Evaluation proposal to the Danish Health Technology Council regarding Optune®, a medical device that delivers Tumor Treating Fields (TTFields) for treatment of newly diagnosed and recurrent glioblastoma patients

Instructions for applicant

This template is used to submit evaluation proposals to the Danish Health Technology Council for evaluation of a new or existing health technology. The evaluation proposal should be completed by the applicant and aim to provide the Council with a background for initiating evaluations. It is recommended that applicants engage in dialogue with the Danish Health Technology Council secretariat for guidance on completion.

The template is relevant for the overall themes:

- background information
- clinical outcome and safety
- patient perspective
- organisation
- budget and finances
- other relevant information

The scope of the response to each of the themes will depend on the individual health technology. If the applicant considers that a question is not relevant, the applicant should state 'not relevant' with brief supporting arguments. Explanatory text for the questions is in grey and is not exhaustive. It may contain definitions, descriptions that are more detailed, etc. The applicant may delete the explanatory text when the field has been completed. Under relevant enclosures' it is possible to list and enclose relevant publications and other documents, e.g. certificates, etc.

If there is confidential information in the evaluation proposal, this should be clearly marked by applying following to your answer: //CONFIDENTIAL//

The evaluation proposal must contain a reference list, should be kept as short and as precise as possible, possible (<20 pages, excl. Reference list), contain literature citations (Vancouver reference style), and written in either Danish or English.

Should any questions arise in preparation of an evaluation proposal or outline of costs, applicants can contact the Danish Health Technology Council secretariat for assistance or clarification.

The completed evaluation proposal is the applicant’s material.

INTRODUCTION

Tumor Treating Fields as a supplementary entity in the treatment of glioblastoma was introduced in the beginning of this century.

Optune delivers Tumor Treating Fields (TTFields) and is intended for treatment of newly diagnosed and recurrent glioblastoma. Optune is a portable, CE marked medical device (risk class 2 b) carried by the patient and thus an outpatient therapy.

Since the introduction of TTFields a number of scientific articles, as listed in the application, have shown a clear and significant increase in overall survival and a prolonged progression free survival in patients with newly diagnosed and recurrent glioblastoma without device-related severe adverse effects, except mild to moderate skin irritation on the scalp.

Optune is approved for both newly diagnosed and recurrent glioblastoma by FDA in USA, Health Canada in Canada. In Europe Optune obtained EU certificate according to the new Medical Device Regulation on November 4th, 2022.

Optune is an integrated part of the treatment guidelines for glioblastoma in many countries as e.g. USA, Germany, Austria, Sweden, Spain, Israel and China.

Health authorities in Austria, Germany, Israel, Japan, Sweden, and Switzerland have granted reimbursement for newly diagnosed GBM patients within their respective health care systems.

Worldwide, more than 25 000 patients have been treated with Optune.

It is based on this that the evaluation proposal of Optune for the treatment of newly diagnosed and recurrent glioblastoma is send to the Danish Health Technology Council.

1 Background

1.1 State the type of health technology

Optune is a portable, CE-marked medical device (risk class 2b) that delivers Tumor Treating Fields (TTFields). Optune is intended to treat patients with newly diagnosed or recurrent glioblastoma (GBM). TTFields are electric fields that disrupt cancer cell division [1]. Optune is an outpatient treatment and managed by the patients and their caregivers to integrate the therapy in their daily life [2].

Newly diagnosed glioblastoma patients typically receive surgery (biopsy or resection), radiation therapy together with chemotherapy (typically Temozolomide, TMZ) followed by maintenance chemotherapy (TMZ) [3].

1.2 Briefly describe the technology and the current Danish clinical context in which the technology will be used.

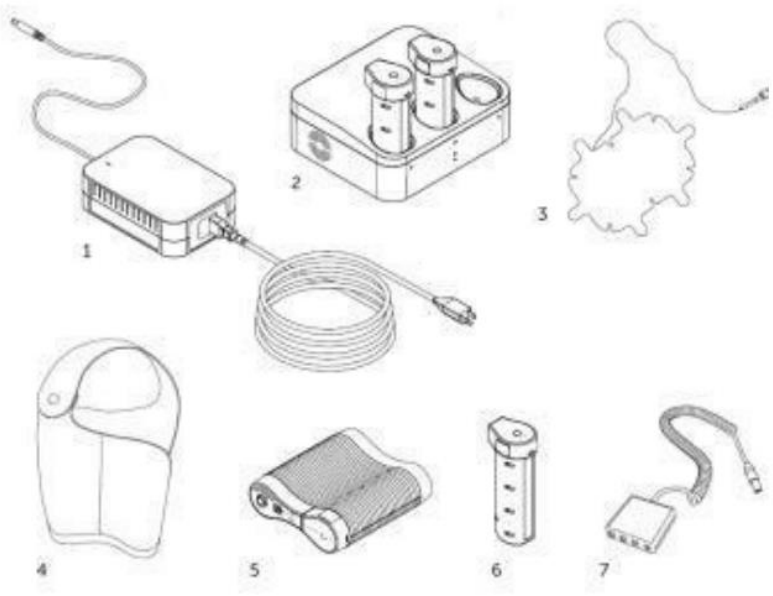
Optune is a portable medical device that delivers Tumor Treating Fields (TTFields). TTFields are alternating electric fields that disrupt the rapid cell division normally exhibited by cancer cells [1].

TTFields therapy employs electric fields in a frequency range of 100 kHz to 300 kHz, which is too high to stimulate healthy tissue, too low to have ionizing or significant heating effects, and allows TTFields to enter cells more effectively [11,13]. TTFields work by exerting electric forces on polar components within cells, disrupting their normal localization and function [14].

TTFields therapy selectively targets cancer cells due to their distinct properties, such as division rate, morphology, and electrical properties without significantly affecting healthy cells[11]. In addition to the anti-mitotic effects, further effects have been described, e.g. downstream induction of immunogenic cell-death and disruption of DNA damage response [11, 15].

Based on preclinical data, the effectiveness of TTFields in controlling tumor growth depends on four key physical factors related to how the fields are delivered: frequency, intensity, time, and direction [1, 12]. TTFields therapy is a noninvasive, locoregional cancer treatment delivered via a portable medical device that is designed to be integrated into daily life, while maintaining patients' quality of life [14].

Optune is comprised of two main components: 1) an Electric Field Generator (the Optune device); and 2) INE Transducer Arrays (Arrays). In addition, the following components are also included in the Optune Treatment Kit (NovoTTF-200A): power supply, portable battery, battery rack, battery charger, connection cable and carrying case. Fig. 1 below



1	Plug in power supply (Model SPS9100)
2	Charger for batteries (Model ICH9100)
3	Insulated Transducer array (INE) – (Model INE9020 and INE9020W)
4	Device & battery carrying bag (Model BAG9100)
5	Optune electric field generator (the Device) (Model TFH9100)
6	Battery (Model IBH9100)
7	Connection cable & box (Model CAD9100)

Fig. 1 Optune® (NovoTTF-200A) components

TTFields have been shown to significantly extend median progression-free and overall survival in newly diagnosed patients with glioblastoma (ndGBM) while maintaining health-related quality of life as measured for up to one year, except itchy skin [6].

The current application is regarded for Optune® (NovoTTF-200A).

NovoTTF-200A (Optune) Treatment Kit is intended for the treatment of patients with ndGBM, after surgery and radiotherapy with adjuvant Temozolomide, concomitant to maintenance Temozolomide. The treatment is intended for adult patients, 18 years of age or older, and should be started more than 4 weeks after surgery and radiation therapy with adjuvant Temozolomide. Treatment may be given together with maintenance Temozolomide (according to the prescribing information in the Temozolomide package insert) and after maintenance Temozolomide is stopped.

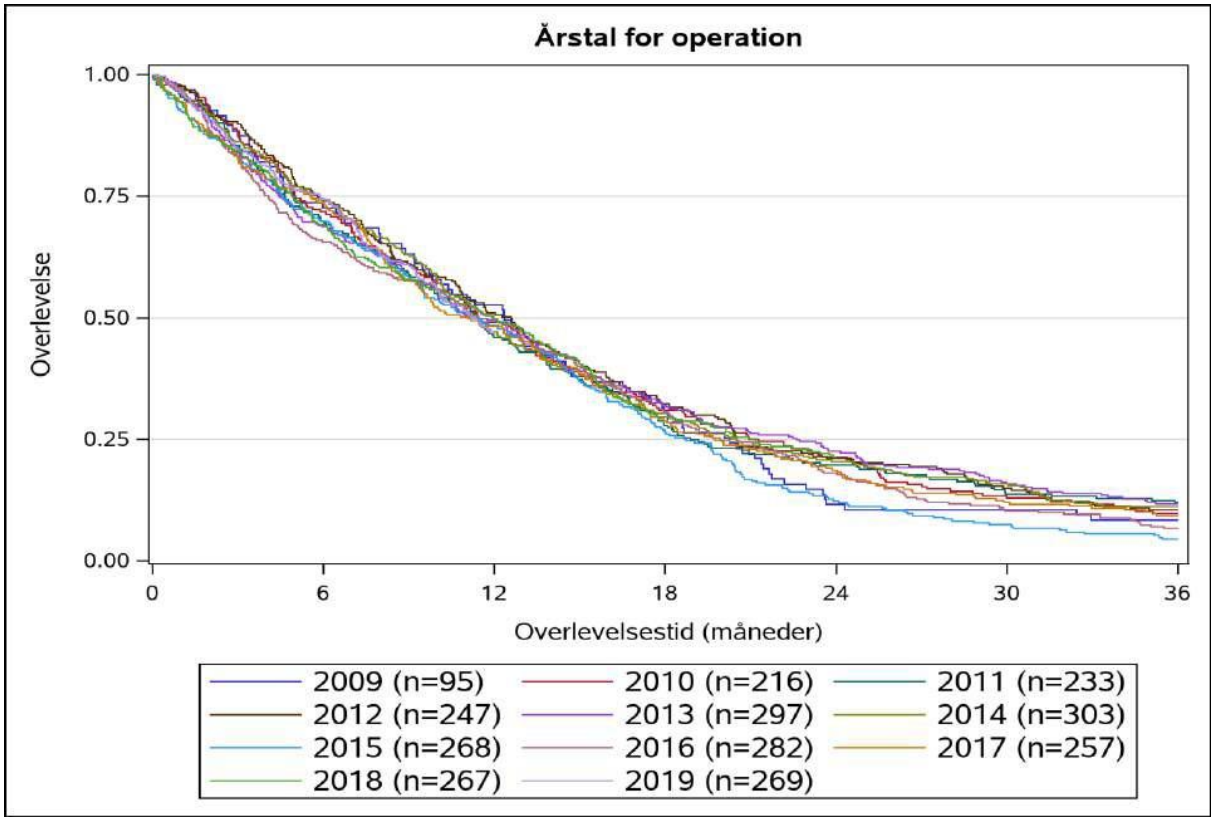
For the treatment of recurrent GBM, Optune is intended as a mono therapy following histologically- or radiologically-confirmed recurrence in the supratentorial region of the brain after receiving chemotherapy, as an alternative to standard medical therapy for GBM after surgical and radiation options have been exhausted.

For further information on indications, contraindications, warnings and precautions, please refer to the complete user manual https://www.optune.de/wp-content/uploads/2021/07/Optune_User_Manual_ver2.0.pdf

1.3 Describe the expected patient population

GBM is an aggressive malignant tumor that occurs in the brain or spinal cord. ndGBM is a rare disease with 307 newly diagnosed GBM patients in 2020. The median age was 66 years in Denmark [39].

GBM is the most common primary central nervous system (CNS) cancer. The prognosis of patients with glioblastoma that receive optimal treatment of surgery, radiation therapy and chemotherapy is about 15 months (median overall survival) [16, 39].



Log-rank test (p = 0.44) shows no significant difference in survival between patients operated on in the years 2009-2019.

Fig. 2: Three-year postoperative survival for all patients with glioblastoma (GBM), broken down by year of surgery 2009-2019 [39].

Patients that are expected to receive Optune are adult newly diagnosed glioblastoma patients that underwent surgery (biopsy or resection) and received radiation therapy plus chemotherapy. Treatment with Optune is intended to be concomitant to maintenance chemotherapy and after chemotherapy is stopped.

According to DNOR registry, 138 patients with GBM initiated concomitant radio-chemotherapy (TMZ) during high-dose radiation therapy in 2020. [39]

The characteristics of the GBM patient population in Denmark correspond to patients in the EF-14 trial. [16, 39]

For adults with recurrent glioblastoma Optune can be used as monotherapy. [16]

1.4 Describe the current status for use in Denmark and abroad

Treatment with Optune has not and is not being used or put into service for patients with ndGBM in Denmark.

Optune is currently only available through an investigator initiated sponsored trial (IST) for patients with recurrent GBM. (NCT02893137 and NCT04223999) [17, 18].

Abroad, usage of Optune is extensive with over 25 000 patients treated globally.
https://www.novocure.com/wp-content/uploads/2022/11/NVCR_Corp-Presentation_October-2022-PDF.pdf

In Sweden, approx. 400 patients have used Optune over a period of 3 years.

Optune is commercialized by Novocure in the USA, Canada, Germany, Austria, Switzerland, Sweden, Israel and Japan. In China Optune is commercialized by Novocure's collaborator Zai Lab.

1.5 State completed or ongoing health technology evaluations performed by health technology assessment (HTA) organisations.

HTA of the Swedish Dental and Pharmaceutical Benefits Agency (TLV):

https://www.tlv.se/download/18.3d5ca496161de47811d16065/1519905690094/bes180222_optune_eng_version.pdf

In 2017, Sweden's TLV published a HTA report for the use of Optune in ndGBM [50]. The TLV concluded that the clinical evidence was convincing and the reported survival benefits were relevant [50].

New Terapies (NT) Council recommendation :

https://janusinfo.se/download/18.46ffb4bf1643b6f9fb02116/1566894729188/Optune-180628.pdf

Based on the HTA report, the NT Council's judged that the cost was reasonable in relation to the treatment benefits. The recommendation to the county councils was: Optune should be used in the maintenance treatment of newly diagnosed patients with supratentorial glioblastoma together with temozolomide after undergoing maximal resection in accordance with the clinical study, as well as discontinuing radiotherapy and concomitant chemotherapy [37].

Rapid report by the German Institute for Quality and Efficiency in Health Care (IQWiG):

https://www.iqwig.de/download/n18-02_tumour-treating-fields-for-glioblastoma_extract-of-rapid-report_v1-1.pdf

In 2019, IQWiG released a benefit assessment that included one study in patients with ndGBM who had previously undergone resection (or biopsy) and completed RT and chemotherapy. In this study, TTFields was started as part of maintenance therapy as first-line treatment, and therapy could be continued after tumor progression [36].

For the outcome of OS, an indication of greater benefit was reported with TTFields as an add-on to the current standard treatment with TMZ in comparison with TMZ monotherapy. For morbidity, a hint of greater benefit was present with TTFields as an add-on to the current standard therapy for the outcomes of cognitive functioning and activities of daily living. For one (itchy skin) out of the three examined symptoms, the potential for greater harm with TTFields as an add-on to the current standard therapy was based on an early analysis time point. In terms of HRQoL, serious AEs as well as the two other examined symptoms (pain and leg weakness) were evaluated. No hint of greater benefit or harm was found with TTFields as an add-on to the current standard treatment in comparison with TMZ monotherapy [36].

1.6 State Danish or international clinical guidelines on use of the technology.

Optune is currently not recommended by the Danish Clinical Guidelines.

Many national and international professional Societies have integrated Optune into their guidelines (see overview table below [23]).

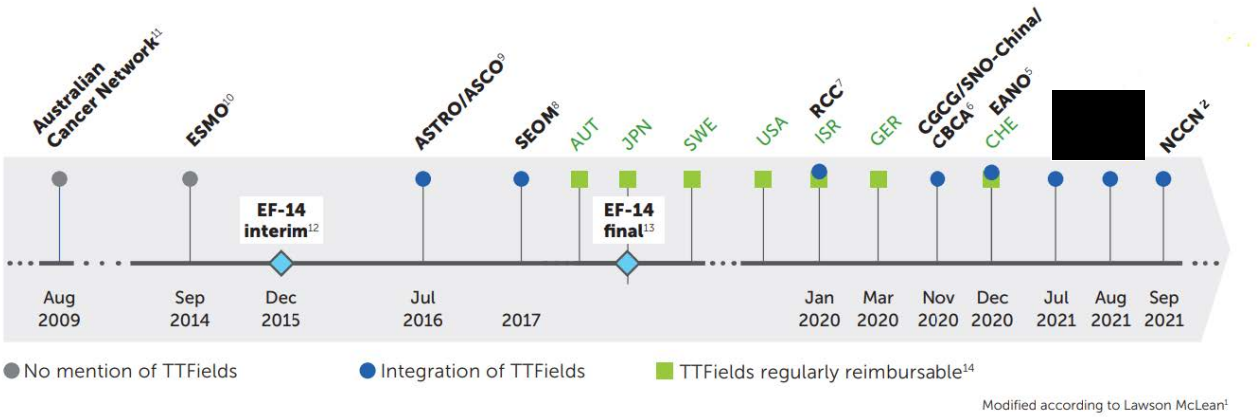
Guidelines of the professional societies[1]	Latest publication date	TTFields Integration
National Comprehensive Cancer Network (**NCCN**; USA)[2]	September 2021	**Yes**
German Society of Hematology and Medical Oncology (**DGHO**), Austrian Society for Hematology and Medical Oncology (OeGHO)[3]	August 2021	**Yes**
German Society for Neurology (**DGN**), Austrian Society of Neurology (**ÖGN**)[4]	July 2021	**Yes**
European Association of Neuro-Oncology (**EANO**)[5]	December 2020	**Yes**
Chinese Glioma Cooperative Group (CGCG), Society for Neuro-Oncology of China (SNO-China), Chinese Brain Cancer Association (CBCA)[6]	November 2020	**Yes**
Regionala Cancercentrum I Samverkan (**RCC**; Sweden)[7]	January 2020	**Yes**
Spanish Society of Medical Oncology (**SEOM**)[8]	October 2017	**Yes**
American Society for Radiation Oncology (**ASTRO**; USA), endorsed by the American Society of Clinical Oncology (**ASCO**; USA)[9]	July 2016	**Yes**
European Society for Medical Oncology (**ESMO**)[10]	September 2014	**No**
Australian Cancer Network[11]	August 2009	**No**

Modified according to Lawson McLean[1]

Tabel. 1. TTFields in glioblastoma clinical practice guidelines

Leading neuro-oncological societies recognize the efficacy of TTFields therapy and have successively incorporated it into their guidelines in recent years.

Guidelines that do not currently integrate TTFields have not been updated since the publication of the interim analysis of the 2015 EF-14 study.



Modified according to Lawson McLean[1]

Fig. 3. TTFields in glioblastoma clinical practice guidelines: An analysis of contemporary North American and European recommendations, AACR Virtual Meeting II, 2020 [19, 20, 21, 22, 23]

In the US, Optune is recommended by the NCCN guidelines with evidence-level category 1 recommendation for the treatment of patients with newly diagnosed GBM [38].

The Swedish authorities have included Optune into the National Guideline Recommendations for the Treatment of Brain tumors, 2020 following a positive evaluation and reimbursement recommendation by the Swedish TLV in 2017.[35].

The recently published Consensus Review of the Society of Neuro-Oncology (SNO) and the European Association of Neuro-Oncology (EANO) include TTFields as part of the standard of care treatment paradigm for newly diagnosed GBM patients [5].

Health authorities in Austria, Germany, Israel, Japan, Sweden, Switzerland have granted reimbursement for newly diagnosed GBM patients within their respective health care systems.

1.7 Describe the best existing, widely implemented alternative(s) to the technology.

TTFields is a novel treatment modality. Being the first of its kind for therapy, there is no comparative therapy to benchmark against Optune. TTFields as treatment modality is considered as an add-on therapy to existing treatment regimens.

Current standard of care (Stupp protocol) is based on the phase 3 study that lead to the approval of TMZ published by Dr. Stupp in 2005 that demonstrated an increase in median overall survival. TMZ is the current SOC chemotherapy for the treatment of ndGBM [25].

For comparison, adding TTFields to maintenance TMZ in the pivotal EF-14 study increased median overall survival by 4.9 months in patients with ndGBM [2]. Until the final publication of the pivotal EF-14 study by Dr. Stupp in 2017, there was no positive phase 3 study that showed an increase in median progression-free or overall survival [2].

2 Clinical outcome and safety

2.1 Briefly describe the most significant clinical outcomes from the health technology compared with the alternative.

Efficacy Summary:

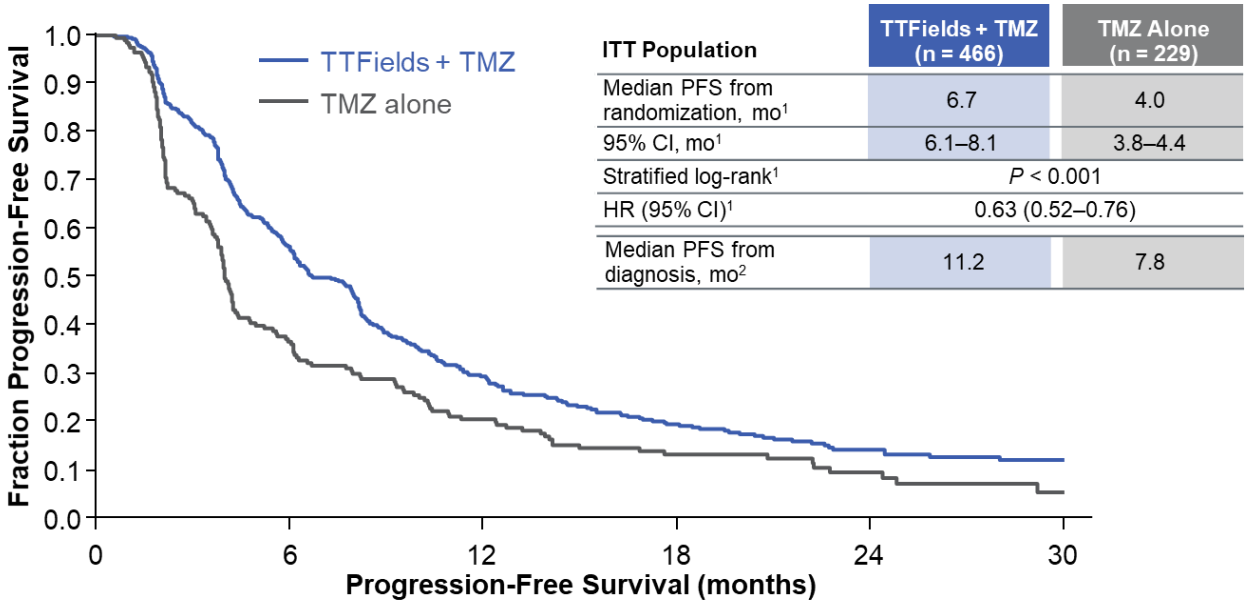
- Optune + TMZ provided an unprecedented long-term survival benefit that increased with more time on Optune [2].
- Optune + TMZ significantly improved median PFS from diagnosis compared with TMZ alone (6.7 vs 4.0 months; P<0.001, HR 0.63) [2].
- Median OS was significantly extended with Optune–by nearly 5 months compared with TMZ alone (20.9 vs 16.0; P<0.001, HR 0.63) [2].
- Survival with Optune + TMZ vs TMZ alone was significantly better at the 2- and 5-year landmark analyses (43% vs 31% and 13% vs 5%, respectively) [2].

EF-14 was a pivotal phase 3, randomized, open-label, active comparator trial that compared the efficacy and safety outcomes of ndGBM subjects treated with Optune (TTFields) plus TMZ to those treated with TMZ alone.[34] The study was multicenter and multinational, being conducted at 83 global centers in the US, Canada, Europe, Israel, and South Korea [26].

Between July 2009 and November 2014, 695 of the 700 planned patients were randomized in a 2:1 ratio to receive either Optune plus TMZ or TMZ alone [26]. Patients were randomized through a central web-based randomization system and stratified based on the extent of resection and MGMT methylation status [26]. An interim analysis, a final analysis, and a post-hoc analysis on both patient groups were conducted [26, 27].

Primary Endpoint Progression-Free Survival

After a median follow-up of 40 months, as shown in the figure 3 below, the median PFS in the ITT population was significantly higher (P<0.001; HR 0.63 [95% CI 0.52 to 0.76]; for the Optune plus TMZ group (6.7 months; 95% CI 6.1 to 8.1 months) relative to the TMZ alone group (4.0 months; 95% CI 3.8 to 4.4 months). At 6 months, 56% (95% CI 51% to 61%) of patients in the Optune plus TMZ group and 37% (95% CI 30% to 44%) of patients in the TMZ alone showed no disease progression (P<0.001) [3].

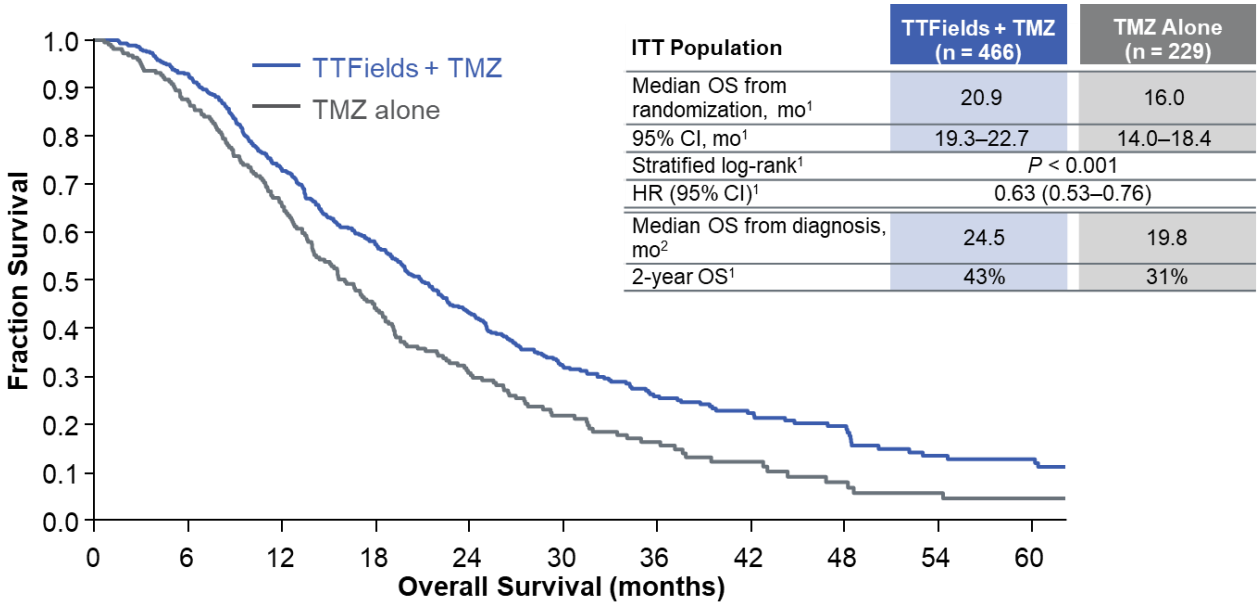


ITT Population	TTFields + TMZ (n = 466)	TMZ Alone (n = 229)
Median PFS from randomization, mo[1]	6.7	4.0
95% CI, mo[1]	6.1–8.1	3.8–4.4
Stratified log-rank[1]	*P* < 0.001	
HR (95% CI)[1]	0.63 (0.52–0.76)	
Median PFS from diagnosis, mo[2]	11.2	7.8

Fig 4. Progression-Free Survival

Secondary Endpoint – Overall Survival

The median OS was significantly higher (P<0.001; HR 0.63 [95% CI 0.53 to 0.76]) in the Optune plus TMZ treatment arm (20.9 months; 95% CI 19.3 to 22.7) than in the TMZ-alone treatment arm (16.0 months; 95% CI 14.0 to 18.4; figure below) [3].



ITT Population	TTFields + TMZ (n = 466)	TMZ Alone (n = 229)
Median OS from randomization, mo[1]	20.9	16.0
95% CI, mo[1]	19.3–22.7	14.0–18.4
Stratified log-rank[1]	*P* < 0.001	
HR (95% CI)[1]	0.63 (0.53–0.76)	
Median OS from diagnosis, mo[2]	24.5	19.8
2-year OS[1]	43%	31%

Fig 5. Overall Survival

Long-term survival rates

Long-term survival was significantly better with Optune plus TMZ vs TMZ alone (figure below). At 2 years from randomization, 43% (95% CI 39% to 48%) of the patients in the Optune plus TMZ treatment arm and 31% (95% CI 25% to 38%; P<0.001) in the TMZ-alone treatment arm were alive. At 5 years, 13% (95% CI 9% to 18%) and 5% (95% CI 2% to 11%; P=0.004) of patients were alive in the respective treatment arms [3].

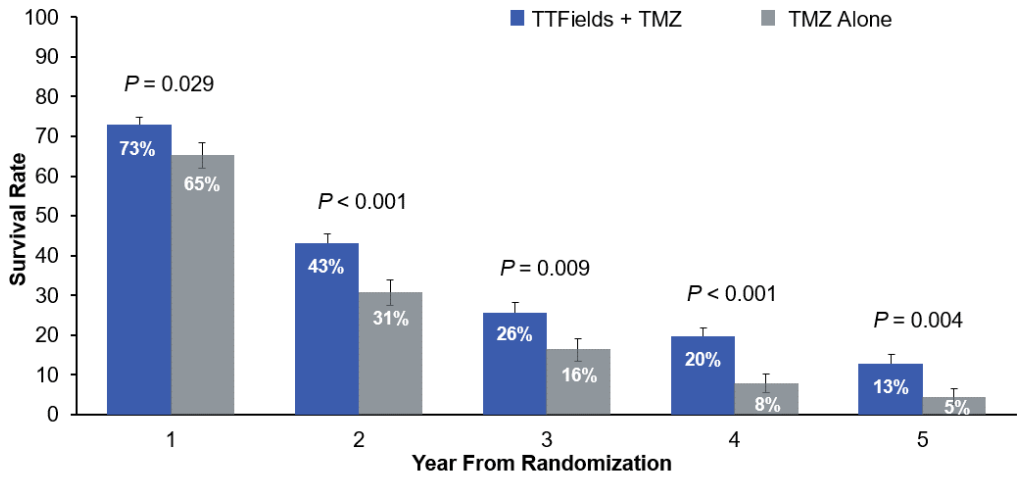


Fig. 6. Long-term survival rates

EF-14 TTFields use after first progression (as per study protocol)

A planned post-hoc analysis of the EF-14 trial was conducted to examine patients in the Optune plus TMZ and TMZ only treatment arms, after a first recurrence and treatment with second-line chemotherapy with or without Optune.[35, 36] The OS of patients who continued treatment with Optune after the first recurrence and received concomitant chemotherapy lived longer than patients who received only chemotherapy (11.8 months vs 9.2 months; P=0.0489; HR 0.695). When considering patients on bevacizumab, Optune use was still associated with significantly longer survival (11.8 months vs 9.0 months; P=0.0428; HR 0.606) [28].

EF-14 subgroup and post-hoc analyses

In post-hoc analyses, Optune use plus TMZ treatment was associated with a significant increase in PFS and OS in all subgroups (P<0.05 within each subgroup; Of note, patients aged ≥65 years experienced a shorter, though still significant OS benefit compared to younger patients (HR 0.51; 95% CI 0.33 to 0.77 and HR 0.67; 95% CI 0.55 to 0.82, respectively). In addition, patients with unmethylated MGMT promoters had significantly shorter OS compared to those that had MGMT promoter methylation, though Optune treatment was still associated with longer OS in both groups (HR 0.66; 95% CI 0.49 to 0.85) [3].

EF-14 TTFields usage and efficacy

Among patients in the Optune plus TMZ arm, the 265 patients treated with Optune for ≥18 hours a day on average in the first 6 months survived longer than the 185 patients treated for shorter periods (22.6 months [95% CI 19.7 to 25.1 months] vs 19.1 months [95% CI 16.5 to 21.9]; HR 0.65 [95% CI 0.49 to 0.85] P=0.009) [3].

Toms et al (2019) examined the effect of usage time on PFS and OS in the EF-14 trial in more detail [37]. Patient usage was calculated by recording the average percentage of each month that Optune was delivering TTFields. The data was obtained by analyzing each device's log file and dividing the total device 'ON' time by the number of 1-month courses of treatment prescribed. PFS and OS from the Optune plus TMZ arm were analyzed in subgroups [29]. Fig. 5

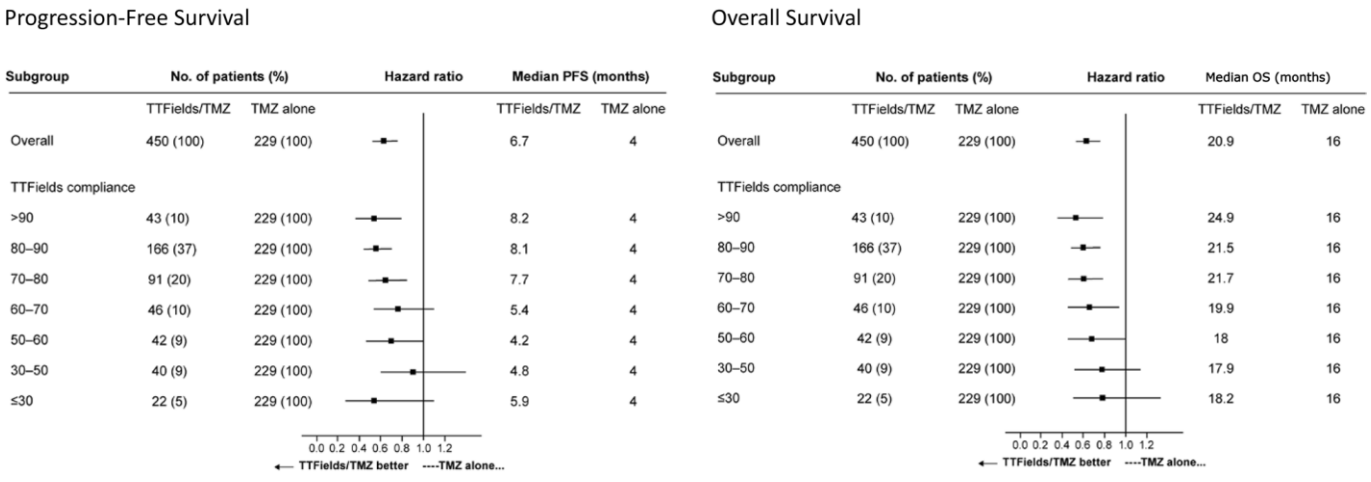


Fig. 7. Forest plots show the effect of treatment compliance with TTFields plus TMZ on PFS and OS.
A threshold value of 50% compliance with TTFields plus TMZ was needed to show a significant extension of OS compared to TMZ alone. Both PFS and OS were extended with treatment compliance levels > 50%. A trend in favor of longer PFS and OS was seen with higher rates of treatment compliance

Results showed similar baseline characteristics between the separate percent usage groups and between each group and the full data set of EF-14. A trend in favor of longer PFS and OS was seen in groups with progressively higher usage rates starting at ≥50% average monthly usage time with Optune, indicating that patients using Optune at least 12 hours/day will receive treatment benefits. Those with >90% usage time showed maximum survival benefits with a 5-year survival rate of 29.3% and median PFS of 8.2 months in the Optune plus TMZ group vs 4.0 months in the TMZ alone group (HR 0.538, 95% CI 0.365 to 0.794; P=0.0047), and an median OS of 24.9 months since randomization in the Optune plus TMZ group vs 16.0 months in the TMZ alone group (HR 0.522, 95% CI 0.347 to 0.787; P=0.0007) [29]. Fig.5.

EF-14 TTFields dose

Ballo et al (2019) conducted a simulation of the EF-14 study to examine the effect of Optune dosage (local minimum field intensity [LMiFI] and local minimum power density [LMiPD]) on treatment efficacy. The authors used data from 340/466 patients from the EF-14 study and divided the patients into groups based on median OS. When LMiFI was ≥1.06 V/cm in the tumor bed, the median OS was 24.3 months (95% CI 19.6 to 33.0) vs 21.6 months (95% CI 18.7 to 24.1) in the <1.06 V/cm group (P=0.0298; HR 0.687). Likewise, PFS was 8.1 months (95% CI 6.1 to 10.6) vs 7.9 (95% CI 6.1 to 8.4) in the ≥1.06 V/cm and <1.06 V/cm LMiFI groups, respectively (P=0.034; HR 0.647).

Adjusting for patients and treatment characteristics confirmed that a higher LMiFI was independently associated with improved outcomes (OS HR 0.694 and PFS HR 0.708). When LMiPD was ≥1.15 mW/cm3, the OS was 24.9 months (95% CI 20.8 to 37.7) and PFS was 8.2 months (95% CI 6.4 to 11.2). When LMiPD was <1.15 mW/cm3, the OS was 21.5 (95% CI 18.7 to 23.9) and PFS was 7.9 (95% CI 5.8 to 8.2). Higher LMiPD was independently associated with improved outcomes, as well as with improved prolongation of survival until deterioration of global health (P=0.004) [30].

2.2 Briefly describe the most important risks associated with use of the health technology compared with the alternative.

In the EF-14 pivotal study adding Optune to TMZ treatment was not associated with a significant increase of systemic AEs compared to TMZ alone (48% vs 44% respectively, P=0.58), with similar overall incidence, distribution, and severity of AEs between groups. Due to the delayed progression seen in the Optune plus TMZ group, patients were treated with TMZ for longer than those receiving TMZ-alone , leading to a non-significant higher incidence of some AEs. These differences were nullified when AE incidence was normalized to duration of treatment, except for localized skin effects. Mild to moderate skin irritation was observed in 52% and Grade 3 skin involvement occurred in 2% of patients receiving Optune plus TMZ [3].

A global post-marketing safety surveillance analysis included more than 11,000 patients with high-grade glioma that were treated with Optune (TTFields) in clinical practice. This safety analysis revealed no new safety concerns, with a favorable safety profile comparable with published data on TTFields therapy in GBM. The safety profile remained consistent among subgroups including elderly patients [32].

Optune is generally well-tolerated, with mild-to-moderate skin irritation as the most common device-related AE.

- Optune was used with TMZ in ndGBM patients with no significant increase in severe AEs compared with TMZ alone [2].
- Mild-to-moderate skin irritation, the most common device-related adverse event with Optune, was manageable, reversible, and did not usually result in treatment discontinuation [2].
- The management of device-related dermatologic AEs has been assessed and was published to provide guidance for clinicians in daily practice. Management strategies include both, preventive measures and treatment advices [33, 34].

2.3 State ongoing and/or completed clinical studies of the technology in the table.

Study ID	Study name	Indication	Study design	N	Comparator	Published data	Status
Novocure sponsored trials							
PMID: 17551011	EF-07	rGBM ndGBM	interventional	20	No	[12]	Completed
NCT00379470	EF-11	rGBM	RCT, Interventional	236	Yes	[45]	Completed
NCT00916409	EF-14	ndGBM	RCT, Interventional	695	Yes	[2]	Completed
NCT04471844	EF-32	ndGBM	RCT, Interventional	950	Yes		Ongoing
NCT04492163	EF-33	rGBM	interventional	25	No		Ongoing
NCT00749346	EF-15	NSCLC	Interventional	42	No	[46]	Completed
NCT02397928	STELLAR	Mesothelioma	interventional	82	No	{Ceresoli, 2019 #1169}	
NCT02973789	LUNAR	NSCLC	RCT, Interventional	276	Yes		Ongoing
NCT04892472	Keynote B36	NSCLC	Interventional	66	No		Ongoing
NCT02831959	METIS	NSCLC	RCT, Interventional	270	Yes		Ongoing
NCT01971281	PANOVA	Pancreatic cancer	interventional	40	No	[47]	Completed
NCT03377491	PANOVA-3	Pancreatic cancer	RCT, Interventional	556	Yes		Ongoing
NCT02244502	INNOVATE	Ovarian Cancer	Interventional	31	No	[48]	Completed
NCT03940196	INNOVATE-3	Ovarian cancer	RCT, Interventional	540	Yes		Fully Enrolled
NCT03606590	HEPANOVA	Liver cancer	Interventional	25	No		Completed
NCT04281576	ZLB-8301-001	Gastric cancer	Interventional		No		Ongoing
Ongoing Investigator Sponsored Trials in ndGBM							
NCT03869242		ndGBM	RCT, Interventional	60	Yes		Ongoing
DRKS-ID: DRKS00016667	PriCoTTF	ndGBM	RCT, Interventional	33	Yes		Ongoing
NCT03501134		ndGBM	Observational	36	No		
NCT03405792	2-THE-TOP	ndGBM	Interventional	32	No		Ongoing
NCT03223103		ndGBM	Observational	20	No		Ongoing
NCT04469075	PROTECT	ndGBM	interventional	58	No		Ongoing
NCT04474353		ndGBM	interventional	12	No		Ongoing

2.4 State and describe any important data on clinical outcome and safety which has not yet been published.[1]

Not applicable

3 Patient perspective

3.1 State and describe data concerning patient experience as regards the choice between the technology and comparator(s).

A secondary analysis of the EF-14 study focused on the HRQoL of the 639 patients who completed at least one scale at baseline [6]. Over the 12 months assessed, mean changes from baseline were stable (<10-point change) for all predefined scales in both treatment arms, except for itchy skin. A clinically significant deterioration in itchy skin was observed in the Optune plus TMZ arm at 3 months mean increase [standard deviation, SD] 10.4 [30.1]) vs an improvement of 2.3 [24.4] in the TMZ only arm (P=0.005). This trend continued with patients in the Optune plus TMZ arm experiencing significantly itchier skin at 6 months (P=0.008) and 9 months (P=0.04), but not at 12 months (P=0.66). More patients in the Optune plus TMZ arm reported a significant difference from baseline in stable or improved global health status, physical functioning, pain, and leg weakness vs TMZ-only patients (all P≤0.001) [6].

HRQoL data from the EF-14 trial was examined in the per-protocol population, which included only patients who received their original allocated treatments (some patients in the TMZ group crossed over to Optune plus TMZ and were excluded from this analysis).[39] Patient independence in activities of daily living remained stable over the first year in both treatment groups as measured by KPS ratings. Mean percentage change from baseline was between -4.3 (month 7) and -1.6 (month 1) in the Optune plus TMZ group, and between -4.2 (month 8) and -0.4 (month 2) in the TMZ alone group. Likewise, mean cognitive status stayed ≥27 out of 30 in both groups (note: a test result of 27-30 points is considered normal function) [3, 31].

There were no documented differences in Mini-Mental Status Exam scores between groups, with mean percentage changes ranging from -2.4 (month 1) to 4.8 (month 8) in the Optune plus TMZ arm and from -0.5 (month 2) to 3.8 (month 8) in the TMZ alone arm.[39] HRQoL initially improved in patients in the Optune plus TMZ arm at 3 and 6 months by 24% and 13% vs -7% and -17% in the TMZ alone arm, respectively, though at 9 months the change from baseline in the Optune plus TMZ arm slowed to 2.9% and was 7.8% in the TMZ alone arm. There were no significant changes from baseline in any HRQoL scales and no significant differences in any of the EORTC QLQ-30 functional scales. Patients receiving Optune plus TMZ reported numerically higher scores for “itchy skin”. Self-reported neurological results on the BN20 were comparable between groups and reflected the increase in symptoms expected from TMZ administration [31].

The time to a sustained 6-point decline in the Mini-Mental State Examination score was significantly longer in the Optune plus TMZ study arm than in the TMZ-alone arm [3]:

- Optune plus TMZ: 16.7 months (95% CI 14.7 to 19.0 months)
- TMZ alone: 14.2 months (95% CI 12.7 to 17.0 months)
- HR 0.79 (95% CI 0.66 to 0.95); P=0.01

[1] The Danish Health Technology Council may include unpublished and possibly confidential data concerning clinical outcome and safety in its evaluations, provided that a number of criteria have been met. See the principles from the Danish Health Technology Council for use of unpublished data. https://behandlingsraadet.dk/in-english

The time to a sustained 10-point decrease in KPS was also significantly longer in the Optune plus TMZ study arm than in the TMZ alone arm [3]:

- Optune plus TMZ: 5.5 months (95% CI 5.0 to 6.3 months)
- TMZ alone: 3.9 months (95% CI 3.1 to 5.2 months)
- HR 0.80 (95% CI 0.67 to 0.95); P=0.009)

QoL was maintained with Optune + TMZ over time and across predefined daily-functioning domains, as measured up to 1 year [6]:

- Physical, role, social, emotional, and cognitive functioning for patients with ndGBM treated with Optune + TMZ all remained stable and comparable with the TMZ alone arm.
- Patients with recurrent GBM who were treated with Optune had improved cognitive and emotional functioning when compared with patients treated with TMZ alone.

3.2 State and describe any issues regarding accessibility and inequality for specific patient groups in use of the health technology.

Novocure cannot identify any issues regarding accessibility and inequality for specific patient groups in the use of Optune.

4 Organisation

4.1 State and describe the organisational conditions in the health care sectors which are likely to be changed or influenced if the Danish Health Technology Council recommends use* of the health technology.

Optune does not alter organizational conditions in the health care sector.

4.2 Describe current experience with the health technology and its use.

The treatment is intended for adult patients, 18 years of age or older, to be used at home, after receiving training from qualified personnel, such as a doctor, nurse, other medical personnel, or Novocure Device Support Specialist (DSS), who have completed a training course given by the device manufacturer (Novocure). Training is provided to patient and caregiver and it is extended until the patient can use the device with an appropriate level of confidence. Training includes a detailed review of the User Manual and practice in the use of the system, how to shave the scalp, how to position and how to change the transducer arrays. In addition, patient is trained in what to do if there are problems with treatment and is provided with contact details of both assigned DSS and 24-hour technical support [7, 8, 9, 10].

5 Budget and finances

5.1 State and describe a list of published, peer-reviewed economic analyses of the technology

Bernard-Arnoux, Lamure, Ducray, Aulagner, Honnorat, Armoiry. 2016. The cost-effectiveness of tumor-treating fields therapy in patients with newly diagnosed glioblastoma.

- Cost-effectiveness analysis, 3-state Markov model, effect measured using ICER=Cost gain/Life-Year Gain, French National Health Insurance perspective, used interim not final EF-14 data
- Adding Optune to standard of care increased the life expectancy of patients by 4.08 months.
- In the base-case analysis the estimated ICER was €549,909 per LYG. The discounted ICER was €596,411 per LYG.
- Optune had a 0% chance of being cost-effective at a willingness-to-pay threshold of €100,000/LYG.

Connock, Auguste, Dussart, Guyotat, Armoiry. 2019. Cost-effectiveness of tumor-treating fields added to maintenance temozolomide in patients with glioblastoma: an updated evaluation using a partitioned survival model.

- Cost-effectiveness analysis, 3-state partitioned survival model, effect measured using ICER=Cost gain/Life-Year Gain, French National Health Insurance perspective
- Optune increased patient survival by .604 Life-Years at a cost of €453,848.
- The discounted ICER estimate was €510,273 per LYG.
- Optune was not cost-effective at a willingness-to-pay threshold of €100,000/LYG.

Guzauskas, Pollom, Stieber, Wang, Garrison. 2019. Tumor treating fields and maintenance temozolomide for newly-diagnosed glioblastoma: a cost-effectiveness study.

- Cost-effectiveness analysis, area under the curve 3-state model, effect measured using ICER=Cost gain/QALY gain, US payer perspective
- Adding Optune to maintenance TMZ increased the estimated mean lifetime survival and quality-adjusted survival for newly diagnosed GBM patients by 1.25 Life-Years and .96 QALYs respectively.
- In a US cost-utility analysis, the estimated ICER for Optune was $197,336 per QALY gained for newly diagnosed GBM patients.
- Optune may be considered cost-effective by current standards of willingness-to-pay for cancer treatment in the US of $100,000–$300,000 per QALY gained.

5.2 Describe the overall results from the completed outline of costs*.

See above results described.

[49]

6 Other relevant enclosures

Relevant publications and documents will go to the Danish Health Technology Council secretariat, but they will not be forwarded to the Council for their decision. However, applicants may choose to insert references to publications, for example hyperlinks, so the Council can search them itself.

6.1 State and attach relevant publications on the health technology.

Applicants should consider any issues concerning copyright or similar.

Please see reference list below in the appendix for publications.

6.2 State and attach relevant documents on the health technology.

Including, for example CE certificates from notified bodies.

Please see reference list below in the appendix for publications.

Appendix

List of abbreviations

Abbreviation	Definition
BBB	Blood-brain barrier
CE Mark	Product has been assessed by the manufacturer and deemed to meet EU safety, health and environmental protection requirements
CNS	Central nervous system
EANO	European Association for Neuro-Oncology
ECG	electrocardiogram
FDA	Food and Drug Administration
GBM	Glioblastoma multiforme
GVD	Global value dossier
GSPR	General Safety and Performance Requirements
HAS	Hatue Autorité de Santé
HRQoL	Health-related quality of life
HTA	Health technology assessment
ICER	Incremental Cost Effectiveness Ratio
IQWiG	Institute for Quality and Efficiency in Health Care

IST	Investigator Sponsored Trial
ITT	Intent-to-treat
KPS	Karnofsky Performance Score
LYG	Life Years Gained
MGMT	Methyl-guanine methyl transferase
NA	Not applicable
NCCN	National Comprehensive Cancer Network
ndGBM	Newly diagnosed glioblastoma
NICE	National Institute for Health and Care Excellence
NT Council	New Therapies Council
OS	Overall survival
PFS	Progression-free survival
PRiDe	Patient Registry Dataset
QALY	Quality Adjusted Life Years
rGBM	Recurrent glioblastoma
RT	Radiation therapy
SD	Standard deviation
SNO	Society for Neuro-Oncology
SOC	Standard of Care
Stuup Protocol	Standard of care for GBM
TENS	transcutaneous electrical nerve stimulation
TLV	The Swedish Dental and Pharmaceutical Benefits Agency
TMZ	Temozolomide
TTF	Tumor Treating Fields
TTFields	Tumor Treating Fields
TRIDENT	EF-32 clinical trial is evaluating the safety and efficacy of Tumor Treating Fields (TTFields) delivered by the Optune® treatment paired with radiation therapy and temozolomide in newly diagnosed GBM patients
US	United States
WHO	World Health Organization

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