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Tumor Treating Fields (TTF) Therapy

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Related Policies (if applicable)
None

Disclaimer

Carefully check state regulations and/or the member contract.
Each benefit plan, summary plan description or contract defines which services are covered, which services are excluded, and which services are subject to dollar caps or other limitations, conditions or exclusions. Members and their providers have the responsibility for consulting the member's benefit plan, summary plan description or contract to determine if there are any exclusions or other benefit limitations applicable to this service or supply. **If there is a discrepancy between a Medical Policy and a member's benefit plan, summary plan description or contract, the benefit plan, summary plan description or contract will govern.**

Coverage

Tumor treating fields (TTF) therapy to treat glioblastoma multiforme (GBM) until disease progression **is considered medically necessary** as an adjunct to standard maintenance therapy with temozolomide in individuals with newly diagnosed GBM following maximal debulking surgery and completion of radiation therapy together with concomitant standard of care chemotherapy, under the following conditions:

- Individuals ≥18 years of age; and
- Supratentorial tumor; and
- Karnofsky Performance Status (KPS) score ≥60%; and
- Patient understands the device use, including the requirement for a shaved head, and is willing to comply with use criteria according to the U.S. Food and Drug Administration (FDA) label.

Tumor treating fields (TTF) therapy to treat glioblastoma multiforme (GBM) until disease progression **is considered medically necessary** as a monotherapy in individuals with recurrent

GBM following treatment with chemotherapy after surgical and radiation treatments have been exhausted, under the following conditions:

- Individuals ≥18 years of age; and
- Supratentorial tumor; and
- Karnofsky Performance Status (KPS) score ≥60%; and
- Patient understands the device use, including the requirement for a shaved head, and is willing to comply with use criteria according to the U.S. Food and Drug Administration (FDA) label.

Tumor treating fields therapy **is considered experimental, investigational and/or unproven** in all other conditions, including but not limited to the following situations:

- As an adjunct to standard medical therapy (e.g., bevacizumab, chemotherapy) for individuals with progressive (see **NOTE 2**) or recurrent glioblastoma multiforme; or
- As an adjunct to standard medical therapy (pemetrexed and platinum-based chemotherapy) for individuals with malignant pleural mesothelioma; or
- For brain metastases; or
- For cancer in areas other than the brain; or
- For use in individuals with an active implanted device (e.g., spinal cord stimulator, pacemaker, defibrillator, programmable shunt, stent, clips or coils, device leads, drug delivery reservoir); or
- For use in individuals with a skull defect (e.g., missing bone with no replacement); or
- For use in individuals with bullet fragments; or
- For use in individuals with known sensitivity to conductive hydrogels.

The use of treatment planning software (i.e., NovoTAL™) for use with TTFs for any indication **is considered experimental, investigational and/or unproven**.

Policy Guidelines

NOTE 1: The FDA label for the Optune® device includes the following notices:

- Individuals should use Optune for at least 18 hours a day to get the best response to treatment.
- Individuals should finish at least 4 full weeks of therapy to get the best response to treatment. Stopping treatment before 4 weeks lowers the chances of a response to treatment.

NOTE 2: Progression was defined in the EF-14 trial (Stup et al. [2015, 2017]) according to the MacDonald criteria (tumor growth >25% compared with the smallest tumor area measured in the individual during the trial OR appearance of 1 or more new tumors in the brain that are diagnosed radiologically as GBM).

Description

Glioblastoma Multiforme

Glioblastomas, also known as glioblastoma multiforme (GBM), are the most common form of malignant primary brain tumor in adults. (1) Glioblastomas are grade IV astrocytomas, a rapidly progressing and deadly type of glial cell tumor that is often resistant to standard medical therapy (e.g., bevacizumab, chemotherapy). Together, anaplastic astrocytomas and glioblastomas comprise approximately 49.1% of all primary malignant brain tumors. Mean age at GBM diagnosis is 65 years. Glioblastomas have the lowest survival rate of any central nervous system tumor; the 5-year survival rate and average length of survival is estimated at 6.9% and 8 months, respectively. (2)

Treatment of Newly Diagnosed Glioblastoma Multiforme

The primary treatment for patients newly diagnosed with GBM is to resect the tumor to confirm a diagnosis while debulking the tumor to relieve symptoms of increased intracranial pressure or compression. If total resection is not feasible, subtotal resection and open biopsy are options. During surgery, some patients may undergo implantation of the tumor cavity with a carmustine (bis-chloroethylnitrosourea) impregnated wafer. Due to the poor efficacy of local treatment, postsurgical treatment with adjuvant radiotherapy (RT), chemotherapy (typically temozolomide), or a combination of these 2 therapies is recommended. After adjuvant therapy, patients may undergo maintenance therapy with temozolomide. Maintenance temozolomide is given for 5 days of every 28-day cycle for 6 cycles. Response and overall survival rates with temozolomide are higher in patients who have O^6-methylguanine-DNA methyltransferase (*MGMT*) gene promoter methylation.

Prognostic factors for therapy success are age, histology, performance status or physical condition of the patient, and extent of resection. National Comprehensive Cancer Network recommendations include patient age and Karnofsky Performance Status score as important determinants of postsurgical treatment choice. (3) For patients with good performance status, the most aggressive treatment (standard RT plus temozolomide) is recommended. For patients with poor performance status, only single treatment cycles or even palliative or supportive care are recommended. Hypofractionated RT is indicated for patients with poor performance status because it is better tolerated, and more patients are able to complete RT.

Treatment of GBM is rarely curative, and tumors will recur in essentially all patients.

Treatment of Recurrent Glioblastoma Multiforme

When disease recurs, additional debulking surgery may be used if the recurrence is localized. Due to radiation tolerances, re-radiation options for patients with recurrent GBM who have previously received initial external-beam RT are limited. There is no standard adjunctive treatment for recurrent GBM. Treatment options for recurrent disease include various forms of systemic medications such as the antivascular endothelial growth factor drug bevacizumab, alkylating agents such as nitrosoureas (e.g., lomustine, carmustine), or retreatment with temozolomide. Medical therapy is associated with side effects that include hematologic toxicity, headache, loss of appetite, nausea, vomiting, and fatigue. Response rates in recurrent disease are less than 10%, and the progression-free survival rate at 6 months is less than 20%.

(4) There is a need for new treatments that can improve survival in patients with recurrent GBM or reduce the side effects of treatment while retaining survival benefits.

Malignant Pleural Mesothelioma
Malignant pleural mesothelioma (MPM) is an aggressive tumor that is associated with significant morbidity and mortality. It is associated with asbestos exposure and has a latency period of about 40 years after asbestos exposure. Recommendations for treatment are mainly chemotherapy as first line with pemetrexed plus platinum. Surgical cytoreduction is also recommended in selected patients with early-stage disease. Adjuvant radiation can be offered for patients who have resection of intervention tracts found to be histologically positive or for palliation of symptomatic patients.

Regulatory Status
In April 2011, the NovoTTF-100A™ System (Novocure; assigned the generic name of TTF) was approved by the U.S. Food and Drug Administration (FDA) through the premarket approval process. (5) The FDA approved label reads as follows: "The NovoTTF-100A System is intended as a treatment for adult patients (22 years of age or older) with confirmed GBM, following confirmed recurrence in an upper region of the brain (supratentorial) after receiving chemotherapy. The device is intended to be used as a stand-alone treatment and is intended as an alternative to standard medical therapy for recurrent GBM after surgical and radiation options have been exhausted."

In September 2014, the FDA approved Novocure's request for a product name change from NovoTTF-110A System to Optune®. (6)

In October 2015, the FDA expanded the indication for Optune in combination with temozolomide to include newly diagnosed GBM. (7) The device was granted priority review status in May 2015 because there was no legally marketed alternative device available for the treatment of newly diagnosed GBM, a life-threatening condition. In July 2016, a smaller, lighter version of the Optune device, called the Optune System (NovoTTF-200A System), received FDA approval.

The FDA-approved label for newly diagnosed GBM reads as follows: "This device is indicated as treatment for adult patients (22 years of age or older) with histologically-confirmed glioblastoma multiforme (GBM). Optune with temozolomide is indicated for the treatment of adult patients with newly diagnosed, supratentorial glioblastoma following maximal debulking surgery and completion of radiation therapy together with concomitant standard of care chemotherapy."

In May 2019, the FDA approved a modified version of the Optune System (NovoTTF-100A System), which is now called the Optune Lua® System (NovoTTF™-100L System), for "treatment of adult patients with unresectable, locally advanced or metastatic, malignant pleural mesothelioma (MPM) to be used concurrently with pemetrexed and platinum-based chemotherapy. The indication was modified from that granted for the Humanitarian Device

Exemption designation to more clearly identify the patient population the device is intended to treat and in which the safety and probable benefit of the device is supported by the available clinical data." (8)

In September 2021, the FDA granted breakthrough designation to the NovoTTF-200T System for use together with atezolizumab and bevacizumab for the first-line treatment of patients with unresectable or metastatic liver cancer. (9)

To date, all of the existing tumor treating fields products fall under the brand name Optune. In March 2020, the manufacturer of Optune products announced a plan to include a suffix after the brand name for newly approved indications to further delineate specific indications for individual products (e.g., Optune Lua). (10) Optune was renamed Optune Gio® in 2023. (11)

NovoTAL™

The NovoTAL™ (transducer array layout) system is optional simulation software for use in clinical treatment planning with Optune therapy that may be leased from the manufacturer. Its purpose is to determine the optimal location of the transducer arrays based on the patient's most recent magnetic resonance imaging (MRI) scan, head size, and tumor location.

Rationale

Medical policies assess the clinical evidence to determine whether the use of a technology improves the net health outcome. Broadly defined, health outcomes are length of life, quality of life, and ability to function including benefits and harms. Every clinical condition has specific outcomes that are important to patients and to managing the course of that condition. Validated outcome measures are necessary to ascertain whether a condition improves or worsens; and whether the magnitude of that change is clinically significant. The net health outcome is a balance of benefits and harms.

To assess whether the evidence is sufficient to draw conclusions about the net health outcome of a technology, 2 domains are examined: the relevance and the quality and credibility. To be relevant, studies must represent 1 or more intended clinical use of the technology in the intended population and compare an effective and appropriate alternative at a comparable intensity. For some conditions, the alternative will be supportive care or surveillance. The quality and credibility of the evidence depend on study design and conduct, minimizing bias and confounding that can generate incorrect findings. The randomized controlled trial (RCT) is preferred to assess efficacy; however, in some circumstances, nonrandomized studies may be adequate. Randomized controlled trials are rarely large enough or long enough to capture less common adverse events and long-term effects. Other types of studies can be used for these purposes and to assess generalizability to broader clinical populations and settings of clinical practice.

For this literature review, 3 indications are evaluated: 1) tumor treating fields (TTF) as an adjunct to maintenance chemotherapy in newly diagnosed glioblastoma multiforme (GBM) patients following initial treatment with surgery, radiotherapy (RT) and chemotherapy; 2) TTF as an adjunct or alternative to medical therapy (e.g., bevacizumab, chemotherapy) in progressive or recurrent GBM; and 3) as treatment of adult patients with unresectable, locally advanced or metastatic malignant pleural mesothelioma (MPM) to be used concurrently with pemetrexed and platinum-based chemotherapy.

Tumor Treating Fields Therapy as an Adjunct to Standard Maintenance Care for Newly Diagnosed Glioblastoma Multiforme

Clinical Context and Therapy Purpose

The purpose of TTF therapy, also referred to as alternating electrical field therapy, is to provide a treatment option that is an alternative to or an improvement on existing therapies for individuals with newly diagnosed GBM. Tumor treating fields therapy has been investigated as an adjunct to temozolomide for the treatment of newly diagnosed GBM and as an alternative or adjunct to medical therapy for progressive or recurrent GBM.

The following PICO was used to select literature to inform this policy.

Populations

The relevant populations of interest is individuals who have newly diagnosed GBM and good performance status. Newly diagnosed patients would have undergone initial treatment with surgery, RT, and chemotherapy and be receiving maintenance chemotherapy.

Interventions

Tumor treating fields therapy is a noninvasive technology intended to treat GBM on an outpatient basis and at home using electrical fields. (4, 12, 13) Tumor treating fields therapy exposes rapidly dividing cancer cells to electric fields of low intensity and intermediate frequency (200 kHz) that alternate in perpendicular orientation. Tumor treating fields therapy is proposed to inhibit tumor growth by 2 mechanisms: the arrest of cell proliferation by causing microtubule misalignment in the mitotic spindle of rapidly dividing tumor cells and apoptosis due to movement of macromolecules and organelles during telophase. (12, 13) Preclinical studies have indicated that the electric fields may also make the cells more susceptible to chemotherapy.

Optune branded products (formerly NovoTTF-100A System) are the only legally marketed TTF delivery system available in the United States. The portable, battery-powered device is carried in a backpack or shoulder pack while carrying out activities of daily living. For the treatment of glioblastoma, 4 disposable transducer arrays with insulated electrodes are applied to the patient's shaved head. The transducer array layout is typically determined using specialized software. The patient's scalp is re-shaved and the transducer arrays replaced twice a week by the patient, caregiver, or device technician. The device is worn for up to 24 hours a day for the duration of treatment, except for brief periods for personal hygiene and 2 to 3 days at the end

of each month. The minimum daily treatment is 18 hours. The minimum duration of treatment is 1 month, with the continuation of treatment available until recurrence.

Comparators
The following practice is currently being used to make decisions about newly diagnosed GBM: maintenance chemotherapy with temozolomide alone.

TTF therapy might also be compared with palliative or supportive care, where survival rarely exceeds 3 to 5 months. (4)

Outcomes
The general outcomes of interest are whether TTF improves survival or quality of life during treatment and the time to tumor recurrence because most GBMs recur. Measures of cognitive status and quality of life measures are also of interest to determine whether TTF alters the decline in cognition and quality of life that occur with GBM. Also, adverse events of treatment, such as side effects of chemotherapy and the possibility of seizures, need to be assessed.

Due to the rapid progression of GBM, the time of interest for both progression-free survival (PFS) and overall survival (OS) is months.

Study Selection Criteria

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs.
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Consistent with a "best available evidence approach," within each category of study design, studies with larger sample sizes and longera durations were sought.
- Studies with duplicative or overlapping populations were excluded.

Systematic Reviews

Regev et al. (2021) conducted a systematic review of studies describing the use of TTF therapy for the treatment of GBM. (14) The authors included a total of 20 studies of patients with newly diagnosed GBM and recurrent GBM. For newly diagnosed GBM (n=542), only 1 RCT was identified (Stupp et al., 2017), which is described in further detail in the section below. The remainder of the data for newly diagnosed GBM was observational. The pooled median OS and PFS in newly diagnosed patients was 21.7 months (95% confidence interval [CI], 19.6 to 23.8) and 7.2 months (95% CI, 6.1 to 8.2) months, respectively. The pooled rate of OS at 1, 2, and 3 years was 73.5%, 45.1%, and 29.3%, respectively. The pooled rate of PFS at 6, 12, and 18 months was 55.9%, 32.4%, and 21.7%, respectively. Statistical comparisons to other treatment modalities were not provided.

Randomized Controlled Trials

Stupp et al. (2017) published results of the EF-14 multicenter, open-label phase 3 RCT that evaluated maintenance therapy with TTF for newly diagnosed GBM. (15) The trial included 695 patients from 83 sites who had supratentorial GBM and had completed standard treatment consisting of biopsy or surgical resection followed by RT and chemotherapy (see Table 1). A Karnofsky Performance Status (KPS) score of 70 or higher was an additional inclusion criterion to ensure independence in activities of daily living, and patients with rapidly progressing GBM following radiochemotherapy were excluded from the trial. Patients were randomized in a 2:1 fashion to TTF plus maintenance temozolomide or maintenance temozolomide alone.

All patients were seen monthly for follow-up. Quality of life was assessed every 3 months, and magnetic resonance imaging (MRI) was performed every 2 months until tumor progression. Tumor progression on MRI was adjudicated by a central review committee blinded to treatment group. The primary outcome was PFS, and the secondary outcome was OS. The analysis was by intention-to-treat, including 26 patients from the control arm who crossed over to TTF following the planned interim analysis.

In 2014, an independent data and safety monitoring board concluded from the planned interim analysis that the trial met its predefined boundaries for success (improvement in PFS and OS) and recommended trial termination. The U.S. Food and Drug Administration (FDA) approved the trial termination, and the trial was closed to recruitment with 695 of the planned 700 participants randomized. Control arm participants were allowed to cross over to the experimental treatment at this time. The interim analysis, which the U.S. FDA considered for the 2015 expanded approval of Optune, was published by Stupp et al. (2015). (16) At the time of the interim analysis, data were available for 210 patients randomized to TTF plus temozolomide and 105 patients to temozolomide alone. Follow-up of the remainder of the 695 enrolled patients continued after enrollment was closed.

Table 1. Key Randomized Controlled Trial Characteristics for Newly Diagnosed Glioblastoma

Study; Trial	**Countries**	**Sites**	**Dates**	**Participants**	**Interventions**	
					Active	*Comparator*
Stupp et al. (2017) (15); EF-14	U.S., E.U., South Korea, Israel	83	2009-2016	• 695 newly diagnosed with GBM and treated by radiochemotherapy • KPS score ≥70	TTF >18 h/d plus maintenance temozolomide. (n=466)	Maintenance temozolomide alone (5 d every 28 d for 6 cycles) (n=229)

d: days; E.U.: European Union; GBM: glioblastoma multiforme; h/d: hours per day; KPS: Karnofsky Performance Status; TTF: tumor treatment fields; U.S.: United States.

Results of the final analysis of the EF-14 trial were similar to the interim analysis and are shown in Table 2. Both PFS and OS improved with the addition of TTF therapy to standard maintenance chemotherapy (i.e., temozolomide). PFS increased by 2.7 months (p<.001) and OS

increased by 4.9 months (p<.001) in the TTF group. The time to a decrease in mental function was 2.5 months longer with TTF therapy (p<.01).

There was a similar percentage of dropouts at the final analysis with 49 (11%) patients in the TTF group and 27 (12%) patients in the temozolomide alone group. More treatment cycles with temozolomide were administered in the TTF group (median, 6 for TTF group vs 5 for controls), a finding that is consistent with the longer PFS. Rates of adverse events were similar between the groups, including rates of seizures. In a secondary analysis of patients who had not progressed, there was no reduction in health-related quality of life with TTF compared with temozolomide alone aside from "itchy skin." (15) Interpretation of this result is limited by the low percentage of patients who completed the health-related quality of life assessments at follow-up (65.8% of the 655 patients alive at 3 months and 41.7% of the 473 patients alive at 12 months). A mixed-model analysis, which accounts for missing data, confirmed the results of the mean change from baseline analysis.

Table 2. Key Randomized Controlled Trial Results for Newly Diagnosed Glioblastoma

Study	Final N (%)	Median PFS (95% CI), months	Median OS (95% CI), months	Systemic Adverse Events, n (%)	Seizures, n (%)	Time to 6-Point Decline in MMSE Score (95% CI), months
Stupp et al. (2017) (15)						
TTF +temozolomide	417 (89)	6.7 (6.1 to 8.1)	20.9 (19.3 to 22.7)	218 (48)	26 (6)	16.7 (14.7 to 19.0)
Temozolomide alone	202 (88)	4.0 (3.8 to 4.4)	16.0 (14.0 to 18.4)	94 (44)	13 (6)	14.2 (12.7 to 17.0)
HR (95% CI)		0.63 (0.52 to 0.76)	0.63 (0.53 to 0.76)			0.79 (0.66 to 0.95)
p-value		<0.001	<0.001	0.58		0.01

CI: confidence interval; HR: hazard ratio; MMSE: Mini-Mental State Examination; OS: overall survival; PFS: progression-free survival; TTF: tumor treatment fields.

Tables 3 and 4 display notable limitations identified in this trial; a major limitation is the lack of patient blinding to treatment assignment. However, PFS was assessed by investigators who were blinded to treatment, and placebo effects on OS measurement were expected to be minimal. Investigators considered it practically unfeasible (due to the heat and current of the TTF therapy) and ethically unacceptable to submit the control patients to repeated shaving of the head and continuous wear of a sham device over many months.

Table 3. Study Relevance Limitations

Study; Trial	Population[a]	Intervention[b]	Comparator[c]	Outcomes[d]	Follow-Up[e]

Stupp et al. (2017) (15); EF-14			3. Possible differences in post-progression treatment affecting OS		

OS: overall survival.

The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.

[a] Population key: 1. Intended use population unclear; 2. Study population is unclear; 3. Study population not representative of intended use; 4, Enrolled populations do not reflect relevant diversity; 5. Other.

[b] Intervention key: 1. Not clearly defined; 2. Version used unclear; 3. Delivery not similar intensity as comparator; 4. Not the intervention of interest (e.g., proposed as an adjunct but not tested as such); 5: Other.

[c] Comparator key: 1. Not clearly defined; 2. Not standard or optimal; 3. Delivery not similar intensity as intervention; 4. Not delivered effectively; 5. Other.

[d] Outcomes key: 1. Key health outcomes not addressed; 2. Physiologic measures, not validated surrogates; 3. Incomplete reporting of harms; 4. Not establish and validated measurements; 5. Clinically significant difference not prespecified; 6. Clinically significant difference not supported; 7. Other.

[e] Follow-Up key: 1. Not sufficient duration for benefit; 2. Not sufficient duration for harms; 3. Other.

Table 4. Study Design and Conduct Limitations

Study; Trial	Allocation[a]	Blinding[b]	Selective Reporting[c]	Data Completeness[d]	Power[e]	Statistical[f]
Stupp et al. (2017) (15); EF-14		1. No sham control and not blinded to treatment assignment				

The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.

[a] Allocation key: 1. Participants not randomly allocated; 2. Allocation not concealed; 3. Allocation concealment unclear; 4. Inadequate control for selection bias; 5. Other.

[b] Blinding key: 1. Participants or study staff not blinded; 2. Outcome assessors not blinded; 3. Outcome assessed by treating physician; 4. Other.

[c] Selective Reporting key: 1. Not registered; 2. Evidence of selective reporting; 3. Evidence of selective publication; 4. Other.

[d] Data Completeness key: 1. High loss to follow-up or missing data; 2. Inadequate handling of missing data; 3. High number of crossovers; 4. Inadequate handling of crossovers; 5. Inappropriate exclusions; 6. Not intent to treat analysis (per protocol for noninferiority trials); 7. Other.

[e] Power key: 1. Power calculations not reported; 2. Power not calculated for primary outcome; 3. Power not based on clinically important difference; 4. Other.

[f] Statistical key: 1. Analysis is not appropriate for outcome type: (a) continuous; (b) binary; (c) time to event; 2. Analysis is not appropriate for multiple observations per patient; 3. Confidence intervals and/or p values not reported; 4. Comparative treatment effects not calculated; 5. Other.

Section Summary: Tumor Treating Fields Therapy as an Adjunct to Standard Maintenance Care for Newly Diagnosed Glioblastoma Multiforme

The final analysis of the EF-14 trial, which included 695 patients from 83 sites, found a statistically and clinically significant increase of 2.7 months in PFS and an increase of 4.9 months in OS with the addition of TTF therapy to standard maintenance therapy (i.e., temozolomide) in patients with newly diagnosed GBM. There was no sham control, and patients were not blinded to treatment assignment. However, PFS was assessed by blinded evaluators, and placebo effects on the objective measure of OS were likely to be minimal. There was no evidence of a negative impact of TTF therapy on health-related quality of life, except for itchy skin from the transducers. In a systematic review that included the EF-14 trial along with other observational studies, the pooled median OS and PFS in newly diagnosed patients who received TTF therapy was 21.7 months and 7.2 months, respectively.

Tumor Treating Fields Therapy as an Adjunct or Alternative to Medical Therapy for Progressive or Recurrent Glioblastoma Multiforme

Clinical Context and Therapy Purpose

The purpose of TTF therapy is to provide a treatment option that is an alternative to or an improvement on existing therapies for individuals with progressive or recurrent GBM. Tumor treating fields therapy has been investigated as an alternative or adjunct to medical therapy for progressive or recurrent GBM.

The following PICO was used to select literature to inform this policy.

Populations

The relevant population of interest is individuals who have recurrent GBM with good performance status.

Interventions

The therapy being considered is TTF therapy as an adjunct or alternative to standard medical therapy.

Comparators

The following practice is currently being used to make decisions about progressive or recurrent GBM: standard medical therapy (e.g., bevacizumab, nitrosoureas, temozolomide rechallenge).

Outcomes

The general outcomes of interest are whether TTF improves survival or quality of life during treatment and the time to tumor recurrence because most GBMs recur. Measures of cognitive status and quality of life measures are also of interest to determine whether TTF alters the decline in cognition and quality of life that occur with GBM. Also, adverse events of treatment, such as side effects of chemotherapy and the possibility of seizures, need to be assessed.

Due to the rapid progression of GBM, the time of interest for both PFS and OS is months.

Study Selection Criteria

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs.
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Consistent with a "best available evidence approach", within each category of study design, studies with larger sample sizes and longer durations were sought.
- Studies with duplicative or overlapping populations were excluded.

Systematic Reviews

A systematic review by Regev et al. (2021) is introduced above. (14) For patients with recurrent GBM (n=1094), only 2 RCTs were identified (Stupp et al. [2012] and post hoc analysis of Kesari et al. [2017]), which are described in further detail in the section below. The remainder of the data for recurrent GBM was observational. For patients with recurrent GBM, the pooled median OS and PFS were 10.3 months (95% CI, 8.3 to 12.8) and 5.7 (95% CI, 2.8 to 10) months, respectively. The pooled rate of OS at 1, 2, and 3 years was 43.7%, 21.3%, and 14%, respectively. The pooled rate of PFS at 6, 12, and 18 months was 47.8%, 29.3%, and 19.7%, respectively. As previously noted, statistical comparisons to other treatment modalities were not provided.

Randomized Controlled Trials

The 2011 U.S. FDA approval of the NovoTTF-100A System (now called Optune) was based on a phase 3 multinational RCT (EF-11), results of which were published by Stupp et al. (2012). (4) This trial compared TTF therapy alone with physician's choice medical therapy in 237 adults who had relapsed or progressive glioblastoma (see Table 5). Patients had failed conventional treatment with RT, chemotherapy, and/or surgery, and more than 80% of participants had failed 2 or more prior chemotherapy regimens. In this trial, the term chemotherapy also applied to targeted agents such as bevacizumab. Patient characteristics and performance of additional post-recurrence debulking surgery were similar in the 2 groups.

Table 5. Summary of Key Randomized Controlled Trial Characteristics for Progressive or Recurrent Glioblastoma

Study; Trial	**Countries**	**Sites**	**Dates**	**Participants**	**Interventions**	
					Active	*Comparator*
Stupp et al. (2012) (4); EF-11	U.S., E.U., Israel	28	1987-2013	• 237 adults with relapsed or progressive supratentorial glioblastoma • KPS score ≥70%	120 patients treated with TTF alone, 93 (78%)	117 patients treated with physician's choice of

					completed 1 cycle	medical therapy[a]

EU: European Union; KPS: Karnofsky Performance Status; TTF: tumor treating fields; U.S.: United States.
[a] Medical therapy included bevacizumab, irinotecan, nitrosoureas, platinum-based chemotherapy (i.e., >carboplatin); temozolomide; or a combination of procarbazine, chloroethyl ether, and vincristine.

Participants were followed monthly, which included laboratory tests. Magnetic resonance images were evaluated at 2, 4, and 6 months from initiation of treatment, with subsequent MRIs performed according to local practice until disease progression. Quality of life questionnaires were completed every 3 months. Medical follow-up continued for 2 months after disease progression. Monthly telephone interviews with participants' caregivers were used to assess mortality rates. The primary end point was OS. Secondary end points included PFS, the percentage of patients with PFS at 6 months, time to progression, 1-year survival rate, quality of life, and radiologic response. All end points were evaluated using intention-to-treat analysis.

The trial did not reach its primary end point of improved survival compared with active medical therapy (see Table 6). With a median follow-up of 39 months, 93% of patients had died. There was not a statistically significant difference in survival rates at 1, 2, and 3 years between groups. Patients in the TTF group did not, however, suffer the typical systemic side effects of chemotherapy. The most common adverse event in the TTF group was grade 1 and 2 contact dermatitis on the scalp, which resolved with topical corticosteroids and did not require treatment breaks. Control participants experienced grade 2, 3, or 4 events by organ system related to the pharmacologic activity of chemotherapy agents used. Hematologic events of grade 2 or greater were observed in 17% of chemotherapy patients compared with 3% of TTF patients. Gastrointestinal disorders of grade 2 or greater were identified in 17% of chemotherapy patients compared with 4% of TTF patients. Severe (grades 3 to 4) hematologic and gastrointestinal toxicity was observed in 7% of chemotherapy controls compared with 1% of the TTF group.

Longitudinal quality of life data, available in 63 (27%) participants, showed no meaningful differences between groups for the domains of global health and social functioning. However, cognitive and emotional functioning domains favored TTF therapy. Symptom scale analysis was by treatment-associated toxicity; appetite loss, diarrhea, constipation, nausea, and vomiting were directly related to the chemotherapy administration.

Table 6. Summary of Key Randomized Controlled Trial Results for Recurrent or Progressive Glioblastoma

Study; Trial	LTFU, n (%)	Median OS, mo	Progression-Free Survival		OS (95% CI), %		
			Median, months	Rate at 6 Months (95% CI), %	1 Year	2 Years	3 Years
Stupp et al. (2012) (4); EF-11							

TTF	23 (22)	6.6	2.2	21.4 (13.5 to 29.3)	20	8 (4 to 13)	4 (1 to 8)
PCC	12 (18)	6.0	2.1	15.1 (7.8 to 22.3)	20	5 (3 to 10)	1 (0 to 3)
HR (95% CI)		0.86 (0.66 to 1.12)	0.81 (0.60 to 1.09)				
P value		0.27	0.16	0.13			

CI: confidence interval; HR: hazard ratio; LTFU: loss to follow-up; OS: overall survival; mo: month; PCC: physician's choice
chemotherapy; TTF: tumor treating fields.

Nonrandomized Comparative Studies

Zhu et al. (2022) conducted a prospective, post-marketing registry study (the EF-19 study) to evaluate the safety and efficacy of TTF versus physician's choice standard of care in patients from the EF-11 study with recurrent glioblastoma. (17) The patient population was comprised of patients already enrolled in the PRiDe registry and included a total of 309 patients. Primary and secondary endpoints assessed included OS in the intention-to-treat (ITT) and per-protocol (PP) populations. In the ITT population, median OS in patients treated with TTF was comparable to physician's choice of standard of care (7.4 vs 6.4 months, respectively; log-rank test p=.053). The Cox test HR was 0.66 (95% CI, 0.47 to 0.92; p=.016). In the PP population, median OS in patients treated with TTF was significantly longer than patients treated with standard of care (8.1 vs 6.4 months; log-rank test p=.017). The Cox test HR was 0.60 (95% CI, 0.42 to 0.85; p=.004). Tumor treating fields therapy showed a favorable safety profile as well.

Kesari et al. (2017) conducted a post hoc analysis of the EF-14 trial (see Stupp et al. [2017] above) to evaluate the efficacy of TTF in patients who had the first recurrence. (18) Some patients in the temozolomide alone group crossed over to receive TTF plus chemotherapy after the first recurrence, resulting in 144 patients who received TTF fields plus chemotherapy and 60 patients who received chemotherapy alone for recurrent GBM (see Table 7). Patient characteristics and second-line treatments were well-balanced between the groups, with bevacizumab the most common second-line therapy. The median OS in patients treated with systemic therapy alone was 9.2 months (see Table 8). In comparison, the group of patients who received TTF therapy in addition to systemic therapy had a median OS of 11.8 months (p=.043).

A registry study published by Mrugala et al. (2014) assessed OS data from patients who received NovoTTF therapy in a real-world, clinical practice setting (see Table 7). (19) Concurrent treatment was not captured in the registry, and it is possible that some patients received combination therapy. Median OS in the PRiDe clinical practice dataset (9.6 months) was reported as superior to that attained in the EF-11 pivotal trial (6.6 months, p<.001) (see Table 8). More patients in the PRiDe registry were treated for first recurrence (33% vs 9%), and more

had received bevacizumab as prior therapy (55% vs 19%). The PRiDe investigators reported no novel or unexpected treatment-related adverse events compared with the EF-11 trial.

Table 7. Characteristics of Key Nonrandomized Trial Results

Study	Study Type	Country	Dates	Participants	TTF	Controls	FU
Zhu et al. (2022) (17)	Registry	U.S.	2016-2018	309 patients with recurrent GBM	192 patients treated with TTF already enrolled in the PRiDe registry	117 patients in the SOC cohort from the EF-11 study	12 months
Kesari et al. (2017) (18)	EF-14 post hoc analysis	U.S., E.U., South Korea, Israel	2009-2016	204 patients with first recurrence in the EF-14 trial	144 patients treated with TTF plus second-line chemotherapy	60 patients treated with second-line chemotherapy	12.6 months
Mrugala et al. (2014) (19)	Registry	U.S. (91 centers)	2011-2013	457 patients with recurrent GBM	Patient Registry Dataset (PRiDe)	EF-11	NR

E.U.: European Union; FU: follow-up; GBM: glioblastoma; NR: not reported; SOC: standard of care; TTF: tumor treating fields; U.S.: United States.

Table 8. Summary of Key Nonrandomized Trial Results

Study	**Median OS, months**	**Additional OS outcomes**	
Zhu et al. (2022) (17)	**Median OS with TTF (ITT population), months**	**Median OS with TTF (PP population), months**	
TTF monotherapy	7.4	8.1	
Physician's choice SOC	6.4	6.4	
HR (95%, CI)	0.66 (0.47 to 0.92)	0.60 (0.42 to 0.85)	
p-value	0.16	.004	
Kesari et al. (2017) (18); EF-14	**Median OS without bevacizumab, months**	**Median OS with bevacizumab, months**	
TTF plus chemotherapy	11.8	11.8	
Chemotherapy alone	9.2	9.0	
HR (95% CI)	0.70 (0.48 to 1.00)	0.61 (0.37 to 0.99)	

p-value	0.049	0.043	
Mrugala et al. (2014) (19)	**Median OS with TTF**	**1-Year OS, %**	**2-Year OS, %**
PRiDe Registry	9.6	44	30
EF-11	6.6	20	9
HR (95% CI)	0.66 (0.05 to 0.86)	NR	NR
p-value	<0.001	NR	NR

CI: confidence interval; HR: hazard ratio; ITT: intention-to-treat; NR: not reported; OS: overall survival, PP: per-protocol; SOC: standard of care; TTF: tumor treating fields.

Post hoc analyses of the EF-11 pivotal trial have been reported. Wong et al. (2014) published a subgroup analysis to determine characteristics of responders and nonresponders in the active treatment and active treatment control. (20) They found that responders had a lower grade of histology and lower daily dexamethasone use than nonresponders. A second post hoc analysis by Kanner et al. (2014) of the EF-11 pivotal trial data was performed to evaluate OS among patients who finished at least 1 complete course of TTF or chemotherapy. (21) The investigators reported that median OS was 7.7 months in the TTF group compared with 5.9 months in the chemotherapy group (p=.009). These post hoc analyses are considered to be hypothesis-generating.

Section Summary: Tumor Treating Fields Therapy as an Adjunct or Alternative to Chemotherapy for Progressive or Recurrent Glioblastoma Multiforme

The single RCT for TTF as an alternative to chemotherapy demonstrated no improvement in overall survival, however efficacy and activity with this chemotherapy-free treatment device appears to be comparable to chemotherapy regimens that are commonly used for recurrent GBM. Toxicity and quality of life outcomes favor TTF therapy.

A nonrandomized post hoc evaluation of the EF-14 trial suggests that TTF may improve survival when combined with chemotherapy for recurrent GBM. This analysis should be considered hypothesis-generating, and further study in high-quality RCTs is needed.

Two registry studies also evaluated real-world outcomes in patients enrolled in the PRiDe registry compared to patients in the EF-11 study. In a systematic review that included the RCT and post hoc analysis of the EF-14 trial, along with other observational studies, the pooled median OS and PFS in patients with recurrent GBM who received TTF therapy was 10.3 months and 5.7 months, respectively.

Tumor Treating Fields Therapy as an Adjunct or Alternative to Standard Medical Therapy for Unresectable, Locally Advanced, or Metastatic Malignant Pleural Mesothelioma

Clinical Context and Therapy Purpose

The purpose of TTF therapy as an adjunct or alternative to standard medical therapy is to provide a treatment option that is an alternative to or an improvement on existing therapies for individuals with malignant pleural mesothelioma. Tumor treating fields has been investigated as

an adjunct to pemetrexed and platinum-based chemotherapy for the treatment of unresectable, locally advanced or metastatic, malignant pleural mesothelioma (MPM).

The following PICO was used to select literature to inform this policy.

Populations
The relevant population of interest is individuals with unresectable, locally advanced or metastatic MPM.

Interventions
The therapy being considered is TTF as an adjunct or alternative to standard medical therapy.

Optune branded products (formerly NovoTTF-100A System) are the only legally marketed TTF delivery system available in the United States. For the treatment of MPM, the Optune Lua system is used in the same way as the Optune system is used for glioblastoma; however, the 4 disposable transducer arrays with insulated electrodes are applied to the patient's shaved chest and back.

Comparators
The following practice is currently being used to make decisions about unresectable, locally advanced or metastatic MPM: standard medical therapy with pemetrexed and platinum-based chemotherapy.

Outcomes
The general outcomes of interest are whether TTF improves survival or QOL during treatment.

The time of interest for both PFS and OS is months to years.

Study Selection

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs.
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Consistent with a “best available evidence approach”, within each category of study design, studies with larger sample sizes and longer durations were sought.
- Studies with duplicative or overlapping populations were excluded.

TTF therapy for patients with metastatic MPM has been evaluated in 1 prospective, single-arm study (STELLAR) (22) and a much smaller single-arm retrospective study of 5 patients at a single U.S. center.

Prospective Single-Arm Study

The STELLAR study enrolled 80 patients with inoperable, previously untreated MPM. Study characteristics and results are summarized in Tables 9 and 1102. Patients were treated with cisplatin or carboplatin in combination with TTF therapy delivered by the NovoTTF-100L System at 12 sites outside the U.S. The primary outcome was OS as measured from start of study treatment until date of death. Secondary outcomes were PFS based on investigator assessment of computed tomography (CT) scan imaging, radiological response rate, 1 and 2 year survival rates, and safety.

In STELLAR the median OS was 18.2 months and median PFS was 7.6 months. Seventy-two of the 80 patients enrolled had at least 1 follow-up CT scan. Of those, 40% had a partial response, 57% had stable disease, and 3% progressed. The only adverse event associated with TTF treatment was skin reaction; this adverse event was mild to moderate for the majority of patients who experienced it (66%). The limitations of the STELLAR study are summarized in Tables 11 and 12. Because there was no control group, it is not possible to draw conclusions about the effectiveness of TTF therapy compared to standard medical care alone. Additional limitations include the small sample size and no reporting of symptoms or quality of life outcomes.

Table 9. Summary of The STELLAR Single Arm Study

Study	Study Type	Country	Dates	Participants	Treatment	Follow-Up
STELLAR (2019) (22) NCT02397928	Prospective, single-arm, multicenter (12 sites)	E.U.	2015-2017	Age 18 years or older, with mesothelioma, not candidate for curative treatment (surgery or RT), ≥1 evaluable lesion, ECOG Performance Status of 0 to 1, at least 4 weeks since last surgery, life expectancy at least 3 months; and able to operate the device independently or with help of a caregiver	TTF (delivered by the NovoTTF-100L System) or ≥18 hours per day in combination with pemetrexed and cisplatin or carboplatin N=80	Protocol specified minimum follow-up of at least 12 months

ECOG: Eastern Cooperative Oncology Group; E.U.: European Union; RT: radiotherapy; TTF: tumor treating fields.

Table 10. Summary of The STELLAR Single Arm Study Results

Study	Median Overall Survival (95% CI)	Median Progression-free Survival (95% CI)	One-year Survival (95% CI)	2-year Survival (95% CI)	Response
STELLAR (2019) (22) NCT02397928	18.2 months (12.1 to 25.8)	7.6 months (6.7 to 8.6)	62.2% (50.3% to 72.0%)	41.9% (28.0% to 55.2%)	Of 72 who had a follow-up CT scan: • 29/70 (40%) partial response • 41/70 (57%) stable disease • 2/70 (3%) progressed

CI: confidence interval; CT: computed tomography.

Table 11. Study Relevance Limitations

Study	Population[a]	Intervention[b]	Comparator[c]	Outcomes[d]	Follow-Up[e]
STELLAR (2019) (22) NCT02397928			2. No comparator	1. Quality of life not assessed	

The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.

[a] Population key: 1. Intended use population unclear; 2. Study population is unclear; 3. Study population not representative of intended use; 4, Enrolled populations do not reflect relevant diversity; 5. Other.

[b] Intervention key: 1. Not clearly defined; 2. Version used unclear; 3. Delivery not similar intensity as comparator; 4. Not the intervention of interest (e.g., proposed as an adjunct but not tested as such); 5: Other.

[c] Comparator key: 1. Not clearly defined; 2. Not standard or optimal; 3. Delivery not similar intensity as intervention; 4. Not delivered effectively; 5. Other.

[d] Outcomes key: 1. Key health outcomes not addressed; 2. Physiologic measures, not validated surrogates; 3. Incomplete reporting of harms; 4. Not establish and validated measurements; 5. Clinically significant difference not prespecified; 6. Clinically significant difference not supported; 7. Other.

[e] Follow-Up key: 1. Not sufficient duration for benefit; 2. Not sufficient duration for harms; 3. Other.

Table 12. Study Design and Conduct Limitations

Study	Allocation[a]	Blinding[b]	Selective Reporting[d]	Data Completeness [e]	Power[d]	Statistical[f]
STELLAR (2019) (22) NCT02397928	1. Not randomized	1. Not blinded		1. 8 patients lost to follow-up (10%)		

The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.
[a] Allocation key: 1. Participants not randomly allocated; 2. Allocation not concealed; 3. Allocation concealment unclear; 4. Inadequate control for selection bias.
[b] Blinding key: 1. Not blinded to treatment assignment; 2. Not blinded outcome assessment; 3. Outcome assessed by treating physician.
[c] Selective Reporting key: 1. Not registered; 2. Evidence of selective reporting; 3. Evidence of selective publication.
[d] Data Completeness key: 1. High loss to follow-up or missing data; 2. Inadequate handling of missing data; 3. High number of crossovers; 4. Inadequate handling of crossovers; 5. Inappropriate exclusions; 6. Not intent to treat analysis (per protocol for noninferiority trials).
[e] Power key: 1. Power calculations not reported; 2. Power not calculated for primary outcome; 3. Power not based on clinically important difference.
[f] Statistical key: 1. Analysis is not appropriate for outcome type: (a) continuous; (b) binary; (c) time to event; 2. Analysis is not appropriate for multiple observations per patient; 3. Confidence intervals and/or p values not reported; 4. Comparative treatment effects not calculated.

Retrospective Studies

Kutuk et al. (2022) published a single-arm retrospective study of 5 patients with unresectable MPM who received TTF therapy from 2019 to 2021 at a single center in the US. (23) The median follow-up was 5.4 months (range, 1.1 to 20.9). All patients were also treated with pemetrexed plus platinum-based chemotherapy. The median number of 4-week TTF cycles was 5 (range, 2 to 7) and the median TTF device usage in the first 3 months was 12.5 hours per day (range, 5 to 16.8). Treatment-related dermatitis was the only side effect associated with TTF and was reported as grade 1 to 2 in all patients; no patient had grade 3+ device-related toxicities. The authors note that this was the first publication of real-world implementation of TTF for MPM.

Section Summary: TTF Therapy as an Adjunct or Alternative to Standard Medical Therapy for Unresectable, Locally Advanced, or Metastatic Malignant Pleural Mesothelioma

For patients with metastatic MPM, TTF therapy has been evaluated in a prospective, single-arm study conducted in 80 patients (STELLAR) and a retrospective study of 5 US patients. The STELLAR study enrolled 80 patients with inoperable, previously untreated MPM who were treated with cisplatin or carboplatin in combination with TTF therapy at 12 sites outside the U.S. Median OS was 18.2 months and median PFS was 7.6 months. Seventy-two of the 80 patients enrolled had at least 1 follow-up CT scan. Of those, 40% had a partial response, 57% had stable disease, and 3% progressed. Because there was no control group, it is not possible to draw conclusions about the effectiveness of TTF therapy compared to standard medical care alone. Additional limitations include the small sample size and no reporting of symptoms or quality of life outcomes. The retrospective study is the first publication of real-world implementation of TTF for MPM.

NovoTAL™

There is limited data related to the use of the NovoTAL™ treatment planning software which includes a small case series (24) and a user group survey (25). Published literature does not indicate that use of the NovoTAL™ treatment planning software is superior to using Optune TTF

therapy with preset settings or that it improves clinical outcomes. To date, there is insufficient data to support improved long-term health outcomes with its use, therefore the NovoTAL™ treatment planning software is considered experimental, investigational and/or unproven.

Summary of Evidence

For individuals who have newly diagnosed glioblastoma multiforme (GBM) on maintenance therapy after initial treatment who receive tumor treating fields (TTF) therapy as an adjunct to standard maintenance therapy, the evidence includes a randomized controlled trial (RCT) and a systematic review. Relevant outcomes include overall survival (OS), disease-specific survival, symptoms, functional outcomes, quality of life, and treatment-related morbidity. The EF-14 trial found a significant increase of 2.7 months in progression-free survival (PFS) and an increase of 4.9 months in OS with the addition of TTF therapy to standard maintenance therapy (i.e., temozolomide) in patients with newly diagnosed GBM. Although patients were not blinded to treatment assignment, PFS was assessed by blinded evaluators, and the placebo effects on the objective measure of OS are expected to be minimal. In a systematic review that included the EF-14 trial along with other observational studies, the pooled median OS and PFS in newly diagnosed patients who received TTF therapy was 21.7 months and 7.2 months, respectively. This technology represents a clinically significant option in the treatment of patients with GBM, for whom options are limited. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have progressive or recurrent GBM who receive TTF therapy as an adjunct or alternative to standard medical therapy, the evidence includes an RCT, nonrandomized comparative studies, and a systematic review of this data. Relevant outcomes are OS, disease-specific survival, QOL, and treatment-related morbidity. The single RCT evaluating TTF therapy for recurrent GBM did not show superiority of TTF therapy for the primary outcome (overall survival) compared with physicians' choice chemotherapy. Because no serious adverse effects have been identified with TTF therapy, this raises the possibility that treatment with TTF might reduce the toxicity associated with treatment for recurrent GBM. A reduction in chemotherapy-associated toxicity without loss of efficacy would be considered a net health benefit. The evidence is considered sufficient to determine that the technology results in a meaningful improvement in the net health outcome when given as a monotherapy after medical therapy has been exhausted. The highest quality study of TTF combined with medical treatment for recurrent GBM is a post hoc analysis of the EF-14 trial. Two registry studies also evaluated real-world outcomes in patients enrolled in the PRiDe registry compared to patients in the EF-11 study. In a systematic review that included the RCT and post hoc analysis of the EF-14 trial, along with other observational studies, the pooled median OS and PFS in patients with recurrent GBM who received TTF therapy was 10.3 months and 5.7 months, respectively. A high-quality, prospective RCT is needed. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome when given as an adjunct to standard medical therapy.

For individuals who have unresectable, locally advanced or metastatic, malignant pleural mesothelioma (MPM) who receive TTF therapy as an adjunct to standard maintenance therapy,

the evidence includes a single-arm prospective study conducted in 80 patients and a retrospective study of 5 US patients. Relevant outcomes include OS, disease-specific survival, symptoms, functional outcomes, QOL, and treatment-related morbidity. In patients who received TTF therapy in combination with pemetrexed and cisplatin or carboplatin, median OS was 18.2 months (95% confidence interval [CI], 12.1 to 25.8 months). Because there was no comparison group, it is not possible to make conclusions about the effectiveness of the intervention compared to medical therapy alone. The retrospective study is the first publication of real-world implementation of TTF for MPM. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

Clinical Input From Physician Specialty Societies and Academic Medical Centers

Clinical input found majority support, but not consensus, for the use of TTF therapy as an adjunct to maintenance treatment following initial therapy for GBM. There was mixed support for the use of TTF as an alternative to chemotherapy in advanced or recurrent GBM.

Practice Guidelines and Position Statements

National Comprehensive Cancer Network

National Comprehensive Cancer Network guidelines on central nervous system cancers (V.3.2024) include recommendations for the treatment of glioblastoma (see Table 13). (3) For the initial treatment of patients with glioblastoma with good performance status and either methylated or unmethylated or indeterminate O^6-methylguanine-DNA methyltransferase promotor status, treatment with standard brain radiotherapy plus concurrent temozolomide and adjuvant temozolomide plus alternating electric field therapy is a category 1 recommendation. Alternating electric currents therapy is only an option for patients with supratentorial disease. Consideration of alternating electric field therapy for recurrent glioblastoma is a category 2B recommendation.

Table 13. Guidelines for Adjuvant Treatment of Glioblastoma, by Age and Performance Status

Age, y	KPS Score, %	Treatment Options	Category
≤70	≥60	• Standard RT plus concurrent and adjuvant temozolomide plus TTF (preferred) • Standard RT plus concurrent and adjuvant temozolomide	1
≤70	≥60	• Standard RT alone (for unmethylated MGMT promoter status only)	2A
≤70	≥60	• Standard RT plus concurrent and adjuvant lomustine and temozolomide (for methylated or indeterminate MGMT promoter status only)	2B
≤70	<60	• Hypofractionated RT with/without concurrent or adjuvant temozolomide • Temozolomide alone • Palliative/best supportive care	2A

>70	≥60	• Hypofractionated RT plus concurrent and adjuvant temozolomide (for methylated or indeterminate MGMT promoter status only) • Standard RT plus concurrent and adjuvant temozolomide plus TTF	1
>70	≥60	• Standard RT plus concurrent and adjuvant temozolomide • Temozolomide alone (for methylated or indeterminate MGMT promoter status only) • Hypofractionated brain RT alone (for unmethylated MGMT promoter status only)	2A
>70	≥60	• Hypofractionated RT alone (for methylated or indeterminate MGMT promoter status only)	2B
>70	<60	• Hypofractionated brain RT alone • Temozolomide alone • Palliative/best supportive care	2A

KPS: Karnofsky Performance Status; MGMT: O^6-methylguanine-DNA-methyltransferase; RT: radiotherapy; TTF: tumor treating fields; y: year.

The National Comprehensive Cancer Network guidelines on malignant pleural mesothelioma (V. 2.2024) do not address TTF as a treatment option for malignant pleural mesothelioma. (26)

Congress of Neurological Surgeons

In 2022, the Congress of Neurological Surgeons released guidelines on role of cytotoxic chemotherapy and other cytotoxic therapies in the management of progressive glioblastoma. (27) In regard to TTF use in adult patients with progressive glioblastoma, the Congress states that "the use of TTF with other chemotherapy may be considered when treating adult patients with progressive glioblastoma [pGBM]. There is insufficient evidence to recommend TTF to increase overall survival in adult patients with pGBM."

Ongoing and Unpublished Clinical Trials

Some currently ongoing and/or unpublished trials that might influence this policy are listed in Table 14. Of particular note are phase 3 trials evaluating TTF therapy in non-small-cell lung cancer and pancreatic cancer. TTF therapy is an active area of research for mechanisms underlying its effects on cancer cells.

Table 14. Summary of Key Trials

NCT Number	Trial Name	Planned Enrollment	Completion Date
Ongoing			
NCT02831959[a]	Pivotal, Open-label, Randomized Study of Radiosurgery with or without Tumor	270	Dec 2024

	Treating Fields (TTFields) (150kHz) for 1-10 Brain Metastases from Non-Small Cell Lung Cancer (NSCLC) (METIS)		
NCT02973789[a]	LUNAR: Pivotal, Randomized, Open-label Study of Tumor Treating Fields (TTFields) Concurrent with Standard of Care Therapies for Treatment of Stage 4 Non-small Cell Lung Cancer (NSCLC) Following Platinum Failure	276	Sep 2023
NCT03377491[a]	EF-27 Pivotal, Randomized, Open-label Study of Tumor Treating Fields (TTFields, 150kHz) Concomitant with Gemcitabine and Nab-paclitaxel for Front-line Treatment of Locally-advanced Pancreatic Adenocarcinoma (PANOVA-3)	556	Oct 2024
NCT04471844[a]	EF-32: Pivotal, Randomized, Open-Label Study of Optune® (Tumor Treating Fields, 200kHz) Concomitant With Radiation Therapy and Temozolomide for the Treatment of Newly Diagnosed Glioblastoma	950	Aug 2026
Unpublished			
NCT02663271[a]	A Phase 2, Multi-center, Single Arm, Histologically Controlled Study Testing the Combination of TTFields and Pulsed Bevacizumab Treatment in Patients	18	Mar 2022 (terminated)
NCT03940196[a]	ENGOT-ov50 / GOG-3029 / INNOVATE-3: Pivotal, Randomized, Open-label Study of Tumor Treating Fields (TTFields, 200kHz) Concomitant With Weekly Paclitaxel for the Treatment of Platinum-resistant Ovarian Cancer (PROC)	540	May 2023 (completed)
NCT01971281[a]	A Phase II Study of TTFields (150 kHz) Concomitant with Gemcitabine and TTFields Concomitant with Gemcitabine Plus Nab-paclitaxel for Front-line Therapy of Advanced Pancreatic Adenocarcinoma	40	Dec 2017 (unknown)
NCT01894061[a]	A Prospective Phase II Trial of NovoTTF-100A With Bevacizumab (Avastin) in Patients with Recurrent Glioblastoma	40	Jul 2019 (completed)

NCT: national clinical trial.

[a] Denotes industry-sponsored or cosponsored trial.

Coding

Procedure codes on Medical Policy documents are included **only** as a general reference tool for each policy. **They may not be all-inclusive.**

The presence or absence of procedure, service, supply, or device codes in a Medical Policy document has no relevance for determination of benefit coverage for members or reimbursement for providers. **Only the written coverage position in a Medical Policy should be used for such determinations.**

Benefit coverage determinations based on written Medical Policy coverage positions must include review of the member's benefit contract or Summary Plan Description (SPD) for defined coverage vs. non-coverage, benefit exclusions, and benefit limitations such as dollar or duration caps.

CPT Codes	64999
HCPCS Codes	A4555, E0766

*Current Procedural Terminology (CPT®) ©2024 American Medical Association: Chicago, IL.

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Centers for Medicare and Medicaid Services (CMS)

The information contained in this section is for informational purposes only. HCSC makes no representation as to the accuracy of this information. It is not to be used for claims adjudication for HCSC Plans.

The Centers for Medicare and Medicaid Services (CMS) does not have a national Medicare coverage position. Coverage may be subject to local carrier discretion.

A national coverage position for Medicare may have been developed since this medical policy document was written. See Medicare's National Coverage at <https://www.cms.hhs.gov>.

Policy History/Revision

Date	Description of Change
02/01/2025	Document updated with literature review. The following change was made to Coverage: Removed criterion limitation of “up to 24 months” specific to length of therapy for newly diagnosed glioblastoma multiforme. Added/updated the following references: 1, 3, 11, and 26.
03/15/2024	Document updated with literature review. The following changes were made to Coverage: 1) Lowered Karnofsky Performance Status (KPS) score criteria from ≥70% to ≥60%; and 2) Added criteria limitations specific to length of therapy. Added/updated the following references: 2, 3, 9, 14, 17, 23, 26, and 27.
10/01/2022	Reviewed. No changes.
11/01/2021	Document updated with literature review. The following change was made to Coverage: Added conditional coverage for patients with recurrent glioblastoma multiforme as a monotherapy following treatment with chemotherapy after surgical and radiation treatments have been exhausted. Added/updated the following references: 1, 3, 9, 10, 19, and 22.
09/15/2020	Reviewed. No changes.
10/15/2019	Document updated with literature review. The following change was made to Coverage: Malignant pleural mesothelioma added to list of conditions for

	which the therapy is considered experimental, investigational and/or unproven. The following references were added/updated: 3 and 8.
05/01/2019	Document updated with literature review. The following changes were made to Coverage: 1) Modified conditional criteria for tumor treating fields (TTF) therapy to treat glioblastoma multiforme (GBM) in newly diagnosed GBM; 2) Added additional indications to the experimental, investigational, and/or unproven statement; 3) Added the use of treatment planning software (i.e., NovoTAL™) for use with tumor treatment fields (TTFs) for any indication, is considered experimental, investigational and/or unproven; 4) Added NOTE 1 for additional FDA label notices. 5) Added NOTE 2 to define progression. Added references 2, 9, 10, 12, 13. Title changed from Tumor-Treatment Fields For Glioblastoma.
06/15/2017	Document updated with literature review. The following change was made to Coverage: Added conditional coverage for newly diagnosed Glioblastoma.
05/01/2016	Document updated with literature review. Coverage unchanged.
12/012015	Document updated with literature review. Coverage unchanged.
01/01/2014	New medical document. Tumor treatment fields therapy to treat glioblastoma is considered experimental, investigational and/or unproven.