Electric Tumor Treatment Field Therapy

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➲ Instructions for Use

Table of Contents **Page**

Application 1
Coverage Rationale 1
Medical Records Documentation Used for Reviews 2
Definitions 2
Applicable Codes 3
Description of Services 3
Clinical Evidence 4
U.S. Food and Drug Administration 13
References 13
Policy History/Revision Information 15
Instructions for Use 15

Related Commercial/Individual Exchange Policy

- Clinical Trials

Community Plan Policy

- Electric Tumor Treatment Field Therapy

Application

UnitedHealthcare Commercial

This Medical Policy applies to UnitedHealthcare Commercial benefit plans.

UnitedHealthcare Individual Exchange

This Medical Policy applies to Individual Exchange benefit plans.

Coverage Rationale

The following is proven and medically necessary for treating newly diagnosed, histologically confirmed Supratentorial glioblastoma (GBM):

- The use of U.S. Food and Drug Administration (FDA)–approved devices to generate electric tumor treatment fields (TTFs) when used according to FDA-labeled indications, contraindications, warnings, and precautions and when all the following criteria are met:
  - Debulking surgery has been completed; and
  - Treatment with radiation therapy has been completed; and
  - Individual is receiving Temozolomide as the only cancer drug; and
  - Individual has a Karnofsky Performance Status (KPS) score of ≥ 60 or Eastern Cooperative Oncology Group (ECOG) Scale of Performance Status of ≤ 2; and
  - Individual has been counseled that the electric TTF device must be worn for at least 18 hours daily

When all the above criteria are met for newly diagnosed GBM, an initial 3 months of electric TTF therapy will be approved.

The following is proven and medically necessary for treating radiologically confirmed recurrence of GBM (rGBM) in the Supratentorial region of the brain:

- The use of FDA-approved devices to generate electric TTF after initial chemotherapy when used according to FDA-labeled indications, contraindications, warnings, and precautions and when all the following criteria are met:
  - The device is used as the only treatment; and
  - Individual has a KPS score of ≥ 60 or ECOG performance status of ≤ 2; and
  - Individual has been counseled that the electric TTF device must be worn for at least 18 hours daily

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When all the above criteria are met for rGBM, an initial 3 months of electric TTF therapy will be approved.

Subsequent approval(s) for continuation beyond the initial 3 months of electric TTF for treatment of histologically confirmed Supratentorial GBM is based on:

- Magnetic resonance imaging scan has been performed ≤ 2 months prior to the request and documents no evidence of disease progression; and
- Individual with newly diagnosed GBM continues to receive Temozolomide as the only cancer drug, or the device is used as the only treatment for an individual with rGBM; and
- KPS score of ≥ 60 or ECOG performance status of ≤ 2; and
- Documentation that the individual has been using the electric TTF device for at least 18 hours daily

Due to insufficient evidence of efficacy, the use of devices to generate electric TTF is unproven and not medically necessary when the criteria above are not met and for all other indications, including but not limited to the following:

- Treatment of tumors other than GBM
- Use of electric TTF therapy with concurrent medical therapy (e.g., bevacizumab or chemotherapy) for the treatment of rGBM

Medical Records Documentation Used for Reviews

Benefit coverage for health services is determined by the member specific benefit plan document and applicable laws that may require coverage for a specific service. Medical records documentation may be required to assess whether the member meets the clinical criteria for coverage but does not guarantee coverage of the service requested; refer to the guidelines titled Medical Records Documentation Used for Reviews.

Definitions

Eastern Cooperative Oncology Group (ECOG) Scale of Performance Status: A standard criterion for measuring how the disease impacts a person's level of functioning in terms of their ability to care for themselves, daily activity, and physical ability (e.g., walking, working, etc.) (ECOG-ACRIN Cancer Research Group).

Grade	ECOG Performance Status
0	Fully active, able to carry on all predisease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light housework, office work
2	Ambulatory and capable of all self-care but unable to carry out any work activities; up and about more than 50% of waking hours
3	Capable of only limited self-care; confined to bed or chair more than 50% of waking hours
4	Completely disabled; cannot carry on any self-care; totally confined to bed or chair
5	Dead

Karnofsky Performance Status: A standard way of measuring the ability of patients with cancer to perform ordinary tasks. Karnofsky Performance Status (KPS) scores range from 0 to 100; a higher score means that a person is better able to carry out daily activities. For example, a KPS of 60 means that a person requires occasional assistance but is able to care for most of their personal needs. KPS may be used to determine a patient's prognosis, to measure changes in a patient's ability to function, or to decide if a patient could be included in a clinical trial [National Cancer Institute (NCI), 2019; West and Jin, 2015].

Grade	Karnofsky Performance Status (KPS)
100	Normal, no complaints; no evidence of disease
90	Able to carry on normal activity; minor signs or symptoms of disease
80	Normal activity with effort, some signs or symptoms of disease
70	Cares for self but unable to carry on normal activity or to do active work
60	Requires occasional assistance but is able to care for most of personal needs
50	Requires considerable assistance and frequent medical care

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Grade	Karnofsky Performance Status (KPS)
40	Disabled; requires special care and assistance
30	Severely disabled; hospitalization is indicated although death not imminent
20	Very ill; hospitalization and active supportive care necessary
10	Moribund
0	Dead

(Table: ECOG-ACRIN Cancer Research Group)

Supratentorial: A term that is used to describe the upper portion of the brain that comprises the cerebrum, ventricles, choroid plexus, hypothalamus, pineal gland, pituitary gland, and optic nerve (NCI, 2019).

Temozolomide: An oral alkylating chemotherapy drug that is used in the treatment of some brain cancers. It is a first-line treatment for glioblastoma (NCI, 2019).

Applicable Codes

The following list(s) of procedure and/or diagnosis codes is provided for reference purposes only and may not be all inclusive. Listing of a code in this policy does not imply that the service described by the code is a covered or non-covered health service. Benefit coverage for health services is determined by the member specific benefit plan document and applicable laws that may require coverage for a specific service. The inclusion of a code does not imply any right to reimbursement or guarantee claim payment. Other policies and guidelines may apply.

HCPCS Code	Description
A4555	Electrode/transducer for use with electrical stimulation device used for cancer treatment, replacement only
E0766	Electrical stimulation device used for cancer treatment, includes all accessories, any type
E0767	Intrabuccal, systemic delivery of amplitude-modulated, radiofrequency electromagnetic field device, for cancer treatment, includes all accessories

Description of Services

Electric tumor treatment field (TTF) therapy (also known as tumor-treating fields, TTFields, and ETTFs) is based on the principle that low-intensity, intermediate-frequency electric fields (100 to 300 kHz) disrupt cell division and may destroy proliferating cells in brain tumors (Rulseh et al., 2012).

Glioblastoma multiforme is the most prevalent and primary malignant brain tumor in adults; for those with newly diagnosed glioblastoma, the initial standard treatment consists of debulking surgery (when feasible), followed by radiation and chemotherapy [National Comprehensive Cancer Network® (NCCN®), 2025].

Refer to the U.S. Food and Drug Administration (FDA) section for additional information.

The Optune kit contains the portable electric field generator (Optune device), insulated electrode transducer arrays, power supply, and additional supplies. Prior to treatment, transducer arrays are placed on the individual's scalp according to the tumor's location, which is then covered by a lightweight white cap that resembles a bandage. The individual receives the noninvasive TTF treatment for at least 18 continuous hours per day for a minimum of 4 weeks. As the Optune device is portable, individuals can carry out everyday activities. Treatment parameters are preset by the manufacturer so that no electrical output adjustments are available to the individual being treated. The individual being treated or caregiver must learn to change and recharge depleted device batteries and to connect to an external power supply overnight. In addition, the transducer arrays need to be replaced once to twice a week, and the scalp needs to be reshaved to maintain optimal contact.

TTF technology is also being studied through ongoing clinical trials as a treatment for other solid tumors, such as non-small cell lung cancer, brain metastasis, pancreatic cancer, ovarian cancer, and mesothelioma.

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Clinical Evidence

Glioblastoma

Khagi et al. (2025) reported the EF-14 clinical study, which is a global, randomized, pivotal, phase 3 trial that enrolled participants with newly diagnosed and histologically confirmed supratentorial glioblastoma [World Health Organization (WHO) grade 4 astrocytoma]. Participants received tumor-treating field (TTField) therapy concomitantly with maintenance temozolomide (TMZ) or TMZ alone. TTField therapy delivered alternating electric fields through transducer arrays placed on the skin surrounding the tumor, using individualized treatment planning software. There is considerable evidence that TTField therapy extends survival in individuals with glioblastoma while maintaining quality of life. There are limitations, including the lack of methodological detail for the summarized studies, such as sample size, randomization, and statistical approach, which hinders reproducibility and prevents evaluation of study rigor and validity.

Chen et al. (2025) conducted a phase 2 single-arm study (2-THE-TOP) that evaluated adjuvant TTFields combined with pembrolizumab and TMZ in participants with newly diagnosed glioblastoma (ndGBM) following standard chemoradiation. Eligible participants had a Karnofsky Performance Status (KPS) of at least 70%, adequate hematologic and metabolic reserves, and a dexamethasone dose of 4 mg/day or less; 40 participants were screened, 31 were enrolled, and 26 received the allocated intervention per protocol, with none lost to follow-up. TTFields began with cycle 1 of TMZ, and pembrolizumab 200 mg intravenously every 3 weeks was added at cycle 2. The primary end point was progression-free survival (PFS) compared with case-matched controls treated with TTFields and TMZ alone, assessed by brain magnetic resonance imaging (MRI) every 9 weeks. Among 26 per-protocol participants, median PFS was 12.0 months vs 5.8 months in controls [hazard ratio (HR), 0.377; 95% CI, 0.217-0.653; p = 0.0026], and median overall survival (OS) was 24.8 months vs 14.6 months (HR, 0.522; 95% CI, 0.301-0.905; p = 0.0477). The prespecified secondary end points included OS, safety, objective response, and immune correlates. Adjuvant TTFields combined with anti–programmed cell death 1 protein immunotherapy and TMZ was well tolerated and associated with survival benefits, particularly in participants with large, inoperable tumors. Key limitations include the single-arm design and small sample size, particularly in the biopsy-only cohort, which restrict a definitive evaluation of the regimen's efficacy and limit statistical power. There are limitations in measurement and analysis, as peripheral blood mononuclear cells were used as a surrogate for central nervous system immune changes, and statistical comparisons relied on small group sizes with simple t tests. The single-arm design also limits the ability to distinguish treatment effects from potential influences of prior chemoradiation or differences in comorbid conditions between resection groups. Another limitation is that the study did not directly assess the impact of adjuvant TMZ on immune phenotypes, which may affect the interpretation of immunologic outcomes.

Ballo et al. (2023) performed a systematic review and meta-analysis on the association of TTField therapy with survival in ndGBM. The authors reviewed the literature to identify clinical studies that evaluated OS in individuals who were treated with TTFields. Overall, 1,430 individuals were included in the studies that compared the addition of TTField therapy with standard-of-care (SOC) chemoradiotherapy vs SOC alone. The meta-analysis included comparative studies that showed a significant improvement in OS in those receiving TTFields and SOC vs SOC alone. This systematic review and meta-analysis showed a median OS of 22.6 months in those who received TTFields and 17.4 months in those who did not receive TTFields. In those reporting data on device usage (n = 1,015), an average usage rate of ≥ 75% was consistently associated with prolonged survival. The limitations of the study include the risk of bias and overestimations of treatment effects. The authors concluded that adding TTFields to standard chemoradiotherapy significantly prolongs OS in those who were newly diagnosed with glioblastoma multiforme (GBM) and treated in the real world. Future studies are essential for investigating the role of TTField treatment duration in individuals' outcomes and assessing the clinical benefits in populations with high unmet needs.

Li et al. (2022) explored studies to evaluate the efficacy and safety of TTFields for treating recurrent glioblastoma (rGBM) through a systematic review and meta-analysis. The outcomes measured were OS, HR, 1-year survival rate, and cutaneous toxicity. The results of the exploration included a total of 1,048 individuals who had rGBM and received TTField treatment. The individuals were divided into two groups: the TTField group and the control group. The OS time between the TTField and control groups showed an HR of 0.75, with a pooled 1-year OS rate and incidence of cutaneous toxicity of 0.47 and 0.48, respectively. The authors concluded that TTField therapy is effective for rGBM. However, the most relevant trials should assess individuals with rGBM's baseline characteristics such as age, KPS, methylguanine-DNA methyltransferase (MGMT) methylation status, and the number of recurrent tumors. The risk of rashes caused by long-term wearing of devices should be considered.

Li et al. (2022) conducted a systematic review and meta-analysis to review the literature about the influencing factors on the efficacy of TTFields with two experimentally supported factors: the dose of dexamethasone and compliance of TTFields to perform a meta-analysis. The results of the exploration revealed that the median OS was conspicuously

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longer in the TTFields group when the dexamethasone dose was ≤ 4.1 mg, and those whose compliance with TTFields treatment was ≥ 75% had a significantly lower OS risk than those compliant with TTField treatment of < 75%. The limitations of this exploration include significant heterogeneity in the analysis of the dose of dexamethasone, restricted English articles, and a small number of included articles. The authors concluded that TTFields are a safe and efficient treatment modality. The dose of dexamethasone of ≤ 4.1 mg of TTField treatment and the compliance of TTField treatment of ≥ 75%, ≥ 18 h per day, are beneficial to the prognosis in those with glioblastoma (included in the 2019 ECRI Clinical Evidence Assessment).

Dongpo et al. (2022) guided a network meta-analysis on the efficacy and safety of bevacizumab (BEV) combined with other therapeutic regimens for treating rGBM and to further explore the differences in the effectiveness of each treatment in randomized controlled trials (RCTs) and non-RCTs. The results of this exploration showed that in 6 months, the OS in those receiving BEV combination therapy was ranked from high to low, as follows: BEV + rindopepimut, BEV + lomustine (CCNU), CCNU, TTFields + BEV, BEV, BEV + irinotecan (Iri), BEV + TMZ, BEV + vorinostat, BEV + onartuzumab, BEV + dasatinib, BEV + carboplatin, BEV + trebananib, BEV + VB-111, TMZ, PCV, VB-111, and carboplatin. Ranked from high to low, the PFS was ranked as follows: BEV + CCNU, BEV + rindopepimut, BEV + dasatinib, BEV + vorinostat, BEV, BEV + Iri, BEV + TMZ, CCNU, BEV + carboplatin, TMZ, BEV + VB-111, PCV, BEV + trebananib, carboplatin, and VB-111. The authors compared the total incidence of serious adverse events (AEs; ≥ 3) and discovered that the BEV + vorinostat and BEV + trebananib were safer than BEV, while other regimens were not as safe. A descriptive analysis showed that BEV + rindopepimut also appeared safer than BEV. In a subgroup analysis, BEV + CCNU therapy had the highest 6-month OS and 6-month PFS among RCTs. Among non-RCTs, BEV + Iri therapy showed the highest 6-month OS and good 6-month PFS. The limitations of the study include the small number of noncontributing trials, small sample sizes, and the paucity of relevant, high-quality, large-sample, original studies, which reduce the strength of the evidence. According to the network meta-analysis results, the authors concluded that both BEV + CCNU and BEV + rindopepimut could be considered effective therapies for treating rGBM. Among them, BEV + rindopepimut therapy seems safer and more effective. Moreover, the authors found that BEV + Iri was an effective therapy in a retrospective study. An analysis of the evidence is necessary, which should include a larger number of relevant, high-quality, large-sample RCTs and non-RCTs.

Regev et al. (2021) conducted a systematic review and meta-analysis of evaluating the mechanism of action, safety, and efficacy of TTFields for both ndGBM and rGBM. Overall, 20 studies met the predefined inclusion criteria, including 1,636 individuals (542 ndGBM and 1,094 rGBM) and 11,558 individuals (6,403 ndGBM and 5,155 rGBM) who were analyzed for the clinical outcomes and safety end points separately. This study demonstrated improved clinical efficacy and a good safety profile of TTFields. For ndGBM, pooled median OS and PFS was 21.7 months (95% CI, 19.6-23.8 months) and 7.2 months (95% CI, 6.1-8.2 months), respectively. For rGBM, pooled median OS and PFS was 10.3 months (95% CI, 8.3-12.8 months) and 5.7 months (95% CI, 2.8-10 months), respectively. Compliance of ≥ 75% was associated with an improved OS, and the predominant AEs were dermatologic, with a pooled prevalence of 38.4% (95% CI, 32.3%-44.9%). Preclinical studies demonstrated TTFields' diverse molecular mechanism of action, potential synergistic efficacy, and suggested possible benefits for certain populations. The findings showed that TTFields had significantly better emotional function and reported significantly lower incidence of side effects. Also, TTField users had better emotional, physical, and cognitive functions compared with social and role functioning. The study showed that TTFields frequently affected multiple aspects of individuals' daily lives; however, 70% would recommend TTFields to others, and 67% would reuse the device. This study supports the clinical benefit, safety, and potential therapeutic synergism of TTFields for treating GBM alongside the SOC treatment protocol (included in the 2019 ECRI Clinical Evidence Assessment). (Mrugala et al., 2014, Stupp et al., 2017, and Wong et al., 2015, are included in this review.)

Chen et al. (2021) performed a systematic review and bayesian network meta-analysis to compare and rank active therapies in rGBM. The authors obtained a treatment hierarchy using the surface under the cumulative ranking curve and mean ranks. A cluster analysis was conducted to aggregate the separated results of three outcomes. Overall, 1,667 citations were identified, and 15 eligible articles with 17 treatments remained in the final network meta-analysis. Pairwise comparison showed no difference in the 6-month PFS rate, objective response rate (ORR), and OS. Among the reports, CCNU corresponded to the highest grade 3 to 4 AE rates. Ranking and cluster analysis indicated that BEV plus CCNU and regorafenib had a higher efficacy in the ORR, 6-month PFS rate, and OS and that BEV monotherapy or BEV combined with active drug therapies was advantageous for the ORR and 6-month PFS rate. Additionally, TTFields plus BEV showed a higher surface under the cumulative ranking curve value in OS. The authors concluded that according to ranking and cluster analysis, BEV plus CCNU and regorafenib are the primary recommendations for treatment. BEV monotherapy alone or combined with active drug therapies is recommended in those with severe neurological symptoms. Limitations include inconsistency among researchers, which may have biased the statistical results. In addition, the published results lag behind current therapy options.

Dono et al. (2021) performed a retrospective review of an institutional database that included 530 patients with infiltrating gliomas to evaluate the survival effects of TTFields in a cohort of those with isocitrate dehydrogenase wild-type (*IDH*-WT)

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rGBM and to investigate the possible clinical characteristics or genomic alterations that may predict responsiveness to TTFields. People with *IDH*-WT rGBM who were receiving TTFields at first recurrence were included. Tumors were evaluated by next-generation sequencing for mutations in 205 cancer-related genes. The log-rank and multivariate Cox regression analysis examined postprogression survival (PPS). Overall, 149 patients with rGBM were identified, of whom 29 (19%) were treated with TTFields. No difference in median PPS was seen between those with rGBM who received vs those who did not receive TTFields (13.9 vs 10.9 months; p = 0.068). However, in the TTFields-treated group (n = 29), PPS was improved in PTEN-mutant (n = 14) vs PTEN-WT (n = 15) rGBM (22.2 vs 11.6 months; p = 0.017). In the PTEN-mutant group [n = 70 (47%)], those treated with TTFields (n = 14) had longer median PPS (22.2 vs 9.3 months; p = 0.005). No PPS benefit was observed in PTEN-WT patients who were receiving TTFields [n = 79 (53%)]. TTField therapy conferred a PPS benefit in PTEN-mutant rGBM. The authors concluded that understanding the molecular mechanisms underpinning the differences in response to TTField therapy could help elucidate the mechanism of action of TTFields and identify the individuals with rGBM who are most likely to benefit from this therapeutic option. This study is limited by its retrospective observations. In addition, a small sample size makes it difficult to decide whether these conclusions can be generalized to a larger population. Further research that includes RCTs is needed to confirm these findings.

Ram et al. (2021) performed a subgroup analysis of the multicenter, phase 3 EF-14 randomized clinical trial subgroup analysis in participants with ndGBM to evaluate the safety and efficacy of TTFields in elderly people. All 134 participants who were ≥ 65 years of age were included (TTFields/TMZ combination, n = 89; TMZ monotherapy, n = 45; 2:1 ratio of randomization). PFS and OS were analyzed using Kaplan-Meier methodology (α = 0.05). Health-related quality of life (HRQOL) was assessed using the European Organisation for Research and Treatment of Cancer (EORTC) quality-of-life questionnaire (QLQ-C30) supplemented with the brain tumor module (QLQ-BN20). AEs were evaluated using Common Terminology Criteria for Adverse Events (CTCAE) v4.0. The PFS was 6.5 months in those randomized to the treatment group with TTFields/TMZ combination vs 3.9 months in those treated with TMZ monotherapy (HR, 0.47; 95% CI, 0.30-0.74; p = 0.0236). The OS was 17.4 months in those treated with TTFields/TMZ combination vs 13.7 months in people treated with TMZ monotherapy (HR, 0.51; 95% CI, 0.33-0.77; p = 0.0204). Annual survival rates with TTFields/TMZ vs TMZ monotherapy were 39% (95% CI, 29%-50%) vs 27% (95% CI, 15%-41%; p = 0.072) at 2 years, 19% (95% CI, 11%-29%) vs 11% (95% CI, 4%-23%; p = 0.135) at 3 years, and 15% (95% CI, 7%-25%) vs 0% at 5 years, respectively. There were no differences between groups in the preselected items of HRQOL assessment. Grade ≥ 3 systemic AEs were 46% in the TTFields/TMZ group vs 40% in the TMZ monotherapy group, without a statistically significant difference between the two groups. The only TTFields-related AEs were reversible scalp skin reactions, with grades 1 to 2 and grade 3 skin reactions reported by 51% and 2% of participants, respectively. The authors concluded that combining TTFields with maintenance, TMZ improved PFS and OS in older adults with ndGBM in the phase 3 EF-14 clinical trial, without increases in systemic toxicity or negative effects on participant HRQOL. TTFields-related skin AEs were low grade and manageable. Limitations of this analysis include the small sample sizes of both treatment groups due to the limited number of people enrolled in the EF-14 trial who were 65 years of age or older. There is also a lack of available molecular data in approximately 20% of people; 4% of TTFields plus TMZ-treated participants had an *IDH* mutation compared with 0% of the TMZ-treated people. Only one had a 1p/19q codeletion (TTFields plus TMZ group). Long-term evaluations of the results and prospective, randomized studies are still needed. (Clinical trial identifier: NCT00916409; the trial has concluded.)

Jin et al. (2020) conducted a systematic review and meta-analysis to compare the efficacy and safety of treatments based on the Stupp protocol in older adults with ndGBM and to determine the optimal treatment option for those with different O^6-MGMT promoter methylation statuses. The authors estimated HRs for OS and odds ratios for AEs of grade 3 or higher (AEs ≥ 3). Overall, 21 RCTs, including 6,478 people treated with 21 different treatment strategies, were included. Results of the pooled HRs indicated that TTFields combined with the Stupp protocol resulted in the most favorable OS for those with or without MGMT promoter methylation. Subgroup analyses by the two MGMT promoter statuses indicated that CCNU-TMZ plus radiotherapy or TTField combination therapy was associated with the best OS in those with methylated MGMT promoter (HR, 1.03; 95% credible interval, 0.54-1.97), and standard cilengitide combination therapy or TTField combination treatment was linked with the best OS in those with unmethylated MGMT promoter (HR, 1.05; 95% credible interval, 0.67-1.64). Regarding AEs of ≥ 3, there were no significant differences in pooled odds ratios. However, bayesian ranking profiles that verified intensive cilengitide combination therapy and TTField combination therapy have a similar possibility of causing the least toxicity. Results showed that TTField combination therapy was associated with increased survival regardless of the MGMT promoter methylation status and that it had a relatively tolerated safety profile compared with other combination treatments. The best treatment options for those with glioblastoma with different MGMT promoter methylation statuses were different. These findings help establish an SOC and plan for adults with ndGBM. (Stupp et al., 2017, and Stupp et al., 2015, are included in this review.)

Marenco-Hillembrand et al. (2020) conducted a systematic review to describe the current status and advances in the survival of those with glioblastoma by analyzing median OS through time and between treatment modalities. Full-text glioblastoma papers that included human individuals who were ≥ 18 years old and had a population of at least 25

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individuals were included for evaluation. The central tendency of median OS was 13.5 months (2.3-29.6 months), and cumulative 5-year survival was 5.8% (0.01%-29.1%), with a significant difference in survival between studies that predate vs postdate the implementation of TMZ and radiation [12.5 (2.3-28) vs 15.6 (3.8-29.6) months; p < 0.001]. In clinical trials, the highest median OS involved TTFields with 20.7 months (range, 20.5-20.9 months). According to the authors, therapies such as TTField provide a means of prolonging the survival of those with glioblastoma.

Kim et al. (2020) reported on Korean participants who were newly diagnosed with GBM and participated in the EF-14 trial. Overall, 39 participants in the EF-14 trial were enrolled at eight sites in South Korea. Participants (24 TTFields/TMZ; 14 TMZ alone) received TTFields (200 kHz) for > 18 hours per day; TMZ was received at 120 to 150 mg for 5 days per a 28-day cycle. Safety and efficacy were assessed. Baseline characteristics were balanced in the two arms, and the mean age was 52.1 years; 66.7% were male, with a mean KPS of 90. Safety incidence was comparable between the two arms. In the TTFields/TMZ arm, 30% experienced skin irritation vs 52% in the entire study population. No TTFields-related serious AEs were reported. The median PFS in the TTFields/TMZ arm was 6.2 months (95% CI, 4.2-12.2 months) vs 4.2 months (95% CI, 1.9-11.2 months) with TMZ alone (p = 0.67). Median OS was 27.2 months (95% CI, 21 months to NA) with TTFields/TMZ vs 15.2 months (95% CI, 7.5-24.1 months; HR, 0.27; p = 0.01) with TMZ alone. The authors concluded that median OS and 1- and 2-year survival rates were higher with TTFields/TMZ and similar to those in the entire EF-14 population. According to the authors, these results demonstrate the efficacy and safety of TTFields in this population of participants with ndGBM.

Shi et al. (2020) performed a retrospective analysis with unsolicited, postmarketing surveillance data from TTFields-treated patients with high-grade glioma (October 2011 to February 2019) using Medical Dictionary for Regulatory Activities (MedDRA) v21.1 preferred terms, stratified by region (U.S.; Europe, Middle East, and Africa; and Japan), diagnosis (ndGBM, rGBM, anaplastic astrocytoma/oligodendroglioma, and other brain tumors), and age [< 18 (pediatric), 18-64 (adults), and ≥ 65 (older adult) years of age]. This analysis aimed to assess the safety of TTFields in real-world clinical practice settings using global postmarketing surveillance data from a large cohort. Of 11,029 patients, 53% were diagnosed with ndGBM, and 39% were diagnosed with rGBM at any line of disease recurrence. Most were adults (73%), 26% were older adults, and the male-to-female ratio was approximately 2:1 (close to published ratios in typical GBM populations). The most commonly reported TTFields-related AE was array-associated skin reaction, occurring in those with ndGBM (38%), rGBM (29%), anaplastic astrocytoma/oligodendroglioma (38%), or other brain tumors (31%) as well as 37% of pediatric patients, 34% of adults, and 36% of older adults. Most skin AEs were mild/moderate and manageable. Other TTFields-related AEs in those with ndGBM/rGBM included under-array heat sensation (warmth; 11% and 10%, respectively), electric sensation (tingling; 11% and 9%, respectively), and headache (7% and 6%, respectively). The authors concluded that this TTField safety surveillance analysis in > 11,000 people revealed no new safety concerns, with a favorable safety profile comparable with that seen in published TTFields/GBM trials. The safety profile remained consistent among subgroups, suggesting feasibility in multiple populations, including older adults. Limitations include the retrospective and observational design. Safety data were collated only from those who were TTFields treated and reported AEs; therefore, the incidence in the overall cohort and subgroups is likely overestimated. In addition, no efficacy, survival, or standardized quality-of-life assessment data were included. This analysis did not translate research data into guidelines to improve individuals' care, and there is no evidence that this analysis will affect individuals' management (included in the systematic review and meta-analysis by Regev et al., 2021).

ECRI conducted a Clinical Evidence Assessment in 2019, updated in 2024, on the Optune Gio (Novocure, Ltd.) for treating rGBM. Evidence from three systematic reviews shows that Optune Gio and best standard care (BSC) chemotherapy results are similar in OS in those with rGBM. However, TTField enables individuals to avoid chemotherapy-associated AEs (e.g., serious hematologic AEs, diarrhea, nausea, infection, anorexia, muscle weakness) but does result in more skin site reactions and falls than BSC. Whether TTFields has clinical value in those with rGBM may depend on which outcomes are most important to the individuals and clinician. TTField plus BEV may increase OS in some people more than BSC alone, but additional studies are needed to ensure firm conclusions. When comparing the Optune Gio with other treatments for rGBM, the evidence is favorable for the Optune Gio, and there is moderate confidence in the evidence for OS for TTField vs BSC.

Toms et al. (2019) analyzed the compliance data from participants who received TTFields/TMZ in a subgroup analysis of the phase 3 EF-14 trial (Stupp et al., 2017) to correlate TTField compliance with PFS and OS and identify potential lower boundary for compliance with improved clinical outcomes. Compliance was assessed by usage data from the NovoTTF-100A device and calculated as a monthly percentage of TTField delivery. Those who were treated with TTFields/TMZ were segregated into subgroups by percent monthly compliance. A Cox proportional hazards model that was controlled for sex, extent of resection, MGMT methylation status, age, region, and performance status was used to investigate the effect of compliance on PFS and OS. A threshold value of 50% compliance with TTFields/TMZ improved PFS and OS vs TMZ alone, with improved outcomes as compliance increased. At compliance of > 90%, median survival was 24.9 months (28.7 months from diagnosis), and the 5-year survival rate was 29.3%. The authors concluded that a compliance

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threshold of 50% with TTFields/TMZ correlated with significantly improved OS and PFS vs TMZ alone. People with compliance of > 90% had extended median and 5-year survival rates.

Stupp et al. (2017) reported final outcomes from the randomized open-label trial in 695 participants with glioblastoma whose tumor was resected or biopsied and who had completed concomitant radiochemotherapy (median time from diagnosis to randomization, 3.8 months) and Optune therapy. Of the 695 randomized participants [median age, 56 years; IQR, 48-63 years; 473 men (68%)], 637 (92%) completed the trial. Median PFS from randomization was 6.7 months in the TTFields-TMZ group and 4.0 months in the TMZ-alone group (HR, 0.63; 95% CI, 0.52-0.76; p < 0.001). Median OS was 20.9 months in the TTFields-TMZ group vs 16.0 months in the TMZ-alone group (HR, 0.63; 95% CI, 0.53-0.76; p < 0.001). Systemic AE frequency was 48% in the TTFields-TMZ group and 44% in the TMZ-alone group. Mild to moderate skin toxicity underneath the transducer arrays occurred in 52% of those who received TTFields-TMZ vs no participants who received TMZ alone. In the final analysis of this randomized clinical trial in those with glioblastoma who had received standard radiochemotherapy, the addition of TTFields to maintenance TMZ chemotherapy vs maintenance TMZ alone resulted in statistically significant improvement in PFS and OS. These results are consistent with those of the previous interim analysis (included in the 2023 systematic review and meta-analysis by Ballo et al., 2023, and the systematic review and meta-analysis by Regev et al., 2021).

Taphoorn et al. (2018) created a secondary analysis of the Stupp et al. (2017) trial and examined the association of TTField therapy with PFS and HRQOL among participants with glioblastoma. Of the 695 participants in the study, 639 (91.9%) completed the baseline HRQOL questionnaire. Of these participants, 437 (68.4%) were men; the mean (SD) age was 54.8 (11.5) years. HRQOL did not differ significantly between treatment arms, except for itchy skin. Deterioration-free survival was significantly longer with TTFields for global health (4.8 vs 3.3 months; p < 0.01), physical (5.1 vs 3.7 months; p < 0.01) and emotional functioning (5.3 vs 3.9 months; p < 0.01), pain (5.6 vs 3.6 months; p < 0.01), and leg weakness (5.6 vs 3.9 months; p < 0.01), likely related to improved PFS. Time to deterioration, reflecting the influence of treatment, did not differ significantly, except for itchy skin (TTFields worse; 8.2 vs 14.4 months; p < 0.001) and pain (TTFields improved; 13.4 vs 12.1 months; p < 0.01). Role, social, and physical functioning were not affected by TTFields. The addition of TTFields to standard treatment with TMZ in those with glioblastoma results in improved survival, without a negative influence on HRQOL, except for more itchy skin, which is an expected consequence of the transducer arrays.

In a multinational, open-label, randomized phase III trial (EF-14 trial), Stupp et al. (2015) compared Optune in combination with TMZ to TMZ alone in 700 individuals aged 18 and over with ndGBM. The interim report revealed that in the intent-to-treat population, those treated with TTFields plus TMZ showed a statistically significant increase in PFS, the primary endpoint, compared to TMZ alone (median PFS 7.1 months versus 4.0 months, HR = 0.62, p = 0.0013). In the per-protocol population, those treated with TTFields plus TMZ demonstrated a statistically significant increase in OS, a powered secondary endpoint, compared to TMZ alone (median OS 20.5 months versus 15.6 months, HR = 0.64, p = 0.0042). In the intent-to-treat population, the median OS was 19.6 months versus 16.6 months, respectively, HR = 0.74 (p = 0.0329). The two-year survival rate was 50 percent greater with TTFields plus TMZ versus TMZ alone: 43 percent versus 29 percent. The trial's independent data monitoring committee concluded that the study met its endpoints at its pre-specified interim analysis of the first 315 participants with 18 months or more of follow-up., which, according to the authors, was easily managed, reversible, and did not result in treatment discontinuation. This clinical trial has some important limitations. Patient enrollment occurred only after the end of radiochemotherapy, leading to some variation in the delivery of standard treatment of TMZ and radiotherapy. Participants who had progressed early during radiochemotherapy were not eligible for randomization, thus excluding those with very poor prognoses. There is likely reporting bias for second-line therapies after tumor progression because, in the TTFields plus TMZ group, TTFields were to be continued, and thus, more detailed treatment information has been tracked for this group.

Tumors Other Than Glioblastoma

There is a lack of published evidence from RCTs that examine the long-term safety and effectiveness of TTField as a treatment for tumors other than GBM, including non-small cell lung cancer (NSCLC), brain metastasis, pancreatic cancer, ovarian cancer, and mesothelioma.

Hayes (2025) developed an Evidence Analysis Research Brief on the Optune Lua (Novocure GmbH) for treating metastatic NSCLC (mNSCLC). Optune Lua (Novocure GmbH) is a novel cancer treatment modality for mNSCLC that delivers low-intensity, intermediate-frequency, alternating electric fields, also known as TTField therapy, through skin-applied transducer arrays to disrupt the rapid cell division exhibited by cancer cells. TTField therapy can be used with either the chemotherapy drug docetaxel or an immune checkpoint inhibitor for the treatment of mNSCLC that has developed during or after chemotherapy. The purpose of this Evidence Analysis Research Brief was to summarize the volume of publications and to determine whether there is adequate published, peer-reviewed literature to evaluate the evidence related to Optune Lua (Novocure GmbH) for the treatment of mNSCLC. A review of abstracts suggests that there currently is not enough published, peer-reviewed literature to evaluate the evidence related to Optune Lua

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(Novocure GmbH) for the treatment of mNSCLC in a full assessment. One RCT that evaluated Optune Lua compared with standard systemic therapy was identified. No studies that evaluated Optune Lua compared with another technology were identified. One study that evaluated treatment guided by Optune Lua was identified. No systematic reviews or meta-analyses were identified. Optune Lua has U.S. Food and Drug Administration (FDA) approval for marketing in the United States. One guideline was identified. Based on a review of full-text clinical practice guidelines and position statements, guidance appears to confer no/unclear support for TTField therapy for the treatment of mNSCLC.

Babiker et al. (2025) conducted PANOVA-3, which was a global, randomized, open-label, multicenter, phase 3 trial, at 196 sites in 20 countries that evaluated TTFields with gemcitabine/nab-paclitaxel vs gemcitabine/nab-paclitaxel alone in adults with unresectable, locally advanced, biopsy-confirmed pancreatic adenocarcinoma. Eligible participants were aged 18 years or older, had an Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 2, and had no implantable electronic devices or severe hypersensitivity to adhesives or study drugs. Overall, 571 participants were randomized 1:1 (285 to TTFields plus chemotherapy; 286 to chemotherapy alone), with 198 and 207 completing at least one treatment cycle, respectively. The primary end point was OS, which was defined as the time from randomization to death or censoring, analyzed hierarchically with PFS using Kaplan-Meier and log-rank tests in the intention-to-treat population. Median OS was 16.2 months (95% CI, 15.0-18.0 months) with TTFields plus gemcitabine/nab-paclitaxel vs 14.2 months (95% CI, 12.8-15.4 months) with chemotherapy alone (HR, 0.82; 95% CI, 0.68-0.99; p = 0.039). The prespecified secondary end points included PFS, local PFS, 1-year survival rate, pain-free survival, puncture-free survival, overall response rate, resectability rate, and safety. The authors concluded that TTFields combined with gemcitabine/nab-paclitaxel significantly improved OS, pain-free survival, and distant PFS, without additional systemic toxicity, supporting its role as a new treatment paradigm for unresectable, locally advanced pancreatic adenocarcinoma. Key limitations include the open-label design and absence of a sham device in the control arm, which may have introduced assessment bias despite rigorous data collection procedures. There are limitations in study design and conduct, as OS in both arms was lower than that in comparable trials, possibly due to differences in participant selection and trial procedures. The study was further limited by the lack of crossover to TTFields at progression and the prohibition of TTFields continuation beyond local progression, which may have influenced treatment outcomes. These limitations, together with potential inclusion of participants with more advanced disease and investigator-based imaging assessments, restrict the ability to draw firm conclusions about the impact of TTFields on resectability.

Mehta et al. (2026) conducted the phase 3 METIS trial, which was a prospective, open-label, randomized, international study that enrolled adults who were aged 18 years or older, had one to 10 newly diagnosed NSCLC brain metastases that were suitable for stereotactic radiosurgery, and did not have known actionable mutations. Eligible participants had a KPS of at least 70 and were randomized 1:1 to receive stereotactic radiosurgery followed by TTField therapy at 150 kHz or stereotactic radiosurgery alone. Overall, 379 participants were screened, and 298 were enrolled (149 per arm), with efficacy analyzed by intention to treat and safety, including 287 treated participants. The primary end point was time to intracranial progression, a composite of local progression, clinical worsening, or neurological death, which was assessed by independent radiological review using Response Assessment in Neuro-Oncology Brain Metastases criteria and analyzed with Fine-Gray and Cox models. TTFields significantly delayed intracranial progression compared with stereotactic radiosurgery alone (HR, 0.72; 95% CI, 0.53-0.98; Fine-Gray p = 0.044), with 12-month intracranial progression rates of 46.9% vs 59.4%. The secondary end points included OS, time to neurocognitive failure, radiological response, and HRQOL. Device-related AEs were mainly grade 1 to 2 skin events, and no deterioration in quality of life or neurocognitive function was observed. The authors concluded that TTField therapy following stereotactic radiosurgery significantly prolonged time to intracranial progression, without worsening quality of life or cognitive function, and represents an effective treatment option for individuals with NSCLC brain metastases. Key limitations include the lack of a sham device and the open-label design, which may have introduced bias despite central blinded assessment of the primary end point. There are limitations related to data completeness, as the ability to detect changes in HRQOL was constrained by the small number of participants who completed questionnaires and by declining data availability due to poor health. Additional limitations include the broad and insufficiently characterized participant population, with undefined prior treatments and molecular pathology, which may limit interpretability and generalizability.

Vergote et al. (2025) conducted a pivotal, phase 3, randomized, open-label, multicenter trial (ENGOT-ov50/GOG-3029/INNOVATE-3) that evaluated TTField therapy plus paclitaxel vs paclitaxel alone in adult women with platinum-resistant epithelial ovarian cancer. Eligible participants were aged 18 years or older with an ECOG performance status of 0 to 1, evaluable disease per Response Evaluation Criteria in Solid Tumors v1.1, and up to five prior therapy lines, while those with platinum-refractory disease or implantable electrical devices were excluded. Overall, 558 participants were randomized 1:1 (TTFields plus paclitaxel, n = 280; paclitaxel, n = 278), with efficacy analyzed in intention-to-treat and modified intention-to-treat populations using Kaplan-Meier and stratified log-rank tests at α of 0.05. The primary end point was OS, defined from randomization to death, and the secondary end points were PFS, ORR, and safety. Median OS was 12.2 months (95% CI, 10.3-13.8 months) with TTFields plus paclitaxel vs 11.9 months (95% CI, 10.8-13.6 months) with paclitaxel alone (HR, 1.01; 95% CI, 0.83-1.24; p = 0.89). Grade 3 or higher AEs were similar between groups, and

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TTFields-related skin events were mostly grade 1 to 2. The authors concluded that TTFields plus paclitaxel did not significantly improve OS compared with paclitaxel alone, and no new safety signals were identified. Key limitations include high attrition with unclear handling of nontreated participants in the intention-to-treat analyses, which may have introduced attrition bias and inflated efficacy estimates. The modified intention-to-treat definition that required completion of at least one full 28-day cycle may have excluded early discontinuations and introduced selection bias, favoring participants with better tolerance or response. Exploratory post hoc subgroup and multivariable analyses, without prespecified hypotheses, present a limitation, as they increase the risk of data-driven bias and false-positive findings.

Leal et al. (2023) conducted a randomized, open-label, pivotal, phase 3 (LUNAR) study of TTField therapy in metastatic NSCLC. Overall, 276 participants from 130 sites in 19 countries who had metastatic NSCLC that progressed on or after platinum-based therapy, squamous or nonsquamous histology, and an ECOG performance status of 2 or less were included. The participants of the study were randomly assigned (1:1) to TTField therapy and standard systemic therapy (n = 137) or standard therapy alone (n = 139). The primary outcome that was measured was OS in the intention-to-treat population and the safety of those who received any study therapy according to the treatment received. The study's results demonstrated that OS was significantly longer with TTField therapy and standard therapy than with standard therapy alone. In the safety population (n = 267), serious AEs of any cause were reported in 70 of 133 participants (53%) who were receiving TTField therapy plus standard therapy and 51 of 134 (38%) who were receiving standard therapy alone. The most frequent grade 3 to 4 AEs were leukopenia [37 of 267 (14%)], pneumonia [28 (10%)], and anemia [21 (8%)]. TTField therapy–related AEs were reported in 95 of 133 participants (71%); these were mostly [81 (85%)] grade 1 to 2 skin and subcutaneous tissue disorders. There were three deaths that were related to standard therapy (two due to infections and one due to pulmonary hemorrhage) and no deaths associated with TTField therapy. Study limitations include the open-label design and enrollment of a small number of participants with brain metastases, potentially affecting the generalizability of these findings to that population. Additionally, participant accrual proceeded more slowly than planned in the original study design. LUNAR was started before the advent of standard genetic profiling by next-generation sequencing in NSCLC; thus, little information about the relationship between TTField therapy efficacy and tumor genetic subtype is available. The authors concluded that TTField therapy added to standard therapy significantly improved OS compared with standard therapy alone in metastatic NSCLC after progression on platinum-based therapy, without exacerbating systemic toxicities. These data suggest that TTField therapy is efficacious in metastatic NSCLC and should be considered as a treatment option to manage the disease in this setting. The study is registered at ClinicalTrials.gov (NCT02973789).

Ceresoli et al. (2019) conducted a prospective, single-arm, phase 2 trial (STELLAR) to test the activity of TTFields delivered to the thorax in combination with systemic chemotherapy for the front-line treatment of participants with unresectable, malignant pleural mesothelioma. Participants were at least 18 years old, had an ECOG performance status of 0 to 1, and had at least one measurable or evaluable lesion according to modified Response Evaluation Criteria in Solid Tumors for mesothelioma. Participants received continuous TTFields at a frequency of 150 kHz to the thorax and concomitant chemotherapy with intravenous pemetrexed (500 mg/m^2 on day 1) plus intravenous platinum (either cisplatin 75 mg/m^2 on day 1 or carboplatin area under the curve five on day 1) every 21 days for up to six cycles. Those not progressing after completion of chemotherapy received TTFields as maintenance treatment until progression, participant or physician decision, or unacceptable toxic effects. The primary end point of the trial was OS. Survival analyses were done in the intention-to-treat population, and safety analyses were done in all participants who received at least 1 day of TTFields treatment. Overall, 80 participants were enrolled in the study. The median follow-up was 12.5 months. Median OS was 18.2 months (95% CI, 12.1-25.8 months). The most common grade 3 or worse AEs were anemia [nine (11%) participants], neutropenia [seven (9%)], and thrombocytopenia [four (5%)]. Skin reaction was the only AE that was associated with TTFields and was reported as grade 1 to 2 in 53 participants (66%) and as grade 3 in four people (5%). No treatment-related deaths were observed. According to the authors, the trial showed encouraging OS results, with no increase in systemic toxicity. TTFields (150 kHz) delivered to the thorax concomitant with pemetrexed and platinum was an active and safe combination for front-line treatment of unresectable, malignant pleural mesothelioma. The lack of a comparison group limits the conclusions that can be drawn from the study. The authors indicated that further investigation in a randomized trial is warranted.

Clinical Practice Guidelines

American Society of Clinical Oncology (ASCO)

In 2022, ASCO launched living clinical practice guidelines on systemic therapy in patients with stage IV NSCLC with or without driver alterations. Both have been updated recently. Based on routine literature searches (up to September 16, 2024), this version of the stage IV NSCLC without driver alterations living guidelines reviews new evidence to assess if recommendations are up to date. The guideline expert panel reviewed new evidence from three studies that met the systematic review inclusion criteria and reviewed and approved the updated recommendations. Evidence that supports unchanged recommendations is reviewed in previous publications of this guideline. The literature states, "Given the

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potential lifestyle implications of wearing a device for 18 hours per day, the lack of evidence in the immunotherapy-pretreated population, and the absence of data in the first-line setting for immunotherapy-naive patients, there are insufficient data to definitively recommend the addition of TTFields to systemic therapy for most patients. Additional clinical studies are needed to recommend this device's use in the immunotherapy-naive first-line setting and in the chemo-immunotherapy pretreated setting. Additional studies to promote external generalizability of the use of TTFields in patients with advanced NSCLC are also needed if this novel technology is to be widely adopted. ASCO believes that cancer clinical trials are vital to inform medical decisions and improve cancer care and that all patients should have the opportunity to participate" (Leighl et al., 2025).

American Society of Clinical Oncology (ASCO)/Society for Neuro-Oncology (SNO)

In 2022, Mohile et al. published the ASCO and SNO clinical guidelines on therapy for diffuse astrocytic and oligodendroglia tumors in adults. This guideline recommends that alternating electric field therapy may be added to adjuvant TMZ in people with newly diagnosed supratentorial glioblastoma, *IDH*-WT, and CNS WHO grade 4 who have completed chemoradiation therapy (type: evidence based, benefits outweigh harms; evidence quality: moderate; strength of recommendation: weak).

European Association of Neuro-Oncology (EANO)

In 2021, Weller et al. published updated recommendations from the EANO due to the revision of the WHO Classification of Tumors of the Central Nervous System. The revisions have led to major changes in how EANO routinely diagnoses and treats those with gliomas.
Recommendations:

- The SOC for patients with *IDH*-WT glioblastoma who are aged < 70 years and have a KPS of ≥ 70 includes resection, as feasible, or biopsy followed by involved-field radiotherapy and concomitant radiotherapy and six cycles of maintenance TMZ chemotherapy (EORTC 26981-NCIC CE.3). C: I; L: A.
- TMZ might only be active in patients with MGMT promoter-methylated tumors, while its activity in those with MGMT promoter-unmethylated tumors is probably marginal. C: II; L: B.
- Older adults who are not considered candidates for TMZ chemoradiotherapy should be treated based on MGMT promoter methylation status (NOA-08, Nordic Trial) with radiotherapy (such as 15 × 2.66 Gy) or TMZ (5 of 28 days) alone. C: II; L: B.
- At recurrence, SOCs are less well defined. Surgery and radiotherapy might be considered. Nitrosourea regimens, TMZ rechallenge, and, considering the country-specific label, BEV are options for pharmacotherapy, but their impact on OS remains unproven. When available, recruitment into appropriate clinical trials should be considered. C: II; L: B.

Furthermore, EANO advocates against using any treatment beyond confirmed progression on that same treatment, including BEV and TTFields, because the clinical benefit of this practice has not been established. Several chemotherapy regimens that are commonly used to treat other tumor types, including Iri and platinum compounds, are known not to be active against gliomas and should not be used in this setting.

NCCN

The NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for central nervous system cancers, adult glioma, glioblastoma, recommend alternating electric field therapy as the only option for those with supratentorial disease (GLIO-10).

- For patients who are diagnosed with glioblastoma and are ≤ 70 years of age with a good performance status (KPS ≥ 60) with methylated or indeterminate to consider a clinical trial (preferred for eligible patients) or radiation therapy (RT) plus concurrent TMZ and adjuvant TMZ + alternating electric field therapy (preferred; category 1) or RT + concurrent TMZ and adjuvant TMZ (category 1).
- For patients who are diagnosed with glioblastoma and are ≤ 70 years of age with a good performance status (KPS ≥ 60) with unmethylated to consider a clinical trial (preferred for eligible patients) or RT + concurrent TMZ and adjuvant TMZ + alternating electric field therapy (preferred; category 1) or RT + concurrent temoxolomide and adjuvant TMZ (category 1). Or, RT alone.
- For patients who are diagnosed with glioblastoma and are > 70 years of age with a good performance status (KPS ≥ 60) with methylated or indeterminate disease to consider a clinical trial (preferred for eligible patients). Or, hypofractionated RT + concurrent and adjuvant TMZ (category 1). Or, RT + concurrent TMZ and adjuvant TMZ + alternating electric field therapy (category 1) or RT + concurrent TMZ and adjuvant TMZ or TMZ or hypofractionated RT alone (category 2B).
- For patients who are diagnosed with glioblastoma and are > 70 years of age with a good performance status (KPS ≥ 60) with unmethylated disease to consider a clinical trial (preferred for eligible patients). Or, hypofractionated RT +

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concurrent and adjuvant TMZ or RT + concurrent TMZ + adjuvant TMZ + alternating electric field therapy (category 1) or RT + concurrent TMZ and adjuvant TMZ or hypofractionated RT alone (GLIO-10 and -11).

- For recurrent or progressive disease (WHO grade 3, oligodendroglioma, *IDH1*/2 mutant, and 1p/19q codeleted, KPS of ≥ 60; WHO grade 3 or 4, astrocytoma, *IDH1*/2 mutant, KPS of ≥ 60; glioblastoma; and H3-mutated high-grade glioma having diffuse or multifocal disease), the recommendation is to consider clinical trials (preferred for eligible patients) or systemic therapy or surgery for symptomatic, large lesions or consider alternating electric field therapy for glioblastoma (category 2B) or palliative/best supportive care if there is a poor performance status.
- For recurrent or progressive disease (WHO grade 3, oligodendroglioma, *IDH1*/2 mutant, and 1p/19q codeleted, KPS of ≥ 60; WHO grade 3 or 4, astrocytoma, IDH1/2 mutant, KPS of ≥ 60; glioblastoma; and H3-mutated high-grade glioma having local, resectable disease), consider a clinical trial or resection or a brain MRI, consider clinical trials (preferred for eligible patients) or systemic therapy, consider reirradiation (category 2B), or consider alternating electric field therapy for glioblastoma (category 2B) or palliative/best supportive care if there is a poor performance status.
- For recurrent or progressive disease (WHO grade 3, oligodendroglioma, IDH1/2 mutant and 1p/19q codeleted, KPS of ≥ 60; WHO grade 3 or 4, astrocytoma, *IDH*1/2 mutant, KPS of ≥ 60; glioblastoma; and H3-mutated high-grade glioma having local, unresectable disease), resection is not recommended/elected to consider clinical trials (preferred for eligible patients) or systemic therapy, consider reirradiation (category 2B), or consider alternating electric field therapy for glioblastoma (category 2B) or palliative/best supportive care if there is a poor performance status (GLIO-13).

The NCCN Guidelines® for adult glioma, *IDH*1/2-mutant astrocytoma, and those seeking systemic therapy and adjuvant treatment who have WHO grade 4 and a KPS of ≥ 60, the preferred systemic therapy option is RT + adjuvant TMZ or RT + concurrent and adjuvant TMZ ±alternating electric field therapy (GLIO-A 4 of 10).

The NCCN Guidelines state, “Alternating electric field therapy is also FDA approved for treating recurrent glioblastoma based on the safety results of this medical device from the EF-11 clinical trial. This phase III study randomized 237 patients with recurrent glioblastoma to alternating electric field therapy or the treating oncologist’s choice of chemotherapy. The study did not meet its primary endpoint of demonstrating an improvement in survival in the cohort of patients treated with alternating electric field therapy. Although median OS was similar in both of the treatment arms (6.6 vs 6 months), the study had not been powered for a non-inferiority determination. Due to lack of clear efficacy data for alternating electric field therapy in EF-11, the panel is divided about recommending it for the treatment of recurrent glioblastoma. Similarly, re-irradiation may be reasonable to consider for some recurrent glioblastoma patients, but the panel is also divided about this option.”

“NCCN Recommendations Primary Treatment: When a patient presents with a clinical and radiologic picture suggestive of a high-grade glioma, neurosurgical input is needed regarding the feasibility of maximal safe resection. For first-line treatment of high-grade glioma, the NCCN Guidelines recommend maximal safe resection whenever possible. One exception is when CNS lymphoma is suspected; a biopsy should be performed before steroids are administered, and management should follow the corresponding pathway if the diagnosis is confirmed. When maximal resection is performed, the extent of tumor debulking should be documented with a postoperative MRI scan with and without contrast performed within 48 hours after surgery. Multidisciplinary consultation is encouraged once the pathology is available” (MS-19).

“For patients diagnosed with glioblastoma, the adjuvant options mainly depend on the patient’s age, PS (as defined by KPS), and MGMT promoter methylation status. Category 1 recommendations for patients aged ≤ 70 years with a good PS, regardless of the tumor’s MGMT methylation status, include standard brain RT plus concurrent and adjuvant TMZ with or without alternating electric field therapy. Because patients with newly diagnosed MGMT promoter-unmethylated glioblastoma are likely to receive less benefit from TMZ, RT alone is included as a reasonable option, particularly if the patient is eligible to participate in a clinical trial, which omits the use of upfront TMZ. Category 1 treatment recommendations for patients > 70 years of age with newly diagnosed glioblastoma, a good PS, and MGMT promoter methylated tumors include hypofractionated brain RT plus concurrent and adjuvant TMZ141 or standard brain RT plus concurrent and adjuvant TMZ and alternating electric field therapy. For those patients > 70 years with newly diagnosed glioblastoma, a good PS, and with MGMT-unmethylated or -indeterminant tumors, hypofractionated brain radiation with concurrent and adjuvant TMZ141 is preferred, but standard brain RT plus concurrent and adjuvant TMZ and alternating electric field therapy is also a reasonable option (category 1). For patients > 70 years of age who want to be treated as aggressively as possible. The complete list of recommendations that the panel did not consider category 1 can be found in the treatment algorithms for patients with glioblastoma who are > 70 years” (MS-20) (NCCN v.1., 2026).

National Institute for Health and Care Excellence (NICE)

According to the 2018 (updated 2021) NICE guidelines titled *Brain Tumours (Primary) and Brain Metastases in Over 16s*

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for the management of newly diagnosed grade IV glioma (glioblastoma) following surgery or if surgery is not possible (or has been declined), the guidelines state:

- Do not offer TTField as part of managing a newly diagnosed grade IV glioma (glioblastoma).

For the management of recurrent high-grade glioma (recurrent grade III and grade IV glioma)

- When deciding on treatment options for people with recurrent high-grade glioma, take into account:
  - KPS
  - The person's preferences
  - Time from last treatment
  - Tumor molecular markers
  - What their last treatment was
- Consider PCV or single-agent CCNU as an alternative to TMZ in people with recurrent high-grade glioma.
- Consider best supportive care alone for high-grade glioma if other treatments are not likely to be of benefit or if the person would prefer this.
- For people with focally recurrent high-grade glioma, the multidisciplinary team should also consider the treatment options of:
  - Further surgery
  - Further radiotherapy
- Do not offer BEV, erlotinib, or cediranib, either alone or in combination with chemotherapy, as part of management of recurrent high-grade glioma.
- Do not offer TTFields as part of management of recurrent high-grade glioma.
- If asked, advise people who have recurrent high-grade glioma (and their relatives and carers, as appropriate) that the available evidence does not support the use of:
  - Cannabis oil
  - Immunotherapy
  - Ketogenic diets
  - Metformin
  - Statins
  - Valganciclovir

U.S. Food and Drug Administration (FDA)

This section is to be used for informational purposes only. FDA approval alone is not a basis for coverage.

The Optune treatment kit, formerly the NovoTTF-100A System (Novocure), was approved by the FDA in April 2011 as a novel device to treat adults who are aged 22 years or older with glioblastoma that recurs or progresses after receiving chemotherapy and radiation therapy. The FDA categorizes the Optune as a stimulator, low-electric-field tumor treatment; refer to the following website for the initial premarket approval information: https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpma/pma.cfm?id=P100034. (Accessed May 21, 2026)

A supplemental FDA premarket approval was received in October 2015 for Optune with temozolomide in adults with newly diagnosed supratentorial glioblastoma following maximal debulking surgery and completion of radiation therapy together with concomitant standard-of-care chemotherapy. Refer to the following website for more information: https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpma/pma.cfm?id=P100034S013. (Accessed May 21, 2026)

Refer to the following website for additional information on supplemental FDA approvals for the Optune using product code NZK: http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMA/pma.cfm. (Accessed May 21, 2026)

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Policy History/Revision Information

Date	Summary of Changes
09/01/2026	**Supporting Information** • Updated *Clinical Evidence* and *References* sections to reflect the most current information • Archived previous policy version 2026T0582R

Instructions for Use

This Medical Policy provides assistance in interpreting UnitedHealthcare standard benefit plans. When deciding coverage, the member specific benefit plan document must be referenced as the terms of the member specific benefit plan may differ from the standard plan. In the event of a conflict, the member specific benefit plan document governs. Before using this policy, check the member specific benefit plan document and any applicable federal or state mandates. UnitedHealthcare reserves the right to modify its policies and guidelines as necessary. This Medical Policy is provided for informational purposes. It does not constitute medical advice.

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