Clinical UM Guideline

Subject:	Electric Tumor Treatment Field (TTF) Therapy		
Guideline #:	CG-DME-44	**Publish Date:**	04/01/2026
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Description

This document addresses the use of alternating electrical field therapy known as tumor treatment field (TTF) therapy. The TTF device creates low-intensity, intermediate frequency (100–200 kilohertz [kHz]) electric currents delivered to the malignant tumor site by insulated electrodes placed on the skin surface. TTF therapy causes tumor cell death (apoptosis) by disrupting the assembly of microtubules during later stages of cell division.

Note: For a high-level overview of this document, please see "Summary for Members and Families" below.

Clinical Indications

Medically Necessary:

TTF therapy is considered **medically necessary** for either of the following conditions (I *or* II) when the applicable criteria are met:

I. Histologically-confirmed supratentorial glioblastoma (known also as glioblastoma multiforme [GBM] or World Health Organization [WHO] grade IV astrocytoma) when *both* criteria (A *and* B) are met:
   A. An FDA approved device is used; **and**
   B. Either criteria 1 *or* 2 below are met:
      1. Newly diagnosed GBM when **all** the following criteria are met:
         a. Initial treatment with debulking surgery or biopsy followed by chemoradiation with concomitant temozolomide and radiotherapy has been completed with no documented tumor progression*; **and**
         b. TTF is used in combination with temozolomide; **and**
         c. Individual has Karnofsky Performance Status (KPS) score of 70 or higher **or** Eastern Cooperative Oncology Group (ECOG) performance status 0-1; **and**
         d. Individual or caregiver has been trained and is willing and able to apply and use the device at least 18 hours, per day on average.

         or
      2. Recurrent GBM when **all** the following criteria are met:
         a. TTF is used as a monotherapy; **and**
         b. Individual has KPS score of 70 or higher or ECOG performance status 0-1; **and**
         c. Individual or caregiver has been trained and is willing and able to apply and use the device at least 18 hours, per day, on average.

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Historical

Continuation of TTF therapy to treat GBM beyond the initial 90 days is considered **medically necessary** when *both* of the following criteria are met:

1. Documentation of compliant use must be reported every 90 days as evidenced by the device monitor report showing the individual is using the device at least 18 hours per day, on average; **and**
2. There is no documented tumor progression*, defined as *at least one* of the following:
    a. Tumor growth of greater than 25% of the product of 2 perpendicular diameters compared to the smallest tumor area measured; **or**
    b. Appearance of one or more new tumors in the brain (diagnosed radiologically as GBM).

II. Histologically-confirmed de novo locally advanced pancreatic adenocarcinoma when *all* of the following criteria (A, B, C *and* D) are met:
A. Disease is considered unresectable; **and**
B. Individual has an ECOG performance status of 0-2; **and**
C. TTF is used in combination with gemcitabine and nab-paclitaxel; **and**
D. Individual or caregiver has been trained and is willing and able to apply and use the device at least 12 hours, per day on average.

Continuation of TTF therapy to treat histologically-confirmed de novo locally advanced pancreatic adenocarcinoma beyond the initial 90 days is considered **medically necessary** when *both* of the following criteria are met:

A. Documentation of compliant use must be reported every 90 days as evidenced by the device monitor report showing the individual is using the device at least 12 hours per day, on average; **and**
B. One of the following criteria (1 *or* 2) are met:
    1. There is no documented tumor progression*, as evidenced by *any* of the following (a, b, *or* c):
        a. Increase in size of target lesion as defined by **both** (i *and* ii) of the following:
            i. 20% or greater increase in sum of target lesion diameters; **and**
            ii. 5 mm or greater absolute increase target lesion size;
            or
        b. Worsening of non-target disease requiring a treatment change; **or**
        c. Appearance of new lesions;
        or
    2. Individual reports meaningful pain control with TTF therapy.

*See discussion section regarding *tumor progression*.

Not Medically Necessary:

The use of devices to generate electric tumor treatment fields (TTF) is considered **not medically necessary** when the criteria above are not met.

The use of enhanced computer treatment planning software (such as NovoTal) is considered **not medically necessary** in all cases.

Historical

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Summary for Members and Families

This document describes clinical studies and expert recommendations, and explains whether TTF therapy is appropriate. The following summary does not replace the medical necessity criteria or other information in this document. The summary may not contain all of the relevant criteria or information. This summary is not medical advice. Please check with your healthcare provider for any advice about your health.

Key Information

Tumor Treatment Fields, also called TTF therapy, involves the use of a wearable device that sends low-level electrical fields into a tumor. The device is placed on the skin with adhesive patches. These electrical fields may slow or stop cancer cells from dividing, which may lead to cancer cell death. The main device for brain tumors is called Optune (NovoTTF-100A System). A similar device, Optune Lua, is proposed for some chest cancers. TTF therapy must be worn for many hours each day to work well. Studies show that TTF therapy can help some people with certain cancers live longer when used with standard treatments. However, it has not been proven to help in all cancers. Skin irritation under the patches is the most common side effect. The device can also be heavy and may affect daily life. Each use has benefits and limits.

What the Studies Show

For newly diagnosed glioblastoma, a fast-growing brain cancer, studies compared temozolomide (Temodar) alone to temozolomide plus TTF therapy. People who used TTF with chemotherapy lived longer on average than those who had chemotherapy alone. In one large study, people lived about 20 months with TTF plus temozolomide compared to about 16 months with temozolomide alone. Skin reactions were more common with TTF, but most other side effects were similar between groups. Studies also show that people who wear the device at least 18 hours a day, about 75 percent of the time, tend to live longer than those who use it less often.

For locally advanced pancreatic cancer that cannot be removed with surgery, one large study tested TTF therapy with gemcitabine (Gemzar) and nab-paclitaxel (Abraxane). People who used TTF plus chemotherapy lived longer than those who had chemotherapy alone. They also had a longer time before their cancer worsened and a longer time before pain got worse. TTF did not increase whole body side effects from chemotherapy. Most device related side effects were skin reactions. In other cancers, such as ovarian cancer, studies did not show longer survival with TTF. For pleural mesothelioma and non-small cell lung cancer, results are mixed, and some expert groups do not recommend routine use. Better studies are needed to know if TTF improves health in these cancers.

Summary of Treatment Options

TTF has been approved by the U.S. Food and Drug Administration (FDA) for the treatment of one type of brain cancer glioblastoma. Studies show it may improve survival when added to drug treatment in newly found disease. It may also be used without drug treatment in some people who have been treated for glioblastoma and it has come back. The device must be worn at least 18 hours a day to work properly.

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Some studies have looked at the use of TTF for lung cancer, ovarian cancer, and pancreatic cancer. Some studies show that it may help people live longer, but guidelines from major medical societies do not recommend such use yet. More research is needed to understand if TTF helps in these types of cancer.

Special computer software may be used to help doctors plan where to use TTF. While it may help with setting up, studies have not shown that it improves the result of treatment.

What is Clinically Appropriate?

TTF therapy may be appropriate in these situations:

- Newly diagnosed supratentorial glioblastoma after surgery or biopsy and chemoradiation with temozolomide, when there is no tumor growth; and
- Used together with temozolomide; and
- The person has good physical function, shown by a Karnofsky Performance Status score of 70 or higher or an Eastern Cooperative Oncology Group score of 0 to 1; and
- The person or caregiver is trained and able to use the device at least 18 hours per day on average.

- Recurrent glioblastoma; and
- Used alone without chemotherapy; and
- The person has good physical function, shown by a Karnofsky Performance Status score of 70 or higher or an Eastern Cooperative Oncology Group score of 0 to 1; and
- The person or caregiver is trained and able to use the device at least 18 hours per day on average.

TTF therapy may continue after 90 days for glioblastoma when:

- The device report shows use of at least 18 hours per day on average; and
- There is no tumor progression on brain imaging. Tumor progression means tumor growth of more than 25 percent in size or new brain tumors.

TTF therapy may also be appropriate for newly diagnosed, locally advanced pancreatic adenocarcinoma that cannot be removed by surgery when:

- The cancer is unresectable; and
- The person has moderate to good physical function, shown by an Eastern Cooperative Oncology Group score of 0 to 2; and
- TTF is used with gemcitabine and nab-paclitaxel; and
- The person or caregiver is trained and able to use the device at least 12 hours per day on average.

TTF therapy may continue after 90 days for pancreatic cancer when:

- The device report shows use of at least 12 hours per day on average; and
- There is no tumor progression on imaging, meaning the cancer has not grown by set measurement rules, there are no new tumors, and the cancer has not clearly worsened; or
- The person reports no pain or improved pain compared to before using the device.

Historical

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What is Not Clinically Appropriate?

TTF therapy is not clinically appropriate when the criteria above are not met.

Enhanced treatment planning software, such as NovoTal, is not clinically appropriate in all cases. Small studies looked at how doctors use this software, but they did not show that it improves survival or other health outcomes. Better studies are needed to know if this software improves health.

TTF therapy for cancers other than glioblastoma or locally advanced pancreatic cancer, as listed above, is not clinically appropriate. For example, in ovarian cancer, a large study showed no improvement in survival when TTF was added to chemotherapy. In pleural mesothelioma, the main study did not compare TTF plus chemotherapy to chemotherapy alone in a randomized way. In non-small cell lung cancer, results are limited and some expert groups do not recommend routine use. Because of these limits in the evidence, these uses have not been proven to improve health. Unnecessary or unproven tests or treatments can lead to needless worry, or to treatment that does not help. TTF therapy is not clinically appropriate in scenarios other than those listed above.

(Return to Description)

Coding

The following codes for treatments and procedures applicable to this guideline are included below for informational purposes. Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement policy. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

When services may be Medically Necessary when criteria are met:

CPT

1025T	Alternating electric fields dosimetry and delivery-simulation modeling, creation and selection of patient-specific array layouts, and placement verification

HCPCS

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

ICD-10 Diagnosis

C25.0-C25.9	Malignant neoplasm of pancreas
C71.0-C71.9	Malignant neoplasm of brain
Z85.07	Personal history of malignant neoplasm of pancreas
Z85.841	Personal history of malignant neoplasm of brain

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When services are Not Medically Necessary:
For the procedure and diagnosis codes listed above when criteria are not met, and for all other diagnoses not listed.

When services are also Not Medically Necessary:

CPT	
77299	Unlisted procedure, therapeutic radiology clinical treatment planning [when specified as treatment planning for use of an electrical stimulation device for TTF using enhanced computer software (e.g., NovoTal)]
ICD-10 Diagnosis	
	All diagnoses

Discussion/General Information

Summary

Tumor Treatment Fields (TTF) therapy delivers low-intensity, intermediate-frequency alternating electric fields to disrupt mitosis and induce tumor cell death. The Optune device is FDA-approved for the treatment of GBM or grade IV astrocytomas in both recurrent and newly diagnosed disease. TTF therapy has been demonstrated to improve survival when combined with temozolomide, and the National Comprehensive Cancer Network® (NCCN) has a category 1 recommendation for adjuvant therapy (category 2B for recurrence); compliance ≥ 75% is recommended to optimize clinical benefit. The FDA also approved Optune Lua® for malignant pleural mesothelioma with pemetrexed/platinum chemotherapy and for metastatic non-small cell lung cancer (NSCLC) after platinum therapy, though the NCCN and American Society of Clinical Oncology (ASCO) guidelines do not recommend use.

In pancreatic cancer, the phase III PANOVA-3 trial demonstrated a statistically significant improvement in overall survival with the addition of TTF therapy to gemcitabine/nab-paclitaxel, without increased systemic toxicity and with preservation of quality-of-life measures. Based on these findings, TTF therapy will be considered medically necessary for pancreatic cancer when defined clinical criteria are met. In contrast, evidence in ovarian cancer has not demonstrated improvement in survival outcomes, and national guidelines continue to endorse TTF therapy primarily for the treatment of GBM.

Discussion

Glioblastoma Multiforme (GBM)

Glioblastoma (WHO grade IV astrocytoma), also known as GBM (National Cancer Institute [NCI], 2025), has a peak incidence between the ages of 45 and 70 years. GBM is the most frequently occurring brain tumor accounting for approximately 12% to 15% of all brain tumors and 50% to 60% of all astrocytic tumors. Giant cell glioblastoma

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and gliosarcoma are two histologic variants of GBM. The 5-year survival rate for GBM is between 1% and 19%, depending upon age. Treatment of GBM is challenging due to the inability of most systemic therapy agents to cross the blood-brain barrier and the propensity of high-grade gliomas to recur (NCCN Central Nervous System Cancers [CNS], V2.2025). The delivery of low-intensity, intermediate-frequency alternating electric fields has been demonstrated to have an inhibitory effect on proliferating cells. Exposure to the alternating fields leads to mitotic disruption and ultimately mitotic cell death. Nonproliferating cells remain unaffected by these fields (Fabian, 2019).

NovoTTF™-100A System (NovoCure™ Ltd., Portsmouth, NH; Haifa, Israel) received FDA premarket approval (PMA) in 2011. The device is now marketed as Optune® (NovoCure Ltd., Portsmouth, NH, Haifa, Israel). Optune, a portable, non-invasive device designed for the delivery of TTF therapy to the head, should be worn at least 18 hours a day in order to obtain the best treatment response. The device was originally approved as a novel device to treat adults aged 22 years or older with GBM that recurs or progresses after receiving chemotherapy and radiation therapy. On October 5, 2015, the FDA approved the use of Optune in combination with temozolomide for the treatment of adults with newly diagnosed, supratentorial GBM following maximal debulking surgery and radiation therapy.

The first generation Optune system weighed approximately 6 pounds, the weight of the second generation Optune system has been reduced to 2.7 pounds. The second-generation device has also been redesigned to generate significantly less noise. These improvements may result in increased compliance. In a study by Kinzel and associates (2019), 10 individuals with GBM who were currently using the first generation TTF device, were transitioned to the second-generation device. Compliance improved in 4 users, was maintained in 5 users and decreased in 1 user. A total of 3/10 users had not reached 75% compliance level with the first-generation device but did achieve ≥ 75% compliance following transition to the second-generation device.

Newly diagnosed GBM

Current standard treatment for newly diagnosed GBM consists of tumor resection followed by daily low dose temozolomide administered concurrently with external beam radiotherapy followed by adjuvant temozolomide with alternating electric field therapy (NCCN CNS, V2.2025). Radiochemotherapy is followed by adjuvant temozolomide given for 6 to 12 months. The prognosis for individuals with GBM is poor, with a 1-year survival rate of less than 40%.

Stupp and colleagues (2015) evaluated the safety and efficacy of TTF therapy in individuals with newly diagnosed GBM following chemoradiation therapy. In a multi-center clinical trial, 695 individuals were randomized (2:1) to either TTF therapy (worn at least 18 hours/day) with temozolomide or temozolomide alone. The primary endpoint was identified as progression-free survival (PFS) time in the intent-to-treat (ITT) population (significant threshold, $p \leq 0.01$).

An interim analysis conducted on the first 315 participants who had completed at least 18 months of follow-up revealed median PFS in the TTF therapy plus temozolomide group of 7.1 months (95% confidence interval [CI], 5.9-8.2 months) compared to 4.0 months (95% CI, 3.3-5.2 months) in the temozolomide group (Hazard Ratio [HR], 0.62; 98.7% CI, 0.43-0.89; stratified log-rank, p=0.001). Median overall survival (OS, secondary endpoint) in the

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per-protocol population was 20.5 months (95% CI, 16.7-25.0 months) in the TTF therapy plus temozolomide group compared to 15.6 months (95% CI, 13.3-19.1 months) (HR, 0.64; 99.4% CI, 0.42-0.98; p=0.004) in the temozolomide alone group. Based on the interim analysis results, the study was terminated and individuals in the control group were offered TTF therapy in addition to temozolomide. A total of 11 individuals crossed over and began using TTF therapy. With the exception of a higher incidence of localized skin reactions in the TTF therapy plus temozolomide group, the incidence, distribution, and severity of adverse events (AEs) were similar across both treatment groups. The final analysis of the data was consistent with the interim analysis results (Stupp, 2017).

Kirson and associates (2009b) reported on the results from an industry-sponsored pilot study of TTF therapy alone and TTF therapy in combination with chemotherapy for individuals with diagnosed GBM. In this single arm study, the first group included 10 individuals with recurrent GBM after failure of maintenance temozolomide, and 10 individuals with newly diagnosed GBM treated with TTF therapy combined with temozolomide were in the second cohort. All 20 individuals were treated for an average of 1 year (range 2.5-24 months) continuously. The first group was compared to a matched group of 18 concurrent controls who received salvage chemotherapy for relapsed/recurrent GBM. The TTF-chemotherapy group was compared to a matched group of 32 concurrent controls who received temozolomide alone. The OS for both cohorts was also compared to matched historical control data. Data for the first group were reported by Kirson and colleagues in 2007. For the group of 10 individuals with newly diagnosed GBM, PFS was significantly different (HR, 3.32; 95% CI, 1.9-5.9; p=0.0002) between the TTF-chemotherapy group compared to the matched concurrent and historical controls. The difference in OS was also significant (p=0.0018). The authors concluded TTF therapy may also be an effective sensitizer when used concurrently with chemotherapeutic agents.

Ballo and colleagues (2023) published a meta-analysis focusing on whether the use of TTF therapy added to standard of care (SOC) therapy in newly diagnosed individuals with GBM resulted in a consistent survival benefit as observed in the real-world setting. The analysis included one RCT and eight retrospective cohort studies, six of these retrospective studies included a control group who were not treated with TTF therapy. Treatment which included TTF therapy resulted in a significantly improved OS (HR, 0.63; 95% CI: 0.53–0.75; p<0.001). The pooled median OS in the SOC alone was 17.4 months compared to the SOC plus TTF therapy group was 22.6 months. In the studies which evaluated device usage and OS (n=5), usage of ≥ 75% was associated with improved OS compared to device usage ≤ 75% (HR, 0.60; 95% CI: 0.48–0.73; p<0.001).

The use of adjuvant alternating electric field therapy when used as an initial therapy along with temozolomide for individuals with anaplastic gliomas/glioblastoma with good performance status following standard radiotherapy and concurrent temozolomide is a NCCN category 1 recommendation.

Recurrent or Progressive GBM

Stupp and associates (2012) conducted a phase III, pivotal, multinational, randomized controlled trial (RCT) upon which the initial PMA was based. Between September 2006 and May 2009, 28 clinical centers enrolled 237 adult participants with relapsed or progressive GBM despite conventional therapy (e.g., surgery and chemo-radiotherapy followed by chemotherapy). A total of 120 participants were randomized in a 1:1 ratio to receive monotherapy with TTF therapy and 117 participants were randomized to the group treated with available best standard care (BSC)

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chemotherapies as practiced at each of the participating clinical centers. Chemotherapy agents considered as BSC during the trial included platinum-based chemotherapy (i.e., carboplatin); nitrosureas (BCNU); procarbazine; combination of procarbazine, lomustine and vincristine (PCV); temozolomide; and bevacizumab. A period of 28 days of treatment with the TTF device was considered one full treatment course. Participants treated with the TTF device were allowed to take breaks from treatment up to an hour, twice per day for personal needs such as showers. The primary endpoint of the study was OS. Secondary endpoints included PFS at 6 months (PFS6), time-to-progression (TTP), 1-year survival rate, quality of life (QOL), and radiological response. Participants were seen in clinic monthly, and magnetic resonance imaging (MRI) was performed after 2, 4, and 6 months from initiation of treatment and subsequent MRIs were done according to local practice until disease progression. Medical follow-up continued for 2 months after disease progression. Monthly telephone interviews with the participants' caregivers were used to assess participant mortality rates.

A total of 97% (116) of 120 enrollees in the TTF therapy group started treatment and 93 participants (78%) completed 1 cycle (4 weeks) of therapy. Discontinuation of TTF therapy occurred in 27 participants due to noncompliance or the inability to handle the device. For each TTF therapy treatment month, the median compliance was 86% (range 41-98%), which equaled a mean use of 20.6 hours per day. In the BSC (active control) group, 113 (97%) of the 117 assigned participants received chemotherapy, 112/113 participants completed one full treatment course. In the BSC cohort, 21 participants did not return to the site and details on disease progression and toxicity were not available. The median survival of 6.6 months in the TTF therapy group was marginally longer than 6 months in the BSC group (HR, 0.86; 95% CI, 0.66-1.12; p=0.27). For both groups, 1-year survival was 20%. The survival rates for 2 and 3 years were 8% (95% CI: 4, 13) and 4% (95% CI: 1, 8) versus 5% (95% CI: 3, 10) and 1% (95% CI: 0, 3) for the TTF therapy cohort compared to the BSC cohort, respectively. With a median follow-up of 39 months, 93% (220 participants) had died. Objective radiological responses (partial response [PR] and complete response [CR]) were noted in 14 participants in the TTF therapy group and 7 in the BSC group, with a calculated response rate of 14.0% (95% CI, 7.9-22.4%) compared to 9.6% (95% CI, 3.9-18.8%), respectively. Individuals in the TTF therapy group reported localized reactions which resolved with topical steroids. BSC participants experienced grade 2-4 events by organ system related to the pharmacologic activity of chemotherapy agents utilized. This trial represents the first phase III clinical trial of the TTF therapy device using the first-generation device. The primary endpoint of the trial, improved OS compared to chemotherapy, was not reached. The TTF therapy group did demonstrate similar efficacy to chemotherapy regimens with a lower toxicity profile and better quality of life (Fabian, 2019).

In 2014, Mrugala and associates analyzed the registry data of all individuals with recurrent GBM who had undergone therapy with the TTF device in 91 cancer centers (n=457). The median survival rate was 9.6 months. This was significantly longer than the 6.6 months reported in the Stupp (2012) trial. The individuals included in the registry data analysis also reported more than double the overall 1- and 2-year survival rates than reported in the Stupp 2012 trial. This may have been associated with the number of recurrences experienced prior to the application of the TTF device. Individuals in the data registry cohort were more likely experiencing their first recurrence (33%) compared to individuals in the Stupp (2012) trial (9%). Compliance is also a prognostic factor of OS. Individuals with 75% or greater compliance, defined as daily compliance ≥ 75% or ≥ 18 hours daily, had a median OS of 13.5 months compared to 4.0 months in those with suboptimal compliance.

Historical

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Vymazal and colleagues (2015) analyzed the response patterns in individuals with recurrent GBM who exhibited an objective response in two previous studies in order to evaluate the baseline characteristics of those individuals who responded and to evaluate the relationship between compliance with use and efficacy outcomes. The analysis was completed on one pilot study (n=10) and a phase III trial (n=237) in which TTF therapy was compared to standard chemotherapy. Between both studies, TTF was administered as monotherapy in 130 individuals. Across both trials, there was a 15% response rate (16/110 with a 4% CR rate). There were no significant differences in baseline characteristics between the responder and non-responder groups. In those in which a response was noted, there was frequently a delayed response; the tumor would initially continue to grow before responding to treatment. Analysis supported that an increase in compliance was associated with better treatment response and longer OS. The extent of treatment response in those who exhibited a response was significantly dependent on compliance.

Treatment recommendations for brain tumors include surgical resection, radiation therapy and/or chemotherapy as treatment options. There is no established second-line therapy for recurrent gliomas (NCI, 2025; NCCN CNS, V2.2025). The NCCN panel designates a 2B recommendation for alternating electric field therapy in the treatment of recurrent GBM. The evidence supports that the use of TTF therapy in recurrent GBM is associated with improved OS when used consistently with a trend towards higher levels of survival associated with increasing compliance (Toms, 2019).

Locally advanced pancreatic adenocarcinoma

Pancreatic ductal adenocarcinoma is a highly aggressive malignancy and the third leading cause of cancer-related death, typically presenting late because early symptoms are nonspecific; individuals often develop weight loss, abdominal or back pain, jaundice (particularly with head lesions), and declining performance status. At diagnosis, only about 15% of individuals have (borderline) resectable disease, approximately 35% present with locally advanced pancreatic cancer (LAPC), and roughly 50% have metastatic disease. LAPC is characterized by extensive vascular involvement that is unresectable and carries a substantial risk of distant spread; indeed, pancreatic cancer is considered a systemic disease with many individuals harboring occult micrometastases at baseline. Staging broadly includes resectable, borderline resectable, locally advanced (unresectable), and metastatic disease based on vascular involvement and presence of distant metastases. For LAPC, standard treatment consists of systemic chemotherapy, most commonly modified FOLFIRINOX or gemcitabine/nab-paclitaxel (NCCN Pancreatic Adenocarcinoma, V2.2025). In a limited group of individuals without progression, consolidative radiotherapy such as stereotactic body radiotherapy (SBRT) may be considered. In metastatic disease, systemic chemotherapy remains the mainstay of treatment, with FOLFIRINOX demonstrating superior OS compared with gemcitabine in advanced pancreatic cancer. Overall, outcomes remain poor across stages, with disease progression driven by both local tumor effects and high rates of distant metastasis.

Babiker (2025) reported results from the randomized, open-label phase III PANOVA-3 trial (n=571) evaluating TTF therapy in combination with gemcitabine and nab-paclitaxel in adults with newly diagnosed biopsy-confirmed unresectable locally advanced pancreatic adenocarcinoma. Participants reflected a population of largely ambulatory and able to tolerate systemic therapy and were required to have an ECOG performance status of 0–2. The study protocol recommended TTF therapy be used at least 75% of the time, corresponding to a minimum of 18 hours per day. Median device usage in the trial was 62% (approximately 15 hours/day), exceeding 12 hours per day on

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average. TTF therapy did not increase systemic toxicity beyond chemotherapy; device-related AEs were primarily mild-to-moderate dermatologic reactions, with grade ≥ 3 skin events in 7.7% of participants and no TTF therapy related deaths.

The addition of TTF therapy to chemotherapy produced statistically and clinically meaningful improvements in key survival outcomes. In the ITT population, median OS improved to 16.2 months vs. 14.2 months with chemotherapy alone (HR 0.82; p=0.039), with an even greater benefit in the modified ITT population (18.3 vs. 15.1 months; HR 0.77; p=0.023). PFS, a highly relevant endpoint in unresectable pancreatic cancer, was significantly prolonged to 15.2 months compared with 9.1 months (HR 0.74; p=0.027), representing a greater than 6-month delay in clinically meaningful pain progression. This is a significant 6.1-month extension in time to pain progression. Distant progression-free survival was also significantly extended (13.9 vs. 11.5 months; HR 0.74; p=0.022), supporting improved systemic disease control in a setting where micrometastatic spread is common. While overall PFS, local PFS, and ORR were not significantly different, the consistent improvements in OS, pain control, and distant disease progression, achieved without added systemic toxicity and with sustained daily device usage, represent a meaningful therapeutic advance for individuals with unresectable LAPC, a population with historically limited treatment progress.

Pain management in locally advanced pancreatic adenocarcinoma

Pain management is a concern in individuals with pancreatic adenocarcinoma. The NCCN clinical practice guideline on pancreatic adenocarcinoma (V2.2025) notes “Most patients with locally advanced or metastatic pancreatic cancer experience cancer-related pain.” Pancreatic cancer pain results from direct neural invasion and neurogenic inflammation, producing both nociceptive and neuropathic components. The disease commonly infiltrates the dense retroperitoneal nerve plexuses surrounding the pancreas, particularly the celiac and splanchnic pathways, and its pain has a “complex physiopathology” involving neural invasion and inflammatory changes. Because the pancreas is primarily a retroperitoneal organ rich in neural tissue, tumor cells readily invade peripheral nerves, leading to intractable upper abdominal and back pain. Visceral afferent fibers from the pancreas travel via the splanchnic nerves to the celiac plexus; tumor-related irritation or infiltration of these pathways amplifies pain transmission. Together, perineural invasion, neural inflammation, and propagation through the splanchnic–celiac network contribute to the severe, often refractory pain seen in advanced pancreatic cancer (Lambert, 2019; Luo, 2025). Current pain management techniques include around-the-clock analgesics, radiation therapy or celiac plexus neurolysis.

In the PANOVA-3 trial, pain was measured using a participant-reported visual analog scale (VAS), with baseline pain established at the time of randomization and used as the reference point for longitudinal comparison. Pain-free survival was defined as the time from randomization to either a 20 point or greater increase from baseline VAS score or death, making this threshold the prespecified measurable event indicating clinically meaningful worsening. Participants without a VAS-defined event were censored at their last VAS assessment, and deaths within 8 weeks of the last VAS were counted as events. In this trial, *meaningful* reflects both statistical significance and attainment of the predefined VAS threshold for clinically important pain worsening (20-point or greater increase from baseline), consistent with established minimal clinically important difference standards cited in the trial methodology.

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Tumor progression (Return to Clinical Indications)

MacDonald and colleagues (1990) categorize 4 response categories: complete response, partial response, progressive disease and stable disease in supratentorial malignant glioma. Tumor progression can be defined in 3 ways: increasing tumor size, new areas of tumor and unequivocal neurologic deterioration. Measurement of tumor size is commonly determined using two-dimensional tumor measurements on computed tomography (CT) or magnetic resonance imaging (MRI) (Wen, 2010).

Tumor progression in GBM, based on the Macdonald criteria was defined by Stupp (2015) as at least one of the following:

- Tumor growth of greater than 25% of the product of 2 perpendicular diameters compared to the smallest tumor area measured, also calculated as a greater than 25% increase in sum of the products of perpendicular diameters of enhancing lesions compared with the smallest tumor measurement.
- Appearance of one or more new tumors in the brain (diagnosed radiologically as GBM).

Macdonald (1990) defines the measure of size as the largest cross-sectional area (the largest cross-sectional diameter multiplied by the largest diameter perpendicular to it). The goal of this calculation is to measure the response as a change of a product of the maximal cross-sectional enhancing diameters (Aykan, 2020). The smallest tumor measurement is considered the size at baseline or the size at best response (Wen, 2010).

In the pivotal PANOVA-3 trial assessing locally advanced pancreatic cancer, local disease progression was quantified using the Revised Response Evaluation Criteria in Solid Tumors (RECIST v1.1) tool, which measures tumor burden changes via imaging. At baseline, up to five measurable target lesions (maximum two per organ) are selected and their longest diameters are summed to establish a reference value. Progressive disease is defined as at least a 20% increase in the sum of diameters of target lesions compared with the smallest sum recorded on study (including baseline if smallest), with a required absolute increase of at least 5 mm to avoid over-calling minor measurement variation. Progression may also be declared with the unequivocal worsening of non-target disease or the appearance of one or more new lesions on imaging. These criteria provide an objective, reproducible framework for determining whether pancreatic tumors are growing despite therapy and are widely used in clinical trials and treatment.

Compliance with therapy

The TTF device is designed for continuous application, with at least 18 hours of daily use required to maintain therapeutic efficacy (Regev, 2021). The compliance rate is an independent predictor of OS in individuals with glioblastoma (Toms, 2019). Device adherence is often expressed as usage percentage, where ≥ 75% reflects at least 18 hours per day (Ballo, 2023). Compliance is objectively tracked through internal device log files, ensuring accurate measurement of usage patterns.

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A systematic review and meta-analysis further demonstrated that individuals with glioblastoma with ≥ 75% daily usage achieved a longer survival (10.3 months) compared to those with < 75% (5.7 months); 6-, 9-, and 12-month OS rates were also consistently higher in the higher compliance group (Regev, 2021). A retrospective single-institution study by Riegel and associates (2025) evaluated outcomes for newly diagnosed glioblastoma treated with standard therapy with or without TTF therapy. A total of 208 individuals were included, and survival analysis demonstrated that adding TTF therapy improved median OS (21.7 vs. 17.7 months) and PFS (12.4 vs. 9.6 months) compared to standard therapy alone. Device usage was a critical determinant of benefit: when TTF therapy was applied at least 75% of the time (averaging 18 hours per day), both OS and PFS were significantly prolonged after controlling for prognostic factors, underscoring the dose–response effect of consistent device adherence.

The PANOVA-3 protocol and device labeling recommend an average use of at least 18 hours per day (≥ 75% daily usage) in individuals with locally advanced pancreatic cancer. In the pivotal trial, median daily usage was approximately 62% (about 11–12 hours per day), and treatment benefit was observed even at this level. The physicians Instructions for Use recommend use at least 12 hours/day. However, both the FDA Summary of Safety and Effectiveness Data and the Instructions for Use emphasize that longer daily usage is associated with improved outcomes and that individuals should aim for continuous use with only short breaks for personal needs.

Malignant Pleural Mesothelioma

Pleural mesothelioma cancer develops in the mesothelial surface of the lungs and is primarily associated with asbestos exposure. Malignant mesothelioma is rare in the United States, with approximately 2500 new cases diagnosed each year. Pleural mesothelioma accounts for more than 75% of mesothelioma cases. Most individuals present with advanced disease limiting treatment options available. Median OS is 1 year with a 5-year OS of about 10% (NCCN Mesothelioma, V2.2025).

In May 2019, the FDA approved the use of a modified version of the TTF device (Optune Lua previously known as NovoTTF™-100L) for the first-line treatment of adults with unresectable, locally advanced or metastatic malignant pleural mesothelioma to be used concurrently with pemetrexed and platinum-based chemotherapy. The device was approved under the Humanitarian Device Exemption (HDE) and identifies the specific population that the modified device is intended to treat. The HDE was not reviewed by the FDA advisory panel, the approval is based upon the previous review and approval of the similar GBM device. The Optune Lua operates on the same principle as the device used to treat GBM but includes different technological characteristics and area of application.

Ceresoli and colleagues (2019) evaluated the activity of TTF therapy used in combination with systemic chemotherapy in treating Stage IV unresectable malignant pleural mesothelioma (STELLAR study). Participants in the Phase II, prospective, single arm study (n=80) were treated with pemetrexed and cisplatin or carboplatin in combination with TTF therapy to the thorax until radiological disease progression or unacceptable toxicity was seen. The primary endpoint was OS time from diagnosis until the date of death. The median OS was 18.2 months (95% CI, 12.1-25.8). The 1-year survival rate was 62% and the 2-year survival rate was 42%. This OS was compared to the OS reported in two recent randomized trials involving malignant pleural mesothelioma chemotherapy regimens. These studies evaluated the addition of bevacizumab or nintedanib to a standard cisplatin and pemetrexed regimen. Both studies reported increased OS in the study groups compared to control groups, 18.8

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months (95% CI, 15.9-2.6) and 18.3 months (15.2-28.8) compared to 16.1 months (14.0-17.9) and 14.2 months (95% CI 12.3-20.9) respectively. A total of 32 individuals (40%) reported severe AEs during the study, with anemia and neutropenia being unrelated to device use. Device-related AEs primarily consisted of skin reactions and were reported in 66% of the individuals, with 5% of these reactions being severe enough to result in treatment interruption. Randomized trials which compare standard chemotherapy with and without concurrent TTF therapy are needed to further evaluate any potential incremental benefit of this therapy over the current standard of care.

In summary, the available evidence regarding the use of TTF therapy in treating stage IV non-curative mesothelioma in combination with standard chemotherapy does not demonstrate that use provides cost effective, therapeutically equivalent outcomes over the use of standard chemotherapy therapy alone.

NSCLC

Leal and associates (2023) reported on the LUNAR study, a randomized open-label, pivotal phase 3 study comparing the OS in individuals with metastatic NSCLC who were treated with SOC with or without TTF therapy. Eligible individuals had metastatic NSCLC (squamous or non-squamous) with radiological progression at any site during or after platinum-based systemic therapy. Participants were randomly assigned to standard systemic therapy of the clinical investigator's choice without TTF therapy (control; n=139) or with TTF therapy (test; n=137). At data collection cutoff, the median follow-up was 10.6 months in the test group compared to 9.5 months in the control group. The median OS was significantly longer in the SOC with TTF therapy group compared to SOC alone (13.2 months [95% CI: 10.3–15.5] compared to 9.9 months [95% CI: 8.1–11.5]; HR, 0.74 [95% CI: 0.56–0.98; p=0.035] respectively). Among those treated with an immune checkpoint inhibitor plus TTF therapy, the median OS was 7.7 months longer than those receiving the immune checkpoint inhibitor alone. There was no significant improvement in median OS in individuals who received docetaxel therapy. (Fennell, 2023). The median TTF therapy device usage for individuals in the study was 56-57%, which is below the manufacturers recommended use of at least 18 hours/day (≤ 75%). The study was initiated prior to the advent of standard genetic profiling by next-generation sequencing in NSCLC (now considered SOC), which complicates interpretation in the current therapeutic milieu. While there were no serious AEs associated with the device itself, there was a higher rate of serious AEs in the TTF therapy group (53%, 70/133) compared to the SOC group (38%, 51/134). The study did show there may be a potential benefit to TTF therapy when combined with immune checkpoint inhibitor therapy. Further studies are needed to investigate potential benefits of TTF therapy when used with or following immune checkpoint inhibitor therapy with a phase 3 study currently recruiting (NCT 06216301; LUNAR-2).

On October 15, 2024, the FDA approved the Optune Lua as a treatment of metastatic NSCLC when disease has progressed on or after a platinum-based regimen. The device is intended to be used concurrently with PD-1/PD-L1 inhibitors or docetaxel. The device should be worn for at least an average of 12 hours each day. The approval is based upon the results of the LUNAR trial, noting that an extension of over 3 months compared to SOC alone is considered clinically meaningful.

ASCO guidelines for stage IV NSCLC (Owen, 2025) highlight that TTF combined with standard therapy after platinum chemotherapy demonstrated a survival benefit in the LUNAR trial, with the greatest effect observed in the immunotherapy-naïve, second line group; however, because of low-quality evidence, lifestyle burdens of device

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use, and limited relevance to current treatment patterns, TTF therapy is not broadly recommended. For pleural mesothelioma, ASCO (Kindler, 2025) reported encouraging outcomes when TTF therapy was added to pemetrexed-platinum chemotherapy, but as a single-arm, nonrandomized trial, the evidence was deemed insufficient for ASCO to recommend routine use.

The NCCN clinical practice guideline for NSCLC (V2.2025) does not reference TTF therapy as a potential treatment. In summary, use of TTF therapy for NSCLC is not currently supported by credible scientific evidence published in peer-reviewed medical literature, or national physician specialty society recommendations.

Other Solid Tumors

A pivotal phase 3 RCT evaluated TTF therapy in combination with paclitaxel for platinum-resistant ovarian cancer (Vergote, 2025). The study showed no improvement in OS or PFS compared to paclitaxel alone, with median OS nearly identical between groups (12.2 vs. 11.9 months; HR, 1.01, p=0.89). While exploratory post-hoc analyses suggested possible benefit in pegylated liposomal doxorubicin–naïve cases, the primary findings did not support the addition of TTF therapy to ovarian cancer treatment.

Trials are underway in other types of malignancies. The FDA has granted breakthrough device designation to the NovoTTF-200T for liver cancer. This designation was granted based upon the unpublished results of a phase 2 study evaluating the safety and efficacy of TTF therapy when used with sorafenib to treat advanced liver cancer.

Treatment Planning Software

In 2013, the FDA approved NovoTal through a PreMarket Approval (PMA) supplement. NovoTal is an algorithmic software package which allows treating physicians, who have completed a certification program, to create individualized treatment maps. The standard treatment plan developed by the manufacturer uses post-contrast MRI sequences to develop a treatment plan. Treating physicians using NovoTal are able to incorporate additional imaging data and other clinical considerations into TTF treatment planning (Connelly, 2016). There is a paucity of literature reporting on planning approaches in TTF therapy and their effect on clinical outcomes. Connelly and colleagues (2016) reported on the use of NovoTal in a case series of 8 individuals with grades 2-4 GBMs. In addition to contrast enhancing MRI imaging, other clinical considerations, such as the heterogeneity in contrast enhancement in tumors, were taken into account during the planning process. The authors discuss the use of alternative MRI sequences during the planning stage of treatment, but do not report on clinical outcomes, noting:

> this case series demonstrates that treatment planning beyond the extent of contrast enhancement is clinically feasible and should be prospectively compared to standard treatment planning in a clinical trial setting, in order to determine the impact on patient outcomes.

Chaudhry and associates (2015) compared physician performance using the NovoTal system to conduct transducer array layout mapping to the mapping laid out by the Novocure in-house clinical team. Neuro-oncologists, medical oncologists and neurosurgeons (n=14) evaluated 5 cases of recurrent GBM and developed treatment plans. While the study demonstrated a high level of concordance in transducer array layout planning between NovoTal certified

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physicians and the Novocure in-house clinical team, the study did not address whether clinical outcomes were affected. The evidence does not support that the use of enhanced treatment planning software is considered effective in the use of TTF therapy.

Definitions

Cytokinesis: The cytoplasmic changes accompanying mitosis. The cleavage of the cytoplasm into daughter cells following nuclear division.

Eastern Cooperative Oncology Group (ECOG) Performance Status: A scale used to determine the individual's level of functioning. This scale may also be referred to as the WHO or Zubrod score which is based on the following scale:

0 Fully active, able to carry on all pre-disease 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

Glioblastoma multiforme: Stage IV glioblastoma, which includes WHO recognized variants, giant cell glioblastoma and gliosarcoma.

Karnofsky Performance Status Score: A 10-point scale used by healthcare providers to quickly evaluate how an individual is feeling on any given day.

100 Able to work. Normal; No complaints; No evidence of disease.
90 Able to work. Able to carry on normal activity; Minor symptoms.
80 Able to work. Normal activity with effort; Some symptoms.
70 Independent; not able to work. Cares for self; Unable to carry on normal activity.
60 Disabled; dependent. Requires occasional assistance; cares for most needs.
50 Moderately disabled; dependent. Requires considerable assistance and frequent care.
40 Severely disabled; dependent. Requires special care and assistance.
30 Severely disabled. Hospitalized, death not imminent.
20 Very sick. Active supportive treatment needed.
10 Moribund. Fatal processes are rapidly progressing

Macdonald criteria for disease progression is defined as *at least one* of the following:

- Tumor growth of greater than 25% of the product of 2 perpendicular diameters compared to the smallest tumor area measured
- Appearance of one or more new tumors in the brain (diagnosed radiologically as GBM).

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Mitosis: The process by which a single parent cell divides to make two new daughter cells. Each daughter cell receives a complete set of chromosomes from the parent cell, allowing the body to grow and replace cells.

Progressive disease: Disease that is growing, spreading or getting worse.

Recurrent disease or recurrence: Disease that has recurred (come back), usually after a period of time during which the disease could not be detected. In the case of cancer, the disease may come back to the same place as the original (primary) tumor or to another place in the body (metastatic).

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NovoTTF-100A System
NovoTTF-100L System
Optune Gio
Optune Lua
Tumor Treatment Field (TTF)

The use of specific product names is illustrative only. It is not intended to be a recommendation of one product over another, and is not intended to represent a complete listing of all products available.

History

Status	Date	Action
Revised	03/12/2026	Revised title to add "therapy". Added MN criteria for locally advanced pancreatic adenocarcinoma. Reformatted the MN criteria for GBM and grade IV astrocytoma to reflect additional MN criteria. Removed "and for all other malignant tumors" from a NMN statement. Revised Discussion and References sections. Revised Coding section to add ICD-10 diagnosis codes C25.0-C25.9, Z85.07.
Reviewed	11/06/2025	Medical Policy & Technology Assessment Committee (MPTAC) review. Added 'Summary for Members and Families' section. Revised Description, Discussion, References, and Websites sections. Updated Coding section with 01/01/2026 CPT changes, added 1025T.
Reviewed	11/14/2024	MPTAC review. Updated Description, Discussion and References sections.
Revised	11/09/2023	MPTAC review. Removed criteria requiring treatment begin within 7 weeks of completion of temozolomide and radiotherapy. Revised criteria to add definition of tumor progression to the clinical indications. Reformatted criteria to limit criteria to one requirement per line. Updated Description, Discussion, Definitions and References sections.
Revised	11/10/2022	MPTAC review. Added medically necessary criteria for recurrent glioblastoma multiforme. Revised reference to see rationale for discussion

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		about tumor progression criteria without change in intent. Updated Discussion and References sections.
Reviewed	08/11/2022	MPTAC review. Updated Discussion and References sections.
Revised	08/12/2021	MPTAC review. Added medically necessary indications for continuation therapy. Updated Discussion and References sections.
Revised	08/13/2020	MPTAC review. Revised definition of tumor progression to refer reader to Discussion section. Updated Discussion and References sections. Reformatted Coding section.
Reviewed	08/22/2019	MPTAC review. Updated Discussion and References sections.
Revised	03/21/2019	MPTAC review.
Revised	03/20/2019	Hematology/Oncology Subcommittee review. Added a not medically necessary statement for treatment mapping and planning computer software. Updated Discussion and References sections.
New	05/03/2018	MPTAC review.
New	05/02/2018	Hematology/Oncology Subcommittee review. Initial document development. Moved content of DME.00035 Electric Tumor Treatment Field (TTF) to new clinical utilization management guideline document with the same title.

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