,273	42.7
Progression costs (standard TMZ)	− 20	535,000	52.0
	+ 20	168,773	− 52.0
Stable utility (long-term TMZ)	− 5	Dominant	N/A
	+ 5	136,624	− 61.2
Stable utility (standard TMZ)	− 5	142,929	− 59.4
	+ 5	Dominant	N/A
Progression utility (long-term TMZ)	− 5	663,600	88.6
	+ 5	238,215	− 32.3
Progression utility (standard TMZ)	− 5	226,595	− 35.6
	+ 5	774,200	120

ICER incremental cost-effectiveness ratio, *QALY* quality-adjusted life-year, *TMZ* temozolomide, *N/A* not applicable

Table 6 One-way sensitivity analysis (model 2)

Parameter	Range	ICER (Costs/QALY)	Change in ICER (%)
Stable costs (long-term TMZ)	−20%	90,722	−28.3
	+20%	162,206	28.3
Stable costs (standard TMZ)	−20%	148,258	17.2
	+20%	104,670	−17.2
Progression costs (long-term TMZ)	−20%	71,742	−43.3
	+20%	181,175	43.3
Progression costs (standard TMZ)	−20%	169,814	34.3
	+20%	83,103	−34.3
Stable utility (long-term TMZ)	−5%	165,398	30.8
	+5%	100,825	−20.3
Stable utility (standard TMZ)	−5%	102,225	−19.2
	+5%	161,763	27.9
Progression utility (long-term TMZ)	−5%	153,338	21.3
	+5%	105,902	−16.3
Progression utility (standard TMZ)	−5%	109,040	−13.8
	+5%	148,691	17.6
Overall survival (long-term TMZ)	−2 weeks	130,558	3.2
	+2 weeks	121,421	−4.0
Overall survival (standard TMZ)	−2 weeks	119,657	−5.4
	+2 weeks	131,912	4.3
PFS (long-term TMZ)	−2 weeks	138,369	9.4
	+2 weeks	114,760	−9.3
PFS (standard TMZ)	−2 weeks	110,464	−12.7
	+2 weeks	144,012	13.9

ICER incremental cost-effectiveness ratio, *QALY* quality-adjusted life-year, *TMZ* temozolomide, *PFS* progression-free survival

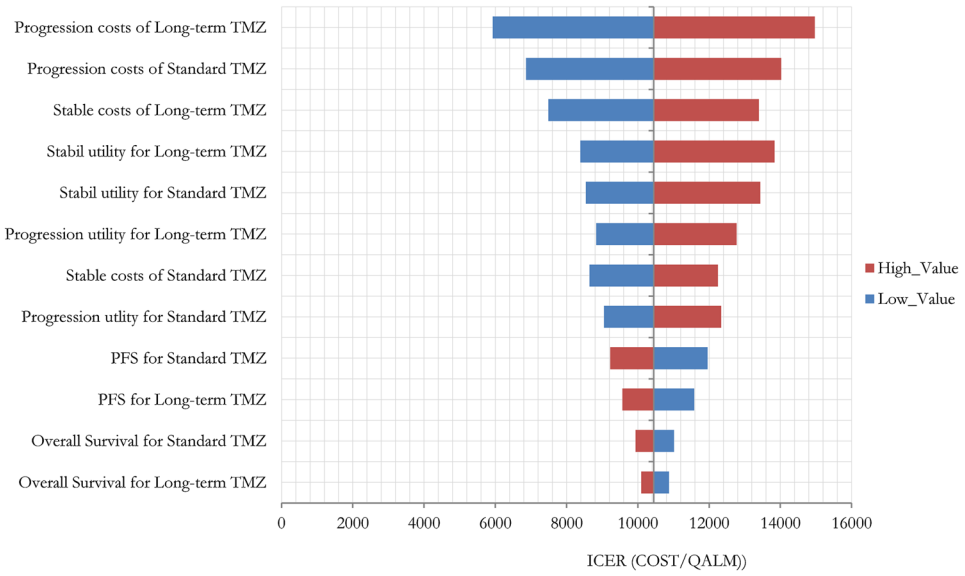

Fig. 1 One-way sensitivity analysis tornado diagrams; calculated with incremental cost-effectiveness ratio (ICER) which was 10,455 €/additional quality-adjusted life-month (QALM). Variations on variables were ±2 weeks for survival parameters, ±20% for costs, and ±5% of the utilities

Discussion

We evaluated the cost-effectiveness of long-term therapy with temozolomide for patients newly diagnosed with glioblastoma using a Markov model with two types of transition probabilities. Only a small number of published studies have examined the cost-effectiveness of TMZ for patients newly diagnosed with glioblastoma. Comparing the results of our analysis with other publication results is difficult because of the different study methods, cost perspectives and geographical regions used in the studies.

Messali et al. [10] investigated the ICER of chemotherapy with TMZ in addition to the standard therapy with surgery and radiation. The authors considered the costs for additional QALYs from a societal perspective in the US, accounting for both direct and indirect costs. Cost-effectiveness was demonstrated for both Temodar® (ICER: US$102,364 per QALY) and generic TMZ (ICER: US$8875 per QALY). Garside et al. [17] evaluated adjuvant temozolomide treatment in a cost-effectiveness analysis from the perspective of the UK's national health care system and calculated an ICER of £35,861 per QALY; the therapy being compared was irradiation only without any chemotherapy.

According to the results of the two Markov models, the long-term use of temozolomide is effective in producing a gain in QALYs. As expected, long-term treatment with temozolomide in the stable state causes higher costs, resulting in an ICER of €351,909 and €125,340 per QALY. Similar to the findings from a recent study by Bernard-Arnoux et al. [19], there is no doubt about the clinical effectiveness of the alternative treatment arm, yet the costs for gaining QALYs are rather high. Bernard-Arnoux calculated an ICER of €596,411 for one life-year gained (LYG) by using an additional treatment with "tumor treating fields" for glioblastoma patients and concluded that such costs would be "far beyond conventional thresholds". The outcome measure used by the authors was explicitly LYG, not QALY, as stated by the author, because of the lack of published data on health state utilities associated with glioblastoma. In our study, we used QALYs as an outcome measure referring to the data from Garside et al. [17]. The authors used standard gamble to elicit preference for glioblastoma health states from a small number of the general United Kingdom population. The resulting health state utilities are certainly worth to be discussed. Surprisingly, the utility value for health-related quality of life during TMZ therapy is only slightly above the value for the stage of progression (0.743 vs. 0.731, see Supplementary Table S1). In contrast, Taphoorn et al. [27] found significantly better quality of life data during TMZ therapy compared with the stage of progression. Based on data from HRQoL, which were collected in parallel by several centers during the Stupp et al. study, the authors were able to show, that the additional treatment with TMZ does not lead to any loss of health-related quality of life. Moreover, there was no statistically significant difference in quality of life between the groups "TMZ + RT" and "RT alone". Data from the AVAglio study [28] could confirm these results.

Nonetheless, the resulting ICERs in our study are much higher than the commonly cited US$50,000 per QALY for indicating a treatment is cost-effective. This limit is still based on the results of a cost-effectiveness analysis of dialysis treatment for patients with chronic renal insufficiency from 1982 in the US. On the basis of these data, a willingness-to-pay threshold of US$50,000 per quality-adjusted life-year is still propagated within the framework of health economic analyses [29–31].

The WHO pursues a different approach according to its report from 2002 [32]: "The recent report of the Commission on Macroeconomics and Health suggested that interventions costing less than three times gross domestic product (GDP) per capita for each DALY averted represent good value for money." Considering the development of GDP per capita in Germany since 2000, this figure has grown by almost 50% (2016: €37,800; 2000: €25.980); therefore, when using current data on Germany's GDP, the result would be a threshold of approximately €113,000 for acceptance of a treatment as cost-effective in Germany (using purely Euro amounts). Consistently, a rising number of publications suggest the adoption of a cost-effectiveness limit to values between US$100,000 and US$200,000 per QALY [33–35].

The two models differ significantly with regard to the extent of the ICER, perhaps because the time-dependent Markov model maps the actual conditions more precisely and realistically. The main difference is likely to be the constant transition probabilities for the traditional model, which can be generated from data on the median OS and PFS. However, from a mathematical perspective, the respective life expectancy at time (t) and the median survival are not the same. Life expectancy corresponds to the arithmetic mean of the survival times of all individuals still living at the respective time (t). By contrast, the median survival corresponds to the time point from randomization, where half of all individuals are still alive. All other studies on temozolomide use either a traditional Markov model or no Markov model at all. The validity of our time-dependent model should be relatively higher such that the ICER of €351,909/QALY is more likely to represent natural conditions than the value of €125,340/QALY from the traditional Markov model.

As shown in the sensitivity analyses, costs and health state utilities for the "stable" and "progression" states were the main drivers in both models. In terms of costs, the use of temozolomide, especially in therapy arm 2, was

clearly the most influencing factor. Cost reduction by only 20% in the stable state would reduce the ICER by 66.5% to €117,818/QALY. Under these conditions, long-term temozolomide therapy would be close to the threshold of three times GDP per capita, as proposed by the WHO [32]. Two parameters, namely the health state utility of the stable state in both therapy arms, showed a negative lower-bound ICER. Despite the clinical superiority of the therapy (median OS 17.1 vs. 14.6 months), it would no longer be effective with regard to quality-adjusted survival. Here it becomes clear, how much clinical effectiveness, and thus cost-effectiveness, depends on the utility value for the respective disease stage.

The present study has some limitations. The data source inputs for standard temozolomide therapy were taken from the Stupp et al. study, which was a randomized controlled study with 573 patients in 85 departments from 15 countries. For the long-term temozolomide therapy arm, we selected a small number of patients from a single center in Germany, where data were collected prospectively but reanalyzed retrospectively. Therefore, these data are unlikely to be comparable to the data in the standard temozolomide therapy arm. Furthermore, since 2010, with the revision of the RANO criteria [36], change has occurred in the radiological assessment of progress in glioblastomas. Until 2010, including the Stupp study, progress has always been diagnosed by means of T1 contrast-enhanced magnetic resonance imaging (MRI) scans. After revision in 2010, the co-assessment of T2 hyperintensity had been integrated into these criteria. Though diagnosis of progress is always made in the clinical context, the radiological criteria support an increasing frequency of first, the radiological diagnosis, and second, the integrated clinical diagnosis of progress. The patients given long-term temozolomide were largely treated after 2010, such that the relative frequency and the time to occurrence of progress cannot be easily compared between the two patient groups. However, this fact could not be included in the Markov modeling, because the literature lacks reliable data on whether diagnosis of progress has increased in frequency since this update.

In conclusion, the use of long-term temozolomide was more effective than standard therapy. Although this open-ended temozolomide therapy is very expensive, the ICER of this therapy is comparable to that of standard temozolomide therapy for patients newly diagnosed with glioblastoma. Furthermore, this study demonstrates that a time-dependent Markov model can provide more precise and realistic results.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflicts of interest.

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