Tumor treating fields, (Optune®) - re-review

Final evidence report

October 17, 2018

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List of Abbreviations

AE	Adverse events	NR	Not reported
CI	Confidence interval	NS	Not significant
CPG	Clinical practice guideline	QOL	Quality of life
CQ	Cost question	RCT	Randomized controlled trial
EQ	Efficacy question	SQ	Safety question
FDA	U.S. Food and Drug Administration	TMZ	Temozolomide
GBM	Glioblastoma multiforme	TTF	Tumor treating fields
HTA	Health technology assessment	U.K.	United Kingdom
KPS	Karnofsky performance score	U.S.	United States

Executive Summary

Structured Abstract

Purpose: To conduct a health technology assessment (HTA) on the efficacy, safety, and cost of tumor treating fields (TTF).

Data Sources: PubMed from inception through June 16, 2018; clinical trial registry; government, payor, and clinical specialty organization websites; hand searches of bibliographies, relevant clinical practice guidelines (CPGs), and systematic reviews.

Study Selection: Using a priori criteria, we selected English-language primary research studies published in any year that were conducted in very highly developed countries that enrolled pediatric or adult patients with histologically confirmed cancer who were treated with TTF. We selected studies that evaluated efficacy outcomes (overall survival, progression-free survival, quality of life and functional status), safety outcomes (serious adverse events (AEs), dermatologic AEs, other AEs), and cost outcomes (cost, cost-effectiveness). We also selected relevant CPGs for quality appraisal and synthesis.

Data Extraction: One research team member extracted data and a second checked for accuracy. Two investigators independently assessed risk of bias of included primary research studies and conducted a quality assessment of included CPGs.

Data Synthesis: We included 11 primary research studies from 15 articles published between 2007 and 2018. Six studies (2 randomized controlled trials [RCTs], 4 observational studies) provided evidence on efficacy, 10 studies (2 RCTs, 8 observational studies) provided evidence on safety, and one study provided evidence on cost. The two included RCTs were rated as having some concerns of bias for overall and progression-free survival efficacy outcomes and safety outcomes but rated as high risk of bias for quality of life outcomes. Almost all the observational comparative studies were rated high risk of bias for all outcomes. All studies were among adult patients with glioblastoma multiforme (GBM) except for 3 case series among adult or pediatric patients with other cancers.

One RCT (n=695) and a small controlled cohort study (n=42) studied the addition of TTF to usual care with temozolomide (TMZ) for newly diagnosed GBM. TTF increased overall and progression-free survival; in the RCT over a median follow up of 40 months, median overall survival was 21 months in the TTF+TMZ group and 16 months among patients receiving TMZ alone (strength of evidence: very low [cohort] to low [RCT]). One RCT (n=237) and 3 observational studies (n=1,446) compared TTF, with or without second-line therapy, with second-line therapy for recurrent GBM; there was heterogeneity of results with no difference in efficacy outcomes between groups in the trial data (strength of evidence: very low) and some increased survival with TTF from the observational data (strength of evidence: very low). Patients with newly diagnosed and recurrent GBM experienced some improvements in quality of life and functional status with TTF use (strength of evidence: very low). Studies reported no serious AEs; dermatologic reactions were common with TTF, and other AEs were attributed to

other aspects of treatment or disease (strength of evidence: very low to low). TTF for newly diagnosed GBM was not found to be cost effective; the incremental cost-effectiveness ratio was estimated at $817,001 from the payor perspective. We found no evidence on which to make conclusions about the effect of TTF on any outcomes among patients with non-GBM cancers or the cost-effectiveness of TTF for recurrent GBM.

We identified 6 CPGs of various quality with substantial disagreement regarding recommendations for treatment with TTF for both newly diagnosed and recurrent GBM.

Limitations: Limited published evidence exists for the clinical effectiveness and safety of TTF for the treatment of newly diagnosed and recurrent GBM and no comparative evidence exists for other cancers. The small body of evidence was limited by increased risk of bias related to lack of participant and outcome assessor blinding, selection bias, attrition, and treatment adherence. Most studies were underpowered, resulting in heterogeneous magnitudes of effect and imprecision. This HTA was limited to English-language studies.

Conclusions: Findings are based on a small body of evidence graded as low or very low certainty because of a paucity of RCT data and comparative observational studies rated high risk of bias. We conclude with very low to low certainty that the addition of TTF to usual care with TMZ increases overall and progression-free survival among patients with newly diagnosed GBM. For patients with recurrent GBM, there may or may not be survival benefits associated with TTF treatment with or without second-line therapy (very low certainty). We conclude with very low certainty from RCT data that TTF improves quality of life and functional status among patients with newly diagnosed or recurrent GBM. We found evidence of minimal harm attributed to TTF treatment for GBM; TTF is likely safe for newly diagnosed and recurrent GBM (very low to low certainty), though likely not cost-effective for newly diagnosed GBM (low certainty). We found no evidence on which to draw conclusions about the cost-effectiveness of TTF for recurrent GBM or the impact of TTF treatment on non-GBM cancers.

ES-1. Background

We designed this health technology assessment (HTA) to assist the State of Washington's independent Health Technology Clinical Committee with determining coverage for tumor treating fields (TTF) (Optune®).

ES-1.1 Clinical Background

In 2018, an estimated 1,735,350 new cancer cases will occur in the United States (U.S.).[1] Among adults, an estimated 23,880 new cases of brain and other central nervous system cancers will be diagnosed in the U.S. in 2018.[1] Glioblastomas, hereafter referred to as glioblastoma multiforme (GBM), are high-grade (i.e., grade IV) gliomas that are astrocytic in origin and most commonly present in the supratentorial region of the brain. From 2006 to 2010, the age-adjusted incidence rate of GBM in the U.S. was 3.19 per 100,000 persons and the median age at diagnosis was 64 years.[2] Of 609,640 cancer deaths in the U.S. in 2018, an estimated 16,830 are from brain and other nervous system cancers.[1] GBM is a highly aggressive disease with a very poor prognosis; less than 5 percent of all patients survive 5 years after a GBM diagnosis. The median survival is 14 to 15 months[3] and only 3 months in untreated patients.[2]

Cancer is typically treated by surgery, radiation therapy, or systemic therapy (e.g., chemotherapy). The current standard of care for patients with newly diagnosed GBM consists of surgical resection followed by 6 weeks of radiotherapy, together with concomitant chemotherapy with temozolomide (TMZ). Once chemoradiotherapy is complete, a minimum of 6 months of adjuvant treatment with TMZ is typical.[4] Patients are typically followed every 2 to 3 months.[5] At the time of disease recurrence, there is no established standard of care and treatment options are limited; approximately 25% of patients may undergo repeat surgery.[5] For the majority of recurrent GBM patients, chemotherapy is indicated; the type of chemotherapy drug used varies widely. Other novel therapies with different mechanisms of action against GBM and reduced toxicity are needed.

ES-1.2 Technology Description

Another modality for cancer treatment uses noninvasive, alternating electrical fields to disrupt mitosis (i.e., cell division) of the malignant cells. The alternating electric fields enter the cancer cell and disrupt mitotic spindle microtubule assembly, resulting in dielectrophoretic dislocation of proteins such as tubulin and septin and interference of cell division; ultimately, this interference results in cancer cell death (i.e., apoptosis).[6] This therapy, known as tumor treating fields (TTF), externally delivers alternating electric fields that are very-low intensity and of intermediate frequency (i.e., 100 to 300 kilohertz [kHz]) to an area of proliferating cancer cells during the late metaphase and anaphase of mitosis. The specific frequency used in treatment is inversely related to the size of the specific cancer cells; for example, 200 kHz is used for treatment of GBM and ovarian cancer while 150 kHz is used for treatment of pancreatic and non-small cell lung cancers. Normal cells, which are affected at -50 kHz, remain unaffected by the frequencies used to treat cancer cells.

TTF are clinically delivered in paired orthogonal directions, left–right and anterior–posterior, using Optune®, previously referred to as the NovoTTF-100A System or Novocure (Novocure

Inc.; Haifa, Israel).[7] Unlike chemotherapy, Optune® therapy does not have a half-life. Therefore, it requires continuous application to be effective. Patients are instructed to use the device at least 18 hours per day; the manufacturer recommends a minimal treatment course duration of 4 weeks.[8-10] The Optune® system is portable and operated by the patient. TTF are delivered through transducer arrays that are applied to the shaved scalp for GBM or to the abdomen, torso, or pelvic areas for other cancers. The patient, caregiver, or doctor can apply Optune® by placing the transducer arrays according to the doctor's instruction.[11] The transducer arrays are composed of insulated ceramic discs that are separated from the skin by a layer of conductive hydrogel. The locations of the arrays are calculated for each individual patient to optimize field intensity based on head size and tumor location.[12,13]

The Optune® device is contraindicated in patients with active implanted electronic medical devices such as deep brain stimulators, pacemakers, and programmable shunts, and in patients with skull defects such as a missing bone flap, because of the risk of skin toxicity and tissue damage. It should also not be used in patients with known hypersensitivity to conductive hydrogels or in patients with infratentorial disease.[7]

ES-1.3 Regulatory Status

The U.S. Food and Drug Administration (FDA) approved TTF for recurrent GBM in April 2011[14] based on the phase 3 EF-11 randomized controlled trial (RCT) that showed TTF exhibited similar efficacy with improved quality of life and a reduced rate of serious adverse events (AEs) compared with clinician's chemotherapy of choice.[15] In October 2015, the FDA approved TTF in combination with TMZ for the treatment of newly diagnosed GBM[16] based on interim results from the phase 3 EF-14 RCT that demonstrated the increased efficacy of TTF plus TMZ versus TMZ alone on progression-free and overall survival following chemoradiotherapy in patients with newly diagnosed GBM.[17]

ES-1.4 Policy Context

The State of Washington's Health Technology Clinical Committee (HTCC) voted in January 2016 to decline coverage of Optune®. The State of Washington Health Care Authority (HCA) selected Optune® as a topic for re-review based on newly available published evidence, ranking as high concerns for efficacy, low concerns for safety, and high concerns for cost. This HTA is designed to assist the State of Washington's independent HTCC in determining coverage for TTF (Optune®).

The State of Washington HCA examined information on the use of TTF from 2014 to 2017 (*Appendix A*). Utilization and cost data were examined from Medicaid programs (fee for service and managed care organization), as well as the Public Employees Benefit Board Uniform Medical Plan and Medicare. Because the aggregate number of patients receiving TTF was less than the minimum allowed for reporting, utilization data are suppressed.

ES-2.   Methods

This health technology assessment (HTA) includes two separate, but related components. The first component is a systematic review of primary research studies and the second component is a quality appraisal and synthesis of relevant clinical practice guidelines (CPGs).

ES-2.1 Research Questions and Analytic Framework for Systematic Review of Primary Research Studies

We developed the following research questions and analytic framework (*Figure ES-1*) to guide the systematic evidence review of primary research studies:

Efficacy Question 1 (EQ1). What is the clinical effectiveness of tumor treating fields for the treatment of newly diagnosed glioblastoma multiforme, recurrent glioblastoma multiforme, and other cancers?

Efficacy Question 1a (EQ1a). Does the clinical effectiveness of tumor treating fields vary by clinical history or patient characteristics (e.g., age, sex, Karnofsky performance score, surgical resection)?

Safety Question 1 (SQ1). What are the harms associated with tumor treating fields for the treatment of newly diagnosed glioblastoma multiforme, recurrent glioblastoma multiforme, and other cancers?

Safety Question 1a (SQ1a). Do the harms associated with tumor treating fields vary by clinical history or patient characteristics (e.g., age, sex, Karnofsky performance score, surgical resection)?

Cost Question 1 (CQ1). What are the costs and cost-effectiveness of tumor treating fields?

Figure ES-1. Analytic framework for HTA on TTF (Optune®)
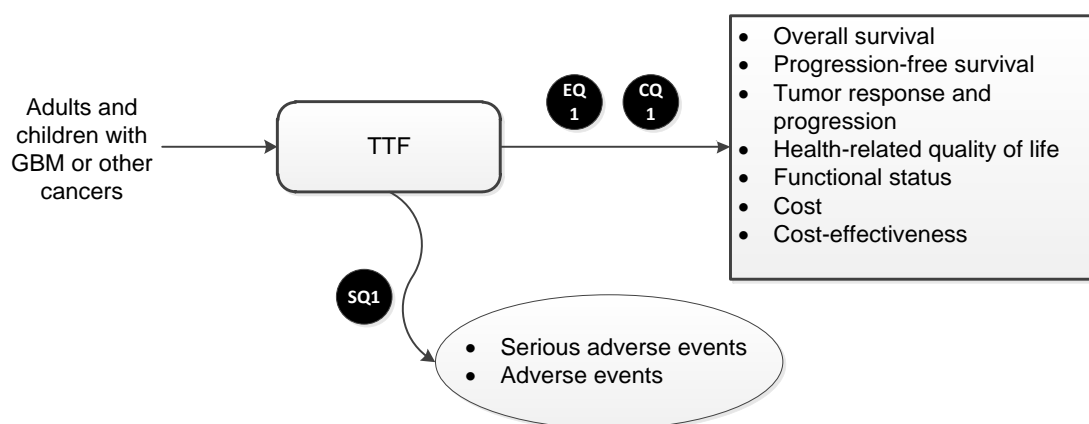
Abbreviations: CQ = cost question; EQ = efficacy question; GBM = glioblastoma multiforme; SQ = safety question; TTF = tumor treating fields.

ES-2.1.1 Data Sources and Search

The search strategy is detailed in **Appendix B**. We searched MEDLINE® (via PubMed) from inception, the Cochrane Library, and a clinical trials registry (clinicaltrials.gov) for relevant English-language studies. We searched the Centers for Medicare and Medicaid Services and United States (U.S.) Food and Drug Administration (FDA) websites, selected payer and health care professional society websites, and websites of other organizations that conduct and disseminate HTAs. In addition, we reviewed the reference lists of relevant studies, systematic reviews, practice guidelines, and other HTAs on this topic to identify any relevant primary research studies not found through the electronic search. We used medical subject headings (MeSH terms) and text words associated with tumor treating fields (TTF).

ES-2.1.2 Study Selection

Table ES-1 summarizes the study selection criteria related to the population, intervention, comparator, outcomes, time period, and setting that defined the scope of this HTA. We screened titles and abstracts and full-text articles based on these study selection criteria.

Table ES-1.   Population, intervention, comparator, outcome, timing, setting and other study selection criteria for HTA on TTF (Optune®)

Domain	Included	Excluded
Population	Adults or children with a histologically confirmed diagnosis of incident or recurrent GBM or other cancer (e.g., non-small cell lung cancer, ovarian cancer, pancreatic cancer)	Adults or children without a histologically confirmed diagnosis of cancer Adults or children for whom treatment with TTF is contraindicated Studies conducted in animals, in vitro, or in silico
Intervention	TTF with or without concomitant therapy	All other interventions including surgery, radiation therapy, or systemic therapy (i.e., chemotherapy, targeted therapies such as hormone therapy)
Comparator	Chemotherapy; TTF plus chemotherapy or other adjunctive treatments; placebo; no comparator	None
Outcomes	**EQ**: Overall survival; progression-free survival; tumor response and progression; health-related quality of life; functional status (e.g., cognitive function measured by the Karnofsky Performance Scale) **SQ**: Serious adverse events; adverse events (e.g., dermatitis, insomnia, headaches) **CQ**: Cost; cost-effectiveness	Quality of life and functional outcomes not measured using valid and reliable instruments or scales
Timing	No time restrictions	None
Setting	Countries[a] categorized as "very high human development" according to the United Nations Development Programme's 2016 Human Development Report[18]	Countries not categorized as "very high human development" according to the United Nations Development Programme's 2016 Human Development Report[18]

(continued)

Table ES-1. Population, intervention, comparator, outcome, timing, setting and other study selection criteria for HTA on TTF (Optune®) (continued)

Domain	Included	Excluded
Study Design	**EQ:** CCTs; RCTs; cohort studies with concurrent or historical comparator group; case-control studies **SQ:** All of the designs listed for EQ plus studies without a comparator (e.g., case series) **CQ:** CEA, CUA, or CBA performed from the societal or payor perspective	Editorials, comments, or letters; narrative or systematic reviews (or similar publications); conference abstracts; case reports Reviews will be hand searched to identify relevant primary studies

Abbreviations: CBA = cost-benefit analysis; CCT = controlled clinical trial; CEA = cost-effectiveness analysis; CQ = cost question; CUA = cost-utility analysis; EQ = efficacy question; GBM = glioblastoma multiforme; HTA = health technology assessment; RCT = randomized controlled trial; SQ = safety question; TTF = tumor treating fields.

[a] Andorra, Argentina, Australia, Austria, Bahrain, Belgium, Brunei Darussalam, Canada, Chile, Croatia, Cyprus, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hong Kong China (SAR), Hungary, Iceland, Ireland, Israel, Italy, Japan, Korea (Republic of), Kuwait, Latvia, Liechtenstein, Lithuania, Luxembourg, Malta, Montenegro, Netherlands, New Zealand, Norway, Poland, Portugal, Qatar, Romania, Russian Federation, Saudi Arabia, Singapore, Slovakia, Slovenia, Spain, Sweden, Switzerland, United Arab Emirates, United Kingdom, United States.

ES-2.1.3 What is Excluded from This HTA

This review did not include studies published in languages other than English or conducted in countries not designated as "very high human development" based on the United Nations Human Development Index.[18]

ES-2.1.4 Data Abstraction and Risk of Bias Assessment

One team member extracted relevant study data into a structured abstraction form and another checked it for accuracy. We used the Cochrane Risk of Bias (RoB 2.0) tool to assess the risk of bias for each included trial.[19] Domains assessed with this tool include: bias arising from randomization process, bias due to deviations from intended interventions, bias due to missing outcome data, bias in measurement of the outcome, and bias in selection of the reported result. Risk of bias was assessed as "high," "some concerns," or "low" at the study level unless different outcomes within a single study required outcome-level risk of bias ratings. We used the Risk Of Bias In Non-randomized Studies – of Interventions (ROBINS-I) instrument to assess the quality of nonrandomized studies with comparator groups;[20] risk of bias ratings were translated to analogous low, some concerns, and high ratings to be consistent with the RoB 2.0 tool. Case series were not evaluated for risk of bias due to the absence of a comparator group. We used the Quality of Health Economic Studies (QHES) instrument to assess the quality of included cost analyses.[21] Two team members conducted independent risk of bias or quality assessments on all included studies.

ES-2.1.5 Data Synthesis and Analysis

Study characteristics and results were qualitatively synthesized for each research question in tabular and narrative formats; quantitative synthesis was not possible because of the limited evidence. For cost outcomes, we adjusted all reported outcomes in foreign currency to U.S. dollars based on the U.S. Department of Treasury mid-year exchange rate for the year reported by study authors (*Appendix C*).

We graded the strength of evidence among comparative studies using a modification to GRADE, which assesses the strength of evidence based on domains relating to risk of bias, inconsistency, imprecision, indirectness, and other considerations, such as publication bias,[22] for outcomes broadly defined as overall survival, progression-free survival, health-related quality of life, and adverse events (AEs). Additionally, we stratified the strength of evidence assessments by specific treatment comparison and indication for treatment (i.e., new and recurrent glioblastoma multiforme [GBM]). To assess the consistency domain within GRADE, we evaluated both the consistency in the direction and magnitude of treatment effect; we modified the conventional GRADE by downgrading this domain when there was only a single-study body of evidence to evaluate. To assess the precision domain, we considered width of confidence intervals, when provided, and whether they included a null effect or clinically meaningful benefit or harm. We applied the GRADE system to the cost-effectiveness study in a similar fashion. With GRADE, the strength of evidence represents the overall certainty of the findings and can be graded as "very low," "low," "moderate," or "high." **Table ES-2** defines these levels of certainty.[23]

Table ES-2.   Strength of evidence grades and definitions[23]

GRADE	Definition
High	**We are very confident that the estimate of effect lies close to the true effect for this outcome.** The body of evidence has few or no deficiencies. We believe that the findings are stable, that is, another study would not change the conclusions.
Moderate	**We are moderately confident that the estimate of effect lies close to the true effect for this outcome.** The body of evidence has some deficiencies. We believe that the findings are likely to be stable, but some doubt remains.
Low	**We have limited confidence that the estimate of effect lies close to the true effect for this outcome.** The body of evidence has major or numerous deficiencies (or both). We believe that additional evidence is needed before concluding either that the findings are stable or that the estimate of effect is close to the true effect.
Very Low	**We have very limited confidence that the estimate of effect lies close to the true effect for this outcome.** The body of evidence has numerous major deficiencies. We believe that substantial additional evidence is needed before concluding either that the findings are stable or that the estimate of effect is close to the true effect.

ES-2.2 Clinical Practice Guideline Synthesis

In addition to the systematic evidence review portion of this HTA, we also identified relevant CPGs and conducted a quality assessment of each guideline using the Appraisal of Guidelines for Research & Evaluation II (AGREE) instrument.[24] With this instrument, six domains are assessed and an overall score of between 1 (lowest possible) and 7 (highest possible) is assigned to reflect the overall quality of the guideline. We synthesized CPGs in a tabular format and discussed the results qualitatively in the accompanying text.

ES-3. Results

ES-3.1 Literature Yield

We identified and screened 423 unique citations. We excluded 346 citations after title and abstract review. We reviewed the full text of 77 articles and included a total of 11 studies reported in 15 articles published between 2007 and 2018. Six studies (10 articles) provided evidence on efficacy (EQ1), 10 studies (10 articles) provided evidence on safety (SQ1), and one

study (1 article) provided evidence on costs or cost-effectiveness (CQ1). The Full Report includes individual study and population characteristics and findings for all included studies (*Appendix D*), the list of articles we screened but excluded at the full-text stage (*Appendix E*), and risk of bias or quality assessments for included studies (*Appendix F)*.

ES-3.2 New GBM

We identified two eligible studies, described in three articles, which investigated the efficacy and safety[25-27] and one study which investigated the cost-effectiveness[28] of tumor treating fields (TTF) in patients with newly diagnosed glioblastoma multiforme (GBM).

ES-3.2.1 Efficacy

Two studies reported outcomes related to the efficacy of TTF for newly diagnosed GBM (EQ1). One study is a randomized controlled trial (RCT), the EF-14 trial.[25,26] We also identified a small cohort study of newly diagnosed GBM patients (n=10) who received treatment with TTF and maintenance temozolomide (TMZ) and were compared to historical and concurrent comparator groups of newly diagnosed GBM patients who received only maintenance TMZ treatment.[27] Efficacy subgroup analyses (EQ1a) were reported by one study, the EF-14 trial, for the overall survival outcome.[25] In the EF-14 trial, there were some concerns of bias for the survival outcomes[25] and high risk of bias for the quality of life (QOL) outcomes.[26] Overall and progression-free survival outcomes were assessed as high risk of bias in the cohort study conducted by Kirson et al.; the cohort study did not provide data on QOL.[27] A summary of the findings and strength of evidence ratings for the efficacy of TTF in patients with newly diagnosed GBM is presented in *Table ES-3*.

Table ES-3. Summary of findings and strength of evidence ratings comparing TTF plus maintenance TMZ to maintenance TMZ alone for efficacy in persons with newly diagnosed GBM (EQ1)

Certainty Assessment		Summary of Findings	CERTAINTY/ Direction of Effect
№ of Studies (№ of Patients)	Risk of Bias Inconsistency[a] Indirectness Imprecision		
Overall survival			
1 RCT (695)[25]	**Risk of Bias**: Serious[b] **Inconsistency**: Unknown **Indirectness**: Not serious **Imprecision**: Not serious	Median OS was 20.9 months with TTF+TMZ and 16.0 months with TMZ alone; HR 0.63 (95% CI, 0.53 to 0.76) over median 40 months of follow up.	⊕⊕◯◯ LOW For benefit with TTF
1 Cohort (NR)[27]	**Risk of Bias**: Very serious[c] **Inconsistency**: Unknown **Indirectness**: Not serious **Imprecision**: Very serious[d]	Observational study consistent with RCT in direction of effect (but not magnitude); median OS was >39 months with TTF+TMZ and 14.7 months with TMZ alone.	⊕◯◯◯ VERY LOW For benefit with TTF

(continued)

Table ES-3.   Summary of findings and strength of evidence ratings comparing TTF plus maintenance TMZ to maintenance TMZ alone for efficacy in persons with newly diagnosed GBM (EQ1) (continued)

Certainty Assessment		Summary of Findings	CERTAINTY/ Direction of Effect
Progression-free survival			
1 RCT (695)[25]	**Risk of Bias**: Serious[b] **Inconsistency**: Unknown **Indirectness**: Not serious **Imprecision**: Not serious	Median PFS was 6.7 months with TTF+TMZ and 4.0 months with TMZ alone; HR 0.63 (95% CI, 0.52 to 0.76) over median 40 months of follow up; at 6 months, 56% of TTF+TMZ group and 37% of TMZ alone group were progression-free.	⊕⊕◯◯ LOW For benefit with TTF
1 Cohort (42)[27]	**Risk of Bias**: Very serious[c] **Inconsistency**: Unknown **Indirectness**: Not serious **Imprecision**: Very serious[e]	Observational study consistent with RCT in direction of effect (but not magnitude); median PFS was 38.8 months with TTF+TMZ and 7.8 months with TMZ alone.	⊕◯◯◯ VERY LOW For benefit with TTF
Quality of life and functional status			
1 RCT (695)[25,26]	**Risk of Bias**: Very serious[b] **Inconsistency**: Unknown **Indirectness**: Not serious **Imprecision**: Serious[f]	Time to sustained decline in KPS and MMSE scores was significantly longer with TTF+TMZ than TMZ alone [KPS: HR 0.79 (95% CI, 0.66 to 0.95); MMSE: HR 0.80 (95% CI, 0.67 to 0.95)]; significantly more patients in TTF+TMZ than TMZ alone group experienced stable or improved global health status, pain, weakness of legs, and physical/cognitive/emotional functioning.	⊕◯◯◯ VERY LOW For benefit with TTF

Abbreviations: CI = confidence interval; EQ = efficacy question; GBM = glioblastoma multiforme; HR = hazard ratio; KPS = Karnofsky Performance Scale; MMSE = Mini Mental State Examination; NA = not applicable; NR = not reported; OS = overall survival; PFS = progression-free survival; RCT = randomized controlled trial; TMZ = temozolomide; TTF = tumor treating fields.

[a] When the body of evidence is a single study, consistency is unknown; a rating of "serious" is entered in the GRADE tool for the purposes of calculating the overall strength of evidence.

[b] The EF-14 trial was rated some concerns for bias for the overall survival, progression-free survival, and safety outcomes and high risk of bias for the quality of life outcomes.

[c] This study was rated high risk of bias for all outcomes.

[d] Results are very imprecise due to a sample size of only 10 patients receiving TTF+TMZ (intervention) and an indeterminate number of patients receiving TMZ alone (comparator).

[e] Results are very imprecise due to a sample size of only 10 patients receiving TTF+TMZ (intervention) and 32 patients receiving TMZ alone (comparator).

[f] Results are somewhat imprecise due to 91% of patients providing data on quality of life outcomes and some EORTC QLQ-C30 subscale results including the both benefit and harm.

Overall Survival

Overall survival was a secondary endpoint in the EF-14 trial. Over a median follow-up period of 40 months, the EF-14 trial reported median overall survival of 20.9 months and 16.0 months in the intervention and comparator groups, respectively. The HR favored treatment with TTF and maintenance TMZ (HR 0.63, 95% CI, 0.53 to 0.76) compared with TMZ alone.[25] Results from the cohort study conducted by Kirson et al. were consistent with the results from the EF-14 trial in direction of effect, but were of greater magnitude among the patients receiving TTF.[27]

In subgroup analyses (EQ1a) of the EF-14 trial data, median overall survival was significantly higher only among patients who were adherent (i.e., used continuous TTF therapy for ≥18 hours

per day) (22.6 months, 95% CI, 19.7 to 25.1) than among patients who were not adherent (19.1 months, 95% CI, 16.5 to 21.9) (HR 0.65, 95% CI, 0.49 to 0.85).[25]

Progression-free Survival

Progression-free survival was the primary endpoint in the EF-14 trial. Over a median follow-up period of 40 months, the EF-14 trial reported median progression-free survival of 6.7 months and 4.0 months in the intervention and comparator groups, respectively. The HR favored treatment with TTF and maintenance TMZ (HR 0.63, 95% CI, 0.52 to 0.76) compared to TMZ alone. Results from the cohort study by Kirson et al. were consistent with the results from the EF-14 trial in direction of effect, but not magnitude. Median progression-free survival was greater than 38.75 months (reported as 155 weeks) among the 10 patients who received TTF with maintenance TMZ therapy and 7.75 months (reported as 31 weeks) among the patients in the historical comparator group who only received maintenance TMZ (P=0.0002).[27]

No subgroup analyses (EQ1a) were reported for the progression-free survival outcome.

Quality of Life and Functional Status

In the EF-14 trial, health-related quality of life (HRQoL) and functional status were self-reported by patients. In intention-to-treat (ITT) analyses, the median time to a sustained 6-point decrease on the Mini-Mental State Examination (MMSE) (i.e., a decrease in function) was 16.7 and 14.2 months in the intervention and comparator groups, respectively (HR 0.79, 95% CI, 0.66 to 0.95). The median time to a sustained 10-point decrease on the Karnofsky Performance Scale (KPS) (i.e., a decrease in function) was 5.5 and 3.9 months in the intervention and comparator groups, respectively (HR 0.80, 95% CI, 0.67 to 0.95). In analyses among patients with baseline HRQoL data (n=639; 92% of randomized), the percentage of patients with stable or improved HRQoL was significantly higher in the intervention group than the comparator group for global health status (54% versus 38%); physical functioning (54% versus 38%); cognitive functioning (50% versus 39%); emotional functioning (55% versus 44%); pain (57% versus 36%); and weakness of legs (59% versus 42%) but not role functioning (48% versus 41%), social functioning (48% versus 41%), or itchy skin (42% versus 47%).

No subgroup analyses (EQ1a) were reported for the QOL and functional status outcomes.

Summary

We concluded with low certainty from RCT evidence and very low certainty from observational study evidence that the addition of TTF to usual care treatment with TMZ improved overall and progression-free survival among patients with newly diagnosed GBM. We also concluded with very low certainty from RCT evidence that the addition of TTF to usual care treatment with TMZ improved quality of life and functional status among patients with newly diagnosed GBM (*Table ES-3*).

ES-3.2.2 Safety

The two studies included for the efficacy research questions (EQ1, EQ1a) also contributed data to the safety research question (SQ1) for newly diagnosed GBM. No subgroup analyses (SQ1a) were reported for the safety outcomes. In the EF-14 trial[25] there were some concerns of bias. In the cohort study by Kirson et al., safety outcomes were only reported for the 10 patients who received TTF with maintenance TMZ therapy and as such, we did not rate the risk of bias for safety outcomes.[27] A summary of the findings and strength of evidence ratings for the safety of TTF in patients with newly diagnosed GBM is presented in **Table ES-4**.

Table ES-4. **Summary of findings and strength of evidence ratings comparing TTF plus maintenance TMZ to maintenance TMZ alone for safety in persons with newly diagnosed GBM (SQ1)**

Certainty Assessment			
№ of Studies (№ of Patients)	Risk of Bias Inconsistency[a] Indirectness Imprecision	Summary of Findings	CERTAINTY/ Direction of Effect
Adverse events			
1 RCT (672)[25]	**Risk of Bias:** Serious[b] **Inconsistency:** Unknown **Indirectness:** Not serious **Imprecision:** Not serious	Mild to moderate dermatologic AEs were reported by half of patients receiving TTF; the addition of TTF to TMZ treatment did not significantly increase the rates of systemic AEs (P=0.58).	⊕⊕◯◯ LOW For minimal harm with TTF

Abbreviations: AE = adverse event; GBM = glioblastoma multiforme; RCT = randomized controlled trial; SQ = safety question; TMZ = temozolomide; TTF = tumor treating fields.

[a] When the body of evidence is a single study, consistency is unknown; a rating of "serious" is entered in the GRADE tool for the purposes of calculating the overall strength of evidence.

[b] The EF-14 trial was rated some concerns for bias for the overall survival, progression-free survival, and safety outcomes and high risk of bias for the quality of life outcomes.

There were no serious adverse events (AEs) among the 10 patients who received TTF and maintenance TMZ treatment in the small cohort study.[27]

Among 456 patients in the EF-14 trial with grade 3 or grade 4 GBM (98% of 466 randomized to TTF plus maintenance TMZ), more than half (52%) experienced mild to moderate site reactions under the TTF transducer arrays and 2 percent experienced a severe (i.e., grade 3) site reaction.[25] All 10 patients in the cohort study by Kirson et al. reported grade 1 or 2 (i.e., mild to moderate) dermatitis and none reported grade 3 or 4 (i.e., severe or disabling) dermatitis.[27]

The EF-14 trial reported no significant difference between groups with respect to participants experiencing one or more grade 3 or 4 (i.e., severe or disabling) AEs (P=0.58 for between-group comparison) and differences between groups for specific safety outcomes disappeared once treatment duration was taken into account.[25] All of the mild to moderate AEs reported among the 10 patients in the cohort study were attributed to underlying disease, TMZ treatment, or other treatments; no severe or disabling AEs were reported.[27]

We concluded with low certainty from RCT data that the addition of TTF to usual care treatment with TMZ among patients with newly diagnosed GBM introduced minimal harm (**Table ES-4**). We did not grade strength of evidence from the observational study by Kirson et al.[27] since

safety outcomes were reported only for the patients receiving treatment with TTF (i.e., there was no comparative analysis).

ES-3.2.3 Cost

We identified one eligible study that investigated the cost-effectiveness of TTF in patients with newly diagnosed GBM.[28] Bernard-Arnoux et al.[28] used effectiveness data from the interim analysis of the EF-14 trial[17] to conduct a cost-effectiveness study comparing TTF plus maintenance TMZ to maintenance TMZ alone from the French health care system payor perspective. The authors entered a hypothetical cohort of 1,000 people into a Markov decision model with the same characteristics and receiving the same intervention as those in the EF-14 trial.[17] We rated this study as good quality using the Quality of Health Economic Studies (QHES) instrument. A summary of the findings and strength of evidence rating for the cost-effectiveness of TTF in patients with newly diagnosed GBM is presented in ***Table ES-5***.

The incremental cost-effectiveness ratio (ICER) was $817,000 (in 2014 United States Dollars [USD]) (95% CI, $612,352 to $1,021,651) per life year gained and remained robust across sensitivity analyses. According to the authors, if the monthly costs for the Optune® system and support were reduced to $2,740 per month from $27,398 per month (price discounted by approximately 90%), the discounted ICER would be $97,562.

We concluded with low certainty that TTF is not cost-effective among patients with newly diagnosed GBM (***Table ES-5***).

Table ES-5. Summary of findings and strength of evidence ratings comparing TTF plus maintenance TMZ to maintenance TMZ alone for cost-effectiveness in persons with newly diagnosed GBM (CQ1)

№ of Studies (№ of Patients)	Certainty Assessment Risk of Bias Inconsistency[a] Indirectness Imprecision	Summary of Findings[b]	CERTAINTY/ Direction of Effect
Cost-effectiveness			
1 study (1000)[28]	**Risk of Bias:** Not serious **Inconsistency:** Unknown **Indirectness:** Not serious **Imprecision:** Not serious	The discounted payor perspective ICER was $817,001 (95% CI, $612,352 to $1,021,651) per life year gained.	⊕⊕◯◯ LOW[c] Not cost-effective

Abbreviations: CI = confidence interval; CQ = cost question; GBM = glioblastoma multiforme; ICER = incremental cost-effectiveness ratio; TMZ = temozolomide; TTF = tumor treating fields.

[a] When the body of evidence is a single study, consistency is unknown; a rating of "serious" is entered in the GRADE tool for the purposes of calculating the overall strength of evidence.

[b] All costs are reported here in 2014 U.S. Dollars. The costs for the year and currency reported in the published studies is in ***Appendix D***, ***Table D-6***.

[c] As a cost effectiveness study, the starting GRADE for this study was "low" (i.e., the approach taken with observational research). The study was then downgraded for unknown inconsistency and upgraded for the large effect size.

ES-3.3 Recurrent GBM

We identified 4 eligible studies, described in 7 articles, which investigated the efficacy of TTF among patients with recurrent GBM.[9,15,29-33] The same studies also investigated the safety of TTF

among patients with recurrent GBM, described in 4 articles,[9,15,32,33] along with one additional eligible study.[13] No eligible studies evaluated the cost-effectiveness of TTF among patients with recurrent GBM.

ES-3.3.1 Efficacy

One RCT, the EF-11 trial,[15,29-31] and 3 observational studies[9,32,33] investigated the efficacy of TTF among patients with recurrent GBM (EQ1). One observational study included patients from the Patient Registry Dataset (PRiDe) who were compared to both groups of the EF-11 trial.[9] Another observational study by Kirson et al. included a small cohort of patients with recurrent GBM (n=10) who were compared to multiple historical comparator groups.[33] The final observational study included patients originally enrolled in the EF-14 trial of TTF for newly diagnosed GBM[25] who experienced a recurrence during follow up;[32] patients received TTF with second-line therapy or second-line therapy alone. All other studies, including the EF-11 trial, evaluated TTF monotherapy compared with second-line therapy alone. Efficacy subgroup analyses (EQ1a) were reported by 3 studies, in 5 articles,[9,29-32] for the overall survival outcome and one study[29] for the progression-free survival outcome. In the EF-11 trial, there were some concerns of bias for the overall survival and progression-free survival outcomes[15,29-31] and high risk of bias for the QOL outcomes.[15] There were some concerns of bias for all efficacy outcomes in the PRiDe study.[9] The small cohort study by Kirson et al.[33] and the post-hoc analysis of EF-14 patients who experienced a recurrence by Kesari et al.[32] were rated high risk of bias for all efficacy outcomes. A summary of the findings and strength of evidence ratings for the efficacy of TTF in patients with recurrent GBM is presented in *Table ES-6*.

Table ES-6. Summary of findings and strength of evidence ratings for efficacy of TTF in persons with recurrent GBM (EQ1)

Certainty Assessment			
№ of Studies (№ of Patients) **Treatment Comparison**	**Risk of Bias** **Inconsistency[a]** **Indirectness** **Imprecision**	**Summary of Findings**	**CERTAINTY/ Direction of Effect**
Overall survival			
1 RCT (237)[15] TTF versus Second-line therapy	**Risk of Bias**: Serious[b] **Inconsistency**: Unknown **Indirectness**: Not serious **Imprecision**: Serious[c]	Median OS was similar in the intervention and comparator groups (6.6 and 6.0 months, respectively) in the EF-11 trial; [HR 0.86, 95% CI, 0.66 to 1.12; P=0.27].	⊕◯◯◯ VERY LOW For no benefit with TTF
2 Cohort (1,479)[9,33] TTF versus Second-line therapy	**Risk of Bias**: Very serious[b] **Inconsistency**: Serious[d] **Indirectness**: Not serious **Imprecision**: Serious[e]	Studies were consistent in direction but not magnitude of effect with each other and the RCT. Patients in PRiDe registry reported "significantly longer" OS than EF-11 patients receiving second-line therapy (6.0 months).[9] Median OS in 10 TTF patients (16 months) was "more than double" that of historical controls (range 6 to 10 months) in the pilot study for EF-11.[33]	⊕◯◯◯ VERY LOW For benefit with TTF
1 Cohort (204)[32] TTF + Second-line therapy versus Second-line therapy	**Risk of Bias**: Very serious[b] **Inconsistency**: Unknown **Indirectness**: Not serious **Imprecision**: Serious[c]	Median OS was similar in the intervention and comparator groups (11.8 and 9.2 months, respectively) [HR 0.70, 95% CI, 0.48 to 1.00; P=0.05].	⊕◯◯◯ VERY LOW For no benefit with TTF

(continued)

Table ES-6.   Summary of findings and strength of evidence ratings for efficacy of TTF in persons with recurrent GBM (EQ1) (continued)

Certainty Assessment		Summary of Findings	CERTAINTY/ Direction of Effect
№ of Studies (№ of Patients) **Treatment Comparison**	**Risk of Bias Inconsistency[a] Indirectness Imprecision**		
Progression-free survival			
1 RCT (237)[15] TTF versus Second-line therapy	**Risk of Bias**: Serious[b] **Inconsistency**: Unknown **Indirectness**: Not serious **Imprecision**: Serious[c]	Median PFS was 2 months in both the intervention and comparator groups in the RCT [HR 0.81, 95% CI, 0.60 to 1.09]; 21% of TTF patients and 15% of second-line therapy patients were progression-free at 6 months (P=0.13).	⊕◯◯◯ VERY LOW For no benefit with TTF
1 Cohort (785)[33] TTF versus Second-line therapy	**Risk of Bias**: Very serious[b] **Inconsistency**: Unknown **Indirectness**: Not serious **Imprecision**: Very serious[e]	The historical comparator groups in the observational study reported similar results (9%-19% were progression-free at 6 months) but a much higher proportion (50%) of the 10 TTF patients were progression-free at 6 months; this is consistent in direction but not magnitude of effect with the RCT. Authors report that the median time to progression was more than double for the TTF than the second-line therapy patients; confidence intervals were very wide in the TTF group.	⊕◯◯◯ VERY LOW For benefit with TTF
Quality of life and functional status			
1 RCT (63)[15] TTF versus Second-line therapy	**Risk of Bias**: Very serious[b] **Inconsistency**: Unknown **Indirectness**: Not serious **Imprecision**: Very serious[e]	After 3 months, TTF participants showed larger improvements on the EORTC QLQ-C30 emotional functioning subscale, less of a decline on the role functioning subscale, and improvement (compared to a decline with chemotherapy) on the cognitive functioning subscale. Patients receiving second-line therapy experienced less of a decline on the physical functioning subscale. There were no "meaningful" differences between TTF and second-line therapy with respect to the global health status and social functioning subscales.	⊕◯◯◯ VERY LOW For benefit with TTF

Abbreviations: CI = confidence interval; EORTC QLQ-C30 = European Organization for Research and Treatment Quality of Life Questionnaire; EQ = efficacy question; GBM = glioblastoma multiforme; HR = hazard ratio; OS = overall survival; PFS = progression-free survival; PRiDe = Patient Registry Dataset; RCT = randomized controlled trial; TTF = tumor treating fields.

[a] When the body of evidence is a single study, consistency is unknown; a rating of "serious" is entered in the GRADE tool for the purposes of calculating the overall strength of evidence.

[b] The EF-11 trial[15] was rated some concerns for bias for overall survival, progression-free survival, and safety outcomes and high risk of bias for the quality of life outcomes. The PRiDe[9] study was rated some concerns for bias for overall and progression-free survival and high risk of bias for safety outcomes. All other studies[32,33] were rated high risk of bias for all outcomes. When considering multiple studies, the higher risk of bias was considered for the purposes of calculating the overall strength of evidence.

[c] Results are imprecise due to small sample size, with confidence intervals that include both benefit and harm.

[d] Results are consistent between the two studies in direction of effect but not magnitude of effect.

[e] Results are imprecise due to very small sample size in at least one study group.

Overall Survival

Overall survival was the primary endpoint in the EF-11 trial. Over a median follow-up period of 39 months, the median overall survival did not differ between the intervention (6.6 months) and

the comparator group (6.0 months) (HR 0.86, 95% CI, 0.66 to 1.12; P=0.27).[15] Mrugula et al.[9] reported that median overall survival among patients in the PRiDe registry (9.6 months) was "markedly longer" and "significantly longer" than EF-11 trial patients receiving TTF treatment or second-line therapy. In the pilot study by Kirson et al., the median overall survival in the intervention group (62 weeks; range 20 to 124 weeks) was "more than doubled" the median overall survival in 5 historical comparator groups (range of medians 24 to 39 weeks).[33] In the post-hoc analysis of patients with recurrence from the EF-14 trial, Kesari et al. reported that over a median follow-up period of 12.6 months, the median overall survival was higher among patients receiving TTF treatment with second-line therapy (11.8 months) than patients receiving second-line therapy alone (9.2 months) (P=0.049).[32]

Several subgroup analyses (EQ1a) of the EF-11 trial data have been reported.[15,29-31] When the intervention group was restricted to patients who received at least one cycle of TTF treatment (i.e., 28 days) (93 of 120 randomized [78%]), median survival increased to 7.8 months (from 6.6 months among all randomized patients) and the comparison between groups was significant (HR 0.69, 95% CI, 0.52 to 0.92; P=0.0093); all patients randomized to second-line therapy received at least one course of treatment.[15] Median overall survival was significantly higher in the intervention group than in the comparator group among patients with the following: previous failed treatment with bevacizumab (P=0.0156); prior low-grade glioma diagnosis (P=0.0493); tumor size $\geq$18 cm^2 (P=0.009); baseline KPS score $\geq$80 (P=0.0453); and higher rate of adherence to treatment (P=0.039).[30] Mrugula et al. also reported subgroup analyses for the PRiDe registry. Among the 457 patients in the PRiDe registry who received TTF treatment, median overall survival was significantly higher for patients with the following attributes: first recurrence, $\geq$75 percent daily adherence to treatment, KPS scores between 90 and 100, and no prior bevacizumab use.[9] For further subgroup analyses, please refer to the Full Report.

Progression-free Survival

Over a median follow up of 39 months, the median progression-free survival in the EF-11 trial was 2.2 months among the intervention group and 2.1 months among the comparator group (HR 0.81, 95% CI, 0.60 to 1.09). Twenty-one percent (95% CI, 13.5% to 29.3%) of TTF patients and 15 percent (95% CI, 7.8% to 22.3%) of second-line therapy patients were progression-free at 6 months (P=0.13). In the small cohort study of 10 patients receiving TTF treatment, Kirson et al. reported that median time to disease progression (26.1 weeks; range 3 to 124 weeks) was more than double the reported medians of the 5 historical comparator groups (range of medians 8.1 to 12.4 weeks).[33]

In subgroup analyses (EQ1a) of the EF-11 trial, the median progression-free survival was higher among responders (n=21) than nonresponders (n=216) within both the TTF (P=0.0007) and second-line therapy (P=0.0222) groups and was numerically higher among patients receiving TTF treatment than patients receiving second-line therapy, regardless of response.[29]

Quality of Life and Functional Status

The EF-11 trial investigators reported that there were "no meaningful differences" between the intervention and comparator groups with respect to the global health status and social

functioning subscales from the EORTC QLQ-C30 at 3 months. The TTF intervention group was favored with respect to multiple subscales; patients experienced larger improvements, less of a decline, and improvement rather than a decline when compared to the second-line therapy group on the emotional, role, and cognitive functioning subscales, respectively.[15] The EF-11 trial did not report any subgroup analyses (EQ1a) and none of the other included studies for EQ1 provided data on QOL or functional status.

Summary

Evidence on the efficacy of TTF for recurrent GBM varied by study design. We concluded with very low certainty from RCT data that there are no differences in survival outcomes between TTF monotherapy and second-line therapy; however, QOL is improved with TTF monotherapy. From observational data, we concluded that there is a survival benefit with TTF monotherapy (very low certainty).

For the comparison of TTF with second-line therapy and second-line therapy alone among patients with recurrent GBM, we concluded with very low certainty (from one observational study) that there are no differences in overall survival outcomes between the groups. There was no evidence on which to draw a conclusion about the potential benefit of TTF with respect to progression-free survival, QOL, or functional status (***Table ES-6***).

ES-3.3.2 Safety

The 4 studies included for the efficacy research questions (EQ1, EQ1a) also contributed data to the safety research question (SQ1). We additionally identified one case series of patients with recurrent GBM by Lacouture et al. that contributed data to the safety question (SQ1).[13] No subgroup analyses (SQ1a) were reported for the safety outcomes. In the EF-11 trial,[15] there were some concerns of bias for the safety outcomes; all other comparative studies[9,13,32,33] were rated as high risk of bias for the safety outcomes.

A summary of the findings and strength of evidence ratings for the safety of TTF in patients with recurrent GBM is presented in ***Table ES-7***. Adverse effects were similar across the studies that compared TTF, with or without second-line therapy, with second-line therapy alone.

Table ES-7. Summary of findings and strength of evidence ratings for safety of TTF in persons with recurrent GBM (EQ1)

Certainty Assessment		Summary of Findings	CERTAINTY/ Direction of Effect
№ of Studies (№ of Patients) Treatment Comparison	Risk of Bias Inconsistency[a] Indirectness Imprecision		
Adverse Events			
1 RCT (207)[15] TTF versus Second-line therapy	**Risk of Bias**: Serious[b] **Inconsistency**: Unknown **Indirectness**: Not serious **Imprecision**: Serious[c]	Mild to moderate contact dermatitis beneath the TTF transducer arrays was reported by 16% of the patients in the TTF group; no severe or disabling dermatologic AEs were reported in either group. Moderate to disabling AEs were reported by 6% of the TTF group and 16% of the second-line therapy group (P=0.022); only 3% of patients overall experienced a severe or disabling AE.	⊕◯◯◯ VERY LOW For minimal harm with TTF
2 Cohort (1,479)[9,33] TTF versus Second-line therapy	**Risk of Bias**: Very serious[b] **Inconsistency**: Serious[d] **Indirectness**: Not serious **Imprecision**: Serious[c]	No serious AEs reported with TTF; range of 24% to 90% of TTF patients experienced a skin reaction/contact dermatitis with TTF; other AEs were rare (≤10%) or not attributed to TTF treatment.	⊕◯◯◯ VERY LOW For minimal harm with TTF
1 Cohort (204)[32] TTF + Second-line therapy versus Second-line therapy	**Risk of Bias**: Very serious[b] **Inconsistency**: Unknown **Indirectness**: Not serious **Imprecision**: Serious[c]	Site reactions beneath the TTF transducer arrays were reported by 13% of patients in the intervention group; though 49% of the TTF group experienced at least one grade 3 or 4 AE[e], compared to 33% of the second-line therapy group, none were related to TTF treatment.	⊕◯◯◯ VERY LOW For minimal harm with TTF

Abbreviations: AE = adverse event; GBM = glioblastoma multiforme; RCT = randomized controlled trial; SQ = safety question; TTF = tumor treating fields.

[a] When the body of evidence is a single study, consistency is unknown; a rating of "serious" is entered in the GRADE tool for the purposes of calculating the overall strength of evidence.

[b] The EF-11 trial[15] was rated some concerns for bias for overall survival, progression-free survival, and safety outcomes and high risk of bias for the quality of life outcomes. The PRiDe[9] study was rated some concerns for bias for overall and progression-free survival and high risk of bias for safety outcomes. All other studies[32,33] were rated high risk of bias for all outcomes. When considering multiple studies, the higher risk of bias was considered for the purposes of calculating the overall strength of evidence.

[c] Study sample sizes across studies were relatively small, especially for rare serious adverse events.

[d] Results are consistent between the two studies in direction of effect but not magnitude of effect.

[e] Authors did not explicitly define what is meant by grade 3 or 4, but patients were originally enrolled in the EF-14 trial[25], where grade 3 or 4 was defined as severe or disabling, according to the NCI Common Terminology Criteria for Adverse Events v3.0.[34,35]

Authors of the EF-11 trial report that serious AEs were significantly lower in the intervention group than in the comparator group (6% versus 16%, P=0.022) but do not define serious AEs or provide additional details.[15] No treatment-related serious AEs occurred among 10 patients who were compared to multiple historical comparator groups in the pilot study by Kirson et al.;[33] none of the other eligible observational studies reported data on serious AEs.

Sixteen percent of the intervention group in the EF-11 trial reported a mild to moderate (grade 1 or 2) contact dermatitis beneath the transducer arrays and no patients experienced a grade 3 or 4 (i.e., severe or disabling) dermatologic AE in either group.[15] Transducer array site reactions were commonly reported by patients receiving TTF in the observational studies (range 13%[32] to

90%[33]). In Lacouture et al.'s case series of 540 patients receiving TTF treatment, the median time to dermatologic AE onset was 32.5 days (range 2 to 250).[13]

Authors of the EF-11 trial reported that patients in the active comparator group experienced chemotherapy-related AEs, including significantly more hematological (17%), gastrointestinal (17%), and infection-related (8%) AEs than the TTF group (3%, 4%, and 4%, respectively).[15] Kirson et al.'s post-hoc analysis of EF-14 patients (who experienced a recurrence) reported that 49 percent of patients receiving TTF treatment experienced one or more grade 3 or 4 (not otherwise defined by study authors, presumably severe or disabling) AE compared to 33 percent of patients receiving second-line therapy; however, none of the AEs in the intervention group were attributed to the TTF treatment and, as suggested by the investigators, may have been related to the longer duration of follow-up in the TTF plus second-line therapy group compared to the second-line therapy alone group.[32] Likewise, none of the other AEs experienced by patients in the intervention groups of the EF-11 trial,[15] the PRiDe study,[9] or the patients in the pilot study by Kirson et al.[33] were attributed to TTF treatment.

We concluded with very low certainty that there is minimal harm with TTF, with or without second-line therapy, compared with second-line therapy alone for patients with recurrent GBM (*Table ES-7*).

ES 3.4 Other Cancers

We identified three studies[12,36,37] that investigated the safety of TTF and no studies that investigated the efficacy or cost-effectiveness of TTF in patients with other cancers. Due to the lack of comparator groups, we did not assess ROB or grade strength of evidence for the safety outcomes from these case series.

In the case series of NSCLC patients by Pless et al., none of the serious AEs reported were considered TTF-related over a follow-up period of 9.5 months.[12] No serious AEs were reported among patients in the other two case series.[36,37]

In regard to dermatological AEs, Pless et al. reported only one NSCLC patient who had a severe or disabling dermatologic AE (rash/dermatitis/erythema). Mild or moderate rash/dermatitis/erythema was the most common dermatologic AE reported among the NSCLC patients (24%); the remaining dermatologic AEs were also mild or moderate and included blister (7%), pruritus (5%), alopecia (2%), and ulceration (2%).[12] In the case series by Green et al., one (20%) of the pediatric glioma patients reported a scalp ulceration, categorized by the authors as a grade 2 skin breakdown.[36] Three patients (50%) in the multi-cancer case series by Salzberg et al. reported a grade 1 (not otherwise defined by study authors) skin irritation with reddening of the skin under the transducer arrays.[37]

Pless et al. was the only study that reported nondermatologic AEs. Less than 10 percent of patients reported any of the AEs, except for respiratory AEs (dyspnea: 29% and cough: 27%) that were expected due to the natural history of lung cancer.[12]

ES-3.5 Synthesis of Clinical Practice Guidelines

We identified several clinical practice guidelines (CPGs) for the treatment of GBM, 6 of which include a discussion of TTF as a treatment modality. These are summarized in ***Table ES-8***. Please refer to the [Full Report](#) for additional details.

Overall, recommendations were mixed. TTF for the treatment of recurrent GBM was addressed in all 6 guidelines; 3 of 6 CPGs addressed use of TTF for newly diagnosed GBM. The NCCN[38] and the AANN[39] both recommend TTF as an adjunct to chemotherapy for patients with recurrent GBM, whereas neither the SEOM[40], EANO[41], nor ESMO[42] include TTF as a recommended treatment, stating that treatment with TTF failed to prolong survival compared with second-line chemotherapy. Similarly, NICE recommends against TTF for the management of recurrent GBM, stating that there is evidence of some clinical benefit but that indirect published health economic evidence in people with newly diagnosed high-grade gliomas found that treatment with TTF is not an efficient use of the United Kingdom's (U.K.'s) National Health System's (NHS) resources.[43] Of the 3 guidelines addressing TTF for newly diagnosed GBM, the NCCN recommends TTF as an adjunct to standard radiotherapy plus chemotherapy for patients of any age with a good Karnofsky performance score (>60 KPS). It recently updated the strength of that recommendation (based on results from the EF-14 trial[25]) from a category 2A recommendation (based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate) to a category 1 recommendation (based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate).[38] Conversely, the EANO does not recommend the use of TTF for newly diagnosed GBM.[41] Similarly, NICE also recommends against TTF for the management of newly diagnosed GBM based on the published health economic evidence.[28]

Table ES-8. Clinical practice guidelines that include TTF treatments

Organization *Guideline Title (Year)* Guideline Quality Rating[a]	Evidence Base	Recommendation[b]	Rating/Strength of Evidence Narrative Assessment[c]
National Comprehensive Cancer Network (NCCN) *NCCN Clinical Practice Guidelines in Oncology. Central Nervous System Cancers Version 1.2018 (2018)[38]* Quality Rating: 5 out of 7	2 RCTs	For patients of any age with newly diagnosed GBM and with good performance status (KPS >60), and any MGMT promoter status: Recommend standard brain radiotherapy + concurrent temozolomide and adjuvant temozolomide + **alternating electric field therapy.[d]** For patients with recurrent glioblastoma: consider **alternating electric field therapy.[d]**	Authors rated the recommendation for newly diagnosed GBM Category 1 and recurring GBM Category 2B[e]
U.K. National Institute for Health and Care Excellence (NICE) *Brain tumours (primary) and brain metastases in adults (2018)[43]* Quality Rating: 7 out of 7	2 RCTs	For patients newly diagnosed glioblastoma: Do not offer **TTF** as part of management. For patients with recurrent glioblastoma: Do not offer **TTF** as part of management.	NICE chooses to reflect the concept of strength in the wording of the recommendation

(continued)

Table ES-8.   Clinical practice guidelines that include TTF treatments (continued)

Organization *Guideline Title (Year)* Guideline Quality Rating[a]	Evidence Base	Recommendation[b]	Rating/Strength of Evidence Narrative Assessment[c]
American Association of Neuroscience Nurses (AANN) *Care of the Adult Patient with a Brain Tumor (2014)[39] (Revised 2016)* Quality Rating: 4 out of 7	1 RCT, 1 Narrative Expert Review	Nurses should be aware that use of electrical **TTF** may be considered a comparable treatment option to chemotherapy for patients with recurrent malignant glioma, particularly when hematologic, infectious, or gastrointestinal toxicities limit treatment options (Level 1 recommendation). When **TTF** are used, nurses should assess the skin for topical dermatitis (Level 1 recommendation). Nurses should educate patients about measures to improve comfort and compliance with the system (Level 3 recommendation).	Authors rated two recommendations Level 1 and one recommendation Level 3[f]
Medical Oncology Spanish Society (SEOM) *SEOM clinical guidelines for diagnosis and treatment of glioblastoma (2017)[40]* Quality Rating: 3 out of 7	Unclear	For recurrent GBM, **TTF** failed to prolong survival compared with second-line chemotherapy.	Authors rated the evidence level II grade D[g]
European Association for Neuro-Oncology (EANO) *EANO guideline on the diagnosis and treatment of adult astrocytic and oligodendroglial gliomas (2017)[41]* Quality Rating: 5 out of 7 overall. 3 out of 7 for the guidelines handling of TTF	2 RCTs	TTF was not recommended. The following two statements were included in the text: <u>Newly diagnosed GBM:</u> Questions about the mode of action, interpretation of data, and effect on quality of life have been raised, and the role and cost-effectiveness of **TTF** in the treatment of newly diagnosed glioblastoma remain to be defined. <u>Recurrent GBM:</u> **TTF** were not superior to best physician's choice in a randomized phase III trial.	No rating was given when a treatment was not recommended
European Society for Medical Oncology (ESMO) *High-grade glioma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up (2014)[42]* Quality Rating: 2 out of 7	1 RCT	TTF was not recommended. The guideline included the following statement for recurrent GBM "**TTF** failed to prolong survival compared with second-line chemotherapy."	Authors rated the TTF evidence level I grade A[h]

Abbreviations: AGREE II = Appraisal of Guidelines for Research & Evaluation II; CT = controlled trial; GBM = glioblastoma; KPS = Karnofsky Performance Score; MGMT = 06-methylguanine-DNA Methyltransferase; NCCN = National Comprehensive Cancer Network; RCT = randomized controlled trial; SR = systematic review; TTF = tumor treating fields; U.K. = United Kingdom.

[a] Results of our independent quality assessment using the AGREE II tool (version 2017.21). Unless otherwise noted, the Rating refers to the quality of the overall guideline including the guidelines handling of the TTF evidence. A score of 1 indicates the lowest quality possible, a score of 7 indicated the highest quality possible.

[b] Only recommendations from the guideline pertinent to TTF for the treatment of GBM are summarized.

[c] Refers to the quality rating/ strength of the recommendation as described in the guideline by the authors of the CPG.

[d] Alternating electric field therapy is only an option for patients with supratentorial disease.

[e] Category 1 evidence: based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate. Category 2B: Based upon lower-level evidence, there is NCCN consensus that the intervention is appropriate. Note the recommendation for newly diagnosed GBM was changed from category 2A (based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate) to category 1 in a flash update to the 2018 guideline.

[f] Level 1 recommendations are supported by Class 1 evidence. Class I = Randomized controlled trials without significant limitations or meta-analysis. Level 3 recommendations are supported by Class III and IV evidence. Class III = Qualitative study, case study, or series Class IV = Evidence from expert committee reports and expert opinion of the AANN guideline panel; standards of care and clinical protocols that have been identified.

[g] Level 2 Evidence = Small randomized trials or large randomized trials with a suspicion of bias (lower methodological quality) or meta-analyses of such trials or of trials with demonstrated heterogeneity. Grade D = Moderate evidence against efficacy or for adverse outcome, generally not recommended.

[h] Level 1 = Evidence from at least one large randomized, controlled trial of good methodological quality (low potential for bias) or meta-analyses of well-conducted randomized trials without heterogeneity, Grade A= Strong evidence for efficacy with a substantial clinical benefit, strongly recommended.

ES-4. Discussion

ES-4.1 Summary of the Evidence

Limited evidence on the efficacy, safety, and cost-effectiveness of tumor treating fields (TTF) treatment among patients with cancer exists. We included only one eligible randomized controlled trial (RCT) that compared TTF plus maintenance temozolomide (TMZ) with maintenance TMZ alone among adult patients with newly diagnosed glioblastoma multiforme (GBM)[25] and one eligible RCT that compared TTF with second-line therapy among adult patients with recurrent GBM;[15] no eligible RCTs evaluated the use of TTF among pediatric patients or patients with non-GBM malignancies. The observational data were limited to one cohort study among trial participants who experienced recurrent GBM,[32] 3 cohorts that were compared to concurrent or historical comparator groups from other studies for both newly diagnosed GBM and recurrent GBM patients,[9,27,33] one case series of patients with recurrent GBM[13], and 3 small case series (sample sizes of 5, 6, and 42) of patients with non-GBM cancers.[12,36,37] Only one study evaluated the cost-effectiveness of TTF (for treatment of newly diagnosed GBM).[28]

Table ES-9 provides an overall summary of findings and strength of evidence ratings for efficacy outcomes (overall survival, progression-free survival, quality of life (QOL) and functional status) (EQ1), safety outcomes (SQ1), and cost outcomes (CQ1) by treatment comparison and study design among patients with newly diagnosed or recurrent GBM. No eligible comparative studies on which to rate strength of evidence were identified by this health technology assessment (HTA) among patients with non-GBM indications.

Table ES-9.   Overall summary of findings and strength of evidence ratings (certainty and direction of effect) by indication and treatment comparison

Outcomes	New GBM	Recurrent GBM	
	TTF+TMZ Versus TMZ	TTF Versus Second-line therapy	TTF + Second-line therapy Versus Second-line therapy
OS	SOE$_{RCT}$: ⊕⊕◯◯ LOW DOE$_{RCT}$: For benefit with TTF SOE$_{OBS}$: ⊕◯◯◯ VERY LOW DOE$_{OBS}$: For benefit with TTF	SOE$_{RCT}$: ⊕◯◯◯ VERY LOW DOE$_{RCT}$: For no benefit with TTF SOE$_{OBS}$: ⊕◯◯◯ VERY LOW DOE$_{OBS}$: For benefit with TTF	SOE$_{RCT}$: No evidence SOE$_{OBS}$: ⊕◯◯◯ VERY LOW DOE$_{OBS}$: For no benefit with TTF
PFS	SOE$_{RCT}$: ⊕⊕◯◯ LOW DOE$_{RCT}$: For benefit with TTF SOE$_{OBS}$: ⊕◯◯◯ VERY LOW DOE$_{OBS}$: For benefit with TTF	SOE$_{RCT}$: ⊕◯◯◯ VERY LOW DOE$_{RCT}$: For no benefit with TTF SOE$_{OBS}$: ⊕◯◯◯ VERY LOW DOE$_{OBS}$: For benefit with TTF	No evidence
QOL, Functional Status	SOE$_{RCT}$: ⊕◯◯◯ VERY LOW DOE$_{RCT}$: For benefit with TTF SOE$_{OBS}$: No evidence	SOE$_{RCT}$: ⊕◯◯◯ VERY LOW DOE$_{RCT}$: For benefit with TTF SOE$_{OBS}$: No evidence	No evidence
Safety	SOE$_{RCT}$: ⊕⊕◯◯ LOW DOE$_{RCT}$: For minimal harm with TTF SOE$_{OBS}$: No evidence	SOE$_{RCT}$: ⊕◯◯◯ VERY LOW DOE$_{RCT}$: For minimal harm with TTF SOE$_{OBS}$: ⊕◯◯◯ VERY LOW DOE$_{OBS}$: For minimal harm with TTF	SOE$_{RCT}$: No evidence SOE$_{OBS}$: ⊕◯◯◯ VERY LOW DOE$_{OBS}$: For minimal harm with TTF
Cost	SOE$_{RCT}$: No evidence SOE$_{OBS}$: ⊕⊕◯◯ LOW DOE$_{OBS}$: TTF not cost-effective	No evidence	No evidence

Abbreviations: DOE = direction of effect, GBM = glioblastoma multiforme; OBS = observational study; OS = overall survival; PFS = progression-free survival; QOL = quality of life; RCT = randomized controlled trial; SOE = strength of evidence; TMZ = temozolomide; TTF = tumor treating fields.

ES-4.2 Limitations of the Evidence Base

The studies we identified for inclusion in this HTA had numerous limitations as summarized in this section. Please refer to the Full Report for a more detailed description of each of these limitations.

- **Limited number of comparative effectiveness trials.** Limited published evidence investigating the clinical effectiveness and safety of TTF for the treatment of newly diagnosed and recurrent GBM exists, and no published trial data exists for other cancers.

- **Risk of bias among included studies.** We rated all efficacy and safety outcomes from all studies as having high or some concerns for risk of bias. Sources of bias across studies included: lack of blinding with the potential to bias patient-reported outcomes related to QOL, functional status, and adverse events; differential adherence, attrition, and crossover rates; and potential selection bias among observational studies that was not addressed in analyses.

- **Heterogeneity and studies underpowered for subgroups of interest.** There were heterogenous populations of patients enrolled in studies that evaluated TTF for treatment of GBM, particularly with respect to number of recurrences and prior treatment. No study was adequately powered to investigate whether the clinical effectiveness or safety of TTF

varied by clinical history or patient characteristics (e.g., age, sex, Karnofsky performance score, surgical resection).

- **Applicability to current standard of care in the United States.** The limited use of bevacizumab for treatment of recurrent GBM in the EF-11 trial may not be representative of current clinical practice. Additionally, findings from the EF-11 trial should be interpreted in the context of a population having failed multiple previous treatments and therefore likely at a more advanced stage of disease. Additionally, whereas efficacy and safety outcomes from studies conducted outside of the United States (U.S.) are likely applicable to U.S. settings, it is not clear that studies conducted using cost data outside of the U.S. would apply to U.S. settings.

ES-4.3 Other Related HTAs

The Swedish Dental and Pharmaceutical Benefits Agency conducted an HTA in 2017[44] on the use of Optune® as an addition to the standard of care treatment for patients with newly diagnosed GBM. The authors summarized efficacy and safety findings from the EF-14 trial[25] and noted that their conclusions were based on one study and study-related abstracts. The manufacturer of Optune® calculated the cost per quality-adjusted life years (QALY) to be approximately 1.8 million Swedish kronor (SEK) ($200,000 United States Dollars [USD] at the time of analysis) in a cost-effectiveness analysis that was not cited and is not publicly accessible. In sensitivity analyses that assumed a horizon of 20 years, higher medical expenses, and lower temozolomide costs, the authors of the Swedish HTA calculated the cost per QALY to be approximately 2.1 million SEK ($233,333 USD at the time of analysis) and assessed the uncertainty level of their model to be medium.

We also identified an HTA that was commissioned by the ECRI Institute Health Technology Assessment Information Service.[45] This 2015 HTA included 3 articles[9,15,33] also included in this HTA and used the GRADE approach to determine the strength of evidence for each outcome. The HTA concluded that patients with recurrent GBM treated with TTF therapy compared to best standard of care had the same overall survival at 24 months (moderate strength of evidence) but that there was insufficient evidence to draw a conclusion on QOL (very low strength of evidence). Compared to best standard of care, it concluded that TTF caused a similar or lower rate of several adverse events (AEs) (low to moderate strength of evidence) and increased rates of dermatologic AEs and falls (low strength of evidence).

ES-4.4 Payer Coverage

The Centers for Medicare and Medicaid Services (CMS) does not have a national coverage determination related to TTF. *Table ES-10* provides an overview of other payer coverage policies; please see the Full Report for complete details.

Table ES-10. Overview of payer coverage policies

Payor	Newly Diagnosed GBM	Recurrent GBM	Other Cancers
Medicare	--	--	--
Premera	✓ a	✗	✗
Regence	✓ a	✗	✗
United Healthcare	✓ a	✓ a	✗
Aetna	✓ a	✓ a	✗
Humana	✓ a	✓ a	✗
Kaiser	✓ a	✗	✗
Cigna	✓ a	✓ a	✗

✓ = covered; ✗ = not covered; — = no policy identified

Abbreviations: GBM = glioblastoma multiforme.

a If specific clinical criteria are met. See Full Report for details.

Aside from Medicare, all assessed payers cover TTF for newly diagnosed GBM patients if clinical criteria are met. The coverage of TTF for recurrent GBM varies by payer. Specific clinical criteria required for TTF coverage for newly diagnosed or recurrent GBM vary but often include histologically confirmed supratentorial GBM and prior debulking, radiation, and/or chemotherapy. Some payers also have an age requirement (minimum age of 18 or 22 years) or Karnofsky Performance Status score requirement (>60 or >70). For newly diagnosed GBM patients, all payors require the patient is also being treated with TMZ unless contraindicated. No payers we assessed cover TTF for non-GBM cancers.

ES-4.5 Limitations of this HTA

This HTA has some limitations related to the scoping, process, and analyses we used to conduct the HTA. This HTA was limited to studies and other information published or publicly available in English. Though studies conducted in countries designated as less than "very high human development" on the United Nations Human Development Report were ineligible, no articles were excluded for country during full-text review. Because of the limited body of evidence, we accepted retrospective studies and studies with comparator groups from other populations (both concurrent and historical) that introduce an inherent risk of bias. The electronic search was limited to only three databases. Our HTA excluded 'as treated' or 'per protocol' analyses, which could offer additional evidence on the efficacy and safety of TTF. The small evidence base made applying the GRADE approach challenging. We mitigated this challenge by using a modified GRADE approach that allowed us to downgrade the consistency domain to unknown when there was a single-study body of evidence. Finally, the AGREE guideline appraisal instrument largely focuses on evaluating the processes through which a guideline is developed; it does not assess how well the evidence included in the guideline was evaluated and interpreted correctly, or whether the conclusions of the guideline are consistent with the evidence. Thus, some guidelines may score artificially high and explains why conclusions may differ between guidelines despite having nearly similar quality scores.

ES-4.6 Ongoing Research and Future Research Needs

We identified 37 clinical trials registered in clinicaltrials.gov that are relevant for this HTA. *Table ES-11* lists the clinical trials by study status and cancer type.

Table ES-11. Relevant clinical trials status[a]

Study Status	Newly diagnosed GBM	Recurrent GBM	Other cancers
Not yet recruiting	0	1	4
Recruiting	9	8	8
Active and not recruiting	2	0	3
Completed	1 (EF-14)	1 (EF-11)	1[b]
Withdrawn	0	1[c]	0
Terminated	0	1[d]	0
Unknown	0	0	2[e]
TOTAL	12	12	18

Abbreviations: GBM = glioblastoma multiforme; HTA = health technology assessment; NSCLC = non-small cell lung cancer.

[a] Several clinical trials enroll participants with newly diagnosed GBM, recurrent GBM, and/or other cancers; therefore, totals do not add up to 37 trials.

[b] This clinical trial evaluated the efficacy and safety of TTF in NSCLC patients. One case series included in this HTA provides published results.[37]

[c] Withdrawn due to poor participant accrual.[46]

[d] Terminated due to amendment of study protocol.[47]

[e] Both clinical trials were last updated September 21, 2016 and reported as active, not recruiting with a study completion date of July 2017[48] and December 2016.[49]

Among newly diagnosed and recurrent GBM clinical trials, one trial in newly diagnosed GBM (EF-14)[50] and one trial in recurrent GBM (EF-11)[51] are reported as completed. This HTA includes published results from both completed trials.[15,26,29-32,52] Two trials currently recruiting newly diagnosed and recurrent GBM patients evaluate the feasibility and safety of TTF in pediatric populations.[53,54] Please see the [Full Report](#) for further information on relevant ongoing clinical trials in newly diagnosed and recurrent GBM patients*.*

Additional RCTs may change the certainty of findings from this HTA for newly diagnosed and recurrent GBM patients. Upcoming trial completions will likely provide further information on efficacy, safety, and cost outcomes, particularly for other cancers. Moreover, additional research on patient preferences and values related to timing of treatment and subgroups analyses would advance research in this area. Advanced analytic and statistical techniques could be used within observational studies to mitigate biases introduced by nonrandomized study designs, potentially broadening the evidence base available to address important research questions. Publishing results in journal articles as well as or instead of conference abstracts would also help expand the available evidence.

ES-5. Conclusion

Findings are based on a small body of evidence graded as low or very low certainty because of a paucity of RCT data and comparative observational studies that we rated high risk of bias. We

conclude with very low to low certainty that the addition of TTF to usual care with TMZ increases overall and progression-free survival among patients with newly diagnosed GBM. For patients with recurrent GBM, there may or may not be survival benefits associated with TTF treatment with or without second-line therapy (very low certainty). We conclude with very low certainty from RCT data that TTF improves quality of life and functional status among patients with newly diagnosed or recurrent GBM. We found evidence of minimal harm attributed to TTF treatment for GBM; TTF is likely safe for newly diagnosed and recurrent GBM (very low to low certainty), though likely not cost-effective for newly diagnosed GBM (low certainty). We found no evidence on which to draw conclusions about the cost-effectiveness of TTF for recurrent GBM or the impact of TTF treatment on non-GBM cancers.

Full Technical Report

Structured Abstract

Purpose: To conduct a health technology assessment (HTA) on the efficacy, safety, and cost of tumor treating fields (TTF).

Data Sources: PubMed from inception through June 16, 2018; clinical trial registry; government, payor, and clinical specialty organization websites; hand searches of bibliographies, relevant clinical practice guidelines (CPGs), and systematic reviews.

Study Selection: Using a priori criteria, we selected English-language primary research studies published in any year that were conducted in very highly developed countries that enrolled pediatric or adult patients with histologically confirmed cancer who were treated with TTF. We selected studies that evaluated efficacy outcomes (overall survival, progression-free survival, quality of life and functional status), safety outcomes (serious adverse events (AEs), dermatologic AEs, other AEs), and cost outcomes (cost, cost-effectiveness). We also selected relevant CPGs for quality appraisal and synthesis.

Data Extraction: One research team member extracted data and a second checked for accuracy. Two investigators independently assessed risk of bias of included primary research studies and conducted a quality assessment of included CPGs.

Data Synthesis: We included 11 primary research studies from 15 articles published between 2007 and 2018. Six studies (2 randomized controlled trials [RCTs], 4 observational studies) provided evidence on efficacy, 10 studies (2 RCTs, 8 observational studies) provided evidence on safety, and one study provided evidence on cost. The two included RCTs were rated as having some concerns of bias for overall and progression-free survival efficacy outcomes and safety outcomes but rated as high risk of bias for quality of life outcomes. Almost all the observational comparative studies were rated high risk of bias for all outcomes. All studies were among adult patients with glioblastoma multiforme (GBM) except for 3 case series among adult or pediatric patients with other cancers.

One RCT (n=695) and a small controlled cohort study (n=42) studied the addition of TTF to usual care with temozolomide (TMZ) for newly diagnosed GBM. TTF increased overall and progression-free survival; in the RCT over a median follow up of 40 months, median overall survival was 21 months in the TTF+TMZ group and 16 months among patients receiving TMZ alone (strength of evidence: very low [cohort] to low [RCT]). One RCT (n=237) and 3 observational studies (n=1,446) compared TTF, with or without second-line therapy, with second-line therapy for recurrent GBM; there was heterogeneity of results with no difference in efficacy outcomes between groups in the trial data (strength of evidence: very low) and some increased survival with TTF from the observational data (strength of evidence: very low). Patients with newly diagnosed and recurrent GBM experienced some improvements in quality of life and functional status with TTF use (strength of evidence: very low). Studies reported no serious AEs; dermatologic reactions were common with TTF, and other AEs were attributed to

other aspects of treatment or disease (strength of evidence: very low to low). TTF for newly diagnosed GBM was not found to be cost effective; the incremental cost-effectiveness ratio was estimated at $817,001 from the payor perspective. We found no evidence on which to make conclusions about the effect of TTF on any outcomes among patients with non-GBM cancers or the cost-effectiveness of TTF for recurrent GBM.

We identified 6 CPGs of various quality with substantial disagreement regarding recommendations for treatment with TTF for both newly diagnosed and recurrent GBM.

Limitations: Limited published evidence exists for the clinical effectiveness and safety of TTF for the treatment of newly diagnosed and recurrent GBM and no comparative evidence exists for other cancers. The small body of evidence was limited by increased risk of bias related to lack of participant and outcome assessor blinding, selection bias, attrition, and treatment adherence. Most studies were underpowered, resulting in heterogeneous magnitudes of effect and imprecision. This HTA was limited to English-language studies.

Conclusions: Findings are based on a small body of evidence graded as low or very low certainty because of a paucity of RCT data and comparative observational studies rated high risk of bias. We conclude with very low to low certainty that the addition of TTF to usual care with TMZ increases overall and progression-free survival among patients with newly diagnosed GBM. For patients with recurrent GBM, there may or may not be survival benefits associated with TTF treatment with or without second-line therapy (very low certainty). We conclude with very low certainty from RCT data that TTF improves quality of life and functional status among patients with newly diagnosed or recurrent GBM. We found evidence of minimal harm attributed to TTF treatment for GBM; TTF is likely safe for newly diagnosed and recurrent GBM (very low to low certainty), though likely not cost-effective for newly diagnosed GBM (low certainty). We found no evidence on which to draw conclusions about the cost-effectiveness of TTF for recurrent GBM or the impact of TTF treatment on non-GBM cancers.

1.   Background

We designed this health technology assessment (HTA) to assist the State of Washington's independent Health Technology Clinical Committee with determining coverage for tumor treating fields (TTF) (Optune®).

1.1   Clinical Background

1.1.1 Cancer Incidence

In 2018, an estimated 1,735,350 new cancer cases will occur in the United States (U.S.).[1] Although cancer incidence has declined by approximately 2 percent per year among males since 2005, it has remained relatively stable among females. Among males, the decline in incidence is attributable to reductions in lung, colorectal, and prostate cancer diagnoses. Among females, decreases in lung and colorectal cancer incidence have been offset by increasing or stable incidence rates of breast, uterine, and thyroid cancers, as well as melanoma.[1]

Among adults, an estimated 23,880 new cases of brain and other central nervous system (CNS) cancers will be diagnosed in the U.S. in 2018.[1] Gliomas, a broad category of brain and spinal cord tumors, are the most common tumors of the CNS, and account for approximately 80 percent of all primary brain cancers.[3] They are generally astrocytic, oligodendrocytic, or a combination of these two cell types; ependymomas are another, less common, type of glioma. Glioblastomas, also referred to as glioblastoma multiforme (GBM), are high-grade (i.e., grade IV) gliomas that are astrocytic in origin and most commonly present in the supratentorial region of the brain (i.e., frontal, temporal parietal, and occipital lobes). From 2006 to 2010, the age-adjusted incidence rate of GBM in the U.S. was 3.19 per 100,000 persons, accounting for more than 54 percent of all gliomas and 16 percent of all primary brain cancers.[2] Incidence rates for GBM are higher in males than females (3.97 versus 2.53 per 100,000 persons, respectively) and increase with age; the median age at diagnosis is 64 years.[2]

In 2018, an estimated 10,590 children 0 to 14 years of age will be diagnosed with cancer in the U.S.; incidence rates have been relatively stable for the past 5 data years.[1] In 2014, an estimated 2,240 new cases of brain and CNS malignancies among children 0 to 14 years of age and 540 new cases among adolescents 15 to 19 years of age were diagnosed; these cancers were the second (21%) and third (10%) most common cancers among children and adolescents, respectively.[55] According to National Program of Cancer Registries (NPCR) and Surveillance, Epidemiology, and End Results Program (SEER) data from 2010 through 2014, the average age-adjusted incidence rate of primary brain and CNS cancer was 3.48 per 100,000 children and adolescents.[56] Gliomas account for more than half of brain tumors among children and for one third of brain tumors among adolescents (incidence rate [IR] 0.66 per 100,000 [95% CI, 0.64 to 0.69]). High-grade astrocytomas (World Health Organization [WHO] grades III and IV), a subtype of glioma, include glioblastoma; only about 3 percent of brain tumors among children and adolescents were glioblastoma (IR 0.17 per 100,000 [95% CI, 0.16 to 0.19]) in 2010 through 2014.[56]

1.1.2 Cancer Mortality

In 2018 an estimated 609,640 cancer deaths among adults will occur in the U.S. in 2018, equivalent to almost 1,700 deaths from cancer per day. According to data from the National Center for Health Statistics, cancer was the second leading cause of death (behind heart disease) in the U.S. in both 2014 and 2015; it was the number one cause of death among females, aged 40 to 79 years, and males, aged 60 to 79 years, in 2015. Among the top 10 causes of death in the U.S., however, cancer is the only cause whose rates declined relatively (by 1.7%) between 2014 and 2015. The most common cause of cancer death was lung cancer, followed by prostate and colorectal cancers among males and breast and colorectal cancers among females.[1]

Of the estimated 609,640 cancer deaths in the U.S. in 2018, an estimated 16,830 are from brain and other nervous system cancers. Brain and other CNS cancers are the tenth highest cause of cancer death among females overall (7,340 cancer deaths in 2018) and are the leading cause of cancer death among males aged less than 39 years and females aged less than 20 years.[1] GBM is a highly aggressive disease with a very poor prognosis; less than 5 percent of all patients survive 5 years after a GBM diagnosis. The median survival is 14 to 15 months[3] and only 3 months in untreated patients.[2]

In 2018, an estimated 1,180 children 0 to 14 years of age will die from cancer,[1] down from 1,350 cancer deaths in 2014.[55] Among adolescents 15 to 19 years of age in 2014, there were an estimated 610 deaths from cancer.[55] Brain tumors are the second leading cause of cancer death among both children and adolescents.[57] The average mortality rate for brain and other CNS tumors among children 0 to 14 years of age was 0.71 per 100,000 children in 2010 through 2014.[56] In 2003 through 2009, the 5-year survival rate among children and adolescents was 75 percent for brain and CNS cancers.[55] In 2010 through 2014, the 5-year survival rate among children and adolescents was 64% (95% CI, 62% to 66%) for glioma and only 18% (95% CI, 14% to 22%) for glioblastoma.[56]

1.1.3 Cancer Treatment

Cancer is typically treated by surgery, radiation therapy, or systemic therapy (e.g., chemotherapy). Targeted cancer therapies such as hormone therapy (e.g., tamoxifen for breast cancer) or immunotherapy (e.g., rituximab for non-Hodgkin lymphoma) are systemic therapies that are used to interfere with specific molecules involved in cancer cell growth. Targeted drugs can (a) block or turn off molecular signals that control cell division and proliferation, (b) change proteins within the cancer cells so they are no longer viable, (c) stop making new blood vessels that feed cancer cells, (d) trigger the immune system to kill the cancer cells, or (e) carry toxins to cancer cells to kill them. Radiation therapy is a physical method that uses high-energy beams to kill cancer cells; although it is typically administered from a source outside of the body, it can also be delivered internally (e.g., brachytherapy).

The current standard of care for patients with newly diagnosed GBM consists of surgical resection followed by 6 weeks of radiotherapy, together with concomitant chemotherapy with temozolomide (TMZ). Once chemoradiotherapy is complete, a minimum of 6 months of adjuvant treatment with TMZ is typical.[4] Patients are typically followed every 2 to 3 months;

radiologic diagnosis with magnetic resonance imaging is the reference for follow up.[5] Criteria to assess progression have been established by the Response Assessment in Neuro-Oncology Working Group.[58] Most patients experience a recurrence of disease because GBM is a genetically and phenotypically heterogeneous disease, complete resection of GBM tumors is rare, and chemotherapeutic agents cannot optimally cross the blood brain barrier.[59] At the time of disease recurrence, there is no established standard of care and treatment options are limited; approximately 25% of patients may undergo repeat surgery.[5] Experts suggest that tumor involvement in certain critical brain regions, poor performance scores, and large tumor volume are associated with poor repeat surgery outcomes;[60] the patient's clinical condition and chemoresistance resulting from prior treatments may also negatively impact the outcomes of recurrence treatment. Carmustine polymer wafers may be placed intraoperatively in the surgical cavity during repeat surgery. Rarely, patients may undergo reirradiation. For the majority of recurrent GBM patients, chemotherapy is indicated; the type of chemotherapy drug used varies widely. In the U.S., combination treatment with chemotherapy and the angiogenesis inhibitor bevacizumab has been approved for recurrent GBM and certain other cancers.[15] However, approximately 40 percent to 60 percent of recurrent GBM patients are either unresponsive to bevacizumab or experience serious adverse events (AEs) following treatment.[30] These serious side effects include hemorrhage, thromboembolism, infection, hypertensive crisis, and renal failure. Furthermore, although some patients may be initially responsive to bevacizumab, the tumor eventually progresses.[61] Other novel therapies with different mechanisms of action against GBM and reduced toxicity are needed.

1.2   Technology Description

Another modality for cancer treatment uses noninvasive, alternating electrical fields to disrupt mitosis (i.e., cell division) of the malignant cells. The alternating electric fields enter the cancer cell and disrupt mitotic spindle microtubule assembly, resulting in dielectrophoretic dislocation of proteins such as tubulin and septin and interference of cell division; ultimately, this interference results in cancer cell death (i.e., apoptosis).[6] This therapy, known as tumor treating fields (TTF), externally delivers alternating electric fields that are very-low intensity and of intermediate frequency (i.e., 100 to 300 kilohertz [kHz]) to an area of proliferating cancer cells during the late metaphase and anaphase of mitosis. The specific frequency used in treatment is inversely related to the size of the specific cancer cells; for example, 200 kHz is used for treatment of GBM and ovarian cancer while 150 kHz is used for treatment of pancreatic and non-small cell lung cancers. Normal cells, which are affected at -50 kHz, remain unaffected by the frequencies used to treat cancer cells.

TTF have been shown to arrest cell proliferation and destroy cancer cells during division in animal models and human cancer cell lines.[33,62-66] The first preclinical study published in 2004 by Kirson et al. demonstrated that electric fields could slow tumor replication in vitro and in vivo.[66] The in vitro results showed that multiple cell lines had impaired growth under electric fields and that this effect persisted for at least 72 hours after treatment. In mouse models, generating electric fields through surgically implanted wires resulted in an average 47 percent reduction in melanoma tumor size (P=0.001). Studies on other animal models and tumor types, such as lung, pancreatic, and brain primary malignancy, have also shown the efficacy of electric

fields.[33,63-66] In addition, several investigators reported that chemotherapy efficacy is potentiated in TTF treated animals.[27,65,67] Introducing a less invasive technique, a study by Kirson et al. in 2007 reported that externally placed electrodes showed a 53 percent reduction in tumor growth of intracranial GBM in mice (P=0.01).[33] The work with in vivo models allowed TTF technology to mature into a clinically feasible and minimally invasive tool for human trials.

TTF are clinically delivered in paired orthogonal directions, left–right and anterior–posterior, using Optune®, previously referred to as the NovoTTF-100A System or Novocure (Novocure Inc.; Haifa, Israel).[7] Unlike chemotherapy, Optune® therapy does not have a half-life. Therefore, it requires continuous application to be effective. Patients are instructed to use the device at least 18 hours per day; the manufacturer recommends a minimal treatment course duration of 4 weeks.[8-10] The Optune® system is portable and operated by the patient. It comprises an electrical field generator device, four insulated transducer arrays, a connector cable, and a power source (battery or electrical outlet). Treatment parameters for GBM are preset (200 kHz and a minimal field intensity of 0.7 volts per centimeter [V/cm] in the brain) and no output adjustments are available to the patient. TTF are delivered through transducer arrays that are applied to the shaved scalp for GBM or to the abdomen, torso, or pelvic areas for other cancers. The patient, caregiver, or doctor can apply Optune® by placing the transducer arrays according to the doctor's instruction.[11] The transducer arrays are composed of insulated ceramic discs that are separated from the skin by a layer of conductive hydrogel. The locations of the arrays are calculated for each individual patient to optimize field intensity based on tumor location and head size in the case of GBM. The NovoTAL™ System is an optional simulation software that may be used to determine optimal placement of the transducer arrays; the placement plan is patient-specific and can be modified over time by utilizing information from the most recent magnetic resonance images (MRIs).[68] Patients or caregivers replace transducer arrays 1 to 2 times per week and reshave the skin to maintain optimal contact with the arrays.[12,13] The Optune® device is contraindicated in patients with active implanted electronic medical devices such as deep brain stimulators, pacemakers, and programmable shunts, and in patients with skull defects such as a missing bone flap, because of the risk of skin toxicity and tissue damage. It should also not be used in patients with known hypersensitivity to conductive hydrogels or in patients with infratentorial disease.[7]

1.3   Regulatory Status

The U.S. Food and Drug Administration (FDA) approved TTF for recurrent GBM in April 2011[14] based on the phase 3 EF-11 randomized controlled trial (RCT) that showed TTF exhibited similar efficacy with improved quality of life and a reduced rate of serious AEs compared with clinician's chemotherapy of choice.[15] In October 2015, the FDA approved TTF in combination with TMZ for the treatment of newly diagnosed GBM[16] based on interim results from the phase 3 EF-14 RCT that demonstrated the increased efficacy of TTF plus TMZ versus TMZ alone on progression-free and overall survival following chemoradiotherapy in patients with newly diagnosed GBM.[17] *Table 1* lists the current FDA-approved indications and contraindications for TTF.

Table 1.   FDA regulatory status of TTF (Optune®)

Recurrent GBM (FDA approval in April 2011)[14]
Indications: • Age 22 years or older   • GBM in supratentorial location   • Confirmed recurrent GBM after chemotherapy   • To be used as monotherapy   • As alternative to standard medical therapy after surgical and radiation options exhausted   Contraindications: • Active implanted medical device present (brain, spinal cord, or vagus nerve stimulators, pacemaking, defibrillators, programmable shunts)   • Skull defect present   • Known sensitivity to conductive hydrogels
Newly Diagnosed GBM (FDA approval in October 2015)[16]
Indications: • Age 22 years or older   • GBM in supratentorial location   • Confirmed newly diagnosed GBM following maximal debulking surgery and completion of radiation therapy with concomitant standard-of-care chemotherapy   • To be used with temozolomide   Contraindications: • Active implanted medical device present (brain, spinal cord, or vagus nerve stimulators, pacemaking, defibrillators, programmable shunts)   • Skull defect present   • Known sensitivity to conductive hydrogels

Abbreviations: FDA = United States Food and Drug Administration; GBM = glioblastoma multiforme; TTF = tumor treating fields.

1.4   Policy Context

The State of Washington's Health Technology Clinical Committee (HTCC) voted in January 2016 to decline coverage of Optune®. The State of Washington Health Care Authority (HCA) selected Optune® as a topic for re-review based on newly available published evidence, ranking it as high concerns for efficacy, low concerns for safety, and high concerns for cost.[69,70] This HTA is designed to assist the State of Washington's independent HTCC in determining coverage for TTF (Optune®).

1.5   Washington State Agency Utilization Data

The State of Washington HCA examined information on the use of TTF from 2014 to 2017 (*Appendix A*). Utilization and cost data were examined from Medicaid programs (fee for service and managed care organization), as well as the Public Employees Benefit Board Uniform Medical Plan and Medicare. Because the aggregate number of patients receiving TTF was less than the minimum allowed for reporting, utilization data are suppressed.

2.   Methods

This health technology assessment (HTA) includes two separate, but related components. The first component is a systematic review of primary research studies and the second component is a quality appraisal and synthesis of relevant clinical practice guidelines (CPGs).

2.1   Research Questions and Analytic Framework for Systematic Review of Primary Research Studies

We developed the following research questions and analytic framework (*Figure 1*) to guide the systematic evidence review of primary research studies:

Efficacy Question 1 (EQ1). What is the clinical effectiveness of tumor treating fields for the treatment of newly diagnosed glioblastoma multiforme, recurrent glioblastoma multiforme, and other cancers?

Efficacy Question 1a (EQ1a). Does the clinical effectiveness of tumor treating fields vary by clinical history or patient characteristics (e.g., age, sex, Karnofsky performance score, surgical resection)?

Safety Question 1 (SQ1). What are the harms associated with tumor treating fields for the treatment of newly diagnosed glioblastoma multiforme, recurrent glioblastoma multiforme, and other cancers?

Safety Question 1a (SQ1a). Do the harms associated with tumor treating fields vary by clinical history or patient characteristics (e.g., age, sex, Karnofsky performance score, surgical resection)?

Cost Question 1 (CQ1). What are the costs and cost-effectiveness of tumor treating fields?

The State of Washington Health HTA Program posted a draft of these research questions with study selection criteria for public comment from June 1, 2018 to June 14, 2018. The final key questions are available at the Program's website[71]; no public comments on the draft key questions were received.

Figure 1.   Analytic framework for HTA on TTF (Optune®)
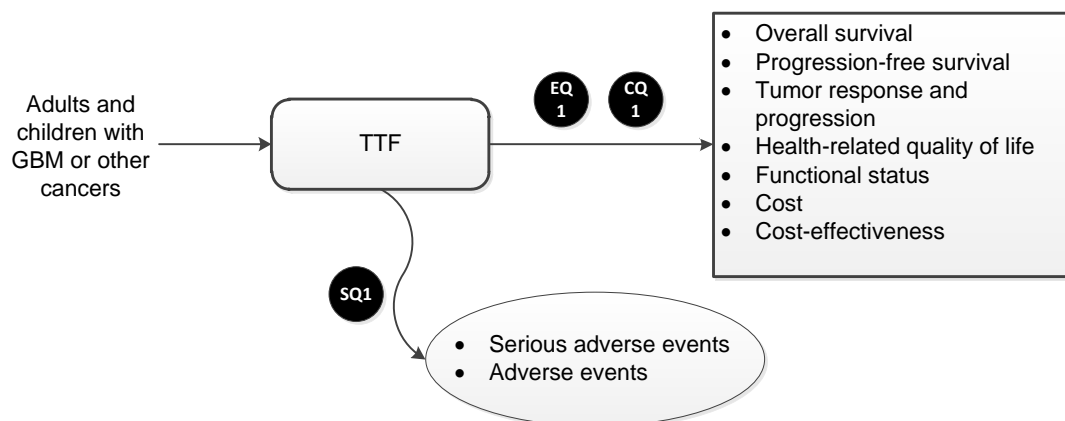
Abbreviations: CQ = cost question; EQ = efficacy question; GBM = glioblastoma multiforme; SQ = safety question; TTF = tumor treating fields.

2.1.1 Data Sources and Searches

We searched MEDLINE® (via PubMed) from inception, the Cochrane Library, and a clinical trials registry (clinicaltrials.gov) for relevant English-language studies. We searched the Centers for Medicare and Medicaid Services and United States (U.S.) Food and Drug Administration (FDA) websites, selected payer and health care professional society websites, and websites of other organizations that conduct and disseminate HTAs. In addition, we reviewed the reference lists of relevant studies, systematic reviews, practice guidelines, and other HTAs on this topic to identify any relevant primary research studies not found through the electronic search. The detailed search strategy is provided in *Appendix B.*

In brief, we used medical subject headings (MeSH terms) and text words associated with tumor treating fields (TTF). We limited the search by eliminating studies indexed using terms for selected animals. We used MeSH terms to select studies most likely to be trials or systematic reviews and to remove editorials, letters, and publication types that do not represent primary research studies.

2.1.2 Study Selection

Table 2 summarizes the study selection criteria related to the population, intervention, comparator, outcomes, time period, and setting that defined the scope of this HTA; these are further described following the table. We screened titles and abstracts and full-text articles based on these study selection criteria. Two team members screened the title/abstracts. The lead investigator and one additional team member independently screened all full-text articles; discrepancies were resolved by discussion.

2.1.2.1 Population

Studies were eligible for selection if they enrolled adults or children with a histologically confirmed diagnosis of incident or recurrent glioblastoma multiforme (GBM) or other cancers such as non-small cell lung cancer, ovarian cancer, or pancreatic cancer. Studies that enrolled adults or children without a histologically confirmed diagnosis of cancer or for whom treatment with TTF is contraindicated were excluded.

2.1.2.2 Intervention and Comparator

The use of TTF is approved by the FDA as an adjuvant to maintenance temozolomide (TMZ) treatment for newly diagnosed GBM and as a monotherapy for recurrent GBM. For all research questions, at least one study group had to include treatment with TTF, with or without a concomitant therapy. Studies that evaluated surgery, radiation therapy, or systemic therapies or targeted therapies such as chemotherapy or immunotherapy were excluded. We made no exclusions based on comparator since treatment of cancer, especially recurrent GBM, may include multiple therapies.

2.1.2.3 Outcomes

For the research questions on efficacy (EQ1, EQ1a), studies that reported outcomes related to overall or progression-free survival, tumor response and progression, health-related quality of life, and functional status were eligible for selection. We required studies to use valid and

reliable instruments to measure quality of life and functional status (e.g., Karnofsky Performance Scale[72]). For the research questions on safety (SQ1, SQ1a), studies that reported on serious adverse events or adverse events were eligible for selection. For the research question on cost (CQ1), studies that reported on cost or cost-effectiveness were eligible for selection.

Table 2. **Population, intervention, comparator, outcome, timing, setting and other study selection criteria for HTA on TTF (Optune®)**

Domain	Included	Excluded
Population	Adults or children with a histologically confirmed diagnosis of incident or recurrent GBM or other cancer (e.g., non-small cell lung cancer, ovarian cancer, pancreatic cancer)	Adults or children without a histologically confirmed diagnosis of cancer Adults or children for whom treatment with TTF is contraindicated Studies conducted in animals, in vitro, or in silico
Intervention	TTF with or without concomitant therapy	All other interventions including surgery, radiation therapy, or systemic therapy (i.e., chemotherapy, targeted therapies such as hormone therapy)
Comparator	Chemotherapy; TTF plus chemotherapy or other adjunctive treatments; placebo; no comparator	None
Outcomes	**EQ**: Overall survival; progression-free survival; tumor response and progression; health-related quality of life; functional status (e.g., cognitive function measured by the Karnofsky Performance Scale) **SQ**: Serious adverse events; adverse events (e.g., dermatitis, insomnia, headaches) **CQ**: Cost; cost-effectiveness	Quality of life and functional outcomes not measured using valid and reliable instruments or scales
Timing	No time restrictions	None
Setting	Countries[a] categorized as "very high human development" according to the United Nations Development Programme's 2016 Human Development Report[18]	Countries not categorized as "very high human development" according to the United Nations Development Programme's 2016 Human Development Report[18]
Study Design	**EQ**: CCTs; RCTs; cohort studies with concurrent or historical comparator group; case-control studies **SQ**: All of the designs listed for EQ plus studies without a comparator (e.g., case series) **CQ**: CEA, CUA, or CBA performed from the societal or payor perspective	Editorials, comments, or letters; narrative or systematic reviews (or similar publications); conference abstracts; case reports Reviews will be hand searched to identify relevant primary studies

[a] Andorra, Argentina, Australia, Austria, Bahrain, Belgium, Brunei Darussalam, Canada, Chile, Croatia, Cyprus, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hong Kong China (SAR), Hungary, Iceland, Ireland, Israel, Italy, Japan, Korea (Republic of), Kuwait, Latvia, Liechtenstein, Lithuania, Luxembourg, Malta, Montenegro, Netherlands, New Zealand, Norway, Poland, Portugal, Qatar, Romania, Russian Federation, Saudi Arabia, Singapore, Slovakia, Slovenia, Spain, Sweden, Switzerland, United Arab Emirates, United Kingdom, United States.

Abbreviations: CBA = cost-benefit analysis; CCT = controlled clinical trial; CEA = cost-effectiveness analysis; CQ = cost question; CUA = cost-utility analysis; EQ = efficacy question; GBM = glioblastoma multiforme; HTA = health technology assessment; RCT = randomized controlled trial; SQ = safety question; TTF = tumor treating fields.

2.1.2.4 Settings

Studies that were conducted in countries designated as "very high human development" by the United Nations Human Development Programme were eligible for selection as these countries (Europe, Australia, New Zealand, Japan, South Korea, Singapore, Hong Kong, and selected Middle Eastern countries) are like the United States (U.S.) with respect to available health care and standards of medical practice.[18] We excluded studies conducted in countries designated as less than "very high human development."

2.1.2.5 Study Design

We included controlled clinical trials (CCTs), randomized controlled trials (RCTs), cohort studies with concurrent or historical comparator groups and case-control studies for the research questions related to efficacy and safety (EQ1, EQ1a, SQ1, SQ1a). For the research questions related to safety (SQ1, SQ1a), we also included studies without comparators (e.g., case series). Editorials, comments, letters, and case reports were excluded. We also excluded reviews and conference abstracts but hand searched them to identify relevant primary studies. For the research question on cost (CQ1), cost-effectiveness, cost-benefit, and cost-utility analyses from the societal or payor perspective were eligible for selection.

2.1.2.6 Time Period

We did not restrict included studies based on year conducted or published.

2.1.3 What is Excluded from This HTA

This review did not include studies published in languages other than English or conducted in countries not designated as "very high human development" based on the United Nations Human Development Index.[18]

2.1.4 Data Abstraction and Risk of Bias Assessment

One team member extracted relevant study data into a structured abstraction form and another checked it for accuracy. For consistency in reporting findings across studies, we transposed some treatment effects reported in studies to ensure all our abstracted data represented the effect of the intervention group relative to the comparator group. We used the Cochrane Risk of Bias (RoB 2.0) tool to assess the risk of bias for each included trial.[19] Domains assessed with this tool include: bias arising from randomization process, bias due to deviations from intended interventions, bias due to missing outcome data, bias in measurement of the outcome, and bias in selection of the reported result. Risk of bias was assessed as "high," "some concerns," or "low" at the study level unless different outcomes within a single study required outcome-level risk of bias ratings. We used the Risk Of Bias In Non-randomized Studies – of Interventions (ROBINS-I) instrument to assess the quality of nonrandomized studies with comparator groups;[20] risk of bias ratings were translated to analogous low, some concerns, and high ratings to be consistent with the RoB 2.0 tool. Case series were not evaluated for risk of bias due to the absence of a comparator group. We used the Quality of Health Economic Studies (QHES) instrument to assess the quality of included cost analyses.[21] We considered studies with scores on this instrument above 90 to be good quality, studies with scores between 60 and 89 to be fair quality, and studies with scores below 60 to be poor quality. Two team members conducted independent

risk of bias or quality assessments on all included studies; discrepancies were resolved by discussion, in consultation with the lead investigator if needed.

2.1.5 Data Synthesis and Strength of Evidence Rating

Study characteristics and results were qualitatively synthesized for each research question in tabular and narrative formats; quantitative synthesis was not possible because of the limited evidence. For cost outcomes, we adjusted all reported outcomes in foreign currency to U.S. dollars based on the U.S. Department of Treasury mid-year exchange rate for the year reported by study authors (*Appendix C*).

We graded the strength of evidence among comparative studies using a modification to GRADE, which assesses the strength of evidence based on domains relating to risk of bias, inconsistency, imprecision, indirectness, and other considerations, such as publication bias,[22] for outcomes broadly defined as overall survival, progression-free survival, health-related quality of life, and adverse events (AEs). Additionally, we stratified the strength of evidence assessments by specific treatment comparison and indication for treatment (i.e., new and recurrent GBM); the included studies in which non-GBM cancers were the indication for treatment were not comparative studies and, therefore, not graded for any outcome. To assess the consistency domain within GRADE, we evaluated both the consistency in the direction and magnitude of treatment effect; we modified the conventional GRADE by downgrading this domain when there was only a single-study body of evidence to evaluate. To assess the precision domain, we considered width of confidence intervals, when provided, and whether they included a null effect or clinically meaningful benefit or harm. We applied the GRADE system to the cost-effectiveness study in a similar fashion. With GRADE, the strength of evidence represents the overall certainty of the findings and can be graded as "very low," "low," "moderate," or "high." *Table 3* defines these levels of certainty.[23]

Table 3.   Strength of evidence grades and definitions[23]

GRADE	Definition
High	**We are very confident that the estimate of effect lies close to the true effect for this outcome.** The body of evidence has few or no deficiencies. We believe that the findings are stable, that is, another study would not change the conclusions.
Moderate	**We are moderately confident that the estimate of effect lies close to the true effect for this outcome.** The body of evidence has some deficiencies. We believe that the findings are likely to be stable, but some doubt remains.
Low	**We have limited confidence that the estimate of effect lies close to the true effect for this outcome.** The body of evidence has major or numerous deficiencies (or both). We believe that additional evidence is needed before concluding either that the findings are stable or that the estimate of effect is close to the true effect.
Very Low	**We have very limited confidence that the estimate of effect lies close to the true effect for this outcome.** The body of evidence has numerous major deficiencies. We believe that substantial additional evidence is needed before concluding either that the findings are stable or that the estimate of effect is close to the true effect.

2.2   Clinical Practice Guideline Synthesis

In addition to the systematic evidence review portion of this HTA, we also identified relevant CPGs and conducted a quality assessment of each guideline using the Appraisal of Guidelines for Research & Evaluation II (AGREE) instrument.[24] With this instrument, six domains are

assessed and an overall score between 1 (lowest possible) and 7 (highest possible) is assigned to reflect the overall quality of the guideline. We synthesized CPGs in a tabular format and discussed the results qualitatively in the accompanying text.

3.   Results

3.1   Literature Search

Figure 2 depicts the study flow diagram. We identified and screened 423 unique citations. We excluded 346 citations after title and abstract review. We reviewed the full text of 77 articles and included a total of 11 studies reported in 15 articles published between 2007 and 2018. Six studies (10 articles) provided evidence on efficacy (EQ1), 10 studies (10 articles) provided evidence on safety (SQ1), and one study (1 article) provided evidence on costs or cost-effectiveness (CQ1).

Figure 2.   Study flow diagram for HTA on TTF (Optune®)
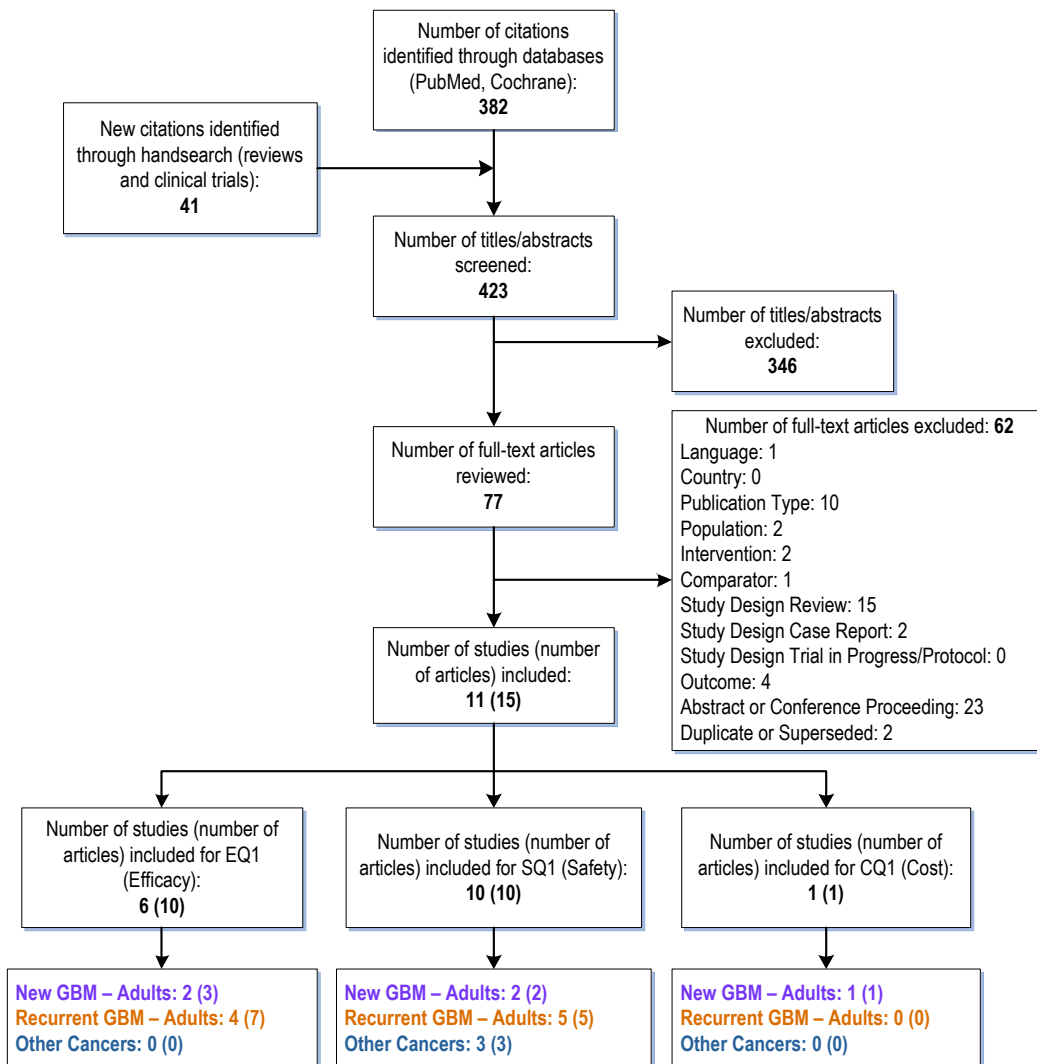
Abbreviations: CQ = cost question; EQ = efficacy question; GBM = glioblastoma multiforme; HTA = health technology assessment; SQ = safety question; TTF = tumor treating fields.

Individual study and population characteristics and findings for all included studies are summarized in *Appendix D*. The list of articles we screened at the full-text stage but excluded, is provided in *Appendix E*. Note that articles may have been excluded based on more than one reason but we report only one reason. We report our individual study risk of bias or quality assessments for included studies in *Appendix F*.

With respect to the findings of our systematic literature review that follow in this section, the results are grouped by indication for treatment (new GBM [purple], recurrent GBM [orange], other indications [blue]). Findings related to the efficacy (EQ), safety (SQ), and cost-effectiveness (CQ) of TTF are presented for each indication.

3.2   Newly Diagnosed GBM

We identified two eligible studies, described in three articles, which investigated the efficacy and safety[25-27] and one study which investigated the cost-effectiveness[28] of tumor treating fields (TTF) in patients with newly diagnosed glioblastoma multiforme (GBM).

3.2.1 Efficacy

Two studies reported outcomes related to the efficacy of TTF for newly diagnosed GBM (EQ1). One study is a randomized controlled trial (RCT), the EF-14 trial.[25,26] We also identified a small cohort study of newly diagnosed GBM patients (n=10) who received treatment with TTF and maintenance temozolomide (TMZ) and were compared to historical and concurrent comparator groups of newly diagnosed GBM patients who received only maintenance TMZ treatment.[27]

Efficacy subgroup analyses (EQ1a) were reported by one study, the EF-14 trial, for the overall survival outcome.[25]

3.2.1.1 Study Characteristics

Study and population characteristics for the two included studies are available in *Appendix D, Tables D-1 and D-2*. Briefly, the EF-14 RCT[25,26] was conducted in 83 centers in the United States (U.S.), Canada, Europe, and South Korea between July 2009 and December 2016. Patients were randomized to receive treatment with TTF and maintenance TMZ (n=466) or maintenance TMZ alone (n=229). The median age of patients was 56 to 57 years and 68 percent of patients were male. Karnofsky Performance Status (KPS) scores were between 60 and 100 (median 90) and Mini-Mental State Examinations (MMSE) scores were between 27 and 30 for 74 percent of patients at baseline; higher KPS and MMSE scores represent better performance/functional status. More than half of patients underwent gross total resection (only 13% of patients had only a biopsy) and 91 percent of patients received a dose of 57 to 63 Gray (Gy) during standard radiotherapy. The mean number of TMZ cycles received prior to the trial was 6 (range 0 to 51) in the intervention group and 5 (range 0 to 33) in the comparator group. Patients were randomized within a mean of 4 months since diagnosis (range 1 to 6 months) and were at least 2 weeks post-radiation therapy (median 36 to 37 days).

The cohort study by Kirson et al. was conducted in the Czech Republic as a pilot to the EF-14 trial and did not provide many details related to the populations in the intervention and two

comparator groups.[27] The intervention group consisting of 10 patients received TTF and maintenance TMZ therapy. A historical comparator group (n not reported), matched to the intervention group on age and KPS score, received maintenance TMZ alone according to the protocol described by Stupp et al.[4] and was included in the analyses of overall survival. A concurrent comparator group (n=32) also received maintenance TMZ alone according to the protocol described by Stupp et al.[4] and was included in the analyses of progression-free survival. All KPS scores at baseline were ≥70 in the intervention group, >60 in the historical comparator group, and not reported in the concurrent comparator group. Patients in the intervention group were at least 4 weeks post-radiation therapy when they were assigned to receive TTF with maintenance TMZ therapy.

We rated risk of bias separately for the overall survival, progression-free survival, and quality of life (QOL) outcomes from the two included studies. In the EF-14 trial, there were some concerns of bias for the survival outcomes[25] and high risk of bias for the QOL outcomes.[26] Overall and progression-free survival outcomes were assessed as high risk of bias in the cohort study conducted by Kirson et al.; the cohort study did not provide data on QOL.[27]

3.2.1.2 Findings

In the EF-14 trial,[25,26] the median duration of TTF treatment was 8.2 months (range 0 to 82) and the median duration of TMZ treatment was 6 months (range 0 to 51) in the intervention group and 5 months (range 0 to 33) in the comparator group. Seventy-five percent of patients in the intervention group achieved treatment adherence of ≥75 percent, defined as use of the device for ≥18 hours per day.[25] The cohort study[27] did not report duration of or adherence to treatment. Details related to the overall survival, progression-free survival, and QOL and functional status outcomes are available in *Appendix D, Tables D-3 and D-4*. A summary of the findings and strength of evidence ratings for the efficacy of TTF in patients with newly diagnosed GBM is presented in *Table 4*.

Table 4.   Summary of findings and strength of evidence ratings comparing TTF plus maintenance TMZ to maintenance TMZ alone for efficacy in persons with newly diagnosed GBM (EQ1)

Certainty Assessment		Summary of Findings	CERTAINTY/ Direction of Effect
№ of Studies (№ of Patients)	Risk of Bias Inconsistency[a] Indirectness Imprecision		
Overall survival			
1 RCT (695)[25]	**Risk of Bias**: Serious[b] **Inconsistency**: Unknown **Indirectness**: Not serious **Imprecision**: Not serious	Median OS was 20.9 months with TTF+TMZ and 16.0 months with TMZ alone; HR 0.63 (95% CI, 0.53 to 0.76) over median 40 months of follow up.	⊕⊕◯◯ LOW For benefit with TTF
1 Cohort (NR)[27]	**Risk of Bias**: Very serious[c] **Inconsistency**: Unknown **Indirectness**: Not serious **Imprecision**: Very serious[d]	Observational study consistent with RCT in direction of effect (but not magnitude); median OS was >39 months with TTF+TMZ and 14.7 months with TMZ alone.	⊕◯◯◯ VERY LOW For benefit with TTF

(continued)

Table 4.   Summary of findings and strength of evidence ratings comparing TTF plus maintenance TMZ to maintenance TMZ alone for efficacy in persons with newly diagnosed GBM (EQ1) (continued)

Certainty Assessment № of Studies (№ of Patients)	Risk of Bias Inconsistency[a] Indirectness Imprecision	Summary of Findings	CERTAINTY/ Direction of Effect
Progression-free survival			
1 RCT (695)[25]	**Risk of Bias**: Serious[b] **Inconsistency**: Unknown **Indirectness**: Not serious **Imprecision**: Not serious	Median PFS was 6.7 months with TTF+TMZ and 4.0 months with TMZ alone; HR 0.63 (95% CI, 0.52 to 0.76) over median 40 months of follow up; at 6 months, 56% of TTF+TMZ group and 37% of TMZ alone group were progression-free.	⊕⊕◯◯ LOW For benefit with TTF
1 Cohort (42)[27]	**Risk of Bias**: Very serious[c] **Inconsistency**: Unknown **Indirectness**: Not serious **Imprecision**: Very serious[e]	Observational study consistent with RCT in direction of effect (but not magnitude); median PFS was 38.8 months with TTF+TMZ and 7.8 months with TMZ alone.	⊕◯◯◯ VERY LOW For benefit with TTF
Quality of life and functional status			
1 RCT (695)[25,26]	**Risk of Bias**: Very serious[b] **Inconsistency**: Unknown **Indirectness**: Not serious **Imprecision**: Serious[f]	Time to sustained decline in KPS and MMSE scores was significantly longer with TTF+TMZ than TMZ alone [KPS: HR 0.79 (95% CI, 0.66 to 0.95); MMSE: HR 0.80 (95% CI, 0.67 to 0.95)]; significantly more patients in TTF+TMZ than TMZ alone group experienced stable or improved global health status, pain, weakness of legs, and physical/cognitive/emotional functioning.	⊕◯◯◯ VERY LOW For benefit with TTF

Abbreviations: CI = confidence interval; EQ = efficacy question; GBM = glioblastoma multiforme; HR = hazard ratio; KPS = Karnofsky Performance Scale; MMSE = Mini Mental State Examination; NA = not applicable; NR = not reported; OS = overall survival; PFS = progression-free survival; RCT = randomized controlled trial; TMZ = temozolomide; TTF = tumor treating fields.

[a] When the body of evidence is a single study, consistency is unknown; a rating of "serious" is entered in the GRADE tool for the purposes of calculating the overall strength of evidence.

[b] The EF-14 trial was rated some concerns for bias for the overall survival, progression-free survival, and safety outcomes and high risk of bias for the quality of life outcomes.

[c] This study was rated high risk of bias for all outcomes.

[d] Results are very imprecise due to a sample size of only 10 patients receiving TTF+TMZ (intervention) and an indeterminate number of patients receiving TMZ alone (comparator).

[e] Results are very imprecise due to a sample size of only 10 patients receiving TTF+TMZ (intervention) and 32 patients receiving TMZ alone (comparator).

[f] Results are somewhat imprecise due to 91% of patients providing data on quality of life outcomes and some EORTC QLQ-C30 subscale results including the both benefit and harm.

Overall Survival

Overall survival was a secondary endpoint in the EF-14 trial, which had 80 percent power (allowing for 10% loss to follow up) to detect a hazard ratio (HR) of 0.76. Over a median follow-up period of 40 months, the EF-14 trial reported median overall survival of 20.9 months and 16.0 months in the intervention and comparator groups, respectively. The HR favored treatment with TTF and maintenance TMZ (HR 0.63, 95% confidence interval [CI], 0.53 to 0.76) compared with TMZ alone.[25] Results from the cohort study conducted by Kirson et al. were consistent with the results from the EF-14 trial in direction of effect, but were of greater magnitude among the patients receiving TTF. Median overall survival was greater than 39 months (exact median not

reported [NR]) among the 10 patients who received TTF with maintenance TMZ therapy and 14.7 months among the patients from a historical comparator group who only received maintenance TMZ (P=0.0018).[27]

In subgroup analyses (EQ1a) of the EF-14 trial data, median overall survival was significantly higher among patients who were adherent (i.e., used continuous TTF therapy for ≥18 hours per day) (22.6 months, 95% CI, 19.7 to 25.1) than among patients who were not adherent (19.1 months, 95% CI, 16.5 to 21.9) (HR 0.65, 95% CI, 0.49 to 0.85).[25] Other subgroup analyses found no significant differences between subgroups with respect to overall survival defined by age (<65 versus ≥65 years), sex (men versus women), resection history (biopsy versus partial resection versus gross total resection), or KPS score at baseline (90 to 100 versus ≤80).[25]

Progression-free Survival

Progression-free survival was the primary endpoint in the EF-14 trial, which had 80 percent power (allowing for 10% loss to follow up) to detect a HR of 0.78 or less. Over a median follow-up period of 40 months, the EF-14 trial reported median progression-free survival of 6.7 months and 4.0 months in the intervention and comparator groups, respectively. The HR favored treatment with TTF and maintenance TMZ (HR 0.63, 95% CI, 0.52 to 0.76) compared to TMZ alone. Fifty-six percent of the intervention group was progression-free at 6 months, compared to 37 percent of the comparator group.[25]

Results from the cohort study by Kirson et al. were consistent with the results from the EF-14 trial in direction of effect, but not magnitude. Median progression-free survival was greater than 38.75 months (reported as 155 weeks) among the 10 patients who received TTF with maintenance TMZ therapy and 7.75 months (reported as 31 weeks) among the patients in the historical comparator group who only received maintenance TMZ (P=0.0002).[27]

No subgroup analyses (EQ1a) were reported for the progression-free survival outcome.

Quality of Life and Functional Status

In the EF-14 trial, health-related quality of life (HRQoL) and functional status were self-reported by patients using the MMSE, the KPS, and 9 preselected subscales of the European Organisation for Research and Treatment of Cancer (EORTC) QLQ-C30 and QLQ-BN20. In intention-to-treat (ITT) analyses, the median time to a sustained 6-point decrease on the MMSE (i.e., a decrease in function) was 16.7 and 14.2 months in the intervention and comparator groups, respectively (HR 0.79, 95% CI, 0.66 to 0.95). The median time to a sustained 10-point decrease on the KPS (i.e., a decrease in function) was 5.5 and 3.9 months in the intervention and comparator groups, respectively (HR 0.80, 95% CI, 0.67 to 0.95). In analyses among patients with baseline HRQoL data (n=639; 92% of randomized), the percentage of patients with stable or improved HRQoL was significantly higher in the intervention group than the comparator group for global health status (54% versus 38%); physical functioning (54% versus 38%); cognitive functioning (50% versus 39%); emotional functioning (55% versus 44%); pain (57% versus 36%); and weakness of legs (59% versus 42%) but not role functioning (48% versus 41%), social functioning (48% versus 41%), or itchy skin (42% versus 47%). Results within the HRQoL subscales were similar

with respect to median months of deterioration-free survival. Itchy skin increased for the intervention group at 3, 6, 9, and 12-month assessments, compared to baseline, while it decreased for the comparator group. Itchy skin was an expected side effect from the transducer arrays among patients receiving TTF plus maintenance TMZ.[27]

No subgroup analyses (EQ1a) were reported for the QOL and functional status outcomes.

Summary

We concluded with low certainty from RCT evidence and very low certainty from observational study evidence that the addition of TTF to usual care treatment with TMZ improved overall and progression-free survival among patients with newly diagnosed GBM. We also concluded with very low certainty from RCT evidence that the addition of TTF to usual care treatment with TMZ improved quality of life and functional status among patients with newly diagnosed GBM (**Table 4**).

3.2.2 Safety

The two studies included for the efficacy research questions (EQ1, EQ1a) also contributed data to the safety research question (SQ1) for newly diagnosed GBM. No subgroup analyses (SQ1a) were reported for the safety outcomes.

3.2.2.1 Study Characteristics

Study and population characteristics for the two studies are available in **Appendix D, Tables D-1 and D-2** and are described in section 3.2.1.1 above. In the EF-14 trial[25] there were some concerns of bias. In the cohort study by Kirson et al., safety outcomes were only reported for the 10 patients who received TTF with maintenance TMZ therapy and as such, we did not rate the risk of bias for safety outcomes.[27]

3.2.2.2 Findings

Details related to the safety outcomes are available in **Appendix D, Table D-5**. A summary of the findings and strength of evidence ratings for the safety of TTF in patients with newly diagnosed GBM is presented in **Table 5**.

There were no serious adverse events (AEs) among the 10 patients who received TTF and maintenance TMZ treatment in the small cohort study.[27]

Among 456 patients in the EF-14 trial with grade 3 or grade 4 GBM (98% of 466 randomized to TTF plus maintenance TMZ), more than half (52%) experienced mild to moderate site reactions under the TTF transducer arrays and 2 percent experienced a severe (i.e., grade 3) site reaction.[25] All 10 patients in the cohort study by Kirson et al. reported grade 1 or 2 (i.e., mild to moderate) dermatitis and none reported grade 3 or 4 (i.e., severe or disabling) dermatitis.[27]

The EF-14 trial reported no significant difference between groups with respect to participants experiencing one or more grade 3 or 4 (i.e., severe or disabling) AEs (P=0.58 for between-group comparison) and differences between groups for specific safety outcomes disappeared once

treatment duration was taken into account.[25] All of the mild to moderate AEs reported among the 10 patients in the cohort study were attributed to underlying disease (headache, seizures), TMZ treatment (anemia, thrombocytopenia, leucopenia), or other treatments (elevated liver function, hyperglycemia); no severe or disabling AEs were reported.[27]

We concluded with low certainty from RCT data that the addition of TTF to usual care treatment with TMZ among patients with newly diagnosed GBM introduced minimal harm (***Table 5***). We did not grade the strength of evidence from the observational study by Kirson et al.[27] since safety outcomes were reported only for the patients receiving treatment with TTF (i.e., there was no comparative analysis).

Table 5.   **Summary of findings and strength of evidence ratings comparing TTF plus maintenance TMZ to maintenance TMZ alone for safety in persons with newly diagnosed GBM (SQ1)**

Certainty Assessment		Summary of Findings	CERTAINTY/ Direction of Effect
№ of Studies (№ of Patients)	Risk of Bias Inconsistency[a] Indirectness Imprecision		
Adverse events			
1 RCT (672)[25]	**Risk of Bias:** Serious[b] **Inconsistency:** Unknown **Indirectness:** Not serious **Imprecision:** Not serious	Mild to moderate dermatologic AEs were reported by half of patients receiving TTF; the addition of TTF to TMZ treatment did not significantly increase the rates of systemic AEs (P=0.58).	⊕⊕◯◯ LOW For minimal harm with TTF

Abbreviations: AE = adverse event; GBM = glioblastoma multiforme; RCT = randomized controlled trial; SQ = safety question; TMZ = temozolomide; TTF = tumor treating fields.

[a] When the body of evidence is a single study, consistency is unknown; a rating of "serious" is entered in the GRADE tool for the purposes of calculating the overall strength of evidence.

[b] The EF-14 trial was rated some concerns for bias for the overall survival, progression-free survival, and safety outcomes and high risk of bias for the quality of life outcomes.

3.2.3 Cost

We identified one eligible study that investigated the cost-effectiveness of TTF in patients with newly diagnosed GBM.[28]

3.2.3.1 Study Characteristics

Study and population characteristics for the study are available in ***Appendix D, Tables D-1 and D-2***. Bernard-Arnoux et al.[28] used effectiveness data from the interim analysis of the EF-14 trial[17] to conduct a cost-effectiveness study comparing TTF plus maintenance TMZ to maintenance TMZ alone. The study was from the French health care system payor perspective using a lifetime horizon, discounted at 4 percent, and based on costs in 2014 Euros (€). The authors entered a hypothetical cohort of 1,000 people into a Markov decision model with the same characteristics and receiving the same intervention as those in the EF-14 trial.[17] The model used direct health care costs excluding the cost of surgery and concomitant radiotherapy and TMZ. The model looked at life expectancy after each 1-month treatment cycle and did not use quality adjusted-life-years (QALY) because of the lack of relevant published data on health-state utilities associated with GBM.

We rated this study as good quality using the Quality of Health Economic Studies (QHES) instrument.

3.2.3.2 Findings

Details related to the cost outcomes are available in *Appendix D, Table D-6*. A summary of the findings and strength of evidence rating for the cost-effectiveness of TTF in patients with newly diagnosed GBM is presented in *Table 6*.

Table 6.   **Summary of findings and strength of evidence ratings comparing TTF plus maintenance TMZ to maintenance TMZ alone for cost-effectiveness in persons with newly diagnosed GBM (CQ1)**

Certainty Assessment		Summary of Findings[b]	CERTAINTY/ Direction of Effect
№ of Studies (№ of Patients)	Risk of Bias Inconsistency[a] Indirectness Imprecision		
Cost-effectiveness			
1 study (1000)[28]	**Risk of Bias:** Not serious **Inconsistency:** Unknown **Indirectness:** Not serious **Imprecision:** Not serious	The discounted payor perspective ICER was $817,001 (95% CI, $612,352 to $1,021,651) per life year gained.	⊕⊕◯◯ LOW[c] Not cost-effective

Abbreviations: CI = confidence interval; CQ = cost question; GBM = glioblastoma multiforme; ICER = incremental cost-effectiveness ratio; TMZ = temozolomide; TTF = tumor treating fields.

[a] When the body of evidence is a single study, consistency is unknown; a rating of "serious" is entered in the GRADE tool for the purposes of calculating the overall strength of evidence.

[b] All costs are reported here in 2014 U.S. Dollars. The costs for the year and currency reported in the published studies is in *Appendix D*, *Table D-6*.

[c] As a cost effectiveness study, the starting GRADE for this study was "low" (i.e., the approach taken with observational research). The study was then downgraded for unknown inconsistency and upgraded for the large effect size.

The incremental cost-effectiveness ratio (ICER) was $817,000 (in 2014 United States Dollars [USD]) (95% CI, $612,352 to $1,021,651) per life year gained and remained robust across sensitivity analyses. According to the authors, if the monthly costs for the Optune® system and support were reduced to $2,740 per month from $27,398 per month (price discounted by approximately 90%), the discounted ICER would be $97,562.

We concluded with low certainty that TTF is not cost-effective among patients with newly diagnosed GBM.

3.3   Recurrent GBM

We identified 4 eligible studies, described in 7 articles, which investigated the efficacy of TTF among patients with recurrent GBM.[9,15,29-33] The same studies also investigated the safety of TTF among patients with recurrent GBM, described in 4 articles,[9,15,32,33] along with one additional eligible study.[13] No eligible studies evaluated the cost-effectiveness of TTF among patients with recurrent GBM.

3.3.1 Efficacy

One RCT, the EF-11 trial,[15,29-31] and 3 observational studies[9,32,33] investigated the efficacy of TTF among patients with recurrent GBM (EQ1). One observational study included patients from the Patient Registry Dataset (PRiDe) who were compared to both groups of the EF-11 trial.[9] Another observational study by Kirson et al. included a small cohort of patients with recurrent GBM (n=10) who were compared to multiple historical comparator groups.[33] The final observational study included patients originally enrolled in the EF-14 trial of TTF for newly diagnosed GBM[25] who experienced a recurrence during follow up;[32] patients received TTF with second-line therapy or second-line therapy alone. All other studies, including the EF-11 trial, evaluated TTF monotherapy compared with second-line therapy alone.

Efficacy subgroup analyses (EQ1a) were reported by 3 studies, in 5 articles,[9,29-32] for the overall survival outcome and one study[29] for the progression-free survival outcome.

3.3.1.1 Study Characteristics

Study and population characteristics for the 4 included studies are available in *Appendix D, Tables D-7 and D-8*. Briefly, the EF-11 RCT[15,29-31] was conducted in 28 centers in the U.S. and Europe between September 2006 and May 2009. Patients with recurrent GBM were randomized to receive treatment with TTF (n=120) or best available chemotherapy according to local practice and physician's choice (n=117) until disease progression or intolerance. Some patients in the comparator group received combination treatment; almost one third of patients received bevacizumab (31%) and irinotecan (31%). The median age of patients was 54 years (range 24 to 80 years) and 70 percent of patients were male. KPS scores ranged from 50 to 100 (median 80); higher KPS scores represent better performance/functional status. Most of the enrolled patients were experiencing their second or greater recurrence (91% and 85% of the intervention and comparator groups, respectively); patients randomized to TTF treatment were a median 12 months (range 3 to 99 months) and patients randomized to best chemotherapy were a median 11 months (range 3 to 77 months) from their initial diagnosis. Eighty-two percent of patients underwent surgical resection at some point during the course of their disease, and almost a quarter of patients underwent surgical resection just prior to enrollment in the EF-11 trial. Most patients received TMZ with radiotherapy (84%) and as maintenance therapy (80%) and 19 percent of patients had previously received bevacizumab.[15]

The cohort study by Mrugula et al.[9] compared 457 patients enrolled in PRiDe in the U.S. between October 2011 and November 2013 with historical comparator groups from the EF-11 trial (i.e., patients with recurrent GBM who received TTF [n=120] or best chemotherapy according to physician's choice [n=117]). Patients from PRiDe were not restricted by number of recurrences, but more than half were experiencing their second or greater recurrence. The median age of patients in PRiDe was 55 years (range 18 to 86 years) and the median KPS score was 80 (range 10 to 100). Patients in PRiDe were similar to those in the EF-11 trial with respect to history of debulking surgery and radiotherapy with TMZ, but 55 percent (compared to 19% in the EF-11 trial) had previously received bevacizumab.[9]

Kirson et al. presented data on a small cohort of 10 patients with recurrent GBM who received TTF treatment until disease progression (up to a maximum of 18 months) as part of a pilot study for EF-11. These 10 patients were compared to 5 historical comparator groups from phase II studies of chemotherapy published between 1999 and 2004; the comparator groups included a total of 775 patients who received a variety of different chemotherapies, some in combination. The median age was 51 years among the TTF patients and median ages ranged from 45 to 54 years across the historical comparator groups. The median KPS score at baseline was 90 in the intervention group (range 70 to 100) and the range of KPS scores was 60 to 100 among the comparator groups. Patients in the intervention group were experiencing their first recurrence of disease, were at least 4 weeks removed from surgery, and at least 8 weeks removed from radiotherapy. Patients in the comparator groups were not excluded based on number of recurrences.[33]

The final study was a post-hoc analysis of participants in the EF-14 trial[17] by Kesari et al.[32] A total of 144 of 466 (31%) patients randomized to receive TTF plus maintenance TMZ and 60 of 229 (26%) patients randomized to receive maintenance TMZ alone experienced a first recurrence of GBM and were included in the post-hoc analysis. The intervention group continued to receive TTF with second-line chemotherapy and the comparator group received second-line chemotherapy until second progression of disease (or a maximum of 24 months). The median age of patients followed was 57 years (range 29 to 83 years) in the intervention group and 58 years (range 22 to 75 years) in the comparator group; the median KPS score at first recurrence was 90 (range 60 to 100 across both groups).

We rated risk of bias separately for the overall survival, progression-free survival, and QOL of life outcomes from the 4 included studies. In the EF-11 trial, there were some concerns of bias for the overall survival and progression-free survival outcomes[15,29-31] and high risk of bias for the QOL outcomes.[15] There were some concerns of bias for all efficacy outcomes in the PRiDe study.[9] The small cohort study by Kirson et al.[33] and the post-hoc analysis of EF-14 patients who experienced a recurrence by Kesari et al.[32] were rated high risk of bias for all efficacy outcomes.

3.3.1.2 Findings

In the EF-11 trial, 93 patients (78% of randomized) completed 4 weeks of TTF treatment; median monthly compliance (i.e., using TTF ≥75% of the time) was 86 percent (range 41% to 98%), translating to a mean use of 20.6 hours per day.[30] Ninety-six percent of patients in the comparator group completed one cycle (i.e., 1 month) of second-line therapy.[15]

The median daily compliance rate among patients receiving TTF treatment in the PRiDe study was 70 percent (range 12% to 99%) and less than half of patients (i.e., 44%) achieved compliance of ≥75 percent per day.[9] The median durations of treatment in the PRiDe study[9] were 4.1 months (95% CI, 3.5 to 4.8 months) for patients receiving TTF treatment (n=457), 2.3 months (95% CI, 2.1 to 2.4) for patients receiving TTF treatment in the EF-11 trial (n=120), and 2.1 months (95% CI, 2.0 to 2.9) for patients receiving second-line therapy in the EF-11 trial (n=117). None of the other studies providing results for efficacy outcomes reported duration of treatment.[15,32,33]

Details related to the overall survival, progression-free survival, and QOL and functional status outcomes are available in *Appendix D, Tables D-9 and D-10*. A summary of the findings and strength of evidence ratings for the efficacy of TTF in patients with recurrent GBM is presented in *Table 7*.

Table 7.   Summary of findings and strength of evidence ratings for efficacy of TTF in persons with recurrent GBM (EQ1)

Certainty Assessment			
№ of Studies (№ of Patients) Treatment Comparison	Risk of Bias Inconsistency[a] Indirectness Imprecision	Summary of Findings	CERTAINTY/ Direction of Effect
Overall survival			
1 RCT (237)[15] TTF versus Second-line therapy	**Risk of Bias**: Serious[b] **Inconsistency**: Unknown **Indirectness**: Not serious **Imprecision**: Serious[c]	Median OS was similar in the intervention and comparator groups (6.6 and 6.0 months, respectively) in the EF-11 trial; [HR 0.86 (95% CI, 0.66 to 1.12); P=0.27].	⊕◯◯◯ VERY LOW For no benefit with TTF
2 Cohort (1,479)[9,33] TTF versus Second-line therapy	**Risk of Bias**: Very serious[b] **Inconsistency**: Serious[d] **Indirectness**: Not serious **Imprecision**: Serious[e]	Studies were consistent in direction but not magnitude of effect with each other and the RCT. Patients in PRiDe registry reported "significantly longer" OS than EF-11 patients receiving second-line therapy (6.0 months).[9] Median OS in 10 TTF patients (16 months) was "more than double" that of historical controls (range 6 to 10 months) in the pilot study for EF-11.[33]	⊕◯◯◯ VERY LOW For benefit with TTF
1 Cohort (204)[32] TTF + Second-line therapy versus Second-line therapy	**Risk of Bias**: Very serious[b] **Inconsistency**: Unknown **Indirectness**: Not serious **Imprecision**: Serious[c]	Median OS was similar in the intervention and comparator groups (11.8 and 9.2 months, respectively) [HR 0.70 (95% CI, 0.48 to 1.00); P=0.05].	⊕◯◯◯ VERY LOW For no benefit with TTF
Progression-free survival			
1 RCT (237)[15] TTF versus Second-line therapy	**Risk of Bias**: Serious[b] **Inconsistency**: Unknown **Indirectness**: Not serious **Imprecision**: Serious[c]	Median PFS was 2 months in both the intervention and comparator groups in the RCT [HR 0.81 (95% CI, 0.60 to 1.09); 21% of TTF patients and 15% of second-line therapy patients were progression-free at 6 months (P=0.13).	⊕◯◯◯ VERY LOW For no benefit with TTF
1 Cohort (785)[33] TTF versus Second-line therapy	**Risk of Bias**: Very serious[b] **Inconsistency**: Unknown **Indirectness**: Not serious **Imprecision**: Very serious[e]	The historical comparator groups in the observational study reported similar results (9% to 19% were progression-free at 6 months) but a much higher proportion (50%) of the 10 TTF patients were progression-free at 6 months; this is consistent in direction but not magnitude of effect with the RCT. Authors report that the median time to progression was more than double for the TTF than the second-line therapy patients; confidence intervals were very wide in the TTF group.	⊕◯◯◯ VERY LOW For benefit with TTF

(continued)

Table 7.   Summary of findings and strength of evidence ratings for efficacy of TTF in persons with recurrent GBM (EQ1) (continued)

Certainty Assessment			
№ of Studies (№ of Patients) **Treatment Comparison**	**Risk of Bias Inconsistency**[a] **Indirectness** **Imprecision**	**Summary of Findings**	**CERTAINTY/ Direction of Effect**
Quality of life and functional status			
1 RCT (63)[15] TTF versus Second-line therapy	**Risk of Bias**: Very serious[b] **Inconsistency**: Unknown **Indirectness**: Not serious **Imprecision**: Very serious[e]	After 3 months, TTF participants showed larger improvements on the EORTC QLQ-C30 emotional functioning subscale, less of a decline on the role functioning subscale, and improvement (compared to a decline with chemotherapy) on the cognitive functioning subscale. Patients receiving second-line therapy experienced less of a decline on the physical functioning subscale. There were no "meaningful" differences between TTF and second-line therapy with respect to the global health status and social functioning subscales.	⊕○○○ VERY LOW For benefit with TTF

Abbreviations: CI = confidence interval; EORTC QLQ-C30 = European Organization for Research and Treatment Quality of Life Questionnaire; EQ = efficacy question; GBM = glioblastoma multiforme; HR = hazard ratio; OS = overall survival; PFS = progression-free survival; PRiDe = Patient Registry Dataset; RCT = randomized controlled trial; TTF = tumor treating fields.

[a] When the body of evidence is a single study, consistency is unknown; a rating of "serious" is entered in the GRADE tool for the purposes of calculating the overall strength of evidence.

[b] The EF-11 trial[15] was rated some concerns for bias for overall survival, progression-free survival, and safety outcomes and high risk of bias for the quality of life outcomes. The PRiDe[9] study was rated some concerns for bias for overall and progression-free survival and high risk of bias for safety outcomes. All other studies[32,33] were rated high risk of bias for all outcomes. When considering multiple studies, the higher risk of bias was considered for the purposes of calculating the overall strength of evidence.

[c] Results are imprecise due to small sample size, with confidence intervals that include both benefit and harm.

[d] Results are consistent between the two studies in direction of effect but not magnitude of effect.

[e] Results are imprecise due to very small sample size in at least one study group.

Overall Survival

Overall survival was the primary endpoint in the EF-11 trial, which had 80 percent power to detect a HR of 0.63. Over a median follow-up period of 39 months, the median overall survival did not differ between the intervention (6.6 months) and the comparator groups (6.0 months) (HR 0.86, 95% CI, 0.66 to 1.12; P=0.27).[15] The proportion of patients that survived in the intervention and comparator groups, respectively, was 20 percent and 20 percent at 1 year, 8 percent and 5 percent at 2 years, and 4 percent and 1 percent at 5 years.[15] Mrugula et al.[9] reported that median overall survival among patients in the PRiDe registry (9.6 months) was "markedly longer" and "significantly longer" than EF-11 trial patients receiving TTF treatment or second-line therapy. Forty-four percent of the patients in the PRiDe registry were alive at 1 year, compared to 20 percent of the patients in the EF-11 trial. At two years, 30 percent of patients in the PRiDe registry were alive compared to 8 percent of patients in the EF-11 trial.[9] In the pilot study by Kirson et al., 67.5 percent of the cohort of 10 patients receiving TTF treatment were alive at 1 year. The median overall survival in the intervention group (62 weeks; range 20 to 124

weeks) was "more than doubled" the median overall survival in 5 historical comparator groups (range of medians 24 to 39 weeks).[33]

In the post-hoc analysis of patients with recurrence from the EF-14 trial, Kesari et al. reported that over a median follow-up period of 12.6 months, the median overall survival was higher among patients receiving TTF treatment with second-line therapy (11.8 months) than patients receiving second-line therapy alone (9.2 months) (P=0.049).[32]

Several subgroup analyses (EQ1a) of the EF-11 trial data have been reported.[15,29-31] When the intervention group was restricted to patients who received at least one cycle of TTF treatment (i.e., 28 days) (93 of 120 randomized [78%]), median survival increased to 7.8 months (from 6.6 months among all randomized patients) and the comparison between groups was significant (HR 0.69, 95% CI, 0.52 to 0.92; P=0.0093); all patients randomized to second-line therapy received at least one course of treatment.[15] Median overall survival was significantly higher in the intervention group than in the comparator group among patients with the following: previous failed treatment with bevacizumab (P=0.0156); prior low-grade glioma diagnosis (P=0.0493); tumor size $\geq$18 cm^2 (P=0.009); baseline KPS score $\geq$80 (P=0.0453); and higher rate of adherence to treatment (P=0.039).[30] When the comparator group was limited to patients receiving bevacizumab treatment (81 of 117 randomized [69%]), the median overall survival was significantly higher among the intervention group than the comparator group (P=0.0450).[30] No significant differences between the intervention and comparator groups were observed among subgroups defined by age ($\leq$60 years, >60 years) or surgical resection history (biopsy only, any surgery, reoperation at recurrence).[30] Median overall survival was significantly higher among lower-dose (i.e., $\leq$4.1 mg/day) dexamethasone users (P<0.0001) than among higher-dose (i.e., >4.1 mg/day) dexamethasone users (P=0.0015).[31] In the EF-11 trial, responders were defined as those with a complete or partial response and nonresponders were defined as those with stable disease or progression according to Macdonald criteria.[73] In subgroup analyses of responders (n=21) and nonresponders (n=216), the median overall survival was significantly higher within groups among responders than nonresponders (intervention group: P<0.0001; comparator group: P=0.0235).[29] Mrugula et al. also reported subgroup analyses for the PRiDe registry. Among the 457 patients in the PRiDe registry who received TTF treatment, median overall survival was significantly higher for patients with the following attributes: first recurrence, $\geq$75 percent daily adherence to treatment, KPS scores between 90 and 100, and no prior bevacizumab use.[9]

Kesari et al.'s post-hoc subgroup analysis of the EF-14 trial participants who experienced a recurrence demonstrated that median overall survival was significantly higher among patients receiving TTF treatment with second-line therapy (11.8 months) than among patients receiving bevacizumab alone (9.0 months) (P=0.043) when the comparator group was restricted to bevacizumab users.[32] Detailed data are presented in ***Appendix D, Table D-9***.

Progression-free Survival

Over a median follow up of 39 months, the median progression-free survival in the EF-11 trial was 2.2 months among the intervention group and 2.1 months among the comparator group (HR 0.81, 95% CI, 0.60 to 1.09). Twenty-one percent (95% CI, 13.5% to 29.3%) of TTF patients and

15 percent (95% CI, 7.8% to 22.3%) of second-line therapy patients were progression-free at 6 months (P=0.13). The response rate, including partial and complete response according to Macdonald criteria, was 14 percent (95% CI, 7.9% to 22.4%) of TTF patients and 9.6 percent (95% CI, 3.9% to 18.8%) of second-line therapy patients (P=0.19).[15] In the small cohort study of 10 patients receiving TTF treatment, Kirson et al. reported that median time to disease progression (26.1 weeks; range 3 to 124 weeks) was more than double the reported medians of the 5 historical comparator groups (range of medians 8.1 to 12.4 weeks). Fifty percent of the TTF patients (i.e., 5 of 10) were progression-free at 6 months, compared to a range of 9 to 19 percent of the historical comparator groups.[33]

In subgroup analyses (EQ1a) of EF-11 trial, the median progression-free survival was higher among responders (n=21) than nonresponders (n=216) within both the TTF (P=0.0007) and second-line therapy (P=0.0222) groups and was numerically higher among patients receiving TTF treatment than patients receiving second-line therapy, regardless of response.[29] Detailed data are presented in **Appendix D Table D-9**.

Quality of Life and Functional Status

Twenty-seven percent of patients randomized in the EF-11 trial contributed self-reported data from the EORTC QLQ-C30 at baseline and 3 months. The EF-11 trial investigators reported that there were "no meaningful differences" between the intervention and comparator groups with respect to the global health status and social functioning subscales.[15] The TTF intervention group was favored with respect to multiple subscales; patients experienced larger improvements, less of a decline, and improvement rather than a decline when compared to the second-line therapy group on the emotional, role, and cognitive functioning subscales, respectively. The second-line therapy comparator group experienced less of a decline on the physical functioning subscale than the TTF intervention group.[15] The EF-11 trial did not report any subgroup analyses (EQ1a) and none of the other included studies for EQ1 provided data on QOL or functional status.

Summary

Evidence on the efficacy of TTF for recurrent GBM varied by study design. We concluded with very low certainty from RCT data that there are no differences in survival outcomes between TTF monotherapy and second-line therapy; however, QOL is improved with TTF monotherapy. From observational data, we concluded that there is a survival benefit with TTF monotherapy (very low certainty).

For the comparison of TTF with second-line therapy and second-line therapy alone among patients with recurrent GBM, we concluded with very low certainty (from one observational study) that there are no differences in overall survival outcomes between the groups. There was no evidence on which to draw a conclusion about the potential benefit of TTF with respect to progression-free survival, QOL, or functional status (**Table 7**).

3.3.2 Safety

The 4 studies included for the efficacy research questions (EQ1, EQ1a) also contributed data to the safety research question (SQ1). We additionally identified one case series of patients with

recurrent GBM by Lacouture et al. that contributed data to the safety question (SQ1).[13] No subgroup analyses (SQ1a) were reported for the safety outcomes.

3.3.2.1 Study Characteristics

Study and population characteristics are available in **Appendix D, Tables D-7 and D-8** and are described in section 3.3.1.1 above for the 4 studies that contributed data to both the efficacy research questions (EQ1, EQ1a) and the safety research question (SQ1).[9,15,32,33] Mrugula et al.[9] only provided safety data on the patients receiving TTF in the PRiDe registry but did qualitatively compare them to patients in the two arms of the EF-11 trial. The additional fifth study by Lacouture et al. included 540 patients with recurrent GBM who received TTF treatment and reported adverse events as part of a post-marketing surveillance program in the U.S.; no details about the patient population were provided by the authors.[13]

In the EF-11 trial,[15] there were some concerns of bias for the safety outcomes; all other comparative studies[9,13,32,33] were rated as high risk of bias for the safety outcomes.

3.3.2.2 Findings

Details related to the safety outcomes are available in **Appendix D, Table D-11**. A summary of the findings and strength of evidence ratings for the safety of TTF in patients with recurrent GBM is presented in **Table 8**. Adverse effects were similar across the studies that compared TTF, with or without second-line therapy, with second-line therapy alone.

Authors of the EF-11 trial report that serious AEs were significantly lower in the intervention group than in the comparator group (6% versus 16%, P=0.022) but do not define serious AEs or provide additional details.[15] No treatment-related serious AEs occurred among 10 patients who were compared to multiple historical comparator groups in the pilot study by Kirson et al.;[33] none of the other eligible observational studies reported data on serious AEs.

Sixteen percent of the intervention group in the EF-11 trial reported a mild to moderate (grade 1 or 2) contact dermatitis beneath the transducer arrays and no patients experienced a grade 3 or 4 (i.e., severe or disabling) dermatologic AE in either group.[15] Transducer array site reactions were commonly reported by patients receiving TTF in the observational studies (range 13%[32] to 90%[33]). In Lacouture et al.'s case series of 540 patients receiving TTF treatment, the median time to dermatologic AE onset was 32.5 days (range 2 to 250).[13]

Authors of the EF-11 trial reported that patients in the active comparator group experienced chemotherapy-related AEs, including significantly more hematological (17%), gastrointestinal (17%), and infection-related (8%) AEs than the TTF group (3%, 4%, and 4%, respectively).[15] Kesari et al.'s post-hoc analysis of EF-14 patients (who experienced a recurrence) reported that 49 percent of patients receiving TTF treatment experienced one or more grade 3 or 4 (not otherwise defined by study authors, presumably severe or disabling) AE compared to 33 percent of patients receiving second-line therapy; however, none of the AEs in the intervention group were attributed to the TTF treatment and, as suggested by the investigators, may have been related to the longer duration of follow-up in the TTF plus second-line therapy group compared to the second-line therapy alone group .[32] Likewise, none of the other AEs experienced by

patients in the intervention groups of the EF-11 trial,[15] the PRiDe study,[9] or the patients in the pilot study by Kirson et al.[33] were attributed to TTF treatment.

We concluded with very low certainty that there is minimal harm with TTF, with or without second-line therapy, compared to second-line therapy alone for patients with recurrent GBM (*Table 8*).

Table 8.   **Summary of findings and strength of evidence ratings for safety of TTF in persons with recurrent GBM (EQ1)**

Certainty Assessment			
№ of Studies (№ of Patients) Treatment Comparison	Risk of Bias Inconsistency[a] Indirectness Imprecision	Summary of Findings	CERTAINTY/ Direction of Effect
Adverse Events			
1 RCT (207)[15] TTF versus Second-line therapy	**Risk of Bias**: Serious[b] **Inconsistency**: Unknown **Indirectness**: Not serious **Imprecision**: Serious[c]	Mild to moderate contact dermatitis beneath the TTF transducer arrays was reported by 16% of the patients in the TTF group; no severe or disabling dermatologic AEs were reported in either group. Moderate to disabling AEs were reported by 6% of the TTF group and 16% of the second-line therapy group (P=0.022); only 3% of patients overall experienced a severe or disabling AE.	⊕○○○ VERY LOW For minimal harm with TTF
2 Cohort (1,479)[9,33] TTF versus Second-line therapy	**Risk of Bias**: Very serious[b] **Inconsistency**: Serious[d] **Indirectness**: Not serious **Imprecision**: Serious[c]	No serious AEs reported with TTF; range of 24% to 90% of TTF patients experienced a skin reaction/contact dermatitis with TTF; other AEs were rare (≤10%) or not attributed to TTF treatment.	⊕○○○ VERY LOW For minimal harm with TTF
1 Cohort (204)[32] TTF + Second-line therapy versus Second-line therapy	**Risk of Bias**: Very serious[b] **Inconsistency**: Unknown **Indirectness**: Not serious **Imprecision**: Serious[c]	Site reactions beneath the TTF transducer arrays were reported by 13% of patients in the intervention group; though 49% of the TTF group experienced at least one grade 3 or 4 AE[e], compared to 33% of the second-line therapy group, none were related to TTF treatment.	⊕○○○ VERY LOW For minimal harm with TTF

Abbreviations: AE = adverse event; GBM = glioblastoma multiforme; RCT = randomized controlled trial; SQ = safety question; TTF = tumor treating fields.

[a] When the body of evidence is a single study, consistency is unknown; a rating of "serious" is entered in the GRADE tool for the purposes of calculating the overall strength of evidence.

[b] The EF-11 trial[15] was rated some concerns for bias for overall survival, progression-free survival, and safety outcomes and high risk of bias for the quality of life outcomes. The PRiDe[9] study was rated some concerns for bias for overall and progression-free survival and high risk of bias for safety outcomes. All other studies[32,33] were rated high risk of bias for all outcomes. When considering multiple studies, the higher risk of bias was considered for the purposes of calculating the overall strength of evidence.

[c] Study sample sizes across studies were relatively small, especially for rare serious adverse events.

[d] Results are consistent between the two studies in direction of effect but not magnitude of effect.

[e] Authors did not explicitly define what is meant by grade 3 or 4, but patients were originally enrolled in the EF-14 trial[25], where grade 3 or 4 was defined as severe or disabling, according to the NCI Common Terminology Criteria for Adverse Events v3.0.[34,35]

3.4   Other Cancers

We identified three studies[12,36,37] that investigated the safety of TTF and no studies that investigated the efficacy or cost-effectiveness of TTF in patients with other cancers.

3.4.1 Safety

We included three case series that investigated the safety of TTF in patients with other cancers.[12,36,37] Due to the lack of comparator groups, we did not assess ROB or grade strength of evidence for the safety outcomes from these case series.

3.4.1.1   Study Characteristics

Study and population characteristics for the three included case series are available in *Appendix D, Table D-12 and D-13*. One case series by Green et al. reported the AEs related to the use of TTF among 5 male pediatric patients with high-grade glioma in the U.S.; TTF treatment was given on a compassionate use basis with or without other treatment (i.e., radiation or chemotherapy). The mean age at treatment was 14.8 years (range 10 to 20 years) and all patients had previously undergone surgical resection. Two patients were newly diagnosed and 3 patients had recurrent disease.[36] A second case series by Pless et al. of 42 adult patients in Switzerland with advanced stage non-small cell lung cancer (NSCLC) evaluated the safety of TTF with concomitant pemetrexed use. The median age of patients was 63 years (range 44 to 78 years) and almost two-thirds of patients were male. Only 12 percent of patients reported surgical resection; 24 and 90 percent of patients reported radiotherapy or chemotherapy, respectively. The median time since diagnosis was 11.4 months and the median time since last chemotherapy was 3.7 months. Over the course of the study, patients received an average 4.5 cycles (i.e., months) of TTF treatment and 6.1 cycles of pemetrexed.[12] Finally, a third case series by Salzberg et al. of 6 adult patients in Switzerland with locally advanced or metastatic malignancies described the AEs associated with TTF treatment; the cancers included breast cancer (n=3), melanoma (n=1), GBM (n=1), and pleural mesothelioma (n=1). The median age of the patients was 66 years (range 24 to 76 years) and all patients were previously treated with several lines of therapy (i.e., no additional treatment options were available to them).[37]

3.4.1.2   Findings

Details regarding the safety outcomes for the three included case series are available in *Appendix D, Table D-16*. In the case series of NSCLC patients by Pless et al., none of the serious AEs reported were considered TTF-related over a follow-up period of 9.5 months.[12] No serious AEs were reported among patients in the other two case series.[36,37]

In regard to dermatological AEs, Pless et al. reported only one NSCLC patient who had a severe or disabling dermatologic AE (rash/dermatitis/erythema). Mild or moderate rash/dermatitis/erythema was the most common dermatologic AE reported among the NSCLC patients (24%); the remaining dermatologic AEs were also mild or moderate and included blister (7%), pruritus (5%), alopecia (2%), and ulceration (2%).[12] In the case series by Green et al., one (20%) of the pediatric glioma patients reported a scalp ulceration, categorized by the authors as a grade 2 skin breakdown.[36] Three patients (50%) in the multi-cancer case series by Salzberg et al.

reported a grade 1 (not otherwise defined by study authors) skin irritation with reddening of the skin under the transducer arrays.[37]

Pless et al. was the only study that reported nondermatologic AEs. Less than 10 percent of patients reported any of the AEs detailed in ***Appendix D, Table D-16***, except for respiratory AEs (dyspnea: 29% and cough: 27%) that were expected due to the natural history of lung cancer.[12]

3.5   Clinical Practice Guideline Synthesis

We identified several clinical practice guidelines (CPGs) for the treatment of GBM, 6 of which include a discussion of TTF as a treatment modality. These are summarized in ***Table 9*** and include guidelines from the National Comprehensive Cancer Network (NCCN)[38], the American Association of Neuroscience Nurses (AANN)[39], the United Kingdom (U.K.) National Institute for Health and Care Excellence (NICE),[43] the Medical Oncology Spanish Society (SEOM)[40], the European Association for Neuro-Oncology (EANO)[41], and the European Society for Medical Oncology (ESMO)[42]. Guidelines varied widely in the methods employed in their development process including variations in the methods used to search and select evidence, formulate recommendations, and determine the strengths and limitations of the body of evidence. Several guidelines did not include a process for external review, patient engagement in guideline development, or a description of the process for updating the guideline, and all but 2 did not appear to consider conflicts of interest among authors when forming recommendations. The lowest quality score possible was 1 and the highest possible quality score was 7.

Overall, recommendations were mixed. Of the 3 guidelines addressing TTF for newly diagnosed GBM, the NCCN recommends TTF as an adjunct to standard radiotherapy plus chemotherapy for patients of any age with a good Karnofsky performance score (>60 KPS). It recently updated the strength of that recommendation (based on results from the EF-14 trial[25]) from a category 2A recommendation (based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate) to a category 1 recommendation (based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate).[38] Conversely, the EANO does not recommend the use of TTF for newly diagnosed GBM, stating that "Questions about the mode of action, interpretation of data, and effect on quality of life have been raised, and the role and cost-effectiveness of TTF in the treatment of newly diagnosed glioblastoma remain to be defined."[41] Similarly, NICE also recommends against TTF for the management of newly diagnosed GBM based on the published health economic evidence.[28] The NICE guideline states that TTF is not an efficient use of the UK's National Health System's (NHS) resources.[43]

TTF for the treatment of recurrent GBM was addressed in all 6 guidelines; 3 of 6 CPGs addressed use of TTF for newly diagnosed GBM. The EF-11 trial[15] was included in all guidelines addressing use of TTF in recurrent GBM and while guideline authors described the findings of the trial similarly, they differed substantially in their recommendations. The NCCN[38] and the AANN[39] both recommend TTF as an adjunct to chemotherapy for patients with recurrent GBM, whereas neither the SEOM[40], EANO[41], nor ESMO[42] include TTF as a recommended treatment, stating that treatment with TTF failed to prolong survival compared with second-line chemotherapy. Similarly, NICE recommends against TTF for the management of recurrent

GBM, stating that there is evidence of some clinical benefit but that indirect published health economic evidence in people with newly diagnosed high-grade gliomas found that treatment with TTF is not an efficient use of the U.K.'s National Health System's (NHS) resources.[43]

Table 9.   Clinical practice guidelines that include TTF treatments

Organization *Guideline Title (Year)* Guideline Quality Rating[a]	Evidence Base	Recommendation[b]	Rating/Strength of Evidence Narrative Assessment[c]
National Comprehensive Cancer Network (NCCN) *NCCN Clinical Practice Guidelines in Oncology. Central Nervous System Cancers Version 1.2018 (2018)[38]* Quality Rating: 5 out of 7	2 RCTs	For patients of any age with newly diagnosed GBM and with good performance status (KPS >60), and any MGMT promoter status: Recommend standard brain radiotherapy + concurrent temozolomide and adjuvant temozolomide + **alternating electric field therapy.[d]** For patients with recurrent glioblastoma: consider **alternating electric field therapy.[d]**	Authors rated the recommendation for newly diagnosed GBM Category 1 and recurring GBM Category 2B[e]
U.K. National Institute for Health and Care Excellence (NICE) *Brain tumours (primary) and brain metastases in adults (2018)[43]* Quality Rating: 7 out of 7	2 RCTs	For patients newly diagnosed glioblastoma: Do not offer **TTF** as part of management. For patients with recurrent glioblastoma: Do not offer **TTF** as part of management.	NICE chooses to reflect the concept of strength in the wording of the recommendation
American Association of Neuroscience Nurses (AANN) *Care of the Adult Patient with a Brain Tumor (2014)[39] (Revised 2016)* Quality Rating: 4 out of 7	1 RCT, 1 Narrative Expert Review	Nurses should be aware that use of electrical **TTF** may be considered a comparable treatment option to chemotherapy for patients with recurrent malignant glioma, particularly when hematologic, infectious, or gastrointestinal toxicities limit treatment options (Level 1 recommendation). When **TTF** are used, nurses should assess the skin for topical dermatitis (Level 1 recommendation). Nurses should educate patients about measures to improve comfort and compliance with the system (Level 3 recommendation).	Authors rated two recommendations Level 1 and one recommendation Level 3[f]
Medical Oncology Spanish Society (SEOM) *SEOM clinical guidelines for diagnosis and treatment of glioblastoma (2017)[40]* Quality Rating: 3 out of 7	Unclear	For recurrent GBM, **TTF** failed to prolong survival compared with second-line chemotherapy.	Authors rated the evidence level II grade D[g]

(continued)

Table 9.   Clinical practice guidelines that include TTF (continued)

Organization *Guideline Title (Year)* Guideline Quality Rating[a]	Evidence Base	Recommendation[b]	Rating/Strength of Evidence Narrative Assessment[c]
European Association for Neuro-Oncology (EANO) *EANO guideline on the diagnosis and treatment of adult astrocytic and oligodendroglial gliomas (2017)[41]* Quality Rating: 5 out of 7 overall. 3 out of 7 for the guidelines handling of TTF	2 RCTs	TTF was not recommended. The following two statements were included in the text: Newly diagnosed GBM: Questions about the mode of action, interpretation of data, and effect on quality of life have been raised, and the role and cost-effectiveness of **TTF** in the treatment of newly diagnosed glioblastoma remain to be defined. Recurrent GBM: **TTF** were not superior to best physician's choice in a randomized phase III trial.	No rating was given when a treatment was not recommended
European Society for Medical Oncology (ESMO) *High-grade glioma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up (2014)[42]* Quality Rating: 2 out of 7	1 RCT	TTF was not recommended. The guideline included the following statement for recurrent GBM "**TTF** failed to prolong survival compared with second-line chemotherapy."	Authors rated the TTF evidence level I grade A[h]

Abbreviations: AGREE II = Appraisal of Guidelines for Research & Evaluation II; CT = controlled trial; GBM = glioblastoma; KPS = Karnofsky Performance Score; MGMT = 06-methylguanine-DNA Methyltransferase; RCT = randomized controlled trial; SR = systematic review; TTF = tumor treating fields; U.K. = United Kingdom.

[a] Results of our independent quality assessment using the AGREE II tool (version 2017.21). Unless otherwise noted, the Rating refers to the quality of the overall guideline including the guidelines handling of the TTF evidence. A score of 1 indicates the lowest quality possible, a score of 7 indicated the highest quality possible.

[b] Only recommendations from the guideline pertinent to TTF for the treatment of GBM are summarized.

[c] Refers to the quality rating/ strength of the recommendation as described in the guideline by the authors of the CPG.

[d] Alternating electric field therapy is only an option for patients with supratentorial disease.

[e] Category 1 evidence: based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate. Category 2B: Based upon lower-level evidence, there is NCCN consensus that the intervention is appropriate. Note the recommendation for newly diagnosed GBM was changed from category 2A (based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate) to category 1 in a flash update to the 2018 guideline.

[f] Level 1 recommendations are supported by Class 1 evidence. Class I = Randomized controlled trials without significant limitations or meta-analysis. Level 3 recommendations are supported by Class III and IV evidence. Class III = Qualitative study, case study, or series Class IV = Evidence from expert committee reports and expert opinion of the AANN guideline panel; standards of care and clinical protocols that have been identified.

[g] Level 2 Evidence = Small randomized trials or large randomized trials with a suspicion of bias (lower methodological quality) or meta-analyses of such trials or of trials with demonstrated heterogeneity. Grade D = Moderate evidence against efficacy or for adverse outcome, generally not recommended.

[h] Level 1 = Evidence from at least one large randomized, controlled trial of good methodological quality (low potential for bias) or meta-analyses of well-conducted randomized trials without heterogeneity, Grade A= Strong evidence for efficacy with a substantial clinical benefit, strongly recommended.

4. Discussion

4.1   Summary of the Evidence

Limited evidence on the efficacy, safety, and cost-effectiveness of tumor treating fields (TTF) treatment among patients with cancer exists. We included only one eligible randomized controlled trial (RCT) that compared TTF plus maintenance temozolomide (TMZ) with maintenance TMZ alone among adult patients with newly diagnosed glioblastoma multiforme (GBM)[25] and one eligible RCT that compared TTF with second-line therapy among adult patients with recurrent GBM;[15] no eligible RCTs evaluated the use of TTF among pediatric patients or patients with non-GBM malignancies. The observational data were limited to one cohort study among trial participants who experienced recurrent GBM,[32] 3 cohorts that were compared to concurrent or historical comparator groups from other studies for both newly diagnosed GBM and recurrent GBM patients,[9,27,33] one case series of patients with recurrent GBM[13], and 3 small case series (sample sizes of 5, 6, and 42) of patients with non-GBM cancers.[12,36,37] Only one study meeting inclusion criteria evaluated the cost-effectiveness of TTF (for treatment of newly diagnosed GBM).[28]

Table 10 provides an overall summary of findings and strength of evidence ratings for efficacy outcomes (overall survival, progression-free survival, quality of life (QOL) and functional status) (EQ1), safety outcomes (SQ1), and cost outcomes (CQ1) by treatment comparison and study design among patients with newly diagnosed or recurrent GBM. No eligible comparative studies on which to rate strength of evidence were identified by this health technology assessment (HTA) among patients with non-GBM indications.

We concluded with low certainty from RCT evidence and very low certainty from observational study evidence that the addition of TTF to usual care treatment with TMZ improved overall and progression-free survival among patients with newly diagnosed GBM. With respect to treatment for recurrent GBM, we concluded with very low certainty from RCT evidence that TTF monotherapy does not improve overall or progression-survival and from observational evidence that TTF plus second-line therapy does not improve overall survival compared with second-line therapy alone. Observational data among patients with recurrent GBM suggest a survival benefit with TTF monotherapy when compared with second-line therapy (very low certainty). From RCT evidence, we concluded with very low certainty that the addition of TTF to usual care treatment improved QOL and functional status among patients with newly diagnosed GBM and that TTF monotherapy, compared with second-line therapy, improved QOL among patients with recurrent GBM.

With low certainty from RCT evidence among newly diagnosed GBM patients and very low certainty from all other available evidence, we conclude that there is minimal harm associated with TTF; there were no serious adverse events (AEs) related to TTF reported in the eligible studies and most AEs were expected (dermatologic reactions under the TTF transducer arrays) or unrelated to TTF treatment. Finally, we concluded with low certainty that TTF is not a cost-effective treatment among patients with newly diagnosed GBM.

Table 10.   Overall summary of findings and strength of evidence ratings (certainty and direction of effect) by indication and treatment comparison

Outcomes	New GBM	Recurrent GBM	
	TTF + TMZ Versus TMZ	TTF Versus Second-line therapy	TTF + Second-line therapy Versus Second-line therapy
OS	SOE$_{RCT}$: ⊕⊕◯◯ LOW DOE$_{RCT}$: For benefit with TTF SOE$_{OBS}$: ⊕◯◯◯ VERY LOW DOE$_{OBS}$: For benefit with TTF	SOE$_{RCT}$: ⊕◯◯◯ VERY LOW DOE$_{RCT}$: For no benefit with TTF SOE$_{OBS}$: ⊕◯◯◯ VERY LOW DOE$_{OBS}$: For benefit with TTF	SOE$_{RCT}$: No evidence SOE$_{OBS}$: ⊕◯◯◯ VERY LOW DOE$_{OBS}$: For no benefit with TTF
PFS	SOE$_{RCT}$: ⊕⊕◯◯ LOW DOE$_{RCT}$: For benefit with TTF SOE$_{OBS}$: ⊕◯◯◯ VERY LOW DOE$_{OBS}$: For benefit with TTF	SOE$_{RCT}$: ⊕◯◯◯ VERY LOW DOE$_{RCT}$: For no benefit with TTF SOE$_{OBS}$: ⊕◯◯◯ VERY LOW DOE$_{OBS}$: For benefit with TTF	No evidence
QOL, Functional Status	SOE$_{RCT}$: ⊕◯◯◯ VERY LOW DOE$_{RCT}$: For benefit with TTF SOE$_{OBS}$: No evidence	SOE$_{RCT}$: ⊕◯◯◯ VERY LOW DOE$_{RCT}$: For benefit with TTF SOE$_{OBS}$: No evidence	No evidence
Safety	SOE$_{RCT}$: ⊕⊕◯◯ LOW DOE$_{RCT}$: For minimal harm with TTF SOE$_{OBS}$: No evidence	SOE$_{RCT}$: ⊕◯◯◯ VERY LOW DOE$_{RCT}$: For minimal harm with TTF SOE$_{OBS}$: ⊕◯◯◯ VERY LOW DOE$_{OBS}$: For minimal harm with TTF	SOE$_{RCT}$: No evidence SOE$_{OBS}$: ⊕◯◯◯ VERY LOW DOE$_{OBS}$: For minimal harm with TTF
Cost	SOE$_{RCT}$: No evidence SOE$_{OBS}$: ⊕⊕◯◯ LOW DOE$_{OBS}$: TTF not cost-effective	No evidence	No evidence

Abbreviations: DOE = direction of effect, GBM = glioblastoma multiforme; OBS = observational study; OS = overall survival; PFS = progression-free survival; QOL = quality of life; RCT = randomized controlled trial; SOE = strength of evidence; TMZ = temozolomide; TTF = tumor treating fields.

4.2   Limitations of the Evidence Base

The primary research study and clinical practice guideline evidence we identified for inclusion in this HTA has several limitations.

4.2.1 Limited number of comparative effectiveness trials

Limited published evidence investigating the clinical effectiveness and safety of TTF for the treatment of newly diagnosed and recurrent GBM exists, and no published trial data exists for other cancers. We identified only two RCTs comparing TTF to usual care, both of which had some concerns for bias for the survival and safety outcomes and high concerns for risk of bias for QOL and functional status outcomes. The lack of comparative effectiveness trials, and small body of evidence in general, limited our ability to draw conclusions for TTF for patient populations with other cancer types. It should also be noted that both included RCTs were funded by the makers of Optune® with significant input from Optune® staff into the design and conduct of the studies. This in itself does not introduce automatic bias; however, independent verification of study findings would be a valuable addition to the evidence base.

4.2.2 Risk of bias among included studies

We rated all outcomes from all studies as having high or some concerns for risk of bias. Some sources of bias across included studies were common; for example, most studies did not blind

participants, caregivers, or clinicians to treatment allocation nor blind outcome assessors. Endpoints such as overall and progression-free survival were often determined independently of the study personnel and are not likely to be biased. A lack of blinding, however, is problematic for patient-reported outcomes such as QOL, some functional outcomes, and adverse events because these outcomes are somewhat subjective and more susceptible to risk of bias. Although blinding treatment allocation is challenging to perform (i.e., a sham-controlled study of TTF is not practically feasible) and potentially unethical in studies of TTF treatment, the risk of bias nonetheless remains and should be acknowledged for patient-reported outcomes. The direction of bias from nonblinding largely depends on the beliefs and attitudes of participants, clinicians, and outcome assessors, so cannot always be predicted.

Issues of attrition, adherence, and crossover also led to some concerns for bias. In the EF-14 trial of patients with newly diagnosed GBM, 8 percent of patients randomized to TTF plus TMZ treatment were lost to follow up (primarily due to withdrawing consent), compared to 6 percent of patients randomized to TMZ alone.[25] In the EF-11 trial of patients with recurrent GBM, only 78 percent of patients receiving TTF treatment completed at least one month of treatment, usually due to noncompliance or inability to handle the device, compared to 96 percent of patients who completed at least one month of second-line treatment.[15] There were 26 patients (11%) in the TMZ alone group of the EF-14 trial who crossed over to the TTF plus TMZ treatment group after the favorable interim results of the study were released; these patients had more favorable baseline characteristics than the rest of the TMZ alone group.[25] Though this crossover is not surprising given the severity of the disease, limited number of treatment options, and positive interim results from the trial, it still introduces the potential for bias.

Finally, there was likely selection bias in the included observational studies; authors typically did not provide explanations or perform sensitivity analyses to address potential selection bias. As an example, only 50 percent of TTF plus TMZ patients and 60 percent of TMZ alone patients in the EF-14 trial who experienced a recurrence continued receiving treatment during the observational study by Kesari et al.[32] The investigators did not provide explanations for the low enrollment into the study and did not adjust analyses for imbalances between groups related to prior treatment history (including crossover from TMZ alone to TTF plus TMZ treatment).

4.2.3 *Heterogeneity and studies underpowered for subgroups of interest*

No study was adequately powered to investigate whether the clinical effectiveness or safety of TTF varied by clinical history or patient characteristics (e.g., age, sex, Karnofsky performance score, surgical resection). As an example, the EF-11 trial of TTF among patients with recurrent GBM included a heterogeneous population of patients with respect to the number of recurrences and types of prior treatments they had experienced; patients experiencing multiple recurrences have often acquired resistance to treatment(s). Forty-seven percent of patients were enrolled in the trial after their second recurrence and 41 percent were enrolled after their third or greater recurrence; 18 percent of patients reported prior bevacizumab treatment. Additionally, *methyl-guanine methyl-tranferase* (*MGMT*) gene promotor methylation status, a predictive factor for TMZ response, was not assessed in the EF-11 trial. Finally, 84 percent of patients reported TMZ treatment concomitant with radiotherapy and 79 percent of patients reported maintenance TMZ treatment.[15] Authors did not provide results for any outcomes stratified by these clinical histories

or genetic factors, possibly due to prohibitive sample sizes. Any reported findings of differences with respect to subgroups must be considered hypothesis generating.

4.2.4 Applicability to current standard of care in the United States

Although there is no current standard of care for recurrent GBM, treatment with bevacizumab has become a more common practice since 2009 when it was provisionally approved by the United States (U.S.) Food and Drug Administration (FDA); it was rejected by the European Medicines Agency due to a lack of a controlled trial.[5,74,75] The EF-11 trial enrolled patients from countries including the U.S. and several from Europe between September 2006 and May 2009, which was prior to the FDA's provisional approval of bevacizumab for recurrent GBM, and only 31 percent received treatment with bevacizumab.[15] A physician's best choice of chemotherapy in the active comparator group during the trial may not be representative of current clinical practice. Additionally, patients in the EF-11 trial represent a population with a more advanced state of disease. Eighty-eight percent of patients enrolled in the EF-11 trial after their second or higher recurrence of disease. Because of this, 62 percent of participants had failed 2 or more previous treatments, including 20 percent who had previously failed treatment with bevacizumab.[15] Compared to other trials that enrolled patients at the first recurrence of GBM, findings from the EF-11 trial should be interpreted in the context of a population having failed multiple previous treatments and therefore likely at a more advanced stage of disease.

Whereas efficacy and safety outcomes from studies conducted outside of the U.S. are likely applicable to U.S. settings, it is not clear that studies conducted using cost data outside of the U.S. would apply to U.S. settings. The only eligible cost study we identified used effectiveness data from the interim analysis of the EF-14 trial[17] and was conducted from the French health care system payor perspective.[28] Although the effectiveness inputs from non-U.S. studies used in cost-effectiveness analyses are likely applicable, the extreme differences in how health care services are organized and financed between U.S. and non-U.S. countries likely reduces the applicability of the cost inputs used in non-U.S. studies.

4.3   Other Related HTAs

The Swedish Dental and Pharmaceutical Benefits Agency conducted an HTA in 2017[44] on the use of Optune® as an addition to the standard of care treatment for patients with newly diagnosed GBM. The authors summarized efficacy and safety findings from the EF-14 trial[25] and noted that their conclusions were based only on that trial and study-related abstracts. For the assessment of cost-effectiveness, the authors described an analysis performed by the manufacturer of Optune®, which was not cited and does not appear to be publicly accessible. The manufacturer's model inputs included a monthly product cost of 189,000 Swedish kronor (SEK) (i.e., approximately $21,000 U.S. dollars (USD) at the time of the publication) and data from the EF-14 trial that was extrapolated for a lifetime horizon using published data from Surveillance, Epidemiology, and End Results (SEER). The manufacturer calculated the cost per quality-adjusted life years (QALY) to be approximately 1.8 million SEK ($200,000 USD at the time of analysis); in sensitivity analyses that assumed a horizon of 20 years, higher medical expenses, and lower temozolomide costs, the authors of the HTA calculated the cost per QALY to be approximately

2.1 million SEK ($233,333 USD at the time of analysis) and assessed the uncertainty level of their model to be medium.

We also identified an HTA that was commissioned by the ECRI Institute Health Technology Assessment Information Service.[45] This 2015 HTA focused on TTF for recurrent GBM and searched databases and gray literature to identify studies related to the efficacy of TTF compared to other treatment options and palliative care and AEs associated with TTF. It included 3 articles[9,15,33] also included in this HTA and used the GRADE approach to determine the strength of evidence for each outcome. The HTA concluded that patients with recurrent GBM treated with TTF therapy compared to best standard of care had the same overall survival at 24 months (moderate strength of evidence) but that there was insufficient evidence to draw a conclusion on QOL (very low strength of evidence). Compared to best standard of care, it concluded that TTF therapy causes a lower rate of treatment-emergent serious hematologic AEs (moderate strength of evidence), thrombocytopenia, leukopenia, diarrhea, and infections (moderate strength of evidence), and nausea, anorexia, muscle weakness, and alopecia (low strength of evidence), a similar rate of treatment-emergent serious metabolism and nutrition disorders or vascular disorders (low strength of evidence), and a higher rate of skin site reactions, falls, and rashes (low strength of evidence). Evidence was insufficient to determine the difference in treatment-emergent serious gastrointestinal AEs or nervous system disorders (very low strength of evidence). The most common reported AE for TTF was skin reaction at the site of electrodes.

4.4   Selected Payer Coverage Policies

The Centers for Medicare and Medicaid Services (CMS) does not have a national coverage determination related to TTF. *Table 11* provides an overview of other payer coverage policies, and *Table 12* summarizes excerpts from these policies that are relevant to TTF.

Table 11.   Overview of payer coverage policies

Payor	Newly Diagnosed GBM	Recurrent GBM	Other Cancers
Medicare	--	--	--
Premera	✓ a	✗	✗
Regence	✓ a	✗	✗
United Healthcare	✓ a	✓ a	✗
Aetna	✓ a	✓ a	✗
Humana	✓ a	✓ a	✗
Kaiser	✓ a	✗	✗
Cigna	✓ a	✓ a	✗

✓ = covered; ✗ = not covered; — = no policy identified

Abbreviations: GBM = glioblastoma multiforme.

a If specific clinical criteria are met. See *Table 12* for details.

Table 12.   **Selected payer coverage for tumor treating fields (Optune®)**

Payer; Effective Date	Policy
Premera (Blue Cross)[76] November 1, 2017	Tumor treating fields (TTF) therapy to treat glioblastoma is medically necessary when ALL the following are met: - The patient has completed debulking surgery or biopsy; and - The patient has completed radiation therapy; and - The patient is being treated with temozolomide (TMZ); and - TTF therapy is begun within 7 weeks of the final radiation treatment. TTF therapy to treat advanced or recurrent glioblastoma is considered investigational. TTF is considered investigational for all other indications.
Regence (Blue Shield)[77] May 1, 2018	TTF to treat primary supratentorial glioblastoma multiforme (GBM) may be considered medically necessary when all of the following are met: - Patient is 18 years of age or older; and - Documentation of histologically confirmed primary supratentorial GBM; and - Following radiation and chemotherapy; and - Concurrent treatment with TMZ, unless TMZ has been ineffective, not tolerated, or is contraindicated. Due to insufficient research, the use of TTF therapy is considered investigational when the above criteria are not met, including but not limited to patients with recurrent glioblastoma.
United Healthcare[78] November 1, 2017	The use of FDA-approved devices to generate electric TTF to treat histologically-confirmed supratentorial glioblastoma (known also as GBM or World Health Organization [WHO] grade IV astrocytoma) is proven and medically necessary as adjunctive therapy when used according to FDA labeled indications, contraindications, warnings and precautions, and when ALL the following criteria are met: - Initial treatment with debulking surgery or biopsy followed by chemoradiation with concomitant TMZ and radiotherapy has been completed; and - Individual has Karnofsky Performance Status (KPS) score of >60; and - Individual or caregiver has been trained and is willing and able to apply the device daily; and - Individual is willing to wear the device at least 18 hours daily. When all the above criteria are met, an initial 3 months of electric TTF therapy will be approved. Subsequent approval(s) for continuation of electric TTF is based on: - Evidence of no documented disease progression by magnetic resonance imaging (MRI) done at a minimum of every 2 to 4 months. This includes a completed MRI scan with report submitted as part of any request for continuation of electric TTF treatment; and - KPS score of >60; and - Documentation that the individual and/or caregiver have been applying the device daily; and - Documentation that the patient has been wearing the device at least 18 hours daily. The use of devices to generate electric TTF is considered investigational, unproven, and not medically necessary when the criteria above are not met and for all other indications. The FDA has not approved the use of electric TTF devices for indications other than GBM. Further studies are needed to determine the safety and long-term efficacy of electric TTF therapy for other types of cancer.

(continued)

Table 12.   Selected payer coverage for tumor treating fields (Optune®) (continued)

Payer; Effective Date	Policy
Aetna[79] December 6, 2017	Aetna considers combination of devices to generate electric tumor treatment fields (ETTF) and TMZ medically necessary as adjunctive treatment of newly diagnosed histologically confirmed supratentorial glioblastoma following standard treatments that include surgery, chemotherapy, and radiation therapy. Aetna considers devices to generate ETTF medically necessary as monotherapy for persons with histologically confirmed glioblastoma (World Health Organization grade IV astrocytoma), after histologically or radiologically confirmed recurrence in the supratentorial region of the brain after receiving chemotherapy. Aetna considers devices to generate ETTF experimental and investigational for the treatment of other malignant tumors (e.g., breast, lung, melanoma, ovarian cancer, pancreatic cancer, and solid tumor brain metastases; not an all-inclusive list) and for all other indications because their effectiveness has not been established. Aetna considers combined ETTF therapy and chemo-immuno-therapy other than TMZ (e.g., 6-thioguanine, bevacizumab, capecitabine, celecoxib, cisplatin, cyclophosphamide, dacarbazine, doxorubicin, lomustine, paclitaxel, and pemetrexed; not an all-inclusive list) for the treatment of other malignant tumors experimental and investigational because the effectiveness of this approach has not been established.
Humana[80] February 22, 2018	All requests for ETTF require review by a medical director. Humana members may be eligible under the Plan for ETTF for the following indications: • Absence of any contraindication listed in the Coverage Limitations section; and • 22 years of age or older; and • Combined ETTF and TMZ in individuals with histologically-confirmed newly diagnosed GBM limited to the supratentorial region following maximal debulking surgery and completion of radiation therapy together with concomitant standard of care chemotherapy; or • Monotherapy for individuals diagnosed with histologically- or radiologically - confirmed recurrent GBM limited to the supratentorial region following treatment with chemotherapy after surgical and radiation treatments have been exhausted. Humana members may NOT be eligible under the Plan for ETTF for any indications other than those listed above including, but may not be limited to: • Active implanted medical device (e.g., deep brain stimulators, spinal cord stimulators, pacemakers, defibrillators); or • Bullet fragments; or • Pregnancy; or • Shunts; or • Skull defects (e.g., missing bone with no replacement); or • Treatment of other malignant tumors (e.g., breast, lung, pancreas). This is considered experimental/investigational as it is not identified as widely used and generally accepted for any other proposed use as reported in nationally recognized peer-reviewed medical literature published in the English language.

(continued)

Table 12.   Selected payer coverage for tumor treating fields (Optune®) (continued)

Payer; Effective Date	Policy
Kaiser[81] March 21, 2016	TTF to treat primary (not recurrent) supratentorial GBM may be considered medically necessary when ALL the following are met: • Patient is 18 years of age or older; and • KPS is 70% or higher; and • Documentation of histologically-confirmed primary GBM; and • Patient has completed standard concomitant chemoradiation with TMZ; and • Disease did not progress through chemo radiation (possible "pseudo progression" does not exclude patients from receiving TTF); and • TTF will be administered concurrently with TMZ, unless TMZ has been ineffective, not tolerated, or is contraindicated; and • TTF must be started no later than 60 days from the end of chemo radiation. Continued treatment of TTF can be covered until the second radiological progression (meaning 2 consecutive images showing tumor progression) or clinical deterioration.
Cigna[82] July 15, 2018	TTF therapy (i.e., Optune®) is considered medically necessary for individual 22 years of age or older with presence of histologically-confirmed GBM when EITHER of the following criteria are met: • With confirmed recurrence after receiving chemotherapy and the device is being used as a monotherapy • For adjuvant therapy with temozolomide TTF (i.e., Optune®) for any other indication is considered experimental, investigational or unproven.

Abbreviations: ETTF = electric tumor treatment fields; FDA = United States Food and Drug Administration; GBM = glioblastoma multiforme; KPS = Karnofsky Performance Status; TMZ = temozolomide; TTF = tumor treating fields; WHO = World Health Organization.

Aside from Medicare, all assessed payers cover TTF for newly diagnosed GBM patients if clinical criteria are met. The coverage of TTF for recurrent GBM varies by payer. Specific clinical criteria required for TTF coverage for newly diagnosed or recurrent GBM vary but often include histologically confirmed supratentorial GBM and prior debulking, radiation, and/or chemotherapy. Some payers also have an age requirement (minimum age of 18 or 22 years) or Karnofsky Performance Status score requirement (>60 or >70). For newly diagnosed GBM patients, all payors require the patient is also being treated with TMZ unless contraindicated. No payers we assessed cover TTF for non-GBM cancers.

4.5   Limitations of this HTA

This HTA has some limitations related to the scoping, process, and analyses we used to conduct the HTA. This HTA was limited to studies and other information published or publicly available in English. Though studies conducted in countries designated as less than "very high human development" on the United Nations Human Development Report were ineligible, no articles were excluded for country during full-text review. Because of the limited body of evidence, we accepted retrospective studies and studies with comparator groups from other populations (both concurrent and historical) that introduce an inherent risk of bias. The electronic search was limited to three databases. Our HTA excluded 'as treated' or 'per protocol' analyses, which could offer additional evidence on the efficacy and safety of TTF. The small evidence base made applying the GRADE approach challenging. We mitigated this challenge by using a modified GRADE approach that allowed us to downgrade the consistency domain to unknown when there was a single-study body of evidence. Finally, the AGREE guideline appraisal instrument largely focuses on evaluating the processes through which a guideline is developed; it does not assess how well the evidence included in the guideline was evaluated and interpreted correctly, or whether the conclusions of the guideline are consistent with the evidence. Thus, some guidelines may score artificially high and explains why conclusions may differ between guidelines despite having nearly similar quality scores.

4.6   Ongoing Research and Future Research Needs

We identified 37 clinical trials registered in clinicaltrials.gov that are relevant for this HTA. *Table 13* lists the clinical trials by study status and cancer type.

Table 13.   Relevant clinical trials status[a]

Study Status	Newly diagnosed GBM	Recurrent GBM	Other cancers
Not yet recruiting	0	1	4
Recruiting	9	8	8
Active and not recruiting	2	0	3
Completed	1 (EF-14)	1 (EF-11)	1[b]
Withdrawn	0	1[c]	0
Terminated	0	1[d]	0
Unknown	0	0	2[e]
TOTAL	12	12	18

Abbreviations: GBM = glioblastoma multiforme; HTA = health technology assessment; NSCLC = non-small cell lung cancer.

[a] Several clinical trials enroll participants with newly diagnosed GBM, recurrent GBM, and/or other cancers; therefore, totals do not add up to 37 trials.

[b] This clinical trial evaluated the efficacy and safety of TTF in NSCLC patients. One case series included in this HTA provides published results.[37]

[c] Withdrawn due to poor participant accrual.[46]

[d] Terminated due to amendment of study protocol.[47]

[e] Both clinical trials were last updated September 21, 2016 and reported as active, not recruiting with a study completion date of July 2017[48] and December 2016.[49]

Among newly diagnosed and recurrent GBM clinical trials, one trial in newly diagnosed GBM (EF-14)[50] and one trial in recurrent GBM (EF-11)[51] are reported as completed. This HTA includes published results from both completed trials. [15,26,29-32,52] Two trials currently recruiting newly diagnosed and recurrent GBM patients evaluate the feasibility and safety of TTF in pediatric populations.[53,54] Relevant ongoing clinical trials in newly diagnosed and recurrent GBM patients are listed by estimated study completion date in *Table 14* and *Table 15*, respectively.

Table 14.   Relevant ongoing trials in newly diagnosed GBM patients by completion date

Completion Date	Status	NCT Number	Trial Name
February 2019	Recruiting	NCT03128047	HUMC 1612: Optune® NovoTTF-200A System
April 2019	Recruiting	NCT03033992	Feasibility Trial of Optune® for Children With Recurrent or Progressive Supratentorial High-Grade Glioma and Ependymoma
March 2020	Recruiting	NCT03477110	Temozolomide, Radiation Therapy, and Tumor Treating Fields Therapy in Treating Participants With Glioblastoma
March 2020	Recruiting	NCT03258021	TTFields In Germany in Routine Clinical Care
May 2020	Active, not recruiting	NCT03223103	Safety and Immunogenicity of Personalized Genomic Vaccine and Tumor Treating Fields (TTFields) to Treat Glioblastoma
May 2020	Recruiting	NCT02903069	Study of Marizomib With Temozolomide and Radiotherapy in Patients With Newly Diagnosed Brain Cancer
June 2021	Recruiting	NCT02343549	A Phase II Study of Optune® (NovoTTF) in Combination With Bevacizumab and Temozolomide in Patients With Newly Diagnosed Unresectable Glioblastoma
June 2022	Active, not recruiting	NCT02152982	Temozolomide With or Without Veliparib in Treating Patients With Newly Diagnosed Glioblastoma Multiforme
September 2022	Recruiting	NCT03501134	Quality of Life of Patients With Glioblastoma Treated With Tumor-Treating Fields
February 2023	Recruiting	NCT03405792	Study Testing The Safety and Efficacy of Adjuvant Temozolomide Plus TTFields (Optune®) Plus Pembrolizumab in Patients With Newly Diagnosed Glioblastoma (2-THE-TOP)
July 2027	Recruiting	NCT03232424	NovoTTF-200A and Temozolomide Chemoradiation for Newly Diagnosed Glioblastoma

Abbreviations: GBM = glioblastoma multiforme; NCT = National Clinical Trial; TTF = tumor treating fields.

Table 15.   Relevant ongoing trials in recurrent GBM patients by completion date

Completion Date	Status	NCT Number	Trial Name
December 2018	Recruiting	NCT01894061	NovoTTF-100A With Bevacizumab (Avastin) in Patients With Recurrent Glioblastoma
February 2019	Recruiting	NCT03128047	HUMC 1612: Optune® NovoTTF-200A System
March 2019	Recruiting	NCT02663271	TTFields and Pulsed Bevacizumab for Recurrent Glioblastoma
April 2019	Recruiting	NCT03033992	Feasibility Trial of Optune® for Children With Recurrent or Progressive Supratentorial High-Grade Glioma and Ependymoma
March 2021	Recruiting	NCT01954576	NovoTTF Therapy in Treating Patients With Recurrent Glioblastoma Multiforme
August 2021	Not yet recruiting	NCT03430791	Trial of Combination TTF (Optune®), Nivolumab Plus/Minus Ipilimumab for Bevacizumab-naive, Recurrent Glioblastoma
August 2022	Recruiting	NCT02743078	Optune® Plus Bevacizumab in Bevacizumab-Refractory Recurrent Glioblastoma
September 2022	Recruiting	NCT03501134	Quality of Life of Patients With Glioblastoma Treated With Tumor-Treating Fields
December 2026	Recruiting	NCT01925573	Optune® (NOVOTTF-100A)+ Bevacizumab+ Hypofractionated Stereotactic Irradiation Bevacizumab-Naive Recurrent Glioblastoma (GCC 1344)

Abbreviations: GBM = glioblastoma multiforme; NCT = National Clinical Trial; TTF = tumor treating fields.

Clinical trials in other cancers include, but are not limited to, low-grade glioma, non-small cell lung cancer (NSCLC), pancreatic adenocarcinoma, ovarian carcinoma, meningioma, and hepatic

cancer. One clinical trial in NSCLC patients is reported as completed[83] and has published results in a case series included in this HTA.[37] Two clinical trials with unknown study status have past completion dates.[53,54] The first, COMET, was last updated as active, not recruiting with a study completion date of July 2017. The study assesses the effect of TTF in NSCLC patients and has only published interim safety results in a 2015 conference abstract.[84] The second, PANOVA, was last updated as active, not recruiting with a study completion date of December 2016. The study evaluates the efficacy and safety of TTF in advanced pancreatic adenocarcinoma patients and has only published efficacy and safety results in a 2017 conference abstract.[85] Other trials in non-GBM cancers have also only published results as conference abstracts.[86]

Additional RCTs may change the certainty of findings from this HTA for newly diagnosed and recurrent GBM patients. Upcoming trial completions will likely provide further information on efficacy, safety, and cost outcomes, particularly for other cancers. Moreover, additional research on patient preferences and values related to timing of treatment and subgroups analyses would advance research in this area. Advanced analytic and statistical techniques could be used within observational studies to mitigate biases introduced by nonrandomized study designs, potentially broadening the evidence base available to address important research questions. Publishing results in journal articles as well as or instead of conference abstracts would also help expand the available evidence.

5.   Conclusion

Findings are based on a small body of evidence graded as low or very low certainty because of a paucity of RCT data and comparative observational studies that we rated high risk of bias. We conclude with very low to low certainty that the addition of TTF to usual care with TMZ increases overall and progression-free survival among patients with newly diagnosed GBM. For patients with recurrent GBM, there may or may not be survival benefits associated with TTF treatment with or without second-line therapy (very low certainty). We conclude with very low certainty from RCT data that TTF improves quality of life and functional status among patients with newly diagnosed or recurrent GBM. We found evidence of minimal harm attributed to TTF treatment for GBM; TTF is likely safe for newly diagnosed and recurrent GBM (very low to low certainty), though likely not cost-effective for newly diagnosed GBM (low certainty). We found no evidence on which to draw conclusions about the cost-effectiveness of TTF for recurrent GBM or the impact of TTF treatment on non-GBM cancers.

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Appendix A. State of Washington Health Care Authority Utilization and Costs Data

Populations

The Tumor Treatment Field analysis examined member utilization and cost claims data from the following agencies:

• PEBB/UMP (Public Employees Benefit Board Uniform Medical Plan);

• PEBB Medicare;

• Department of Labor and Industries (LNI) Workers' Compensation Plan; and the

• Medicaid Fee-for-Service (FFS) and the Managed Care (MCO) programs.

The analysis period covered four (4) calendar years, 2014 to 2017. Extract inclusion criteria included age greater than 17 years old at time of service AND having at least one designated CPT/HCPCS codes on a paid claim:

E0766

Electrical stimulation device used for cancer treatment, includes all accessories, any type. The analysis excluded denied claims (effective date January 1, 2014).

Findings

Utilization data findings are suppressed. The aggregate number of patients utilizing a Tumor Treatment Field was less than the minimum permitted for public reporting.

Appendix B. Search Strategy

PubMed searched from inception to 6/16/2018

(((("Novocure"[Text Word] OR "Optune"[Text Word] OR "NovoTTF"[Text Word] OR "tumor treating field"[Text Word] OR "tumor treating fields"[Text Word] OR "tumor treatment field"[Text Word] OR "tumor treatment fields"[Text Word] OR "TTfield"[Text Word] OR "TTFfields"[Text Word] OR "alternating electric field"[Text Word] OR "alternating electric fields"[Text Word] OR "tumour treating field"[Text Word] OR "tumour treating fields"[Text Word] OR "tumour treatment field"[Text Word] OR "tumour treatment fields"[Text Word]) NOT ("Comment"[Publication Type] OR "Letter"[Publication Type] OR "Patient Education Handout"[Publication Type] OR "Editorial"[Publication Type] OR "Review"[Publication Type] OR "Meta-Analysis"[Publication Type] OR "systematic review"[Text Word] OR "meta-analysis"[Text Word] OR "systematic reviews"[Text Word] OR "meta-analyses"[Text Word] OR "metaanalysis"[Text Word] OR "metaanalyses"[Text Word] OR "Review Literature as Topic"[Mesh] OR "Meta-Analysis as Topic"[Mesh] OR "review"[Title] OR "reviews"[Title])) NOT ("Animals"[Mesh] NOT "Humans"[Mesh]) OR (("Novocure"[Text Word] OR "Optune"[Text Word] OR "NovoTTF"[Text Word] OR "tumor treating field"[Text Word] OR "tumor treating fields"[Text Word] OR "tumor treatment field"[Text Word] OR "tumor treatment fields"[Text Word] OR "TTfield"[Text Word] OR "TTFfields"[Text Word] OR "alternating electric field"[Text Word] OR "alternating electric fields"[Text Word] OR "tumour treating field"[Text Word] OR "tumour treating fields"[Text Word] OR "tumour treatment field"[Text Word] OR "tumour treatment fields"[Text Word]) AND ("Randomized Controlled Trial"[Publication Type] OR "Clinical Trial"[Publication Type] OR "Clinical Trial, Phase I"[Publication Type] OR "Clinical Trial, Phase II"[Publication Type] OR "Clinical Trial, Phase III"[Publication Type] OR "Clinical Trial, Phase IV"[Publication Type] OR "Pragmatic Clinical Trial"[Publication Type] OR "Controlled Clinical Trial"[Publication Type] OR "Clinical Trials as Topic"[Mesh] OR "trial"[Text Word] OR "trials"[Text Word])) NOT ("Animals"[Mesh] NOT "Humans"[Mesh]) OR (("Novocure"[Text Word] OR "Optune"[Text Word] OR "NovoTTF"[Text Word] OR "tumor treating field"[Text Word] OR "tumor treating fields"[Text Word] OR "tumor treatment field"[Text Word] OR "tumor treatment fields"[Text Word] OR "TTfield"[Text Word] OR "TTFfields"[Text Word] OR "alternating electric field"[Text Word] OR "alternating electric fields"[Text Word] OR "tumour treating field"[Text Word] OR "tumour treating fields"[Text Word] OR "tumour treatment field"[Text Word] OR "tumour treatment fields"[Text Word]) AND ("systematic review"[Text Word] OR "meta-analysis"[Text Word] OR "Review"[Publication Type] OR "meta-analysis"[Publication Type] OR "systematic reviews"[Text Word] OR "meta-analyses"[Text Word] OR "metaanalysis"[Text Word] OR "metaanalyses"[Text Word] OR "Review Literature as Topic"[Mesh] OR "Meta-Analysis as Topic"[Mesh] OR "review"[Title] OR "reviews"[Title])) NOT ("Animals"[Mesh] NOT "Humans"[Mesh])) Filters: English

Total Yield: 359

Cochrane Library Search from inception to 6/16/2018

Terms: Tumor Treating Fields, TTFields, NovoTTF, Novocure, Optune, Alternating Electric Fields

Total Yield: 58

ClinicalTrials.Gov Search from inception to 6/16/2018

Terms: Tumor Treating Fields, TTFields, NovoTTF, Novocure, Optune, Alternating Electric Fields

Total Yield: 43

Other Data

The following websites were searched using the terms tumor treating fields, TTFields, NovoTTF, Novocure, Optune, and alternating electric fields.

United States (U.S.) Food and Drug Administration

Centers for Medicare and Medicaid Services

Aetna

UnitedHealth

Humana

BlueCross BlueShield (Premera and Regence)

Kaiser Permanente

National Institute for Health and Care Excellence (U.K.)

U.S. Agency for Healthcare Research and Quality

Appendix C. Additional Methods

The following exchanges rates were used to convert foreign costs reported to U.S. dollars:

	U.S. $	Euro €
Year 2014	1	0.730

Source: U.S. Department of Treasury. Treasury Reporting Rates of Exchange. Historical Rates for March 31st, 2014. Available at: https://www.fiscal.treasury.gov/fsreports/rpt/treasRptRateExch/historicalRates.htm Accessed July 20, 2018.

Abbreviations: U.S. = United States.

Appendix D. Evidence Tables

Table D-1.   Newly diagnosed GBM — Characteristics of included studies

Study Author(s) (Year(s))	Study Name/Identifier Funding Source(s) Country Study Dates	Study Design Power Risk of Bias	TTF Intervention (G1) TTF Intervention Details Duration of Treatment, months N	Comparator (G2) Comparator Details Duration of Treatment, months N
Bernard-Arnoux (2016)[28]	**Study**: NA **Funding**: None declared **Country**: France **Study dates**: NA	**Study design**: Cost-effectiveness analysis (Markov model) **Power**: NA **ROB**: Low	**Intervention (G1):** TTF and TMZ **Intervention details**: A hypothetical cohort of people receiving the same intervention as that in the EF-14 trial[17] was entered into the model. **Duration of treatment, months:** In the model, people could receive TTF therapy for a maximum of 24 months in the stable-disease state. Patients could be kept on TTF therapy up to the second relapse. Knowing that the time to first progression was 7.1 months and that the median duration of TTF therapy was 9 months, it was assumed that the device was used an average of 2 months in the progressive disease (e.g., until the second relapse). People could be receiving TMZ in stable disease state for up to 6 months. **N enrolled:** 1,000 in entire hypothetical cohort.	**Comparator (G2)**: TMZ **Comparator details**: A hypothetical cohort of people receiving the same comparator as that in the EF-14 trial[17] was entered into the model. **Duration of treatment, months:** In the model, people could receive TMZ in the stable disease state for up to 6 months. **N enrolled:** 1,000 in entire hypothetical cohort

(continued)

Table D-1.   Newly diagnosed GBM — Characteristics of included studies (continued)

Study Author(s) (Year(s))	Study Name/Identifier Funding Source(s) Country Study Dates	Study Design Power Risk of Bias	TTF Intervention (G1) TTF Intervention Details Duration of Treatment, months N	Comparator (G2) Comparator Details Duration of Treatment, months N
Kirson (2009)[a][27]	**Study**: NA **Funding**: Novocure LTD **Country**: Czech Republic **Study dates**: NR	**Study design**: Cohort with historical and concurrent comparator groups **Power**: NR **ROB**: High	**Intervention (G1)**: TTF and TMZ **Intervention details**: Newly diagnosed patients who were at least 4 weeks post-radiation therapy received TTF combined with maintenance TMZ. The patients were hospitalized for 1 to 3 days for observation and then released home where they received multiple 4-week courses of continuous NovoTTF-100A treatment until progression. TTs were applied to the patients using the NovoTTF-100A device set to deliver 200 kHz, 0.7 V/cm fields (at the center of the brain) in 2 perpendicular directions, 1 second in each direction sequentially. The TTF were applied continuously using four insulated electrode arrays, each having a surface area of 22.5 cm^2, placed on opposing sides of the head with the tumor positioned directly between the electrode pairs. **Duration of treatment, months**: NR **N enrolled**: 10	**Comparator (G2)**: TMZ **Comparator details**: Matched historical control group with the same KPS score (>60) and age who received TMZ alone according to the protocol described by Stupp et al. (2005).[4] **Duration of treatment, months**: NR **N analyzed**: NR **Comparator (G3)**: TMZ **Comparator details**: Matched concurrent control group who received TMZ alone according to the protocol described by Stupp et al. (2005).[4] **Duration of treatment, months**: NR **N analyzed**: 32

(continued)

Table D-1.   Newly diagnosed GBM — Characteristics of included studies (continued)

Study Author(s) (Year(s))	Study Name/Identifier Funding Source(s) Country Study Dates	Study Design Power Risk of Bias	TTF Intervention (G1) TTF Intervention Details Duration of Treatment, months N	Comparator (G2) Comparator Details Duration of Treatment, months N
Stupp (2017)[25][b] Taphoorn (2018)[26][c]	**Study**: EF-14/NCT00916409 **Funding**: Novocure Ltd. **Countries**: 83 centers in Austria, Canada, Czech Republic, France, Germany, Israel, Italy, South Korea, Sweden, Switzerland, United States **Study dates**: July 2009 through December 2016	**Study design**: RCT **Power**: 80% power, allowing for 10% loss to follow up, to detect HR of 0.78 or less for PFS (primary endpoint) and HR of 0.76 for OS (secondary endpoint) **ROB**: Some concerns (OS, PFS, safety) to high (QOL)	**Intervention (G1)**: TTF plus TMZ **Intervention details**: Continuous TTF (at least 18 hours/day), delivered by the Optune® device (4 transducer arrays with 9 insulated electrodes each placed on the shaved scalp and connected to a portable device set to generate 200-kHz electric fields within the brain), combined with standard maintenance TMZ chemotherapy (150 to 200 mg/m^2/d for 5 days every 28 days for 6 cycles). **Duration of treatment, months**: Median (range) TTF: 8.2 (0 to 82) TMZ: 6 (0 to 51) **N randomized**: 466	**Comparator (G2)**: TMZ **Comparator details**: Standard maintenance TMZ chemotherapy (150 to 200 mg/m^2/d for 5 days every 28 days for 6 to 12 cycles) **Duration of treatment, months**: Median (range) 5 (0 to 33) **N randomized**: 229

Abbreviations: CI = confidence interval; GBM = glioblastoma multiforme; HR = hazard ratio; kHz = kilohertz; KPS = Karnofsky Performance Scale; NA = not applicable; NR = not reported; OS = overall survival; PFS = progression-free survival; QOL = quality of life; RCT = randomized controlled trial; ROB = risk of bias; TMZ = temozolomide; TTF = tumor treating fields.

[a] Authors describe an additional 10 patients with recurrent GBM in the single-arm clinical trial. No additional data are presented in the article but the authors note, "Both progression-free survival and overall survival in the recurrent GBM salvage therapy group were at least double that of concurrent and historical controls, respectively." Additional details about the 10 patients with recurrent GBM are reported in Kirson (2007)[33] and separately presented in this table.

[b] Stupp, 2015,[17] which was included in the prior HTA, reported the interim primary results for the trial. It is superseded by the final primary results presented in Stupp, 2017.[25]

[c] Interim results related to quality of life are reported in Zhu, 2017[87] but superseded by the final results related to quality of life reported in Taphoorn, 2018[26]

Table D-2.   Newly diagnosed GBM — Population characteristics of included studies at baseline

Study Author(s) (Year(s)) Study Design Risk of Bias	Eligibility Criteria	Demographics	Cancer Diagnosis Details	Prior Treatment Details	Baseline Functional Status
Bernard-Arnoux (2016)[28] **Study design**: Cost-effectiveness analysis (Markov model) **ROB**: Low	The population was a hypothetical cohort of 1,000 people with the same characteristics as those in the EF-14 trial.[17] The whole cohort was entered in the model and started the simulation in the stable-disease state.	See EF-14 trial[17]	See EF-14 trial[17] Newly diagnosed grade IV astrocytoma.	See EF-14 trial[17] Model assumed all patients had previously undergone radiotherapy plus TMZ.	See EF-14 trial[17] KPS≥70
Kirson (2009)[27a] **Study design**: Cohort with historical and concurrent comparator groups **ROB**: High	**Inclusion:** G1: Histologically proven diagnosis of GBM; age over 18 years, Karnofsky scale ≥ 70; participants of child bearing age had to be receiving efficient contraception; willing and able to sign an informed consent prior to participation in the study G2: NR G3: NR **Exclusion:** G1: In another clinical trial; received anti-tumor therapy in prior 4 weeks (steroids are permitted if stable or decreasing dose); suspected of suffering from radiation necrosis; pregnancy; implanted pacemaker or documented arrhythmias; significant renal, hepatic or hematologic disease; seizure disorder unrelated to tumor; preexisting dementia;	**Age, years** G1: NR G2: Median 54 G3: NR Study authors state G1 is matched to G2, in part, by age. **Male, N (%)** NR **Nonwhite, N (%)** NR	**Description of diagnosis** G1: Histologically proven new of GBM G2: NR G3: NR	NR	**Karnofsky performance score** G1 ≥ 70 G2: >60 G3: NR Study authors state G1 is matched to G2, in part, by KPS score.

(continued)

Table D-2.   Newly diagnosed GBM — Population characteristics of included studies at baseline (continued)

Study Author(s) (Year(s)) Study Design Risk of Bias	Eligibility Criteria	Demographics	Cancer Diagnosis Details	Prior Treatment Details	Baseline Functional Status
Kirson (2009)[27a] (continued)	progressive degenerative neurological disorder; meningitis or encephalitis; hydrocephalus associated with increased intracranial pressure. G2: NR G3: NR				
Stupp (2017)[25] Taphoorn (2018)[26] **Study design**: RCT (EF-14) **ROB**: Some concerns (OS, PFS, safety) to high (QOL)	**Inclusion:** Histologically confirmed supratentorial glioblastoma (WHO grade IV astrocytoma);[88] progression-free after maximal safe debulking surgery when feasible or biopsy; completed standard concomitant chemoradiotherapy with temozolomide; 18 years of age or older; KPS score ≥70%; and adequate bone marrow, liver, and renal function. **Exclusion:** Evidence of progressive disease following radio-chemotherapy; Infratentorial tumor location; severe comorbidities.	**Age, years** Median (range) G1: 56 (19 to 83) G2: 57 (19 to 80) **Male, N (%)** G1: 316 (68) G2: 157 (69) **Nonwhite, N (%)** G1: 49 (11) G2: 28 (12)	**Description of diagnosis** Newly diagnosed, histologically confirmed supratentorial glioblastoma (WHO grade IV astrocytoma).[88] Patients were included based on local histological diagnosis; study investigators performed a retrospective pathology review of 434 cases (62%).[b] **Tumor position, N (%)[c]** Corpus callosum G1: 25 (5) G2: 12 (5) Frontal lobe G1: 190 (41) G2: 84 (37) Occipital lobe G1: 58 (12) G2: 27 (12) Parietal lobe G1: 146 (31) G2: 89 (39)	**Resection, N (%)** Biopsy G1: 60 (13) G2: 29 (13) Partial resection G1: 157 (34) G2: 77 (33) Gross total resection G1: 249 (53) G2: 123 (54) **Completed standard radiation therapy, N (%)** 57 to 63 Gy G1: 422 (91) G2: 212 (93) <57 Gy G1: 21 (5) G2: 11 (5) >63 Gy G1: 18 (4) G2: 3 (1) Dose NR G1: 5 (1) G2: 3 (1)	**Karnofsky Performance Status score[e]** Median (range) G1: 90 (60 to 100) G2: 90 (70 to 100) **Mini-Mental State Examination score[f], N (%)** Score of 27 to 30 G1: 356 (76) G2: 160 (70) Score of ≤26 G1: 88 (19) G2: 48 (21) Missing G1: 22 (5) G2: 21 (9)

(continued)

Table D-2.   Newly diagnosed GBM — Population characteristics of included studies at baseline (continued)

Study Author(s) (Year(s)) Study Design Risk of Bias	Eligibility Criteria	Demographics	Cancer Diagnosis Details	Prior Treatment Details	Baseline Functional Status
Stupp (2017)[25] Taphoorn (2018)[26] (continued)			Temporal lobe G1: 191 (41) G2: 90 (40) Missing G1: 3 (1) G2: 3 (1) **Tumor location, N (%)[d]** Left hemisphere G1: 214 (46) G2: 99 (43) Right hemisphere G1: 249 (53) G2: 127 (55) Both hemispheres G1: 4 (1) G2: 2 (1) Corpus callosum G1: 15 (3) G2: 9 (4) Missing G1: 1 (<1) G2: 1 (<1)	**Completed concomitant radiation and TMZ, N (%)** G1: 433 (93) G2: 212 (93) **TMZ cycles** Mean (range) G1: 6 (0 to 51) G2: 5 (0 to 33) **Time from initial diagnosis to randomization, months** Mean (range) G1: 3.8 (1.7 to 6.2) G2: 3.7 (1.4 to 6.3) **Time from last day of radiation therapy to randomization, days** Mean (range) G1: 37 (15 to 128) G2: 36 (15 to 70)	

Abbreviations: GBM = glioblastoma multiforme; Gy = Gray; KPS = Karnofsky Performance Scale; NA = not applicable; NR = not reported; OS = overall survival; PFS = progression-free survival; QOL = quality of life; RCT = randomized controlled trial; ROB = risk of bias; TMZ = temozolomide; TTF = tumor treating fields; WHO = world health organization.

[a] Authors describe an additional 10 patients with recurrent GBM in the single-arm clinical trial. No additional data are presented in the article but the authors note, "Both progression-free survival and overall survival in the recurrent GBM salvage therapy group were at least double that of concurrent and historical controls, respectively." Additional details about the 10 patients with recurrent GBM are reported in Kirson (2007)[33] and separately presented in this table.

[b] Local histological diagnosis was confirmed in 419 of 434 patients (97%). Six cases were later diagnosed as WHO grade II or III and nine cases did not receive a definitive diagnosis based on the available tissue.

[c] Local histological diagnosis was confirmed in 419 of 434 patients (97%). Six cases were later diagnosed as WHO grade II or III and nine cases did not receive a definitive diagnosis based on the available tissue.

[d] Multiple positions/locations allowed per patient for multifocal tumors.

[e] Scores range from 0 to 100 in 10-point increment; a higher score represents better performance status.[72]

[f] Scores range from 1 to 30; a higher score represents better cognitive function.[89]

Table D-3. Newly diagnosed GBM — Individual study findings related to efficacy outcomes (survival, tumor progression and response)

Study Author(s) (Year(s)) Study Design Risk of Bias	G1: TTF Intervention N Randomized N Analyzed G2: Comparator N Randomized N Analyzed Duration of Follow Up, months	Adherence	Overall Survival (OS) Progression-Free Survival (PFS) Other Tumor Response and Progression Outcomes
Bernard-Arnoux (2016)[28] **Study design**: Cost-effectiveness analysis (Markov model) **ROB:** Low	Ineligible for these outcomes.		
Kirson (2009)[27a] **Study design**: Cohort with historical and concurrent comparator groups **ROB:** High	**G1:** TTF and TMZ; N=10 enrolled N=10 analyzed **G2**: TMZ N randomized NR N analyzed NR **G3**: TMZ N randomized NR N=32 analyzed **Duration of follow up, months** NR	NR	**Overall survival, months** G1: Median >39 G2: Median 14.7 Difference between the overall survival Kaplan-Meier curves is significant (log-rank test P=0.0018) **Progression-free survival, weeks** G1: Median 155 G3: Median 31 HR 3.32 (95% CI, 1.9 to 5.9); Difference between the progress free survival Kaplan-Meier curves is significant (log-rank test P=0.0002) **Progression-free at publication, N (%)** G1: 5 (50) G2: NR G3: NR **Alive at publication, N (%)** G1: 8 (80) G2: NR G3: NR

(continued)

Table D-3.   Newly diagnosed GBM — Individual study findings related to efficacy outcomes (survival, tumor progression and response) (continued)

Study Author(s) (Year(s)) Study Design Risk of Bias	G1: TTF Intervention N Randomized N Analyzed G2: Comparator N Randomized N Analyzed Duration of Follow Up, months	Adherence	Overall Survival (OS) Progression-Free Survival (PFS) Other Tumor Response and Progression Outcomes
Stupp (2017)[25] Taphoorn (2018)[26] **Study design**: RCT (EF-14) **ROB**: Some concerns (OS, PFS, safety) to high (QOL)	**G1**: TTF+TMZ N=466 randomized N=466 analyzed (ITT) **G2**: TMZ N=229 randomized N=229 analyzed (ITT) **Duration of follow up, months** Median (range) 40 (IQR 34 to 66) Minimum 24	75% of patients (n=347) achieved treatment adherence of 75% or more (i.e., used the device for ≥18 hours per day)	**Median OS, months[b] (Secondary endpoint)[25]** Overall G1: 20.9 (95% CI, 19.3 to 22.7) G2: 16.0 (95% CI, 14.0 to 18.4) Between-group difference 4.9 (95% CI, 2.3 to 7.9) HR 0.63 (95% CI, 0.53 to 0.76); P<0.001 Subgroup Analysis (G1 vs G2): Age <65 years: HR 0.69 (95% CI, 0.57 to 0.85) ≥65 years: HR 0.51 (95% CI, 0.33 to 0.77) Subgroup Analysis (G1 vs G2): Sex Women: HR 0.64 (95% CI, 0.56 to 0.87) Men: HR 0.63 (95% CI, 0.45 to 0.88) Subgroup Analysis (G1 vs G2): Resection Biopsy: HR 0.50 (95% CI, 0.30 to 0.84) Partial: HR 0.56 (95% CI, 0.41 to 0.77) Gross total: HR 0.70 (95% CI, 0.54 to 0.91) Subgroup Analysis (G1 vs G2): Karnofsky Performance Status Score 90-100: HR 0.70 (95% CI, 0.56 to 0.87) ≤80: HR 0.58 (95% CI, 0.45 to 0.88) Subgroup Analysis (G1 vs G2): MGMT Status Unmethylated: HR 0.66 (95% CI, 0.49 to 0.85) Methylated: HR 0.62 (95% CI, 0.44 to 0.88) Subgroup Analysis (G1 vs G2): Duration of daily TTF therapy ≥18 hours: 22.6 (95% CI, 19.7 to 25.1) <18 hours: 19.1 (95% CI, 16.5 to 21.9) HR 0.65 (95% CI, 0.49 to 0.85), P=0.009

(continued)

Table D-3.   Newly diagnosed GBM — Individual study findings related to efficacy outcomes (survival, tumor progression and response) (continued)

Study Author(s) (Year(s)) Study Design Risk of Bias	G1: TTF Intervention N Randomized N Analyzed G2: Comparator N Randomized N Analyzed Duration of Follow Up, months	Adherence	Overall Survival (OS) Progression-Free Survival (PFS) Other Tumor Response and Progression Outcomes
Stupp (2017)[25] Taphoorn (2018)[26] (continued)			**Median PFS, months (Primary endpoint)[25]** G1: 6.7 (95% CI, 6.1 to 8.1) G2: 4.0 (95% CI, 3.8 to 4.4) Between-group difference 2.7 (95% CI, 2.1 to 4.2) HR 0.63 (95% CI, 0.52 to 0.76); P<0.001 **PFS at 6 months[25]** G1: 56% (95% CI, 51% to 61%) G2: 37% (95% CI, 30% to 44%) Between-group difference 19% (95% CI, 15% to 23%); P<0.001

Abbreviations: CI = confidence interval; GBM = glioblastoma multiforme; HR = hazard ratio; IQR = interquartile range; ITT = intent to treat; NA = not applicable; NR = not reported; OS = overall survival; PFS = progression-free survival; QOL = quality of life; RCT = randomized controlled trial; ROB = risk of bias; TMZ = temozolomide; TTF = tumor treating fields.

[a] Authors describe an additional 10 patients with recurrent GBM in the single-arm clinical trial. No additional data are presented in the article but the authors note, "Both progression-free survival and overall survival in the recurrent GBM salvage therapy group were at least double that of concurrent and historical controls, respectively." Additional details about the 10 patients with recurrent GBM are reported in Kirson (2007)[33] and separately presented in this table.

[b] Subgroup analyses are adjusted for the other subgroups: *MGMT* promotor region methylation status (unmethylated/methylated), resection (biopsy/partial/gross total), region (outside U.S./U.S.), age (<65/≥65 years), Karnofsky Performance Status score (90-100/≤80), and sex (women/men).

Table D-4.   Newly diagnosed GBM — Individual study findings related to efficacy outcomes (health-related quality of life and functional status)

Study Author(s) (Year(s)) Study Design Risk of Bias	G1: TTF Intervention N Randomized N Analyzed G2: Comparator N Randomized N Analyzed Duration of Follow Up, months	Health-Related Quality of Life	Functional Status
Bernard-Arnoux (2016)[28] **Study design**: Cost-effectiveness analysis (Markov model) **ROB:** Low	Ineligible for these outcomes.		
Kirson (2009)[27a] **Study design**: Cohort with historical and concurrent comparator groups **ROB:** High	**G1:** TTF and TMZ; N=10 enrolled N=10 analyzed **G2**: TMZ N randomized NR N analyzed NR **G3**: TMZ N randomized NR N=32 analyzed **Duration of follow up, months** NR	NR	NR

(continued)

Table D-4.   Newly diagnosed GBM — Individual study findings related to efficacy outcomes (health-related quality of life and functional status) (continued)

Study Author(s) (Year(s)) Study Design Risk of Bias	G1: TTF Intervention N Randomized N Analyzed G2: Comparator N Randomized N Analyzed Duration of Follow-Up, months	Health-Related Quality of Life	Functional Status
Stupp (2017)[25] Taphoorn (2018)[26] **Study design**: RCT (EF-14) **ROB**: Some concerns (OS, PFS, safety) to high (QOL)	**G1**: TTF+TMZ N=466 randomized N=466 analyzed (ITT)[25] N=437 analyzed[26] **G2**: TMZ N=229 randomized N=229 analyzed (ITT)[25] N=202 analyzed[26] **Duration of follow up, months** (ITT) Median (range) 40 (IQR 34 to 66) Minimum 24	**European Organisation for Research and Treatment of Cancer QLQ-C30 and QLQ-BN20**[90-92] **Mean change from baseline (SD), G1 vs. G2**[26] **Global health status** 3 months: -2.6 (NR) vs. -1.6 (NR) 6 months: -2.5 (NR) vs. 0.9 (NR) 9 months: -0.7 (NR) vs. -1.7 (NR) 12 months: -4.0 (NR) vs. -1.2 (NR) **Physical functioning** 3 months: -3.7 (NR) vs. -3.3 (NR) 6 months: -5.8 (NR) vs. -2.8 (NR) 9 months: -4.0 (NR) vs. -8.2 (NR) 12 months: -6.6 (NR) vs. -4.8 (NR) **Cognitive functioning** 3 months: -2.3 (NR) vs. -4.3 (NR) 6 months: -4.1 (NR) vs. -2.5 (NR) 9 months: -2.1 (NR) vs. -3.1 (NR) 12 months: -8.0 (NR) vs. -2.9 (NR) **Role functioning** 3 months: -6.1 (NR) vs. 0.0 (NR) 6 months: -6.1 (NR) vs. -0.3 (NR) 9 months: -0.8 (NR) vs. -5.7 (NR) 12 months: -2.3 (NR) vs. -7.6 (NR)	**Time to a sustained 6-point decline in the MMSE, months**[25] G1: 16.7 (95% CI, 14.7 to 19.0) G2: 14.2 (95% CI, 12.7 to 17.0) HR 0.79 (95% CI, 0.66 to 0.95); P=0.01 **Time to a sustained 10-point decrease in the KPS, months**[25] G1: 5.5 (95% CI, 5.0 to 6.3) G2: 3.9 (95% CI, 3.1 to 5.2) HR 0.80 (95% CI, 0.67 to 0.95); P=0.009

(continued)

Table D-4.   Newly diagnosed GBM — Individual study findings related to efficacy outcomes (health-related quality of life and functional status) (continued)

Study Author(s) (Year(s)) Study Design Risk of Bias	G1: TTF Intervention N Randomized N Analyzed G2: Comparator N Randomized N Analyzed Duration of Follow Up, months	Health-Related Quality of Life	Functional Status
Stupp (2017)[25] Taphoorn (2018)[26] (continued)		**Social functioning** 3 months: -4.0 (NR) vs. 1.7 (NR) 6 months: -2.5 (NR) vs. 3.1 (NR) 9 months: -0.6 (NR) vs. 2.9 (NR) 12 months: -3.4 (NR) vs. 1.2 (NR) **Emotional functioning** 3 months: 1.4 (NR) vs. -2.8 (NR) 6 months: -0.1 (NR) vs. -3.5 (NR) 9 months: 0.8 (NR) vs. -1.4 (NR) 12 months: -1.1 (NR) vs. -0.6 (NR) **Itchy skin** 3 months: -10.4 (30.1) vs. 2.3 (24.4); P=0.005 6 months: -8.1 (31.6) vs. 4.2 (31.4); P=0.008 9 months: -5.3 (28.0) vs. 5.2 (29.6); P=0.04 12 months: -4.6 (32.8) vs. 1.9 (36.9); P=0.66 **Pain** 3 months: -1.8 (NR) vs. -3.6 (NR) 6 months: NR (NR) vs. 0.2 (NR) 9 months: 0.6 (NR) vs. -3.9 (NR) 12 months: -3.3 (NR) vs. -4.8 (NR) **Weakness of Legs** 3 months: -0.5 (NR) vs. -4.3 (NR) 6 months: 1.2 (NR) vs. -0.3 (NR) 9 months: 2.5 (NR) vs. -3.2 (NR) 12 months: -1.3 (NR) vs. -4.8 (NR)	

(continued)

Table D-4.   Newly diagnosed GBM — Individual study findings related to efficacy outcomes (health-related quality of life and functional status) (continued)

Study Author(s) (Year(s)) Study Design Risk of Bias	G1: TTF Intervention N Randomized N Analyzed G2: Comparator N Randomized N Analyzed Duration of Follow Up, months	Health-Related Quality of Life	Functional Status
Stupp (2017)[25] Taphoorn (2018)[26] (continued)		**N (%) stable or improved HRQoL during progression-free time,** [b] **G1 vs. G2**[26] **G1 vs. G2, N (%)** **Global health status** 192 (54) vs. 53 (38); P=0.001 **Physical functioning** 195 (54) vs. 54 (38); P=0.001 **Cognitive functioning** 181 (50) vs. 55 (39); P=0.02 **Role functioning** 173 (48) vs. 58 (41); P=0.17 **Social functioning** 173 (48) vs. 58 (41); P=0.14 **Emotional functioning** 196 (55) vs. 62 (44); P=0.03 **Itchy skin** 148 (42) vs. 64 (47); P=0.39 **Pain** 205 (57) vs. 51 (36); P<0.001 **Weakness of Legs** 206 (59) vs. 58 (42); P=0.001 **Median deterioration-free survival,**[c] **months, G1 vs. G2**[26] **Global health status** 4.8 vs. 3.3; HR 0.73 (95% CI, 0.60 to 0.88)	

(continued)

Table D-4.   Newly diagnosed GBM — Individual study findings related to efficacy outcomes (health-related quality of life and functional status) (continued)

Study Author(s) (Year(s)) Study Design Risk of Bias	G1: TTF Intervention N Randomized N Analyzed G2: Comparator N Randomized N Analyzed Duration of Follow Up, months	Health-Related Quality of Life	Functional Status
Stupp (2017)[25] Taphoorn (2018)[26] (continued)		**Physical functioning** 5.1 vs. 3.7; HR 0.73 (95% CI, 0.60 to 0.88) **Cognitive functioning** 4.4 vs. 3.6; HR 0.78 (95% CI, 0.64 to 0.94) **Role functioning** 4.3 vs. 3.8; HR 0.86 (95% CI, 0.71 to 1.02) **Median deterioration-free survival,[c] months, G1 vs. G2[26]** **Global health status** 4.8 vs. 3.3; HR 0.73 (95% CI, 0.60 to 0.88) **Physical functioning** 5.1 vs. 3.7; HR 0.73 (95% CI, 0.60 to 0.88) **Cognitive functioning** 4.4 vs. 3.6; HR 0.78 (95% CI, 0.64 to 0.94) **Role functioning** 4.3 vs. 3.8; HR 0.86 (95% CI, 0.71 to 1.02) **Social functioning** 4.5 vs. 3.9; HR 0.84 (95% CI, 0.70 to 1.06) **Emotional functioning** 5.3 vs. 3.9; HR 0.75 (95% CI, 0.62 to 0.91) **Itchy skin** 3.9 vs. 4.0; HR 1.03 (95% CI, 0.85 to 1.25) **Pain** 5.6 vs. 3.6; HR 0.67 (95% CI, 0.56 to 0.81) **Weakness of Legs** 5.6 vs. 3.9; HR 0.74 (95% CI, 0.61 to 0.89)	

(continued)

Table D-4.   Newly diagnosed GBM — Individual study findings related to efficacy outcomes (health-related quality of life and functional status) (continued)

Study Author(s) (Year(s)) Study Design Risk of Bias	G1: TTF Intervention N Randomized N Analyzed G2: Comparator N Randomized N Analyzed Duration of Follow Up, months	Health-Related Quality of Life	Functional Status
Stupp (2017)[25] Taphoorn (2018)[26] (continued)		**Median time to deterioration,[d] months, G1 vs. G2[26]** **Global health status** 14.1 vs. 9.6; HR 0.81 (95% CI, 0.60 to 1.10) **Physical functioning** 14.2 vs. 14.0; HR 0.90 (95% CI, 0.66 to 1.24) **Cognitive functioning** 10.3 vs. 14.0; HR 0.95 (95% CI, 0.71 to 1.28) **Role functioning** 9.2 vs. 14.0; HR 1.16 (95% CI, 0.86 to 1.56) **Social functioning** 10.6 vs. 14.0; HR 1.25 (95% CI, 0.91 to 1.72) **Emotional functioning** 13.4 vs. 14.0; HR 0.88 (95% CI, 0.64 to 1.21) **Itchy skin** 8.2 vs. 14.4; HR 1.85 (95% CI, 1.33 to 2.57) **Pain** 13.4 vs. 12.1; HR 0.65 (95% CI, 0.48 to 0.89) **Weakness of Legs** 14.2 vs. 14.0; HR 0.71 (95% CI, 0.51 to 0.99)	

Abbreviations: CI = confidence interval; GBM = glioblastoma multiforme; HR = hazard ratio; HRQoL = health-related quality of life; IQR = interquartile range; ITT = intent to treat; KPS = Karnofsky Performance Score; MMSE = Mini-Mental Status Examination; NA = not applicable; NR = not reported; OS = overall survival; PFS = progression-free survival; QLQ = quality of life questionnaire; QOL = quality of life; RCT = randomized controlled trial; ROB = risk of bias; TMZ = temozolomide; TTF = tumor treating fields.

[a] Authors describe an additional 10 patients with recurrent GBM in the single-arm clinical trial. No additional data are presented in the article but the authors note, "Both progression-free survival and overall survival in the recurrent GBM salvage therapy group were at least double that of concurrent and historical controls, respectively." Additional details about the 10 patients with recurrent GBM are reported in Kirson (2007)[33] and separately presented in this table.

[b] Duration of stable or improved HRQoL was shorter in G1 than in G2, though not statistically significant; authors report no significant differences between G1 and G2 for any of the HRQoL subscales while patients were not experiencing tumor progression.

[c] Defined as the time to a greater than 10-point deterioration in scores from baseline with a subsequent ≥10-point in scores compared with baseline, progressive disease, or death in the absence of a previous definitive deterioration before the next assessment.

[d] Definition is similar to deterioration-free survival with the exception that progressive disease was excluded as an event.

Table D-5.   Newly diagnosed GBM — Individual study findings related to safety outcomes

Study Author(s) (Year(s)) Study Design Risk of Bias	G1: TTF Intervention N Randomized N Analyzed G2: Comparator N Randomized N Analyzed Duration of Follow Up, months	Serious Adverse Events	Dermatologic Adverse Events	Other Adverse Events
Bernard-Arnoux (2016)[28] **Study design**: Cost-effectiveness analysis (Markov model) **ROB:** Low	Ineligible for these outcomes.			
Kirson (2009)[27a] **Study design**: Cohort with historical and concurrent comparator groups **ROB:** High	**G1**: TTF and TMZ; N=10 enrolled N=10 analyzed **G2**: TMZ N randomized NR N analyzed NR **G3**: TMZ N randomized NR N=32 analyzed **Duration of follow up, months** NR	**Device-related serious adverse events among G1 only, N (%)** 0 (0) Serious adverse events for G2 and G3 were NR.	**Dermatologic adverse events among G1 only, N (%)** Dermatitis Grade[b] 1 or 2: 10 (100) Dermatitis Grade 3 or 4: 0 (0) Dermatologic adverse events for G2 and G3 were NR.	**Grade 1 or 2 adverse events among G1 only, N (%)** Elevated LFTs: 6 (60) (attributed to anti-epileptic drugs) Hyperglycemia: 4 (40) (attributed to oral steroids) Anemia: 6 (60) (attributed to TMZ) Thrombocytopenia: 2 (20) (attributed to TMZ) Leucopenia: 3 (30) (attributed to TMZ) Headache: 2 (20) (attributed to underlying disease) Seizures: 1 (10) (attributed to underlying disease) None of the 10 patients in G1 reported grade 3 or 4 adverse events for the categories described above. Other adverse events for G2 and G3 were NR.

(continued)

Table D-5.   Newly diagnosed GBM — Individual study findings related to safety outcomes (continued)

Study Author(s) (Year(s)) Study Design Risk of Bias	G1: TTF Intervention N Randomized N Analyzed G2: Comparator N Randomized N Analyzed Duration of Follow Up, months	Serious Adverse Events	Dermatologic Adverse Events	Other Adverse Events
Stupp (2017)[25] Taphoorn (2018)[26] **Study design**: RCT (EF-14) **ROB**: Some concerns (OS, PFS, safety) to high (QOL)	**G1**: TTF+TMZ N=466 randomized N=456 analyzed[c] **G2**: TMZ N=229 randomized N=216 analyzed **Duration of follow up, months** Median (range) 40 (IQR 34 to 66) Minimum 24	NR	**Site reaction beneath the TTF transducer arrays, % in G1** Mild to moderate: 52 Severe (grade 3):[d] 2	**≥1 grade 3/4 adverse event, N (%)** G1: 218 (48) G2: 94 (44) P=0.58 **Adverse event[d]: N (%) in G1, N (%) in G2** Blood and lymphatic system disorders: 50 (13), 23 (11) Thrombocytopenia: 39 (9), 11 (5) Gastrointestinal disorders: 23 (5), 8 (4) Asthenia, fatigue, and gait disturbance: 42 (9), 13 (6) Infections: 32 (7), 10 (5) Injury, poisoning, and procedural complications:[e] 24 (5), 7 (3) Metabolism and nutrition disorders[f]: 16 (4), 10 (5) Musculoskeletal and connective tissue disorders: 21 (5), 9 (4) Nervous system disorders: 109 (24), 43 (20) Seizures: 26 (6), 13 (6) Respiratory, thoracic, and mediastinal disorders[h]: 24 (5), 11 (5)

(continued)

Table D-5.   Newly diagnosed GBM — Individual study findings related to safety outcomes (continued)

Study Author(s) (Year(s)) Study Design Risk of Bias	G1: TTF Intervention N Randomized N Analyzed G2: Comparator N Randomized N Analyzed Duration of Follow Up, months	Serious Adverse Events	Dermatologic Adverse Events	Other Adverse Events
Stupp (2017)[25] Taphoorn (2018)[26] (continued)				NS differences between G1 and G2 regarding anxiety, confusion, insomnia, headaches, and seizures

Abbreviations: GBM = glioblastoma multiforme; IQR = interquartile range; LFT = liver function test; NA = not applicable; NR = not reported; NS = not significant; OS = overall survival; PFS = progression-free survival; QOL = quality of life; RCT = randomized controlled trial; ROB = risk of bias; TMZ = temozolomide; TTF = tumor treating fields.

[a] Authors describe an additional 10 patients with recurrent GBM in the single-arm clinical trial. No additional data are presented in the article but the authors note, "Both progression-free survival and overall survival in the recurrent GBM salvage therapy group were at least double that of concurrent and historical controls, respectively." Additional details about the 10 patients with recurrent GBM are reported in Kirson (2007)[33] and separately presented in this table.

[b] Grading system was not explicitly defined.

[c] Analysis restricted to patients with grade 3 or grade 4 disease.

[d] Authors utilized NCI's Common Terminology Criteria for Adverse Events, version 3.0, for adverse event reporting. Severity is defined by the grade: 1=mild, 2=moderate, 3=severe, 4=life-threatening or disabling, and 5=death.[35]

[e] The numerically higher rate of some adverse events is due to longer treatment duration and observational time in G1. The differences between groups disappear when treatment duration is taken into account.

[f] Falls and medical device site reactions

[g] Anorexia, dehydration, and hyperglycemia

[h] Pulmonary embolism, dyspnea, and aspiration pneumonia

Table D-6.   Newly diagnosed GBM — Individual study findings related to cost outcomes

Study Author(s) (Year(s)) Study Design Risk of Bias	Indication for Treatment Intervention Comparator Health States Outcome	Study Methods	Results (as Reported by Study)	Results (Converted to 2014 USD)
Bernard-Arnoux (2016)[28] **Study design**: Cost-effectiveness analysis (Markov model) **ROB:** Low	**Indication for treatment:** Newly diagnosed grade IV astrocytoma (EF-14 population[17]); **Intervention**: TTF and TMZ **Comparator**: TMZ **Health states:** Stable disease, progressive disease, and death state **Outcome**: Life expectancy, total cost, ICER	**Study design:** Cost-effectiveness analysis (Markov model) **Year/unit of currency reported:** 2014 Euros **Discount rate:** 4% **Perspective:** Payor (French Health Insurance system) **Time horizon:** Lifetime **Cycle length:** 1 month **Costs included:** TTF device and support, chemotherapy drugs (front-line and at tumor recurrence), hospital stays, specialized medical visits, outpatient procedures (imaging, laboratory test), and medicalized transportation. Note that the cost of surgery and concomitant radiotherapy and temozolomide are not included. Total costs were divided by the mean duration of survival (reported at 20.1 months) to obtain monthly costs except costs for chemotherapies at relapse, which were divided by the time from relapse to death or last follow-up date (found at 7.9 months)	**Life expectancy, months (undiscounted)** G1: 22.08 (95% CI, NR) G2: 18.0 (95% CI, NR) Incremental effectiveness: 4.08 (95% CI, NR) **Life expectancy, months (discounted)** G1: NR (95% CI, NR) G2: NR (95% CI, NR) Incremental effectiveness: 3.6 (95% CI, NR) **Total cost (undiscounted)** G1: €243,141 (95% CI, NR) G2: €57,665 (95% CI, NR) Incremental cost: €185,476 (95% CI, NR) **Total cost (discounted)** G1: NR (95% CI, NR) G2: NR (95% CI, NR) Incremental cost: €180,431 (95% CI, NR) **ICER (undiscounted, payor perspective)** €549,909 (95% CI, NR) **ICER (discounted, payor perspective)** €596,411 (95% CI, €447,017 to €745,805) The threshold sensitivity analysis on the cost of TTF showed that at a cost of €10,000/month, the ICER would be €292,353.	**Life expectancy, months (undiscounted)** G1: 22.08 (95% CI, NR) G2: 18.0 (95% CI, NR) Incremental effectiveness: 4.08 (95% CI, NR) **Life expectancy, months (discounted)** G1: NR (95% CI, NR) G2: NR (95% CI, NR) Incremental effectiveness: 3.6 (95% CI, NR) **Total cost (undiscounted)** G1: $333,069 (95% CI, NR) G2: $78,993 (95% CI, NR) Incremental cost: $254,077 (95% CI, NR) **Total cost (discounted)** G1: NR (95% CI, NR) G2: NR (95% CI, NR) Incremental cost: $247,166 (95% CI, NR) **ICER (undiscounted, payor perspective)** $753,300 (95% CI, NR) **ICER (discounted, payor perspective)** $817,001 (95% CI, $612,352 to $1,021,651) The threshold sensitivity analysis on the cost of TTF showed that at a cost of $13,699/month, the ICER would be $400,484.

(continued)

Table D-6.   Newly diagnosed GBM — Individual study findings related to cost outcomes (continued)

Study Author(s) (Year(s)) Study Design Risk of Bias	Indication for Treatment Intervention Comparator Health States Outcome	Study Methods	Results (as Reported by Study)	Results (Converted to 2014 USD)
Bernard-Arnoux (2016)[28] (continued)		**Other:** TTF device and support costs are as reported by the company at €21,000/month ($27,398/month in 2014 USD). All other costs are from a study on GBM from the perspective of the French Health Insurance system in 2014 euros.[93,94] **Effectiveness Threshold:** ICER €100,000	At a cost of €3,000/month, the discounted ICER would be €98,862. At a cost of €2,000/month (price discounted by approximately 90%), the discounted ICER would be €71,220. ICERs presented as discounted, payor perspective.	At a cost of $4,110/month, the discounted ICER would be $135,427. At a cost of $2,740/month (price discounted by approximately 90%), the discounted ICER would be $97,562. ICERs presented as discounted, payor perspective.
Kirson (2009)[27a] **Study design:** Cohort with historical and concurrent comparator groups **ROB:** High	Ineligible for these outcomes.			
Stupp (2017)[25] Taphoorn (2018)[26] **Study design:** RCT (EF-14) **ROB:** Some concerns (OS, PFS, safety) to high (QOL)	Ineligible for these outcomes.			

Abbreviations: CI = confidence interval; GBM = glioblastoma multiforme; ICER = incremental cost-effectiveness ratio; NR = not reported; OS = overall survival; PFS = progression-free survival; QOL = quality of life; RCT = randomized controlled trial; ROB = risk of bias; TTF = tumor treating fields; USD = United States Dollars.

[a] Authors describe an additional 10 patients with recurrent GBM in the single-arm clinical trial. No additional data are presented in the article but the authors note, "Both progression-free survival and overall survival in the recurrent GBM salvage therapy group were at least double that of concurrent and historical controls, respectively." Additional details about the 10 patients with recurrent GBM are reported in Kirson (2007)[33] and separately presented in this table.

Table D-7.   Recurrent GBM — Characteristics of included studies

Study Author(s) (Year(s))	Study Name/Identifier Funding Source(s) Country Study Dates	Study Design Power Risk of Bias	TTF Intervention (G1) TTF Intervention Details Duration of Treatment, months N	Comparator (G2) Comparator Details Duration of Treatment, months N
Kesari (2017)[32]	**Study**: EF-14/NCT00916409 **Funding**: Novocure Ltd. **Countries**: 83 centers in Austria, Canada, Czech Republic, France, Germany, Israel, Italy, South Korea, Sweden, Switzerland, United States **Study dates**: July 2009 through December 2016	**Study design**: Prospective cohort (post-hoc analysis of EF-14 trial) **Power**: NR **ROB**: High	**Intervention (G1)**: Tumor treating field therapy (TTF) plus second-line therapy **Intervention details**: Continuous TTF, delivered by the Optune® device, combined with second-line therapy that included bevacizumab, a monoclonal antibody drug, or chemotherapy (i.e., lomustine, carmustine, fotemustine, temozolomide, irinotecan, carboplatin, procarbazine) **Duration of treatment, months**: NR; until second progression for a maximum of 24 months **N enrolled**: 144 (466 patients were randomized in the original trial)	**Comparator (G2)**: Second-line therapy **Comparator details**: Bevacizumab, a monoclonal antibody drug, or chemotherapy (i.e., lomustine, carmustine, fotemustine, temozolomide, irinotecan, carboplatin, procarbazine) **Duration of treatment, months**: NR; until second progression for a maximum of 24 months **N enrolled**: 60 (229 patients were randomized in the original trial)
Lacouture (2014)[13]	**Study**: NA **Funding**: Novocure **Country**: United States **Study dates**: NR	**Study design**: Case series (adverse events submitted in post-marketing surveillance program) **Power**: NR **ROB**: NA[a]	**Intervention (G1)**: TTF **Intervention details**: NR **Duration of treatment, months**: NR **N enrolled**: 570 (patients who submitted adverse events)	NA

(continued)

Table D-7.   Recurrent GBM — Characteristics of included studies (continued)

Study Author(s) (Year(s))	Study Name/Identifier Funding Source(s) Country Study Dates	Study Design Power Risk of Bias	TTF Intervention (G1) TTF Intervention Details Duration of Treatment, months N	Comparator (G2) Comparator Details Duration of Treatment, months N
Mrugala (2014)[9]	**Study**: Patient Registry Dataset (PRiDe) **Funding**: Novocure, Inc **Country**: United States **Study dates**: October 2011 to November 2013	**Study design**: Cohort with historical comparator groups **Power**: NR **ROB**: Some concerns (OS) to high (safety)	**Intervention (G1):** TTF **Intervention details**: Participants were not restricted to the number or types of prior therapies or recurrences. Information about combination use of TTF as part of the prescription-use program was not captured. Some participants may have received combination therapy (chemotherapy or anti-vascular endothelial growth factor agents) rather than monotherapy. **Duration of treatment, months:** Median 4.1 (95% CI, 3.5 to 4.8) **N enrolled:** 457	The comparator groups are from the EF-11 phase III trial.[15] **Comparator (G2):** TTF **Comparator details**: NovoTTF therapy **Duration of treatment, months:** Median 2.3 (95% CI, 2.1 to 2.4) **N randomized:** 120 **Comparator (G3):** Chemotherapy **Comparator details**: Best chemotherapy according to physician's choice **Duration of treatment, months:** Median 2.1 (95% CI, 2.0 to 2.9) **N randomized:** 117

(continued)

Table D-7.   Recurrent GBM — Characteristics of included studies (continued)

Study Author(s) (Year(s))	Study Name/Identifier Funding Source(s) Country Study Dates	Study Design Power Risk of Bias	TTF Intervention (G1) TTF Intervention Details Duration of Treatment, months N	Comparator (G2) Comparator Details Duration of Treatment, months N
Kirson (2007)[33]	**Study**: NA **Funding**: Novocure Ltd. **Country**: Czech Republic **Study dates**: NR	**Study design**: Cohort with historical comparator groups **Power**: NR **ROB**: High	**Intervention (G1)**: TTF **Intervention details**: TTF were applied using the NovoTTF-100A device (Novo-Cure Ltd., Haifa, Israel). The area of each insulated electrode array used was 22.5 cm². Fields of 1–2 V/cm were generated by controlling the current density through the electrodes <31 mA/cm². The maximal power density beneath the electrodes was kept beneath 0.22 W/cm². Patients received treatment continuously until disease progression or for a maximum of 18 months. Treatment was applied daily for an average of 18 hours per day. No concomitant chemotherapy was allowed. **Duration of treatment, months**: NR **N enrolled**: 12 (10 analyzed)	The historical comparator groups are from five phase II studies that were published between 1999 and 2004. **Comparator (G2)**: Gefitinib[95] **Comparator details**: NR **Duration of treatment, months**: NR **N analyzed**: 57 **Comparator (G3)**: Temozolomide[96] **Comparator details**: NR **Duration of treatment, months**: NR **N analyzed**: 142 **Comparator (G4)**: Temozolomide[97] **Comparator details**: NR **Duration of treatment, months**: NR **N analyzed**: 126

(continued)

Table D-7.   Recurrent GBM — Characteristics of included studies (continued)

Study Author(s) (Year(s))	Study Name/Identifier Funding Source(s) Country Study Dates	Study Design Power Risk of Bias	TTF Intervention (G1) TTF Intervention Details Duration of Treatment, months N	Comparator (G2) Comparator Details Duration of Treatment, months N
Kirson (2007)[33] (continued)			**Duration of treatment, months:** NR **N enrolled**: 12 (10 analyzed)	**Comparator (G5):** Temozolomide and procarbazine[98] **Comparator details**: NR **Duration of treatment, months:** NR **N analyzed:** 225 **Comparator (G6):** Meta-analyses of multiple chemotherapies[99] **Comparator details**: NR **Duration of treatment, months:** NR **N analyzed:** 225
Stupp (2012)[15] Wong (2014);[29] Kanner (2014);[30] Wong (2014)[31]	**Study**: EF-11/NCT00379470 **Funding**: Novocure, Ltd. **Countries**: 28 institutions in Austria, Czech Republic, France, Germany, Israel, Switzerland, and the United States **Study dates**: September 2006 until May 2009 (enrollment)	**Study design:** RCT **Power:** 80% power at a significance level of 0.05 to detect a 60% increase in median overall survival (HR for death=0.63) **ROB:** Some concerns (OS, PFS, safety) to high (QOL, subgroup analyses)	**Intervention (G1):** TTF **Intervention details:** Continuous TTF monotherapy, delivered by the NovoTTF-100A device. 4 transducer arrays were placed on the shaved scalp and set to generate 200 kHz electric fields within the brain in two perpendicular directions (operated sequentially).	**Comparator (G2):** Chemotherapy **Comparator details**: Best available chemotherapy according to local practice and depending on prior treatment exposure, prescribed at the local investigator's discretion Active control chemotherapy, N (%) Bevacizumab: 36 (31) Irinotecan: 36 (31)

(continued)

Table D-7.   Recurrent GBM — Characteristics of included studies (continued)

Study Author(s) (Year(s))	Study Name/Identifier Funding Source(s) Country Study Dates	Study Design Power Risk of Bias	TTF Intervention (G1) TTF Intervention Details Duration of Treatment, months N	Comparator (G2) Comparator Details Duration of Treatment, months N
Stupp (2012)[15] Wong (2014);[29] Kanner (2014);[30] Wong (2014)[31] (continued)			Field intensity was set at >0.7 V/cm at the center of the brain. **Duration of treatment, months:** NR (treatment was continued until disease progression or intolerance) **N randomized: 120**	Nitrosoureas: 29 (25) Carboplatin: 15 (13) Temozolomide: 13 (11) Other[b]: 21 (15) Some therapies given in combination **Duration of treatment, months**: NR (treatment was continued until disease progression or intolerance) **N randomized**: 117

Abbreviations: CI = confidence interval; GBM = glioblastoma multiforme; HR = hazard ratio; kHz = kilohertz; NA = not applicable; NR = not reported; OS = overall survival; PFS = progression-free survival; PRiDe = Patient Registry Dataset; QOL = quality of life; RCT = randomized controlled trial; ROB = risk of bias; TMZ = temozolomide; TTF = tumor treating fields.

[a] We did not formally assess the quality or risk of bias in case series that were included for SQ.

[b] Other chemotherapy treatments included PCV (combination of procarbazine, lomustine, and vincristine); procarbazine; etoposide; imatinib; and hydroxyurea.

Table D-8.   Recurrent GBM — Population characteristics of included studies at baseline

Study Author(s) (Year(s)) Study Design Risk of Bias	Eligibility Criteria	Demographics	Cancer Diagnosis Details	Prior Treatment Details	Baseline Functional Status
Kesari (2017)[32] **Study design:** Prospective cohort **ROB:** High	**Inclusion:** Participants in the EF-14 trial[b] who experienced a first progression of disease at the time of the trial's interim analysis **Exclusion:** Participants in the EF-14 trial[b] who had not experienced a first progression of disease at the time of the trial's interim analysis	**Age, years** Median (range) G1: 57 (29 to 83) G2: 58 (22 to 75) **Male, N (%)** G1: 108 (75) G2: 45 (75) **Nonwhite, N (%)** G1: NR G2: NR	**Description of diagnosis** First progression of newly diagnosed, histologically confirmed supratentorial glioblastoma (WHO grade IV astrocytoma).[88] Progression was defined as tumor growth of >25% of the product of two perpendicular diameters compared with the smallest tumor area measured and the appearance of one or more new GBM tumors in the brain. When MRI was not available, clinical progression was determined according to the following criteria: decline in functional status as indicated by a decrease of ≥20 points in KPS, decline in neurologic function as indicated by a decrease of ≥2 points on the Medical Research Council Scale, or an increase of ≥50% in steroid dose.	**Resection, N (%)** Biopsy G1: 20 (14) G2: 10 (17) Partial resection G1: 40 (28) G2: 16 (27) Gross total resection G1: 84 (58) G2: 34 (57)	**Karnofsky Performance Status score[d]** Median (range) G1: 90 (60 to 100) G2: 90 (70 to 100)

(continued)

Table D-8.   Recurrent GBM — Population characteristics of included studies at baseline (continued)

Study Author(s) (Year(s)) Study Design Risk of Bias	Eligibility Criteria	Demographics	Cancer Diagnosis Details	Prior Treatment Details	Baseline Functional Status
Lacouture (2014)[13] **Study design:** Case series **ROB:** NA[a]	**Inclusion:** Recurrent GBM patients **Exclusion:** NR	**Age, years** NR **Male, N (%)** NR **Nonwhite, N (%)** NR	**Description of diagnosis** Recurrent GBM	NR	NR
Mrugala (2014)[9] **Study design:** Cohort with historical comparator group **ROB:** Some concerns (OS) to high (safety)	**Inclusion:** G1: >18 years old with recurrent GBM who began commercial treatment with NovoTTF Therapy in the United States between October 2011 and November 2013. Participants were not restricted to the number or types of prior therapies or recurrences. G2: NR G3: NR **Exclusion:** NR	**Age, years** Median (range) G1: 55 (18 to 86) G2: 54 (24 to 80) G3: 54 (29 to 74) **Male, N (%)** G1: NR (67.6) G2: NR (77) G2: NR (62) **Nonwhite, N (%)** NR	**Description of diagnosis** G1: Recurrent GBM defined as histologically-confirmed, supratentorial GBM (World Health Organization grade IV astrocytoma) with radiologically confirmed evidence of disease progression, as defined by the Macdonald criteria.[100] G2: NR G3: NR **Recurrence** Median (range) G1: 2 (1 to 5) G2: 2 (1 to 5) G3: 2 (1 to 4) First recurrence, N (%) G1: NR (33.3) G2: NR (9) G2: NR (15)	**Debulking surgery, N (%)** G1: NR (63.9) G2: NR (79) G3: NR (85) **Radiotherapy and temozolomide, N (%)** G1: 356 (77.9) G2: NR (86) G3: NR (82) **Bevacizumab, N (%)** G1: NR (55.1) G2: NR (19) G3: NR (18) **Carmustine wafers, N (%)** G1: NR (3.7) G2: NR G3: NR	**Karnofsky performance score[d]** Median (range) G1: 80 (10 to 100) G2: 80 (50 to 100) G3: 80 (50 to 100) 10 to 60 points, N (%) G1: NR (19.0) G2: NR G3: NR 70 to 80 points, N (%) G1: NR (46.6) G2: NR G3: NR 90 to 100 points, N (%) G1: NR (30.9) G2: NR G3: NR Unknown score, N (%) G1: NR (3.5) G2: NR G3: NR

(continued)

Table D-8.   Recurrent GBM — Population characteristics of included studies at baseline (continued)

Study Author(s) (Year(s)) Study Design Risk of Bias	Eligibility Criteria	Demographics	Cancer Diagnosis Details	Prior Treatment Details	Baseline Functional Status
Mrugala (2014)[9] **(continued)**			Second recurrence, N (%) G1: NR (26.9) G2: NR (48) G3: NR (46) Third to fifth recurrence, N (%) G1: NR (27.4%) G2: NR (43%) G3: NR (39%) Unknown Recurrence, N (%) G1: NR (12.5%) G2: 0 (0%) G3: 0 (0%)		
Kirson (2007)[33] **Study design:** Cohort with historical comparator groups **ROB:** High	**Inclusion:** G1: GBM recurrence based on Macdonald criteria; >18 years old; histologically established GBM (World Health Organization grade IV); KPS score ≥ 70; were at least 4 weeks from any brain surgery and at least 8 weeks from radiotherapy; could be at any recurrence and may have received other salvage therapies; multifocal disease was allowed G2: Recurrent GBM patients, first relapse G3: Recurrent GBM patients, any recurrence	**Age, years** Median (SD) G1: 50.7 (11.3) G2: 54 (NR) G3: 53 (NR) G4: 54 (NR) G5: 52 (NR) for temozolomide patients, 51 (NR) for procarbazine patients G6: 45 **Male, N (%)** G1: 7 (70) G2: NR G3: NR G4: NR G5: NR G6: NR	**Description of diagnosis** G1: Histologically established GBM (World Health Organization grade IV) G2: Recurrent GBM patients, first relapse G3: Recurrent GBM patients, any recurrence; histological verification not needed G4: Recurrent GBM patients, first relapse G5: Recurrent GBM patients, first relapse; enhancing lesion necessary but no size limit G6: Recurrent GBM patients	**Surgery, N (%)** G1: NR G2: NR (100) G3: NR G4: NR (89) at initial diagnosis and NR (13) at relapse G5: NR (87) for temozolomide patients, NR (91) for procarbazine patients at initial diagnosis G6: NR (34%) had two prior surgeries and NR (7) had more than two prior surgeries **Radiotherapy, N (%)** G1: NR G2: NR (100)	**Karnofsky performance score**[d] Median, range G1: 90 (70 to 100) G2: NR (60 to 100) G3: 80 (≥70) G4: NR (70 to 100) G5: NR (70 to 100) G6: 80 (60 to 100)

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Table D-8.   Recurrent GBM — Population characteristics of included studies at baseline (continued)

Study Author(s) (Year(s)) Study Design Risk of Bias	Eligibility Criteria	Demographics	Cancer Diagnosis Details	Prior Treatment Details	Baseline Functional Status
Kirson (2007)[33] (continued)	G4: Recurrent GBM patients, first relapse G5: Recurrent GBM patients, first relapse G6: Recurrent GBM patients **Exclusion:** G1: Concomitant chemotherapy; significant comorbidities; infratentorial tumors; implanted pacemakers or documented clinically significant arrhythmias G2: NR G3: NR G4: NR G5: NR G6: NR	**Nonwhite, N (%)** NR	**Tumor location in G1, N (%)** Right temporal-parietal: 3 (30) Right temporal: 1 (10) Right parietal: 1 (10) Right parieto-occipital: 1 (10) Right fronto-temporal: 1 (10) Left fronto-parietal: 1 (10) Left temporo-occipital: 1 (10) Left temporal: 1 (10)	G3: NR (100) G4: NR (100) G5: NR (100) G6: NR (100) **Chemotherapy, N (%)** G1: 10 (100) G2: NR (66) had up to five previous chemotherapy agents and NR (17) had gliadel wafer G3: NR (44) had previous nitrosurea therapy G4: NR (29) had adjuvant nitrosurea therapy G5: NR (65) of temozolomide patients and NR (68) of procarbazine patients had adjuvant nitrosurea therapy G6: NR (77) had prior chemotherapy	

(continued)

Table D-8.   Recurrent GBM — Population characteristics of included studies at baseline (continued)

Study Author(s) (Year(s)) Study Design Risk of Bias	Eligibility Criteria	Demographics	Cancer Diagnosis Details	Prior Treatment Details	Baseline Functional Status
Stupp (2012)[15] Wong (2014);[29] Kanner (2014);[30] Wong (2014)[31] **Study design:** RCT (EF-11) **ROB:** Some concerns (OS, PFS, safety) to high (QOL)	**Inclusion:** Histologically confirmed glioblastoma (WHO grade IV astrocytoma); radiologically confirmed disease progression according to Macdonald criteria;[100] KPS score ≥70%; adequate hematologic, renal, and hepatic function (absolute neutrophil count ≥1000/mm^3; hemoglobin ≥100 g/L platelet count, ≥100,000/mm^3; serum creatinine level ≤1.7 mg/dL (<150 µmol/L); total serum bilirubin level ≤ the upper limit of normal and liver function levels, <3 times the upper limit of normal); ≥18 years of age; prior therapy must have included radiotherapy **Exclusion:** Infra-tentorial tumor location; patients with implanted electronic medical devices e.g., pacemaker, programmable ventriculo-peritoneal shunt)	**Age, years** Median (range) G1: 54 (24 to 80) G2: 54 (29 to 74) **Male, N (%)** G1: 92 (77) G2: 73 (62) **Nonwhite, N (%)** G1: NR G2: NR	**Description of diagnosis** Histologically confirmed glioblastoma (WHO grade IV astrocytoma) and radiographically confirmed progression according to Macdonald criteria.[100] **Histology, N (%)** Prior lower grade glioma G1: 10 (8) G2: 9 (8) **Largest tumor diameter at randomization,** Median (range) G1: 6.1 cm (0 to 15.2 cm) G2: 5.5 cm (0 to 16.2 cm) **Time since initial glioma diagnosis, months** Median (range) G1: 11.8 (3.2 to 99.3) G2: 11.4 (2.9 to 77.1)	**Surgery, N (%)** Debulking before enrollment G1: 33 (28) G2: 29 (25) Debulking at any stage G1: 95 (79) G2: 99 (85) Biopsy only G1: 25 (21) G2: 18 (15) **Recurrence, N (%)** First G1: 11 (9) G2: 17 (15) Second G1: 58 (48) G2: 54 (46) Third or greater G1: 51 (43) G2: 46 (39) **Radiotherapy, N (%)** With concomitant TMZ G1: 103 (86) G2: 96 (82) Without concomitant TMZ G1: 15 (13) G2: 20 (17) Unknown G1: 2 (1) G2: 1 (1)	**Karnofsky Performance Status score**[d] Median (range) G1: 80 (50 to 100) G2: 80 (50 to 100)

(continued)

Table D-8.   Recurrent GBM — Population characteristics of included studies at baseline (continued)

Study Author(s) (Year(s)) Study Design Risk of Bias	Eligibility Criteria	Demographics	Cancer Diagnosis Details	Prior Treatment Details	Baseline Functional Status
Stupp (2012)[15] Wong (2014);[29] Kanner (2014);[30] Wong (2014)[31] (continued)				**Prior adjuvant (maintenance) TMZ, N (%)** G1: 100 (83) G2: 89 (76) Cycles, median (range) G1: 4 (0 to 19) G2: 3 (0 to 27) **Prior bevacizumab, N (%)** G1: 23 (19) G2: 21 (18) **Steroid use at enrollment, N (%)** G1: 55 (46) G2: 62 (53)	

Abbreviations: CI = confidence interval; GBM = glioblastoma multiforme; kHZ = kilohertz; KPS = Karnofsky Performance Score; NA = not applicable; NR = not reported; OS = overall survival; PFS = progression-free survival; QOL = quality of life; RCT = randomized controlled trial; ROB = risk of bias; SD = standard deviation; TMZ = temozolomide; TTF = tumor treating fields; WHO = world health organization.

[a] We did not formally assess the quality or risk of bias in case series that were included for SQ.

[b] Inclusion criteria for the EF-14 trial included histologically confirmed supratentorial glioblastoma (WHO grade IV astrocytoma); progression-free after maximal safe debulking surgery when feasible or biopsy; completed standard concomitant chemoradiotherapy with temozolomide; 18 years of age or older; KPS score ≥70%; and adequate bone marrow, liver, and renal function.

[c] Exclusion criteria for the EF-14 trial included Infratentorial tumor location or severe comorbidities.

[d] Scores range from 0 to 100 in 10-point increment; a higher score represents better performance status.[72]

Table D-9.   Recurrent GBM — Individual study findings related to efficacy outcomes (survival, tumor progression and response)

Study Author(s) (Year(s)) Study Design Risk of Bias	G1: TTF Intervention N Randomized N Analyzed G2: Comparator N Randomized N Analyzed Duration of Follow Up, months	Adherence	Overall Survival (OS) Progression-Free Survival (PFS) Other Tumor Response and Progression Outcomes
Kesari (2017)[32] **Study design:** Prospective cohort **ROB:** High	**G1**: TTF + second-line therapy N=466 randomized in the original trial N=144 enrolled N=144 analyzed **G2**: Second-line therapy N=229 randomized in the original trial N=60 enrolled N=60 analyzed **Duration of follow up, months** Median (range) 12.6 (NR)	NR	**Median OS, months** G1: 11.8 G2: 9.2 HR 0.70 (95% CI, 0.48 to 1.00); P=0.049 <u>Subgroup analysis among bevacizumab users only</u> G1: 11.8 G2: 9.0 HR 0.61 (95% CI, 0.37 to 0.99); P=0.043
Lacouture (2014)[13] **Study design:** Case series **ROB:** NA[a]	Ineligible for these outcomes.		

(continued)

Table D-9.   Recurrent GBM — Individual study findings related to efficacy outcomes (survival, tumor progression and response) (continued)

Study Author(s) (Year(s)) Study Design Risk of Bias	G1: TTF Intervention N Randomized N Analyzed G2: Comparator N Randomized N Analyzed Duration of Follow Up, months	Adherence	Overall Survival (OS) Progression-Free Survival (PFS) Other Tumor Response and Progression Outcomes
Mrugala (2014)[9] **Study design:** Cohort with historical comparator group **ROB:** Some concerns (OS) to high (safety)	**G1:** TTF N=457 enrolled N= 457 analyzed (adherence data only available for 287 (63%)) **G2:** TTF N=120 randomized N=120 analyzed **G3:** Chemotherapy N=117 randomized N=117 analyzed **Duration of follow up, months** NR	Daily compliance, % Median (range) G1: 70 (12 to 99) G2: NR G3: NR **Daily compliance > 75% each day, N (%)** G1: 127 (44) G2: NR G3: NR **Daily compliance < 75% each day, N (%)** G1: 160 (56) G2: NR G3: NR	**Median overall survival, months** G1: 9.6 G2: 6.6 G3: 6.0 Authors report that median overall survival is "markedly longer" in G1 compared to G2 and "significantly longer" in G1 compared to G3. **Subgroup analyses within G1: Median overall survival, months** **Recurrence** First recurrence: 20 (reference) Second recurrence: 8.5 Third to fifth recurrence: 4.9 HR 0.6 (95% CI, 0.4 to 0.9); P=0.0271 for second recurrence compared to first recurrence HR 0.3 (95% CI, 0.2 to 0.5); P<0.0001 for third to fifth recurrence compared to first recurrence **Compliance** Daily compliance < 75% each day: 4.0 (reference) Daily compliance > 75% each day: 13.5 HR 0.4 (95% CI, 0.3 to 0.6); P<0.001 **Karnofsky performance status** 90 to 100 points: 14.8 (reference) 70 to 90 points: 7.7 10 to 60 points: 6.1

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Table D-9. **Recurrent GBM — Individual study findings related to efficacy outcomes (survival, tumor progression and response) (continued)**

Study Author(s) (Year(s)) Study Design Risk of Bias	G1: TTF Intervention N Randomized N Analyzed G2: Comparator N Randomized N Analyzed Duration of Follow Up, months	Adherence	Overall Survival (OS) Progression-Free Survival (PFS) Other Tumor Response and Progression Outcomes
Mrugala (2014)[9] (continued)			HR 0.6 (95% CI, 0.4 to 0.9); P=0.0070 for 70 to 90 points compared to 90 to 100 points HR 0.4 (95% CI, 0.2 to 0.6); P<0.0001 for 10 to 60 points compared to 90 to 100 points **Bevacizumab use** Prior use: 7.2 (Reference) Naïve: 13.4 HR 0.5 (95% CI, 0.4 to 0.7); P<0.0001 **Debulking surgery** Yes (any surgery): 9.8 (reference) No: 8.9 HR 1.1 (95% CI, 0.8 to 1.5); P=0.7927 **1-year overall survival, N (%)** G1: NR (44) G2: NR (20) G3: NR (20)

(continued)

Table D-9.   Recurrent GBM — Individual study findings related to efficacy outcomes (survival, tumor progression and response) (continued)

Study Author(s) (Year(s)) Study Design Risk of Bias	G1: TTF Intervention N Randomized N Analyzed G2: Comparator N Randomized N Analyzed Duration of Follow Up, months	Adherence	Overall Survival (OS) Progression-Free Survival (PFS) Other Tumor Response and Progression Outcomes
Kirson (2007)[33] **Study design:** Cohort with historical comparator groups **ROB:** High	**G1:** TTF N=12 enrolled N=10 analyzed **G2**: Gefitinib N enrolled NR N=57 analyzed **G3**: Temozolomide N enrolled NR N=142 analyzed **G4:** Temozolomide N enrolled NR N=126 analyzed **G5:** Temozolomide and procarbazine N enrolled NR N=225 analyzed **G6:** Meta-analyses of multiple chemotherapies N enrolled NR N=225 analyzed	NR	**2-year overall survival, N (%)** G1: NR (30) G2: NR (9) G3: NR (7) **Median time to disease progression, weeks** G1: 26.1 (range 3 to 124) G2: 8.1 (95% CI, 7.9 to 9.1) G3: 10 (range 9 to 14) G4: 9.1 G5: 12.4 for temozolomide patients; 8.32 for procarbazine patients G6: 9 (95% CI, 8 to 10) Study authors state that the median time to disease progression value for G1 is more than double the reported median of the historical control patients **Progression-free survival at 6 months, %** G1: 50 (95% CI, 23 to 77) G2: 13 G3: 18 G4: 18 (95% CI, 11 to 24) G5: 19 (95% CI, 11 to 27) for temozolomide patients; 9 (95% CI, 3 to 14) for procarbazine patients G6: 15 (95% CI, 10 to 19) **Median overall survival, weeks** G1: 62.2 (range 20.3 to 124.0) G2: 39.4 (95% CI, 24.3 to 59.4) G3: 32 (range 27 to 36)

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Table D-9.   Recurrent GBM — Individual study findings related to efficacy outcomes (survival, tumor progression and response) (continued)

Study Author(s) (Year(s)) Study Design Risk of Bias	G1: TTF Intervention N Randomized N Analyzed G2: Comparator N Randomized N Analyzed Duration of Follow Up, months	Adherence	Overall Survival (OS) Progression-Free Survival (PFS) Other Tumor Response and Progression Outcomes
Kirson (2007)[33] (continued)	**Duration of follow up, months** NR; Adverse events occurring during treatment or up to 60 days after termination of therapy		**Median overall survival, weeks** G1: 62.2 (range 20.3 to 124.0) G2: 39.4 (95% CI, 24.3 to 59.4) G3: 32 (range 27 to 36) G4: 23.5 G5: 31 for temozolomide patients; 25 for procarbazine patients G6: 25 (95% CI, 21 to 28) Study authors state that the OS value for G1 is more than double the reported median of the historical control patients **1-year survival, N (%)** G1: NR (67.5) G2: NR G3: NR G4: NR G5: NR G6: NR

(continued)

Table D-9.   Recurrent GBM — Individual study findings related to efficacy outcomes (survival, tumor progression and response) (continued)

Study Author(s) (Year(s)) Study Design Risk of Bias	G1: TTF Intervention N Randomized N Analyzed G2: Comparator N Randomized N Analyzed Duration of Follow Up, months	Adherence	Overall Survival (OS) Progression-Free Survival (PFS) Other Tumor Response and Progression Outcomes
Stupp (2012)[15] Wong (2014);[29] Kanner (2014);[30] Wong (2014)[31] **Study design:** RCT (EF-11) **ROB:** Some concerns (OS, PFS, safety) to high (QOL)	**G1:** TTF N=120 randomized N=120 analyzed (ITT) N= 93 analyzed (mITT)[b] **G2:** Chemotherapy N=117 randomized N=117 analyzed (ITT) N= 117 analyzed (mITT)[c] **Duration of follow up, months** Median (range) 39 (NR)	G1: 116 (97%) of patients started treatment[d] and 93 (78%) completed 4 weeks of treatment (1 cycle); median compliance was 86% (range 41% to 98%) of the time in each treatment month, translating into a mean use of 20.6 hours per day; median (range) duration of device use among 14 treatment responders was 22 (13 to 23) hours/day. G2: 113 (97%) of patients started chemotherapy[e] and 112 completed one full treatment course.	**Median survival, months** ITT analysis[15] G1: 6.6 (NR) G2: 6.0 (NR) HR 0.86 (95% CI, 0.66 to 1.12); P=0.27 mITT analysis[30] G1: 7.8 (NR) G2: 6.0 (NR) HR 0.69 (95% CI, 0.52 to 0.92); P=0.0093 Subgroup analysis (ITT): Compliance level (G1 only)[30] 40-59% compliance (n=10): 5.8 (NR) 60-79% compliance (n=33): 6.0 (NR) 80-100% compliance (n=77): 7.7 (NR) P for trend=0.039 Subgroup analysis (ITT): Prior bevacizumab failure[30] G1 (n=23): 6.0 G2 (n=21): 3.3 HR 0.43 (95% CI, 0.22 to 0.85); P=0.0156 Subgroup analysis (ITT): Non-bevacizumab failure[30] G1 (n=97): 6.7 G2 (n=96): 7.2 HR 0.95 (95% CI, 0.71 to 1.27); P=0.7136 Subgroup analysis (ITT): Prior low-grade glioma[30] G1 (n=12): 25.3 G2 (n=9): 7.7 HR 0.31 (95% CI, 0.09 to 0.99); P=0.0493

Table D-9.   Recurrent GBM — Individual study findings related to efficacy outcomes (survival, tumor progression and response) (continued)

Study Author(s) (Year(s)) Study Design Risk of Bias	G1: TTF Intervention N Randomized N Analyzed G2: Comparator N Randomized N Analyzed Duration of Follow Up, months	Adherence	Overall Survival (OS) Progression-Free Survival (PFS) Other Tumor Response and Progression Outcomes
Stupp (2012)[15] Wong (2014);[29] Kanner (2014);[30] Wong (2014)[31] (continued)			Subgroup analysis (ITT): Primary recurrent GBM[30] G1 (n=108): 6.64 G2 (n=108): 5.8 HR 0.95 (95% CI, 0.72 to 1.26); P=0.7436 Subgroup analysis (ITT): Tumor size ≥18cm^2 [101] G1 (n=39): 5.6 G2 (n=41): 3.3 HR 0.53 (95% CI, 0.32 to 0.85); P=0.009 Subgroup analysis (ITT): Tumor size <18cm^2 [30] G1 (n=81): 7.3 G2 (n=76): 8.3 HR 0.99 (95% CI, 0.71 to 1.37); P=0.9405 Subgroup analysis (ITT): KPS ≥80[30] G1 (n=83): 7.9 G2 (n=77): 6.1 HR 0.71 (95% CI, 0.51 to 0.99); P=0.0453 Subgroup analysis (ITT): KPS <80[30] G1 (n=37): 4.8 G2 (n=40): 5.4 HR 1.26 (95% CI, 0.79 to 2.02); P=0.3375 Subgroup analysis (ITT): G2 limited to bevacizumab[30] G1 (n=120): 6.6 G2 (n=36): 4.9 HR 0.64 (95% CI, 0.41 to 0.99); P=0.0450

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Table D-9.   Recurrent GBM — Individual study findings related to efficacy outcomes (survival, tumor progression and response) (continued)

Study Author(s) (Year(s)) Study Design Risk of Bias	G1: TTF Intervention N Randomized N Analyzed G2: Comparator N Randomized N Analyzed Duration of Follow Up, months	Adherence	Overall Survival (OS) Progression-Free Survival (PFS) Other Tumor Response and Progression Outcomes
Stupp (2012)[15] Wong (2014);[29] Kanner (2014);[30] Wong (2014)[31] (continued)			Subgroup analysis (ITT): G2 limited to non-bevacizumab[30] G1 (n=120): 6.6 G2 (n=81): 6.6 HR 0.92 (95% CI, 0.69 to 1.24); P=0.5860 Subgroup analysis (ITT): Age ≤60 years[30] G1 (n=85): 7.4 G2 (n=83): 6.2 HR 0.74 (95% CI, 0.54 to 1.02); P=0.0631 Subgroup analysis (ITT): Age >60 years[30] G1 (n=35): 4.8 G2 (n=81): 5.7 HR 1.31 (95% CI, 0.78 to 2.19); P=0.3087 Subgroup analysis (ITT): Biopsy only[30] G1 (n=25): 7.9 G2 (n=18): 5.8 HR 0.54 (95% CI, 0.27 to 1.09); P=0.0848 Subgroup analysis (ITT): Any surgery[30] G1 (n=95): 6.2 G2 (n=99): 6.0 HR 0.99 (95% CI, 0.74 to 1.33); P=0.9590 Subgroup analysis (ITT): Reoperation before randomization[30] G1: 7.4 G2: 7.4 Subgroup analysis (ITT): No reoperation before randomization[30] G1: 6.3 G2: 5.3

(continued)

Table D-9. **Recurrent GBM — Individual study findings related to efficacy outcomes (survival, tumor progression and response) (continued)**

Study Author(s) (Year(s)) Study Design Risk of Bias	G1: TTF Intervention N Randomized N Analyzed G2: Comparator N Randomized N Analyzed Duration of Follow Up, months	Adherence	Overall Survival (OS) Progression-Free Survival (PFS) Other Tumor Response and Progression Outcomes
Stupp (2012)[15] Wong (2014);[29] Kanner (2014);[30] Wong (2014)[31] (continued)			Subgroup analysis (ITT): Response Status[29] Responders G1 (n=14): 24.8 (95% CI, 17.5 to N/A) G2 (n=7): 20.0 (95% CI, 14.5 to N/A) Nonresponders G1 (n=106): 6.2 (95% CI, 5.0 to 7.7) G2 (n=110): 6.8 (95% CI, 5.8 to 8.5) Responders vs. Nonresponders G1: P<0.0001 G2: P=0.0235 Subgroup analysis (ITT): Dexamethasone dose[31] ≤4.1 mg/day G1 (n=56): 11.0 (95% CI, 8.8 to 16.6) G2 (n=63): 8.9 (95% CI, 7.2 to 16.1) >4.1 mg/day G1 (n=64): 4.8 (95% CI, 3.9 to 6.0) G2 (n=54): 6.0 (95% CI, 3.5 to 8.3) ≤4.1 mg/day vs. >4.1 mg/day G1: P<0.0001 G2: P=0.0015 **Survival proportion, %** 1 year G1: 20 G2: 20

Table D-9. **Recurrent GBM — Individual study findings related to efficacy outcomes (survival, tumor progression and response) (continued)**

Study Author(s) (Year(s)) Study Design Risk of Bias	G1: TTF Intervention N Randomized N Analyzed G2: Comparator N Randomized N Analyzed Duration of Follow Up, months	Adherence	Overall Survival (OS) Progression-Free Survival (PFS) Other Tumor Response and Progression Outcomes
Stupp (2012)[15] Wong (2014);[29] Kanner (2014);[30] Wong (2014)[31] (continued)			2 year G1: 8 (95% CI, 4 to 13) G2: 5 (95% CI, 3 to 10) ≤4.1 mg/day vs. >4.1 mg/day G1: P<0.0001 G2: P=0.0015 **Survival proportion, %** 1 year G1: 20 G2: 20 2 year G1: 8 (95% CI, 4 to 13) G2: 5 (95% CI, 3 to 10) 3 year G1: 4 (95% CI, 1 to 8) G2: 1 (95% CI, 0 to 3) **Death** ITT analysis[15] HR 0.86 (95% CI, 0.66 to 1.12); P=0.27 **Median progression-free survival, months** ITT analysis[15] G1: 2.2 G2: 2.1 HR 0.81 (95% CI, 0.60 to 1.09); P=0.16

(continued)

Table D-9.   Recurrent GBM — Individual study findings related to efficacy outcomes (survival, tumor progression and response) (continued)

Study Author(s) (Year(s)) Study Design Risk of Bias	G1: TTF Intervention N Randomized N Analyzed G2: Comparator N Randomized N Analyzed Duration of Follow Up, months	Adherence	Overall Survival (OS) Progression-Free Survival (PFS) Other Tumor Response and Progression Outcomes
Stupp (2012)[15] Wong (2014);[29] Kanner (2014);[30] Wong (2014)[31] (continued)			Subgroup analysis (ITT)[f]: Response Status[29] Responders G1 (n=14): 17.8 (95% CI, 11.5 to N/A) G2 (n=7): 11.5 (95% CI, 11.4 to N/A) Nonresponders G1 (n=106): 10.5 (95% CI, 10.4 to 10.6) G2 (n=110): 7.9 (95% CI, 7.8 to 8.6) Responders vs. Nonresponders G1: P=0.0007 G2: P=0.0222 **Progression-free survival at 6 months, %** ITT analysis[15] G1: 21.4 (95% CI, 13.5 to 29.3) G2: 15.1 (95% CI, 7.8 to 22.3) P=0.13 **Radiological response rate (complete and partial)[g]** ITT analysis[15] G1: 14 (95% CI, 7.9 to 22.4) G2: 9.6 (95% CI, 3.9 to 18.8) P=0.19

(continued)

Table D-9.   Recurrent GBM — Individual study findings related to efficacy outcomes (survival, tumor progression and response) (continued)

Study Author(s) (Year(s)) Study Design Risk of Bias	G1: TTF Intervention N Randomized N Analyzed G2: Comparator N Randomized N Analyzed Duration of Follow-Up, months	Adherence	Overall Survival (OS) Progression-Free Survival (PFS) Other Tumor Response and Progression Outcomes
Stupp (2012)[15] Wong (2014);[29] Kanner (2014);[30] Wong (2014)[31] (continued)			**Median time to response, months, among responders[29]** G1 (n=14): 8.4 (95% CI, 6.9 to 9.9) G2 (n=7): 5.8 (95% CI, 3.6 to 8.0) P=0.5755 **Median response duration, months, among responders[29]** G1 (n=14): 7.3 (95% CI, 0.0 to 16.6) G2 (n=7): 5.6 (95% CI, 3.8 to 7.5) P=0.0009

Abbreviations: CI = confidence interval; GBM = glioblastoma multiforme; HR = hazard ratio; ITT = intent to treat; KPS = Karnofsky Performance Score; mITT = modified intent to treat; NA = not applicable; NR = not reported; OS = overall survival; PFS = progression-free survival; QOL = quality of life; RCT = randomized controlled trial; ROB = risk of bias; SQ = safety question; TMZ = temozolomide; TTF = tumor treating fields.

[a] We did not formally assess the quality or risk of bias in case series that were included for SQ.

[b] All patients randomized to G1 who received at least one course (i.e., 28 days) of TTF therapy.

[c] All patients randomized to G2 who received at least one course of chemotherapy.

[d] Four patients experienced pre-treatment events related to disease and never began treatment.

[e] Four patients received hospice care because of disease-related events that prevented them from starting chemotherapy treatment.

[f] Simon-Makuch adjusted[102]

[g] Determined by blinded central radiology review, according to Macdonald criteria[100]

Table D-10.   Recurrent GBM — Individual study findings related to efficacy outcomes (health-related quality of life and functional status)

Study Author(s) (Year(s)) Study Design Risk of Bias	G1: TTF Intervention N Randomized N Analyzed G2: Comparator N Randomized N Analyzed Duration of Follow Up, months	Health-Related Quality of Life	Functional Status
Kesari (2017)[32] **Study design:** Prospective cohort **ROB:** High	**G1**: TTF + second-line therapy N=466 randomized in the original trial N=144 enrolled N=144 analyzed **G2**: Second-line therapy N=229 randomized in the original trial N=60 enrolled N=60 analyzed **Duration of follow up, months** Median (range) 12.6 (NR)	NR	NR
Lacouture (2014)[13] **Study design:** Case series **ROB:** NA[a]	Ineligible for these outcomes.		

(continued)

Table D-10.   Recurrent GBM — Individual study findings related to efficacy outcomes (health-related quality of life and functional status) (continued)

Study Author(s) (Year(s)) Study Design Risk of Bias	G1: TTF Intervention N Randomized N Analyzed G2: Comparator N Randomized N Analyzed Duration of Follow Up, months	Health-Related Quality of Life	Functional Status
Mrugala (2014)[9] **Study design:** Cohort with historical comparator group **ROB:** Some concerns (OS) to high (safety)	**G1:** TTF N=457 enrolled N= 457 analyzed (adherence data only available for 287 (63%)) **G2:** TTF N=120 randomized N=120 analyzed **G3:** Chemotherapy N=117 randomized N=117 analyzed **Duration of follow up, months** NR	NR	NR
Kirson (2007)[33] **Study design:** Cohort with historical comparator groups **ROB:** High	**G1:** TTF N=12 enrolled N=10 analyzed **G2**: Gefitinib N enrolled NR N=57 analyzed	NR	NR

(continued)

Table D-10. **Recurrent GBM — Individual study findings related to efficacy outcomes (health-related quality of life and functional status) (continued)**

Study Author(s) (Year(s)) Study Design Risk of Bias	G1: TTF Intervention N Randomized N Analyzed G2: Comparator N Randomized N Analyzed Duration of Follow Up, months	Health-Related Quality of Life	Functional Status
Kirson (2007)[33] (continued)	**G3**: Temozolomide N enrolled NR N=142 analyzed **G4:** Temozolomide N enrolled NR N=126 analyzed **G5:** Temozolomide and procarbazine N enrolled NR N=225 analyzed **G6:** Meta-analyses of multiple chemotherapies N enrolled NR N=225 analyzed **Duration of follow up, months** NR; Adverse events occurring during treatment or up to 60 days after termination of therapy		

(continued)

Table D-10.   Recurrent GBM — Individual study findings related to efficacy outcomes (health-related quality of life and functional status) (continued)

Study Author(s) (Year(s)) Study Design Risk of Bias	G1: TTF Intervention N Randomized N Analyzed G2: Comparator N Randomized N Analyzed Duration of Follow Up, months	Health-Related Quality of Life	Functional Status
Stupp (2012)[15] Wong (2014);[29] Kanner (2014);[30] Wong (2014)[31] **Study design:** RCT (EF-11) **ROB:** Some concerns (OS, PFS, safety) to high (QOL)	**G1:** TTF N=120 randomized N=36 analyzed **G2:** Chemotherapy N=117 randomized N=27 analyzed **Duration of follow up, months** Median (range) 39 (NR)	**European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30)** [90,91] **Change from baseline to 3 months**[15] No "meaningful" differences between groups with respect to the **global health** and **social functioning** domains. TTF was favored over chemotherapy with respect to several domains: • Larger improvement in **emotional functioning** • Less of a decline in **role functioning** • **Cognitive functioning** improved with TTF but declined with chemotherapy Chemotherapy was favored over TTF with respect to the **physical functioning** domain; there was a smaller decline with chemotherapy than TTF	NR

Abbreviations: GBM = glioblastoma multiforme; NA = not applicable; NR = not reported; OS = overall survival; PFS = progression-free survival; QLC = quality of life questionnaire; QOL = quality of life; RCT = randomized controlled trial; ROB = risk of bias; TMZ = temozolomide; TTF = tumor treating fields.

Table D-11.   Recurrent GBM — Individual study findings related to safety outcomes

Study Author(s) (Year(s)) Study Design Risk of Bias	G1: TTF Intervention N Randomized N Analyzed G2: Comparator N Randomized N Analyzed Duration of Follow Up, months	Serious Adverse Events	Dermatologic Adverse Events	Other Adverse Events
Kesari (2017)[32] **Study design:** Prospective cohort **ROB:** High	**G1**: TTF + second-line therapy N=466 randomized in the original trial N=144 enrolled N=144 analyzed **G2**: Second-line therapy N=229 randomized in the original trial N=60 enrolled N=60 analyzed **Duration of follow up, months** Median (range) 12.6 (NR)	NR	**Site reaction beneath the TTF transducer arrays, % in G1** Any: 19 (13) Severe: 0	**≥1 grade 3/4ᵃ adverse event, N (%)** G1: 70 (49) G2: 20 (33) No grade 3/4 events were attributed to TTF treatment. **Adverse event: N (%) in G1, N (%) in G2** Blood and lymphatic system disorders: 16 (11), 2 (3) Thrombocytopenia: 10 (7), 1 (2) Lymphopenia: 6 (4), 1 (2) Leukopenia: 4 (3), 0 (0) Gastrointestinal disorders: 5 (3), 0 (0) General disorders and administration site conditions: 12 (8), 4 (7) Fatigue: 5 (3), 2 (3) Gait disturbance: 3 (2), 1 (2) Infections and infestations:9 (6), 0 (0) Meningitis: 3 (2), 0 (0) Metabolism and nutrition disorders: 4 (3), 4 (7) Musculoskeletal and connective tissue disorders: 5 (3), 2 (3) Nervous system disorders: 40 (28), 11 (18)

(continued)

Table D-11. Recurrent GBM — Individual study findings related to safety outcomes (continued)

Study Author(s) (Year(s)) Study Design Risk of Bias	G1: TTF Intervention N Randomized N Analyzed G2: Comparator N Randomized N Analyzed Duration of Follow Up, months	Serious Adverse Events	Dermatologic Adverse Events	Other Adverse Events
Kesari (2017)[32] (continued)				Epilepsy: 3 (2), 2 (3) Convulsion: 8 (6), 2 (3) Hemiparesis: 6 (4), 0 (0) Headache: 5 (3), 2 (3) Cognitive disorder: 4 (3), 1 (2) Neurological decompensation: 3 (2), 1 (2) Psychiatric disorders: 6 (4), 1 (2) Mental status changes: 4 (3), 0 (0) Vascular disorders: 5 (3), 1 (2)
Lacouture (2014)[13] **Study design:** Case series **ROB:** NA[b]	**G1:** TTF N enrolled NR N=540 analyzed **Duration of follow up, months** NR	NR	**Non-serious dermatologic adverse events, N (%)** 156 (21.8) (some patients reported more than one event) **Skin ulcer, N (%)** 4 (0.7) **Time to dermatologic adverse event onset, days** Median, range 32.5 (2 to 520)	NR

(continued)

Table D-11.   Recurrent GBM — Individual study findings related to safety outcomes (continued)

Study Author(s) (Year(s)) Study Design Risk of Bias	G1: TTF Intervention N Randomized N Analyzed G2: Comparator N Randomized N Analyzed Duration of Follow Up, months	Serious Adverse Events	Dermatologic Adverse Events	Other Adverse Events
Mrugala (2014)[9] **Study design:** Cohort with historical comparator group **ROB:** Some concerns (OS) to high (safety)	**G1:** TTF N=457 enrolled N= 457 analyzed (adherence data only available for 287 (63%)) **G2:** TTF N=120 randomized N=120 analyzed **G3:** Chemotherapy N=117 randomized N=117 analyzed **Duration of follow up, months** NR	NR	**Adverse events among G1 only, %** Skin reaction: 24.3 Heat sensation: 11.3 Electric sensation: 7.7	"No new adverse events were detected in PRiDe compared to those found in EF-11." **Adverse events among G1 only, %** Neurological disorder: 10.4 Seizure: 8.9 Headache: 5.7 Pain/discomfort: 4.7 Fall: 3.9 Psychiatric disorder: 2.9 Gastrointestinal disorder: 2.9 Fatigue: 2.5 Vascular disorder: 1.6 Weakness: 1.4 Infections: 1.4 Eye disorder: 1.3
Kirson (2007)[33] **Study design:** Cohort with historical comparator groups **ROB:** High	**G1:** TTF N=12 enrolled N=10 analyzed **G2:** Gefitinib N enrolled NR N=57 analyzed **G3:** Temozolomide N enrolled NR N=142 analyzed	**Treatment-related serious adverse events among G1 only, N (%)** 0 (0)	**Mild to moderate contact dermatitis, N (%)** G1: 9 (90) G2: NR G3: NR G4: NR G5: NR G6: NR	**G1:** Partial seizures unrelated to treatment were reported by 2 patients (20%); elevated liver enzymes, attributed to anti-epileptic drugs, were reported "consistently" (Number of patients NR) **G2:** Treatment-related adverse events included diarrhea (40%), conjunctivitis (11%), onycholsysis, liver enzyme elevation, anorexia, and weight loss

(continued)

Table D-11.   Recurrent GBM — Individual study findings related to safety outcomes (continued)

Study Author(s) (Year(s)) Study Design Risk of Bias	G1: TTF Intervention N Randomized N Analyzed G2: Comparator N Randomized N Analyzed Duration of Follow Up, months	Serious Adverse Events	Dermatologic Adverse Events	Other Adverse Events
Kirson (2007)[33] (continued)	**G4:** Temozolomide N enrolled NR N=126 analyzed **G5:** Temozolomide and procarbazine N enrolled NR N=225 analyzed **G6:** Meta-analyses of multiple chemotherapies N enrolled NR N=225 analyzed **Duration of follow up, months** NR; Adverse events occurring during treatment or up to 60 days after termination of therapy		**Rash, N (%)** G1: NR G2: NR (60) G3: NR G4: NR G5: NR G6: NR	**G3:** Treatment-related adverse events included hematologic (25%), gastrointestinal (2%), allergy, fatigue, and hepatic **G4:** Treatment-related adverse events included nausea (26%), emesis (24%), thrombocytopenia (10%), leukopenia (7%), neutropenia (4.5%), fatigue, and anorexia **G5:** Treatment-related adverse events included nausea (38%), emesis (32%), fatigue (27%), constipation (15%), anorexia (11%), and headache (12%) for the temozolomide patients and nausea (34%), emesis (27%), fatigue (15%), constipation (10%), anorexia (8%), and headache (8%) for the procarbazine patients **G6:** Treatment-related adverse events NR

(continued)

Table D-11.   Recurrent GBM — Individual study findings related to safety outcomes (continued)

Study Author(s) (Year(s)) Study Design Risk of Bias	G1: TTF Intervention N Randomized N Analyzed G2: Comparator N Randomized N Analyzed Duration of Follow Up, months	Serious Adverse Events	Dermatologic Adverse Events	Other Adverse Events
Stupp (2012)[15] Wong (2014);[29] Kanner (2014);[30] Wong (2014)[31] **Study design:** RCT (EF-11) **ROB:** Some concerns (OS, PFS, safety) to high (QOL)	**G1:** TTF N=120 randomized N=116 analyzed **G2:** Chemotherapy N=117 randomized N=91 analyzed **Duration of follow up, months** Median (range) 39 (NR)	**Severe adverse events[c], %** **G1:** 6% **G2:** 16% P=0.022	**Skin rash: % (% grade 3 or 4)[d,15]** G1: 2 (0) G2: 0 (0) **Mild to moderate (grade 1 or 2) contact dermatitis[15]** on the scalp beneath the transducer arrays occurred in 16% of G1	**Adverse event: % (% grade 3 or 4) in G1, % (% grade 3 or 4) in G2[15]** Hematological system: 3 (0), 17 (4) Leucopenia: 0 (0), 5 (1) Neutropenia: 0 (0), 2 (1) Thrombocytopenia: 1 (1)[e], 7 (2) Gastrointestinal disorders: 4 (1), 17 (3) Abdominal pain: 0 (0), 3 (0) Diarrhea: 0 (0), 6 (2) Nausea/vomiting: 2 (0), 7 (0) General deterioration and malaise: 5 (1), 6 (1) Infections:4 (0), 8 (1) Metabolism and nutrition disorders: 4 (1), 6 (3) Musculoskeletal disorders: 2 (0), 5 (0) Nervous system disorders: 30 (7), 28 (7) Brain edema: 0 (0), 2 (0) Cognitive disorder: 2 (1), 2 (1) Convulsion: 7 (2), 5 (2) Dysphasia: 2 (0), 1 (0) Headache: 8 (1), 6 (0) Hemianopsia: 1 (0), 3 (1) Hemiparesis: 3 (1), 2 (1) Neuropathy peripheral: 2 (0), 2 (0)

(continued)

Table D-11.   Recurrent GBM — Individual study findings related to safety outcomes (continued)

Study Author(s) (Year(s)) Study Design Risk of Bias	G1: TTF Intervention N Randomized N Analyzed G2: Comparator N Randomized N Analyzed Duration of Follow Up, months	Serious Adverse Events	Dermatologic Adverse Events	Other Adverse Events
Stupp (2012)[15] Wong (2014);[29] Kanner (2014);[30] Wong (2014)[31] (continued)				Psychiatric disorders: 5 (0), 4 (0) Renal and urinary disorders: 3 (1), 3 (0) Respiratory disorders: 1 (0), 3 (1) Vascular disorders: 3 (1), 4 (3) Pulmonary embolism: 1 (1), 2 (2) Hypertension: 1 (0), 1 (1) Deep vein thrombosis: 1 (0), 1 (0)

Abbreviations: GBM = glioblastoma multiforme; NA = not applicable; NR = not reported; OS = overall survival; PFS = progression-free survival; PRiDe = Patient Registry Dataset; QOL = quality of life; RCT = randomized controlled trial; ROB = risk of bias; TMZ = temozolomide; TTF = tumor treating fields.

[a] Grading system was not explicitly defined.

[b] We did not formally assess the quality or risk of bias in case series that were included for SQ.

[c] Authors report severe adverse events rates of 6% and 16% in G1 and G2, respectively. However, data reported in Table 2 and in text of the article report that only 3% of patients overall experienced a severe to disabling adverse event, suggesting that the "severe adverse event" rates actually include a larger proportion of grade 2 (i.e., moderate) adverse events.

[d] Authors utilized NCI's Common Terminology Criteria for Adverse Events, version 3.0, for adverse event reporting. Severity is defined by the grade: 1=mild, 2=moderate, 3=severe, 4=life-threatening or disabling, and 5=death.[35]

[e] From prior chemotherapy.

Table D-12.   Other cancers — Study characteristics of included studies

Study Author(s) (Year(s))	Study Name/Identifier Funding Source(s) Country Study Dates	Study Design Power Risk of Bias	TTF Intervention (G1) TTF Intervention Details Duration of Treatment, months N	Comparator (G2) Comparator Details Duration of Treatment, months N
Green (2017)[36]	**Study**: NA **Funding**: NR **Country**: United States **Study dates**: NR	**Study design**: Case series **Power**: NR **ROB**: NA[a]	**Intervention (G1):** TTF with chemotherapy and/or radiation **Intervention Details**: TTF was used on a compassionate use basis. Patients received TTF along with chemotherapy and/or radiation. Two patients (40%) received concurrent bevacizumab, two patients (40%) received concurrent bevacizumab and lomustine, and one patient (20%) received no concurrent therapies. **Duration of treatment, months:** Range 1 to 6 **N enrolled**: 5	NA

(continued)

Table D-12.   Other cancers — Study characteristics of included studies (continued)

Study Author(s) (Year(s))	Study Name/Identifier Funding Source(s) Country Study Dates	Study Design Power Risk of Bias	TTF Intervention (G1) TTF Intervention Details Duration of Treatment, months N	Comparator (G2) Comparator Details Duration of Treatment, months N
Pless (2013)[12]	**Study**: EF-15/NCT00749346 **Funding**: Novocure, Inc **Country**: Switzerland **Study dates**: May 2008 to September 2009	**Study design**: Case series **Power**: NA (power calculation is for ineligible outcome) **ROB**: NA[a]	**Intervention (G1):** TTF and pemetrexed **Intervention details**: NovoTTF-100L generates TTF at an intensity of 1–2 V/cm within the entire chest cavity and upper abdomen (including the liver). The TTF were delivered to patients through four insulated surface transducer arrays. The four single-use transducer arrays were placed on the thorax so as to generate perpendicular fields in the chest of the patient. Special attention was given to include the liver within the electrical field. Treatment was given continuously for at least 12 h per day until disease progression. Pemetrexed was given at the standard dose of 500 mg/m^2 iv, q3w, together with adequate supportive therapy (dexamethasone, folic acid and vitamin B12); **Duration of treatment, months:** TTF: 4.5 (range 0.25 to 8) Pemetrexed: 6.1 cycles (range 1 to 33 cycles) **N enrolled:** 42	NA

(continued)

Table D-12. Other cancers — Study characteristics of included studies (continued)

Study Author(s) (Year(s))	Study Name/Identifier Funding Source(s) Country Study Dates	Study Design Power Risk of Bias	TTF Intervention (G1) TTF Intervention Details Duration of Treatment, months N	Comparator (G2) Comparator Details Duration of Treatment, months N
Salzberg (2008)[37]	**Study**: NR **Funding**: NR **Country**: Switzerland **Study dates**: NR	**Study design:** Case series **Power:** NR **ROB**: NA[a]	**Intervention (G1):** TTF **Intervention details**: Therapy was initiated under medical supervision for the first 6 hours of treatment. Thereafter, patients were released to continue treatment on an ambulatory basis. These TTF are applied to the patient by means of surface electrodes that are electrically insulated, thereby ensuring that resistively coupled electric currents are not delivered to the patient. The electrodes are placed on the patient's shaved skin over a layer of adhesive hydrogel and held in place with hypoallergenic adhesive strips. Patients received continuous TTF treatment at 100–200 kHz at a field intensity of 0.7 V/cm root mean square. Patients were allowed to disconnect from the device for up to 30 min, twice a day **Duration of treatment, months:** Range 13 to 46 days; Two patients received 2 weeks and four patients received at least 4 weeks of continuous TTF therapy. **N enrolled:** 6	NA

Abbreviations: cm = centimeter; GBM = glioblastoma multiforme; kHz = kilohertz; NA = not applicable; NR = not reported; ROB = risk of bias; SQ = safety question; TMZ = temozolomide; TTF = tumor treating fields.

[a] We did not formally assess the quality or risk of bias in case series that were included for SQ.

Table D-13. Other cancers — Population characteristics of included studies at baseline

Study Author(s) (Year(s)) Study Design Risk of Bias	Eligibility Criteria	Demographics	Cancer Diagnosis Details	Prior Treatment Details	Baseline Functional Status
Green (2017)[36] **Study design:** Case series **ROB:** NA[a]	**Inclusion:** Pediatric high-grade glioma patients treated at one institution on a compassionate use basis **Exclusion:** NR	**Age, years** 14.8 (4.32) (range 10 to 20) **Male, N (%)** 5 (100) **Nonwhite, N (%)** NR	**Description of diagnosis** Pediatric high-grade glioma **Cancer type, N (%)** Anaplastic oligodendroglioma: 1 (20) Epithelioid GBM: 1 (20) Gliomatosis cerebri: 1 (20) GBM: 1 (20) H3K27M Diffuse Midline Glioma: 1 (20) **Recurrence, N (%)** TTF started after: Primary radiotherapy: 2 (40) Recurrence radiotherapy: 1 (20) Second recurrence: 2 (40) **Tumor position, N (%)** Bifrontal: 2 (40) Right frontal: 1 (20) Right temporal: 1 (20) Left thalamic: 1 (20)	**Surgery, N (%)** Primary treatment Subtotal resection surgery: 5 (100) Recurrence treatment Stereotactic radiosurgery: 2 (40) **Radiotherapy, N (%)** 5 (100) **Chemotherapy primary treatment, N (%)** Temozolomide: 4 (80) Vincristine: 1 (20) Cetuximab: 4 (80) Irinotecan: 1 (20) **Recurrence treatment, N (%)** Temozolomide: 1 (20) Procarbazine: 1 (20) Lomustine: 1 (20) Bevacizumab: 2 (40) **Cycles of TTF treatment** Mean (range) 4.4 (1 to 6)[b]	NR

(continued)

Table D-13.   Other cancers — Population characteristics of included studies at baseline (continued)

Study Author(s) (Year(s)) Study Design Risk of Bias	Eligibility Criteria	Demographics	Cancer Diagnosis Details	Prior Treatment Details	Baseline Functional Status
Pless (2013)[12] **Study design:** Case series **ROB:** NA[a]	**Inclusion:** Patients with histologically or cytologically confirmed NSCLC, stage IV or IIIB (malignant pleural effusion per TNM classification 6th edition), or locally advanced NSCLC not otherwise amenable to local treatment; at least one line of prior chemotherapy; measurable disease; age ≥18 years; life expectancy of at least 12 weeks; ECOG performance status 0 to 2; adequate bone marrow function, renal function, hepatic function tests. **Exclusion:** Brain metastases or meningeal carcinomatosis; serious concomitant conditions; myocardial infarction within 1 year; uncontrolled hypertension or arrhythmias; implanted electric devices; history of significant neurologic or psychiatric disorders; pregnancy; active infection requiring iv	**Age, years** Median, range 63 (44 to 78) **Male, N (%)** 26 (63.4) **Nonwhite, N (%)** NR	**Description of diagnosis** Histologically or cytologically confirmed NSCLC, stage IV or IIIB (malignant pleural effusion per TNM classification 6th edition), or locally advanced NSCLC not otherwise amenable to local treatment (surgery or radiotherapy). **Cancer histology, N (%)** Adenocarcinoma: 32 (78.0) Squamous cell: 7 (17.0) Large cell: 2 (4.8) **Cancer stage, N (%)** IIIB (pleural effusion): 10 (24.4) IV: 31 (75.6) **Tumor location** 36 (88) of patients had disease that was confined to the effective region of the TTF treatment	**Surgery, N (%)** 5 (12.2%) **Radiotherapy, N (%)** 10 (24.4%) **Chemotherapy, N (%)** Platinum: 37 (90.2) CR/PR, best response platinum: 10 (27.0) CR/PR, best response all chemotherapy: 13 (31.7) SD: 15 (36.6) PD/unknown: 13 (31.7) **Time since diagnosis, months** Median 11.4 **Time since last chemotherapy, months** Median 3.7	**ECOG performance score, N (%)** 0 or 1 points: 31 (75.6) 2 points: 7 (17.1) Unknown: 3 (7.3)

(continued)

Table D-13.   Other cancers — Population characteristics of included studies at baseline (continued)

Study Author(s) (Year(s)) Study Design Risk of Bias	Eligibility Criteria	Demographics	Cancer Diagnosis Details	Prior Treatment Details	Baseline Functional Status
Pless (2013)[12] (continued)	antibiotics; active ulcer; unstable diabetes mellitus or other contraindication to corticosteroid therapy; concurrent treatment with other experimental drugs.				
Salzberg (2008)[37] **Study design:** Case series **ROB:** NA[a]	**Inclusion:** Patients with histologically proven, locally advanced or metastatic malignant tumors were recruited; age ≥ 18 years; at least 1 measurable lesion; tumor location accessible to field application through externally placed electrodes; ECOG performance[103] ≤ 2; no additional standard therapy available; no concomitant anti-tumor therapy. **Exclusion:** NR	**Age, years** Median (range) 66 (24 to 76) **Male, N (%)** NR **Nonwhite, N (%)** NR	**Description of diagnosis** Histologically proven, locally advanced or metastatic malignant tumors. **Primary cancer type, N (%)** Invasive ductal breast cancer: 2 (33.3) Malignant melanoma: 1 (16.7) Pleural mesothelioma: 1 (16.7) Adenocarcinoma of the breast: 1 (16.7) GBM: 1 (16.7) **Recurrence** Study authors state that all patients were previously treated with several lines of therapy and no additional standard treatment option was available to them.	NR	NR

(continued)

Table D-13.   Other cancers — Population characteristics of included studies at baseline (continued)

Study Author(s) (Year(s)) Study Design Risk of Bias	Eligibility Criteria	Demographics	Cancer Diagnosis Details	Prior Treatment Details	Baseline Functional Status
Salzberg (2008)[37] (continued)			**Tumor location** Locations of treated lesions included right chest wall (invasive ductal breast cancer), left thigh (malignant melanoma), retroperitoneum (pleural mesothelioma), left chest wall (invasive ductal breast cancer and adenocarcinoma of the breast), and left hemisphere of the brain (GBM)		

Abbreviations: CR = complete response; ECOG = Eastern Cooperative Oncology Group; GBM = glioblastoma multiforme; NA = not applicable; NR = not reported; NSCLC = non-small cell lung carcinoma; PR = partial response; ROB = risk of bias; SD = stable disease; SQ = safety question; TNM = tumor (T), nodes (N), and metastases (M); TTF = tumor treating fields.

[a] We did not formally assess the quality or risk of bias in case series that were included for SQ.

[b] Mean cycles of TTF treatment were calculated from reported number of cycles: 1, 4, 5, 6, and 6.

Table D-14.   Other cancers — Individual study findings related to efficacy outcomes (survival, tumor progression and response)

Study Author(s) (Year(s)) Study Design Risk of Bias	G1: TTF Intervention N Randomized N Analyzed G2: Comparator N Randomized N Analyzed Duration of Follow Up, months	Adherence	Overall Survival (OS) Progression-Free Survival (PFS) Other Tumor Response and Progression Outcomes
Green (2017)[36] **Study design:** Case series **ROB:** NA[a]	Ineligible for these outcomes.		
Pless (2013)[12] **Study design:** Case series **ROB:** NA[a]	Ineligible for these outcomes.		
Salzberg (2008)[37] **Study design:** Case series **ROB:** NA[a]	Ineligible for these outcomes.		

Abbreviations: GBM = glioblastoma multiforme; NA = not applicable; ROB = risk of bias; SQ = safety question; TTF = tumor treating fields.

[a] We did not formally assess the quality or risk of bias in case series that were included for SQ.

Table D-15.   Other cancers — Individual study findings related to efficacy outcomes (health-related quality of life and functional status)

Study Author(s) (Year(s)) Study Design Risk of Bias	G1: TTF Intervention N Randomized N Analyzed G2: Comparator N Randomized N Analyzed Duration of Follow Up, months	Health-Related Quality of Life	Functional Status
Green (2017)[36] **Study design:** Case series **ROB:** NA[a]	Ineligible for these outcomes.		
Pless (2013)[12] **Study design:** Case series **ROB:** NA[a]	Ineligible for these outcomes.		
Salzberg (2008)[37] **Study design:** Case series **ROB:** NA[a]	Ineligible for these outcomes.		

Abbreviations: GBM = glioblastoma multiforme; NA = not applicable; ROB = risk of bias; SQ = safety question; TTF = tumor treating fields.

[a] We did not formally assess the quality or risk of bias in case series that were included for SQ.

Table D-16. Other cancers — Individual study findings related to safety outcomes

Study Author(s) (Year(s)) Study Design Risk of Bias	G1: TTF Intervention N Randomized N Analyzed G2: Comparator N Randomized N Analyzed Duration of Follow Up, months	Serious Adverse Events	Dermatologic Adverse Events	Other Adverse Events
Green (2017)[36] **Study design:** Case series **ROB:** NA[a]	**G1:** TTF with chemotherapy and/or radiation N=5 enrolled N=5 analyzed **Duration of follow up, months** NR	None reported	**Skin breakdown (Grade 2),[b] N (%)** 1 (20)	None reported
Pless (2013)[12] **Study design:** Case series **ROB:** NA[a]	**G1:** TTF N=42 enrolled N=41 analyzed **Duration of follow up, months** Median 9.5 months	The study authors state that none of the serious adverse events reported during the phase II trial were considered TTF-related.	**Rash/dermatitis/erythema, N (%)** CTC grade 3 to 4: 1 (2.4) CTC grade 1 to 2: 10 (24.4) **Blister, N (%)** CTC grade 3 to 4: 0 (0) CTC grade 1 to 2: 3 (7.3) **Pruritus, N (%)** CTC grade 3 to 4: 0 (0) CTC grade 1 to 2: 2 (4.9) **Alopecia, N (%)** CTC grade 3 to 4: 0 (2.4)[c] CTC grade 1 to 2: 1 (2.4) **Ulceration, N (%)** CTC grade 3 to 4: 0 (0) CTC grade 1 to 2: 1 (2.4)	**Constitutional system** **Arrhythmia, N (%)** CTC grade 3 to 4: 0 (0%) CTC grade 1 to 2: 1 (2.4%)[d] (patient with known cardiac risk factors, assessed as unrelated to the study device and resolved with pharmacological treatment under continuous TTF therapy) **Fatigue, N (%)** CTC grade 3 to 4: 1 (2.4) CTC grade 1 to 2: 9 (21.9) **Asthenia, N (%)** CTC grade 3 to 4: 0 (0) CTC grade 1 to 2: 2 (4.9) **Insomnia, N (%)** CTC grade 3 to 4: 0 (0) CTC grade 1 to 2: 3 (7.3) **Night sweats, N (%)** CTC grade 3 to 4: 0 (0) CTC grade 1 to 2: 3 (7.3)

(continued)

Table D-16.   Other cancers — Individual study findings related to safety outcomes (continued)

Study Author(s) (Year(s)) Study Design Risk of Bias	G1: TTF Intervention N Randomized N Analyzed G2: Comparator N Randomized N Analyzed Duration of Follow Up, months	Serious Adverse Events	Dermatologic Adverse Events	Other Adverse Events
Pless (2013)[12] (continued)				**Fever, N (%)** CTC grade 3 to 4: 0 (0) CTC grade 1 to 2: 2 (4.9) **Gastrointestinal system** **Anorexia, N (%)** CTC grade 3 to 4: 2 (4.9) CTC grade 1 to 2: 3 (7.3) **Diarrhea, N (%)** CTC grade 3 to 4: 2 (4.9) CTC grade 1 to 2: 2 (4.9) **Nausea, N (%)** CTC grade 3 to 4: 0 (0) CTC grade 1 to 2: 3 (7.3) **Constipation, N (%)** CTC grade 3 to 4: 0 (0) CTC grade 1 to 2: 4 (9.7) **Vomiting, N (%)** CTC grade 3 to 4: 0 (0) CTC grade 1 to 2: 3 (7.3) **Infectious** **Urinary infection, N (%)** CTC grade 3 to 4: 2 (4.9) CTC grade 1 to 2: 0 (0)

(continued)

Table D-16.   Other cancers — Individual study findings related to safety outcomes (continued)

Study Author(s) (Year(s)) Study Design Risk of Bias	G1: TTF Intervention N Randomized N Analyzed G2: Comparator N Randomized N Analyzed Duration of Follow Up, months	Serious Adverse Events	Dermatologic Adverse Events	Other Adverse Events
Pless (2013)[12] (continued)				**Neurological system** **Dizziness, N (%)** CTC grade 3 to 4: 1 (2.4) CTC grade 1 to 2: 1 (2.4) **Neuropathy, N (%)** CTC grade 3 to 4: 0 (0) CTC grade 1 to 2: 2 (4.9) **Thoracic/chest/rib pain, N (%)** CTC grade 3 to 4: 2 (4.9) CTC grade 1 to 2: 3 (7.3) **Pain** **Limb pain, N (%)** CTC grade 3 to 4: 0 (0) CTC grade 1 to 2: 4 (9.7) **Abdominal pain, N (%)** CTC grade 3 to 4: 0 (0) CTC grade 1 to 2: 3 (7.3) **Headache, N (%)** CTC grade 3 to 4: 0 (0) CTC grade 1 to 2: 3 (7.3) **Electric pain, N (%)** CTC grade 3 to 4: 1 (2.4) CTC grade 1 to 2: 0 (0) **Cervical pain, N (%)** CTC grade 3 to 4: 1 (2) CTC grade 1 to 2: 0 (0)

(continued)

Table D-16.   Other cancers — Individual study findings related to safety outcomes (continued)

Study Author(s) (Year(s)) Study Design Risk of Bias	G1: TTF Intervention N Randomized N Analyzed G2: Comparator N Randomized N Analyzed Duration of Follow Up, months	Serious Adverse Events	Dermatologic Adverse Events	Other Adverse Events
Pless (2013)[12] (continued)				**Pain (general), N (%)** CTC grade 3 to 4: 0 (0) CTC grade 1 to 2: 2 (4.9) **Respiratory system** **Dyspnea, N (%)** CTC grade 3 to 4: 4 (10) CTC grade 1 to 2: 8 (19) **Cough, N (%)** CTC grade 3 to 4: 0 (0) CTC grade 1 to 2: 11 (27)
Salzberg (2008)[37] **Study design:** Case series **ROB:** NA[a]	**G1:** TTF N=6 enrolled N=6 analyzed **Duration of follow up, months** NR	None reported	**Grade 1[e] skin irritation with reddening of the skin, N (%)** 3 (50)	None reported

Abbreviations: CTC = Common Terminology Criteria; GBM = glioblastoma multiforme; NA = not applicable; NR = not reported; ROB = risk of bias; SQ = safety question; TTF = tumor treating fields.

[a] We did not formally assess the quality or risk of bias in case series that were included for SQ.

[b] Authors report, but do not define, grade 2.

[c] Error in paper.

[d] Paroxysmal atrial fibrillation.

[e] Authors report, but do not define, grade 1.

Appendix E. Excluded Articles

List of Exclusion Codes

X1: Language

X2: Country

X3: Publication Type

X4: Population

X5: Intervention

X6: Comparator

X7: Study Design Review

X8: Study Design Case Report

X9: Study Design Trial in Progress/Protocol

X10: Outcome

X11: Abstract or Conference Proceeding

X12: Duplicate or Superseded

1. Health technology assessment report in support of county council decision-making. https://www.tlv.se/download/18.3d5ca496161de47811d16065/1519905690094/bes180222_optune_eng_version.pdf. Published 2017. Updated October 3. Accessed October 11, 2018. Exclusion code: X3.

2. Tumor treating fields therapy for recurrent glioblastoma. *Manag Care.* 2012;21(12):43-44. PMID: 23304737. Exclusion code: X3.

3. Alexiades N, McKhann GM, 2nd. A Shock to the System: Tumor-Treating Fields Plus Temozolomide for Glioblastoma. *Neurosurgery.* 2018;82(5):E115-e116. PMID: 29669122. doi: 10.1093/neuros/nyy044. Exclusion code: X3.

4. Ansstas G, Tran DD. Treatment with Tumor-Treating Fields Therapy and Pulse Dose Bevacizumab in Patients with Bevacizumab-Refractory Recurrent Glioblastoma: A Case Series. *Case Rep Neurol.* 2016;8(1):1-9. PMID: 26889149. doi: 10.1159/000442196. Exclusion code: X10.

5. Benavides M, Guillen C, Rivera F, Gallego J, Lopez-Martin J, Kung M. PANOVA: a phase II study of TTFields (150 kHz) concomitant with standard chemotherapy for front-line therapy of advanced pancreatic adenocarcinoma- Updated efficacy results. *J Clin Oncol.* 2017;35(15 Supplement 1). PMID: CN-01398087. doi: 10.1200/JCO.2017.35.15_suppl.e15790. Exclusion code: X11.

6. Bender E, Kozak K, Howard S, Hayes L, Bayouth J, Robins HI. The effect of Optune Tumor Treating Fields transducer arrays on skin radiation dose during radiotherapy. *J Clin Neurosci.* 2017;42:172-175. PMID: 28427800. doi: 10.1016/j.jocn.2017.04.002. Exclusion code: X4.

7. Benson L. Tumor Treating Fields Technology: Alternating Electric Field Therapy for the Treatment of Solid Tumors. *Semin Oncol Nurs.* 2018;34(2):137-150. PMID: 29631935. doi: 10.1016/j.soncn.2018.03.005. Exclusion code: X7.

8. Brozova H, Lucas A, Salmaggi A, Vymazal J. BMET-06COMET: a Phase II randomized study of TTFIELDS versus supportive care in non-small cell lung cancer patients with 1-5 brain metastases-initial safety results. *Neuro Oncol.* 2015;17(Suppl 5):v46. Exclusion code: X11.

9. Calzón FS, Llanos MA. Tumor treating fields therapy (TTF) for glioblastoma. A systematic review of the literature (Structured abstract). *Health Technology Assessment Database.* 2013(4). http://cochranelibrary-wiley.com/o/cochrane/clhta/articles/HTA-32013000378/frame.html. Exclusion code: X7.

10. Ceccon G, Lazaridis L, Stoffels G, et al. Use of FET PET in glioblastoma patients undergoing neurooncological treatment including tumour-treating fields: initial experience. *Eur J Nucl Med Mol Imaging.* 2018. PMID: 29564490. doi: 10.1007/s00259-018-3992-5. Exclusion code: X5.

11.   Cloughesy TF, Lassman AB. NovoTTF: where to go from here? *Neuro Oncol.* 2017;19(5):605-608. PMID: 28453750. doi: 10.1093/neuonc/nox014. Exclusion code: X3.

12.   Davies AM, Weinberg U, Palti Y. Tumor treating fields: a new frontier in cancer therapy. *Ann N Y Acad Sci.* 2013;1291:86-95. PMID: 23659608. doi: 10.1111/nyas.12112. Exclusion code: X7.

13.   Fonkem E, Wong ET. NovoTTF-100A: a new treatment modality for recurrent glioblastoma. *Expert Rev Neurother.* 2012;12(8):895-899. PMID: 22708931. doi: 10.1586/ern.12.80. Exclusion code: X3.

14.   Gervais C, Feuvret L. AERIO news in brief: maintenance therapy with tumor-treating fields plus temozolomide vs temozolomide alone for glioblastoma. A randomized clinical trial. *Oncologie.* 2016;18(5):355-357. http://cochranelibrary-wiley.com/o/cochrane/clcentral/articles/343/CN-01178343/frame.html. Exclusion code: X1.

15.   Gourd E. Tumour-treating fields complement glioblastoma treatment. *Lancet Oncol.* 2018;19(3):e145. PMID: 29429911. doi: 10.1016/s1470-2045(18)30088-3. Exclusion code: X3.

16.   Guzauskas GF, Salzberg M, Wang BC. Estimated lifetime survival benefit of tumor treating fields and temozolomide for newly diagnosed glioblastoma patients. *CNS Oncol.* 2018. PMID: 30124334. doi: 10.2217/cns-2018-0010. Exclusion code: X10.

17.   Halasz LM, Mitin T. Tumor-Treating Fields: Answering the Concern About Quality of Life. *JAMA Oncol.* 2018;4(4):504-505. PMID: 29392273. doi: 10.1001/jamaoncol.2017.5062. Exclusion code: X3.

18.   Harris D, Kumar V, Mehan W, et al. Enhanced therapeutic benefits of tumor treating fields (TTfields) on superficially located glioblastoma multiforme (GBM). *Neuro-oncology. Conference: 21st annual scientific meeting and education day of the society for neuro-oncology. United states. Conference start: 20161117. Conference end: 20161120.* 2016;18:vi180. http://cochranelibrary-wiley.com/o/cochrane/clcentral/articles/980/CN-01303980/frame.html. Exclusion code: X11.

19.   Hayes, Inc. Novocure (tumor treating fields) (Structured abstract). *Health Technology Assessment Database.* 2016(4). http://cochranelibrary-wiley.com/o/cochrane/clhta/articles/HTA-32016000778/frame.html. Exclusion code: X7.

20.   Hottinger AF, Pacheco P, Stupp R. Tumor treating fields: a novel treatment modality and its use in brain tumors. *Neuro Oncol.* 2016;18(10):1338-1349. PMID: 27664860. doi: 10.1093/neuonc/now182. Exclusion code: X7.

21.   Kanner AA, Wong ET, Villano JL, Ram Z. No-065. Tumor Treating Fields (TTFields) In Recurrent Gbm. An Updated Subgroup Analysis Of The Phase III Data. *Neuro Oncol.* 2013;15(suppl_3):iii98–iii135. Exclusion code: X11.

22.   Kumar V, Harris D, Linendoll N, et al. Compliance and duration of treatment with tumor treating fields (TTFIELDS) in adjuvant treatment for newly diagnosed glioblastomas (GBMS) improves progression-free survival (PFS) and overall survival (OS). *Neuro-oncology. Conference: 21st annual scientific meeting and education day of the society for neuro-oncology. United states. Conference start: 20161117. Conference end: 20161120.* 2016;18:vi180. http://cochranelibrary-wiley.com/o/cochrane/clcentral/articles/982/CN-01303982/frame.html. Exclusion code: X11.

23.   Li T, Shukla G, Peng C, Lockamy V, Liu H, Shi W. Dosimetric Impact of a Tumor Treating Fields Device for Glioblastoma Patients Undergoing Simultaneous Radiation Therapy. *Front Oncol.* 2018;8:51. PMID: 29594036. doi: 10.3389/fonc.2018.00051. Exclusion code: X4.

24.   Lu G, Rao M, Delumpa LC, Liu Z, Hsu S, Zhu J-J. Survival Benefit with Triple Chemotherapy and TTFields for Glioblastoma. Paper presented at: Neuro-Oncology 2016. Exclusion code: X11.

25.   Lukas RV, Ratermann KL, Wong ET, Villano JL. Skin toxicities associated with tumor treating fields: case based review. *J Neurooncol.* 2017;135(3):593-599. PMID:

28849343. doi: 10.1007/s11060-017-2612-8. Exclusion code: X8.

26. Magouliotis DE, Asprodini EK, Svokos KA, Tasiopoulou VS, Svokos AA, Toms SA. Tumor-treating fields as a fourth treating modality for glioblastoma: a meta-analysis. *Acta Neurochir (Wien).* 2018;160(6):1167-1174. PMID: 29696502. doi: 10.1007/s00701-018-3536-6. Exclusion code: X7.

27. Mehta M, Gondi V, Brown P. TTFields and radiosurgery for 1-10 brain metastases from NSCLC: the Phase 3 METIS study. *Annals of oncology. Conference: 7th european lung cancer conference, ELCC 2017. Switzerland.* 2017;28(Supplement 2):iii55. http://cochranelibrary-wiley.com/o/cochrane/clcentral/articles/246/CN-01429246/frame.html. Exclusion code: X11.

28. Mittal S, Klinger NV, Michelhaugh SK, Barger GR, Pannullo SC, Juhasz C. Alternating electric tumor treating fields for treatment of glioblastoma: rationale, preclinical, and clinical studies. *J Neurosurg.* 2018;128(2):414-421. PMID: 28298023. doi: 10.3171/2016.9.Jns16452. Exclusion code: X7.

29. Mrugala MM, Ruzevick J, Zlomanczuk P, Lukas RV. Tumor Treating Fields in Neuro-Oncological Practice. *Curr Oncol Rep.* 2017;19(8):53. PMID: 28664468. doi: 10.1007/s11912-017-0611-8. Exclusion code: X7.

30. Odia Y, Schulte J, Iwamoto F. Rates and impact of combination immunotherapy with tumor treating fields in a glioma cohort. *Cancer research. Conference: american association for cancer research annual meeting 2017. United states.* 2017;77(13 Supplement 1) (no pagination). http://cochranelibrary-wiley.com/o/cochrane/clcentral/articles/046/CN-01424046/frame.html. Exclusion code: X11.

31. Onken J, Staub-Bartelt F, Vajkoczy P, Misch M. Acceptance and compliance of TTFields treatment among high grade glioma patients. *J Neurooncol.* 2018. PMID: 29644485. doi: 10.1007/s11060-018-2858-9. Exclusion code: X10.

32. Pless M, Betticher D, Buess M, et al. A phase II study of tumor treating fields (TTFields) in combination with pemetrexed for advanced non small cell lung cancer (NSCLC). Paper presented at: Annals of Oncology 2010. Exclusion code: X11.

33. Pless M, Weinberg U. Tumor treating fields: concept, evidence and future. *Expert Opin Investig Drugs.* 2011;20(8):1099-1106. PMID: 21548832. doi: 10.1517/13543784.2011.583236. Exclusion code: X3.

34. Raizer JJ, Fitzner KA, Jacobs DI, et al. Economics of Malignant Gliomas: A Critical Review. *J Oncol Pract.* 2015;11(1):e59-65. PMID: 25466707. doi: 10.1200/jop.2012.000560. Exclusion code: X7.

35. Ram Z, Gutin P, Stupp R. Subgroup and quality of life analyses of the phase III clinical trial of NovoTTF-100A versus best standard chemotherapy for recurrent glioblastoma. Paper presented at: 15th Annual Meeting of the Society for Neuro-Oncology (SNO) 2010. Exclusion code: X11.

36. Ram Z, Wong ET, Gutin PH. Comparing the effect of NovoTTF to bevacizumab in recurrent GBM: A post-HOC sub-analysis of the phase III trial data. Paper presented at: Neuro-Oncology2011. Exclusion code: X11.

37. Rehman AA, Elmore KB, Mattei TA. The effects of alternating electric fields in glioblastoma: current evidence on therapeutic mechanisms and clinical outcomes. *Neurosurg Focus.* 2015;38(3):E14. PMID: 25727223. doi: 10.3171/2015.1.Focus14742. Exclusion code: X7.

38. Rick J, Chandra A, Aghi MK. Tumor treating fields: a new approach to glioblastoma therapy. *J Neurooncol.* 2018;137(3):447-453. PMID: 29349613. doi: 10.1007/s11060-018-2768-x. Exclusion code: X7.

39. Rulseh AM, Keller J, Klener J, et al. Long-term survival of patients suffering from glioblastoma multiforme treated with tumor-treating fields. *World J Surg Oncol.* 2012;10:220. PMID: 23095807. doi: 10.1186/1477-7819-10-220. Exclusion code: X10.

40. Saria MG, Kesari S. Efficacy and Safety of Treating Glioblastoma With Tumor-Treating

Fields Therapy. *Clin J Oncol Nurs.* 2016;20(5 Suppl):S9-s13. PMID: 27668388. doi: 10.1188/16.Cjon.S1.9-13. Exclusion code: X7.

41.   Sim HW, Morgan ER, Mason WP. Contemporary management of high-grade gliomas. *CNS Oncol.* 2018;7(1):51-65. PMID: 29241354. doi: 10.2217/cns-2017-0026. Exclusion code: X7.

42.   Stupp R, Hegi ME, Idbaih A, et al. Abstract CT007: Tumor treating fields added to standard chemotherapy in newly diagnosed glioblastoma (GBM): final results of a randomized, multi-center, phase III trial. AACR; 2017. Exclusion code: X11.

43.   Stupp R, Idbaih A, Steinberg DM, et al. LTBK-01: Prospective, multi-center phase III trial of tumor treating fields together with temozolomide compared to temozolomide alone in patients with newly diagnosed glioblastoma. Oxford University Press US; 2016. Exclusion code: X11.

44.   Stupp R, Kanner A, Engelhard H, et al. A prospective, randomized, open-label, phase III clinical trial of NovoTTF-100A versus best standard of care chemotherapy in patients with recurrent glioblastoma. *J Clin Oncol.* 2010;28(18_suppl):LBA2007-LBA2007. Exclusion code: X11.

45.   Stupp R, Ram Z. OS07. 9 Standard of care temozolomide chemotherapy±tumor treating fields (TTFields) in newly diagnosed glioblastoma. Final results of the phase III EF-14 clinical trial. *Neuro Oncol.* 2017;19(Suppl 3):iii15. Exclusion code: X11.

46.   Stupp R, Taillibert S, Kanner A, et al. Tumor treating fields (TTFields): a novel treatment modality added to standard chem oand radiotherapy in newly diagnosed glioblastoma-first report of the full dataset of the EF14 randomized phase III trial. *J Clin Oncol.* 2015;33(15 suppl. 1). http://cochranelibrary-wiley.com/o/cochrane/clcentral/articles/339/CN-01130339/frame.html. Exclusion code: X11.

47.   Stupp R, Taillibert S, Kanner AA, et al. Maintenance therapy with tumor-treating fields plus temozolomide vs temozolomide alone for glioblastoma: a randomized clinical trial. *JAMA.* 2015;314(23):2535-2543. PMID:

26670971. doi: 10.1001/jama.2015.16669. Exclusion code: X12.

48.   Stupp R, Taphoorn M, Driven L, et al. Tumor treating fields (TTFields): A novel cancer treatment modality: translating preclinical evidence and engineering into a survival benefit with delayed decline in quality of life. *International journal of radiation oncology biology physics. Conference: 59th annual meeting of the american society for radiation oncology, ASTRO 2017. United states.* 2017;99(5):1316. http://cochranelibrary-wiley.com/o/cochrane/clcentral/articles/742/CN-01437742/frame.html. Exclusion code: X11.

49.   Stupp R, Wong E, Scott C. Interim analysis of the EF-14 trial: a prospective, multicenter trial of NovoTTF-100A together with temozolomide compared to temozolomide alone in patients with newly diagnosed GBM. Paper presented at: Society for Neuro-Oncology; November 13–16, 2014; Miami, FL. Exclusion code: X11.

50.   Toms SA, Tapinos N. Recent Advances in the Treatment of Gliomas - Comprehensive Brain Tumor Center. *R I Med J (2013).* 2017;100(6):43-46. PMID: 28564669. Exclusion code: X3.

51.   Turner SG, Gergel T, Wu H, Lacroix M, Toms SA. The effect of field strength on glioblastoma multiforme response in patients treated with the NovoTTF-100A system. *World J Surg Oncol.* 2014;12:162. PMID: 24884522. doi: 10.1186/1477-7819-12-162. Exclusion code: X8.

52.   Vergote I, Moos R, Manso L, Sessa C. INNOVATE: a phase II study of TTFields (200 kHz) concomitant with weekly paclitaxel for recurrent ovarian cancer-Updated safety and efficacy results. *Journal of clinical oncology. Conference: 2017 annual meeting of the american society of clinical oncology, ASCO. United states.* 2017;35(15 Supplement 1) (no pagination). http://cochranelibrary-wiley.com/o/cochrane/clcentral/articles/547/CN-01397547/frame.html. Exclusion code: X11.

53.   Vymazal J, Wong ET. Response Patterns of Recurrent Glioblastomas Treated With Tumor-Treating Fields. *Semin Oncol.*

2014;41:S14-S24. doi: 10.1053/j.seminoncol.2014.09.009. Exclusion code: X6.

54. Weinberg U, Fresard I, Kueng M. An open label pilot study of tumor treating fields (TTFields) in combination with pemetrexed for advanced non-small cell lung cancer (NSCLC). Paper presented at: 2010 ERS Annual Congress2010. Exclusion code: X11.

55. Wong ET, Lok E, Swanson KD. Clinical benefit in recurrent glioblastoma from adjuvant NovoTTF-100A and TCCC after temozolomide and bevacizumab failure: a preliminary observation. *Cancer Medicine.* 2015;4(3):383-391. doi: 10.1002/cam4.421. Exclusion code: X5.

56. Wong ET, Lok E, Swanson KD. An Evidence-Based Review of Alternating Electric Fields Therapy for Malignant Gliomas. *Curr Treat Options Oncol.* 2015;16(8):40. PMID: 26143265. doi: 10.1007/s11864-015-0353-5. Exclusion code: X7.

57. Wong ET, Phung M, Barron L, Lok E. NTCT-12 Updated Safety Analysis of Bevacizumab Plus Alternative Electric Fields Therapy in Patient with Recurrent Malignant Gliomas. *Neuro Oncol.* 2015;17(Suppl 5):v174-v174. PMID: PMC4639111. doi: 10.1093/neuonc/nov226.12. Exclusion code: X11.

58. Wong ET, Ram Z, Gutin PH, Stupp R. Ot-09. Updated Survival Data Of The Phase III Clinical Trial Of NovoTTF-100a Versus Best Standard Chemotherapy For Recurrent Glioblastoma. *Neuro Oncol.* 2011;13(suppl_3):iii85–iii91. Exclusion code: X11.

59. Zhang I, Knisely JP. Tumor-Treating Fields-A Fundamental Change in Locoregional Management for Glioblastoma. *JAMA Oncol.* 2016;2(6):813-814. PMID: 26986446. doi: 10.1001/jamaoncol.2016.0081. Exclusion code: X3.

60. Zhu JJ, Demireva P, Kanner AA, et al. Health-related quality of life, cognitive screening, and functional status in a randomized phase III trial (EF-14) of tumor treating fields with temozolomide compared to temozolomide alone in newly diagnosed glioblastoma. *J Neurooncol.* 2017;135(3):545-552. PMID: 28849310. doi: 10.1007/s11060-017-2601-y. Exclusion code: X12.

61. Zhu J-J, Pannullo S, Mehdorn M, et al. ATCT-35 quality of life, cognitive function and functional status in the EF-14 trial: A prospective, multi-center trial of ttfields with temozolomide compared to temozolomide alone in patients with newly diagnosed GBM. *Neuro Oncol.* 2015;17(Suppl 5):v9. Exclusion code: X11.

62. Zhu P, Zhu JJ. Tumor treating fields: a novel and effective therapy for glioblastoma: mechanism, efficacy, safety and future perspectives. *Chin Clin Oncol.* 2017;6(4):41. PMID: 28841803. doi: 10.21037/cco.2017.06.29. Exclusion code: X7.

Appendix F. Individual Study Risk of Bias Assessments

Table F-1.   Randomized control trial risk of bias ratings — Overall rating and randomization process

Study Author(s) (Year(s)) Study Name Indication Outcome(s)	Overall Bias		Randomization Process Bias				
	Overall Risk of Bias Rating	Overall Rationale for Risk of Bias Rating	Was the allocation sequence random?	Was allocation sequence concealed until participants were recruited and assigned to interventions?	Were there baseline imbalances that suggest a problem with the randomization process?	Bias arising from randomization or selection?	Comments
Stupp (2017)[25] EF-14 New GBM OS, PFS, Safety	Some concerns	39 patients in G1 and 14 patients in G2 were lost to follow up (8% total), primarily due to withdrawing consent. Only crossover was from G2 (TMZ) to G1 (TTF+TMZ); the 26 patients (11%) who crossed over had more favorable baseline characteristics than the rest of G2 (KPS 80-100; 31 days between radiotherapy and randomization; received more cycles of TMZ, median 10.5). Crossover occurred after December 2014/when interim results were released. There are some concerns that some harms may not have been captured and that harms among the 26 patients who crossed over may have biased.	Yes	No information	No	Low	Authors do not report on whether allocation sequence was concealed until randomization. Note that that Zhu (2017)[87] (interim HRQoL analysis) reports that the randomization was performed through a central web-based system, suggesting allocation may have been concealed.

(continued)

Table F-1.   Randomized control trial risk of bias ratings — Overall rating and randomization process (continued)

Study Author(s) (Year(s)) Study Name Indication Outcome(s)	Overall Bias		Randomization Process Bias				
	Overall Risk of Bias Rating	Overall Rationale for Risk of Bias Rating	Was the allocation sequence random?	Was allocation sequence concealed until participants were recruited and assigned to interventions?	Were there baseline imbalances that suggest a problem with the randomization process?	Bias arising from randomization or selection?	Comments
Taphoorn (2018)[26] EF-14 New GBM HRQoL	High	See individual domains. The authors utilized appropriate analyses and performed sensitivity analyses and multiple comparison corrections to deal with the challenges of the data but there was substantial missing data and what was collected was self-reported quality of life data, which is highly subjective.	Yes	No information	No	Low	Authors do not report on whether allocation sequence was concealed until randomization. Note that Zhu (2017)[87] (interim HRQoL analysis) reports that the randomization was performed through a central web-based system, suggesting allocation may have been concealed.
Stupp (2012)[15] EF-11 Recurrent GBM OS, PFS, Safety	Some concerns	See individual domains. There are some concerns related to an imbalance between groups at baseline with respect to prior treatments and number of imbalances, differential adherence to assigned treatment (despite the use of intention-to-treat analyses), a lack of safety data) among the active control group, and self-reported safety data, which had the potential to be influenced by knowledge of treatment assignment.	Yes	No information	Probably yes	Some concerns	Randomization used random block sizes and was stratified by center and according to whether patients underwent surgery for recurrence prior to entry into the trial. No information was reported on allocation concealment methods prior to randomization. Authors do not report on how balanced the groups were at randomization. There were some imbalances between groups with respect to prior therapies. The TTF group had more multiple recurrences and less debulking at any stage and were more likely to have received TMZ during prior radiotherapy than the chemo group. It's not clear whether these were statistically significant or clinically meaningful differences. Prior therapy and number of recurrences (both related to prognosis/outcome) may be imbalanced between the two groups.

(continued)

Table F-1.   Randomized control trial risk of bias ratings — Overall rating and randomization process (continued)

Study Author(s) (Year(s)) Study Name Indication Outcome(s)	Overall Bias		Randomization Process Bias				
	Overall Risk of Bias Rating	Overall Rationale for Risk of Bias Rating	Was the allocation sequence random?	Was allocation sequence concealed until participants were recruited and assigned to interventions?	Were there baseline imbalances that suggest a problem with the randomization process?	Bias arising from randomization or selection?	Comments
Stupp (2012)[15] EF-11 Recurrent GBM QOL	High	A very small proportion of patients provided data for QOL at 3 months (i.e., 27%) and patient self-report of HRQoL outcomes may have been influenced by knowledge of the intervention that was received.	Yes	No information	Probably yes	Some concerns	Randomization used random block sizes and was stratified by center and according to whether patients underwent surgery for recurrence prior to entry into the trial. No information was reported on allocation concealment methods prior to randomization. Authors do not report on how balanced the groups were at randomization. There were some imbalances between groups with respect to prior therapies. The TTF group had more multiple recurrences and less debulking at any stage and were more likely to have received TMZ during prior radiotherapy than the chemo group. It's not clear whether these were statistically significant or clinically meaningful differences. Prior therapy and number of recurrences (both related to prognosis/outcome) may be imbalanced between the two groups.

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Table F-1.   Randomized control trial risk of bias ratings — Overall rating and randomization process (continued)

Study Author(s) (Year(s)) Study Name Indication Outcome(s)	Overall Bias		Randomization Process Bias				
	Overall Risk of Bias Rating	Overall Rationale for Risk of Bias Rating	Was the allocation sequence random?	Was allocation sequence concealed until participants were recruited and assigned to interventions?	Were there baseline imbalances that suggest a problem with the randomization process?	Bias arising from randomization or selection?	Comments
Kanner (2014)[30] Wong (2014)[29] Wong (2015)[31] EF-11 Recurrent GBM OS and PFS Subgroup Analyses	High	See individual domains.	Yes	No information	Probably yes	Some concerns	Randomization used random block sizes and was stratified by center and according to whether patients underwent surgery for recurrence prior to entry into the trial. No information was reported on allocation concealment methods prior to randomization. Authors do not report on how balanced the groups were at randomization. There were some imbalances between groups with respect to prior therapies. The TTF group had more multiple recurrences and less debulking at any stage and were more likely to have received TMZ during prior radiotherapy than the chemo group. It's not clear whether these were statistically significant or clinically meaningful differences. Prior therapy and number of recurrences (both related to prognosis/outcome) may be imbalanced between the two groups.

Abbreviations: GBM = glioblastoma multiforme; HRQoL = health-related quality of life; NA = not applicable; NR = not reported; OS = overall survival; PFS = progression-free survival; QOL = quality of life; TMZ = temozolomide; TTF = tumor treating fields.

Table F-2.   Randomized control trial risk of bias — Deviations from intended interventions

Study Author(s) (Year(s)) Study Name Indication Outcome(s)	Were the participants aware of their assigned intervention?	Were carers and trial personnel aware of participants' assigned intervention?	Were there deviations from the intended intervention beyond what would be expected in usual practice?	Were these deviations unbalanced between groups and likely to have affected the outcome?	Were any participants analyzed in a group different from the one they were assigned?	Was there potential for a substantial impact of analyzing participants in the wrong group?	Bias arising from deviations from intended interven-tions?	Comments
Stupp (2017)[25] EF-14 New GBM OS, PFS, Safety	Yes	Yes	Probably yes	Probably yes	No	NA	Some concerns	Open-label trial. ITT analysis. 10 patients in G1 (2%) and 13 patients in G2 (6%) withdrew consent after randomization. 39 patients in G1 and 14 patients in G2 were lost to follow up, primarily due to withdrawing consent. Only crossover was from G2 (TMZ) to G1 (TTF+TMZ); the 26 patients (11%) who crossed over had more favorable baseline characteristics than the rest of G2 (KPS 80-100; 31 days between radiotherapy and randomization; received more cycles of TMZ, median 10.5). Crossover occurred after December 2014/when interim results were released. 75% of patients (n=347) achieved treatment adherence of 75% or more (i.e., used the device for ≥18 hours per day); 26/229 (11%) patients randomized to TMZ crossed over to receive TTF after the interim results were released. In a patient population this ill, it is not surprising that patients withdrew consent/were lost to follow up and some G2 patients crossed over to the experimental treatment (received by G1), especially given the positive interim results that were published. Patients were censored for progression when treatment was changed before evidence of progression (at the date of treatment change), at the date of their last MRI if LTF, or upon reaching the cutoff date without progression. Primary efficacy analysis was ITT. Most randomized patients (97%) contributed to the safety analysis.

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Table F-2.   Randomized control trial risk of bias — Deviations from intended interventions (continued)

Study Author(s) (Year(s)) Study Name Indication Outcome(s)	Were the participants aware of their assigned intervention?	Were carers and trial personnel aware of participants' assigned intervention?	Were there deviations from the intended intervention beyond what would be expected in usual practice?	Were these deviations unbalanced between groups and likely to have affected the outcome?	Were any participants analyzed in a group different from the one they were assigned?	Was there potential for a substantial impact of analyzing participants in the wrong group?	Bias arising from deviations from intended interven-tions?	Comments
Taphoorn (2018)[26] EF-14 New GBM HRQoL	Yes	Yes	Probably yes	Probably yes	No	NA	Some concerns	Open-label trial. ITT analysis. 10 patients in G1 (2%) and 13 patients in G2 (6%) withdrew consent after randomization. 39 patients in G1 and 14 patients in G2 were lost to follow up, primarily due to withdrawing consent. Only crossover was from G2 (TMZ) to G1 (TTF+TMZ); the 26 patients (11%) who crossed over had more favorable baseline characteristics than the rest of G2 (KPS 80-100; 31 days between radiotherapy and randomization; received more cycles of TMZ, median 10.5). Crossover occurred after December 2014/when interim results were released. 75% of patients (n=347) achieved treatment adherence of 75% or more (i.e., used the device for ≥18 hours per day); 26/229 (11%) patients randomized to TMZ crossed over to receive TTF after the interim results were released. In a patient population this ill, it is not surprising that patients withdrew consent/were lost to follow up and some G2 patients crossed over to the experimental treatment (received by G1), especially given the positive interim results that were published.

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Table F-2. **Randomized control trial risk of bias — Deviations from intended interventions (continued)**

Study Author(s) (Year(s)) Study Name Indication Outcome(s)	Were the participants aware of their assigned intervention?	Were carers and trial personnel aware of participants' assigned intervention?	Were there deviations from the intended intervention beyond what would be expected in usual practice?	Were these deviations unbalanced between groups and likely to have affected the outcome?	Were any participants analyzed in a group different from the one they were assigned?	Was there potential for a substantial impact of analyzing participants in the wrong group?	Bias arising from deviations from intended interven-tions?	Comments
Stupp (2012)[15] EF-11 Recurrent GBM OS, PFS, Safety	Yes	Yes	Yes	Probably yes	No	NA	Some concerns	The patients randomized to the TTF group discontinued treatment early, usually due to noncompliance or inability to handle the device. There is potential that noncompliance/inability to handle the device is related to prognosis/outcome. The noncompliance/lack of adherence was almost entirely among the group receiving TTF. Only 78% of TTF patients (93/120) while 96% of chemo patients (112/117) completed at least one course of treatment. Lack of adherence treatment is differentially limited to the group receiving TTF.
Stupp (2012)[15] EF-11 Recurrent GBM QOL	Yes	Yes	Yes	Probably yes	No	NA	Some concerns	The patients randomized to the TTF group discontinued treatment early, usually due to noncompliance or inability to handle the device. There is potential that noncompliance/inability to handle the device is related to prognosis/outcome. The noncompliance/lack of adherence was almost entirely among the group receiving TTF. Only 78% of TTF patients (93/120) while 96% of chemo patients (112/117) completed at least one course of treatment. Lack of adherence treatment is differentially limited to the group receiving TTF.

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Table F-2.   Randomized control trial risk of bias — Deviations from intended interventions (continued)

Study Author(s) (Year(s)) Study Name Indication Outcome(s)	Were the participants aware of their assigned intervention?	Were carers and trial personnel aware of participants' assigned intervention?	Were there deviations from the intended intervention beyond what would be expected in usual practice?	Were these deviations unbalanced between groups and likely to have affected the outcome?	Were any participants analyzed in a group different from the one they were assigned?	Was there potential for a substantial impact of analyzing participants in the wrong group?	Bias arising from deviations from intended interven-tions?	Comments
Kanner (2014[30] Wong (2014)[29] Wong (2015)[31] EF-11 Recurrent GBM OS and PFS Subgroup Analyses	Yes	Yes	Yes	Probably yes	No	NA	High	The patients randomized to the TTF group discontinued treatment early, usually due to noncompliance or inability to handle the device. There is potential that noncompliance/inability to handle the device is related to prognosis/outcome. The noncompliance/lack of adherence was almost entirely among the group receiving TTF. Only 78% of TTF patients (93/120) while 96% of chemo patients (112/117) completed at least one course of treatment. One subgroup analysis (a mITT analysis) is among adherent patients and is likely biased due to the differential adherence between groups. One of the subgroup analyses was a modified ITT analysis that only included patients who were randomized and adhered to the treatment.

Abbreviations: GBM = glioblastoma multiforme; HRQoL = health-related quality of life; ITT = intent to treat; mITT = modified intent to treat; NA = not applicable; OS = overall survival; PFS = progression-free survival; QOL = quality of life; TMZ = temozolomide; TTF = tumor treating fields.

Table F-3.   Randomized control trial risk of bias — Missing outcome data

Study Author(s) (Year(s)) Study Name Indication Outcome(s)	Were outcome data available for all, or nearly all, participants randomized?	Are the proportions of missing outcome data and reasons for missing outcome data similar across intervention groups?	Is there evidence that results were robust to the presence of missing outcome data?	Bias arising from missing outcome data?	Comments
Stupp (2017)[25] EF-14 New GBM OS, PFS, Safety	Probably yes	NA	NA	Low	76 patients (11%) withdrew consent or were lost to follow up. Analyses of the efficacy endpoints were done as ITT; the analysis of safety endpoints was performed on most randomized patients (97%).
Taphoorn (2018)[26] EF-14 New GBM HRQoL	No	Probably yes	Probably yes	Some concerns	639 of 695 randomized patients completed at least one HRQoL at baseline (94% of G1 and 88% of G2). Completion rate of HRQoL decreased at each follow-up timepoint (3, 6, 9, and 12 months); adherence was 92% at baseline, 66% at 3 months, and 42% at 12 months. Decrease in adherence over time was similar between G1 and G2, both among patients alive at each timepoint and among patients who were alive and progression-free. Baseline: Demographics of patients who completed the baseline HRQoL were similar to those of the ITT population and were balanced between groups. Authors noted that their mixed-model analyses accounted for missing data and confirmed the results found in the mean change from baseline analyses; the sensitivity analysis used multiple imputation among complete cases to check the robustness of the treatment effect over time. There is substantial missing data over time. While not surprising given the general prognosis of GBM, the data that are available represent the healthier patients with longer survival. There isn't a clear indication that missing data was differential between groups and authors note their mixed-model analyses.
Stupp (2012)[15] EF-11 Recurrent GBM OS, PFS, Safety	No	No	Probably yes	Some concerns	Data for the primary endpoint of OS were relatively complete; only 3% and 4% of the TTF and active control groups, respectively, were lost to survival follow up. Safety data were not available on a substantial proportion of patients in the active control group. Much higher loss to follow up in G2 for safety outcomes.

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Table F-3.   Randomized control trial risk of bias — Missing outcome data (continued)

Study Author(s) (Year(s)) Study Name Indication Outcome(s)	Were outcome data available for all, or nearly all, participants randomized?	Are the proportions of missing outcome data and reasons for missing outcome data similar across intervention groups?	Is there evidence that results were robust to the presence of missing outcome data?	Bias arising from missing outcome data?	Comments
Stupp (2012)[15] EF-11 Recurrent GBM QOL	No	No information	No information	High	QOL data were only available for patients who remained on study therapy for 3+ months and for whom QOL data were available; this was only on 27% of the patients overall (30% in G1 and 23% in G2). Availability of QOL was equally low in both groups; however, reasons for missing data were not described so it's unclear whether the missingness was related to therapy discontinuation or missing QOL data. No sensitivity analyses were reported.
Kanner (2014)[30] Wong (2014)[29] Wong (2015)[31] EF-11 Recurrent GBM OS and PFS Subgroup Analyses	Yes	NA	NA	Low	Data for the primary endpoint of OS was relatively complete; only 3% and 4% of the TTF and active control groups, respectively, were lost to survival follow up.

Abbreviations: GBM = glioblastoma multiforme; HRQoL = health-related quality of life; ITT = intent to treat; NA = not applicable; OS = overall survival; PFS = progression-free survival; QOL = quality of life; TTF = tumor treating fields.

Table F-4. Randomized control trial risk of bias — Measurement of the outcome

Study Author(s) (Year(s)) Study Name Indication Outcome(s)	Were outcome assessors aware of the intervention received by study participants?	Was the assessment of the outcome likely to be influenced by knowledge of intervention received?	Bias arising from measurement of the outcome?	Comments
Stupp (2017)[25] EF-14 New GBM OS, PFS, Safety	No	NA	Low	MRIs were reviewed by two blinded central independent radiologists and were evaluated for tumor response and progression according to the Macdonald criteria. A third blinded radiologist adjudicated disagreements.
Taphoorn (2018)[26] EF-14 New GBM HRQoL	Yes	Probably yes	High	HRQoL data were self-reported by patients, who knew which group they were allocated to. There is a possibility that knowledge of group assignment influenced self-report. Adherence and results were similar between groups, however. Authors did not discuss the potential effect of non-blinding on the results.
Stupp (2012)[15] EF-11 Recurrent GBM OS, PFS, Safety	Probably yes	Probably yes	Some concerns	Unclear how overall survival was ascertained. Tumor response and progression were ascertained by blinded radiology review. Safety was self-reported by patient who knew the intervention they received. Safety results have the potential to be influenced by knowledge of intervention; OS and PFS outcomes were not likely influenced. Safety results have the potential to be influenced by knowledge of intervention; OS and PFS outcomes were not likely influenced.
Stupp (2012)[15] EF-11 Recurrent GBM QOL	Yes	Probably yes	High	Patient self-report. It is conceivable that knowledge of assigned intervention influenced patient self-reported outcomes related to HRQoL.

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Table F-4.   Randomized control trial risk of bias — Measurement of the outcome (continued)

Study Author(s) (Year(s)) Study Name Indication Outcome(s)	Were outcome assessors aware of the intervention received by study participants?	Was the assessment of the outcome likely to be influenced by knowledge of intervention received?	Bias arising from measurement of the outcome?	Comments
Kanner (2014([30] Wong (2014)[29] Wong (2015)[31] EF-11 Recurrent GBM OS and PFS Subgroup Analyses	Probably no	Probably no	Some concerns	Unclear how overall survival was ascertained but it is an objective measure so unlikely to be biased. Tumor response and progression were ascertained by blinded radiology review.

Abbreviations: GBM = glioblastoma multiforme; HRQoL = health-related quality of life; MRI = magnetic resonance imaging; NA = not applicable; OS = overall survival; PFS = progression-free survival; QOL = quality of life.

Table F-5.   Randomized control trial risk of bias — Selection of the reported result

Study Author(s) (Year(s)) Study Name Indication Outcome(s)	Are the reported outcome data likely to have been selected on the basis of results from multiple outcome measurements within the outcome domain?	Are the reported outcome data likely to have been selected on the basis of results from multiple analyses of the data?	Bias arising from selection of reported results?	Comments
Stupp (2017)[25] EF-14 New GBM OS, PFS, Safety	No	Probably no	Low	Interim analysis was preplanned; final analysis is consistent with the interim analysis.
Taphoorn (2018)[26] EF-14 New GBM HRQoL	Yes	Probably no	Some concerns	Authors analyzed 9 preselected HRQoL subscales at multiple timepoints (baseline, 3, 6, 9, and 12 months). Authors preselected the subscales and timepoints and used the Hochberg procedure to adjust for multiple comparisons.
Stupp (2012)[15] EF-11 Recurrent GBM OS, PFS, Safety	No	No	Low	None.
Stupp (2012)[15] EF-11 Recurrent GBM QOL	Yes	No	High	Prespecified, multiple subdomains and symptom scales from the QOL questionnaire between two timepoints (baseline and 3 months). Analysis of the HRQoL outcomes are unadjusted. Authors do not mention the use of a multiple comparison adjustment.

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Table F-5.   Randomized control trial risk of bias — Selection of the reported result (continued)

Study Author(s) (Year(s)) Study Name Indication Outcome(s)	Are the reported outcome data likely to have been selected on the basis of results from multiple outcome measurements within the outcome domain?	Are the reported outcome data likely to have been selected on the basis of results from multiple analyses of the data?	Bias arising from selection of reported results?	Comments
Kanner (2014([30] Wong (2014)[29] Wong (2015)[31] EF-11 Recurrent GBM OS and PFS Subgroup Analyses	No	Yes	High	Substantial number of subgroup analyses. One set of subgroup analyses were limited to the randomized patients who adhered to treatment (and were then analyzed as responders and nonresponders to treatment). Substantial number of post-hoc subgroup analyses.

Abbreviations: GBM = glioblastoma multiforme; HRQoL = health-related quality of life; OS = overall survival; PFS = progression-free survival; QOL = quality of life.

Table F-6.   Observational study risk of bias — Overall rating

Study Author(s) (Year(s)) Study Name Indication Outcome(s)	Overall Risk of Bias Rating	Overall Rationale for Risk of Bias Rating
Kirson (2009)[27] NA New GBM OS, PFS	High	There is very little information for the comparator groups and the intervention group is very small because the study was a pilot trial.
Mrugala (2014)[9] PRiDe Recurrent GBM OS, Compliance, Safety	Some concerns (OS) to high (safety)	For the most part, results are reported for the intervention group only; the study design is more akin to a single-arm cohort study/large case series. The comparator groups from the EF-11 trial only contribute to the OS analysis as a qualitative point of comparison. The intervention group consisted of more patients with their first recurrence than the comparator groups from the EF-11 trial; comparing the OS results among the groups may be misleading due to differences between the groups at baseline and the fact that the intervention group is real-world data and the comparator groups are ITT/trial data. Safety outcomes are self-reported for the intervention and NR for the comparator groups. Harms outcomes are participant self-reported from trial registry data.
Kesari (2017)[32] NA Recurrent GBM OS	High	Selection of patients from initial trial into this post-hoc analysis/prospective cohort at time of first progression was not described and only approximately half of eligible patients continued to receive second line treatment, with or without TTF; those that elected to continue may have had a better prognosis than those who did not continue. 13 patients crossed over to the group receiving TTF so prior treatment history between the groups is heterogeneous. Analyses are unadjusted.
Kirson (2007)[33] NA Recurrent GBM OS, PFS, Safety	High	There is very little information for the historical comparator groups and the intervention group is very small because the study was a pilot trial. Safety outcomes are self-reported and likely to be influenced by knowledge of the intervention received.

Abbreviations: GBM = glioblastoma multiforme; NR = not reported; OS = overall survival; PFS = progression-free survival; PRiDe = Patient Registry Dataset; TTF = tumor treating fields.

Table F-7.   Observational study risk of bias — Confounding

Study Author(s) (Year(s)) Study Name Indication Outcome(s)	Is there potential for confound-ing of the effect of interven-tion?	Was the analysis based on splitting participants' follow-up time according to intervention?	Were intervention discon-tinuations or switches likely related to factors prognostic for the outcome?	Did the authors use appropriate analyses method that controlled for all the important confounding domains?	Were confounding domains measured validly and reliably by the variables available?	Did the authors control for any post-intervention variables that could have been affected by the intervention?	Did the authors use appropriate analyses that adjusted for all important confounding domains and time varying confounding?	Were confounding domains adjusted for measured validly and reliably by the variables available?	Overall bias due to con-founding	Comments
Kirson (2009)[27] NA New GBM OS, PFS	Probably yes	No	NA	No	NA	No	No	NA	High	The authors did not control for any potential confounders, especially when making qualitative comparisons with the comparator groups.
Mrugala (2014)[9] PRiDe Recurrent GBM OS, Compliance, Safety	Yes	No	NA	No	Probably yes	Yes	No	NA	High	Survival analyses were unadjusted but compared between the intervention and comparator groups despite baseline differences between groups with respect to number of recurrences and prior treatments. Authors did stratify analyses among the intervention group on potential confounders related to disease history and compliance, but without the same analysis performed in the comparator groups, the potential for confounding remains high. Safety outcomes were reported for only the intervention group.

(continued)

Table F-7.   Observational study risk of bias — Confounding (continued)

Study Author(s) (Year(s)) Study Name Indication Outcome(s)	Is there potential for confound-ing of the effect of interven-tion?	Was the analysis based on splitting participants' follow-up time according to intervention?	Were intervention discon-tinuations or switches likely related to factors prognostic for the outcome?	Did the authors use appropriate analyses method that controlled for all the important confounding domains?	Were confounding domains measured validly and reliably by the variables available?	Did the authors control for any post-intervention variables that could have been affected by the intervention?	Did the authors use appropriate analyses that adjusted for all important confounding domains and time varying confounding?	Were confounding domains adjusted for measured validly and reliably by the variables available?	Overall bias due to con-founding	Comments
Kesari (2017)[32] NA Recurrent GBM OS	Yes	Yes	Yes	No information	No information	No information	No information	No information	High	Patients were initially randomized into TTF + chemo or chemo only groups. At first recurrence, 13 patients in the chemo only group crossed over to the TTF + second line tx group; this was not accounted for in the analysis in any way (though, the groups were generally balanced on a number of factors). The groups, however, were heterogeneous for prior treatment history. Second-line treatment was based on local practice and was not controlled for. Survival analyses appear to be unadjusted; authors did not describe any methods utilized for addressing confounding.

(continued)

Table F-7.   Observational study risk of bias — Confounding (continued)

Study Author(s) (Year(s)) Study Name Indication Outcome(s)	Is there potential for confounding of the effect of intervention?	Was the analysis based on splitting participants' follow-up time according to intervention?	Were intervention discontinuations or switches likely related to factors prognostic for the outcome?	Did the authors use appropriate analyses method that controlled for all the important confounding domains?	Were confounding domains measured validly and reliably by the variables available?	Did the authors control for any post-intervention variables that could have been affected by the intervention?	Did the authors use appropriate analyses that adjusted for all important confounding domains and time varying confounding?	Were confounding domains adjusted for measured validly and reliably by the variables available?	Overall bias due to con-founding	Comments
Kirson (2007)[33] NA Recurrent GBM OS, PFS, Safety	Probably yes	No	NA	No	NA	No	No	NA	High	The authors did not control for any potential confounders, especially when making qualitative comparisons with the multiple historical comparator groups

Abbreviations: GBM = glioblastoma multiforme; NA = not applicable; OS = overall survival; PFS = progression-free survival; PRiDe = Patient Registry Dataset; TTF = tumor treating fields; tx = treatment.

Table F-8.   Observational study risk of bias — Selection of participants into the study

Study Author(s) (Year(s)) Study Name Indication Outcome(s)	Was selection of participants into the study based on participant characteristics observed after the start of intervention?	Were the post-intervention variables that influenced selection likely associated with the intervention?	Were the post-intervention variables that influenced selection likely influenced by the outcome or a cause of the outcome?	Do start of follow up and start of intervention coincide for most participants?	Were adjustment techniques used that likely correct for selection biases?	Overall bias in selection of participants into the study	Comments
Kirson (2009)[27] NA New GBM OS, PFS	Probably no	NA	NA	Probably yes	NA	Some concerns	No information on the selection of patients in the comparator groups. Selection of patients into the intervention group was appropriate.
Mrugala (2014)[9] PRiDe Recurrent GBM OS, Compliance, Safety	Probably no	NA	NA	Probably yes	NA	Some concerns	PRiDe registry data includes all patients in U.S. receiving TTF therapy so selection is not likely to be an issue. No information is provided about patient selection into the EF-11 trial (comparator groups). There are baseline differences between the groups with respect to disease history (see confounding domain). The PRiDe registry represents real-world data compared to the data from an RCT (trial), which is highly selective.
Kesari (2017)[32] NA Recurrent GBM OS	Yes	Yes	Yes	No	No information	High	Only 50% of TTF + chemo patients and 60% of chemo only patients who experienced a first recurrence continued to receive either TTF + second line tx or second line treatment only. Of those in the second line treatment group, 13 crossed over to the TTF + second line tx group. The authors don't provide any explanation for the substantial number of patients in both groups that were eligible to continue but didn't. It is very likely that continuation was related to prognosis/outcome.

(continued)

Table F-8.   Observational study risk of bias — Selection of participants into the study (continued)

Study Author(s) (Year(s)) Study Name Indication Outcome(s)	Was selection of participants into the study based on participant characteristics observed after the start of intervention?	Were the post-intervention variables that influenced selection likely associated with the intervention?	Were the post-intervention variables that influenced selection likely influenced by the outcome or a cause of the outcome?	Do start of follow up and start of intervention coincide for most participants?	Were adjustment techniques used that likely correct for selection biases?	Overall bias in selection of participants into the study	Comments
Kirson (2007)[33] NA Recurrent GBM OS, PFS, Safety	Probably no	NA	NA	Probably yes	NA	Some concerns	No information on the selection of patients in the historical comparator groups. Selection of patients into the intervention group was appropriate.

Abbreviations: GBM = glioblastoma multiforme; NA = not applicable; OS = overall survival; PFS = progression-free survival; PRiDe = Patient Registry Dataset; RCT = randomized controlled trial; TTF = tumor treating fields; tx = treatment; U.S. = United States.

Table F-9.   Observational study risk of bias — Classification of intervention

Study Author(s) (Year(s)) Study Name Indication Outcome(s)	Were intervention groups clearly defined?	Was the information used to define intervention groups recorded at the start of the intervention?	Could classification of intervention status have been affected by knowledge of the outcome or risk of the outcome?	Overall bias in classification of intervention	Comments
Kirson (2009)[27] NA New GBM OS, PFS	No information	No information	Probably no	Some concerns	There is very little information on the interventions in the comparator groups.
Mrugala (2014)[9] PRiDe Recurrent GBM OS, Compliance, Safety	Yes	Probably yes	Probably no	Low	None.
Kesari (2017)[32] NA Recurrent GBM OS	Yes	Yes	No	Low	None.
Kirson (2007)[33] NA Recurrent GBM OS, PFS, Safety	No information	No information	Probably no	Some concerns	There is very little information on the interventions in the historical comparator groups.

Abbreviations: GBM = glioblastoma multiforme; NA = not applicable; OS = overall survival; PFS = progression-free survival; PRiDe = Patient Registry Dataset.

Table F-10. Observational study risk of bias — Deviation from intended intervention

Study Author(s) (Year(s)) Study Name Indication Outcome(s)	Were there deviations from the intended intervention beyond what would be expected in usual practice?	Were these deviations from intended intervention unbalanced between groups and likely to have affected the outcome?	Overall bias due to deviation from intended intervention	Comments
Kirson (2009)[27] NA New GBM OS, PFS	No information	No information	Some concerns	There were no deviations from TTF in the intervention group; no information was provided on the comparator groups.
Mrugala (2014)[9] PRiDe Recurrent GBM OS, Compliance, Safety	No information	No information	Some concerns	Compliance data for the TTF patients were only collected for 63% of the patients in the registry and no compliance data were reported for the comparator groups. For the TTF patients, compliance was approximately 70%, which may be lower than ideal but probably not unexpected in this patient population (i.e., very ill patients). Compliance is likely to be related to the outcomes studied.
Kesari (2017)[32] NA Recurrent GBM OS	Yes	Yes	High	18% of patients with first recurrence who were to receive second line therapy crossed over and received TTF + second line tx. No patients from the TTF + chemo group crossed-over/discontinued use of TTF. Given the interim results of the trial and the fact that this is a very ill patient population, it's not unexpected that 18% of patients elected to try TTF. However, the groups are unbalanced due to the crossover and there is a potential for the bias to favor the second line treatment group since the TTF + second line tx group now contains a number of patients who did not initially receive TTF.
Kirson (2007)[33] NA Recurrent GBM OS, PFS, Safety	No information	No information	Some concerns	There were no deviations from TTF in the intervention group; no information was provided on the historical comparator groups.

Abbreviations: GBM = glioblastoma multiforme; NA = not applicable; OS = overall survival; PFS = progression-free survival; PRiDe = Patient Registry Dataset; TTF = tumor treating fields; tx = treatment.

Table F-11.   Observational study risk of bias — Missing data

Study Author(s) (Year(s)) Study Name Indication Outcome(s)	Were outcome data available for all, or nearly all, participants?	Were participants excluded due to missing data on intervention status?	Were participants excluded due to missing data on other variables needed for the analysis?	Are the proportion of participants and reasons for missing data similar across interventions?	Is there evidence that results were robust to the presence of missing data?	Overall bias due to missing data	Comments
Kirson (2009)[27] New GBM NA OS, PFS	No information	No information	No information	No information	No information	Some concerns	Missing data is not a problem in the intervention group; no information is provided on the missingness of data in the comparator groups.
Mrugala (2014)[9] PRiDe Recurrent GBM OS, Compliance, Safety	No information	Probably no	Probably no	No information	No information	Some concerns	Very little information provided about the presence of or potential for missing data. It's unlikely that patients were excluded for missing intervention status and since analyses are unadjusted, it is unlikely that patients were excluded because of other missing data. However, safety data is self-reported and it is not known how many adverse events occurred without being reported. No information is reported for the comparator groups.
Kesari (2017)[32] NA Recurrent GBM OS	Probably yes	No	No	NA	NA	Low	None.
Kirson (2007)[33] NA Recurrent GBM OS, PFS, Safety	No information	No information	No information	No information	No information	Some concerns	Missing data is not a problem in the intervention group; no information is provided on the missingness of data in the historical comparator groups.

Abbreviations: GBM = glioblastoma multiforme; NA = not applicable; OS = overall survival; PRiDe = Patient Registry Dataset; PFS = progression-free survival.

Table F-12. Observational study risk of bias — Measurement of outcomes

Study Author(s) (Year(s)) Study Name Indication Outcome(s)	Could the outcome measure have been influenced by knowledge of the intervention received?	Were outcome assessors aware of the intervention received by study participants?	Were the methods of outcome assessment comparable across intervention groups?	Were any systematic errors in measurement of the outcome related to intervention received?	Overall bias in measurement of outcomes	Comments
Kirson (2009)[27] NA New GBM OS, PFS	Probably no	Yes	No information	No information	High	It is unlikely that OS and PFS were influenced by knowledge of the intervention received, but very few details are presented.
Mrugala (2014)[9] PRiDe Recurrent GBM OS, Compliance, Safety	Probably no	Yes	No information	No information	Some concerns	The survival outcome is unlikely to be affected by knowledge of the intervention; no information is provided for the comparator groups but OS data for the intervention group was ascertained from the Social Security Death Date Registry and obituaries. Safety outcomes were self-reported for intervention group and possibly influenced by knowledge of the intervention; no safety data were provided for the comparator groups.
Kesari (2017)[32] NA Recurrent GBM OS	No	No information	No information	Probably no	Low	Though authors do not describe their methods for obtaining overall survival data, it is unlikely that such an objective outcome would be biased or related to the intervention.
Kirson (2007)[33] NA Recurrent GBM OS, PFS, Safety	Probably no	Yes	No information	No information	High	It is unlikely that OS and PFS were influenced by knowledge of the intervention received, but very few details are presented. Safety data are self-reported in the intervention group and presumably self-reported, at least to an extent, in the historical comparator groups; again, very little information is presented. Self-report of safety outcomes may have been influenced by knowledge of the intervention received.

Abbreviations: GBM = glioblastoma multiforme; NA = not applicable; OS = overall survival; PFS = progression-free survival; PRiDe = Patient Registry Dataset.

Table F-13.   Observational study risk of bias — Selection of reported results

Study Author(s) (Year(s)) Study Name Indication Outcome(s)	Is the reported effect estimate likely to be selected, on the basis of the results, from multiple outcome measurements within the outcome domain?	Is the reported effect estimate likely to be selected, on the basis of the results, from multiple analyses of the intervention outcome relationship?	Is the reported effect estimate likely to be selected, on the basis of the results, from different subgroups?	Overall bias in selection of the reported result	Comments
Kirson (2009)[27] NA New GBM OS, PFS	No	No	No	Low	None.
Mrugala (2014)[9] PRiDe Recurrent GBM OS, Compliance, Safety	No	No	Probably no	Some concerns	Multiple subgroup analyses among the intervention group only; no correction for multiple comparisons.
Kesari (2017)[32] NA Recurrent GBM OS	No	No	No	Low	None.
Kirson (2007)[33] NA Recurrent GBM OS, PFS, Safety	No	No	No	Low	None.

Abbreviations: GBM = glioblastoma multiforme; NA = not applicable; OS = overall survival; PFS = progression-free survival; PRiDe = Patient Registry Dataset.

Table F-14.   Quality of health economic studies — Part 1

Study Author(s) (Year(s)) Study Name Indication Outcome(s)	Overall Quality Rating (Score[a])	Was the study objective presented in a clear, specific, and measurable manner?	Were the perspective of the analysis (societal, third-party payer, and so on) and reasons for its selection stated?	Were variable estimates used in the analysis from the best available source (i.e., Randomized Control Trial-Best, Expert Opinion-Worst)?	If estimates came from a subgroup analysis, were the groups pre-specified at the beginning of the study?	Was uncertainty handled by: (i) statistical analysis to address random events; (ii) sensitivity analysis to cover a range of assumptions?
Bernard-Arnoux (2016)[28] NA New GBM Cost, cost-effectiveness	Good (93)	Yes	Yes	Yes	NA	Yes

Abbreviations: GBM = glioblastoma multiforme; NA = not applicable.

[a] Based on scale of 0 (worst quality) to 100 (best quality).

Table F-15.   Quality of health economic studies — Part 2

Study Author(s) (Year(s)) Study Name Indication Outcome(s)	Was incremental analysis performed between alternatives for resources and costs?	Was the methodology for data abstraction (including value health states and other benefits) stated?	Did the analytic horizon allow time for all relevant and important outcomes? Were benefits and costs that went beyond 1 year discounted (3–5%) and justification given for the discount rate?	Was the measurement of costs appropriate and the methodology for the estimation of quantities and unit costs clearly described?	Was the primary outcome measure(s) for the economic evaluation clearly stated and were the major short-term, long-term and negative outcomes included?
Bernard-Arnoux (2016)[28] NA New GBM Cost, cost-effectiveness	Yes	Yes	Yes	Yes	Yes

Abbreviations: GBM = glioblastoma multiforme; NA = not applicable.

Table F-16.   Quality of health economic studies — Part 3

Study Author(s) (Year(s)) Study Name Indication Outcome(s)	Were the health outcomes measures/scales valid and reliable? If previously tested valid and reliable measures were not available, was justification given for the measures/scales used?	Were the economic model (including structure), study methods and analysis, and the components of the numerator and denominator displayed in a clear transparent manner?	Were the choice of economic model, main assumptions and limitations of the study stated and justified?	Did the author(s) explicitly discuss direction and magnitude of potential biases?	Were the conclusions/recommendations of the study justified and based on the study results?	Was there a statement disclosing the source of funding for the study?
Bernard-Arnoux (2016)[28] NA New GBM Cost, cost-effectiveness	Yes	Yes	Yes	No	Yes	Yes

Abbreviations: GBM = glioblastoma multiforme; NA = not applicable.