Application for the assessment of Optune plus temozolomide for Danish patients with newly diagnosed glioblastoma multiforme

November, 2023

Updated version

Behandlingsrådets bemærkninger from 2. november 2023, is incorporated

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1 List of abbreviations

AE	Adverse event
BIA	Budget impact analysis
CCI	Charlson comorbidity index
CE	Conformité européenne
CI	Confidence interval
CT	Computer tomography
CTCAE	Common terminology criteria for adverse events
CUA	Cost-utility analysis
DHTC	Danish Health Technology Council
DKK	Danish Kroner
DNA	Deoxyribonucleic acid
DNOR	Danish neuro-oncological report
DSS	Device support specialist
EANO	European Association of Neuro-Oncology
EORTC	European Organization for Research and Treatment of Cancer
ESMO	European Society for Medical Oncology
EQ-VAS	EuroQol-Visual Analogue Scale
EQ-5D-5L	EuroQol-5dimensions-5levels
EU	European Union
EUR	Euro
FDA	Food and Drug Administration
GBM	Glioblastoma multiforme
GDPR	General Data Protection Regulation
GP	General practitioner
HR	Hazard ratio
HRQoL	Health-related quality-of-life
HTA	Health technology assessment
ICER	Incremental cost-effectiveness ratio
KPS	Karnofsky performance score
LY	Life year
MGMT	O6-methylguanine-deoxyribonucleic acid methyltransferase
MMSE	Mini-Mental Status Examination

MRI	Magnetic resonance imaging
N/A	Not applicable
NCCN	National Comprehensive Cancer Network
ndGBM	Newly diagnosed glioblastoma multiforme
NICE	National Institute for Health and Care Excellence
OS	Overall survival
OWSA	One-way sensitivity analyses
PFS	Progression-free survival
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PSA	Probabilistic sensitivity analysis
QALY	Quality-adjusted life year
QLQ-BN20	Quality-of-life questionnaire brain neoplasm 20
QLQ-C30	Quality-of-life questionnaire core 30
RANO	Response assessment in neuro-oncology
RCC	Regionala Cancercentrum i samverkan
RCT	Randomized control trial
rGBM	Recurrent glioblastoma multiforme
SEK	Swedish Kroner
SNO	Society of Neuro-Oncology
TLV	Swedish Tandvårds- och Läkemedelsförmånsverket
TMZ	Temozolomide
TTD	Time to deterioration
TTFields	Tumor-treating fields
UK	United Kingdom
US	United States
USD	United States dollar
WHO	World Health Organization

2 Summary of the key results of the application

Glioblastoma multiforme (GBM) is a highly aggressive form of brain or spinal cord tumor that is observed in adults and quickly leads to death if left untreated (1). Among other things, the patient can suffer from intracranial hypertension, motor deficit, and visual or speech deficit, all of which greatly impair quality of life. With a poor prognosis and a low five-year survival rate of around 5%, GBM presents significant treatment challenges (2,3). GBM is an orphan disease with approximately 300 new diagnoses in Denmark every year (1,4,5). The conventional treatment modalities for patients with GBM, including surgical resection, radiation, and chemotherapy such as temozolomide (TMZ) demonstrate limited efficacy and substantial side effects (3,5,6). Therefore, there is a high need for new treatments that provide durable response rates, improve survival while maintaining health-related quality of life (HRQoL).

To address these challenges, Novocure has developed a locoregional, portable, and non-invasive device, Optune, that generates alternating electrical fields, known as tumor-treating fields (TTFields), which inhibit tumor growth while preserving healthy cells (7). The device received United States (US) Food and Drug Administration (FDA) approval in 2011 and 2015 for the treatment of patients with recurrent GBM (rGBM) and newly diagnosed (ndGBM), respectively (8). Optune also obtained the Conformité Européenne (CE) mark certification, permitting commercial distribution in Europe in 2009 (7). Optune therapy utilizing TTFields has shown significant clinical effectiveness and a favorable safety profile, particularly in patients with ndGBM. TTFields therapy has demonstrated a good safety profile with no known systemic toxicity. Mild-to-moderate dermatologic adverse events (AEs) are the most common and predominant reported AEs (9,10). Clinical effectiveness studies have shown that TTFields significantly improve survival outcomes with no meaningful difference in HRQoL compared to the control group, particularly in patients with ndGBM (10).

EF-14 was a randomized, open-label phase 3 trial evaluating the efficacy and safety of TTFields plus maintenance TMZ in patients with ndGBM. In terms of the population, according to Danish GBM experts, the baseline demographics of the EF-14 trial are very to the target demographic of patients typically treated with Optune in Denmark. The study found that TTFields therapy has led to a significant improvement in pooled median overall survival (OS) and progression-free survival (PFS) by 4.9 and 2.7 months, respectively (2). The study also reported annual survival with significantly better long-term survival outcomes, with an 8% increase in five-year survival (13% vs 5%) (2). A meta-analysis of studies conducted in a real-world setting showed a median survival difference between Optune plus TMZ compared to TMZ alone of 10.8 months, a 12-month survival of 12.3% points, and a 24-month survival of 18.7% points. No new risks associated with Optune plus TMZ were identified. Treatment compliance with TTFields therapy has been reported to be a key prognostic factor in survival outcomes and influencing patient outcomes (9,10).

TTFields demonstrates improved survival and a similar effect on HRQoL (measured with the EORCT QLQ-BN-20 questionnaire) compared to TMZ, except for more itchy skin (11). The assessment of HRQoL over time was however identified as challenging and imprecise. Therefore, to address this issue, utility scores will be derived from utility values corresponding to various health states relevant to ndGBM (12). There is also similar effect on cognitive status compared to TZM alone, as measured by MMSE. The evidence indicates, however, that the time to a sustained 6-point decline in MMSE score is significantly longer in the group receiving TTFields plus TMZ compared to TMZ alone (2).

Novocure has developed a cost-utility model based on efficacy data from the clinical trial EF-14; a partitioned survival model including the states progression-free/stable, progression/progressed disease, and dead. The model has been validated and calibrated against Danish data and long-term survival modeling has been carried out in line with Danish Health Technology Council (DHTC) and the Danish Medicines Council guidelines. Utilities in the base-case are based on disease-progression-state-related utility scores based on EuroQol-5dimensions-5levels (EQ-5D-5L) data from Palmer et al. (2021) with Danish utilities from Jensen et al.

(2021) (12,13). The incremental cost-effectiveness ratios (ICERs) were determined to be DKK 1.7 million per life year (LY) gained and DKK 2.4 million per quality-adjusted life year (QALY) gained using the list price. The cost of Optune was identified as a key driver of the ICER. The budget impact for recommending Optune as a supplement to TMZ was DKK 17.9 million in year one with 113 patients eligible for Optune treatment and DKK 96.4 million in year five with 157 patients eligible for Optune treatment, when using public purchase price for Optune.

The results demonstrate that treatment with Optune plus TMZ produces significant health gains for patients with a very severe disease and where few treatment options are available. Additionally, the technology enables treatment outside of the hospital setting, potentially resulting in improved patient convenience and decreased healthcare costs (14–17). Successful implementation of Optune therapy requires clinician training, certification, patient acceptance, and compliance. These requirements are already incorporated into the cost of Optune, with no additional cost to the patient, the healthcare providers, or the Danish Regions.

Optune therapy utilizing TTFields has shown clinical effectiveness, a favorable safety profile, and potential healthcare system benefits for patients with GBM. Overall, Optune provides a valuable treatment option for patients with GBM with a distinct and unique mechanism of action, adding to conventional therapies, and addressing the high unmet needs of adult patients with ndGBM, and improving survival outcomes.

Optune should therefore receive a positive recommendation from the DHTC to be used as standard treatment for patients with GBM as add-on therapy to existing treatment regimens and is intended for use together with maintenance TMZ and after TMZ is stopped.

3 Introduction

The following section will provide a brief introduction to Optune and its area of application. This includes a description of the patient population and characteristics of newly diagnosed World Health Organization (WHO) grade IV gliomas, of which Optune is indicated for. Grade IV gliomas most notably include glioblastoma (GBM) which will be described in more detail in the following section. Additionally, the current clinical practice will be described including the comparator, which will be referred to mainly as TMZ alone and standard of care. Lastly, key characteristics of the Optune device will be presented, as well as a summary of the current evidence, along with existing international guidelines and recommendations.

3.1 Patient/target population

Glioma grade IV are rare, highly aggressive malignant tumors that occur in the brain or spinal cord. Grade IV gliomas are an orphan disease with approximately 300 new diagnoses in Denmark every year (1,4,5). It is, however, the most common tumor to occur in the brain or central nervous system (3). The OS of the disease is poor and has a considerable impact on both patients and their families' physical, psychological, and social health (1,3,18).

3.1.1 Definition and classification

Glioma grade IV belongs to a family of central nervous system tumors called gliomas, which are classified into subtypes according to the histology of glial cells and the degree of malignancy. Among glioma types, glioma grade IV is the most common in adults (1,3), and is the highest degree of malignancy, according to the WHO (19). The classifications include astrocytic tumors (grade I–III), oligodendroglia tumors (grade II–III), ependymomas (grade I–III), and GBM, which is the most common diagnosis within glioma grade IV. Glioma grade IV also include Glioblastoma IDH wildtype and Astrocytoma IDH mutant (19). Glioma grade IV can be classified as either primary which occurs de novo or secondary and develops from diffuse astrocytoma or other astrocytoma precursors (WHO grade II–III) (20,21).

In some glioma patients, the O6-methylguanine-deoxyribonucleic acid (DNA) methyltransferase (MGMT) gene promotor serves as a biomarker. Hypermethylation of the MGMT gene promotor leads to reduced expression of the subsequent DNA repair protein, lessening tumor resistance to chemotherapy. The MGMT promotor methylation status is, therefore, a biomarker of both prognostic and therapeutic importance in grade IV glioma, as hypermethylation has a better outcome and more favorable response to chemotherapy, especially in the setting of chemotherapy with TMZ (22–24). Glioma grade IV can originate from various glial cells in the brain such as neural stem cells, glial precursor cells, or the more differentiated glial cells (25,26). The tumors typically present as a single, large, irregular lesion primarily in the white matter of the cerebral hemispheres, predominantly (95%) in the supratentorial region and more rarely in the cerebellum, brainstem, and spinal cord (27).

Throughout the remainder of the document, "glioma grade IV" refers to all WHO grade IV gliomas. Since glioma grade IV is a newer classification, much clinical research pertains not to glioma grade IV, but to GBM. Whether the terms "glioma grade IV" or "GBM" are used in this report will depend on the terminology used in the cited literature.

3.1.2 Symptoms and pathophysiology

Grade IV glioma has a substantial symptom burden, owing to increased pressure caused by the tumor on the brain tissue. Intracranial hypertension is responsible for 30% of clinical signs and symptoms in GBM, followed by a motor deficit (20%), loss of body weight and condition (17%), confusion (15%) and visual or speech deficit (13%) (28). Epilepsy is also fairly common (15%-24%), and thus, some patients present with seizures (1,29). Patients with GBM often present with headaches (38%), nausea, vomiting, confusion, memory loss, personality changes, and/or focal neurologic deficits (e.g., weakness in the extremities, visual

disturbances, or language problems) (1,28). Other common symptoms of GBM include intracranial edema, depression, anxiety, and fatigue (27,30–32).

3.1.3 Incidence

The annual incidence rates of GBM vary between countries, with ranges from 0.51 and 6.3 per 100,000 people (1,3,4,33–35), The age-standardized incidence rate in Denmark was 6.3 for men and 3.9 for women per 100,000 people, based on registry data from 2009 to 2014 (4). The age-standardized incidence rate in 2009 for the overall Danish population was 5.1 per. 100,000 people based on Danish Neuro-Oncological Report (DNOR) data (1). The total incidence of glioma grade IV was 319 new diagnoses in 2021 in Denmark, confirmed through initial operation (5). The incidence differs per year ranging from 256 to 319 in the last five years (5).

GBM can occur at any age, but is most common in individuals aged 60 to 79, with a median age of 64 at diagnosis (1,4,5). It is approximately 1.5 times more common in men than in women and Caucasians have a higher incidence rate compared to other ethnicities (36). Out of all Danish GBM patients between 2013 and 2018, 72% had a Charlson Comorbidity Index (CCI) value of zero, 21% had a CCI of one to two, and 7% of patients had high comorbidity with a CCI equal to or above three (37). CCI is a weighted index to predict the risk of death within one year for patients with specific comorbid conditions, with each condition assigned a weight from one to six. A score of zero indicates that no comorbidities were found. The higher the score, the more likely the predicted outcome will result in mortality or higher resource use (38).

Glioma grade IV is the most frequently occurring brain tumor in Denmark, with around 300 newly diagnosed patients annually; in 2020, 315 patients were diagnosed with glioma grade IV in Denmark (5). Most patients with grade IV glioma with performance status of zero to two will be offered surgery (5,39), but it is estimated that only about half of patients diagnosed with grade IV glioma are suitable to receive surgery/biopsy and radiotherapy. In 2020, 162 patients out of the 315 diagnosed with grade IV glioma completed the entire course of surgery and subsequent radiotherapy and were able to start adjuvant TMZ chemotherapy (4,5). According to DHTC, the patient population size eligible for treatment with Optune is estimated to be 162 annually corresponding to approximately 50% of the newly diagnosed patients.

3.1.4 Mortality and survival

Although GBM rarely metastasizes extracranially and is typically removed surgically after diagnosis, it is essentially incurable, and the prognosis for patients is poor, with a median survival in Denmark at approximately 11.2 months (4). Out of all gliomas, GBMs are the most lethal, and the prognosis for patients is abysmal with only 0.05% to 10% of patients surviving five years past diagnosis (2,3,40).

The risk of progression in GBM is high, with over 80% experiencing recurrence (22). Despite surgical removal of the initial tumor, some cells will likely remain. Because of the infiltrative and proliferative nature of GBM, a new tumor is highly likely to form. Most recurrences are near (within <2 cm) from the original tumor; however, a small proportion may occur in distant regions of the brain (22). Despite surgery and treatment, GBM recurs in virtually all patients. According to the Danish Neuro-Oncological Group (DNOG), the one-year survival rate after surgery in Denmark is approximately 50% while the three-year survival rate is between 4% and 12% (5). Median survival in Denmark is approximately 11.2 months (4), and the survival rate decreases with increasing age, comorbidities, the aggression of the tumors, lower ability to withstand brain injury caused by GBM, and inability to complete treatment (4).

3.1.5 Current clinical practice

The clinical practice for the treatment of GBM will be described in the current section with a focus on how the diagnosis is established. The treatment following diagnosis will be described in Section 3.2.

In most suspected GBM cases, the patient initially contacts either their general practitioner (GP) or the emergency department. In cases of well-founded suspicion of a brain tumor, an urgent magnetic resonance imaging (MRI) scan with contrast is performed. If that is not possible, a computer tomography (CT) scan is used instead. The GP assesses the patient clinically and refers them urgently to the local neurological department. Clinical assessment and relevant imaging diagnostics are conducted in the local neurological department. After initial diagnostic evaluation, including clinical neurological examination and contrast-enhanced MRI of the brain, the patient should be referred to the regional neurosurgical department for further assessment, primary surgical treatment, and final diagnosis. After the final pathological diagnosis, a referral should be made for oncological evaluation and post-treatment care (5).

3.2 Comparator

TTFields are a novel treatment modality. Being the first of its kind to deliver this modality, there is no direct comparative therapy to Optune. TTFields as a treatment modality is considered an add-on therapy to existing approved treatment regimens and is intended for use together with maintenance TMZ and after maintenance TMZ is stopped in the treatment of ndGBM. The present section will therefore present the current treatment for ndGBM in Denmark with an emphasis on chemotherapy.

The current clinical recommendations for the treatment of GBM in Denmark were published in 2022 by DNOG. The recommendations are an adaption of the European Association of Neuro-Oncology (EANO) guidelines for gliomas, supplemented by a literature search and adapted to Danish conditions (5).

3.2.1 Surgery

According to the Danish Guidelines, surgery is the preferred initial treatment option for primary GBM brain tumors as it can ensure diagnosis while reducing the tumor burden and symptoms (5). The MGMT promotor status should be determined in patients with GBM, as it is an important prognostic marker for survival and response to chemotherapy with TMZ. In neurosurgery, as much of the tumor as possible is removed either by macro total or partial removal, or just a diagnostic biopsy depending on the individual patient (5).

3.2.2 TMZ and radiation therapy

After surgery, an early postoperative MRI scan should be performed within 72 hours as a quality control measure regarding the degree of tumor removal and the possibility of re-operation (5,41,42). Post-operative treatment is tailored to the patient's performance status, age, and comorbidities. To assess the patient's disease progression, the Eastern Cooperative Oncology Group (ECOG) performance status should be used to grade the progression of the disease on a scale from 0 to five; 0 being fully active without restrictions and five being dead (39):

- Patients with a performance status of zero to two should be offered postoperative radiotherapy of 60 Gy over 30-33 fractions concurrent with TMZ daily over a period of 42 days (43), followed by six cycles of TMZ as monotherapy, one cycle consisting of daily TMZ for five days every four weeks (44).
- For patients with a performance status of zero to two above the age of 70 with significant comorbidity, postoperative hypofractionated radiotherapy (34Gy/10F or 40Gy/15F), concurrent with TMZ, may be considered and subsequently evaluated for six cycles of TMZ.
- Patients with a performance status of zero to two with methylated MGMT can be treated with TMZ alone, while unmethylated MGMT can be treated with hypofractionated radiotherapy.
- Patients with a performance status of three to four should be offered palliative treatment (41,42).

TMZ is a chemotherapy and is used for malignant brain tumors. It is the most common chemotherapy used for the treatment of grade IV glioma patients in Denmark, with 197 patients with grade IV glioma receiving TMZ concomitant with radiotherapy and 25 receiving adjuvant TMZ as the first registered chemotherapy, out of a total of 319 grade IV glioma patients in 2021 (5). TMZ is an oral alkylating agent that inhibits tumor growth by causing DNA damage and promoting tumor cell apoptosis (21). TMZ has widely replaced other

chemotherapies because of its oral administration and favorable toxicity profile. The dose of TMZ depends on body surface area (calculated using the patient's height and weight) and ranges from 75 to 200 mg per square meter, once a day (43).

In summary, GBM patients typically receive surgery (biopsy or resection), and radiation therapy concurrent with chemotherapy, followed by maintenance chemotherapy, where the most common chemotherapy is TMZ. This is in accordance with the Stupp treatment regimen (45).

3.2.3 Recurrence

As treatment of GBM is not curative, recurrence of the disease is common, usually in the form of local tumor progression (46). The literature differs in its use of the terms "rGBM" and "progression". In the Danish clinical guidelines, rGBM is referred to as progression, based on the reasoning that microscopically, gliomas (WHO grade II-IV) are never completely gone (5). The choice of treatment for tumor progression depends on the patient's performance status and treatment preferences. A renewed surgical operation supplemented with oncologic treatment may be appropriate for patients with good performance status. Patients should be evaluated for treatment with TMZ, lomustine, or bevacizumab, possibly in combination with irinotecan, as tumor control is essential for the patient's quality of life (5).

3.3 Intervention

Optune is a portable device that provides continuous treatment for glioma grade IV using TTFields. Optune is an outpatient treatment managed by the patients and their caregivers to integrate the therapy into daily life (2). It is intended as a treatment for adult patients over the age of 18 with ndGBM following maximal debulking surgery and completion of radiation therapy with concomitant TMZ. Treatment with Optune may be given concomitantly with maintenance TMZ and after TMZ is ceased. For the treatment of recurrent grade IV glioma, the device is indicated for use as a monotherapy and as an alternative to standard medical therapy after surgical and radiation options have been exhausted (47). Optune is indicated for use as monotherapy in recurrent grade IV glioma, as it has demonstrated efficacy comparable to that of chemotherapy (48).

It should be noted that throughout this report, Optune will be referred to as both "Optune" and "TTFields". The specific terminology used will depend on the literature being referenced. In general, "TTFields" will be used to describe Optune's mechanism of action, and "Optune" will be used to refer to the device. Optune and TTFields are not always interchangeable, as TTFields is also used in Optune LUA (49). However, it should be emphasized that Optune LUA is not mentioned in this report, and therefore, both the term TTFields and Optune refer to Novocure's Optune technology when mentioned in this report.

3.3.1 Mechanism of action

Optune is a device that uses TTFields. TTFields is a technology that delivers alternating electrical fields to inhibit cell division, minimally affecting resting, non-proliferating cells (see Figure 3.1). Electric fields have different effects on the human body depending on their frequency. Electric field therapy is well-known in high and low frequencies with different uses in medical practice, leading to diverse applications in healthcare (50). Lower-frequency alternating fields (<1 kHz) mainly affects the cell membrane potential of excitable tissues, causing depolarization to produce action potentials, such as during nerve electrical stimulation and cardiac pacing (51–54). High-frequency alternating fields (>10 mHz) mainly generate a dielectric loss, causing significant heating effects in tissues. It is commonly used in radiofrequency tumor ablation and other contexts (53,55,56).

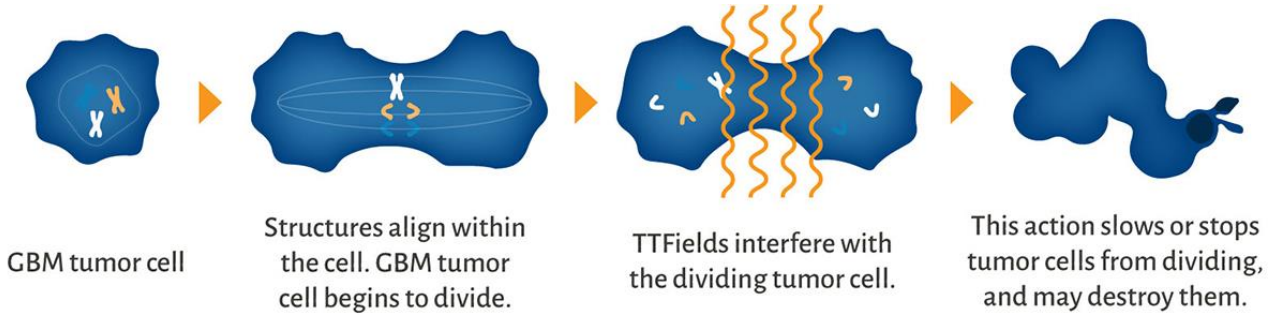


Figure 3.1 Mechanism of action for TTFields (57).
GBM, glioblastoma multiforme; TTFields, tumor-treating fields.

Optune delivers TTFields at an intermediate frequency (100-300 kHz) and low intensity (one to three volt per cm), which is too high to stimulate healthy tissue, and too low to have ionizing or significant heating effects. Preclinical studies have established that the optimal frequency of TTFields used to treat patients with GBM is 200 kHz (47,50,58).

The TTFields technology inhibits cell division (mitosis) minimally affecting resting, non-proliferating cells. TTFields interfere with cell division by affecting the formation of filament threads in the metaphase and by causing dielectrophoretic movements of intracellular molecules and organelles in the telophase, as well as disturbing the distribution of intracellular molecules and organelles to the daughter cells (15,47,59,60). Through its mechanism, TTFields technology disrupts the localization and function of polar molecules, such as tubulin and septin, which drive cancer cell behaviors, including division and movement.

The effect of TTFields on polar components in cancer cells ultimately leads to cell stress, aberrant mitotic effects, and cell death (60,61). Preclinical evidence demonstrates that TTFields disrupt the mitotic spindle in cancer cells, which can lead to prolonged mitotic arrest, slippage, and aneuploid daughter cell formation, ultimately culminating in cell death (60). Studies on isolated cells have also shown that TTFields can impair the migration and invasion of glioma cells (15,59).

3.3.2 Treatment

Optune is a non-invasive CE marked battery or power supply-operated device carried in an over-the-shoulder bag or backpack (see Figure 3.2). TTFields are applied to the patient by electrically insulated surface transducer arrays which are disposable and need to be replaced at least every four days. Optune is comprised of two main components: an electric field generator (the Optune device); and insulated transducer arrays (the transducer arrays). In addition, the following components are also included in the Optune treatment kit: power supply, portable battery, battery rack, battery charger, connection cable, and carrying case (see Figure 3.2) (47,62). Optune uses one battery at a time and each battery lasts two to four hours.

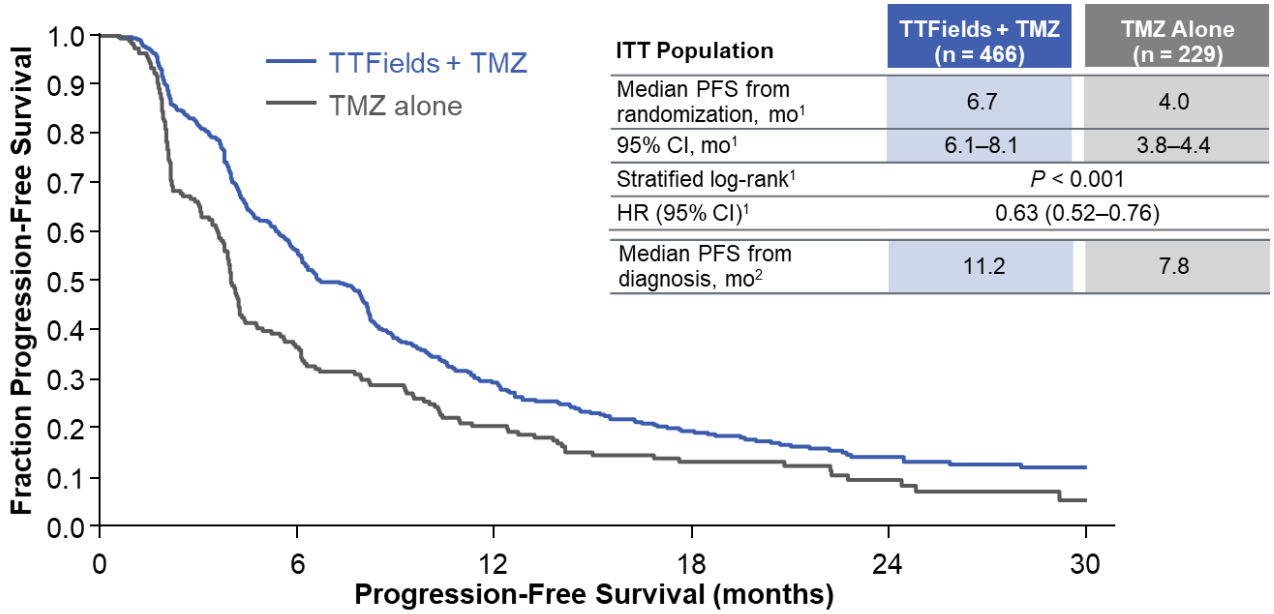
TTFields are applied to the patient by electrically insulated surface transducer arrays (62). These are adhesive bandages that hold the insulated ceramic discs needed to deliver treatment, along with the wiring that connects the discs with the field generator and allows the device to monitor and regulate treatment (62,63). Patients are advised to wear Optune for more than 18 hours per day (corresponding to a minimum of 75% of the treatment time) (64). However, due to the mechanism of action of TTFields, the longer Optune is worn throughout the day, the higher the probability of successful treatment, with clinical benefit observed at ≥50% average monthly usage time, indicating that patients using Optune at least 12 hours per day will receive treatment benefits (65).

Optune uses individualized layout maps, using MRI and a series of measurements to help determine where to place the transducer arrays to optimize the intensity of TTFields at the tumor (66).

Figure 3.2 Overview of the Optune treatment kit (62).

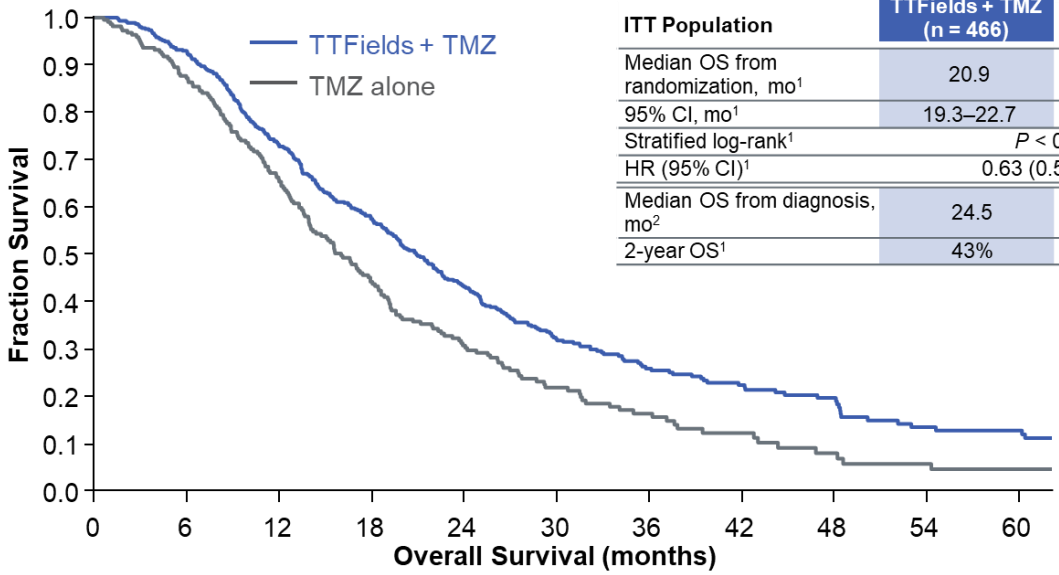
3.3.3 Current evidence

The EF-14 trial authored by Stupp et al. (2017) is the largest multinational trial of TTFields therapy (2). The study is an open-labelled, randomized control trial (RCT). The objective of the study is to investigate whether TTFields improve the PFS and OS of patients with ndGBM. Results from the pivotal trial authored by Stupp et al. formed the basis for the approval of Optune for use in ndGBM in many countries. Stupp et al. demonstrated significantly improved PFS and OS for TTFields therapy concomitant with TMZ vs TMZ alone (2) (see Figures 3.3 and 3.4). Stupp et al. demonstrated that adding TTFields to maintenance TMZ increased median OS by 4.9 months in patients with ndGBM and a significant increase in PFS by 2.7 months. The study also reported annual survival with significantly better survival, with an 8% increase in five-year survival (13% vs 5%).



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

Figure 3.3 Kaplan-Meier estimates of progression-free survival in Optune plus TMZ vs. TMZ alone (2).
CI, confidence interval; HR, hazard ratio; MO, months; PFS, progression-free survival; TTFields, tumor-treating fields; TMZ, temozolomide.



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%

Figure 3.4 Kaplan-Meier estimates of overall survival in Optune plus TMZ vs. TMZ alone (2).
CI, confidence interval; HR, hazard ratio; MO, months; OS, overall survival; TTFields, tumor-treating fields; TMZ, temozolomide.

A secondary analysis of Stupp et al. focusing on the HRQoL showed that patients maintain HRQoL (measured for up to one year in the trial), with the only significant AE being skin irritations (2,11). A global post-marketing safety surveillance analysis, that included more than 11,000 patients with high-grade glioma that were treated with Optune (TTFields) in clinical practice, supports the findings from Stupp et al. (67).

A real-world cross-sectional study reporting HRQoL outcomes showed similar results. The study conducted surveys on patients actively using TTFields for the treatment of GBM in the US and Europe. The study concluded that longer time using TTFields was associated with improved mobility, self-care, usual activities, and EQ-Visual Analogue Scale (EQ-VAS) overall (68).

Optune is generally well-tolerated, with mild-to-moderate skin irritation as the most common device-related AE. 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 advice (69,70).

3.3.4 International guidelines

Several leading neuro-oncological societies have recognized the efficacy of TTFields therapy and have incorporated it into their guidelines in recent years, including NCCN (National Comprehensive Cancer Network), ESMO (European Society for Medical Oncology), RCC (Regionala Cancercentrum i samverkan), SNO (Society of Neuro-Oncology) and more (41,42). As of now, Optune is not included in any existing Danish clinical guideline. Furthermore, while several national European guidelines are in place, Optune has not been integrated into the EANO guidelines yet. This is primarily due to the fact that Optune is not available in all European countries yet.

In the United States (US), Optune is recommended by the NCCN guidelines with evidence-level category one recommendation for the treatment of patients with ndGBM which includes treatment using Optune. The Swedish authorities have included Optune in the National Guideline Recommendations for the Treatment of Brain Tumors, 2020 following a positive evaluation and reimbursement recommendation by the Swedish Tandvårds- och Läkemedelsförmånsverket (TLV) in 2017, leading to approximately 400 patients in Sweden having used Optune over a period of three years (71). The recently published Consensus Review of the SNO and EANO includes TTFields as part of the standard of care treatment paradigm for ndGBM patients (72).

Furthermore, Optune was approved by the US FDA in 2011 as a monotherapy for the treatment of progressive and rGBM, and in 2015 for ndGBM in combination with TMZ following standard treatment. In 2016, the FDA approved the second-generation Optune which is lighter than the original device. In Europe, the second-generation Optune was CE marked in 2015 and is approved for use in Germany, Switzerland, Austria and Sweden, Japan, Israel, and Australia (15).

Treatment with Optune is not being used for patients with grade IV glioma in Denmark and is currently only available through an investigator-initiated sponsored trial for patients with rGBM (73,74). However, usage of Optune outside of Denmark is extensive with over 25,000 patients treated globally as of 2022 (75).

4 Evidence base

As part of the preparation of the DHTC's evaluation design, a systematic literature search is carried out with the aim of identifying existing published literature that document the examined health technology within the four perspectives, including clinical effectiveness and safety, the patient perspective, organizational implications, and health economics.

The identification of existing scientific literature is carried out in three steps. The first step aims to identify existing health technology assessment (HTA) reports on which the evaluation of Optune can be based either partly or initially. After that, the second step is initiated with a systematic literature search for systematic reviews. The last step in the search strategy is to carry out a systematic search for primary studies. The following sections will review the literature search and selection of relevant studies.

4.1 Systematic literature search

Based on the DHTC's method guidelines, a search has been carried out for published HTA reports, which can be used in whole or in part in answering the analysis question. The search was carried out in various databases (see Appendix 11.1) with the search term: Optune, Novocure, Tumor Treating Fields, Tumor Treating Fields, and TTFields. Based on the search for HTA reports, ten reports were identified. Out of these, primarily the HTA reports from Canada, France, the US, and Sweden were used to elucidate the research question formulated in the DHTC's evaluation design. However, an update of the systematic literature search was also performed to ensure an up-to-date evidence base in this rapidly developing field of research.

In addition to the search for HTA reports, a literature search was carried out based on synonyms for the parameter Intervention (I) from the PICO specification, which consists of the keywords "Optune" and "Tumor treating fields". The systematic literature search was therefore carried out to identify primary and secondary literature as a knowledge base for the application. The literature search was carried out following DHTC's search strategy, and the search was restricted to literature published from 2003 to 2023 and selected languages, including English, Danish, Norwegian, and Swedish. The literature search was carried out on PubMed, Embase, Cochrane, and Scopus, which are search engines that jointly form the basis of the existing health and biomedical scientific literature. The search was carried out on 11.05.2023 with the search string described in Appendix 11.1. The systematic literature search was divided into primary and secondary literature, of which RCTs have been assessed for inclusion in the present analysis. No additional study was identified by a manual search.

With the defined search terms, no systematic reviews were identified. Table 4.1 shows the databases, number of search results, and date of the searches for the third step in the search strategy after primary studies. 569 primary studies were identified after duplicate handling in EndNote. All studies are then reviewed in Covidence (76) and assessed for relevance.

Database	Results	SR	RCT	Date
PubMed	PubMed.gov	24	72	11.05.2023
Embase	Embase.com	22	155	11.05.2023
Cochrane Library	Wiley	2	292	11.05.2023
Scopus	Scopus.com	40	313	11.05.2023
Total Minus duplicates via. EndNote		**88** 50	**832** 569	

Table 4.1 Search results for relevant studies.
SR, search results; RCT, randomized control trial.

4.2 Selection of relevant studies

As a head-to-head study with the relevant comparator for the patient population with the relevant outcomes has been carried out, the literature search has been omitted. The identified HTA reports were screened independently by two Nordic Institute of Health Economics employees to sort out irrelevant reports. Disagreements were resolved by discussion until an agreement was reached. Based on this screening, four HTA reports were deemed relevant as shown in Table 4.2.

	Clinical effectiveness and safety	Patient perspective	Organisational implications	Health economics
Studies	Ballo (2022) (77)	Kessler (2020) (78)	Gentilal (2022) (79)	Bernard-Arnoux (2016) (80)
	Garside (2007) (12)	Kinzel (2019) (63)	Kinzel (2019) (63)	Brodbelt (2018) (81)
	Kirson (2009) (82)	Kumthekar (2021) (83)	Stupp (2017) (2)	Connock (2019) (84)
	Ma (2022) (85)	Lacouture (2015) (69)		Garside (2007) (12)
	Magouliotis (2018) (86)	Lacouture (2020) (70)		Guzaukas (2018) (87)
	Osoba (1997) (88)	Miller (2022) (89)		Korshoej (2016) (90)
	Palmer (2021) (68)	Mittal (2018) (91)		Kovic (2015) (92)
	Regev (2021) (10)	Mrugala (2014) (93)		Lamers (2008) (94)
	Shah (2020) (95)	Olubajo (2022) (96)		Martikainen (2005) (97)
	Stupp (2017) (2)	Onken (2018) (98)		Messali (2013) (99)
	Taphoorn (2018) (11)	Onken (2019) (100)		Polley (2011) (101)
	Vymazal (2023) (102)	Pandey (2016) (103)		Porter (2011) (104)
	Zhu (2017a) (105)	Regev (2021) (10)		Stupp (2015) (106)
	Zhu (2017b) (107)	Taphoorn (2018) (11)		Stupp (2017) (2)
	Zhu (2022) (48)			Wu (2012) (108)
Other data		NVC trend analysis (2022) (109)	Clinical guidelines (41,42)	CADTH HTA report (2018) (14)
		NVC survey (2022) (110)	NVC user manuals, global value dossier, company procedures	ACE HTA report (2023) (17)
		NVC survey (2023) (111)	CADTH HTA report (2018) (14)	WA HTA report (2018) (16)
			ACE HTA report (2023) (17)	TLV HTA report (2017) (15)
			WA HTA report (2018) (16)	Drummond (2015) (112)
			TLV HTA report (2017) (15)	Statistics Denmark (113)

Table 4.2 List of studies and other data.
ACE, Agency for Care Effectiveness; CADTH, Canada's Drug and Health Technology Agency; EANO, European Association for Neuro-Oncology; HTA, Health Technology Assessment; NVC, Novocure; TLV, Tandvårds- och Läkemedelsförmånsverket; WA, Washington State Health Care Authority.

Primary literature identified in the systematic search was also screened by two Nordic Institute of Health Economics employees using Covidence systematic review software (Veritas Health Innovation, Melbourne, Australia, www.covidence.org). Two employees reviewed the studies at the title/abstract level and, subsequently, full-text level (see Table 4.2). Before the literature selection, inclusion, and exclusion criteria

were drawn up, these are listed in Appendix 11.1. If there were discrepancies between the reviewers' inclusion or exclusion of a study, the study was discussed until an agreement was reached. Studies where only an abstract is available have been excluded and categorized as "not available".

The result of the systematic search is presented in Chapter 5, while the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) diagram appears in Figures 4.1a and 4.1b.

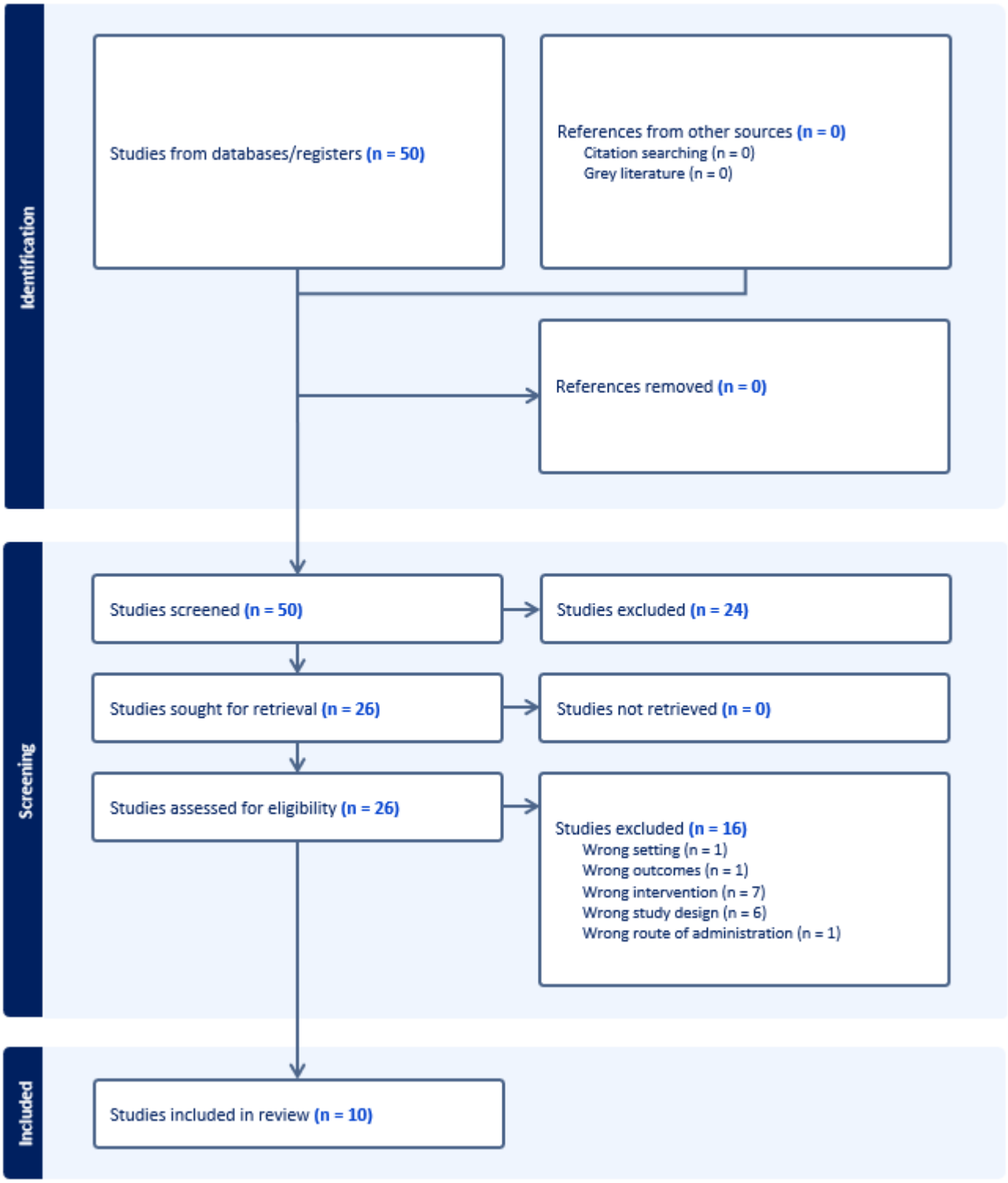


Figure 4.1a PRISMA flowchart of Optune Novocure secondary literature (76).
PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

The primary literature search identified ten studies that were also included in the secondary literature search, indicating overlap between the two sets of studies. Therefore, only 31 additional studies were included in the primary literature search beyond those identified in the secondary literature search.

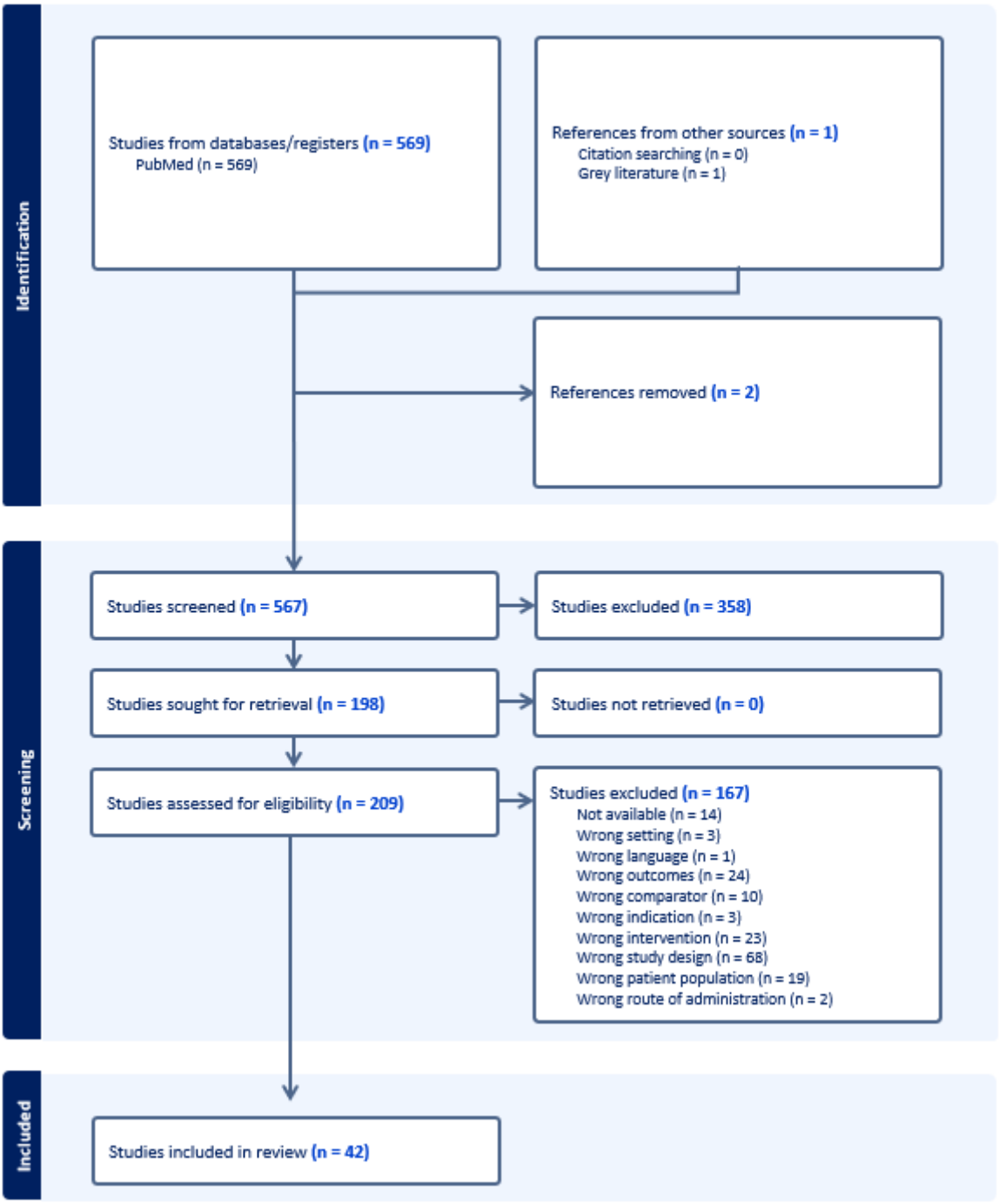


Figure 4.1b PRISMA flowchart of Optune Novocure primary literature (76).
PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

5 Clinical effectiveness and safety

The following section presents the results concerning clinical effectiveness and safety regarding the use of Optune for adult patients with newly diagnosed grade IV glioma. The outcome measures relevant to the use of Optune plus TMZ compared to TMZ alone as determined by the DHTC is the following:

- Survival, including median OS, 12-month survival, and 24-month survival.
- HRQoL, including difference in index score measured with EORTC QLQ-BN-20 and EQ-5D questionnaire.
- Cognitive functions, including difference in index score measured with mini-mental state examination (MMSE).

Reference (first author, year)	Identification no. (NCT, EudraCT or similar)	Intervention	Comparator	Used for clinical question
Stupp, 2017 (2)	NCT00916409	Optune plus TMZ	SOC	1
Vymazal, 2023 (102)	DOI:10.3389/fonc.2022.1014455	Optune plus TMZ	SOC	1
Ballo, 2022 (114)	DOI: 10.1007/s11060-023-04348-w	Optune plus TMZ	SOC	1
Pandey 2022 (115)	DOI: 10.1093/noajnl/vdac096	Optune plus TMZ	SOC	1
Kirson, 2009 (82)	DOI:10.1186/1756-6649-9-1	Optune plus TMZ	SOC	1
Taphoorn, 2018 (11)	NCT00916409	Optune plus TMZ	SOC	1
Regev, 2021 (10)	DOI: 10.1093/nop/npab026	Optune plus TMZ	SOC	1

Table 5.1 List of primary studies used in the analysis of clinical effectiveness and safety.
N/A, not applicable; TMZ, temozolomide, SOC, Stansard of care.

5.1 Study and population characteristics

From the systematic literature search, 15 articles relevant to the analysis of clinical effectiveness and safety were found (see Table 4.2). Appendix 11.2 show important study and baseline characteristics for the included studies. The studies are distributed as follows in relation to outcome measures determent by the DHTC:

- Five studies address overall survival (OS).
- Four studies address progression free survival (PFS).
- Two studies address health related quality of life (HRQoL).
    - One study addresses HRQoL measured with EORTC QLQ-BN-20
    - One study addresses HRQoL measured with EQ-5D-5L.
- Three studies address safety and adverse events (AE).

The studies that address OS and PFS include one RCT (2), one single-arm study (82), three retrospective cohort studies (102,114,115), and one systematic review (10). The systematic review was included with various limitations. The specific details regarding these limitations will be provided in sections 5.1.5, and 5.2.2 of the application.

The most prominent of the included studies is the Stupp et al. (2017) (2). This study represents the best current evidence for evaluating the efficacy of TTFields in ndGBM and reports outcome measures for both PFS, OS, HRQoL, and AEs including skin irritation. Study and population characteristics for the included studies are available in Appendix 11.2 and will be described in the following sections.

5.1.1 Stupp et al. (2017)

The EF-14 trial authored by Stupp et al. (2017) is the largest multinational trial of TTFields therapy (2). The study is an open-label phase 3 RCT. The objective of the study is to investigate whether TTFields improve the PFS and OS of patients with ndGBM.

5.1.1.1 Study population

Patients included had ndGBM, were progression-free after surgery or biopsy, had completed chemotherapy with TMZ, were over 18 years, and had a Karnofsky Performance Score (KPS) of ≥ 70, as well as satisfactory

bone marrow, liver, and renal function (The KPS ranking runs from 100 to zero, where 100 is "perfect" health and zero is death (116). Practitioners occasionally assign performance scores in between standard intervals of ten). Exclusion criteria included early tumor progression during chemoradiotherapy, infratentorial tumor localization, increased intracranial pressure, and severe comorbidity, as well as patients who were not able to complete primary treatment and those who could not tolerate TMZ chemotherapy were also excluded.

The study consisted of 695 patients from 83 different centers in the US, Canada, Europe (Austria, Czech Republic, France, Sweden, Germany, Italy, Spain), Israel, and South Korea. Baseline characteristics were well balanced between the two treatment groups (as can be seen in Appendix 11.2.1).

5.1.1.2 Study design and treatment

Patients who were progression-free after completion of radiotherapy were randomized within four to seven weeks at a ratio of 2:1, between June 2009 and November 2014 to obtain one of the following treatments:

- TTFields (>18 hours/day) and adjuvant TMZ (150-200 mg/m2 per day for five days every 28 days) (n=466)
- TMZ alone (n=229)

Patients in the TTFields plus TMZ group received continuous TTFields combined with maintenance TMZ. TTFields were delivered through a portable device in an outpatient setting. Patients were seen monthly for medical follow-up and routine laboratory examinations.

The median time from diagnosis to randomization was 3.8 months for both groups. The groups were stratified by the extent of resection and MGMT status, and second-line chemotherapy was offered according to local practice when tumor progression occurred. The median duration of treatment with TMZ was the same for both groups, 9 months. The treatment duration with Optune was a median of 8.2 months. The median medical follow-up time was 40 months. Patients in both study groups received monthly medical follow-ups.

In the TTFields and TMZ group, treatment with TTFields could continue until the second radiological progression, or clinical deterioration, for up to a maximum of 24 months. Subjects receiving TTFields were taught to place the electrodes and operate the device independently. Neither clinicians nor subjects were blinded. Subjects had monthly follow-up visits for physical examinations and laboratory studies.

5.1.1.3 Outcomes

The primary outcome was PFS, and the secondary outcome was OS. Exploratory endpoints included PFS at six months, annual survival rates, quality of life, time to a significant decline in the MMSE, KPS, and AEs.

Progression was defined as a radiologic progression as determined by two blinded radiologists using the McDonald criteria. A third radiologist made the final decision in the event of a tie. A brain MRI with and without contrast was completed two weeks before starting maintenance therapy and every two months until the second radiographic progression or 24 months had elapsed. A brain MRI was also performed within one week of a clinician being alerted of a clinical change.

Analysis was conducted with the intent to treat, as 26 patients (11%) in the TMZ alone control group crossed over and received TTFields after December 2014, following the release of the results of the interim analysis of the trial. These 26 patients had more favorable baseline characteristics than the rest of the control group and received more cycles of TMZ. To avoid possible bias, these patients were analyzed as randomized in the control group according to the intent-to-treat principle. Of note, the reported survival times, including both OS and PFS were measured from the time of randomization, which was done after completion of radiation and initial chemotherapy.

AEs were noted up to two months after treatment discontinuation and the treatment adherence with Optune was collected electronically and reviewed every month. AEs are recorded prospectively according to the

National Cancer Institute's Common Terminology Criteria for AE (CTCAE) (version 3.0) until two months after treatment discontinuation. AEs are presented descriptively as the number and percentage of patients with each adverse event term for all patients available at the time of the interim analysis. Treatment adherence with TTFields was recorded electronically by the device as average daily use in hours per day and information was reviewed and transferred at the monthly follow-up visit.

Patients completed questionnaires assessing cognitive screening with the Mini-Mental Status Exam (MMSE), which were repeated once monthly during office visits. The MMSE is a brief cognitive screening measure that has been translated into multiple languages and is designed to sample orientation (place and time), registration, attention, recall, language, and visual construction with a maximum total score of 30 points (107). A cut-off of 27 points was chosen to discriminate between cognitively impaired versus cognitively intact participants. Given that cognitive status, functional status, and HRQoL were secondary endpoints, analysis was performed on the per-protocol patient population. (2,107)

5.1.1.4 Statistical analysis

The primary outcome of PFS was assessed by an independent review panel (80% power; Hazard Ration (HR), 0.78; 2-sided α level of 0.05). The study was also designed to have 80% power (HR, 0.76; 2-sided α level of 0.05) to examine OS as a secondary outcome. To avoid an increase in the risk of a false positive result, OS was to be tested statistically only if the primary outcome was met (106). The primary outcome of the final analysis would be achieved if PFS was significantly longer in the TTFields plus TMZ group using a stratified log-rank test. The secondary endpoint would be achieved if OS was significantly longer in the TTFields plus TMZ group using a stratified log-rank.

For the analysis of PFS, patients were censored for progression when treatment was changed before evidence of progression (at the date of treatment change), at the date of their last MRI if lost to follow-up, or upon reaching the cutoff date without progression. For the analysis of OS, patients without a known date of death were censored at the last known date they were documented to be alive.

Cox proportional hazards models were used to analyze both PFS and OS controlling for the treatment group, age, sex, MGMT methylation status, tumor location in the brain, and country of residence.

Differences in the incidence of adverse events between groups were tested using a $\chi 2$ test at an α of 0.05. The incidence of AEs was compared between groups. Differences in the time to decline in KPS and MMSE were tested using a log-rank test at an α of 0.05.

5.1.1.5 Summary

Stupp et al. is the only randomized clinical trial to assess the efficacy and safety of TTFields plus maintenance TMZ compared to TMZ alone in patients with ndGBM. The trial is the largest study conducted within the field, with 695 patients with ndGBM. Both Swedish TLV's clinical experts and experts from a roundtable discussion described in Mehta et al. (2017) consider the evidence from Stupp et al. to be convincing and regards the survival benefit reported in the study as being clinically relevant (15,117). The results fromStupp et al. will therefore carry much weight in the assessment of clinical effectiveness and safety in this report.

5.1.2 Kirson et al. (2009)

The single-arm trial by Kirson et al. (also referred to as EF-07 trial) was conducted in the Czech Republic, at a single center in Prague (Na Homolce Hospital in Prague), as a pilot to Stupp et al. (82). The objective of the trial was to assess the safety and efficacy of TTFields treatment in 20 patients with GBM, this included ten patients with ndGBM and ten with rGBM. Results were reported separately for the patients with ndGBM and rGBM. The focus of following description will focus on aspects relevant to the analysis of the patients with ndGBM, and outcomes reported in 5.2.2.1 and 5.2.2.2 will exclusively include results from analysis conducted on the ndGBM patients.

5.1.2.1 Study population

The different groups used for different analyses in the study can be listed as followed:

- Ten patients with ndGBM receiving TTFields and adjuvant TMZ.
- Ten patients with rGBM receiving TTFields.
- Matched historical control data matched on KPS (>60) and age used for the analysis of OS (n=unknown)
- Group of concurrent control patients (n=32) matched to group one for the assessment of PFS

The study did not provide a detailed description of the populations in the intervention and the two comparator groups. However, the inclusion criteria included a histologically proven diagnosis of GBM, age over 18 years, and a KPS ≥ 70. Patients were excluded if they received any anti-tumor therapy in the four weeks prior to trial initiation or had severe comorbidity (elaboration in Appendix 11.2.2).

5.1.2.2 Study design and treatment

The intervention group consisted of ten ndGBM patients who had completed at least four weeks of radiation therapy and received TTFields therapy combined with maintenance TMZ. Prior to initiation of treatment, all patients underwent a baseline contrast MRI. The patients were hospitalized for one to three days for observation and then released home where they received multiple four-week courses of continuous TTFields treatment until progression. The patients were seen once per month at an outpatient clinic where they underwent an examination similar to the initial one. Patients in the intervention group were treated continuously for an average of one year (range 2.5 to 24 months).

5.1.2.3 Outcomes and statistical analysis

The outcome endpoints of the study included safety, OS, and PFS. Assessment of tumor response was based on monthly MRIs according to the McDonald criteria. Median OS and PFS were assessed using Kaplan-Meier curves.

PFS in the intervention group, consisting of ten ndGBM patients treated with TTFields and TMZ, was compared to the PFS of a matched group of concurrent control patients (n=32) who received TMZ alone at the same center as the intervention group was treated at (Na Homolce Hospital in Prague). OS was compared to matched historical control data (n not known) matched on the KPS (>60) and age (45). All KPS scores at baseline were ≥70 in the intervention group, >60 in the historical comparator group, and not reported in the concurrent comparator group.

5.1.3 Vymazal et al. (2023)

The study by Vymazal et al. is a retrospective cohort study conducted at a single center in Prague (Na Homolce Hospital in Prague) (102). The objective of the study was to describe outcomes of TTFields therapy for a consecutive cohort of ndGBM patients treated both within clinical trials as well as in routine clinical practice settings over a period of 18 years (see Appendix 11.2.3).

5.1.3.1 Study population

The study included 55 patients with ndGBM who were treated with TTFields between 2004 and 2022 and compared to 54 control patients. The inclusion criteria also allowed for the inclusion of patients with astrocytoma grade IV, as per the WHO definition of grade IV gliomas, although the number of patients included according to the new classification is not specified. The only selection criteria for control patients were data completeness, PFS of more than four months after surgery, and KPS of 70 or more.

Of the 55 patients who received TTFields, eleven patients (20%) were treated between 2004 and 2006 in the Kirson et al. (2009) (82), eight patients (15%) as a part of Stupp et al. (2017) (2), and 36 patients (65%) in the routine clinical setting. All patients had a KPS of 70 or more at the initiation of TTFields therapy, and the median age at diagnosis was 47.6 years (21.9 to 77.8). Patient characteristics between the TTFields group and the control group are generally compatible.

Only ten patients with ndGBM were included in the pilot trial by Kirson et al. (2009) (82) as described in 5.1.3, however, Vymazal et al. (102) included 11 patients from this study with ndGBM. The authors of Vymazal et al. explained upon request from the Nordic Institute of Health Economics that the eleventh patient (who was included as recurrent in the EF-07 trial) was included after reexamination of the EF-07 trial patient population.

5.1.3.2 Study design and treatment

Both groups received standard treatment, consisting of either gross total or subtotal/partial resection of the tumor (one patient with biopsy was included), followed by radiotherapy with concomitant TMZ. No significant differences in therapeutic strategy were observed between the groups.

All patients underwent regular MRI examinations and clinical evaluation by a board-certified neurologist or neurosurgeon. In Kirson et al. (2009) the interval between MRI and clinical evaluation was one month (82). Patients were scanned every month during the trial and surviving patients at the time Vymazal et al. were published were examined annually. Patients from Stupp et al. were examined every two months and those from the clinical TTFields group in Vymazal et al. were examined every two to three months (102).

The principle of TTFields treatment did not change throughout the study period. The Optune device did, however, become more patient-friendly between the years 2004 and 2022 since Novocure has developed several modifications of the device throughout the years. All treatment was done on an outpatient basis. The patients and their families or caregivers were trained to operate the device independently. The compliance of TTFields treatment was followed in each patient monthly.

The median interval between surgery (the time of diagnosis) and TTFields initiation was 3.8 months in Stupp et al. (2) and 4.38 months in patients treated as a part of routine clinical practice. The compliance of 36 clinical patients was mean of 74.8% (median 82%; percentage of day treatment applied).

5.1.3.3 Outcomes and statistical analysis

The outcome measures were PFS and OS. Progression was based on MRIs using McDonald and later Response Assessment in Neuro-Oncology (RANO) criteria to confirm progression. Median OS and PFS were assessed using Kaplan-Meier curves.

There was no missing data regarding survival. Censored data indicates that the patient either did not progress or is still alive. All patients lost from the evidence were excluded. In four control patients, it was not possible to assess the progression date. The PFS group is, therefore, reduced by four patients in comparison to the OS group. There is no further information available regarding outcomes and statistical methods used in the study.

5.1.3.4 Summary

Vymazal et al. study covers a period of 18 years at a single center and presents data from clinical trials as well as a group of 36 patients treated with TTFields as a part of routine clinical practice. It is the only study relevant to this report that includes data from routine clinical practice and is therefore considered valuable for this report.

5.1.4. Ballo et al (2022)

Ballo et al is a single center retrospective cohort study. The objective of the study is to analyze real-world outcomes from a single institution incorporating TTFields into standard practice for patients with ndGBM, and to identify factors associated with both initiating TTFields and maintaining the required usage following initiation (appendix 11.2.4).

5.1.4.1 Study population

Patients were identified through the Radiation Oncology departmental brain tumor database. The department started treating ndGBM patients with TTFields plus TMZ in 2015. Between 2015 and 2021, 135 patients were identified.

Patients who received best supportive care alone and patients with less than 9 months of follow-up were excluded leaving a cohort of 91 patients with IDH wild-type glioblastoma. There were no significant imbalances between patient sex, MGMT methylation status, ECOG performance status, radiation dose, and extent of surgical resection. Patients that chose to initiate TTFields were slightly younger than those who chose not to initiate TTFields (mean age: 59 years vs. 63 years, P = .05). Mean age in the TTFields group ranged from 34 to 87 years with a median of 60 years.

5.1.4.2. Study design and treatment

The patients in the cohort study are treated at the Department of Medical Oncology, West Cancer Center and Research Institute, Memphis, Tennessee, USA. The 91 patients underwent maximal surgical debulking, completed radiotherapy (median dose 60 Gy, range 40–60 Gy) with concurrent TMZ, and initiated adjuvant TMZ. Seventy-four patients received 60 Gy, while 17 patients received less than 60 Gy. All patients underwent a complete history and physical examination, and appropriate radiological imaging studies. Fifty-five patients underwent gross total resection, while 25 had a subtotal resection and 11 had a biopsy only. All patients had histological and molecular confirmation of WHO grade IV glioblastoma. MGMT was methylated in 43 patients, while 39 were un-methylated. MGMT methylation status could not be determined in 9 patients. Patient were encouraged to use TTFields ≥18 h per day (equivalent to average monthly compliance of ≥75%). Monthly TTFields usage data were collected on each patient. The median duration of follow-up for the 18 patients alive at last contact was 26 months (range, 10 to 66 months). Disease relapse was scored if there was any clinical or radiographic evidence of tumor regrowth and patients were followed regularly until the time of death.

5.1.4.3 Outcomes and Statistical analysis

The primary outcome was survival, indicated as median OS and actuarial rate of overall survival according to patient, tumor, and treatment characteristics.

Actuarial data for overall survival curves were calculated using the Kaplan–Meier method and tests of significance were based on the Breslow statistic. Multivariate analysis was done with the proportional hazards model using the log-linear relative hazard function of Cox. The date of surgical resection or biopsy was used as time zero. The significance of differences between proportions was tested with the chi-square statistic or with Fisher's exact test and differences between means was tested with the t-test or the nonparametric Mann–Whitney test as appropriate.

5.1.5 Pandey et al (2022)

Pandey et al. is a retrospective multi-institutional study of patients with GBM treated with TTFields. The aim of the study was to identify whether there is a molecular subset of GBM with differential response to TTFields treatment. (114)

5.1.5.1 Study population

Patients with grade IV glioma who had undergone molecular profiling at Caris Life Sciences were identified and their medical records were reviewed at each participating site from which the treatment, and outcome information were extracted. Data were collected from a total of 148 patients. Patients with rGBM, and patients who had any treatment initiated prior to tumor profiling were excluded. 55 patients treated with TTFields, and 57 treated with standard-of-care treatment without TTFields, were included for final analysis. Demographic characteristics were well balanced in the 2 groups. For more details see appendix 11.2.5.

5.1.5.2 Study design and treatment

This study was a retrospective, multi-institutional evaluation of patients with newly diagnosed grade IV glioma treated with TTFields in the first-line setting. Data were collected from genomic profiles following biopsy or surgical resection of GBM tumor specimens from 6 institutions (Barrow Neurological Institute, Arizona; Levine Cancer Institute, Charlotte, North Carolina; West Cancer Center, Memphis, Tennessee; John Wayne Cancer Center, San Diego, California; Karmanos Cancer Institute, Detroit, Michigan; Florida Hospital, Florida) between December 2014 and November 2017.

Molecular profiling was performed by Caris Life Sciences. At each participating institution, clinical records of patients who received TTFields treatment as part of their treatment plan were reviewed and pre-specified data points were recorded by study co-investigators; a control cohort of similar size as the TTFields-treated cohort was reviewed and included as control.

Treatment regimens for both the TTFields group and control group were dominated by the use of concurrent daily TMZ chemotherapy, followed by 5-day TMZ used in 28-day cycles for 6-12 months. In patients treated with TTFields, the average duration of use of TTFields was 198 days, average compliance was 57%, with median use of 60%.

5.1.5.3 Outcomes and statistical analysis

All tumor samples were tested with comprehensive molecular profiling which included NGS on DNA and RNA as well as MGMT promoter methylation testing by pyrosequencing. Genetic variants identified were interpreted by board-certified molecular geneticists and categorized according to the American College of Medical Genetics and Genomics (ACMG) standards. These genomic factors were assessed in relation to their effect on both PFS and OS. However, this report will focus on the difference in OS and PFS between patients who received TTFields treatment and patients who received standard of care treatment.

PFS was calculated from the date of patients' histological diagnosis to the first progression after TTFields treatment start in the TTFields group, and to the first progression after treatment start in the control arm. OS was calculated from the patients' histological diagnosis till patient death or last date of contact. Kaplan-Meier estimates of the PFS and OS were performed on censored data using Cox proportional hazards model. Hazard ratio and P values were calculated for inter-group comparisons and $P < .05$ was considered significant. Biomarker and clinicopathological features in the TTFields and control group were compared using Fisher's exact test.

5.1.6 Taphoorn et al. (2018)

Study characteristics from Taphoorn et al. are listed in Appendix 11.2.6. Taphoorn et al. is a supplementary article based on Stupp et al. (2017) (11). The study design, population, and treatment are therefore the same as in th trial by Stupp et al. and will therefore not be elaborated on in this section. The supplementary study by Taphoorn reports HRQoL. HRQoL data were examined per protocol, and therefore included only patients who received their original allocated treatments, meaning that the patients in the TMZ group who crossed over to TTFields plus TMZ were excluded from the analysis.

5.1.6.1 HRQoL assessment

The evaluation of HRQoL was performed using the validated European Organization for Research and Treatment of Cancer (EORTC) quality-of-life questionnaire-C30 (QLQ-C30) and brain module (QLQ-BN20). These instruments are disease-specific and developed specifically for the assessment of HRQoL of brain cancer patients. The overall aim of these questionnaires is to evaluate the effects of the tumor and its treatment on symptoms, functions, and HRQoL of brain tumor patients, both in clinical trials and clinical practice (11). QLQ-C30 is the most frequently used measurement assessing HRQoL in GBM patients (68). A study examining the validity and reliability of the QLQ-BN20 in a multi-national, multi-lingual setting, concluded

that the QLQ-BN20 module demonstrated adequate psychometric properties and subsequentially recommend the module for use in conjunction with the QLQ-C30 in assessing the HRQoL of brain cancer patients in international studies (11). The validity of QLQ-C30 and QLQ-BN20 for measuring HRQoL in patients with brain cancer has been reported in several other studies, which confirms the legitimacy of the questionnaires in different countries as reliable tools that have been used extensively in the primary brain cancer population (67,118–121).

Questionnaires were self-reported by patients and completed on paper at baseline (prior to randomization) and subsequently every three months for up to 12 months. The number of patients filling the HRQoL questionnaires decreased from 91.9% at baseline to 65.8% at three months and 41.7% at 12 months. Nine scales and items were preselected as important based on relevance for patients with GBM and hypothesized effects of the TTFields delivery device on patients' HRQoL: global health status; physical, cognitive, role, social, and emotional functioning; itchy skin; pain; and weakness of legs. (11)

5.1.6.2 Statistical analysis

The items on the questionnaires were scaled and scored using the EORTC procedures. The raw scores were transformed to a scale ranging from zero to 100, with a higher score representing a higher level of functioning or a higher level of symptoms. Differences of at least ten points (on a zero to 100 scale) were classified as the minimum clinically meaningful change in any HRQoL scale/item.

Descriptive statistics were used to report HRQoL scores as well as the sociodemographic and clinical variables for the population of patients who completed at least one HRQoL scale at baseline. Differences between arms were tested using a 2-sided $\chi 2$ test or an independent 2-tailed, unpaired t-test or Mann-Whitney test at an α value of 0.05 for each variable. Patients who completed the assessments at the time of progression were included in this analysis.

Mean HRQoL scores over time were calculated as well as the mean changes from baseline. Mean change from baseline was plotted to evaluate the longitudinal course of patients' experience of disease and treatment and a linear mixed-model repeated measures analysis was used to estimate the treatment effect over time.

Deterioration-free survival was defined as the time to a greater than ten-point deterioration in scores from baseline without a subsequent ten point or more improvement in scores compared with baseline, progressive disease, or death in the absence of a previous definitive deterioration before the next assessment. Data for patients with missing baseline scores were not included, and patients missing all postbaseline HRQoL assessments were censored at randomization. Time to deterioration (TTD) was defined similarly to deterioration-free survival, with the exception that progressive disease was excluded as an event (i.e., non-missing HRQoL data beyond progression were included). Kaplan-Meier was used to estimate deterioration-free survival and TTD. The difference between treatment arms was compared using a 2-sided stratified log-rank test. HRs were estimated using a stratified (for the extent of resection and MGMT status) Cox proportional hazards regression model. (11)

5.1.7 Garside et al. (2007)

For this evaluation, the DHTC has requested information on the difference in index scores measured with the EQ-5D questionnaire. Our literature search has not identified any study that contains information on EQ-5D utility scores in patients treated with Optune. Therefore, information on utility is based on Garside et al. (2007) (12).

The study by Garside et al. is a health technology assessment from the UK from the HTA Program made to support a decision in the National Institute for Health and Clinical Excellence (NICE). The aim of the study was to assess the clinical and cost-effectiveness of TMZ or carmustine wafers versus radiotherapy in newly diagnosed grade III and grade IV gliomas. The Garside et al. study is relevant because it is the source of

evidence for the quality-of-life measure used in the health economic evaluation in Chapter 8. For more details see Appendix 11.2.7.

The Garside et al. study included a systematic literature review of the evidence of the health-related quality of life in patients newly diagnosed with high-grade glioma. Updated searches were undertaken on 25.08.2005. The search was performed in electronic databases, including MEDLINE PubMed, EMBASE, The Cochrane Library, Science Citation Index, Web of Science Proceedings, DARE, National Health Service EED, and HTA databases. Two researchers independently assessed the relevance of the retrieved abstracts, and the full texts of these papers were obtained and assessed if they fulfill the inclusion criteria. Included study design was Systematic reviews. RCTs and non-randomized evidence were also considered where they gave the best estimates of a required parameter (for example adverse effects or patient preferences) or where RCT data were scanty or uninformative. Included trials were critically appraised for key elements of internal and external validity. Relevant data were extracted, and a narrative synthesis of the evidence was produced.

The Garside et al. study obtains estimates of utility from the NHS Value of Health Panel, a project being led by PenTAG in collaboration with the Universities of Southampton and Sheffield. The Value of Health Panel had 93 members who were familiarized with the standard gamble (SG) method for preference elicitation, and 36-panel members participated in eliciting utility values for glioma. Garside et al. argue that using this method is less likely to introduce a bias into utility values compared to eliciting utilities from patients or clinicians. The panel members expressed their preferences using this technique in relation to short descriptions of health states. The health state scenarios were developed from disease specific quality of life measures identified in their systematic review. Scenarios were developed based particularly on a study by Osoba et al. using the EORTC QLQ-30 questionnaire (88). Content validity of the health state descriptions was sought using three members of the NICE Expert Advisory Group prior to measuring preferences. Data collection from the panel was web-based.

5.1.8 Regev et al. (2021)

The objective of the review by Regev et al. is to establish an understanding of the device's mechanism of action and its efficacy for treating GBM, by means of a systematic literature review and meta-analysis (10). The meta-analysis was conducted according to the PRISMA guidelines (Appendix 11.2.8).

5.1.8.1 Studies identification and selection

A literature search was performed in three database engines: PubMed (Medline), Scopus (ELSEVIER), and Cochrane Central Register of Controlled Studies. The most recent search was conducted on 09.10.2020.

Studies meeting the following criteria were included in the quantitative analysis: (a) written in English; (b) original study (RCTs, cohort studies, observational studies, or case series); (c) patients treated for GBM; (d) patients ≥18 years; (e) report either clinical efficacy, daily compliance, or AEs. For each eligible study, the following data were extracted: authors, year of publication, study type, intervention, GBM status, number of patients, gender, age, KPS, treatment compliance, and number of recurrences. Also, we extracted clinical endpoints: median OS, median PFS, PFS at six months, survival at one, two, and three years, AEs, and Kaplan-Meier curves.

To evaluate the quality and risk of bias in the included studies' methodological design, the Oxford Centre for Evidence-Based Medicine guidelines, the Newcastle-Ottawa Quality Assessment tool for non-RCT studies, and the risk of bias two tools for RCTs.

Of the initial 645 papers identified, 20 studies met the predefined inclusion criteria. The studies consisted of two RCTs (EF-11 trial and EF-14 trial), and five prospective single-arm clinical trials. One prospective observational study, two registry-based studies (PRiDe on US patients), a global post-marketing registry, three retrospective studies, one case series, and three post hoc analyses (two of EF-14 trial, and one of EF-11 trial).

Three conference presentations that were not yet published in peer-reviewed journals were also included. Seven studies included ndGBM, 13 included rGBM, and two included both. The studies include 1,636 (542 ndGBM and 1,094 rGBM) patients analyzed for the clinical outcomes' endpoints, and 11,558 (6,403 ndGBM and 5,155 rGBM) patients analyzed for the safety endpoints (10).

5.1.8.2 Statistical analysis

Pooled Kaplan-Meier curves, median OS, median PFS, and survival rates with a 95% CI were calculated. Pooled median OS and PFS were estimated, as a sensitivity analysis, for all studies reporting median OS and PFS. The pooled prevalence of AEs was calculated using the MetaProp package using the R software. The Cochrane Q chi-square test and I^2 statistics were used to examine the heterogeneity across studies. The fixed-effects model was used for pooled results with low heterogeneity ($I^2 \leq 50\%$); otherwise, the random-effects model was used for analysis. All analyses were performed using the R software.

5.1.8.3 Summary

Regev et al. is the largest and most recent meta-analysis identified in the literature search, that estimates the efficacy and safety of the use of TTFields in GBM. The study will, however, be included in this report with several limitations, due to the pooling of studies with different patient populations (including both ndGBM and rGBM) as well as differences in treatment and comparison, And the inclusion of the study's results is therefore limited.

5.2 Clinical question

The following section will answer the clinical question regarding the Clinical effectiveness of Optune in patients with ndGBM as stated in the evaluation design supplied by the DHTC:

"Should Optune be used to treat patients with newly diagnosed grade IV glioma as a supplement treatment to standard of care?"

The section will include a brief description of differences in included studies, results at the study level as well as a comparative analysis conducted for outcome measures where this was possible.

5.2.1 Studies used

The current section describes differences between the included studies. This includes differences in study design, patient characteristics, and methods of calculation. Differences between the included studies and the description of the outcome measures in the evaluation design will also be described.

5.2.1.1 Study design

This section will focus on differences in study design between the studies described above, focusing on the five studies included for the assessment of OS and PFS. These studies are Stupp et al. (2017) (2), Kirson et al. (2009) (82), Vymazal et al. (2023) (102). Ballo et al. (2022) (114) and Pandey et al. (2022) (115).

Stupp et al. was a multicenter, open-label, phase three RCT with a large sample size (695 patients) and multiple participating centers across different regions. Kirson et al. was a single-arm, pilot trial with a smaller population. Both were conducted at a single center in Prague, while Ballo et al and Pandey et al, were retrospective cohort studies conducted in the US.

An important strength in Stupp et al. is therefore the randomization. The act of randomizing patients into different treatment groups minimizes risk of differences between the control and treatment group apart from whether they received the treatment or not. Randomization reduces the problem with confounders, so the overall risks of developing the outcome in one group become comparable to the risks in the other group, leaving the difference in outcomes between the groups to the differences in treatment (122). In the case of the

Stupp et al., randomization was stratified by the extent of resection (biopsy, partial resection, gross total resection) and by MGMT methylation status (methylated, unmethylated, or unknown). Furthermore, there were no significant differences in baseline characteristics between the TTFields plus TMZ and the TMZ alone group. A testimonial that randomization was successful in Stupp et al. comes from the Washington State HTA, which classifies the risk of bias arising from randomization or selection as low (16). Randomization is therefore an important strength in Stupp et al.

A possible concern for all included studies is that none of the participants were blinded to the treatment they received. Stupp et al. reported that the choice of not including a placebo device in Stupp et al. was made due to the burden of carrying a device that would have no potential for therapeutic benefit. Of note, the methodology in Stupp et al. is similar to the design utilized in trials evaluating other therapies in GBM, specifically technological options such as radiotherapy (117). Patients not being blinded to treatment generally means that the placebo effect cannot be excluded. In this case, response to therapy can be affected by treatment allocation and any placebo effect of the intervention cannot be accounted for. However, this does not have any impact on OS or PFS, as these are objective outcomes that are not affected by a placebo. Furthermore, a panel of experts discussing the results from Stupp et al. noted that no placebo effect was seen in other recent trials lacking a placebo design that failed to demonstrate improved survival with cilengitide or dose-dense TMZ in patients with ndGBM (106,117,123). The lack of patient blinding does therefore not have any significance for OS or PFS. This assessment is echoed in the Washington HTA (16).

A lack of blinding, however, can affect patient-reported outcomes such as HRQoL and AEs in Stupp et al. because these outcomes are somewhat subjective. The direction of bias from nonblinding largely depends on the beliefs and attitudes of participants, clinicians, and outcome assessors, and can therefore not always be predicted (16).

Duration of follow-up differs between the studies. Stupp et al. reports a median follow-up of 40 months. Kirson et al. do not state median follow-up, however, the longest PFS was 180+ weeks according to the Kaplan-Meier curves. Ballo et al had a median follow up of 26 months. Vymazal et al. had a follow-up of over 18 years. The long follow-up and period of patient recruitment can be considered a strength in Vymazal et al.; but the standard of care (including supportive care) may have changed during the follow-up time. It is however not expected that potential treatment changes significantly affect the comparison of outcomes, as the authors report the main difference to be evolving techniques of postoperative radiotherapy from 3D-conformal techniques to intensity-modulated beam radiotherapy, for which no study has confirmed the superiority of one or the other.

Stupp et al. and Kirson et al. were both funded by Novocure. Novocure had a role in the design and conduct of the Stupp et al. trial as well as the collection, management, and analysis of the data. Neither Ballo et al., Pandey et al. nor Vymazal et al. were funded by Novocure, with Vymazal being funded by the Czech Republic Ministry of Health. The Washington state HTA assessed the risk of bias arising from the selection of reported results in Stupp et al. as “low” since the interim analysis was preplanned, and the final analysis is consistent with the interim analysis. (2,82,102,114,115).

5.2.1.2 Patient population

Stupp et al. and Kirson et al. (2009) included patients with histologically confirmed ndGBM. Two of the three populations included in Vymazal et al. (2023) (2,82) were included according to the same inclusion criteria as in the original studies, however patients recruited in the routine clinical setting, were included according to current terminology, and patients with astrocytoma grade IV were therefore also included. Both Ballo et al. (2022) and Pandey et al. (2022) included patients based on WHO's definition of glioma grade IV. However, the patient population in Ballo et al. consists exclusively of patients with IDH wild type glioblastoma.

A strength in Stupp et al. is the randomization that renders patients in the control and comparator groups compatible. All reported baseline characteristics in Stupp et al., Kirson et al. Ballo et al. Pandey et al. and Vymazal et al. are generally compatible between intervention and comparator within each study. Patient characteristics between studies are largely compatible, with the following differences in reported characteristics. An inclusion criterion for both Stupp et al., Vymazal et al., and Kirson et al. was a KPS above 70, however, the median KPS differs slightly with 90 in Stupp et al. and 80 in Vymazal et al. in both the intervention and control group (value not available in Kirson et al.). Ballo et al. and Pandey et al. did however not report KPS.

All patients included in both Stupp et al., Vymazal et al., and Kirson et al. are over the age of 18, however this is not specified in Ballo et al. and Pandey et al. The median age in Vymazal et al. is 47.6 (21.9 to 77.8) in the TTFields group and 51.7 (27 to 76.7) in the control group, while the median age in Stupp et al. is slightly higher with 56.0 (19 to 83) in the TTFields group and (57.7 (19 to 80) in the control group. Patient characteristics for the comparator groups in Kirson et al. are not reported. The mean age in Ballo et al. is 63 in the TTFields group and 59 (26 to 79) in the control group, while the median age in Pandey et al. is 59 (17 to 75) in the TTFields group and 58 in the control group. (2,82,102,114,115).

The median age for the diagnosis of grade IV glioma is approximately 64 years in Denmark. This is similar to the Swedish patient population. TLV's experts assessed that 56 years of age is a reasonable assumption for mean age in clinical practice for treatment with Optune in a Swedish setting. This is justified by the fact that some of the oldest patients cannot be provided with active standard therapy and those offered standard therapy today are generally younger than the median age of glioblastoma diagnosis and are in good general health (15). Due to the large generalizability between the patient population in Denmark and Sweden, we consider the age group of around 56 years of age as a reasonable assumption for mean age in clinical practice for treatment with Optune.

Furthermore, a group of experts discussing the results of Stupp et al. also concluded that there did not appear to be bias in regard to patient selection or imbalance between treatment groups. This was based on the observation that the two treatment groups were well matched for baseline characteristics and were generally similar to those observed in other trials of patients with glioma grade IV who had completed radio chemotherapy, such as the Gilbert et al. (2014) study that failed to show a survival benefit with dose-dense TMZ (117,123).

As Kirson et al. was a pilot study, only sparse information on patient characteristics is available. This, however, is not an issue for further analysis in this report, as Kirson et al. will not be included in the comparative analysis, because all included patients with ndGBM in Kirson et al. are also included in Vymazal et al. Vymazal et al. report more detailed patient characteristics and are generally compatible with the trial population in Stupp et al. (2,82,102,114,115)

5.2.1.3 Treatment protocols

All included studies involved TTFields treatment, but the specific details of treatment administration may differ slightly. The median duration of TTFields treatment in Stupp et al. was 8.2 months (range zero to 82) and the median duration of TMZ treatment was six months (range zero to 51) in the intervention group and five months (range zero to 33) in the comparator group (2). 75% of patients in the intervention group achieved treatment adherence of ≥75%, defined as the use of the device for ≥18 hours per day in the first three months of TTFields treatment. Vymazal et al. (2023) report compliance only for the 36 clinical patients, for which the compliance is compatible with Stupp et al. with 74.8% (102). Kirson et al. (2009) and Ballo et al. (2022) did not report median compliance (77,82).

Pandey et al. (2022) reported lower compliance on 57%, with the study pointing out that the years where the patients were diagnosed and treated (2014-2017) were when TTFields began to be adopted, claiming that more widespread acceptance of TTFields therapy in the first-line setting for ndGBM took hold more widely following that time period. (115)

The version of Optune used in Kirson et al. and Stupp et al. trial was an older version that weighed approximately six pounds. The newer version is lighter at around 2.7 pounds and was likely used in recent years in the Vymazal et al. study (n=unknown). The second-generation Optune system was designed to be more convenient and to make it even easier for patients to incorporate treatment with TTFields into their lives. One can imagine that these changes could mean that compliance with the new and easier version of Optune will be higher than what has been observed in these studies. The impact of Optune on OS and PFS corresponds to the time the device is used (the longer the patient uses Optune, the greater the effect). Therefore, potentially higher compliance could have a positive impact on PFS and OS. Consequently, the effect of Optune could potentially be greater with second-generation Optune compared to what the current studies using first-generation Optune show.

In Kirson et al. the interval between MRI and clinical evaluation was one month. Patients were scanned every month during the trial and surviving patients at the time Vymazal et al. were published were examined annually. Patients in the Stupp et al. study were examined every two months and those from the clinical TTFields group in Vymazal et al. were examined every two to three months (102). Kirson et al. did not report time between examinations for control groups. TTFields patients in Vymazal et al. underwent MRI examinations more frequently in comparison to controls, thus PFS may be shorter in TTFields patients compared to controls due to greater precision. PFS may by this mechanism be somewhat biased because the recurrence is detected earlier in comparison with the control group (102). The same bias cannot be excluded for Kirson et al. This bias would be a negative bias, meaning that this potential bias would lead the observed effect of TTFields plus TMZ compared to TMZ alone to be lower than the true effect. The actual impact of TTFields on PFS may therefore be larger than what has been reported in the studies conducted by Vymazal et al. and potentially Kirson et al. It implies that there might be a potential underestimation or limitation in the reported effects of TTFields on PFS in these studies, and the true effect could be more significant.

5.2.1.4 Outcome measures

All studies define OS and PFS as the length of time from the start of treatment with TTFields that patients are still alive, and the length of time from the start of treatment with TTFields to the progression of the disease respectively. However, Pandey et al. (2022) deviates from this approach by measuring OS and PFS from the time of diagnosis rather than the start of treatment with TTFields. (2,79,99,112,113)

OS and PFS were analyzed as intention to treat in Stupp et al., as 26 patients (11%) in the TMZ alone control group crossed over and received TTFields, following the release of the interim analysis results. These patients had more favorable baseline characteristics than the rest of the control patients, including MGMT, KPS, time from the end of radiotherapy to randomization, and received more cycles of TMZ. According to the interim analysis, OS was supposed to be analyzed per protocol. However, the authors of Stupp et al. acknowledged the bias that patients who crossed over from TMZ alone to TTFields plus TMZ could introduce. This could have potentially introduced a positive bias, leading to an overestimation of the OS outcomes observed in Stupp et al. Therefore, the authors decided to analyze OS based on the intention-to-treat principle. This means that all patients were analyzed according to the group they were initially randomized to. As a result, the patients who received TTFields treatment after the interim analysis were still included in the TMZ alone group. If this group of patients, due to favorable baseline characteristics and receiving the favorable treatment with TTFields, would have better OS, the true benefit in OS from adding TTFields may be underestimated in Stupp et al. (2)

Furthermore, the Washington HTA assessed bias arising from the measurement of the outcome in regard to OS and PFS as "low", as the MRIs were reviewed by two blinded central independent radiologists and were evaluated for tumor response and progression according to the McDonald criteria, with a third blinded radiologist settling disagreements.

Method of calculation for PFS in the Stupp et al study was calculated using a stratified log-rank test (stratified by randomization strata) aimed to detect an HR of 0.78 or less, with 80% power allowing for 10% loss to follow-up of and a 2-sided α=0.05. Statistical methods are less thoroughly described in the remaining studies. Both Kirson et al. and Vymazal et al. conducted a log-rank-test to detect HR for PFS and OS and all studies conducted Kaplan-Meier curves. Ballo et al. based Kaplan–Meier method and tests of significance on the Breslow statistic. Multivariate analysis was done with the proportional hazards model using the log-linear relative hazard function of Cox. Kaplan-Meier estimate were performed on censored data using Cox proportional hazards (PH) model in Pandey et al. (2,82,102,114,115).

MRIs were reviewed by blinded central independent radiologists in the Stupp et al. study. However, the remaining studies did not report whether the radiologist was blinded and could therefore be subjected to bias. These studies in which outcome assessors are not blinded to treatment allocation may suffer an increased risk of type I error. Bias in the measurement of outcomes is, therefore, possible but is however unlikely (16).

5.2.2 Results at study level

Results at the study level for each of the predefined outcome measures will be presented in the current section. These outcome measures include OS, HRQoL, and cognitive abilities. Additional outcome measures that will be presented are PFS and safety measures, including skin irritation. Discrepancies between measurements and definitions of outcomes in the studies and the evaluation design will be highlighted when relevant.

An overview of results per outcome measure is stated in Table 5.2 and will be discussed in the following. Additionally results per study can be seen in appendix 11.2.9 to appendix 11.2.13.

5.2.2.1 Overall Survival

Objectives for OS will include the treatment advisory board's predefined outcome measures: Median survival, 1-year survival, and 2-year survival. Additionally, 5-year survival will also be presented, ss this efficacy measure can provide valuable information about the long-term impact of TTFields on OS.

5.2.2.1.1 Median survival

The literature search identified five studies that investigate OS in patients with ndGBM compared to standard of care. All studies define OS as the length of time from the start of treatment with TTFields that patients are still alive, except for Pandey et al. (2022) which measures OS as time from diagnosis that patients are still alive.

The most prominent of the included studies is Stupp et al. The study reported a median OS of 20.9 months and 16.0 months in the intervention and comparator groups, respectively, resulting in a difference of 4.9 months, favoring treatment with TTFields. The difference in OS was statistically significant with a HR favoring treatment with TTFields and maintenance TMZ (HR 0.63, 95% CI 0.53 to 0.76) compared with TMZ alone. (2)

Results from the cohort study conducted by Kirson et al. were consistent with the results from Stupp et al. in the direction of effect but were of greater magnitude among the patients receiving TTFields. Kirson et al. reported that patients who were treated with TTFields had a longer median OS of more than 39 months compared to the OS of 14.7 in matched historical controls receiving maintenance TMZ alone. Although Kirson et al. do not supply a hazard ratio, the difference between OS curves in a Kaplan-Meier curve is significant (p=0.00018). (82)

The results in the cohort study by Vymazal et al. are consistent with these results in the direction of effect. The median OS for patients receiving treatment with TTFields was 31.67 months versus 24.80 months in the comparator group (p=0.028). The HR is very similar to the Stupp et al. study on 0.61 (95% CI 0.39 to 0.95). The CI was obtained through contact with the authors. The estimates of OS may be biased due to the exclusion of six patients from the control group due to early progression. Additionally, the standard of care (including supportive care) has likely improved since the Stupp et al. study was conducted. The difference in duration of follow-up also affects the results as three patients have been followed for 16-18 years after initial surgery, contributing to much follow-up time in a relatively small study population (102). Results from the cohort study by Ballo et al. (2022) demonstrate the same tendency. Median OS in the TTFields group was 20.7 months and 15 months in the TMZ alone group (P = 0.4). This is a difference of 5.7 months indicating a favorable effect of TTFields. Similarly, Pandey et al. (2022) reports median OS on 25.5 months in the TTFields group and 18.8 months in the control group (HR = 0.54; 95% CI: 0.31-0.94; P = .03), which is a difference of 6.7 months, favoring treatment with TTFields. (77,115)

The positive results achieved with TTFields Stupp et al. are unlikely to be due to placebo effects in regard to OS, which is a categorical event. Also, the magnitude of benefit observed with TTFields was robust (HRs of 0.69 and 0.75 for PFS and OS, respectively), typically beyond what one usually expects with a placebo effect. This is also supported by a panel of experts that engaged in an open debate on the results of Stupp et al. Furthermore, this same panel concluded that these results from Stupp et al., aside from being statistically significant, are also clinically meaningful for cancer therapies (117). Results from all the mentioned studies can be seen in table 5.2.

Study	Group	N	Medan OS, months [95% CI]	Difference, months [95 % CI]	HR [95 % CI]	P value
Stupp et al. (2017)	TTFields plus TMZ	466	20.9 [19.3-22.7]	4.9 [2.3-7.9]	0.63 [0.53-0.76]	< 0.001
	Standard of care	299	16.0 [14.0-18.4]			
Vymazal et al. (2023)	TTFields plus TMZ	55	39	8.87	0.61 [0.39-0.95]	0.028
	Standard of care	54	14,7			
Ballo et al. (2022)	TTFields plus TMZ	59	20.7	5.7	0.63 [0.38-1.05]	N/A
	Standard of care	32	15			
Pandey et al. (2022)	TTFields plus TMZ	55	25.5	6.7	0.54 [0.31-0.94]	0.03
	Standard of care	57	18.8			
Kirson et al. (2009)	TTFields plus TMZ	10	39	24.3	N/A	0.0018
	Standard of care	N/A	14,7			

Table 5.2 Results for median OS. (2,79,99,112,113).
CI, confidence interval; HR, hazard ratio; N/A, not applicable; OS, overall survival; TMZ, temozolomide.

5.2.2.1.1.1 Relationship between compliance and OS

In a subgroup analysis of the Stupp et al. study, median OS was significantly higher among adherent patients (used continuous TTFields therapy for ≥18 hours), with OS of 22.6 months, 95% CI, 19.7 to 25.1, compared to patients who were not adherent (19.1 months, 95% CI 16.5 to 21.9) (HR 0.65, 95% CI 0.49 to 0.85). For patients using TTFields > 22 hours each day, the 5-year survival rate was high, reaching 29.3% (2). The subgroup analysis by Toms et al. and Kesari et al. reports that OS was extended when compliance was increased beyond 50%, indicating progressively increased gains in OS as compliance increases (124,125).

Furthermore, patients were categorized into groups according to level of monthly usage and reported a stepwise improvement in overall survival with progressively increasing use. For their patients with a usage

rate of less than or equal to 30%, 30%–50%, 50%–60%, 60%– 70%, 70%–80%, 80%–90%, and greater than 90% the median overall survival increased from 18.2, 17.9, 18, 19.9, 21.7, and 21.5 to 24.9 months, respectively (2,65)

This tendency is also apparent in Ballo et al., where patients were split into the following three groups: a no use group, with 32 patients that declined TTFields. A low use group with 40 patients that started, with a median usage on 3 months with average monthly compliance ranging from 9% to 87% (median: 57%). And a high use group with 19 patients with a median usage on 9 months, with average monthly compliance ranging from 75% to 96% (median: 84%). Survival in these groups were as followed: The no use group had a median OS of 15 months. The low usage groups had a median OS of 20 months, and the high usage group had a median OS of 28 months (p = .05). Both studies therefore shows that TTFields use and its relationship to overall survival is proportional and that for higher usage is associated with improvement in OS. (114)

5.2.2.1.2 1-year survival

Stupp et al. and Vymazal et al. have reported results for 1-year survival rates. In Stupp et al., the 1-year survival rate was 73% (95% CI 69% to 77%) for patients in the TTFields plus TMZ group, while it was 65% (95% CI 59% to 72%; p<0.001) for patients in the TMZ alone group. This indicates a difference of 8% (95% CI: 0% to 16%) between the two groups, with the difference favoring treatment with TTFields. (2).

In Vymazal et al., the 1-year survival rate in the TTFields plus TMZ group was 87% (95% CI 79% to 96%), and 93% (95% CI 86% to 99%) in the TMZ alone group. This shows an insignificant difference of -6%. However, there are various issues with the results from Vymazal et al. concerning 1-year survival. The study itself points out that the 1-year survival rate in the TMZ alone group is biased due to the exclusion of 6 patients with very early progression. By excluding the most critically ill patients, an unrealistically high survival rate will very likely have been observed. (102)

Considering this significant problem with the 1-year survival results in Vymazal et al. study, it is concluded that the results from Stupp et al. are more reliable.

5.2.2.1.3 2-year survival

Stupp et al. and Vymazal et al. report results for 2-year survival. In Stupp et al., the OS rate 2 years after randomization was 43% (95% CI 39% to 48%) for patients in the TTFields plus TMZ group, while it was 31% (95% CI 25% to 38%; p<0.001) for patients in the TMZ alone group. This indicates a difference of 12% (95% CI 4% to 18%) between the two groups, and the Stupp et al. study thus shows a significantly higher 2-year survival rate in the TTFields plus TMZ group. (2)

Similarly, the results from Vymazal et al. show the same trend. The 2-year survival rate in the TTFields plus TMZ group was 61% (95% CI 49% to 76%), while it was 53% (95% CI 41% to 68%) in the TMZ alone group, resulting in an 8% difference between the two treatment groups. (102)

The 2-year survival results from both studies favor treatment with TTFields, as they demonstrate higher survival rates in the TTFields plus TMZ group compared to the TMZ alone group.

5.2.2.1.4 5-year survival

Stupp et al. and Vymazal et al. have reported results on 5-year survival rates. In the study by Stupp et al., 13% (95% CI 9% to 18%) of patients in the TTFields plus TMZ group were alive 5 years after randomization, whereas only 5% (95% CI 2% to 11%; p=0.004) of patients in the TMZ alone group survived to the 5-year mark. This is a significant difference of 8% (95% CI 2% to 14%) between the two groups. (2)

Similarly, the 5-year survival results from the study conducted by Vymazal et al. show the same trend, though with higher survival rates in both treatment groups. In the TTFields plus TMZ group, the 5-year survival rate

was 24% (95% CI 12% to 45%), while it was 12% (95% CI 06% to 26%) in the TMZ group, resulting in a difference of 12%. (102)

Both studies demonstrate that treatment with TTFields plus TMZ is associated with higher 5-year survival compared to treatment with TMZ alone.

5.2.2.2 PFS

Although PFS is not specifically requested in the evaluation design, it is relevant to address for several reasons. PFS is a primary outcome measure in several studies on the effectiveness of TTFields, including Stupp et al. (2017). Disease progression and the stage of the disease directly impact a patient's quality of life, making longer PFS of great importance for the patient's well-being. Moreover, PFS will also be utilized in the health economics chapter.

PFS is defined as the length of time during and after the treatment of grade IV glioma, that a patient lives with the disease, but where it does not get worse. The literature search identified 4 studies that investigate PFS in patients with ndGBM compared to TMZ alone, for which the results are shown in Table 5.3. All studies define PFS as the length of time from the start of treatment with TTFields to the progression of the disease, except for Pandey et al. (2022) which measures PFS as time from diagnosis until disease progression. Progression was based on MRIs in all studies using McDonald criteria in Kirson et al. and Stupp et al.. Vymazal et al. used the McDonald criteria and later RANO criteria to confirm progression. Criteria for progression was not specified in Pandey et al. (2,82,102,115)

The Stupp et al. study reported a median PFS of 6.7 months in the intervention group and 4.0 months in the comparator group, over a follow-up period of 40 months. The HR favored treatment with TTF and maintenance TMZ (HR 0.63, 95% CI 0.52 to 0.76) compared to TMZ alone ($p<0.001$). (2)

Results from Kirson et al. are consistent with Stupp et al in the direction of effect. The HR in Kirson et al. is 3.32 (95% CI 1.9 to 5.9), for the control group compared to the intervention group. The ratio has been inverted to better compare the HRs between the included studies. The inverted ratio is 0.30 (95% CI 0.17 to 0.53). The magnitude of the effect in Kirson et al. differs from Stupp et al., with a median PFS of 38.75 months (reported as 155 weeks) for the intervention group and 7.75 months (reported as 31 weeks) for the historical comparator group ($p=0.0002$). (82)

The results from Vymazal et al. are compatible with the results from Stupp et al. and Kirson et al. in the direction of effect, but with longer PFS than in the Stupp et al. study. Median PFS was 19.75 months in the TTFields group and 12.45 months in the TMZ alone group. The HR favored treatment with TTFields (HR 0.64, 95% CI 0.42 to 0.96, $p=0.031$). The CI was obtained through contact with the authors. (102)

Similarly, the results from Pandey et al. demonstrate that the TTFields group exhibits a significantly longer PFS compared to the TMZ alone group. Specifically, the PFS in the TTFields group is 15.8 months, whereas it is 6.9 months in the TMZ alone group (HR 0.55, 95% CI 0.35 to 0.86, $p=0.01$). This indicates an improvement of 8.9 months in PFS for patients receiving TTFields treatment (115). Results from all the mentioned studies can be seen in table 5.3.

Study	Group	N	Median PFS, months [95% CI]	Difference, months [95 % CI]	HR [95 % CI]	P value
Stupp et al. (2017)	TTFields plus TMZ	466	6.7 [6.1-8.1]	2.7 [2.1-4.29]	0.63 [0.52-0.76]	< 0.001
	Standard of care	299	4.0 [3.8-4.49]			
Vymazal et al. (2023)	TTFields plus TMZ	55	19.75	7	0.64	0.031
	Standard of care	48	12.75			
Pandey et al. (2022)	TTFields plus TMZ	55	15.8	8.9	0.55 [0.35-0.86]	0.01
	Standard of care	57	6.9			
Kirson et al. (2009)	TTFields plus TMZ	10	38.75	31	0.30 [0.17-0.53]*	0. 0002
	Standard of care	32	7.75			

Table 5.3 Results for median PFS. (2,82,102,114,115).
**Inverted HR from 3.32 [1.9–5.9].*
CI, confidence interval; HR, hazard ratio; N/A, not applicable; PFS, Progression Free Survival; TMZ, temozolomide.

5.2.2.3 HRQoL

HRQoL will be assessed using both EORTC QLQ-BN-20 and EQ-5D-5L instruments, in accordance with the evaluation design. HRQoL can be measured using generic and disease-specific instruments that focus on overall and disease-specific elements expected to impact HRQoL. Generic instruments typically assess general aspects such as pain levels, ability to perform daily activities, energy levels, etc., while disease-specific instruments, such as the one used in Taphoorn et al. (2018) focus on aspects related to the specific disease, and the questionnaire used is therefore specifically designed for brain tumors, thus focusing on the most essential aspects of the patient population.(11)

5.2.2.3.1 EORTC QLQ-BN-20

The literature search identified a study that addresses HRQoL measured with EORTC QLQ-BN-20. The evaluation design requires information on the subscales at 1, 2, and 3 months. However, the results reported in Taphoorn et al. are based on questionnaires collected at 3, 6, 9, and 12 months, making it impossible to obtain results at 1 and 2 months.

In Stupp et al., HRQoL were self-reported by patients. In analyses among patients with baseline HRQoL data (n=639; 92% of randomized), the percentage of patients with stable or improved HRQoL was significantly higher in the intervention group than the comparator group for global health status (54% versus 38%); physical functioning (54% versus 38%); cognitive functioning (50% versus 39%); emotional functioning (55% versus 44%); pain (57% versus 36%); and weakness of legs (59% versus 42%), all $p \leq 0.001$, but not role functioning (48% versus 41%), social functioning (48% versus 41%), or itchy skin (42% versus 47%).

Taphoorn et al. estimated Deterioration-free survival, which was defined as the time to a greater than ten-point deterioration in scores from baseline without a subsequent ten point or more improvement in scores compared with baseline. TTFields plus TMZ resulted in significantly longer deterioration-free survival in global health status, physical and emotional functioning, pain, and weakness of legs, as can be seen in Table 5.4. (11)

Median, months			
	TTFields plus TMZ	**TMZ alone**	**HR (95% CI)**
PFS	6.7	4.0	0.69 (0.57-0.83)
Deterioration free survival			
Global health status	4.8	3.3	0.73 (0.60-0.88)
Physical functioning	5.1	3.7	0.73 (0.60-0.88)
Cognitive functioning	4.4	3.6	0.78 (0.64-0.94)
Role functioning	4.3	3.8	0.86 (0.71-1.02)
Social functioning	4.5	3.9	0.84 (0.70-1.06)
Emotional functioning	5.3	3.9	0.75 (0.62-0.91)
Pain	5.6	3.6	0.67 (0.56-0.81)
Itchy skin	3.9	4.0	1.03 (0.85-1.25)
Weakness of leg	5.6	3.9	0.74 (0.61-0.89)

Table 5.4 Deterioration free survival for HRQoL domains for patients (11).
CI, confidence interval; HR, hazard ratio; HRQoL, health-related quality of life; PFS, progression-free survival; TMZ, temozolomide.

The only HRQoL scale which deteriorated significantly for TTFields plus TMZ was itchy skin. At three months, the mean (SD) increase was 10.4 (30.1) in the TTFields plus TMZ arm vs an improvement of 2.3 (24.4) in the TMZ alone arm (p=0.005). This trend continued with patients in the TTFields plus TMZ arm experiencing significantly itchier skin at six months (p=0.008) and nine months (p=0.04), but not at 12 months (p=0.66). (2,107)

HRQoL initially improved in patients in the TTFields plus TMZ arm at three and six months by 24% and 13% vs -7% and -17% in the TMZ alone arm, respectively; however, at nine months the change from baseline in the TTFields 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.

A limitation of the Taphoorn et al. study is the high rate of missing longitudinal HRQoL data, which may influence the results since patients with better prognostic factors and good treatment responses will be overrepresented at later stages. However, it should be noted that Stupp et al. addressed this limitation using sensitivity analyses, which confirmed their findings (11). However, there are general challenges in measuring HRQoL and changes in HRQoL over time for patients with grade IV glioma, which will be further elaborated in the following section.

5.2.2.3.2 EQ-5D

Garside et al. (2007) selected ten studies (12). Their searches failed to identify any existing sources of utility values that would represent the preferences of the public in relation to health states associated with high-grade glioma. According to Garside et al. quality of life in people with high-grade gliomas is difficult to measure. Specific tumor localities were found to affect the nature and location of AEs and thus, affect the patients' quality of life in different ways. Given the potential for mental and physical deterioration caused by the tumors, Garside et al. conclude that it is also difficult to measure changes in quality of life over the course of the illness. Garside et al. refer to one particular assessment of quality of life that found that half of the patients had dropped out of completing serial quality of life assessments after six months. Those who continued in the study were younger and fitter than the rest of the population and had a greater probability of survival. Such informative censoring gives rise to considerable scope for bias in serial quality of life measurement. The difficulty in serial measurements also means that it is difficult to ascertain the shape of any deterioration in

quality of life over time. It is not clear whether most people experience a steady decline, a stepwise decline, or a period of relative wellness followed by a rapid decline.

Garside et al. conclude their review by suggesting that patient reactions to glioma and its treatment are complex (12). A substantial minority of patients appear not to recognize the fatal nature of their illness. The place of denial and hope in coping with a terminal illness is unclear. This may have implications for the perceived quality of life of these patients. In some instances, AEs are borne because they are felt to indicate that the treatment may be working. For some patients, the time after treatment and diagnosis is dominated by the disease, whereas others are able to continue with aspects of their normal life activities.

5.2.2.3.2.1 Utility values

For these reasons, Garside et al. do not use evidence of quality of life from RCTs in their health economic evaluation of carmustine implants and TMZ for the treatment of newly diagnosed high-grade glioma (12). Instead, they use evidence of quality of life derived from a panel (see below) to estimate utility in different disease stages relevant for patients with glioma.

The health states for which scenarios were developed included ‘stable disease’ and ‘progressive disease’ with no treatment, and four ‘progressive’ disease states with treatment because the symptomatic impact of tumor growth is likely to be different depending on tumor location, resulting not in a general deterioration but in specific impairments.

Based on the information from the main RCTs in the systematic review, Garside et al. assume that of patients taking TMZ, 26% suffered from nausea and vomiting or infections that might require hospitalization in the adjuvant phase of treatment. Therefore, the UK-utility values for health states involving TMZ were estimated as the weighted average of “stable disease” plus “TMZ” equal to 0.8474. Patients with progressed disease have a UK-utility value of 0.7314. Please note, these utility values from UK are similar to (a little higher than) the utility values for DK that we use in this application.

5.2.2.4 Cognitive abilities

Mean cognitive status within either treatment group in Stupp et al. did not decline below the MMSE score of 27 out of 30 and no differences in MMSE (Mini-Mental State Examination) scores were documented between the groups. Mean percentage change in MMSE scores ranged from −2.4 (month 1) to 4.8 (month 8) in the TTFields plus TMZ arm, and from −0.5 (month 2) to 3.8 (month 8) in the TMZ alone group. (2,107)

Patients in Stupp et al. receiving TTFields and TMZ maintained intact cognitive status, as indicated by their cognitive scores staying above the 27-point cut-off for both treatment groups. There were no significant differences in cognitive status between patients receiving TTFields and TZM and TMZ alone (107). These findings suggest that there is no adverse change in cognitive status associated with treatment using TTFields.

However, the study also revealed that the time it took for a sustained 6-point decline in the MMSE score, as measured in the intention-to-treat analysis, was significantly longer in the group receiving TTFields plus TMZ compared to the group receiving TMZ alone. Time to a sustained 6-point decline in MMSE score was 16.7 months (95% CI 14.7 to 19.0) in the TTFields plus TMZ group and 14.2 months (95% CI 12.7 to 17.0) in the TMZ alone group (HR 0.79, 95% CI 0.66 to 0.95; p=0.01) (2)

Based on these results, it can be concluded that there is no negative adverse effect on cognitive status, as measured by MMSE, for GBM patients receiving treatment with TTFields. On the contrary, the study indicates that the time to a sustained 6-point decline in MMSE score is significantly longer in the group receiving TTFields plus TMZ compared to TMZ alone. (2,107)

5.2.2.4 Safety

Adverse events (AE) will be included in this section as they are relevant to the application. It is important to consider AEs, as they can impact patients' HRQoL. Specifically, serious AEs will be addressed, as they are relevant for the health economic analysis in Chapter 8 of this report. Additionally, dermatological adverse events will be examined, as they had an impact on the patient's quality of life, as stated in Section 5.2.2.3.1.

All AEs in the included studies are graded using the National Cancer Institute's CTCAE (2,10). The AEs are graded on a scale ranging from one to five with unique clinical descriptions for each AE. The higher the grade the higher the severity of the AE (126):

- Grade I – Mild AE
- Grade II – Moderate AE
- Grade III – Severe AE
- Grade IV – Life-threatening or disabling AE
- Grade V – Death related to AE

The current literature search consistently demonstrated TTFields having a good safety profile and that the most predominant AEs associated with the use of TTFields are array-associated dermatologic AEs, which include allergic and irritant dermatitis, mechanical lesions, ulcers, and skin infection (2,10,14–16,69,106,117). The following review of results will therefore focus on the proportion of patients experiencing dermatologic AEs, as well as the proportion of patients experiencing severe AEs.

5.2.2.4.1 Serious AEs

Serious AEs are defined as grade III or IV AEs. This definition is based on CTCAE, which is used in the included studies. To elucidate serious AEs, only studies that are consistent with the evaluation design are included, and therefore, the meta-analysis in Regev et al. is not considered applicable for reporting AEs that are not related to dermatologic AE (10). The studies included for reporting severe AEs are thus limited to Stupp et al. and Kirson et al. (no patients in Kirson et al. experience severe AEs) (2,82).

In the study by Stupp et al., adding TTFields to TMZ treatment was not associated with a significant difference between groups with respect to participants experiencing one or more grade III or IV, with 48% in the TTFields plus TMZ group experiencing one or more grade III-IV AE vs 44% in the TMZ alone group (p=0.58) (2). The overall incidence, distribution, and severity of AEs between groups were similar with no significant differences in all reported AEs as can be seen in Table 5.5.

	TTFields plus TMZ (n = 456)	TMZ alone (n = 216)
≥1 AE	**218 (48)**	**94 (44)**
Blood and lymphatic system disorders	**59 (13)**	**23 (11)**
Thrombocytopenia	39 (9)	11 (5)
Gastrointestinal disorders	**23 (5)**	**8 (4)**
Asthenia, fatigue, and gait disturbance	42 (9)	13 (6)
Infections	32 (7)	10 (5)
Injuries, poisonings, and procedural complications (falls and medical device site reactions)	24 (5)	7 (3)
Metabolism and nutrition disorders (anorexia, dehydration, and hyperglycemia)	**16 (4)**	**10 (5)**
Musculoskeletal and connective tissue disorders	**21 (5)**	**9 (4)**
Nervous system disorders	109 (24)	43 (20)
Seizures	**26 (6)**	**13 (6)**
Respiratory, thoracic, and mediastinal disorders (pulmonary embolism, dyspnea, and aspiration pneumonia)	**24 (5)**	**11 (5)**

Table 5.5 Overview of reported AEs in the TTFields plus TMZ group vs the TMZ alone group (2). AE, adverse event; TMZ, temozolomide.

Due to the delayed disease progression seen in the TTFields plus TMZ group, patients were however treated with TMZ for longer than those receiving TMZ alone, leading to a nonsignificant higher incidence of some AEs. These differences were nullified when AE incidence was normalized to the duration of treatment (2). There were no serious AEs among the ten patients who received TTFields and maintenance TMZ treatment in Kirson et al. (82).

5.2.2.4.2 Dermatological AEs

As Optune is a device that delivers TTFields through arrays placed on the scalp, it is assumed that there are no significant differences in the proportion of patients with ndGBM and patients with rGBM experiencing dermatological AEs when using Optune. To shed light on dermatologic AEs, estimates from Stupp et al, Kirson et al., and a meta-analysis by Regev et al. are therefore included, incorporating both patients with ndGBM and rGBM (2,10,82).

Among the 456 patients in the TTFields group in Stupp et al., approximately 52% of patients experienced mild to moderate dermatological AE (grade I-II), and approximately 2% of patients experienced more severe dermatological AE (grade III-IV) (2). All ten patients in the cohort study by Kirson et al. reported grade I or II dermatological AE and none reported grade III or IV (82).

Regev et al. includes twelve studies that report the frequency of AEs among patients treated with TTFields, summing 11,558 patients, most of which are from the global post-marketing safety surveillance of TTFields in clinical practice (10). It should therefore be noted that the studies in Regev et al. include both patients with ndGBM and rGBM, as well as different interventions. However, all interventions share the commonality of including treatment with TTFields. Only two studies by Regev et al. reported severe dermatological AEs (≥ grade III AE). These include Stupp et al. with 2% of TTFields patients reporting a grade III-IV dermatological AE (2) and the global post-marketing safety surveillance, where less than 1% of TTFields patients experienced severe dermatological AEs (10).

All twelve studies included in the meta-analysis in Regev et al. (2021) can be seen in Figure 5.1. Most dermatological AEs were mild to moderate, with a pooled prevalence of 38.4% (95% CI 32.3 to 44.9) among TTFields patients, with both ndGBM and rGBM.

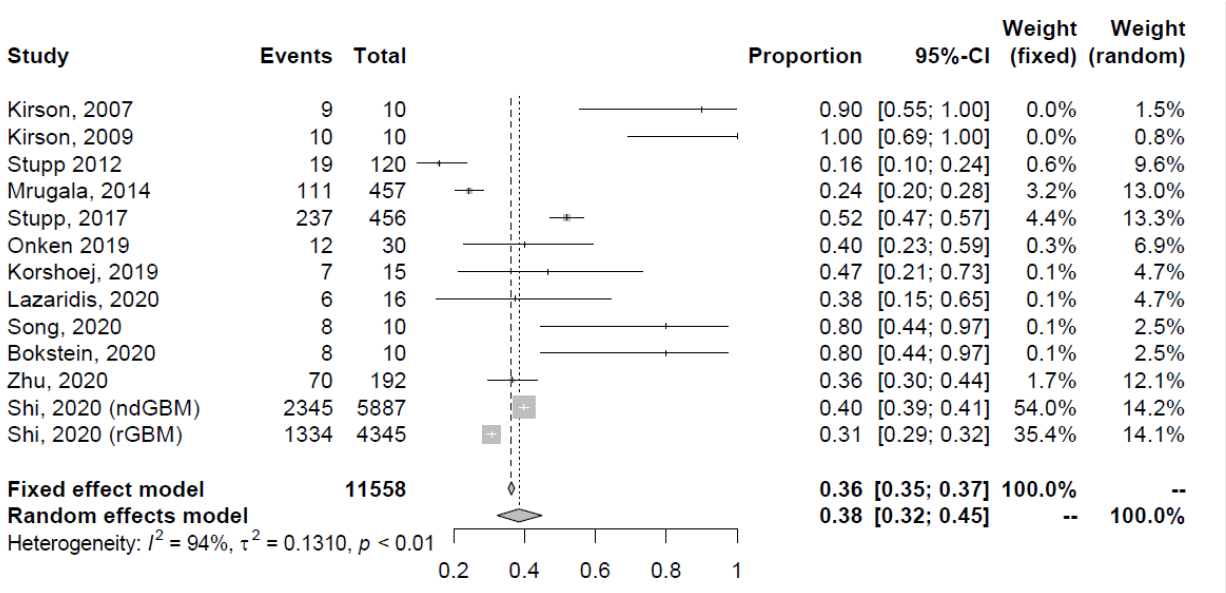


Figure 5.1 Pooled frequency of Mild to Moderate dermatological AEs. I2 was 92% p<0.01, thus the random-effect model used (10). CI, confidence interval.

In summary, the most common, and only significant AE with the use of TTFields is dermatological AE including skin irritation, rash, ulceration, and infections. The irritation is mainly due to repeated shaving of the scalp, application and removal of the transducer arrays, allergic reaction to the hydrogel, and the pressure of the transducers on the skin (10,69,123,126).

5.2.3 Methodologies for the comparative analysis

Since the literature search has not yielded any studies conducting meta-analyses relevant to this application, the applicant has conducted a meta-analysis. The studies included in the meta-analysis of OS are Vymazal et al. (2023), Ballo et al. (2022), and Pandey et al. (2022) (102,114,115). More details about these studies can be seen in appendix 11.2.14. Stupp et al (2017) is not included, as studies of different overall designs should not be included in the same meta-analysis. The results of Stupp et al. (2017), however, should still be considered when assessing OS for TTFields. (2)

5.2.3.1 Clinical endpoints

As an estimate of treatment effect, the outcome of interest was HR for OS and corresponding 95% CIs. The meta-analysis for OS HR derived from the included studies. This approach is grounded in recommendations from the existing literature. For instance, Parmar et al. (1999) concludes that when presenting findings from a randomized controlled trial involving survival-type data, it is advisable to utilize the log hazard ratio along with its corresponding variance as the appropriate summary statistics. Similarly, Sutton et al. (2000) state that the most suitable summary estimate is the (log) hazard ratio. This choice is informed by its unique capability to account for both censoring and time-to-event data. Furthermore, it serves as a metric to quantify the distinction between two Kaplan-Meier survival curves. (127,128)

Further clinical endpoints are median survival, 12-month survival, and 24-month survival. These endpoints were widely reported in the studies and were specified by the DHTC to be included in this analysis. Data extraction involved collecting relevant information from eligible studies. Demographic data, such as the number of patients, mean age, sex, and prior therapy, were recorded.

5.2.3.2 Statistical analysis

In cases where multiple studies analyzed the same population (e.g., series from the same hospital), only the larger study or the one with the longest follow-up (if the sample was similar) was included in the meta-analysis. For this reason, Kirson et al (2009) is not included in. This approach ensured that the analysis was representative and avoided duplication of data from the same cohort.

The meta-analyses was conducted using STATA18 software. A random- effects model was used to assess HRs, applying the DerSimonian-Laird estimation method. Inter-study heterogeneity in the effect estimates was evaluated using the Cochran Q (chi-squared) test and the I2 statistic. Heterogeneity level was considered moderate if I2 values were > 25% (129).Median survival, and 12- and 24-month rate endpoints can be calculated from hazard ratios (HR) by assuming a rate in the control arm, in accordance with methodology described by Tierney et al. (2007) (130)The calculations assume an exponential survival distribution. This is the method recommended by the DHTC. However, notice that applying the method to for instance Stupp (2017) leads to an estimated median OS difference of 9.4 which should be compared to the observed difference of 4.9 months reported in Stupp 2017.

The rate used in the control arm for both median survival, 12-month survival, and 24-month survival is taken from Stupp et al. (2017). This decision was made to obtain the most credible rate for the control arm since Stupp et al. (2017) has the largest population and ranks highest in the hierarchy of evidence among the identified studies. Furthermore, it should be noted that the median survival in the control arm in Stupp et al. (2017) does not significantly differ from the median of the studies included in the meta-analysis, namely Vymazal et al. (2023), Pandey et al. (2022), and Ballo et al. (2022). The implications of choosing the control arm rate for the analysis results will be discussed in conjunction with the analysis results.. For all analyses, significance was established using 95% CIs or $p < 0.05$.

5.2.4 Results of the comparative analysis

The current section will present results from the above-described metaanalysis. Firstly, results from the meta-analysis on HR are presented, accompanied by corresponding forest plot and survival curve. Subsequently, the requested efficacy measures of interest to the DHTC are presented, namely, median survival, 12-month survival rate, and 24-month survival rate. Results of the meta- analysis can be seen in the following forest plot (figure 5.2), and survival curve (figure 5.3).

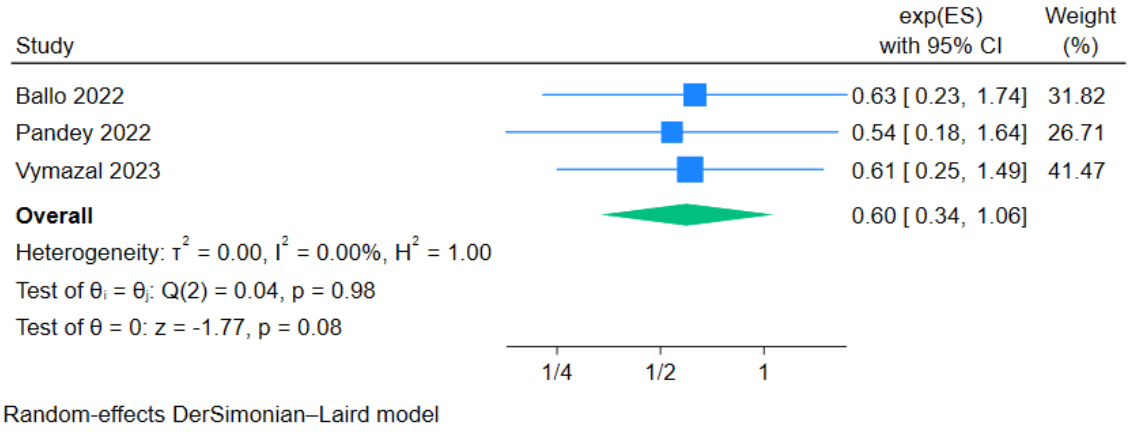


Figure 5.2: Forrest plot for OS HR. The forest plot displays OS HR from the individual studies, along with the results from the meta-analysis. The 95% CIs are indicated by horizontal lines. Marker size represents the relative weight of each study.

A meta-analysis of the results involving patients with ndGBM reported in Ballo 2022, Pandey 2022, and Vymazal 2023 revealed improved (but only significant at a 10 level of significance) OS when patients were treated with TTFields therapy and SOC compared with SOC alone (HR: 0.60; 95% CI 0.34–1.06; p = 0.08. Heterogeneity among studies was very low (I2 = 0.00%, p = 0.98).

5.2.4.1 Median survival

Median survival is defined according to the evaluation design as the difference in median survival from randomization to death. With the exception of the study by Pandey et al. (2022), all studies define median survival in accordance with the evaluation design, whereas Pandey et al. measure median survival from the time of diagnosis. (77,102,115)

Using the median survival from Stupp et al. (2017) of 16.0 months for the SOC group as baseline we get a median survival difference of 10.8 months in favor of TTFields therapy and SOC (95 % CI: -0.9; 31.6) indicating that the benefit of TTFields plus SOC compared to SOC alone in a real world setting results in a median survival increase of 10.8 months. This result therefore meets the DHTC's minimal clinically relevant difference (MKRF) of an increase in median survival of 6 months, although it should be noted that the result of 10.8 months is not statistically significant.

Taking the median survival from Pandey et al. (2022) of 18.8 months for the SOC group as baseline we get a median survival difference of 12.7 months in favor of TTFields therapy and SOC (95 % CI: -1.0; 37.1). Using a control arm with a longer median survival, results in a slightly higher median survival difference, however the result is not statistically significant. This demonstrates that the results do not change substantially, and the rates from Stupp et al (2017) are still considered the most valid control rate.

This gain of 10.8 months in overall survival represents a substantial benefit for this patient population. As mentioned in section 3.1.4 the average survival of patients with grade 4 glioma is approximately 11.2 months in Denmark (4). An additional 10.8 months of survival constitutes a substantial improvement.

This gain in survival is also significant compared to the survival benefit in the current SOC, i.e. the Stupp treatment regimen. The Stupp treatment regimen showed a median survival benefit of 2.5 months compared to the former SOC (surgical resection to the extent feasible, followed by adjuvant radiotherapy). (45)

5.2.4.1.2 12-month survival

The change in 12-month survival rate equals 12.3 % (95 % CI: -1.6 %; 21.5 %), based on the SOC OS rates in Stupp et al. (2017) of 65 % (2). This indicates a 12.3 percentage points higher survival rate in the TTFields plus SOC group compared to the SOC alone group. However, it should be noted that the 12-month survival rate in Vymazal et al. is subject to bias, resulting in an elevated survival rate in the SOC group (see section 5.2.2.1.3) (102).

This difference of 12.3% observed in the meta-analysis concurs with the MKRF of 8% difference between the two aforementioned groups, as defined by the DHTC.

5.2.4.1.3 24-month survival

The change in 24-month survival rate equals 18.7 % (95 % CI: -2.0 %; 36.4 %) based on the rates in the TMZ alone group in Stupp et al (2017) of 31 % (2). The survival rate at 24 months is therefore 18.7% higher in the TTFields plus SOC group compared to the SOC alone group.

This observed increase in survival of 18.7 percentage points is distinctly higher than MKRF of 4% difference between the two groups, as defined by the DHTC.

5.2.4.1.4 Summary

The present meta-analysis has investigated median overall survival, 12-month survival, and 24-month survival for the addition of TTFields to SOC in studies conducted in a real-world setting. All results from the meta-analysis regarding overall survival show favorable outcomes for treatment with TTFields, although they are not statistically significant. It should be noted, however, that although the results of the meta-analysis are not statistically significant, the HR in both Vymazal et al. (2023) and Pandey et al. (2022) are statistically significant. (102,115)

It is also important to consider the results from Stupp et al. (2017) when assessing the survival benefits of TTFields. Stupp et al. (2017) reported median survival difference of 4.9 months (95% CI: 2.3-7.9) favoring treatment with TTFields. The difference in 12-month survival in the study was 8% (95% CI: 0% - 16%) between the two groups, with the difference favoring treatment with TTFields. The difference in 24-month survival was 12% (95% CI: 4% - 18%) between the two groups, and Stupp et al. (2017) thus shows a significantly higher 24-month survival rate in the TTFields plus TMZ group. (2)

5.2.4.2 EORTC QLQ-BN-20

Only one study has been identified for the outcome measure of HRQoL measured with EORTC QLQ-BN-20, which is why a pairwise meta-analysis is not conducted. Please refer to section 5.2.2.3 for results on HRQoL measured with EORTC QLQ-BN-20.

5.2.4.3. EQ-5D-5L

There has not been identified any study that contains information on utility scores measured with the EQ-5D instrument. This evaluation, therefore, cannot answer whether patients experience a change in index scores of 0.13 as requested by the DHTC. For best available information on utility scores see section 5.2.2.4.

5.2.4.4. Cognitive abilities

Only one study has been identified for cognitive abilities measured with the MMSE, for which reason a pairwise meta-analysis is not conducted. Please refer to section 5.2.2.5 for results on cognitive abilities.

All effect estimates requested by the DHTC are provided in Table 5.6. This table presents the results from the meta-analysis. The reader is referred to the aforementioned sections for effect estimates pertaining to HRQoL and cognitive abilities.

Clinical question <1>								
Results per outcome measure	**Studies used in the analysis**	**Groups**	**Total N per group**	**Absolute outcome difference**		**Relative outcome difference**		**Method**
				Estimated outcome difference [95% CI]	**P value**	**Estimated outcome difference [95 % CI]**	**P value**	
Median survival	(102,114, 115)	TTFields	169	10.8 [-0.9;31.6]	N/A	HR: 0.60 [0.34–1.06]	0.008	Meta- analysis. Random effects model (DerSimonian–Laird)
		SOC	143					
12-month survival	(102,114, 115)	TTFields	169	12.3% [-1.6 %; 21.5 %]	N/A	N/A	N/A	Meta- analysis. Random effects model (DerSimonian–Laird)
		SOC	143					
24-month survival	(102,114, 115)	TTFields	169	18.7% [-2.0 %; 36.4 %]	N/A	N/A	N/A	Meta analysis. Random effects model (DerSimonian–Laird)
		SOC	143					
EORTC QNBN20								
EQ-5D questionnaire								
MMSE index score								

Table 5.6 Results of the meta-analysis. CI, confidence interval; MMSE, Mini Mental Health Examination; SOC, standard of care.

6 Patient perspective

In this section, the findings regarding the patient perspective on the use of Optune for adults with ndGBM are presented. As stated in the analysis design, the expert committee identified the following aspects to be addressed as part of the assessment of the patient perspective: Patient Experiences and Compliance, Unwanted incidents, and Accessibility.

As mentioned in Chapter 5, the clinical effectiveness of both PFS and OS is positively associated a compliance of at least 50%. The more a patient uses Optune, the greater the device's effect. It should be considered, though, that patient compliance may be affected by both social and clinical factors. For example, some patients may feel self-conscious due to wearing the arrays on a shaved head, calling attention to their condition (131). Therefore, patients' perceptions and attitudes toward Optune are important for its effectiveness and will be expanded on in this analysis.

6.1 Evidence base

The DHTC's expert committee has assessed that the topics will be best elucidated based on real-world data, but that this can also be supplemented with information from the scientific literature, narratives, and statements from patients who have used Optune, etc. Therefore, the data foundation for the patient perspective consists of various forms of literature. Survey investigations of Optune users' experiences are used, where surveys are conducted at the start of treatment, two months into treatment, and six months into treatment. This survey is Novocure's internal analysis, and the data is not publicly available. The details of these questionnaire surveys are elaborated in section 6.1.1.

Additionally, literature and information used to address the expert committee's focal points for the patient perspective are presented in Table 6.1. Table 6.1 also presents the primary characteristics of the studies, which is why the characteristics of the studies will not be presented in detail in the following.

Reference (author, (year), country)	Objectives	Method	Population	Intervention	Comparator
Stupp (2017), global (2)	To investigate whether TTFields improve PFS and OS of patients with glioblastoma, a fatal disease that commonly recurs at the initial tumor site or in the central nervous system.	Open-label, phase three RCT.	ndGBM	Optune	TMZ alone
Taphoorn (2018), global (11)	To examine the association of TTFields therapy with progression-free survival and HRQoL among patients with glioblastoma.	Secondary analysis of Stupp et al., a phase three RCT.	ndGBM	Optune	TMZ alone
Regev (2021), global (10)	To establish an objective understanding of TTFields' mechanism of action, safety, efficacy, and economic implications	Systematic literature review and meta-analysis.	Patients with ndGBM and rGBM	Optune plus additional treatment	N/A
Onken (2019), Germany (100)	The objective is to assess patient-reported outcome	A two-center, observational study.	Newly diagnosed high-grade glioma	Optune	N/A
Novocure, Trend analyses (2022), Germany, Austria, and Switzerland (109)	Collecting data on satisfaction with the orientation and handling of Optune, and desired improvements in information and therapy materials	Written postal survey in combination with an online survey using a fully structured questionnaire. The mailing was done by Novocure.	All current users of Optune therapy in Germany, Austria, and Switzerland	Optune	N/A
Novocure, Survey (2022), Germany,	Collecting data on satisfaction with the orientation and handling of Optune, and desired	Written postal survey in combination with an online survey using a	All current users of Optune therapy in	Optune	N/A

Austria, and Switzerland (110)	improvements in information and therapy materials	fully structured questionnaire. The mailing was done by Novocure.	Germany, Austria, and Switzerland		
Novocure, Survey (2023), Germany, Austria, and Switzerland (111)	Collecting data on satisfaction with the orientation and handling of Optune, and desired improvements in information and therapy materials	Written postal survey in combination with an online survey using a fully structured questionnaire. The mailing was done by Novocure.	All current users of Optune therapy in Germany, Austria, and Switzerland	Optune	N/A
Onken (2018), Germany (98)	The objective is to investigate the acceptance of TTFields among high-grade glioma patients and factors contributing to therapy compliance	Retrospective study	high-grade glioma patients	Optune	N/A
Olubaju (2022), England (96)	To assess the feasibility of integrating TTFields into a standard UK neuro-oncology service with a focus on patient tolerability, compliance, and treatment delivery.	Prospective study	UK patients with IDH 1 Wild Type, MGMT Unmethylated GBM	Optune	N/A
Pandey (2016), US (103)	To study social, economic, medical conditions, therapy-related and patient behaviors in relation to compliance with Optune	Retrospective study	Patients that were prescribed Optune. TTFields at the West Cancer Center on/after November 2015.	Optune	N/A
Kumthekar (2021), US (83)	Understanding factors that influence the decision of accepting Optune	A qualitative prospective study. Interviewed GBM patients	Adult GBM patients who were offered TTFields	Optune	N/A

Table 6.1 Studies and other data used to describe the patient perspective.
GBM, glioblastoma multiforme; HRQoL, health-related quality of life; IDH, isocitrate dehydrogenase; MGMT, methylguanine- deoxyribonucleic-acid-methyltransferase; N/A, not applicable; ndGBM, newly diagnosed glioblastoma multiforme; OS, overall survival; PFS, progression-free survival; RCT, randomized control trial; rGBM, recurrent glioblastoma multiforme; TTFields, tumor-treating fields; TMZ, temozolomide; UK, United Kingdom; US, United States.

6.1.1 Optune user survey

Novocure has conducted several surveys from 2021 to 2023, with the objective of collecting data on satisfaction with the orientation and handling of Optune, and desired improvements in information and therapy materials (110,111). The surveys were administered to all users of Optune in Germany, Austria, and Switzerland. Optune therapy users were surveyed immediately after starting the therapy (therapy starters), after two months with the therapy (short-term users), and after at least six months of therapy (long-term users). Surveys are conducted for every yearly quarter (Q1, Q2, Q3, Q4), meaning data is obtained four times per year.

The three surveys differ in some of the questions and the purposes of the surveys. The purpose of the first survey given to therapy starters is to learn how the user became aware of Optune and about their personal experience at the start of the treatment. The purpose of the second survey given to short-term users is to learn about how things have gone for the user with Optune in daily life in the first months. The purpose of the third survey given to long-term users is to learn what the user would recommend to future users. All responses are anonymized and treated confidentially.

Written postal surveys in combination with online surveys were administered using fully structured questionnaires. Mindline created three cover letters, three paper editions, and three online questionnaires. Mindline is an independent institute, conducting anonymous surveys among all users of treatment with Optune. The mailing was then performed by Novocure. The collection of all written answers and merging with online data was finally done by Mindline.

Three reports on the results from the surveys will be included in this report. This includes detailed survey results from 2022 (110), including data from Q1 to Q4 of 2022. Survey results from 2022 Q1 to 2023 Q1 (111), and trend analysis of selected questions using data from Q1 of 2021 to Q4 of 2022 (109).

Survey results from Novocure's trend analysis will be given priority as it includes the largest patient population. However, the trend analysis only includes selected questions, which is why Survey 2023, incorporating the latest results, will be used for topics not covered in the trend analysis. Lastly, Survey 2022 will also be included as it incorporates specific questions and quotes that are not included in other surveys.

The response rate is high, with a participation of 44% of users on surveys conducted between 01.01.2022 to 31.03.2023. Out of these users, 82% responded by post and 18% responded to the survey online.

The amount of survey respondents varies between the different reports (109–111), as it is possible with every report version that the bases for the quarterly results will increase. It depends on the participation date of the users. For example, a few therapy starters from Q2 in 2022 answered the questions of the first survey three months later and the questionnaires were therefore received at the beginning of Q4.

Survey	Survey 2022	Survey 2023
1st(n)	235	317
2st(n)	196	257
3st(n)	114	140

Table 6.2 Sample sizes, survey 2022 and survey 2023 (110,111).

Trend analysis								
	2021				2022			
Survey	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4
1st(n)	109	78	74	67	69	48!	66	27
2st(n)	75	70	53	34!	82	47!	31!	34!
3st(n)	22!	10!	23!	19!	30!	28!	31!	14!

Table 6.3 Trend analysis quarterly (Q) sample sizes (109).
! small population sizes.

Note that small population sizes may occur. This will always be pointed out with an exclamation mark, to inform the reader that the results of the survey questionnaire should only be considered a tendency due to the small population base.

It should be noted that the questionnaire surveys are Novocure's internal investigation, and the mentioned results are therefore not publicly available and have subsequentially not been peer-reviewed. The questionnaires also include open-ended questions, and the answering of the expert committee's questions will therefore be supported by quotes. It should be noted that the applicant does not have access to the raw quotes, and the selected quotes have been chosen from among the quotes selected by Mindline that the applicant has deemed relevant.

6.2 Summary of the findings concerning the patient perspective

User experiences and compliance with Optune therapy are generally positive, with the majority of users not considering the visibility of Optune as a significant problem. While some users may feel restricted in certain physical movements and activities, studies suggest that treatment with Optune is favorable for physical functioning compared to treatment with TMZ alone. Some patients may encounter challenges in handling certain components of the Optune treatment kit, particularly the transducer arrays. Changing the transducer arrays is considered somewhat cumbersome and may require assistance, which Novocure addresses by providing training sessions to ensure proper handling and assistance from a Device Support Specialist (DSS). Furthermore, Novocure is developing new array designs to simplify array handling for the patient. The most

common reasons for dissatisfaction with Optune include AEs on the scalp and disease worsening, however overall satisfaction with Optune treatment is high, leading to high median compliance to the therapy, which is regularly above the recommended 75% threshold required for optimal therapeutic efficacy.

Unwanted incidents during Optune treatment can include skin irritations, heat sensations, and headaches. Proper handling of transducer arrays and regular skin care are important, and effective in mitigating the risk of skin irritation. Additionally, the potential impact of Optune on sleep appears to be well-tolerated by users, with a majority reporting satisfactory sleep quality.

In terms of accessibility, language barriers can be overcome with interpreters, and the provided information is generally comprehensible. Basic technological literacy is necessary for Optune usage, and training is provided to ensure proper handling of therapy materials. Geographical location does not restrict access to Optune. Caregiver support and comprehensive training are essential, while no evidence suggests that poor self-care or social status specifically impacts Optune use for glioma grade IV patients.

6.3 Considerations regarding user requirements and accessibility

The present review of the patient perspective will be based on the topics listed in Table 2 of DHTC's evaluation design. The review will be structured according to the following three main topics: a) user experience and compliance, b) AEs, and c) accessibility.

6.3.1 User experience and compliance

This section will uncover users' experiences with the use of Optune. User experiences regarding the use of Optune will be illuminated based on the evaluation design's research questions. This will include user experiences related to the visibility of the disease during use, user-friendliness, and similar aspects. This topic is important as users' experience of Optune facilitates their usage, which is a prerequisite for its effectiveness, as stated in Section 5 of this report.

6.3.1.1 Treatment declination

An abstract for a study conducted by Northwestern University Feinberg School of Medicine, Chicago, IL, US, investigates factors that can influence the decision of accepting Optune treatment. 40 patients were asked about factors shaping their decision to use or not use TTFields. Of the 33 (82.5%) participants who accepted TTFields, 23 (69.7%) reported their physician recommending TTFields, eight (24.2%) reported physician neutrality toward TTFields, and two (6.1%) said their physician advised against TTFields. Among the seven (17.5%) participants who did not choose TTFields, four (57.1%) reported physician neutrality, two (28.6%) reported that their physician advised against TTFields, and one (14.3%) reported that their physician recommended TTFields. Participants who decided against TTFields stated that head shaving, appearing sick, and the inconvenience of wearing/carrying the device most influenced their decision. For those choosing to use TTFields, the most influential factors were extending their life and following their doctor's opinion; other factors included the level of familial support and the clinical evidence supporting TTFields (83).

It should be noted that there are several differences between the Danish and American healthcare systems, and the abstract does not mention whether financial considerations may have also influenced the study population's choices.

The DHTC's Scientific Committee estimates that around 30% of eligible patients will opt out of treatment with Optune before it could potentially be initiated, whereby the relevant patient population includes approximately 113 incident patients with grade IV glioma annually.

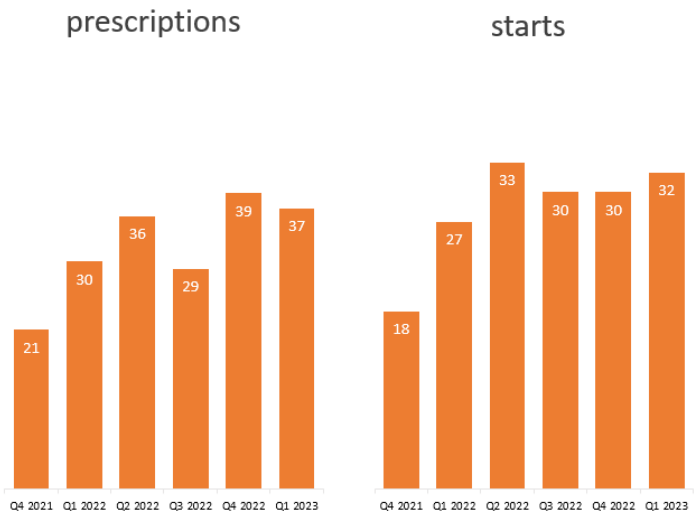


Figure 6.1 Sweden volume trends from Q4 2021 to Q1 2023 (75).

Experiences from Sweden, however, suggest that the number of patients that decline treatment with Optune is significantly lower (see Figure 6.1). Data from one and a half years show that a total of 192 patients with ndGBM in Sweden received a prescription for Optune between Q4 of 2021 and Q1 of 2023. Out of the 192 patients who received a prescription for Optune, 170 initiated the therapy. This results in a treatment decline of only 11.5%.

6.3.1.2 Drop-out

Real-world evidence was collected from patients prescribed Optune at the West Cancer Center on/after November 2015. A retrospective chart review was conducted till June 2016 collecting data on patient characteristics, tumor, and treatment. Treatment adherence data is collected by the Optune device that records average daily use (hours/day), and information is reviewed monthly. The study shows that from November 2015 to June 2016, 33 prescriptions for Optune were written, 23 patients were due to start therapy but 7 did not start due to tumor progression (3 pts), patient refusal (1 pt), other (3 pts; 1 pt herpes simplex virus meningitis, 2 pts social/financial). The patient reported reasons for not using Optune were intolerance of side effects (4 pts), lack of caregiver support (2 pts), interference with lifestyle (2 pts), and others (3 pts) (103).

6.3.1.3 Stigmatization

There is a concern that the need to shave the head and wear noticeable arrays and wires may be experienced as a stigma of cancer, as with hair loss in chemotherapy (14,132). Although no studies have specifically investigated the experience of stigmatization among Optune users, the 2023 survey gathered insights from long-term respondents regarding the challenges they face during Optune therapy:

"My appearance and public perception, as well as the weight of the machine have been major challenges." (Anonymous long-term Optune user, survey 2023 (111)*)*

"(...) I enjoy a good social life and I'm in regular contact with my friends. I am self-conscious about wearing Optune in public, but I have discovered ways of making it less visible and wearing interesting headwear to cover the patches." (Anonymous long-term Optune user, survey 2023 (111)*)*

These quotes are excerpts from long-term Optune users' statements regarding challenges encountered during Optune treatment. These quotes support the assumption that Optune users may experience stigmatization in certain social contexts. However, it should be noted that only 4% of the long-term users in the 2023 survey (total n=140) identified social aspects as a major challenge in response to the question, "Have there been major challenges for you since starting therapy with Optune?" (111).

A study conducted by Onken et al. (2019) using a device-specific questionnaire completed two months after TTFields initiation addressed device-specific complaints (100). This study, which included responses from 30 Optune users with GBM in 2019, reports that 12% of the Optune users experienced the visibility of the arrays as a severe restriction, while 64% view the visibility of the arrays as a mild or moderate restriction.

Additionally, the 2022 survey indicates that short-term Optune users generally do not experience significant issues regarding reactions from their social circle (friends, acquaintances, and colleagues) (110).

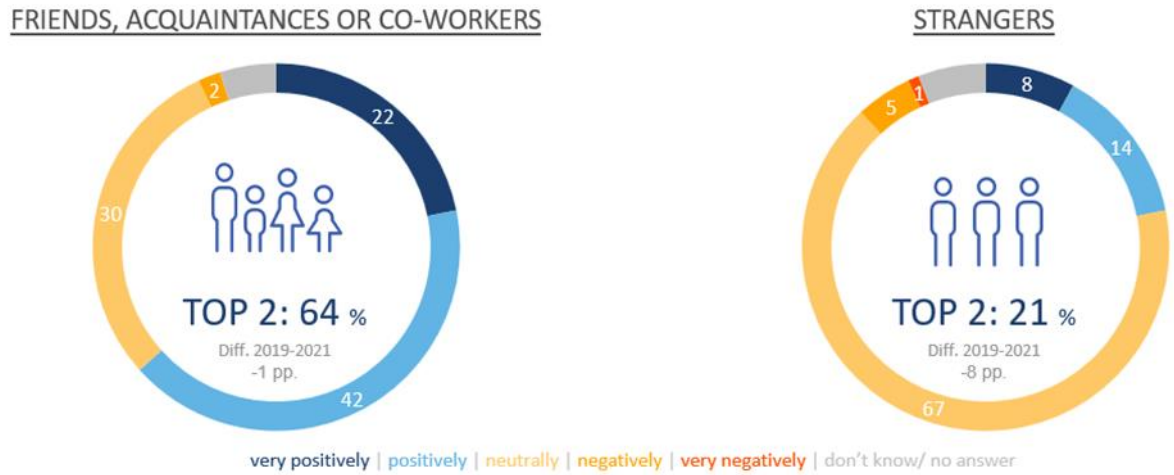


Figure 6.2 Survey results from "Survey 2022" (110). Second survey: Short-term users' reaction to a social setting. Answers to the question: How does your social context react to Optune? (n = 196)

Figure 6.2 illustrates the response to the question "How does your social context react to Optune?". Optune users report that the overall reactions are mostly either positive or neutral. However, they do experience more neutral and somewhat negative reactions from strangers.

When examining the data by gender, it is interesting to note that women seem to find the reactions from their social context predominantly positive. 30% of female respondents indicated that they perceive the reactions from their friends, acquaintances, and coworkers as "very positive," compared to 17% of male respondents (see Figure 6.3). This finding is noteworthy, as one might have expected women to feel a greater sense of loss and visible stigmatization when shaving their hair compared to men.

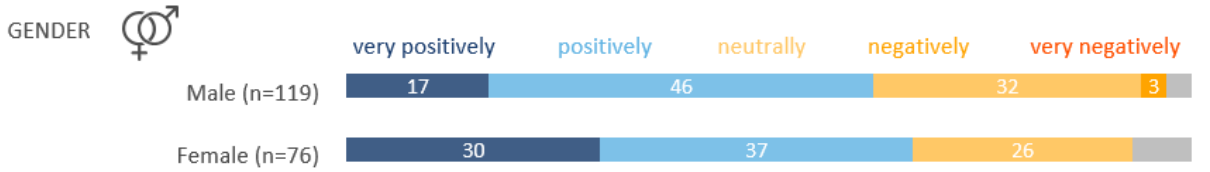


Figure 6.3 Survey results from "Survey 2022" (110). Second survey: Short-term users' reaction to the social setting. Answers to the question split by gender: How does your social context react to Optune?

Taphoorn et al. (2018) hypothesized that the addition of TTFields would result in worse social functioning, due to the visibility of the device, however, this was not confirmed, showing no significant difference in social functioning between TTFields plus TMZ and TMZ alone (11).

Overall, it is observed that Optune can influence patients' perception of their physical appearance and the visibility of their disease. This outcome was anticipated due to the requirements of Optune treatment, which involves patients shaving their heads and wearing noticeable arrays and wires. However, the available literature does not specifically identify the experience of stigmatization and disease visibility as a significant problem among Optune users.

6.3.1.4 Planning of everyday life

In the trend analysis using real-world data from Optune users in Germany, Austria, and Switzerland, short-term users were asked, "How long did it take you to make the therapy part of your daily life?" (109). Figure 6.4 illustrates that over 80% of Optune users reported being able to integrate Optune into their daily lives within the first four weeks of treatment, with approximately 50% stating that it only took them two weeks. However, between 4% and 11% still reported not having integrated Optune into their daily lives by the time of the survey at two months.

In the same survey, both long-term and short-term users were asked the following question: "Overall, how well does Optune fit in with your daily life, i.e., how well can you do house and garden work and leisure activities while using Optune?". The same pattern emerges for both short-term and long-term users. Figure 6.4 illustrates the responses from short-term users (highlighted due to a larger number of respondents). On average, 42% of respondents answered, "very well" or "well," 37% responded "mixed," and 17% indicated "not very well" or "not at all." Similar trends are observed for long-term users, where 40% found that Optune fits very well or well, 39% responded with mixed, and 17% reported not fitting well (at all).

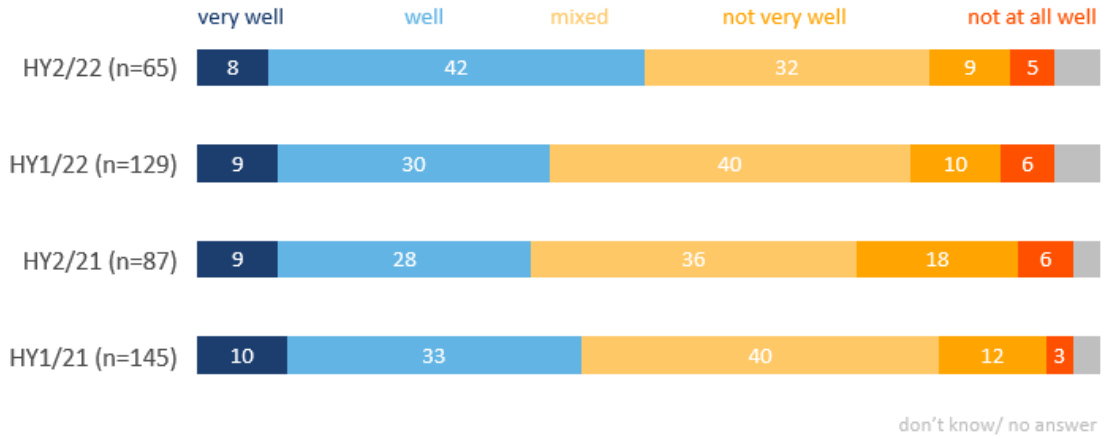


Figure 6.4 Trend analysis (109)*. Base: All short-term users in percentage. Overall, how well do you cope with Optune in daily life, for example, how well can you do household, garden, or leisure activities with Optune?*
HY, half a year.

6.3.1.4.1 Elements of everyday life that are challenging while wearing Optune

The 2022 survey sheds light on various aspects of Optune users' everyday life, where Optune users may experience hindrances in various activities (110). In the survey, long-term users mentioned negative aspects related to gardening (6%), sports (5%), household work (4%), restricted movements due to the device (9%), restrictions in summer due to heat sensitivity (7%), and the weight of the device (6%). This overview of negative mentions is based on an open-ended question. (110)

A smaller tolerability questionnaire was additionally conducted in a small prospective study involving UK patients (n=9, with a median age of 47 years) with isocitrate dehydrogenase 1 wild type, MGMT unmethylated GBM who were treated with TTFields in combination with conventional therapy. The study collected patient compliance data specific to the device. This investigation revealed that the most reported activity hindered by using the device was "showering/bathing" (reported 12 times). This was followed by "exercise/sports" (reported seven times), as well as "no activities affected," "cooking," and "cleaning" (each reported six times respectively) (96).

This indicates that some Optune users feel restricted when it comes to specific physical movements, especially in sports activities. Optune users expressed the following sentiments in the 2022 and 2023 surveys:

"During sport you sweat and then the adhesive comes off. When you bend down, the cable falls forward." (Anonymous short-term Optune user, survey 2023 (111)*)*

"There are many leisure activities I can't do, especially in the summer. For example, swimming and hiking, because either I would have to take the arrays off, or the arrays get hot, or the backpack is too heavy." (Anonymous long-term Optune user, survey 2022 (110)

Some respondents mentioned not being able to swim or engage in high-intensity sports due to issues with the transducer arrays when they become wet. Taphoorn et al. (2018), however, show that the burden of carrying the device is not detrimental to patients' physical functioning, favoring TTFields over TMZ alone (11).

Generally, Optune users perceive themselves to live a relatively normal life, whereas Optune does not hinder their daily life substantially. This is, illustrated in the following quote:

"I lead a relatively normal life. I don't work at the moment, but I am busy managing my home and looking after my two children. As well as being able to exercise, I cook, clean, and work in the garden. I enjoy a good social life and I'm in regular contact with my friends..." (Anonymous long-term Optune user, survey 2023 (111)*)*

As the above quote illustrates, generally Optune users do not experience substantial changes in their daily lives and do not feel restricted by Optune in their everyday activities. Long-term Optune users express that Optune does not prevent them from performing daily activities but rather makes them more time-consuming, and managing Optune takes time out of their daily routines:

"Changes in daily life: Make time for array changing, and activity during rain or summer heat causes alarms. Everything is difficult to begin with. Don't give up!" (Anonymous long-term Optune user, survey 2022 (110)*)*

"Integration of the treatment in daily life (dressing and undressing, driving, doing hobbies). It takes more time and is often a little more complicated. You need to have patience." (Anonymous long-term Optune user, survey 2022 (110)*)*

The above quotes illustrate that some Optune users find that integrating Optune into their daily lives may require time and planning. This is highlighted in relation to hot weather, rain, bathing, dressing, and changing arrays.

6.3.1.5 Satisfaction

As treatment is being shifted to the patient's own homes, this can have implications for their sense of security, convenience, and empowerment. WHO defines empowerment as a process in which individuals gain increased control over decisions and actions that affect their health. The experience of empowerment is described in Schwatz et al. (2016), where an Optune user provided the following quote:

"Out of the very few things I can control during treatment, Optune is fully in my control." (Optune user (Lisa, 63) (133)

This suggests that the Optune device gives the user a sense of agency and control in their treatment journey. Despite facing various challenges and uncertainties, the user, Lisa, feels empowered by having control over the Optune device. It implies that Optune provides a sense of ownership and autonomy for the user, allowing them to actively participate in their treatment process.

One investigator with the EF-14 trial (Stupp et al. (2017)) noted that patients:

"…became psychologically dependent on the TTFields device and saw it as a tangible way to treat their own disease. They were responsible for wearing the device, taking it with them throughout the day, and recharging the batteries. They also had to change their transducer arrays every few days…" (2)

This is in contrast to other cancer treatments where patients are more passive recipients of care. As one US patient who has used the system for two years said: "I wear it and wear it proudly… It's an incredible machine and I'm fine not having hair" (14).

To further elaborate on the topic of user experience and compliance, the patient's satisfaction with Optune will be described. Novocure provides a comprehensive Optune treatment package, and the reporting of

satisfaction will therefore be divided into satisfaction with Novocure, the Optune setup, and overall satisfaction. This topic will largely be based on Novocure's internal surveys.

6.3.1.5.1 Satisfaction with the Optune setup

The DHTC's expert committee highlights in the evaluation design that patients may experience issues with the setup around changing the transducer arrays, among other things. This section aims to uncover patients' experiences with the different components of the Optune setup, with a particular focus on the transducer arrays and the application hereof.

Novocure's Optune User Survey includes questions for both short-term and long-term users regarding how they rate the handling of the different parts of the Optune treatment kit (111). The most detailed reporting of this question is presented in Survey 2023, which is illustrated in Figure 6.5 below.

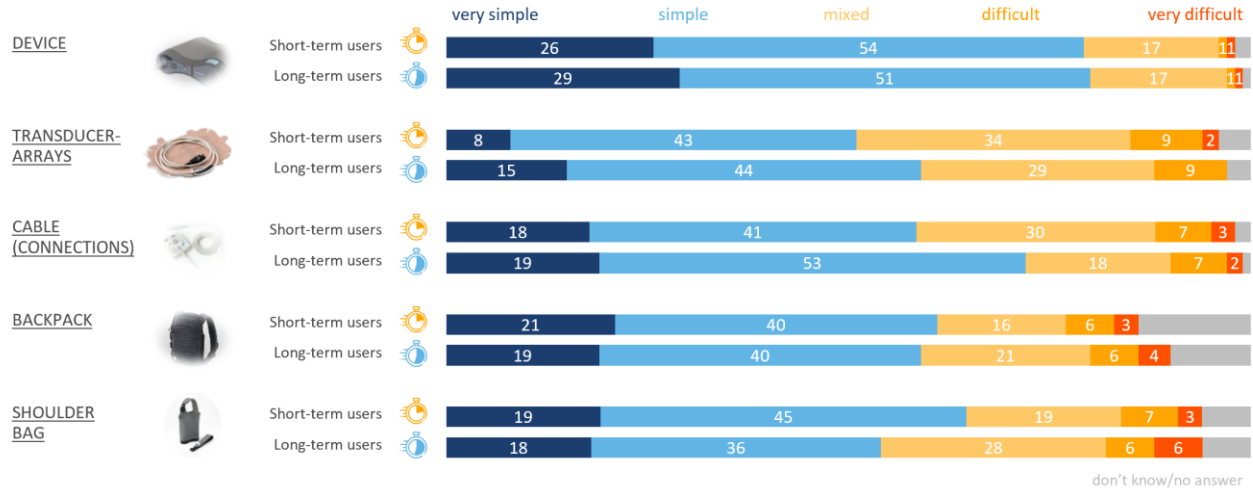


Figure 6.5 Survey 2023 (111). Base: S2 (n=257), S3 (n=140) in percentage. Response to the question "How do you rate the handling of the device, the arrays, and the accessories in daily life?"

As shown in Figure 6.5, both short-term and long-term users perceive the Optune device as the most straightforward component, while the Transducer arrays are considered the least simple part of the Optune treatment kit. Generally, there is a trend indicating that long-term users find the handling of the Optune treatment kit to be simpler than short-term users. However, this trend does not apply to users' perceptions of the backpack and shoulder bag.

6.3.1.5.1.1 Carrying materials.

As depicted in Figure 6.5, the majority of both long-term and short-term users find both the backpack and shoulder bag to be simple to handle. However, patients also express some criticism of the bags. Some patients find the shoulder bag impractical as it tends to slide down and can cause shoulder problems after some time due to excessive weight in one place. Novocure aims to address these issues through the new generation convertible bag, which offers variation in weight distribution as it can be converted into both a shoulder bag and a belt bag. This upgraded module will be further elaborated in Section 8 of this report.

6.3.1.5.1.2 Therapy materials

The therapy materials in the Optune kit consist of the so-called device, the transducer arrays, and the cable. As depicted in Figure 6.5, both long-term and short-term users find the device and cable connections to be straightforward to handle. The most common concern among users appears to be that the device is sometimes perceived as heavy.

6.3.1.5.1.2.1 Changing of the transducer arrays

Changing the transducer arrays is considered less simple and more cumbersome compared to handling the device and cables. Transducer arrays are particularly challenging for patients to handle on their own due to the

difficulty of changing the patches. Patients may therefore require assistance from a caregiver, as one user stated, "You're always dependent on outside assistance" (111). Optune users rely on assistance to ensure proper placement of the arrays on the scalp during regular changes. The dependence on caregivers and the necessary education and training of caregivers will be discussed in a later section.

In most cases, assistance with array changing and Optune maintenance will primarily come from caregivers, such as partners, friends, or relatives. However, if this is not possible or the patient prefers not to rely on caregivers for array changes, the patient may receive assistance from private nurses or publicly assigned home care aides. In such cases, the patient would not be responsible for training and assisting the home care aides in array changes and general handling of the Optune treatment kit. Instead, Novocure offers training sessions conducted by DSSs with home nurses and helpers, ensuring that the burden of training does not fall on the patient. Further details regarding this will be elaborated in Chapter 8, addressing organizational implications.

Based on patients' experiences with the difficulties of changing the arrays, Novocure has developed new arrays to address these concerns which will be further described in Chapter 8 of this report.

6.3.1.5.2 Satisfaction with Novocure services

Satisfaction with Novocure services is very high according to long-term users, in Germany, Austria, and Switzerland, as can be seen in Figure 6.6.

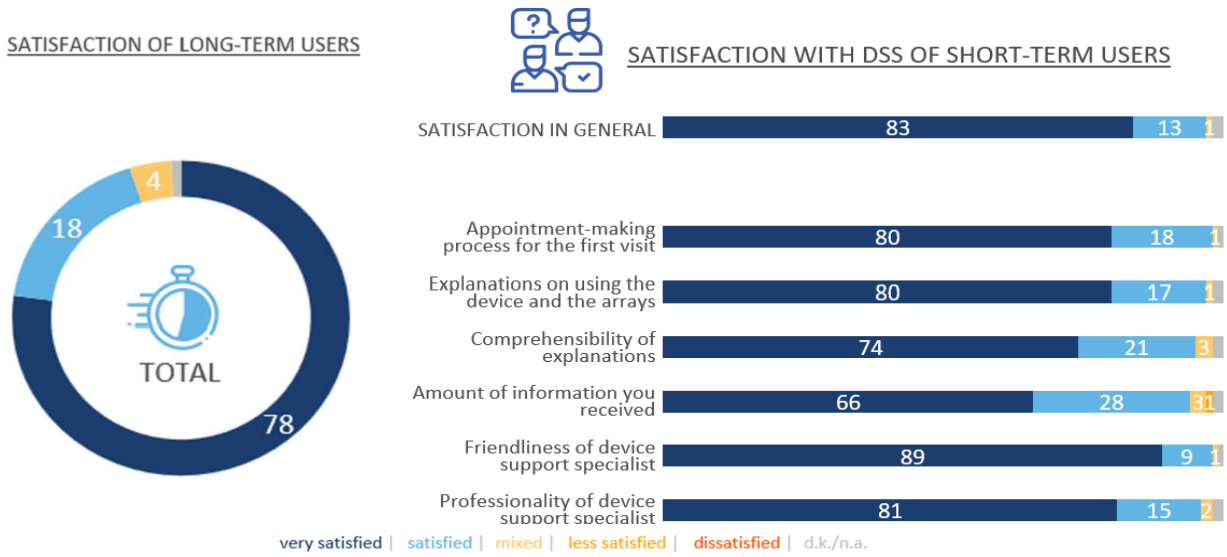


Figure 6.6 Survey 2023 (111). Base: Long-term users (n=140), Therapy starters users (n=317). Q (long-term users): You've been receiving therapy with Optune for six months or more. How satisfied are you with the assistance you get from Novocure staff? Q (Therapy starters): Think back to the first phone call with the DDS or their first visit to your home. How satisfied were you with...?

Survey data from 2023 reveals that a remarkable 96% of long-term users express either satisfaction or high satisfaction with Novocure's services (111). What is defined as "Novocure's Services", are not specified in this satisfaction assessment for long-term users. However, a significant part of Novocure's services that can have particular importance for Optune users is the services provided by the DSSs. When specifically addressing therapy starters satisfaction with DSS, services was at a very high level, with 96% reporting being either satisfied or highly satisfied with DSS overall. Furthermore, it is noteworthy that a significant majority of long-term users (78%) express high satisfaction with Novocure's services. Similarly, 83% of therapy starters users express high satisfaction specifically with DSS services. Therapy starters, exhibit high satisfaction with DSS services and score high across all parameters. The point where satisfaction is comparatively lower, is regarding the "amount of information received." It is observed that 11% of short-term users felt they received an excessive amount of information, while 86% believe that the amount of information received was "just right" (111).

6.3.1.5.3 Overall satisfaction with Optune

Satisfaction with the Optune therapy itself is relatively high, with 82% of therapy starters, 74% of short-term users, and 68% of long-term users being satisfied or very satisfied. The number of satisfied patients does however decline as the therapy continues as can be seen illustrated in Figure 6.7 (111).

Figure 6.7 Survey 2023 (111). Base: Therapy starters (n=226), Short-term users (n=170), long-term users (n=99). Q: How satisfied in general are you with Optune?

When survey respondents were asked to elaborate on reasons for dissatisfaction with Optune therapy, AEs on the scalp and worsening of the disease were the most frequent single mentions as to why short-term and long-term users are not satisfied (Q: why are you not satisfied with the therapy with Optune?) (111).

6.3.1.5.4 Willingness to recommend

The overall satisfaction with Optune treatment is indeed relatively high, which is reflected in an even higher willingness to recommend Optune. In Figure 6.8, it is evident that 71% of short-term users and 72% of long-term users responded that they would be "very likely" to recommend Optune to a friend or acquaintance with glioblastoma. In contrast, only 4% of short-term users and 2% of long-term users responded that they are "unlikely" to recommend Optune (111).

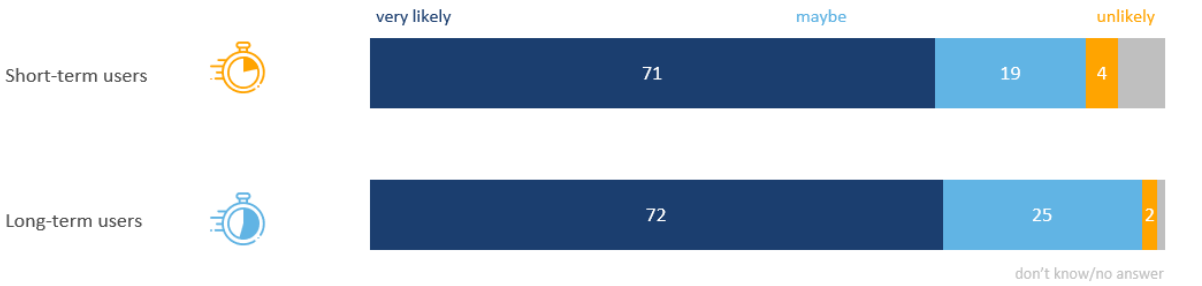


Figure 6.8 Survey 2023 (111). Base: Short-term users (n=170), Long-term users (n=99). Q: How likely is it that you would recommend Optune to a friend or acquaintance with glioblastoma?

Still, the willingness to recommend is quite high among short-term and long-term users alike. Three out of four respondents can sleep (very) well with Optune. A similar trend can be observed in the study conducted by Onken et al. (2019), which involved 30 patients with high-grade glioma receiving TTFields in combination with chemotherapy. In that study, 70% of the participants indicated that they would recommend TTFields to others, and 67% would reuse TTFields treatment again based on their own experience. 16.5% would not repeat TTFields treatment, and 14.8% did not share their opinion on the topic (100).

6.3.1.6 Compliance

Satisfaction with Optune treatment has a considerable impact on patient compliance. Treatment compliance of ≥75% or 18 hours per day has been shown to significantly impact the survival of GBM patients. 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 (10).

6.3.1.6.1 Compliance in clinical trials

In Stupp et al. (2017), 75% of the included patients had a compliance of ≥18 hours per day for the first three months of treatment (2). This level of compliance is comparable to other prospective studies on the use of TTFields for glioma grade IV (10).

In the EF-11 trial, out of 116 patients with rGBM who initiated TTFields treatment, 78% completed at least one four-week cycle (134). The average compliance with treatment was 86% (an average of 20.6 hours per day). 27 patients discontinued TTFields treatment prematurely, either due to not using the system for the recommended hours per day or because of difficulties managing the device.

Compliance data from the PRiDe register were available for approximately two-thirds of the patients (n=287) with recurrent GBM (93). Approximately 44% of the patients (n=127) used TTFields therapy for 18 or more hours per day. Patients with more functional impairment demonstrated lower compliance with TTFields treatment (93).

However, it is problematic to rely solely on compliance data from clinical trials, as patients knowingly participating in a clinical trial are in a different treatment setting than general practice. Therefore, other sources of compliance data are needed to better indicate expected compliance with Optune treatment in a Danish setting, for which reason compliance information from real-world evidence is included in the following.

6.3.1.6.2 Compliance in real-world evidence

Furthermore, a retrospective analysis of 65 patients between 2015 and 2019 assessed patient, tumor, and treatment-related factors of TTFields use and its association with overall survival. All patients underwent maximal surgical debulking, completed external beam radiotherapy with concurrent TMZ chemotherapy, and initiated adjuvant TMZ. The study reported a median compliance for TTFields use of 67.2% (range, 9.4 to 96%) (135).

Another retrospective study reported data from 41 patients with primary GBM or recurrent high-grade glioma who were treated with TTFields at a clinic in Berlin. Compliance reports were generated during the monthly routine check of the device. The study found a mean treatment compliance of 87% in the total population, irrespective of age, sex, and stage of disease (98). Additionally, the study observed that compliance was not negatively correlated with the duration of treatment.

Real-world evidence was collected from 16 patients prescribed Optune at the West Cancer Center from November 2015 to June 2016. Treatment adherence data were collected by the Optune device, which recorded average daily use (hours per day). This study showed that among TTFields users during this period, average compliance was 69.73%, with a range of 7.4-94.93%. Seven patients had compliance below 75%, and data was not available for three patients (103).

A retrospective study by Kessler et al. (2018) identified thirty-four patients diagnosed with glioma grade IV, who were treated with TTFields at University Hospital Würzburg in Germany (78). 28 of the patients were newly diagnosed and the remainder had recurrences. By evaluating monthly compliance reports, the study found that patients with ndGBM were on TTFields therapy for a median of 6.5 months with median treatment

compliance of 86.4%. No significant difference regarding compliance was observed between females (87.1%) and males (81.7%). A comparison of patients with ndGBM and rGBM showed no significant difference in therapy adherence with a median compliance of 80.0%.

Additionally, Regev et al. (2021) summed compliance for nine studies included in the review, where treatment included TTFields and TMZ for both patients with ndGBM and rGBM. The average daily compliance in these studies which included both randomized, progressive, and retrospective studies ranged from 70% to 90% (10).

In summary, TTFields therapy seems to be well accepted by glioma grade IV patients treated with high median compliance to the therapy, which is confirmed by Mittal et al. (2018) claiming that most patients are able to comply with adequate education and support (10,91,124). As mentioned previously, the results from Stupp et al. also revealed a notable trend favoring longer PFS and OS in groups with higher usage rates of Optune. This trend became apparent in patients who utilized Optune for at least 50% of the average monthly time, suggesting that individuals using Optune for at least 12 hours per day can expect to receive significant treatment benefits (2).

6.3.2 Unwanted incidents

Optune works by delivering alternating electric fields (called TTFields) into the tumor area through self-adhesive patches, which can result in unwanted incidents due to the contact between the skin and the transducer arrays, as well as the mechanism of action of TTFields. This section will address the incidence and nature of various AEs. In accordance with the specifications of the evaluation design, the following AEs will be included: feeling of discomfort/nausea/heat and impact on sleep due to discomfort from patches and heat build-up. Serious AEs will not be addressed in the present section. See Chapter 5 for information on the incidence of the occurrence of severe AEs.

6.3.2.1 Patient-reported AEs

It is stated in the DHTC's evaluation design that both the incidence and nature of AEs should be illuminated in the present application. The incidence of relevant AEs will primarily be elucidated based on the systematic review conducted by Regev et al. (2021) (the study is described in more detail in Chapter 5). This study is used to report the incidence of AEs, despite the inclusion of studies involving both non-germinal center B-cell-like (ndGBM), and germinal center B-cell-like (rGBM) subtypes, as there is no assumption of substantial differences in the incidence of AEs between ndGBM and rGBM (see Figure 6.9) (10).

Source	Diagnosis	Patients, No.	Mild-Moderate dAEs	Severe dAEs	Headache	Heat Sensation	Electric Sensation
Kirson et al. 2007	rGBM	10	90%				
Kirson et al. 2009	ndGBM	10	100%		20%		
Stupp et al. 2012 (EF-11)	rGBM	120	16%				
Mrugala et al. 2014 (PRiDe)	rGBM	457	24.30%		5.70%	11.30%	7.70%
Stupp et al. 2017 (EF-14)	ndGBM	456	52%	2%			
Onken et al. 2019	ndGBM + rGBM	30	40%				3%
Korshoej et al. 2019	rGBM	15	47%		60%		
Lazaridis et al. 2020	ndGBM	16	37%				
Song et al. 2020	ndGBM	10	80%		30%		
Bokstein et al. 2020	ndGBM	10	80%				
Zhu et al. 2020 (EF-19)	rGBM	192	36%				
Shi et al. 2020	ndGBM	5887	40%	<1%	8%	11%	11%
	rGBM	4345	31%		7%	10%	9%

Figure 6.9 TTFields-Related Local AEs (10).
dAEs, dermatologic adverse events; rGBM, recurrent glioblastoma; ndGBM, newly diagnosed glioblastoma.

6.3.2.1.1 Skin irritation

Novocure takes a proactive approach in educating healthcare professionals to especially mange skin irritation. Regev et al. (2021) review is comprised of twelve studies that report the frequency of mild to moderate dermatological AEs, summing to 11,558 patients, most of which are from the global post-marketing safety surveillance of TTFields in clinical practice (10). These studies include both patients with ndGBM and rGBM, and all share the common characteristic of undergoing treatment with Optune. The pooled prevalence of mild to moderate skin irritations is 38.4% (95% CI = 32.3-44.9) among TTFields patients, with both ndGBM and rGBM. Severe dermatological AEs (≥ grade III AE) are however much less common, with the PRiDe study reporting incidence in <1% and Stupp et al. reporting an incidence of 2% in patients with ndGBM (2,10,93).

The nature of the AE skin irritation refers to a localized reaction or inflammatory response of the skin that manifests as discomfort, redness, itching, or rash. The occurrence of these dermatological AEs is most probably related to chronic skin exposure to irritants in transducer arrays, shaving of the scalp, and application and removal of the transducer arrays (10,69,117,126).

"(...) Severe long-term skin irritations dictated the time I was able to wear it. I now have the skin problems under control."
(Anonymous long-term Optune user, survey 2023 (111)*)*

This quote highlights that the individual experienced significant and persistent skin irritations as a result of using Optune. These irritations had a direct impact on the duration they were able to wear the device. However, it is mentioned that the user has now managed to gain control over their skin problems, implying that they have found ways to alleviate or mitigate the skin irritations associated with Optune treatment.

When asked about challenges during Optune treatment, 18% of long-term users (n=140) mention inflamed/itching scalp/sores as a challenge (Q: Have there been major challenges for you since starting therapy with Optune? If so, what were they?). Scalp problems were by far the biggest challenge for long-term Optune users (111).

Taphoorn et al. (2018) allows for a direct comparison between TTFields plus TMZ and TMZ alone. For differences between treatment arms, patients treated with TTFields plus significantly worse itchy skin at three, six, and nine months than patients treated with TMZ alone, but not at 12 months (11).

Careful application and removal of transducer arrays are crucial to decrease the risk of cutaneous irritation. Of particular importance is the frequent need to shift transducer locations to minimize direct pressure on the scalp and avoidance of surgical scar lines. Once dermatologic toxicities develop, interventions include treatment interruptions of up to one week, application of topical corticosteroids for irritant or contact dermatitis, and topical antibiotics for infections at the time of array exchanges (69,136).

6.3.2.1.2 Heat sensation

Heat sensations are a possible dermatological AE, which refers to the experience of a heat sensation reported by patients during Optune treatment. Two studies included in the Regev et al. (2021) review measure the incidence of patient-reported heat sensations (10). The incidences in the two studies are very similar ranging from 10% to 11.5%.

The AE heat sensation involves the perception of a noticeable heat by patients at the location where the transducer arrays contact the scalp. Patients have reported feeling a warm or hot sensation in the area of application, which is bothersome to some patients who complain that the patches heat up too much causing the head to sweat (111).

While heat sensation is considered an AE associated with Optune usage, its clinical significance should be interpreted in light of the reported incidence rates ranging from 10% to 11.5% (10). These rates indicate that a

subset of patients may experience this sensation, but the majority of users do not report it as a significant concern.

6.3.2.1.3 Headache

Several studies included in the Regev et al. review (2021) have investigated the incidence of headaches in individuals undergoing Optune treatment (10). The available literature indicates that the reported incidence varies significantly, ranging from 5.7% to 60% across different studies. Notably, the study reported an incidence of 60% must be interpreted with caution due to its small population size (n=15).

The incidence in the two largest studies is respectively 5.7% in the PRiDe study (n=457), 7% for rGBM (n=4,345), and 8% for patients with ndGBM (n=5,887) in Shi et al. (2020) (67,93).

The AE headache refers to the experience of pain or discomfort localized to the head region reported by patients during Optune treatment. The nature of headaches associated with Optune usage can vary in intensity, duration, and accompanying symptoms. It should also be noted that the mentioned studies do not compare the incidence of headaches in glioma grade IV patients using Optune with patients not using Optune. This is important since headaches are a common symptom of glioma grade IV.

Given the wide range of reported incidence rates for headaches in Optune users, it is crucial to consider the clinical significance of this AE. While studies have reported a higher incidence of headaches, including the study with limited evidence, it is essential to interpret these findings cautiously.

Although incidences of AEs such as headaches and heat sensations are relatively infrequent, it is essential to be aware of these potential AEs, as they may impact patients' treatment experience and adherence. Adequate patient education and support regarding the nature of this AE, its transient nature, and the absence of long-term consequences is vital to mitigate concerns and promote patient confidence in Optune therapy.

6.3.2.2 Impact on sleep

The most extensive reports of patients' sleep in the Novocure Optune surveys are found in Survey 2023 (111). These results can be seen as illustrated in Figure 6.10. Patients generally tolerate Optune well while sleeping, both for short-term and long-term users. A significant majority of Optune users, with 72% of short-term users and 74% of long-term users, report sleeping well or very well while using the device. This indicates that Optune treatment does not compromise the ability of the majority of users to achieve satisfactory sleep and suggests that Optune does not significantly disrupt sleep patterns for the majority of individuals undergoing treatment.

Furthermore, it is worth noting that the percentage of users who report not sleeping well with Optune is relatively low, with 10% or less of both long-term and short-term users experiencing sleep difficulties.

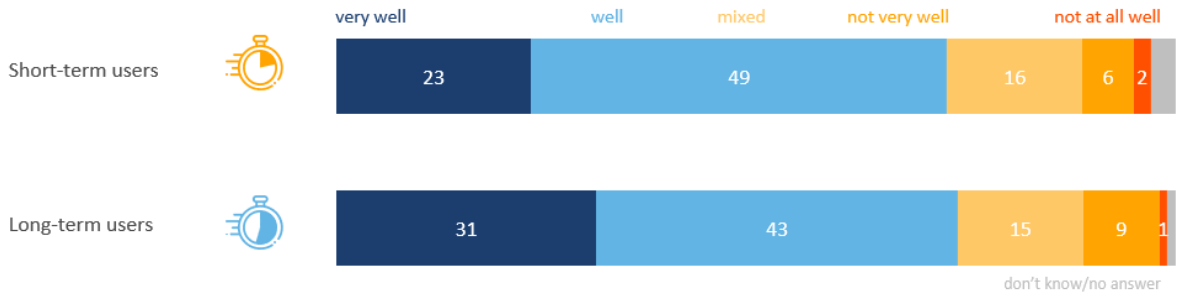


Figure 6.10 Survey 2023 (111). Base: short-term users (n=257), long-term users (n=140). B15, C9: How well can you sleep while wearing Optune?

The negative experiences of some Optune users regarding sleeping while using the device and the potential impact on sleep quality have been highlighted in the following quotes:

"Messages in the middle of the night interfere with sleep. For example when it gets too hot." (Anonymous long-term Optune user, survey 2023 (111)*)*

"They overheat and disturb my sleep." (Anonymous short-term Optune user, survey 2022 (110)*)*

This statement suggests that Optune users may experience interruptions during their sleep due to messages or notifications received from the device. These messages could be related to device functioning, maintenance, or other alerts. Such interruptions may disrupt the continuity of sleep and potentially affect the overall sleep quality of Optune users. These users express that they experience excessive heat, which may contribute to difficulties falling asleep or disrupted sleep patterns.

It is worth noting that individual experiences vary, and not all Optune users encounter sleep-related challenges, as some users state that they have found ways to manage the device while sleeping. One long-term user in the 2023 survey states that they can sleep relatively well with a thick, soft pad on the pillow, and another describes how they will put the cable and the device directly over their head between the mattress and bedstead, so they can move freely (111).

Additionally, the specific impact on sleep quality may depend on various factors, including individual sensitivity to disturbances and comfort levels, as exemplified in the following quote from a user whose husband is a light sleeper.

"(...) Sleeping can also be difficult as I prefer to sleep on my side and the arrays dig into the scalp and are very uncomfortable. Because the machine makes a humming noise at night, my husband, who is a very light sleeper, has to sleep in the spare room." (Anonymous long-term Optune user, survey 2023 (111)*)*

This quote suggests that some Optune users may feel that Optune limits their sleep options. Furthermore, the device itself may emit a humming noise during nighttime operation, which can disturb sleep partners who are sensitive to sound, necessitating adjustments in sleeping arrangements.

6.3.2.3 Impact on consultation patterns

The DHTC has requested an assessment of the potential impact on consultation patterns and additional visits based on the side effect profile of certain treatments, such as consulting a dermatologist for symptom management when using patches alongside steroid cream, among other factors. However, it has been challenging to find relevant literature that specifically addresses this topic.

6.3.3 Accessibility

In this section, possible challenges related to the accessibility of Optune will be highlighted. This includes whether the use of Optune requires specific abilities, such as language skills, health literacy, and technological literacy. Furthermore, it will address whether certain patient groups are unlikely to use or benefit from Optune due to comorbidities, social status, poor self-care, or potential restrictions due to geographical location. Lastly, patient and caregiver education will be discussed.

Not all patients diagnosed with glioma grade IV will have an equal likelihood of being able to use Optune. This may depend on factors such as the presence of other medical conditions, the patient's proficiency in the Danish language, as well as their health literacy and technological literacy to effectively manage Optune. In addition to the patient's own abilities, the assistance provided by caregivers in applying the patches and other aspects of Optune usage is also important. Potential limitations to the use of Optune will be considered and described in the following.

6.3.3.1 Language barrier

Lack of proficiency in Danish can pose a barrier to the optimal use of Optune. Effective communication and understanding of the instructions are crucial for patients to properly operate and manage Optune. Language barriers may hinder patients' ability to comprehend important information regarding handling and adverse

events amongst others. Users who do not have sufficient Danish abilities may therefore want an interpreter. There are, however, currently no specific agreements in place for providing interpretation services, for example in the consultation with the DSS. Patient materials, however, are available in different languages, and in cases where patients have relatives who can communicate in English or Danish, they can assist in facilitating communication between the patient and the DSS team. Novocure is however open to exploring options for interpretation assistance, if required, on a case-by-case basis.

6.3.3.2 Health literacy

The language barrier is, however, not the only barrier to understanding and using informational materials. To enable patients to use Optune, it is important to consider the health literacy of the patient population. Health literacy refers to an individual's ability to access, understand, and effectively use health information and services to make informed decisions about their health. It involves the capacity to read, comprehend, and apply health-related information, as well as the skills to navigate healthcare systems and communicate with healthcare providers. Health literacy is crucial for individuals to be actively engaged in managing their health, making informed decisions, and advocating for their healthcare needs (137).

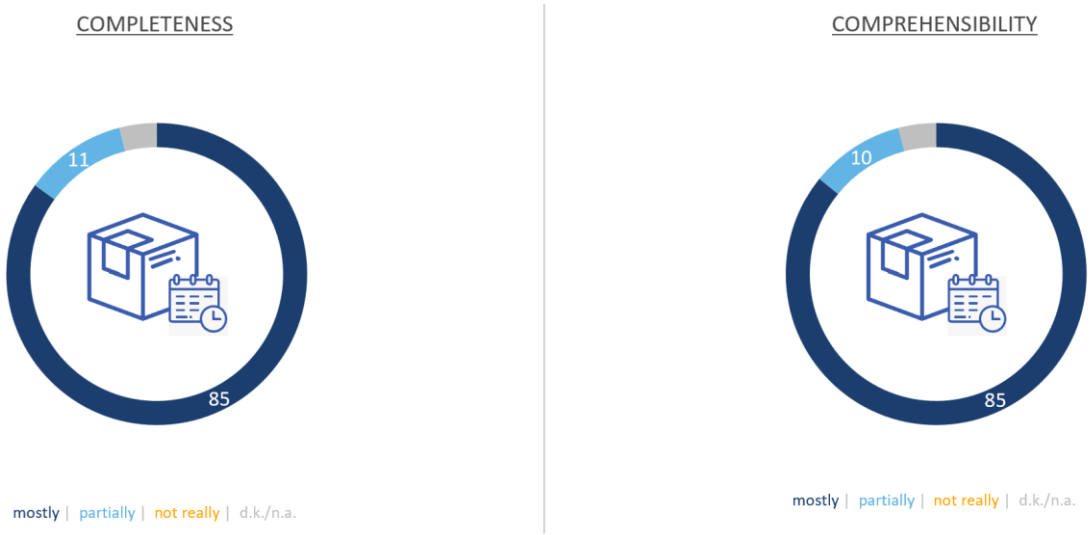


Figure 6.11 Survey 2023 (111). Therapy starters. Base: S1 (n=317). Q: For the therapy, you received a Start-Up Kit from Novocure with various information materials. Was the information in it detailed enough?

The 2023 survey addresses therapy starters' experience with the provided informational material at the beginning of treatment (111). It is not explicitly stated which specific material is being referred to, but it is assumed that patients receive Novocure's patient information and operation manual (62) and instructions for use (47), among other materials.

In Novocure's survey, it is further indicated that 85% of respondents considered the provided information to be mostly comprehensible, while 10% described the information at the beginning of the treatment as partly comprehensible. It is worth noting that despite a large number of respondents, none of them reported experiencing information that was not comprehensible, as can be seen in Figure 6.11. Satisfaction with the informational material given at the beginning of the therapy does not vary significantly with age or gender (111).

Patients will always have varying levels of health literacy, and it is, therefore, crucial to be able to accommodate these differences so that patients with different health literacy levels can understand and use Optune correctly. It is therefore positive that, according to this survey, Optune's materials and instructions are perceived as clear and comprehensible by Optune users.

6.3.3.3 Technological literacy

Technological literacy refers to an individual's knowledge, skills, and understanding of technology and their ability to effectively and confidently use and interact with technological devices or systems. It encompasses both the technical competence to operate the technology and the comprehension of its functions, features, and potential benefits. In relation to Optune use, technological literacy plays a crucial role. Optune is a medical device that incorporates advanced technology, and patients need to have a certain level of technological literacy to navigate and utilize it correctly.

The patient population primarily consists of elderly individuals. Therefore, it is particularly important that the information provided to patients about Optune and the treatment with Optune caters to this specific patient population, as they may face challenges with new technologies.

Referring to Figure 6.5 in Section 6.3.1.5.1, as previously mentioned, the majority of short-term and long-term users find the handling of therapy materials to be simple, with the arrays being the least simple to handle. Interestingly, long-term users consider the handling of cables and cable connections to be simpler compared to short-term users (109,111).

Novocure strives to address any challenges users may have with handling therapy materials through close contact between Optune users and the DSS team. The DSS team is well-equipped to handle various technical issues with Optune and can often provide remote assistance via phone or computer-based communication. However, it is important to note that the patient population predominantly consists of elderly patients. In this context, Survey 2022 indicates a general tendency among individuals over the age of 65 to prefer in-person consultations rather than consultations conducted over the phone or computer. Recognizing this need, the DSS team is prepared to accommodate it and will promptly arrange a visit to the patient's location to provide hands-on support as required (110).

6.3.3.4 Geographical limitations

The geographical location of Optune users does not limit their access to Optune or support from the DSS team. The DSS team supplies 24-hour technical support, is well-equipped to handle various technical challenges, and can often provide remote assistance through phone or computer-based communication. In cases where remote resolution is not possible, the DSS promptly arranges visits to the patient's location to provide hands-on support. Novocure ensures that an adequate number of DSS members are available based on patient volume and geographical distribution, ensuring that patients receive timely assistance regardless of their location. Therefore, geographical barriers do not hinder patients' ability to access Optune treatment and receive the necessary support from the DSS team. Some users may, however, need to wait longer for in-person assistance from the DSS. This could be the case for patients situated on low-populated and hard to get to islands. Prescribing healthcare professionals from Umeå University Hospital have reported positive outcomes in remote areas of Sweden.

6.3.3.5 Assistance from caregivers

Most patients will need help to prepare their scalps and apply the arrays, and for caregivers (such as relatives, neighbors, friends, etc..) support will likely be needed (14). Patients and their caregivers therefore need training in using the device, scalp preparation, and ensuring the correct placement of the transducer arrays. It is essential to ensure that therapists, caregivers, and patients possess the necessary knowledge and abilities to use Optune appropriately (14,62).

Patients and their caregivers will receive comprehensive training and education on the proper use of Optune. Caregivers will participate in training programs along with the patient. The training programs should provide clear instructions on how to use Optune correctly and safely, including guidance on transducer array placement. The simultaneous use of TTFields therapy and chemoradiotherapy can increase dermatological AEs, for which reason patients and caregivers will be educated on dermatological AEs risk, management, and

prevention (138). Patients and their caregivers should also receive education on recognizing and managing potential challenges and AEs. These programs can involve one-on-one training sessions, educational materials, interactive workshops, or online resources. The training duration should be sufficient to ensure that both patients and their caregivers have a thorough understanding of Optune usage and feel confident in managing Optune. Patient and caregiver education will be elaborated on further in Chapter 8.

Generally, a caregiver is required to effectively manage the device with shaving, application, etc., and not all patients are able to manage the logistics associated (139). In cases where patients do not have available caregivers, additional support may be required. Home nurses and assistants can be involved, although there may be challenges related to their consistent availability, particularly during the initial phase when more patients are starting the treatment. Training sessions conducted by DSSs with home nurses and helpers have proven effective in addressing this issue. If the patient does not have a caregiver who can support them, it will be possible to train a homecare nurse.

6.3.3.6 Social status and self-care

In general, poor self-care and low social status are well-known barriers to optimal medical treatment. Certain patient groups may in this sense be less likely to use Optune due to various factors, including social class and poor self-care habits. Patients with poor self-care habits may struggle with adhering to treatment schedules, including consistently using Optune as directed, potentially compromising its effectiveness. Some patients may have underlying mental health conditions that affect their ability to commit to Optune treatment or follow through with necessary care. Problems such as substance abuse can affect overall health and may hinder the optimal utilization and efficacy of Optune treatment (140,141). It is also possible for doctors to assess that patients with such issues should not receive treatment with Optune.

However, there does not appear to be any reason to suggest that poor self-care would be a greater barrier to the treatment of glioma grade IV with Optune compared to TMZ alone. Therefore, patients who are unable to manage treatment with Optune may also be unable to manage the current standard treatment.

The literature search has not identified any evidence addressing the significance of social status and poor self-care in relation to patients' likelihood of using and benefiting from Optune treatment.

6.3.3.7 Second diagnosis

There are secondary diagnoses that often exclude patients from receiving Optune treatment. In Stupp et al., patients were excluded from TTFields treatment if they had significant comorbidities that prevented them from receiving maintenance TMZ treatment, such as thrombocytopenia, liver function impairment, significant renal impairment, implanted pacemaker, defibrillator, deep brain stimulator, or documented clinically significant arrhythmia, infratentorial tumor, among others. It should be noted that there are no additional exclusion criteria for TTFields compared to TMZ alone treatment, and TTFields do not increase health inequality due to secondary diagnoses (2).

Furthermore, patients with a KPS score below 70% were not offered TTFields. Similar to the exclusion criteria in Stupp et al., patients with a KPS score lower than 70% may not be offered treatment with the Stupp protocol and are likely to be offered palliative treatment as a first-line option (2,41,42). However, in individual cases, doctors can assess the patient's eligibility for treatment based on individual assessments.

7 Organizational implications

The organizational implications of offering eligible adult patients with ndGBM Optune treatment are elucidated by seven topics stated in DHTC's evaluation design expected to be addressed in relation to the organizational implications: a) treatment pathway, b) licensing, service and operating agreements, c) implementation, training, and skills, d) information and data management, e) security of supply, f) system requirements and integration into existing systems, and g) expected product modifications. These topics have been addressed using a variety of data sources, either a single or a combination of multiple sources. The included studies and sources are presented in Table 7.1. The primary characteristics of the literature are outlined in the table. Disclaimer: the information presented in this section includes internal experiences and company confidential information obtained from Novocure. Due to the nature of this information, it will not be directly referenced in the text. However, it has been utilized to provide comprehensive insights and enhance the accuracy and completeness of the content.

Reference	Type of study/ type of data	Purpose of the study/ data collection	Context (Year; location; who)	Respondents (number; characteristics)	Comparator
Stupp (2017) (2)	Randomized, open-label phase three trial	To investigate whether TTFields improve the PFS and OS of patients with ndGBM	Multicenter trial (2017; 83 centers in US, Canada, Europe (Austria, Czech Republic, France, Sweden, Germany, Italy, Spain), Israel, and South Korea; Stupp et al. (2017))	Adult patients with ndGBM (695; progression-free after surgery or biopsy, had completed chemotherapy with TMZ, were over 18 years, and had a KPS of ≤ 70, as well as satisfactory bone marrow, liver, and renal function)	TMZ alone
Gentilal (2022) (79)	In-silico study, realistic head models	To evaluate the most optimal placement of the Optune transducer arrays	(2022; N/A; Gentilal et al. (2022))	N/A	N/A
Kinzel (2019) (63)	A patient satisfaction survey	To evaluate the impact of the second-generation Optune system on patient satisfaction and compliance, Novocure identified treating physicians and their patients being treated with the first-generation Optune who were willing and able to switch to the second-generation device and agreed to participate in a patient satisfaction survey	(2022; Germany; Kinzel et al. (2019))	Adult patients with ndGBM and rGBM (10; stable disease or no evidence of disease progression, at least one full month using the first-generation device, a KPS of ≤ 70, no new seizure activity in the past month prior to enrollment, the ability to operate the device)	TMZ alone
Expert statement (2023) (142)	Interview clinical experts	To assess both the current pathway for patients with ndGBM and the changes that the implementation of Optune could bring based on real-life experience with the device	(2023; Aarhus University Hospital Denmark; Dr. Nikola Mikic)	Neurosurgeon who works within the treatment area (one; neurosurgeon with Optune experience)	TMZ alone
DSS interview (2023) (143)	Interview DSSs	To describe the in-depth experience as a DSS, the patient pathway and the collaboration between Novocure and the healthcare providers	(2023; online meeting; Novocure DSSs)	DSS hired by Novocure who works with Optune (two; experienced DSSs)	TMZ alone
EANO (2021) (41)	EANO guidelines on the diagnosis and treatment of diffuse gliomas in adulthood	To validate the patient pathway without Optune based on guidelines from other countries	(2021; Europe; EANO)	N/A	N/A

NCCN (2023) (42)	NCCN guidelines on the diagnosis and treatment of diffuse gliomas in adulthood	To validate the patient pathway with Optune based on guidelines from other countries	(2023; US; NCCN)	N/A	N/A
Novocure_User manual (2022) (144)	User manual new-generation transducer arrays	To describe the expected upcoming modifications of Optune	(2022; N/A; Novocure)	N/A	N/A
Novocure_MyLink (2022)	User manual MyLink	To describe the expected upcoming modifications of Optune	(2022; N/A; Novocure)	N/A	N/A
Novocure_Bag (2023)	User manual convertible bag	To describe the expected upcoming modifications of Optune	(2023; N/A; Novocure)	N/A	N/A
No citation	Confidential information	To elaborate on the requested information formulated in the DHTC's evaluation design	(2023; N/A; Novocure)	N/A	TMZ alone

Table 7.1 Overview of literature and data used to illuminate the organizational implications of implementing Optune in Denmark.
DSS, Device Support Specialist; DHTC, Danish Health Technology Council; Dr., Doctor; EANO, European Association of Neuro-Oncology; KPS, Karnofsky performance score; N/A, not applicable; NCCN, National Comprehensive Cancer Network; ndGBM, newly diagnosed glioblastoma multiforme; OS, overall survival; PFS, progression-free survival; TTFields, tumor-treating fields; TMZ, temozolomide; US, United States.

7.1 Summary of findings regarding the organizational perspective

Optune therapy offers several advantages as a non-invasive treatment option for patients with ndGBM with minimal systemic AEs and compatibility with other treatment modalities such as chemotherapy. It can be used in various clinical settings and is well-tolerated by patients without significantly impacting their quality of life. It is the prescribing healthcare professional that determines the treatment pathway in collaboration with the patients, and Novocure is not involved in the decision-making process. The pricing model will be a leasing agreement for the Optune device while Novocure will provide 24-hour services for patients and healthcare professionals together with other additional services that will be provided without any additional cost. The leasing agreement is initiated by the Hospital/Region for a specific patient. From the day the patient begins to use Optune, Novocure will invoice the Hospital/Region on a monthly basis. If/when the oncologist in cooperation with the patient decides to stop Optune treatment, the Hospital informs Novocure, and the leasing agreement will be terminated by the end of the month. Novocure will then in cooperation with the patient (caregivers) organize to collect the equipment.

In terms of information and data handling, Novocure and the personnel responsible for processing the data comply with General Data Protection Regulation (GDPR) guidelines. Data transfer and storage are conducted securely, and patients retain control over their data. The security of supply is prioritized to ensure uninterrupted access to Optune therapy. Novocure maintains a comprehensive logistics system, strategic partnerships with suppliers, and quality control measures to maintain the specified quality of Optune. Adequate personnel availability and special arrangements are made for patients in restricted locations to ensure continuity of care. Based on several surveys, Novocure is developing new modifications for several components of Optune to enhance user-friendliness and accommodate patients' needs. Therefore, Novocure is introducing new-generation transducer arrays and improved accessories like the convertible bag, as well as the MyLink wireless communication device, to obtain usage data and facilitate quicker technical service to the patient when needed.

Since no Danish clinical guideline exists with Optune incorporated, the uptake of Optune in Denmark requires collaboration between policymakers, healthcare providers, patients, and their caregivers. And although several national European guidelines exist, Optune is not incorporated into the EANO guidelines yet due to variations in Optune reimbursement across European countries. No additional hospital infrastructure is required to support this uptake including no additional MRI to plan the transducer layout for each patient and during

subsequent follow-ups every two to three months. However, healthcare providers need formal training and certification provided by Novocure to ensure optimal experience for the prescriber and patient (understand the setup, read the user reports from the device (healthcare professionals), mitigate risks of skin AEs, etc.). In addition to healthcare professionals, education for patients and their caregivers is crucial in understanding how to effectively incorporate Optune into daily life and utilize the support services provided by Novocure including practice in transducer arrays placement. In situations where patients do not have caregivers who can assist with the placement of the transducer array, the involvement of home nursing staff (from the municipals) is essential to ensure optimal utilization of Optune and proper device application.

7.2 Organizational description

7.2.1 Treatment pathway for Optune

The following description outlines the key steps and processes involved in the treatment pathway for patients receiving Optune (see Figure 7.1). This description entails the entire treatment journey starting from the initial prescription until the treatment is ended no matter the cause. Overall Optune does not alter organizational conditions in the healthcare sector (2,41,42,142).

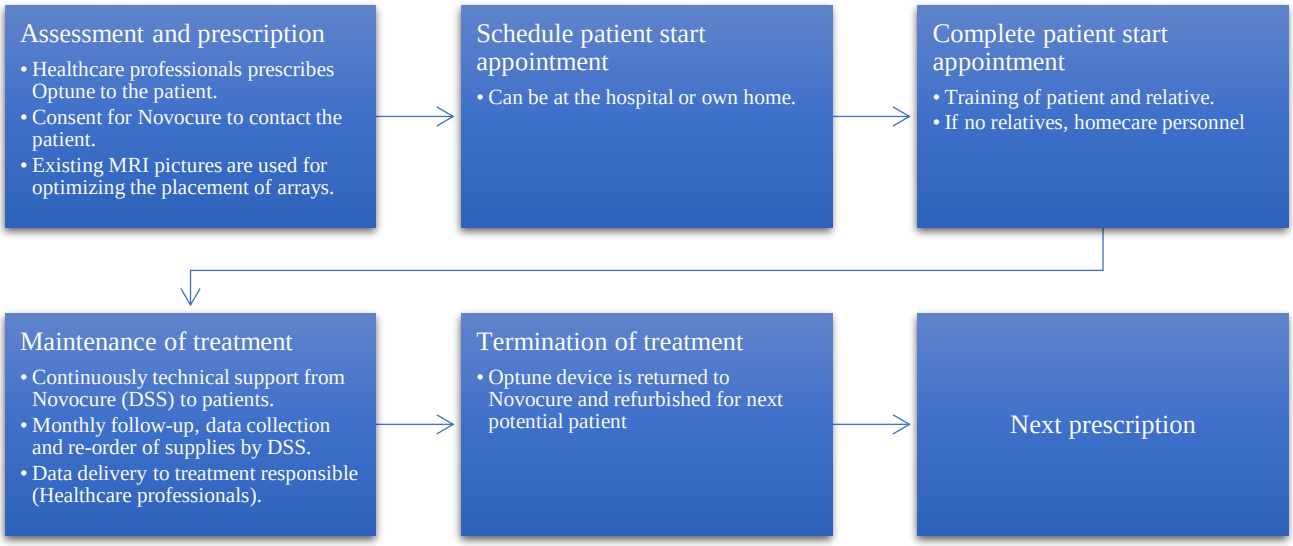


Figure 7.1 Flow diagram of the patient pathway with Optune. Potential Optune candidates are assessed by treatment-responsible healthcare professionals discussing whether the patient should be offered Optune or not. This also includes dialogues with the patient about the potential of Optune. The oncologist prescribes Optune to the patient and consent is gathered for Novocure to contact the patient. Existing MRI pictures are used for optimizing the placement of the transducer arrays. Schedule patients' start appointments which can be at the hospital or their own homes. Complete patients' start appointments including training of patients and relatives. If no relatives, homecare personnel will be involved. The maintenance of treatment includes continuous DSS from Novocure to the patient with monthly follow-up, data collection, and re-order of supplies by DSS. The DSS delivers the data to the treatment responsible (oncology department). At the termination of treatment, the Optune device is returned to Novocure and refurbished for the next potential patient.

7.2.1.1 Assessment and prescription

Healthcare professionals responsible for the patient's treatment assess whether patients are eligible for Optune as a potential treatment option. The decision to initiate and establish treatment with Optune must align with Stupp's treatment regimen. This assessment involves dialogues with the patient regarding the potential benefits and considerations of Optune therapy. If Optune is deemed appropriate, the oncologist prescribes it to the patient, and consent is obtained for Novocure to contact the patient.

7.2.1.2 Imaging material and treatment integration

Optune treatment is expected to supplement the standard treatment regimen, TMZ, according to Stupp's 2015 protocol for managing patients with GBM (106). Although Stupp's regimen may not explicitly require additional imaging material, it is necessary for accurate targeting of the tumor site and optimizing treatment

delivery. The required imaging material is typically obtained through routine MRI examinations conducted as part of the patient's standard follow-up protocol after surgery, therefore, there will be no additional costs or resource use associated with this.

7.2.1.3 Patient eligibility and treatment initiation

The eligibility assessment for Optune therapy is a collaborative decision between the patient and the prescribing doctor. Factors such as the patient's medical history, tumor characteristics, and treatment goals are considered. The decision to initiate Optune treatment must align with the prescribed timeline and therapeutic milestones defined in Stupp's protocol (2). Once Optune has been prescribed, the hospital or healthcare professionals do not provide direct support for using Optune; this responsibility is with the patient together with the Optune support system. The prescriber sends an 'Indication Form', the latest MRI, and the Physician's letter to the Intake Coordinator (by email to SupportEMEA@novocure.com or in a prepaid / FedEx envelope provided by Novocure). Optune therapy is ideally integrated into the patient's overall treatment plan, adhering to the prescribed timeline and therapeutic milestones defined in Stupp's protocol. This ensures that Optune is utilized at the appropriate stages of the treatment course to maximize its potential benefits. The treatment duration is determined by the clinician in close collaboration with the patients.

7.2.1.4 Imaging analysis and device placement

At Novocure, a certified and specialized neuroradiologist, who is employed by Novocure, reviews the patient's medical records, including the imaging materials. Based on the imaging materials scan, the specialized radiologist determines the optimal placement of the transducer arrays on the patient's scalp, which should be placed at least one cm apart from each other (79). This information is then communicated to the appointed DSS who collaborates with the oncologist to schedule the start of Optune treatment, either at the patient's home or hospital. All necessary equipment is delivered directly to the patient's preferred location either at home or to the hospital.

Note that this means that the patient will only have a single point of contact with Novocure because the same DSS will be appointed to the patient throughout the entire treatment period. This ensures that the patient will have a consistent and dedicated point of contact with Novocure throughout their entire treatment journey. By appointing the same DSS to the patient, continuity of personalized support is fostered. This approach allows the DSS to develop a deep understanding of the patient's specific needs, preferences, and treatment progress, leading to a more tailored and effective support system. The patient can rely on their designated DSS for any questions, concerns, or assistance related to the Optune therapy, enhancing the overall treatment experience, and ensuring a seamless and compassionate care process.

7.2.1.5 Training and education

Patients and their caregivers receive comprehensive training and education on the proper use of Optune. This training is typically conducted at treatment facilities and may involve healthcare professionals experienced in Optune therapy or DSSs. These professionals, including nurses and clinicians, provide detailed instructions on Optune application, maintenance, and other relevant aspects (143). Patient compliance and proficiency in using Optune are crucial for optimizing treatment outcomes. For more details see Section 7.2.3.

The patient will only have a single point of contact to Novocure, the dedicated DSS. At the first visit, the DSS will train the patient and the caregiver in how to use Optune and place the arrays. The ideal place for the first visit is the home of the patient. Simply because the patient is home in his/her comfort zone, here is no time pressure getting everything done in a hurry and the DSS may have the opportunity to help the patient where to place the equipment as power cords nearby relevant power outlet in bedroom and living room, as well as handle, where to store arrays and charge batteries at home,

The DSS's second visit will normally take place three to four days after the first visit. The primary aim of this visit is to support changing the arrays. If the patient is confident in managing Optune, there will normally be

scheduled a DSS visit monthly – and in cases where the patient is uncertain about the management with Optune, the DSS will visit the patient with a much higher frequency, always adapted to the individual needs of each patient.

7.2.1.6 Patient acceptance and compliance

Patient acceptance and compliance play crucial roles in facilitating the successful implementation and uptake of the Optune system (144). However, certain factors related to the treatment process may pose challenges for patients. For instance, the requirement for patients to shave their scalps and wear a device with noticeable transducer arrays and wires can potentially contribute to cancer-related stigma and may be burdensome for some individuals. Additionally, most patients would need assistance in preparing their scalps for the proper placement of the arrays.

Ensuring treatment compliance is essential as it directly impacts the effectiveness of Optune. Sustained efforts from patients, caregivers (such as relatives, neighbors, friends, etc.), and healthcare providers are necessary to achieve optimal compliance. Interestingly, anecdotal evidence suggests that Optune encourages patients to take an active role in their treatment, fostering a sense of ownership, in contrast to other cancer treatment approaches where patients may be more passive recipients of care (143).

In cases where patients do not have available caregivers, additional support may be required. Home nurses and assistants can be involved, although there may be challenges related to their consistent availability, particularly during the initial phase when more patients are starting the treatment. Training sessions conducted by DSSs with home nurses and helpers have proven effective in addressing this issue. Furthermore, patients may also learn the procedure themselves.

The time consumption for training home nurses and assistants is approximately 30 minutes. While there may be challenges associated with the turnover of home nurses and assistants, this is primarily a concern during the early stages of treatment initiation when the influx of new patients is higher (143). As the treatment progresses, the training process becomes more established and manageable.

7.2.1.7 Collaboration and coordination between Novocure and the healthcare providers

The collaboration and coordination between Novocure and the departments responsible for patient treatment play a crucial role in the effective utilization of Optune therapy. While there may be areas of intersection or overlap between the two entities, their primary focus lies in ensuring the optimal treatment of patients using Optune. The coordination primarily involves the initiation and ongoing management of the patient's treatment journey. At the start of the treatment, relevant information about the patient is shared between Novocure and the responsible departments. This exchange of information facilitates a comprehensive understanding of the patient's condition and treatment plan.

Throughout the treatment duration, regular communication is maintained, primarily through the submission of usage reports. Every four weeks, Novocure provides a detailed usage report to the treating doctor. This report serves as a valuable tool for the doctor to assess the patient's compliance with Optune therapy. By reviewing the report, the doctor can determine whether the patient is adhering to the recommended treatment regimen.

In addition to monitoring compliance, the management of potential side effects is an important aspect of the collaboration. One AE that may arise is skin problems associated with the use of Optune. In such cases, Novocure and the responsible departments work together to provide guidance and support in managing these issues. By sharing expertise and implementing appropriate measures, they ensure that any skin problems are effectively addressed and managed throughout the treatment process.

7.2.1.8 Ongoing support and follow-up

Patients have access to a dedicated support system to address any questions, challenges, or technical issues they may encounter during their Optune treatment. This support system may involve healthcare professionals at the treatment facility, representatives from Novocure, or a combination of both. The patient continues already planned follow-up meetings and interactions with healthcare professionals. Regular follow-up appointments will be scheduled to monitor treatment progress, assess device functionality, and address any concerns or difficulties faced by the patient. If the patient does not have a caregiver who can support them, it will be possible to train a homecare nurse. Throughout the treatment pathway, the patient continues to engage in planned follow-up meetings and interactions with healthcare professionals to ensure comprehensive care and ongoing evaluation of their treatment progress.

Trained medical providers or Novocure's DSSs may initially assist with fitting the Optune to the patient's scalp. Optune does not require regular maintenance, and Novocure provides a troubleshooting guide with each device and 24-hour technical telephone support.

7.2.1.9 Reporting and treatment discontinuation

Regular reports on time on Optune for the patient on a daily basis with an average for the period are provided to the oncologist on a monthly basis. It is important to note that these reports do not monitor treatment progress and clinical response. In the event that the decision is made to discontinue Optune treatment, the oncologist notifies the DSSs, and the equipment is collected and returned to Novocure. At Novocure, the equipment undergoes appropriate recycling or refurbishment processes to facilitate potential future use. Novocure has implemented a standardized solution for the pickup of used arrays in all European Union (EU) markets.

These used arrays are then disposed of in accordance with certified EU disposal regulations, ensuring compliance with environmental and safety standards. Germany serves as the designated location for array disposal, utilizing a certified EU disposal partner.

Furthermore, at the end of each treatment cycle, all durable components of the Optune system, including the device itself, are collected. These durables undergo a comprehensive cleaning, inspection, and repair process, as necessary, to ensure their optimal condition for subsequent patients. As for Optune accessories, such as bags, Novocure has established a procedure for their return to the respective Operation Center in Eindhoven, Netherlands, for EU markets. The company is actively involved in organizing the disposal process for these accessories, adhering to relevant guidelines and regulations. By implementing these standardized processes and ensuring proper disposal and refurbishment practices, Novocure aims to maintain environmental sustainability while also maintaining a seamless and efficient transition of equipment and accessories between patients.

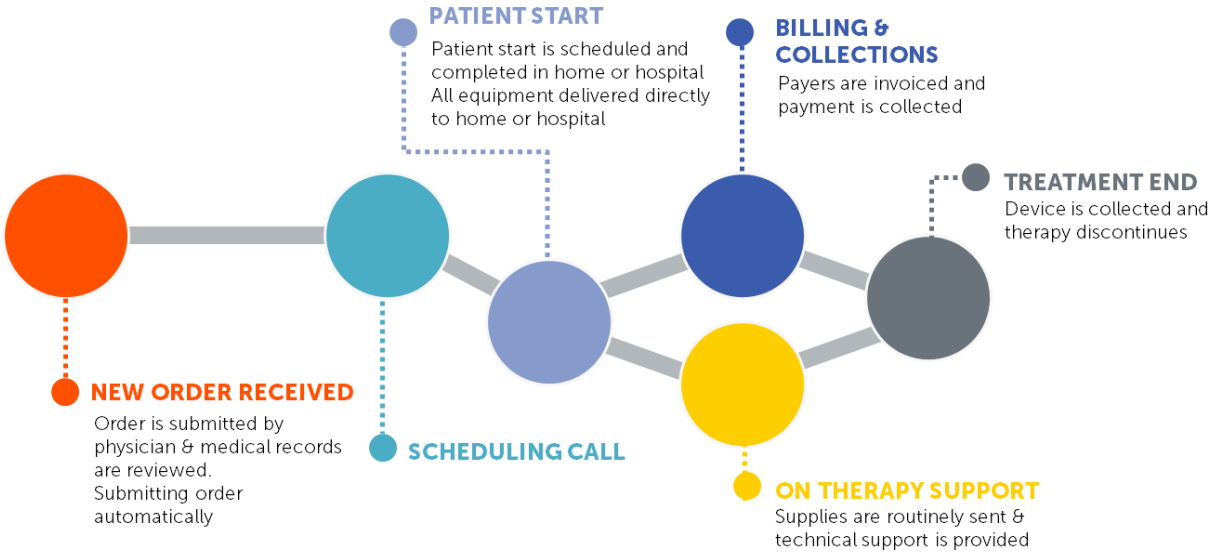


Figure 7.2 Overview of the organization and collaboration between Novocure and the Danish healthcare system when implementing Optune as a treatment option for patients with ndGBM (7).

Overall, the Optune treatment pathway adheres to the established treatment protocols, involves specialized professionals for imaging analysis and device placement, and emphasizes patient training, support, and regular follow-up to optimize treatment outcomes.

Note that even though the patients GBM progress the patient are still able to be treated with Optune. It is important to highlight that Optune treatment can continue even if the patient's GBM progresses. The decision to continue or terminate the treatment lies in the hands of the healthcare professional and the patient, based on their collaborative assessment of the treatment's effectiveness and the patient's overall condition. Optune therapy is not automatically discontinued solely due to GBM progression.

Instead, the healthcare team and the patient continually evaluate the treatment's impact, considering factors such as disease progression, treatment response, and the patient's quality of life. This patient-centered approach ensures that treatment decisions are made in alignment with the patient's best interests and preferences, providing a flexible and personalized treatment plan throughout the disease trajectory.

7.2.2 Licensing, service and operating agreement for Optune

The licensing, service, and operating agreement associated with Optune treatment plays a crucial role in ensuring a seamless experience for patients and healthcare practitioners. It encompasses various aspects that need to be considered, including pricing models, binding periods, contract terms, equipment delivery, service and support provisions, and interpreter assistance. The following description outlines these key features of the agreement. This type of licensing, service and operating agreement is already well known in Denmark since similar agreements exist for other treatments such as homecare dialysis (145).

7.2.2.1 Pricing models

The pricing model for Optune follows a licensing agreement structure. The leasing price for Optune encompasses various components, including equipment, technical support, maintenance, and software updates. The specific terms and pricing details are clearly outlined in the service and operating agreement established between Novocure and the healthcare provider. The service and operating agreement outlines important aspects such as the duration of the leasing period, associated costs, payment terms, and any additional services or features included in the agreement. It is imperative for the applicant to provide precise information regarding the leasing price and to clarify whether software updates are included in the agreement.

In terms of invoicing, billing is typically carried out at the commencement of each treatment period, which spans a duration of one month. This ensures a consistent and transparent billing process for the healthcare provider.

Regarding imaging requirements, the prescription of Optune does not necessitate any additional imaging such as MRI scans. Therefore, there are no extra imaging costs associated with the usage of Optune, providing a streamlined and cost-effective treatment option for patients.

7.2.2.2 Binding periods

There is no binding period for the Optune treatment. However, the payment schedule follows a monthly cycle, whereby payments are made at regular intervals. It is important to note that in the event of termination before the completion of a monthly payment cycle, there will be no refund for the remaining weeks or days between termination and the next scheduled payment.

7.2.2.3 Contractual considerations

Novocure does not reserve the right to refuse to enter contracts with patients or terminate contracts based solely on the doctor's decision, even if the tumor is located outside the indication area as seen in the MRI scan. While Novocure informs healthcare professionals about such cases, the company does not refuse treatment. A specific case in Sweden exemplifies this practice, where a patient was still provided with treatment despite the tumor being located outside the indicated area.

7.2.2.4 Equipment delivery

The delivery of equipment to the patient during the treatment period is handled as follows. All equipment, including disposable items like transducer arrays, is sent directly to the patient's home. Reorders of transducer arrays are also delivered to the patient's home. There are no restrictions on the consumption of equipment, allowing patients to change the arrays more frequently than approximately three times a week, if necessary. In addition, if the patient requires additional equipment such as extra chargers or equipment for a holiday home, Novocure provides these items free of charge. Novocure also facilitates the exchange or replacement of equipment as needed, ensuring that patients have access to functional and appropriate equipment. Importantly, all these services are provided at no extra cost to the patient.

7.2.2.5 Service and support

Service and support for the Optune system are handled by Novocure’s dedicated team of DSSs. These specialists are trained in the technical aspects of the equipment and are responsible for providing assistance, support, and updates to patients. The DSS team operates on a 24/7 basis, ensuring that patients, caregivers, and therapists can reach out for help via phone or text whenever needed (143). The DSS team is equipped to address various technical challenges and can often provide remote assistance over the phone or through computer-based communication. If a situation cannot be resolved remotely, the DSS will promptly arrange a visit to the patient's location to provide hands-on support. Novocure ensures an appropriate number of DSS members based on the patient volume and geographical distribution, ensuring that patients receive timely assistance regardless of their location.

Each patient will generally be allocated one specific DSS (with reservation for personnel changes and vacations etc) as a single point of contact for any devise related support, training, and questions.

Regarding interpretation assistance, currently, there are no specific agreements in place for providing interpretation services. However, patient materials are available in different languages, and in cases where patients have relatives who can communicate in English or Danish, they can assist in facilitating communication between the patient and the DSS team (143). Novocure remains committed to addressing the needs of patients and exploring options for interpretation assistance, if required, on a case-by-case basis.

7.2.3 Implementation, training, and qualifications for Optune use

The implementation of Optune treatment requires specialized qualifications and skills among the healthcare professionals responsible for patient care. It is essential to ensure that therapists and patients possess the necessary knowledge and abilities to use Optune appropriately, therefore, it is crucial to outline the necessary skills enhancement, training programs, and qualifications for therapists and patients involved in Optune therapy. The responsible oncologist has to be certified by Novocure before he/she can order Optune. Other involved healthcare professionals must also be trained and certified by Novocure to secure the most optimal support when interacting with the patient. The following section provides a description of these requirements.

7.2.3.1 Healthcare professional training

Healthcare staff involvement in Optune treatment primarily revolves around reviewing the usage report and potentially issuing prescriptions for managing skin problems. To ensure optimal patient care, it is essential that all healthcare personnel involved in Optune treatment be certified. Certification entails undergoing training provided by the Medical Director, covering general information on Optune's efficacy, AEs, and technical training conducted by a representative familiar with the Optune system.

For healthcare professionals directly involved in Optune treatment, such as oncologists, neurosurgeons, and other staff in oncology departments, specific upskilling is necessary. This includes gaining a comprehensive understanding of Optune's mechanism of action, device operation, treatment guidelines, and patient monitoring procedures. Additionally, nursing staff under municipal auspices who may be involved in patient care should receive minimum upskilling to adequately support Optune treatment.

Training sessions for healthcare professionals can include in-depth seminars, workshops, or online modules conducted by Novocure or authorized training partners. These programs should cover the scientific background of Optune, treatment protocols, device handling, troubleshooting, AE management, patient monitoring, and updates on Optune technology. The duration and frequency of follow-up courses should be clearly specified, considering the dynamic nature of the field and the need for ongoing professional development.

7.2.3.2 Certification of treatment sites and healthcare providers

Novocure determines any user training needed to ensure specific performance and safe use of the medical device. Novocure, therefore, conducts so-called certification training for healthcare professionals (physicians and nurses) as described below:

- Certification training provides a forum for healthcare staff to receive information about Optune and allows them to ask/clarify any open questions they may have. Certification can take place in a medical practice/ hospital or similar, but alternatively, can be conducted online. A typical certification lasts about one hour, depending on the extent of questions and discussions with healthcare professionals about Optune, which always takes place at the end of the certification process to ensure that healthcare professionals are informed about the most important aspects of the therapy. Certification of the Treatment site and the healthcare professional is conducted by Novocure (=certifier). The content of each certification is described below.

On certification day: Certifier hands out the „certification attendees list" to healthcare professionals, which is later sent back to Novocure. In the case of online certifications, the document is sent to the physicians via e-mail (and later returned to Novocure) to make sure that all data about the treatment site and healthcare professional are valid. The actual certification training contains the following topics and materials:

- PowerPoint presentation containing information about Optune indications, clinical trial data, safety, and the prescription process. A link to the most recent Optune user manual is also provided.
- During and after the presentation, questions asked by healthcare professionals about the treatment or Optune device will be clarified.

- In the case of online certification, software that allows sharing of computer screens and conversations between Novocure representatives and healthcare professionals is used. Thus, healthcare professionals can see and hear the presentation and ask questions about Optune.

7.2.3.3 Patient training and education

Patients undergoing Optune therapy require comprehensive training to actively participate in their treatment. The patient training programs aim to provide clear and detailed instructions on the correct and safe usage of Optune, including proper transducer array placement. Additionally, patients should receive education on identifying and managing potential challenges that may arise during treatment.

These training programs are tailored to meet the specific needs of patients and can encompass various approaches, such as one-on-one training sessions, educational materials, interactive workshops, or online resources. The duration of the training is designed to ensure that patients gain a thorough understanding of Optune usage and feel confident in independently managing their treatment. Regarding training for practitioners and patients, the expected time consumption per patient, relatives, and healthcare staff is as follows:

- Initial Patient Training (Start): Approximately three hours.
- Enhanced Training 1: Follow-up call on the next day, lasting approximately ten minutes.
- Enhanced Training 2: DSS visit during the first shift, lasting one and a half to two hours.
- Enhanced Training 3: DSS visit 14 days after treatment initiation, reviewing log files and providing explanations. Monthly visits for regular downloads are scheduled thereafter, with additional visits as needed.

During these visits, the DSS performs various tasks such as checking the equipment, ensuring proper battery charging, ordering necessary equipment, and assisting with the return of used arrays by arranging a pickup.

7.2.4 Information and data handling

When using Optune, specific circumstances apply concerning the collection, sharing, and handling of data. The following description provides an overview of these aspects in accordance with the GDPR and related considerations. Novocure has strict GDPR policies in accordance with Danish standards (see Appendix 11.4.1). Novocure is committed to complying with the applicable data privacy requirements in the countries in which the Company operates including a comprehensive description of safeguards and the processes Novocure has in place for ensuring the privacy and security of applicable patient health information (see Appendix 11.4.2).

7.2.4.1 Data collection and sharing

Optune treatment involves the collection of various data, including personal data, to ensure effective patient care and treatment monitoring. Personal data may include patient demographics, medical history, treatment progress, and device usage information. Novocure and the personnel responsible for processing this data adhere to the GDPR guidelines, ensuring that the collection and handling of personal data complies with relevant privacy laws and regulations. Patient consent is obtained prior to the collection and sharing of their personal data.

7.2.4.2 Data ownership

The ownership of data collected during Optune treatment remains with the patient, as it pertains to their personal medical information. Novocure acts as a custodian of this data and processes it on behalf of the patient and the healthcare professionals involved in their treatment. The patient retains control over their data and can exercise their rights regarding data access, rectification, erasure, and restriction as outlined in the GDPR.

7.2.4.3 Data transfer and storage

Data transfer between Novocure and the personnel responsible for processing occurs securely and in compliance with data protection regulations. Data is typically transferred using secured databases or cloud-based systems with appropriate access controls. The time frame for data storage is determined by regulatory requirements and medical best practices, ensuring data availability for treatment monitoring, research, and potential follow-up purposes. Data retention periods are defined and communicated to patients, reflecting legal obligations and the specific context of Optune treatment.

7.2.4.4 Additional costs associated with data provision or sharing

The provision or sharing of data between Novocure and the personnel responsible for processing does not incur additional costs. Data handling and transfer are considered integral components of Optune treatment and are covered by the overall treatment cost.

7.2.4.5 Data security

Data security is of utmost importance in Optune treatment. Novocure implements robust measures to safeguard data against unauthorized access, loss, or alteration. These measures include secure data transmission, encryption protocols, access controls, regular system audits, and adherence to industry best practices in information security. Patient data is handled in a confidential manner, ensuring that privacy and security requirements are met throughout the treatment process.

7.2.4.6 Integration into existing public systems and data sharing with clinicians

Optune treatment can be integrated into existing public healthcare systems, allowing seamless sharing of relevant treatment data with clinicians responsible for patient care which will be further elaborated in Section 7.2.6. The sharing of data ensures effective coordination between healthcare providers and enables comprehensive treatment monitoring and evaluation. Data sharing is carried out in compliance with applicable laws and regulations, ensuring patient privacy and confidentiality.

7.2.5 Security of supply

Ensuring the security of supply is crucial in Optune treatment to guarantee that patients receive compatible product units of the specified quality, as outlined in the service and operating agreement. The following description highlights how an adequate supply of equipment and personnel is maintained to treat all relevant patients. Additionally, any restrictions related to the delivery and treatment of patients, such as residence in rural areas including non-bridge islands, are considered. Novocure's commitment to a robust supply system enables uninterrupted access to Optune therapy, ensuring optimal treatment outcomes for patients.

7.2.5.1 Equipment supply

To ensure a consistent and reliable supply of Optune equipment, a comprehensive logistics system is established. Novocure, as the provider of Optune, maintains strategic partnerships with suppliers and manufacturers to meet the demand for equipment. Through careful planning and forecasting, inventory levels are regularly monitored to prevent stockouts and ensure timely equipment delivery. Novocure maintains a robust distribution network to promptly deliver Optune equipment to treatment sites, hospitals, and patients' homes.

7.2.5.2 Quality assurance

Maintaining the specified quality of Optune product units is of utmost importance. Novocure adheres to strict quality control measures throughout the manufacturing process to ensure that the equipment meets the required standards. Quality checks, inspections, and adherence to regulatory guidelines are implemented to guarantee the consistent performance and reliability of Optune devices. Regular quality audits and feedback mechanisms help identify and address any potential issues promptly.

7.2.5.3 Personnel availability

Sufficient personnel with the necessary expertise are essential to support the treatment of all relevant patients. Novocure ensures an adequate number of qualified personnel, such as DSS, who are responsible for providing technical support, training, and follow-up assistance to patients. The availability and allocation of DSS personnel are carefully managed to meet patient needs, considering factors such as treatment volume, geographical distribution, and patient-specific requirements (143). Novocure maintains a competent and trained workforce, enabling effective patient support throughout the treatment journey.

7.2.5.4 Delivery and treatment restrictions

In situations where patients reside in locations with delivery or treatment restrictions, such as non-landing islands or remote areas, special arrangements are made to ensure continuity of care. Therefore, Optune therapy can be made available to patients regardless of their geographical location, ensuring equitable access to treatment across different regions. Novocure collaborates with relevant stakeholders, including healthcare providers, logistics partners, and local authorities, to develop tailored solutions. These solutions may involve alternative delivery methods, such as coordination with local shipping providers or establishing dedicated pick-up points. Additionally, remote support systems, including telemedicine and virtual consultations, can be utilized to overcome geographical barriers and provide necessary assistance to patients in restricted areas.

7.2.6 System requirements and integration into existing systems

Optune treatment involves the collection and management of data, and it is important to consider how this data can be integrated into existing IT systems. The following description addresses the integration of Optune data into existing systems, potential compatibility issues, and how challenges are addressed. It also includes information about software updates and their inclusion in the service and operating agreement.

7.2.6.1 Integration into existing IT systems

Optune data can be integrated into existing IT systems within the healthcare sector, allowing for seamless data exchange and integration with other technology platforms. Novocure provides compatible interfaces that enable the integration of Optune data with various IT systems, including electronic patient records, data management systems, and healthcare analytics platforms. These integrations facilitate the flow of relevant patient information, treatment data, and clinical outcomes, enhancing the overall efficiency and effectiveness of patient care.

7.2.6.2 Compatibility and technical challenges

When integrating Optune data with existing IT systems, compatibility issues may arise due to variations in technology, data formats, security protocols, and network configurations. Novocure acknowledges these potential challenges and works closely with healthcare providers to address them effectively. Compatibility assessments are conducted to identify any technical gaps and develop appropriate solutions. Novocure's technical support team collaborates with IT professionals to ensure seamless integration, addressing issues such as firewall configurations, data upload and download mechanisms, and data format conversions.

7.2.6.3 Software updates and service agreements

To maintain optimal system performance and ensure the latest features and enhancements, Novocure provides software updates as part of the service and operating agreement. These updates may include improvements in device functionality, user interface enhancements, and security patches. The frequency and nature of software updates are outlined in the agreement to keep the Optune system up to date and aligned with evolving technological standards and regulatory requirements. The cost of software updates and their inclusion in the leasing price should be specified in the service and operating agreement.

7.2.7 Expected product modifications

TTFields is continuously evolving within the therapeutic area and in new therapeutic areas. TTFields is also being investigated for use in other cancer types, including meningioma, pancreatic, lung, and ovarian cancers.

Separately, the device has also been branded as Optune Lua, and approved by FDA for the treatment of malignant pleural mesothelioma (7).

TTFields therapy is also being evaluated for treating brain metastases in patients with non-small cell lung cancer, advanced pancreatic adenocarcinoma (together with gemcitabine), recurrent ovarian cancer, recurrent atypical anaplastic meningiomas, and malignant mesothelioma (7).

7.2.7.1 User-friendliness and availability

Expected product modifications aim to enhance the user-experience of Optune, making it easier for both healthcare professionals and patients to operate and manage the device. This could include improvements in the user interface, training materials, or support resources. The expected modifications should be discussed in terms of how they will enhance the user experience and ensure the widespread availability of Optune, making it accessible to a larger patient population.

7.2.7.2 New-generation transducer arrays

Patients have reported skin irritations and expressed dissatisfaction with the practicality of the current transducer arrays used with Optune (see Chapter 6) (63). In response to these concerns, Novocure is actively developing a new generation of transducer arrays to address these issues. The newer generation array has been developed and is now available in certain markets.

Figure 7.3 below shows the new polymer-based array, which was designed to be more flexible, 50% thinner, and more than 30% lighter compared to the standard array (144,146). Due to the mechanism of action, the longer Optune is worn throughout the day, the higher the probability of successful treatment (124). Previous device user-experience enhancements have resulted in improved patient use. In a German monitoring study of ten GBM patients, transferring from the first-generation Optune system (6 lbs. or 2.7 kg) to the second-generation Optune system (2.7 lbs. or 1.2 kg) resulted in an increase in ≥75% usage time during the first month of transition (from seven to nine patients).

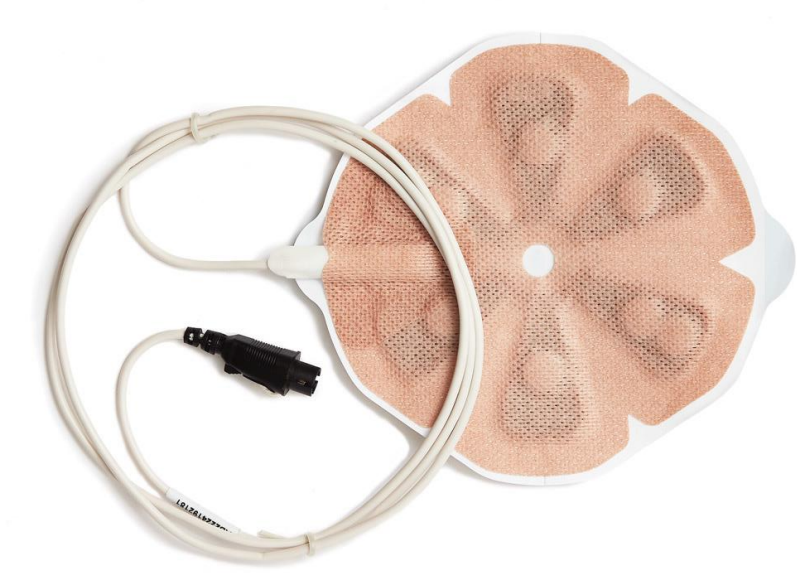


Figure 7.3 The new-generation transducer arrays (144).

7.2.7.3 MyLink

Another expected upgrade and modification of the Optune setup is MyLink. MyLink is a wireless communication device designed to enhance the functionality of the Optune system. It enables real-time data transmission between the patient's Optune device and the healthcare provider, offering several potential benefits and improving the overall treatment experience. One of the key advantages of MyLink is its ability to simplify data collection from the Optune electric field generator. Another advantage which should be

highlighted is the ability for the DSS to troubleshoot the device remotely, which is especially useful for patients in remote areas (147). With MyLink, patients can conveniently upload the log files from their electric field generator to a secure Novocure server directly from their own homes. This feature is particularly beneficial for adult patients receiving treatment at home or under the care of home nursing services.

To use MyLink, patients need access to a mobile network. The device functions as a standalone technical device and facilitates the secure transfer of data to the Novocure server. It is important to note that the uploaded data only includes information about the usage of the Optune device and any errors, ensuring patient privacy and data protection. The MyLink device connects to the electric field generator and downloads the data logs into its internal memory. Subsequently, it uses the mobile network to upload the downloaded data to the secure Novocure server. Throughout the data transfer process, data integrity is maintained, even in the event of interruptions, signal loss, or incomplete transfers.

The download process typically takes between one to three minutes, while the upload process can take up to 15 minutes with a good network connection (147). It is important to ensure that the download mode is completed before initiating the upload mode, which can be done by disconnecting the data cable from the electric field generator.

7.2.7.4 New-generation convertible bag

Regarding the user experience, Novocure acknowledges reported patient dissatisfaction with the current bags used in conjunction with Optune. Patients have expressed concerns about the small size of the backpack and the impracticality of the shoulder bag (see Chapter 6) (63). In response, efforts are being made to develop new versions of the bags to address these concerns.

One of the upcoming modifications is the introduction of a new-generation convertible bag that is specifically designed with patient comfort in mind. This convertible bag offers a range of features to enhance convenience and provide a customized, comfortable fit. It includes a small and lightweight bag, as well as a flexible strap system with both a shoulder strap and a hip strap (148). The convertible bag offers three options for wearing the Optune device throughout the day: a shoulder bag, a hip bag, or a combination of both (see Figure 7.4). This versatility allows patients to choose the most comfortable and convenient way to carry the device based on their preferences and daily activities.

In addition to its flexibility, the new convertible bag incorporates several features to optimize comfort during treatment. It includes a front pocket for personal items such as a mobile phone, wallet, or keys, providing convenient storage. A security latch on top helps keeps the device secure, providing peace of mind for patients. The shoulder strap is equipped with integrated anti-slip material to ensure a more secure fit and prevent slipping or discomfort. Furthermore, the bag features a handle that enables one-handed use, allowing patients to easily lift and grab the bag as needed.

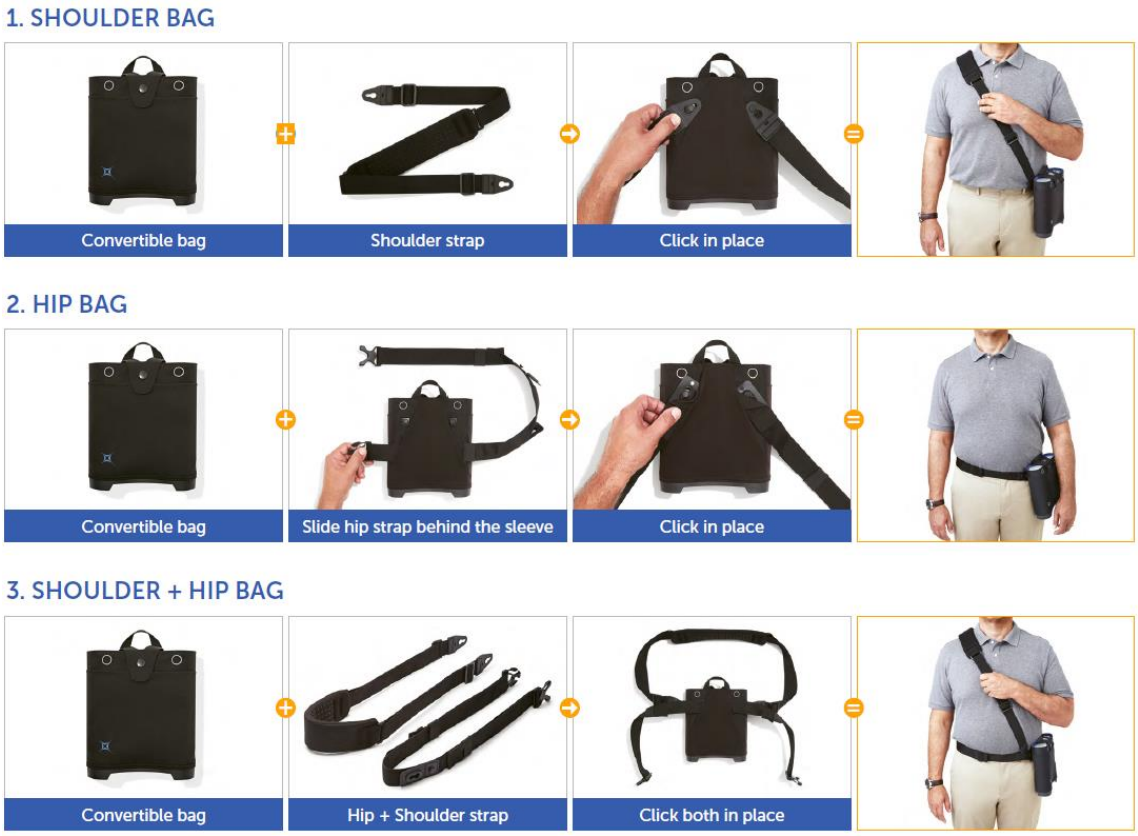


Figure 7.4 The new-generation convertible bag (148).

7.2.8 Ongoing studies of Optune for ndGBM

Several ongoing trials involving the use of TTFields in patients with ndGBM exist (7). These trials mainly aim to provide further evidence on the optimal line of TTFields therapy for patients with GBM.

EF-32 (TRIDENT) is an ongoing, pivotal randomized, open-label global phase three study in patients with ndGBM to determine the efficacy and safety of TTFields plus radiotherapy plus TMZ vs radiotherapy plus TMZ, where after six weeks, patients in both arms will then receive only TTFields plus TMZ. The planned enrollment is 950 patients evenly split between arms. The primary endpoint is OS, and secondary endpoints include PFS, 1-year and 2-year survival, overall radiologic response, next PFS, PFS at six months, safety, change in tumor, quality of life, and dependence of OS on TTFields dose (149).

The 2-THE-TOP study is an ongoing phase two, non-randomized, parallel-assignment, open-label study of the safety and efficacy of TTFields concomitant with TMZ and pembrolizumab in patients with ndGBM. The 2-THE-TOP trial is designed for the treatment of patients with ndGBM. Patients enrolled in the trial underwent maximal tumor resection followed by standard chemoradiation. The primary endpoint is PFS (150).

UNITY is an ongoing, open-label, sequential assignment pilot study of TTFields less than two weeks prior to radiation and TMZ in ndGBM patients after surgery. The primary endpoints are the rate and severity of treatment-related AEs (151).

The ongoing prospective observational study TIGER has enrolled 710 patients with ndGBM to examine the safety, efficacy, usage time, and quality of life associated with TTFields monotherapy. The objective is to obtain real-life data on the use of TTFields in patients with ndGBM in routine clinical care. The trial is performed in a German setting (152).

The non-interventional study (TIGER PRO-Active) investigates change over time in cognitive function, sleep quality, and activity in daily life as important determinants of quality-of-life in GBM patients treated with

TTFields in routine clinical care using low-threshold, electronic patient-reported outcome, and modern automated tracking data analyses. The study enrolled 500 patients with ndGBM (153).

A phase one, single-arm, open-label trial of TTFields started concurrently with stereotactic radiosurgery and TMZ and was initiated in 2021. With an estimated enrollment of 12 participants, the primary endpoint of this study is to determine the safety of this approach (154).

A prospective, randomized, open-label study of TTFields concomitant with radiotherapy and TMZ compared to radiotherapy and TMZ began in 2018 with an estimated enrollment of 60 patients. The primary endpoint is PFS at 12 months (155).

A pediatric trial of TTFields began in 2021. The target sample size is ten patients aged between five and 17 years old. The primary outcome measured is the rate of AEs with causality (156).

7.3 Summary of the transferability of the research setting

Stupp et al. (2017) (2), which served as the basis for evaluating Optune, was conducted in a multicenter setting primarily in the US. While the study provides valuable evidence on the effectiveness and safety of Optune, it is essential to consider its applicability to the Danish healthcare system considering the alignment of the intervention and control processes with the current practice in Denmark. The Stupp treatment regime is in alignment with Danish clinical practices for ndGBM patients (5). The patient characteristics for the included patient populations are also in alignment with Danish patients with ndGBM.

In addition to Stupp et al., insights, and experiences from other countries, especially Sweden and Germany, can provide valuable guidance for the implementation of Optune in Denmark. The healthcare systems in Sweden and Denmark share similarities in terms of organization and patient care delivery. Therefore, the experience of implementing Optune in the Swedish healthcare system can provide valuable insights and lessons that can inform the strategy for introducing Optune in Denmark. The proposed setup for Optune has already been tailored to suit the specific needs and context of the Swedish healthcare system. This adaptation indicates that the necessary adjustments and considerations for integrating Optune into the healthcare system have been carefully made based on the knowledge gained from the Swedish experience. Drawing on the experiences of both patients and healthcare professionals in Sweden, as well as insights from the German context, will contribute to a more comprehensive understanding of the potential challenges and opportunities associated with implementing Optune in Denmark.

8 Health economics

This section provides a comprehensive review of the health economic analyses conducted to evaluate the cost-effectiveness and budget impact of Optune plus TMZ compared to TMZ alone for the treatment of GBM. It encompasses an overview of the existing published economic evaluations and describes the specific health economic analysis conducted in the context of this Danish application.

Currently, Optune plus TMZ is not recommended or utilized in Denmark for adult patients with histologically confirmed ndGBM. However, it is accessible through an investigator-initiated sponsored trial for patients with rGBM (90,157).

For the assessment of the health-economic consequences, a Cost-Utility Analysis (CUA) has been developed by Real Chemistry and adapted to the Danish Healthcare system by York Health Economics Consortium and DLI Market Intelligence (DLIMI) while York Health Economics Consortium developed the Budget Impact Analysis (BIA) model with the support of DLIMI. These models have been used for HTA applications in other countries and have been adapted to fit the Danish clinical practices and the DHTC methodological guidelines. The cost-utility analysis is based on a partition survival analytic model developed to assess the cost-effectiveness of Optune plus TMZ in comparison to TMZ alone incorporating the costs and health outcomes associated with the utilization of Optune plus TMZ and TMZ alone, as well as the management of AEs (87).

In the subsequent section on health economics, headings from the DHTC template that are deemed irrelevant to this analysis are explicitly highlighted with N/A.

8.1 Existing (health) economic analyses

Several health economic analysis studies and HTAs have evaluated the cost-effectiveness of Optune plus TMZ compared to TMZ alone. However, no specific economic evaluations from Denmark were identified. This section provides a summary of the key findings from relevant studies:

TLV HTA report (2017) (15): The TLV conducted an HTA on the use of Optune as an adjunct to standard care for patients with ndGBM. The authors relied on efficacy and safety data from the Stupp et al., acknowledging that their conclusions were based solely on trial and study-related abstracts. The cost-effectiveness analysis was performed by Novocure, but the specific details of this analysis were not accessible. Novocure's model inputs included a monthly product cost and data extrapolated from Stupp et al. for a lifetime horizon. The estimated cost per QALY was approximately Swedish Kroner (SEK) 1.8 million, with sensitivity analyses resulting in a cost per QALY of approximately SEK 2.1 million. The uncertainty level of the model was assessed as medium.

HAS HTA report (2021) (158): In 2021, France’s Medical Device and Health Technology Evaluation Committee (CNEDiMTS) issued an opinion on the use of Optune together with TMZ for maintenance treatment after surgery and radio-chemotherapy. The Committee decided that Optune meets a therapeutic need that is insufficiently covered by pharmacological maintenance treatment based on the use of TMZ alone. Given the seriousness of GBM, its rapid progression, and the impact of Optune on slowing the progression of the disease, the Committee also decided that Optune has a public health benefit. The Expected Service Improvement (ESI) was issued an ASA level III, an improvement in expected benefit from Optune compared to maintenance therapy with TMZ alone. The report’s conclusion on the benefit of Optune stated, that the data provided demonstrated favorable impact of Optune on PFS and OS in the treatment of patients with ndGBM. Furthermore, the report considers Optune to be of therapeutic value in the treatment of ndGBM.

Bernard-Arnoux et al. (2016) (80): The evaluation conducted by Bernard-Arnoux et al. used interim EF-14 data for the survival analysis, which may not adequately represent the long-term outcomes, and relying on

such incomplete information can lead to biased estimates of LYs gained. This study conducted a cost-effectiveness analysis of TTFields therapy in patients with newly diagnosed GBM. Effectiveness data from the interim analysis of the EF-14 trial was utilized to compare TTFields plus TMZ to TMZ alone from the perspective of the French healthcare system payer. The addition of Optune to standard care increased patients' life expectancy by 4.08 months. A hypothetical cohort of 1,000 individuals with similar characteristics to the EF-14 trial participants was entered into a partition survival model. The study reported an ICER of US dollars (USD) 817,000 per LY gained, which remained robust across sensitivity analyses.

Connock et al. (2019) (84): This study employed a partitioned survival model to assess the cost-effectiveness of TTFields plus TMZ in GBM patients from the perspective of French National Health Insurance. The discounted ICER estimate was euro (EUR) 10,273 per LY gained, with Optune increasing patient survival by 0.604 LY at a cost of EUR 453,848.

Guzauskas et al. (2019) (87): The authors conducted a CUA comparing Optune plus TMZ compared to TMZ alone in patients with ndGBM, considering a US payer perspective. They developed a three-state model and found that the addition of Optune to TMZ increased patients' mean survival by 1.25 LYs and 0.96 QALYs. The estimated ICER was USD 197,336 per QALY gained.

These studies provide valuable insights into the cost-effectiveness of Optune plus TMZ compared to TMZ alone, considering different healthcare systems and perspectives. The studies were in agreement suggesting that TTFields therapy with Optune is more effective but also more costly than TMZ alone for GBM patients. The studies, conducted in different healthcare systems and perspectives, consistently report increased survival, LYs, and QALYs for GBM patients treated with Optune compared to TMZ alone.

8.2 Not cost effective at zero price paradox.

The cost effective at zero price paradox is relevant in the case of Optune. This paradox covers scenarios in which clinically effective treatment may be found not to be cost-effective even if they are priced at zero. This is the case when clinically effective treatments, result in additional time being spent in health states with high resource use and/or low health-related quality of life either during or after the treatment period. This pertains healthcare costs beyond the influence of the new drug, specifically, disease background costs, costs of existing drugs used in a combination regimen, and costs of future health interventions patients may become eligible to receive (159,160). In such cases where a clinically effective treatment can be acquired and delivered for zero cost, there are scenarios in which the treatment will fail to demonstrate cost-effectiveness because it increases other aspects of resource use. (160). A report by Briggs et al. states that the paradox poses challenges when assessing treatment combinations, where a novel add-on therapy can fail to be cost-effective even at zero cost (161). At present, there are no established guidelines for addressing situations in which this paradox comes into play. However, there is consensus that other aspects must take precedence. For instance, considerations such as whether there are legal or ethical reasons for recommending the treatment, including the need to distribute health resources in the fairest way in society as a whole. (159,160)

8.3 Economic analysis

To assess the cost-effectiveness and affordability of Optune plus TMZ compared to TMZ alone, several model-based economic evaluations have been conducted, including CUA, several sensitivity analyses, and BIA. The CUA focuses on evaluating the costs and effects associated with the use of Optune plus TMZ compared to TMZ alone. The analysis considers a lifetime horizon of 40 years and employs a three-state partition survival model to simulate patient transitions between different health states. The model is developed based on the best available clinical evidence. The primary outcome of interest in the CUA is the ICER of Optune plus TMZ compared to TMZ alone, which represents the additional cost incurred per additional QALY and LY gained. This comprehensive approach allows for a thorough assessment of the cost-effectiveness of Optune plus TMZ in comparison to TMZ alone, providing insights into the potential economic value of the treatment strategy.

Item	Analysis element	Expert committee specifications	Element applied in the analysis	Elaborated in section
1	**Time horizon**	Lifetime.	Lifetime (40 years).	8.2.3
2	**Intervention**	Optune as a supplement to the standard of care treatment according to Stupp's treatment regime.	Optune plus TMZ.	8.2.2
3	**Comparator(s)**	Standard of care treatment according to Stupp's treatment regime.	TMZ alone.	8.2.2
4	**Analysis method**	Cost-utility analysis.	Cost-utility analysis: a partitioned survival model.	8.2.6
5	**Outcome measure**	QALY.	LY, QALY.	8.2.6
6	**Method of data extrapolation, if relevant**	Carried out to the relevant extent in accordance with the DHTC's technical annex and the Danish Medicines Council's guidance on the use of course data in health economic analyzes.	Carried out to the relevant extent in accordance with the DHTC's technical annex and the Danish Medicines Council's guidance on the use of course data in health economic analyzes.	8.2.5.6
7	**Analysis perspective**	Limited societal perspective.	Limited societal perspective.	8.2.7.3
8	**Minimum cost components to be estimated**	Costs should include but are not limited to: • Costs for using Optune. • Costs for information and training of personnel responsible for processing. • Costs for home nursing and/or home care in connection with the use of Optune (e.g., for changing transducer arrays). • Hospital admissions, including for the administration of chemotherapy and other admissions. • Transport and time (patient and relatives held). Applicant must include the time the patient and their relatives are expected to spend changing transducer arrays.	Costs include but are not limited to components described in DHTC's evaluation design. Hospitalization costs are included in the costs of AEs; furthermore, chemotherapy is not included since TMZ is a capsule that you take once a day which does not require resources from the hospital. Productivity loss is not included due to the limited societal perspective.	8.2.7.3
9	**Sensitivity analyses that should be carried out as a minimum**	The applicant must carry out sensitivity analyses on the following parameters: • The monthly expected cost of using Optune +- 30% of this cost. • Time horizon: application of a time horizon corresponding to available study data on the clinical effect and safety of using Optune, i.e., for the observed time horizon. • Survival: the significance of uncertainty associated with the effect on OS of Optune vs. standard treatment. • Compliance: the importance of compliance (number of hours per day Optune is used) in relation to the effect of Optune (in relation to survival). • The estimate for the patients' HRQoL.	Sensitivity analyses are as follows but not limited to the request in DHTC's evaluation design.	8.2.8.2

Table 8.1 Analysis elements included in the health economic analysis as stated in DHTC's evaluation design.
DHTC; Danish Health Technology Council; LY, life year; TMZ, temozolomide; QALY, quality-adjusted life year.

8.3.1 Patient population

The patient population included in Stupp et al., which served as the basis for the model, consisted of individuals who met specific eligibility criteria (2). These criteria were as follows:

- Patients had histologically confirmed supratentorial ndGBM (WHO grade IV gliomas),
- Were progression-free following maximal safe debulking surgery or biopsy,
- Had completed standard concomitant chemoradiotherapy (radiotherapy 45-70gy concomitant with TMZ).

Additional requirements included:

- Being 18 years of age or older,
- Having a KPS score of 70% or higher (indicating some independence in daily activities),
- Possessing adequate bone marrow, liver, and renal function.

Following completion of chemoradiation, patients were randomized to receive standard maintenance TMZ with or without the addition of TTFields in a 2:1 ratio. TTFields treatment was initiated within a specific timeframe after the last dose of concomitant TMZ and radiotherapy. Within Stupp et al., the patient population primarily consisted of males (62%) and Caucasians (90%), with a median age of 56 years (ranging from 19 to 80). All patients had a KPS score of at least 70, indicating their ability to care for themselves but possibly experiencing symptoms and limitations. The trial excluded individuals with multifocal GBM, prior radiation or chemotherapy treatment, and certain comorbidities such as cardiac pacemakers, implanted defibrillators, or shunts (2).

The model begins from the point of randomization and tracks patients based on their assigned treatment arm. Previous treatments are assumed to be equivalent among patients and therefore not explicitly modeled. The patient population in the model aligns with the CE mark for Optune and has been validated by clinical experts (142,146).

8.3.2 Intervention and comparator

8.3.2.1 Intervention: Optune plus TMZ

The intervention under investigation in the economic evaluation is Optune plus TMZ. Optune is a portable medical device designed to deliver TTFields (alternating electric fields) that disrupt the rapid cell division typically exhibited by cancer cells (see the full description in Section 3.3) (60). The recommended usage of Optune involves applying the device for minimally 75% of a three-day cycle, with an electric field frequency range of 100 kHz to 300 kHz. The optimal treatment duration for Optune is not yet established, as patients in the Stupp et al. study had not completed their treatment at the time of analysis (2). However, it is estimated to be approximately five years, as the majority of patients do not survive beyond this timeframe (3,50). Optune is administered on an outpatient basis and managed by the patients and their caregivers to integrate the treatment into their daily lives (2). In the base-case scenario of the economic evaluation, intervention treatment with Optune will be provided to the average ndGBM patient for 9 months. This is based on the median time on Optune of 8.2 months in the Stupp et al. 2017 and since Optune will be invoiced monthly this is raised to 9 months to cover the costs. Without access to individual-level data from Stupp et al. 2017 it was not possible to calculate the mean time on Optune. The base-case scenario assumes that 9 months is a good estimate of clinical practice considering both early drop out and a few patients having Optune for a longer period of time. Please note, that this assumption is varied in the sensitivity analysis of the budget impact analysis (See 8.4.2.1).

8.3.2.2 Comparator: TMZ alone

According to the clinical guidelines for GBM in Denmark, the current standard of care is maintenance TMZ as monotherapy. TMZ, an oral alkylating agent, is a chemotherapy medication used to treat malignant brain tumors such as GBM. TMZ has become the preferred choice over other chemotherapies due to its oral administration and favorable toxicity profile. The prescribed dose of TMZ varies based on the patient's body

surface area, which is calculated using their height and weight. The dosage typically ranges from 75 to 200 mg per square meter per day for five days every 28 days for 6-12 cycles. The specific dose and duration of treatment depend on factors such as the type of tumor, prior treatments received, whether TMZ is used alone or in combination with other therapies, and the patient's response to treatment (43). In the case of ndGBM, TMZ will be administered to patients until disease progression occurs, at which point second-line systemic therapy will be initiated.

8.3.3 Time horizon

The choice of time horizon plays a crucial role in health economic analyses as it determines the duration over which costs and effects are measured for the compared interventions. In accordance with guidelines for health economic evaluations, the selected time horizon should be long enough to capture all relevant costs and effects related to the decision being evaluated (112).

Additionally, the concept of discounting is employed to account for positive time preferences, which means that future costs and effects are given less weight compared to those occurring in the present. This reflects the general preference for immediate benefits and the opportunity cost of waiting for outcomes to occur in the future.

Considering the potential for a subset of GBM patients to survive beyond the typical prognosis and experience a length of life comparable to the general population, a base-case time horizon of 40 years is utilized. This extended time frame allows for a comprehensive assessment of all relevant costs and outcomes associated with the interventions under investigation. It should be noted that the median age of the patients in this study was 56 years, providing further context for the chosen time horizon.

8.3.3.1 Discounting

In accordance with the guidelines provided by the Danish Ministry of Finance, the base case discounting approach used in this model adheres to gradually decreasing discount rates for both costs and health outcomes over time (162). This approach is recommended for investments spanning a period of 75 years or longer.

Specifically, the discounting profile employed in this analysis involves different interest rates for different time periods. Costs and benefits realized during the initial 35 years are discounted at an annual rate of 3.5% except the first year (undiscounted costs and effects). For the subsequent period spanning years 36 to 70, a discount rate of 2.5% is applied to costs and benefits. Finally, for the remaining years 71 to 75, a discount rate of 1.5% is utilized.

This discounting methodology aligns with the Ministry of Finance's recommendations and ensures that the time preferences for costs and health outcomes are appropriately incorporated into the economic evaluation.

8.3.4 Analysis structure

This section provides an overview of the structure of the model utilized in the health economic evaluation. The analyses are performed using cohort calculations, employing partition survival modeling with a cycle length of one week. This cycle length enables precise capture of the dosing schedules for both the Optune and TMZ regimens. Half-cycle correction was not applied because it would have only very limited impact on the results with a one-week cycle length.

The health economic model has been developed in Microsoft Excel and serves as the foundation for the base-case analysis as well as all the conducted sensitivity analyses. Excel was selected as the modeling platform due to its widespread accessibility and flexibility in accommodating various inputs and calculations required for economic evaluation.

By employing partition survival modeling within the Excel framework, the model facilitates the simulation of patient outcomes over time, considering transitions between different health states, and incorporates relevant

clinical and economic parameters. This modeling approach allows for the estimation of costs, health outcomes, and the cost-effectiveness of Optune plus TMZ compared to TMZ alone.

8.3.4.1 Data from a single trial

The development of the model relied primarily on but was not limited to data from the Stupp et al. study (2). Stupp et al. played a crucial role in providing evidence on the effectiveness of Optune plus TMZ compared to TMZ alone in the treatment of adult patients with ndGBM. The model integrates key parameters related to survival, disease progression, quality of life, and AEs associated with each treatment option. These inputs were derived from a comprehensive analysis of data from Stupp et al. and other pertinent studies.

Stupp et al., which formed the basis for the economic evaluation, enrolled a total of 695 patients across 83 medical centers in eight countries, including the US, Canada, and various European countries. All patients in the trial had histologically confirmed ndGBM and underwent maximal safe resection followed by concurrent chemotherapy with TMZ, representing the standard of care for ndGBM treatment. Subsequently, patients were randomized to receive maintenance TMZ therapy with or without the addition of Optune. For more details on the Stupp et al. study and other studies on clinical effectiveness and safety see Chapter 5.

By incorporating data from the Stupp et al. trial and drawing from a diverse patient population across multiple countries, the model aims to capture a comprehensive representation of the clinical and economic outcomes associated with the use of Optune plus TMZ compared to TMZ alone in the context of ndGBM treatment.

8.3.4.2 Health economic model

The cost-effectiveness model was developed using Microsoft Excel, a widely used software tool for economic modeling. To simulate the economic outcomes associated with different treatment regimens, a three-state partition survival model was employed. This modeling approach is commonly used in oncology research as it allows for patient transitions between distinct health states based on their disease status and the treatment received.

The partition survival model offers several advantages over other modeling techniques, such as the Markov approach. It directly incorporates observed trial results, requiring less data and fewer assumptions. By avoiding the estimation of discrete transition probabilities, the model provides a more straightforward representation of the trial outcomes. Additionally, it reduces the need for complex modeling approaches, making it more accessible and interpretable.

The model consists of three mutually exclusive health states (see Figure 8.1):

- Progression-free/stable,
- Progression/progressed disease,
- Dead.

At the beginning of the model, a hypothetical patient population is placed in the stable disease health state. From there, patients can either remain in the stable state, experience disease progression, or die from cancer or other causes. Patients who transition to the progressed disease state remain there until they either die from progressed cancer or other causes. The dead state serves as an absorbing state.

Throughout the model, patient survival, quality-adjusted survival, and healthcare costs are estimated for each cycle and aggregated over the entire time horizon of the analysis. The treatment options evaluated in the model include TMZ alone and Optune plus TMZ. Patients in the progression-free/stable state have the option to receive either of these treatments, while patients in the progressed state receive the best supportive care. The transitions between health states are determined at the end of each cycle based on the model inputs and assumptions.

By employing this partition survival model, the economic evaluation aims to capture the dynamic nature of disease progression and treatment response, providing insights into the cost-effectiveness of different treatment options for patients with ndGBM.

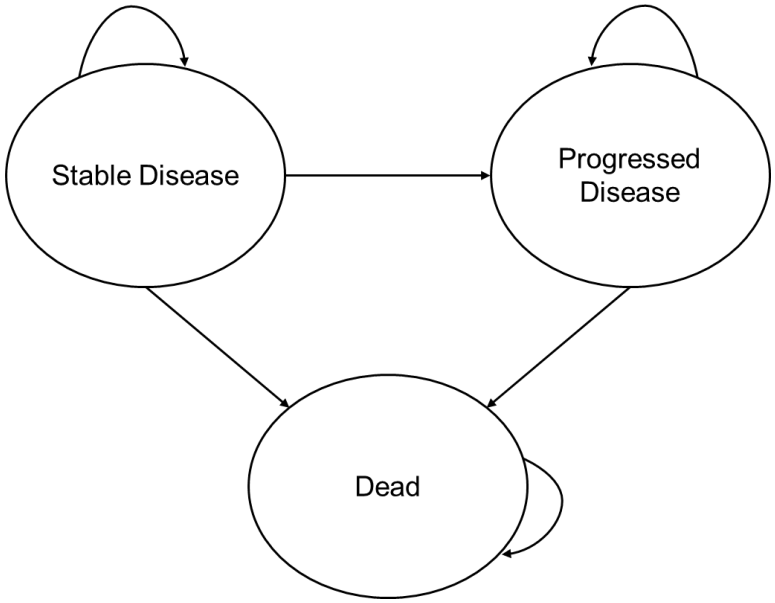


Figure 8.1 Model structure of Optune plus TMZ in ndGBM. This is used to model the effects and costs associated with the use of Optune plus TMZ and TMZ alone. The straight arrows indicate possible transitions between health states.

8.3.4.2.1 Model perspective

The analysis will be conducted from a Danish limited societal perspective in accordance with DHTC's guidelines, which focuses on capturing direct costs associated with the healthcare system and patients, while excluding informal care and productivity costs. Direct costs refer to expenses that are directly incurred and charged, such as medical treatments, hospitalizations, medications, and healthcare professional fees. Patient-related costs concerning transport costs will also be considered. However, informal care, which involves unpaid assistance provided by family members or friends, and productivity costs related to lost work productivity or disability will not be included in the analysis.

8.3.4.2.2 Model validation

No validation study has been published.

8.3.4.3 Sensitivity analyses

According to DHTC's evaluation design, a comprehensive set of sensitivity analyses was conducted to assess the robustness and uncertainty of the health economic model's results. These sensitivity analyses aim to explore the impact of various sources of uncertainty on the model outcomes and identify key drivers of the base-case results. Both deterministic and probabilistic sensitivity analyses (PSA) were performed to address different aspects of uncertainty.

In the deterministic sensitivity analyses, a set of one-way sensitivity analyses (OWSAs) were performed systematically varying one parameter at a time to test the sensitivity of the results. This involved independently varying each parameter within their respective 95% confidence intervals, or if such intervals were not available, by ±20%. The ICER was calculated for each variation, and the upper and lower limits of the ICER were recorded to generate tornado diagrams. These diagrams visually depict the impact of parameter variation on the model results, highlighting the parameters with the greatest influence on the outcomes. For the five OWSAs specified in the DHTC's evaluation design, the results will be presented for the base-case model based on Danish utilities by applying Danish EQ-5D-5L value set from Jensen et al. (2021) to data from a real-world HRQoL study by Palmer et al. (2021) (13,68).

Furthermore, joint parameter uncertainty was explored through PSA. In the PSA, all parameters that were assigned probability distributions were simultaneously varied in multiple model-runs. For each run, input values were randomly selected from the assigned probability distributions using 3,000 2nd-order Monte Carlo simulations. Transition probabilities and utility values were assigned beta distributions, while costs were assigned gamma distributions. The results of these simulations were plotted on a cost-effectiveness scatterplot, which provides a distribution of incremental costs and effects. From this scatterplot, a cost-effectiveness acceptability curve (CEAC) was estimated, illustrating the probability of Optune plus TMZ being cost-effective compared to TMZ alone at different willingness-to-pay thresholds.

8.3.4.3.1 Sensitivity analysis 1 – Cost of Optune

The monthly expected cost of using Optune can be significant for the cost-effectiveness of using Optune, just as it is a parameter that can change significantly over time, e.g., in connection with the tender. Therefore, the significance of increasing and decreasing the cost of Optune ± 30% to 30% above the annual cost for the costliest to 30% below the annual cost for the least costly is examined. The change is made only in relation to the annual cost for Optune.

8.3.4.3.2 Sensitivity analysis 2 – Time horizon

The length of the time horizon is important to the results of the CUA. For this reason, it is examined what the results of the CUA are at a time horizon corresponding to available study data on the clinical effect and safety of using Optune, i.e., for the observed time horizon, which for the Stupp et al. trial is five years (2). All other variables remain the same.

8.3.4.3.3 Sensitivity analysis 3 – Survival outcomes

It is crucial to consider the significance of uncertainty associated with the effect on the OS of Optune. Sensitivity analysis 3 allows the exploration of the impact of this uncertainty by assessing the range of potential outcomes ± 20% when varying the effectiveness on longterm survival of Optune plus TMZ compared to TMZ alone.

8.3.4.3.4 Sensitivity analysis 4 – Compliance

Compliance, measured by the number of hours per day that patients use Optune, plays a critical role in determining the treatment's effectiveness and its impact on survival outcomes. Assessing the importance of compliance allows us to evaluate the effect of Optune on OS by considering variations in compliance levels. To conduct the sensitivity analysis, the compliance rate of Optune usage will be varied according to usage/compliance rate with ICER estimates for 50-60% usage, 60-70% usage, 70-80% usage, 80-90% usage, and >90% usage. The model base-case assumes a usage of 75% or more (≥18hrs a day) referred to as "overall" in table 8.14.

8.3.4.3.5 Sensitivity analysis 5 – HRQoL

N/A in this version of the application.

8.3.4.3.5 Sensitivity analysis 6 – Not cost effective at zero price

Optune is an example of a case where the 'not cost-effective at zero price' paradox comes into play. A sensitivity analysis, in which the price of Optune is set to zero, effectively removing it from the cost-effectiveness model, provides the opportunity to illustrate this paradox. The sensitivity analysis will be conducted by adjusting solely the price of Optune to 0 DKK.

8.3.5 Probability data

The model utilized transition probabilities derived from both clinical trial data and epidemiological data to estimate the likelihood of transitioning between different health states over time.

Clinical trial data, specifically data from the Stupp et al. trial, provided valuable information on the effectiveness of Optune plus TMZ compared to TMZ alone (2). This data informed the estimation of transition probabilities related to disease progression, survival rates, and treatment response (see Table 8.2).

Furthermore, probabilities of adverse events associated with the treatments under investigation were also considered in the model. These probabilities were estimated based on clinical trial data, which provide information on the occurrence and severity of AEs in patients receiving Optune plus TMZ and TMZ alone. In the model, side effects are expected to occur solely during treatment with Optune and not after treatment discontinuation. This is based on results from Stupp et al. (2017), where it is stated that there are no additional side effects except for skin irritation. Skin irritation is associated with the use of Optune's transducer arrays, and skin irritation, therefore, disappears temporarily when treated with dermatologic treatment or during a treatment break (2). By incorporating adverse event probabilities, the model can account for the potential impact of treatment-related complications on patient outcomes and healthcare costs. Adverse events are included as the probability for each event in the first cycle.

Parameter	Estimate		Reference
	Base-case (95% CI)	Probability distribution	
Treatment Details			
Time on TTFields (Median; Months)	8.2 (6.6-9.8)	Normal	Stupp et al. 2017 (2)
Time on TMZ (Median; Months)	7.2 (5.8-8.6)	Normal	Stupp et al. 2017 (2)
TMZ Dose Per Day	150 (120-180)	Normal	Stupp et al. 2017 (2)
Survival Data (0 – 5 Years)			
PFS HR	0.63 (0.52-0.76)	Log-normal	Stupp et al. 2017 (2)
OS HR	0.63 (0.53-0.76)	Log-normal	Stupp et al. 2017 (2)
Survival Data (5+ Years)			
Conditional Survival, Year 10	0.704 (0.56-0.84)	Beta	Porter et al. 2011 (104)
Conditional Survival, Year 15	0.840 (0.67-1.00)	Beta	Porter et al. 2011 (104)
Utility Data			
Progression-Free	0.823 (0.66-0.99)	Beta	Palmer et al. 2021 (68)
Progressed Disease	0.666 (0.53-0.80)	Beta	Palmer et al. 2021 (68)
Grade 3+4 AEs			
Optune plus TMZ			
Pulmonary Embolism	1.97 (1.58-2.36)	Beta	Stupp et al. 2017 (2)
Seizure	7.39 (5.91-8.87)	Beta	Stupp et al. 2017 (2)
Infections	4.93 (3.94-5.92)	Beta	Stupp et al. 2017 (2)
Leukopenia or Lymphopenia	5.42 (4.34-6.50)	Beta	Stupp et al. 2017 (2)
General Disorders*	8.37 (6.70-10.04)	Beta	Stupp et al. 2017 (2)
Thrombocytopenia	9.36 (7.49-11.23)	Beta	Stupp et al. 2017 (2)
TMZ alone			
Pulmonary Embolism	5.94 (4.75-7.13)	Beta	Stupp et al. 2017 (2)
Seizure	7.92 (6.34-9.50)	Beta	Stupp et al. 2017 (2)
Infections	4.95 (3.96-5.94)	Beta	Stupp et al. 2017 (2)
Leukopenia or Lymphopenia	4.95 (3.96-5.94)	Beta	Stupp et al. 2017 (2)
General Disorders*	4.95 (3.96-5.94)	Beta	Stupp et al. 2017 (2)
Thrombocytopenia	2.97 (2.38-3.56)	Beta	Stupp et al. 2017 (2)

*Table 8.2 Display of clinical parameters needed for the model, the base-case source, and the value. *costed as Fatigue. AEs, adverse events; CI, confidence interval; OS, overall survival; PFS, progression-free survival; TMZ, temozolomide; TTFields; tumor-treating fields.*

8.3.5.1 Use of epidemiological data

It is important to account for the impact of background mortality when estimating the long-term survival of patients. Background mortality refers to the mortality rate in the general population which in this model is used as a maximum value for the average GBM to ensure that they do not live longer than the average Dane.

To ensure accurate estimations of survival in economic models, corrections for background mortality are often applied. For more information see Appendix 11.5.

The Danish background mortality data utilized in this analysis were obtained from Statistics Denmark's Table HISB8 for the years 2020 and 2021 (see Table 8.3) (113). These data provide reliable and up-to-date information on mortality rates in the general Danish population.

General population mortality calculations							
Age	**Males**	**Females**	**Weighted**	**Age**	**Males**	**Females**	**Weighted**
0	0,0033	0,0030	0,0032	**50**	0,0025	0,0016	0,0021
1	0,0001	0,0001	0,0001	**51**	0,0028	0,0019	0,0024
2	0,0002	0,0001	0,0001	**52**	0,0030	0,0019	0,0026
3	0,0001	0,0000	0,0001	**53**	0,0036	0,0022	0,0030
4	0,0001	0,0001	0,0001	**54**	0,0044	0,0024	0,0036
5	0,0001	0,0000	0,0001	**55**	0,0046	0,0029	0,0039
6	0,0001	0,0000	0,0001	**56**	0,0050	0,0029	0,0042
7	0,0001	0,0001	0,0001	**57**	0,0064	0,0039	0,0054
8	0,0002	0,0000	0,0001	**58**	0,0060	0,0042	0,0053
9	0,0000	0,0000	0,0000	**59**	0,0077	0,0045	0,0064
10	0,0001	0,0001	0,0001	**60**	0,0081	0,0052	0,0070
11	0,0001	0,0002	0,0001	**61**	0,0079	0,0055	0,0069
12	0,0001	0,0001	0,0001	**62**	0,0098	0,0064	0,0084
13	0,0000	0,0001	0,0000	**63**	0,0118	0,0069	0,0098
14	0,0001	0,0000	0,0001	**64**	0,0120	0,0077	0,0103
15	0,0001	0,0000	0,0001	**65**	0,0139	0,0086	0,0118
16	0,0000	0,0001	0,0000	**66**	0,0145	0,0091	0,0124
17	0,0002	0,0001	0,0001	**67**	0,0162	0,0102	0,0138
18	0,0003	0,0001	0,0002	**68**	0,0171	0,0117	0,0149
19	0,0002	0,0001	0,0002	**69**	0,0184	0,0121	0,0159
20	0,0003	0,0003	0,0003	**70**	0,0209	0,0125	0,0175
21	0,0005	0,0003	0,0004	**71**	0,0220	0,0142	0,0189
22	0,0005	0,0003	0,0004	**72**	0,0241	0,0160	0,0208
23	0,0005	0,0001	0,0003	**73**	0,0255	0,0174	0,0223
24	0,0005	0,0002	0,0004	**74**	0,0293	0,0187	0,0251
25	0,0004	0,0002	0,0003	**75**	0,0317	0,0221	0,0279
26	0,0004	0,0002	0,0003	**76**	0,0346	0,0235	0,0302
27	0,0004	0,0003	0,0003	**77**	0,0406	0,0268	0,0351
28	0,0005	0,0002	0,0004	**78**	0,0407	0,0292	0,0361
29	0,0004	0,0003	0,0004	**79**	0,0463	0,0303	0,0399
30	0,0003	0,0002	0,0003	**80**	0,0523	0,0404	0,0475
31	0,0006	0,0004	0,0005	**81**	0,0605	0,0410	0,0527
32	0,0005	0,0003	0,0004	**82**	0,0650	0,0454	0,0572
33	0,0004	0,0003	0,0004	**83**	0,0745	0,0505	0,0649
34	0,0005	0,0004	0,0005	**84**	0,0832	0,0645	0,0757
35	0,0010	0,0004	0,0007	**85**	0,0977	0,0704	0,0868
36	0,0007	0,0005	0,0006	**86**	0,1052	0,0823	0,0960
37	0,0009	0,0004	0,0007	**87**	0,1219	0,0935	0,1105
38	0,0009	0,0006	0,0008	**88**	0,1315	0,1042	0,1206
39	0,0008	0,0006	0,0007	**89**	0,1529	0,1110	0,1361
40	0,0010	0,0005	0,0008	**90**	0,1710	0,1264	0,1532
41	0,0010	0,0005	0,0008	**91**	0,1798	0,1411	0,1643
42	0,0013	0,0009	0,0012	**92**	0,1969	0,1553	0,1802
43	0,0011	0,0008	0,0010	**93**	0,2167	0,1789	0,2016
44	0,0014	0,0010	0,0012	**94**	0,2364	0,1932	0,2191
45	0,0013	0,0010	0,0012	**95**	0,2657	0,2006	0,2396
46	0,0015	0,0009	0,0013	**96**	0,2556	0,2126	0,2384
47	0,0018	0,0008	0,0014	**97**	0,2773	0,2324	0,2593
48	0,0021	0,0011	0,0017	**98**	0,3141	0,2712	0,2970
49	0,0025	0,0016	0,0021	**99**	0,3810	0,2515	0,3292

Table 8.3 Danish background mortality data (113).

Porter et al. (2011) was selected to represent base-case survival from model years five to 15 because of (a) the availability of estimates up to year 15, (b) its large, homogeneous population composed of 100% pre-TMZ patients, and (c) follow-up maturity versus the relative immaturity of 10+ year data from studies that included TMZ era patients (104). Porter et al. (2011) examined primary malignant and nonmalignant brain tumor cases diagnosed from 1985 to 2005 from selected SEER state cancer registries, including 5,991 GBM patients. This study provided conditional survival probabilities up to years ten and fifteen given survival to years five and ten, respectively. Unlike Polley et al. (101), the patient population was composed of 100% pre-TMZ patients and the long-term follow-up data was more mature; therefore, the conditional survival probabilities estimates are not affected by data cutoff issues. For GBM patients, the probability of surviving to ten years and 15 years given survival to five years and ten years was 70.4% (95% CI 55.6 to 81.2) and 84.0% (95% CI 38.9 to 96.8), respectively. Identical trends were seen for most other tumor groups and for 15-year survival conditioned on having survived five and ten years since diagnosis.

Variable	Study period	Mean probability value (95% CI)	Reference	Probability distribution
Conditional Survival, Year 10	1985-2005	0.704 (0.56-0.84)	Porter et al. 2011 (104)	Beta
Conditional Survival, Year 15	1985-2005	0.840 (0.67-1.00)	Porter et al. 2011 (104)	Beta

Table 8.4 Overview of epidemiological data used in the health economic analysis (104).
CI, confidence interval.

8.3.5.2 Use of data from clinical trials

The EF-14 trial by Stupp et al. (2017) is the largest multinational trial of TTFields therapy. In the final analysis of the trial of patients with GBM who had received standard radiotherapy, the addition of TTFields to TMZ vs TMZ alone resulted in statistically significant improvement in PFS and OS (2). These results are consistent with the previous interim analysis (106). The combination therapy trended towards higher effectiveness, as evidenced by improved OS outcomes. The trial results indicate that Optune plus TMZ offers potential advantages in terms of efficacy when compared to TMZ alone. Besides similarity in safety, a clinical expert has also validated that the patient pathway from diagnosis to treatment, treatment monitoring, etc. is expected to be similar for the two treatments in Danish clinical practice.

Treatment with Optune plus TMZ was associated with AEs such as pulmonary embolism, seizures, and infections advantages over TMZ alone. However, TMZ alone was associated with AEs such as leukopenia or lymphopenia, general disorders, and thrombocytopenia advantages over Optune plus TMZ.

8.3.5.3 Use of proxy outcome measures

N/A

8.3.5.4 Transformation of data

To incorporate these background mortality rates into the survival estimates, they need to be converted into probabilities. The formula used for this conversion is $1 - EXP^{(-rate)}$, where the rate represents the mortality rate per unit of time (e.g., per year) to estimate the probability of surviving each subsequent year. By applying this formula, the mortality rate is transformed into a probability of survival for a given time period.

8.3.5.5 Changes in probabilities over time

N/A

8.3.5.6 Extrapolation of data

The survival data used for this model was solely based on Stupp et al. trial data (2). We employed various parametric functions, such as exponential, Weibull, log-logistic, and log-normal distributions, to fit the Stupp et al. trial PFS and OS Kaplan-Meier data (see Figures 8.2 and 8.3). The goodness of fit for these regression

models was assessed using the Akaike Information Criterion (AIC) and face validity evaluation, following the published methods for extrapolation of survival data (163).

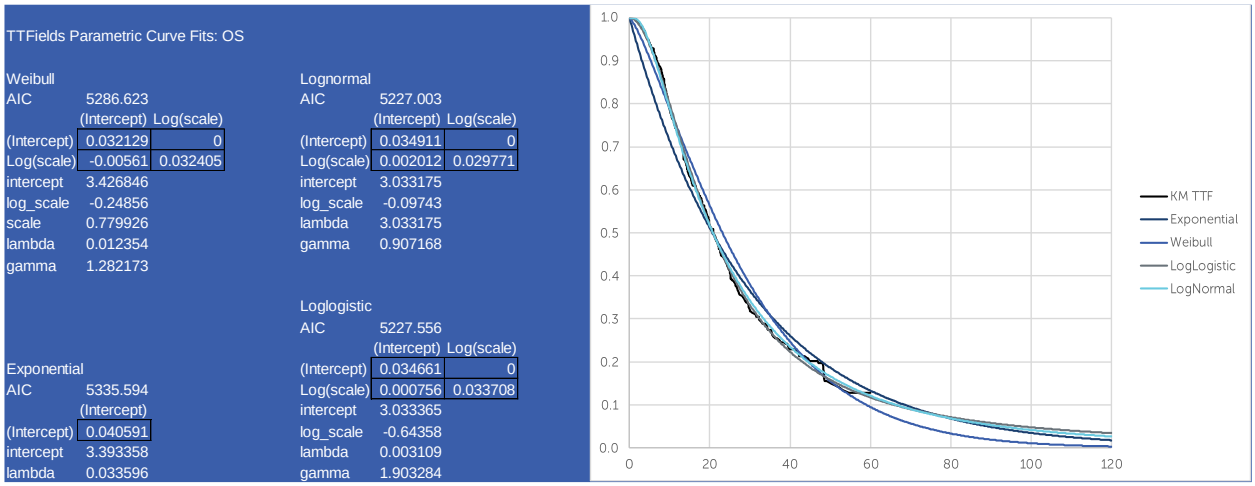


Figure 8.2 Survival data used for the model and parametric function fit of OS for Optune plus TMZ group.
AIC, Akaike Information Criterion; KM, Kaplan-Meier; OS, overall survival; TTFields, tumor-treating fields.

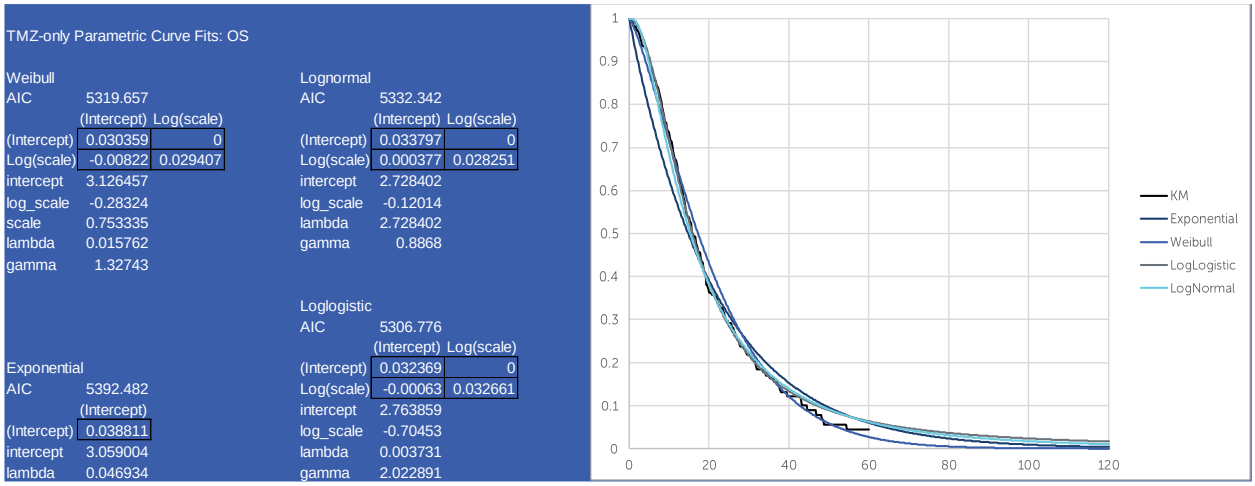


Figure 8.3 Survival data used for the model and parametric function fit of OS for TMZ alone group.
AIC, Akaike Information Criterion; KM, Kaplan-Meier; OS, overall survival; TMZ, temozolomide; TTFields, tumor-treating fields.

However, we observed that the resulting OS curves underestimated the 5-year OS compared to both the Stupp et al. trial data and epidemiological data, which led us to reject these curves based on face validity considerations. Additionally, the assumption of proportional hazards was tested for the PFS and OS curves by plotting log-cumulative hazards, specifically, log(time) vs. log(–log(S(time))). The log-cumulative hazards plots of the Stupp et al. survival data converged over time, indicating that the proportional hazards assumption was not appropriate for the base case analysis.

Furthermore, the survival estimates generated by the regression-based parametric models were inconsistent with both the Stupp et al. data and epidemiological data. These models did not account for a high hazard of death initially, followed by a lower hazard for long-term survivors, which was evident in both the Stupp et al. data and the outcomes reported by Porter et al. (2011) (2,104). Moreover, the parametric models estimated a higher hazard of death after year five for patients treated with TTFields plus TMZ compared to those treated with TMZ alone, which contradicted the Stupp et al. Kaplan-Meier survival data that reported lower mortality rates for TTFields-treated patients throughout the trial period. This discrepancy can be attributed to the inherent constant hazard function in regression-based statistical parametric models, which was not observed in Stupp et al. or previous analyses of GBM survival data (2,101).

Given the inability of the aforementioned approaches to accurately replicate both the Stupp et al. trial and long-term OS outcomes and the availability of epidemiological data, we adopted a three-phase approach to model the mean lifetime survival. This approach integrated the following components: (a) the Stupp et al.trial data up to year five (2), (b) long-term conditional survival probabilities from the epidemiological literature up to year 15 (104), and (c) Danish background mortality for patients who survived beyond year 15 (113). This multi-segment approach has been previously employed when combining clinical trial data with long-term epidemiology data (164). The Stupp et al. trial Kaplan-Meier curves for OS were directly incorporated in the first phase without curve fitting. In the second phase, the long-term conditional survival probabilities from Porter et al. (2011) were converted to weekly mortality probabilities.

For PFS data, we directly incorporated the Stupp et al. trial data into the model and utilized a parametric function to extrapolate survival beyond the available data. The choice of the Weibull distribution was based on its best fit according to AIC testing, given the lack of epidemiology reports on PFS outcomes. For PFS data, several parametric functions were considered initially, including exponential, Weibull, log-logistic, and log-normal distributions, for fitting the PFS data. The model assessment revolved around two key criteria: the Akaike Information Criterion (AIC) and face validity. The AIC helped select the most appropriate parametric function. At the same time, the face validity ensured that the chosen curves aligned with clinical expectations, particularly regarding the 5-year PFS rates, when compared to the EF-14 trial data and relevant epidemiological data. Any PFS curves that failed to meet the face validity criteria, notably those under-estimating 5-year PFS rates, were systematically rejected. To mitigate the lack of epidemiological reports on PFS outcomes, PFS data was directly incorporated from the EF-14 trial. The choice of a parametric function for extrapolation was based on statistical testing, leading to the selection of the Weibull distribution due to its superior fit according to the AIC. This comprehensive methodology ensured the accurate representation and projection of PFS outcomes within the EF-14 trial.

8.3.6 Measurement of outcomes

The health outcomes considered in this model encompass several key measures, including the expected lifetime cost, LYs and QALYs per average patient with and without Optune, and ICER. In the CUA, QALYs serve as the effectiveness measure, providing a comprehensive assessment of overall HRQoL by capturing not only the quantity or duration of life but also the quality of life experienced by patients during that time. This approach accounts for various factors that may influence health outcomes, such as the negative impact of side effects associated with the treatments.

The primary objective of the analysis is to assess the maximum QALY loss or gain while considering the economic implications of utilizing Optune plus TMZ compared to TMZ alone. The ICER, which compares the incremental costs to the incremental QALYs and LYs, is used to assess the cost-effectiveness of Optune plus TMZ relative to TMZ alone.

8.3.6.1 Cost-consequence and cost-effectiveness analyses

N/A

8.3.6.2 Cost-utility analysis

A CUA was performed to evaluate the cost-effectiveness of Optune plus TMZ compared to maintenance TMZ alone for patients with ndGBM. The analysis was conducted from the perspective of the Danish healthcare system, considering relevant costs and health outcomes specific to the Danish context.

To capture the dynamic nature of the disease progression and treatment response, a partition survival model was employed. This modeling approach allows for the representation of three distinct health states: progression-free/stable, progression/progressed disease, and death. Patients transitioned between these states based on their disease status and the treatment received.

The analysis considered various factors, including the total expected costs, LYs, and QALYs, for each treatment option. The total expected costs encompassed both direct medical costs associated with treatment, monitoring, and management of adverse events, as well as other relevant healthcare costs. LYs represented the total number of years lived by patients in each treatment arm, while QALYs incorporated the health-related quality of life during those years, considering the impact of treatment-related side effects.

The ICER was calculated as the difference in costs between Optune plus TMZ and TMZ alone, divided by the difference in QALYs and LYs. This ratio provides a quantitative measure of the additional cost required to gain an additional unit of the health benefit with Optune plus TMZ compared to maintenance TMZ alone.

8.3.6.2.1 HRQoL for Optune

A search of the literature was conducted to identify relevant utility data for patients with GBM. Four sources of utility weights: Messali et al. (2013) (99); Wu et al. (2012) (108); Garside et al. (2007) (12); and Martikainen et al. (2005) (97). Among these studies, both Wu et al. and Messali et al. derived their utility weights from Garside et al., which was a health technology assessment commissioned by NICE in the UK (12). Martikainen et al. utilized proxy respondents using a VAS method. Disutilities are not included in the model due to the low frequency of AEs (see the detailed description of the safety profile in Chapter 5) (2,87).

The utility values utilized in this study were obtained by applying the Danish QALY weights (Jensen et al. 2021) to the EQ-5D scores reported by Palmer et al. (2021). We believe this is a better approach because it relies on Danish utilities and best available evidence of HRQoL at different disease states.

For our analysis, it was assumed that the addition of Optune did not impact the utility values. Specifically, the utility value for patients in a stable condition receiving TMZ alone or TMZ plus Optune was estimated to be 0.823. On the other hand, patients with progressed disease were assigned a utility value of 0.666.

8.3.6.2.2 Data basis for the impact on health-related quality of life

Health state/event	Preference weight, avgerage (95% CI)	Instrument and value set	Probability distribution	Mapping used	Comment	Reference
PFS	0.823 (0,66 – 0,99)	TTO	Beta	No	DK setting	Palmer et al. 2021
Progressive Disease	0.666 (0,53 – 0,8)	TTO	Beta	No	DK setting	Palmer et al. 2021

Table 8.5 List of preference weights ascribed to health states and events (12).
CI, confidence interval; SG, standard gamble; TMZ, temozolomide; UK, United Kingdom.

8.3.7 Cost statement

In the following section, costs included in the health economic analyses are described. The cost included in this model follows the DHTC's methodological guidelines and the cost estimates are based on the best possible evidence from published literature, DRG rates, data from Novocure regarding the costs of Optune, etc. The model takes into account the costs and health outcomes associated with the use of Optune and TMZ including the treatment costs of Optune and TMZ, costs of AEs associated with initial treatments, medical costs, and supportive care costs for progression-free disease and post-progression.

Drug costs were obtained from the Danish Medicines Agency's list of current medicinal product prices in 2022. We assumed an average body weight of 86 kg and an average height of 180 cm. Hospital-related treatment costs were identified from the Danish diagnosis-related groups (DRG) tariffs for 2022. We have not conducted price adjustments. Costs associated with treatment and use of Optune are presented in Table 8.6. Costs related to AEs are provided in Table 8.7.

8.3.7.1 Costs of using Optune and TMZ

Cost component	Cost per patient, DKK (95% CI)	Probability distribution	Annuitized	Allocated	Reference

Optune					
Per month TTFields	156,000 (109,200-202,800)	Gamma	N/A	N/A	Converted from UK cost
Others per month	1,703 (1,362-2,044)	Gamma	N/A	N/A	Behandlingsrådet 2023
Per treatment duration, TTFields (8.2 months)	1,279,200 (895,440-1,662,960)	Gamma	N/A	N/A	Converted from UK cost
Per treatment duration, others (8.2 months)	13,965 (11,172-16,758)	Gamma	N/A	N/A	Behandlingsrådet 2023
TMZ					
Per month	2,288 (1,830-2,745)	Gamma	N/A	N/A	Danish Medicines Agency 2022
Per treatment duration (7.2 months)	16,474 (13,176-19,764)	Gamma	N/A	N/A	Danish Medicines Agency 2022

Table 8.6 Costs of using Optune and its comparator, TMZ.
CI, confidence interval; DKK, Danish Kroner; N/A, not applicable; TMZ, temozolomide; UK, United Kingdom.

The list price of Optune includes several components including Device Support Specialist (DSS) services and Optune device system. The DSSs offer technical training to GBM patients and their caregivers at no additional cost. Novocure offers treatment with the Optune treatment kit for a flat monthly fee of 156,000 DKK + VAT. It is assumed that the patient will need assistance with Optune and that 90% of the patients will get the assistance from relatives and that 10% will get assistance from the municipality. This assumption is based on experiences from Sweden. These costs can be seen in table 8.6 as "others", both listed per months and per treatment duration (8.2 months). The component include nurse home care and patients and relatives home care. The Optune treatment kit contains all technical components for one-month of treatment:

- Rental fee for unrestricted use of the electric field generator.
- Supply of required (unlimited) INE transducer arrays for 1 month at a time.

In addition, the following services and supplements are included:

- Individual planning of the INE Transducer Array treatment layout specific to each tumor (per patient) by trained radiologists.
- On-site patient education and 24/7 technical support by phone from Novocure device support specialists (DSS), both at initial application and throughout the duration of therapy.
- Monthly meeting of the patient with the Novocure device support specialist (DSS).
- Ongoing maintenance as needed of the electric field generator with device replacement if required.
- Download and process the treatment information from the device.
- Transmission of data on therapy conformity to the attending physician

8.3.7.2 Costs associated with health conditions and events

The base-case scenario includes a weekly cost of supportive care for PFS and progressed disease health states. Table 8.7 presents costs associated with health conditions and events, along with a brief explanation of what the cost estimate includes.

A search of the literature was undertaken to examine the cost of progressed GBM. The method by which progressed disease was calculated for each of the studies was also examined. The search found five relevant studies with information related to the cost and or costing of progressed GBM.

The most relevant studies were the Kovic et al. (2015) (92) and Lamers et al. (2008) (94). The study by Lamers et al. was an economic analysis alongside a clinical trial, while the Kovic et al. study was a Canadian cost-effectiveness model, which utilized resource utilization data from the Lamers et al. (92,94). Based on these results our approach to calculating supportive care costs is outlined below.

The cost of supportive care was divided into both the progression-free and progressed disease states. Both sets of costs for supportive care take a micro-costing approach.

Health state/event	Cost component	Valuation, DKK 95% (CI)	Probability distribution	Utilization rate (3 months)		Reference
				Active	After active	
Progression-Free	Physician Visit	3,618	N/A	1,00	0,67	DRG Group 2022: 01MA98 MDC01 1-dagsgruppe, pat. mindst 7 år.
	Lab Tests	87	N/A	3,00	0,67	Agreement on General Good Practice, 2022. Fee schedule.
	MRI scanning	2,057	N/A	1,00	0,67	DRG Group 2022: 30PR03 MR-scanning, ukompliceret
	CT scanning	1,979	N/A	0,00	0,00	DRG Group 2022: 30PR07 CT-scanning, ukompliceret, el. Osteodensitometri
	Hospitalization	5,074	N/A	0,25	0,25	DRG Group 2022: 27MP04 Radiotherapy, complex, 1 fraction, 27MP10 Stereotaksi and 27PR01 Protonterapi
	Neurosurgery	0	N/A	0,00	0,00	Captured within physician visit
	Total cost per week, during active treatment	**392 (314-470)**	**Gamma**	N/A	N/A	
	Total cost per week, after active treatment	**553 (442-663)**	**Gamma**	N/A	N/A	
Progressed Disease	Physician Visit	3,618	N/A	N/A	1,00	DRG Group 2022: 01MA98 MDC01 1-dagsgruppe, pat. mindst 7 år.
	Lab Tests	87	N/A	N/A	1,00	Agreement on General Good Practice, 2022. Fee schedule.
	MRI scanning	2,057	N/A	N/A	1,00	DRG Group 2022: 30PR03 MR-scanning, ukompliceret
	CT scanning	1,979	N/A	N/A	0,00	DRG Group 2022: 30PR07 CT-scanning, ukompliceret, el. Osteodensitometri
	Hospitaitalization					
	Palliative	0	N/A	N/A	0,00	Captured in end-of-life cost
	ICU	454,781	N/A	N/A	0,05	DRG Group 2022: 26MP10 - Intensiv gruppe I: Simpelt organsvigt i et eller to organer and 26MP08 - Intensiv gruppe IV: Alvorligt multiorgansvigt
	Other	136,988	N/A	N/A	1,08	DRG Group 2022: 26MP17 Kranie- og vaskulærkirugi, ukompliceret
	Total cost per week, after active treatment	**13,549 (10,839-16,259)**	**Gamma**	N/A	N/A	

AEs	Pulmonary Embolism	22,502 (18,114-27,171)	Gamma	N/A	N/A	DRG Group 2022: 05MA12 Perifer karsygdom
	Seizure	24,572 (19,770-29,665)	Gamma	N/A	N/A	DRG Group 2022: 01MA18 Observation for sygdom i nervesystemet
	Infections	33,306 (26,757-40,135)	Gamma	N/A	N/A	Calculated Table 8.8
	Leukopenia or Lymphopenia	25,419 (20,448-30,617)	Gamma	N/A	N/A	DRG Group 2022: 16MA10 Øvrige sygdomme i blod og bloddannende organer
	General Disorders*	34,288 (27,543-41,314)	Gamma	N/A	N/A	DRG Group 2022: 23MA02 Symptomer og fund, m. kompl. Bidiag
	Thrombocytopenia	38,408 (30,839-46,258)	Gamma	N/A	N/A	DRG Group 2022: 16MA03 Granulo- og trombocytopeni

Table 8.7 Identification and quantification of cost components associated with different health states and events included in the health economic model.
**Cost as Fatigue*
AEs, adverse events; CI, confidence interval; CT, computer tomography; DKK, Danish Kroner; ICU, intensive care unit; MRI, magnetic resonance imaging; N/A, not applicable.

Infections	Proportion	Source	Unit cost, DKK	Source
Pneumonia	50,00%	Assumption	30,912	DRG Group 2022: 04MA14 Lungebetændelse og pleurit, pat. 18-59 år
Surgical site infection	50,00%	Assumption	35,699	DRG Group 2022: 18MA03 Postoperative og posttraumatiske infektioner, u. kompl. Faktorer

Table 8.8 Estimates of average cost of infections related to the treatment of ndGBM patients.
DKK, Danish Kroner.

8.3.7.3 Limitations of the cost statement

In the absence of real-world cost or healthcare resource utilization rate data in Denmark, the healthcare resource utilization rates reported by Kovic et al. (92) and DNOG (6) were applied to DRG costs in Denmark. The main limitation of this approach is the expectation that real-world patients with GBM in Denmark potentially may consume resources at a different rate than patients that were: a) involved in a clinical trial, and b) located in Austria, Switzerland, Germany, Canada, or the Netherlands. However, due to the data gap, this method of localizing healthcare resource utilization and costs to Denmark is deemed acceptable. Core assumptions were validated by clinical experts and DNOG.

8.3.8 Result of the economic analysis

In the following section, the results of the health economic analyses are presented. First, the evaluation of the health economic model used to conduct the analyses is described. Then, the results of the analyses are presented, followed by the results of the sensitivity analyses that have been performed.

8.3.8.1 Base-case results

The base-case analysis was conducted using the settings for the input parameters and assumptions as described in the previous sections. The expected mean lifetime survival of patients treated with Optune and TMZ was 3.27 years with an incremental LY gain of 1.21 compared to treatment with TMZ alone. The average expected QALYs for patients treated with Optune and TMZ was estimated to be 2.34 with a QALY gain of 0.85 compared to patients treated with TMZ alone. The use of Optune plus TMZ was associated with an incremental cost of DKK 1.5 Mio per patient compared to TMZ alone.

	Optune plus TMZ	TMZ alone
Costs		
Optune cost, total	1,399,195 DKK	0 DKK
TMZ cost, total	42,364 DKK	37,657 DKK
PFS and AEs costs, total	38,637 DKK	27,336 DKK
Progressed costs, total	1,548,134 DKK	918,711 DKK
Other costs, total	14,270 DKK	0 DKK
End-of-life costs, total	55,912 DKK	58,605 DKK
TOTAL COSTS	3,098,514 DKK	1,042,309 DKK
Outcomes		
QALYs	2.34	1.49
LYs	3.27	2.06

Table 8.9 List of costs broken down by sectors and outcomes associated with the examined interventions in the economic analysis. AEs, adverse events; DKK, Danish Kroner; LYs, life years; QALYs, quality-adjusted life years; l; PFS, progression-free survival; TMZ, temozolomide.

Costs in the Optune plus TMZ arm were driven by the cost of Optune. The cost of TMZ, PFS and AEs, progressed disease, and other costs were higher for Optune plus TMZ compared to TMZ alone. These higher costs on the Optune plus TMZ arm were driven by increased survival (TMZ drug cost, PFS costs, and progressed disease costs) and slightly higher costs attributed to AEs. The majority of the cost are located within the regional sector.

Health Outcomes were higher for Optune plus TMZ compared to TMZ alone. Total LYs were 1.20 LYs higher for Optune plus TMZ compared to TMZ alone. Total QALYs were 0.85 QALYs higher for Optune plus TMZ compared to TMZ alone.

The ICER was calculated for Optune plus TMZ vs. TMZ alone using both LYs and QALYs. The estimated ICER was DKK 2.4 million per QALY gained and DKK 1.7 million per LY gained (See Tables 8.10a and 8.10b).

Intervention	Total cost, DKK	Outcome measure, LYs	ΔC, DKK	ΔE, LYs	ICER, DKK/LYs	Statement of dominance
			Vs. relevant comparator			
Optune plus TMZ	3,098,514	3.27	-	-	-	N/A
TMZ alone	1,057,889	2.06	2,040,625	1.20	1,697,942	N/A

Table 8.10a Result of the health economic analysis of cost per LY.
C, cost; DKK, Danish Kroner; E, effect; ICER, incremental cost-effectiveness ratio; LYs, life years; N/A, not applicable; TMZ, temozolomide.

Intervention	Total cost, DKK	The outcome measure, QALYs	ΔC, DKK	ΔE, QALYs	ICER, DKK/QALYs	Statement of dominance
			Vs. relevant comparator			
Optune plus TMZ	3,098,514	2.34	-	-	-	N/A
TMZ alone	1,057,889	1.49	2,040,625	0.85	2,392,874	N/A

Table 8.10b Result of the health economic analysis cost per QALY.
C, cost; DKK, Danish Kroner; E, effect; ICER, incremental cost-effectiveness ratio; N/A, not applicable; QALYs, quality-adjusted life years; TMZ, temozolomide.

8.3.8.2.1 Survival calculations

The OS and PFS curves are shown in five-year time horizons (see Figures 8.4 and 8.5 below).

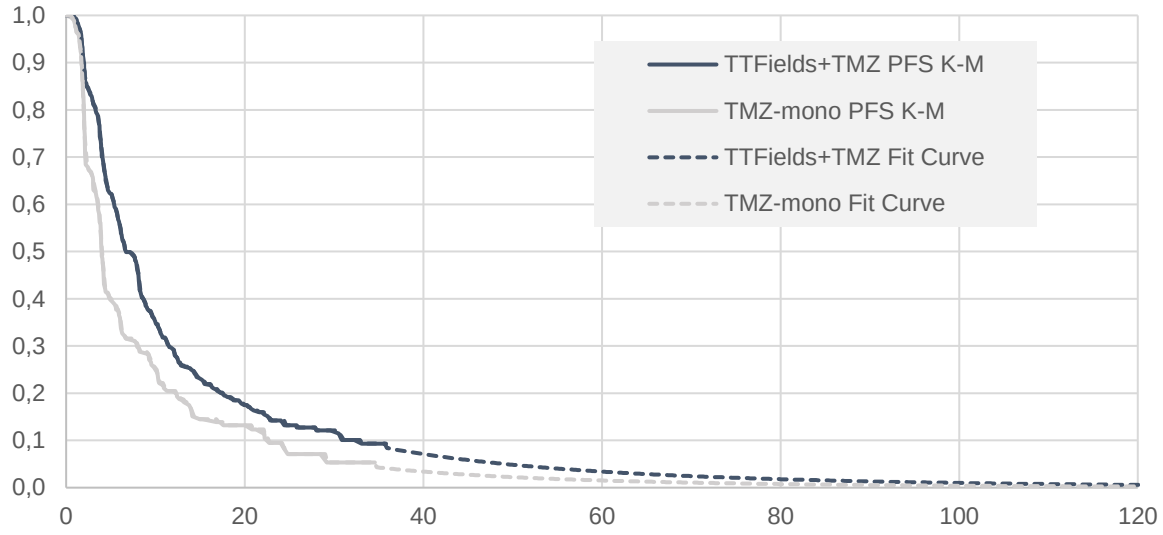


Figure 8.4 PFS curve shown in a ten-year time horizon.
K-M, Kaplan-Meier; PFS, progression-free survival; TMZ, temozolomide; TTFields, tumor-treating fields.

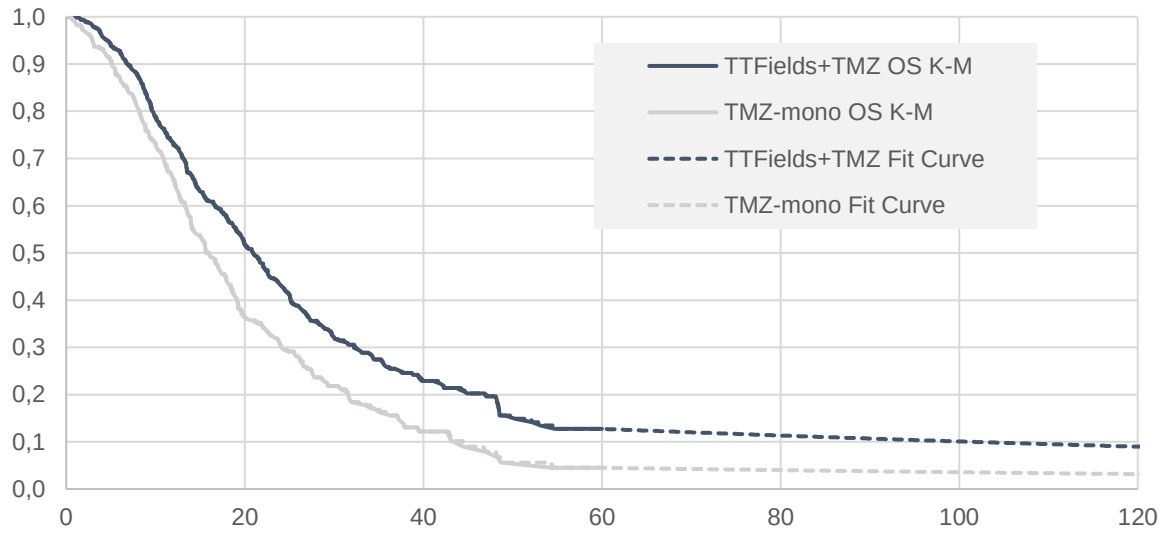


Figure 8.5 OS curve shown in a ten-year time horizon.
K-M, Kaplan-Meier; OS, overall survival; TMZ, temozolomide; TTFields, tumor-treating fields.

The long-term survival calculation is presented in Figure 8.6. At year 20 the Optune plus TMZ arm had 6.7% of patients alive compared to 2.4% for the TMZ alone arm.

Survival		
	TTFields + TMZ	**TMZ Monotherapy**
Year 0	**100%**	**100%**
Year 5	**12,7%**	**4,5%**
Year 10	**9,0%**	**3,2%**
Year 15	**7,5%**	**2,7%**
Year 20	**6,7%**	**2,4%**
Year 25	**5,5%**	**1,9%**
Year 30	**3,9%**	**1,4%**
Year 35	**2,0%**	**0,7%**
Year 40	**0,7%**	**0,2%**

Figure 8.6. Long-term survival calculations.
TMZ, temozolomide; TTFields, tumor-treating fields.

8.3.8.2 Sensitivity analyses

In this section the results of the OWSAs and the PSA will be presented including the five OWSAs specified in the evaluation design by the DHTC. These OWSAs results will be presented compared to the base-case result.

It is important to emphasize that Optune is a case that corresponds to the paradox of not cost effective at zero price. This entails that no matter how low the price will be for Optune, it will never be considered cost-effective within the traditional view of Willingness to pay (160,161). Such an example will be shown in one of the following sensitivity analyses.

8.3.8.2.1 Sensitivity analysis 1

The model was modified so that the Cost of Optune range for the OWSA is ±30%. The results are shown in Table 8.11 below:

	-30%	Base (DKK 156,000)	+30%
Base-case	DKK 1,775,908	DKK 2,392,874	DKK 2,614,557

Table 8.11 Results of sensitivity analysis 1.
DHTC, Danish Health Technology Council; DKK, Danish Kroner.

8.3.8.2.2 Sensitivity analysis 2

The base-case assumption was a time horizon of 40 years. In sensitivity analysis 2 we change this assumption to five years; all other variables remain the same (see Table 8.12).

	5 years	Base (40 years)
Base-case	DKK 4,579,203	DKK 2,392,874

Table 8.12 Results of sensitivity analysis 2.
DHTC, Danish Health Technology Council; DKK, Danish Kroner.

8.3.8.2.3 Sensitivity analysis 3

The impact of varying survival by ±20% is approximated in Table 8.13 below:

	-20%	Base	+20%
Base-case	DKK 2,627,853	DKK 2,392,874	DKK 2,195,232

Table 8.13 Results of sensitivity analysis 3.
DHTC, Danish Health Technology Council; DKK, Danish Kroner.

8.3.8.2.4 Sensitivity analysis 4

ICER results corresponding to different levels of compliance to the TTFields treatment are in Table 8.14 below:

Base-case		
	ICER	Δ vs. overall
Overall	DKK 2,392,874	
50-60 usage	DKK 2,375,909	-0.7%
60-70 usage	DKK 2,588,088	8.2%
70-80 usage	DKK 2,371,121	-0.9%
80-90 usage	DKK 2,131,872	-10.9%
>50 usage	DKK 2,155,791	-9.9%
>90 usage	DKK 1,526,587	-36.2%

Table 8.14 Results of sensitivity analysis 4.
DHTC, Danish Health Technology Council; DKK, Danish Kroner; ICER, incremental cost-effectiveness ration.

8.3.8.2.5 Sensitivity analysis 5

N/A in this updated version.

8.3.8.2.6 Deterministic sensitivity analysis

The OWSAs showed that the model results were most sensitive to the treatment duration of Optune followed by the monthly cost of Optune, and health state utility values for progressed disease and PFS. Figure 8.7 presents a tornado diagram with the results of selected OWSAs.

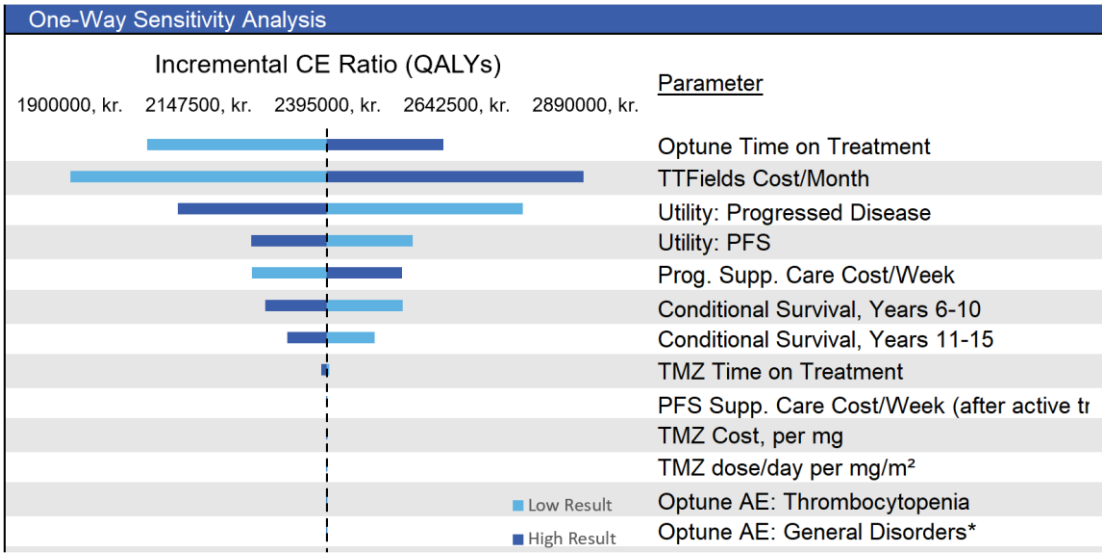


Figure 8.7 Tornado diagram presenting the results of selected OWSAs.
AE, adverse event; Kr, Kroner (Danish); PFS, progression-free survival; TMZ, temozolomide; TTFields, tumor-treating fields.

8.3.8.2.7 PSA

The PSA was performed using 3,000 Monte Carlo simulations. The results of the PSA are presented in the form of a cost-effectiveness scatterplot and CEAC in Figures 8.8 and 8.9.

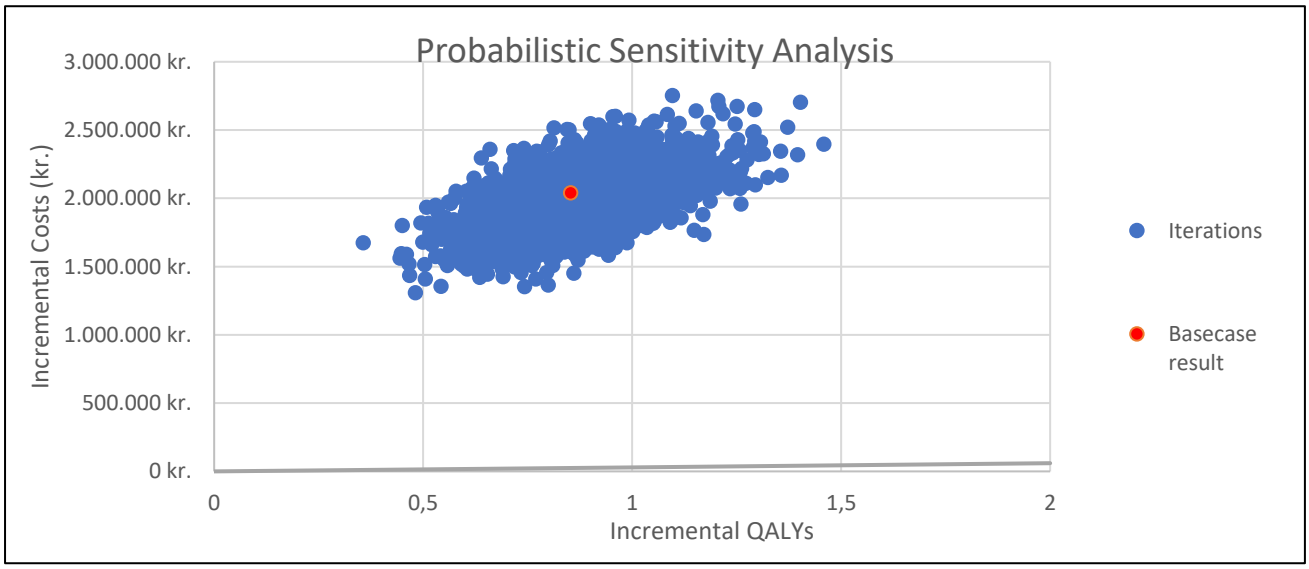


Figure 8.8 Cost-effectiveness scatterplot.
Kr, Kroner (Danish); QALYs, quality-adjusted life years.

All of the simulations are located within the northeast quadrant, which correlates with an intervention that is more effective and more costly than the comparator which is the case of Optune plus TMZ compared to TMZ alone.

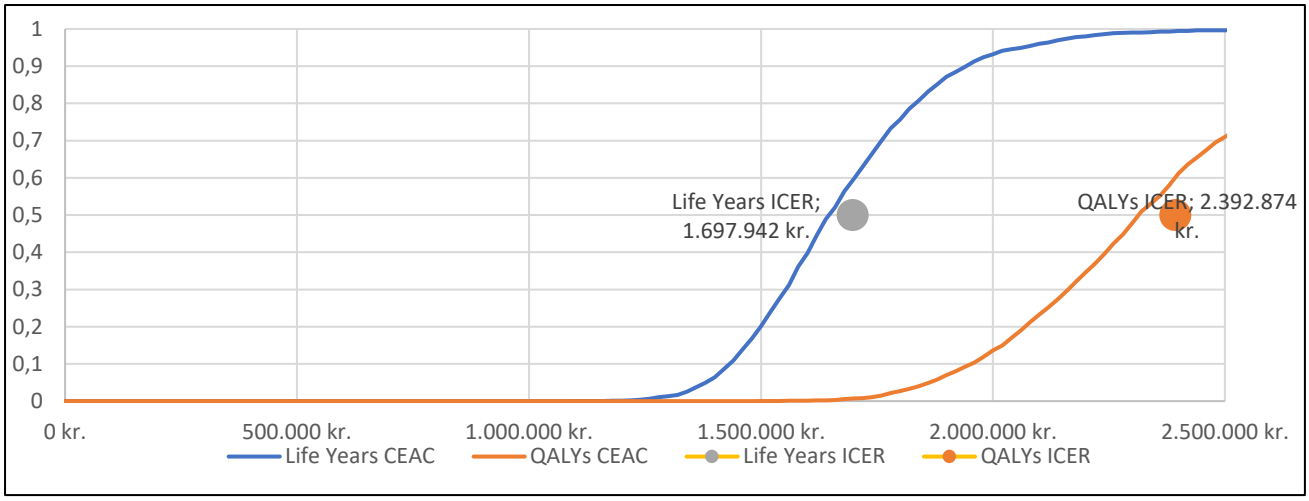


Figure 8.9 Cost-effectiveness acceptability curve.
CEAC, cost-effectiveness acceptability curve; Kr, Kroner (Danish); ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years.

8.3.8.2.8 Sensitivity analysis 6

In this sensitivity analysis, the model has been modified to illustrate the ICER if Optune is priced at zero, compared with the base case. The results are shown in Table 8.11 below:

	DKK 0	Base (DKK 156,000)
Base-case	DKK 752,152	DKK 2,392,874

Table 8.16 Results of sensitivity analysis 6.
DHTC, Danish Health Technology Council; DKK, Danish Kroner.

This sensitivity analysis illustrates that Optune would likely still not be considered cost effective, even priced at zero. This signifies that Optune corresponds to the paradox of not cost effective at zero price. This can largely be attributed to additional costs associated with keeping grade 4 glioma patients alive for a longer period of time.

8.3.8.3 Sub-group analyses

N/A

8.3.8.3.1 Sub-group analysis 1

N/A

8.3.8.3.2 Sub-group analysis 2

N/A

8.3.9 Interpretation of the economic analysis

The value of incorporating Optune into the treatment of patients with ndGBM, as demonstrated in this model, lies in the improvement in long-term survival. When Optune is added to maintenance TMZ, there is a substantial increase in both the estimated mean lifetime survival and quality-adjusted survival for these patients. The health economic evaluation conducted indicates that the use of Optune plus TMZ is associated with an ICER of DKK 2.4 million per QALY gained and DKK 1.7 million per LY gained, compared to TMZ alone.

It is important to note that the results of the analysis are sensitive to certain factors, namely the treatment duration of Optune followed by the supportive care cost associated with progressed disease, and the monthly cost of Optune. These factors have an impact on the cost-effectiveness of using Optune in combination with TMZ.

By considering the ICER and the sensitivity of the results treatment duration and monthly cost of Optune, this provides insights into the economic implications of incorporating Optune into the treatment regimen for ndGBM patients. It offers valuable information to healthcare decision-makers and stakeholders when considering the adoption and reimbursement of Optune in clinical practice.

8.4 Budget impact analysis

A BIA was carried out as per DHTC recommendation. The BIA reflects the estimated budgetary consequences for Danish hospitals if the DHTC recommends a national implementation of Optune as a treatment tool for adult patients with ndGBM. The BIA specifically focuses on exploring the budget impact of introducing Optune in combination with maintenance therapy using TMZ for patients who have undergone surgery followed by radiotherapy plus TMZ. The BIA assesses the budgetary consequences of implementing Optune across the entire Danish patient population with ndGBM, irrespective of their regional affiliation. The analysis takes into account the specific characteristics and requirements of the Danish healthcare system. Patients' own costs are not included, and the costs are not discounted.

The methodology employed in the BIA is described in detail in the subsequent sections. The underlying assumptions and uncertainties in the analysis are also outlined. To complement the results of the BIA, a series of sensitivity analyses were conducted to test the robustness of the findings and evaluate the impact of different assumptions on budgetary outcomes.

In addition to the cost-effectiveness model, a BIA was developed to calculate the projected population-level overall costs of Optune in adults with ndGBM from the healthcare perspective. The BIA was built as an extension of the CUA model. Hence, the BIA model is based on the same data and assumptions as the CUA model. The time horizon of the BIA model will be restricted to five years. For the BIA, the results reflect the potential use of Optune in adults with ndGBM in Denmark. Data on population size represents the best available evidence.

8.4.1 Patient population

The BIA conducted follows the methodological guidelines provided by DHTC. The analysis considers a five-year period, specifically from 2025 to 2029. In accordance with the DHTC's evaluation design, this BIA focuses on adult patients aged 18 years and above, with a median age of 56 years (ranging from 19 to 80 years).

The gross incidence of GBM in the Danish population, reported by the DNOG, is 315 new cases annually (5). As mentioned in Section 3.1.3, 161 patients out of the 315 diagnosed with grade IV glioma completed the entire course of surgery and subsequent radiotherapy and were able to start adjuvant TMZ chemotherapy (4,5). According to DHTC, the patient population size eligible for treatment with Optune is estimated to be 161 annually corresponding to 51.1% of the total number of new cases. However, the DHTC estimates that around 33% of eligible patients will opt out of treatment with Optune before treatment could potentially be initiated, leaving approximately 113 patients that will receive Optune treatment. This corresponds to a 66,1% market uptake over the 5-year period. This is based on historical market uptake in other markets, as well as internal market research. Furthermore, we assume that 25 physicians and 25 nurses (estimated high to be conservative), per year need a one hour training each.

Using these data, we assume that 113 GBM patients are eligible for Optune treatment in the first year of national implementation, gradually increasing to more than 230 GBM patients after three to five years.

These estimates are crucial for determining the expected number of patients expected to be treated over the next five-year period if Optune is introduced (see Tables 8.17 and 8.18).

	Year 1	Year 2	Year 3	Year 4	Year 5
Optune plus TMZ					
Number of patients year 1	15	11	5	1	0
Number of patients year 2	0	40	29	13	4
Number of patients year 3	0	0	63	47	21
Number of patients year 4	0	0	0	76	56
Number of patients year 5	0	0	0	0	76
Total	*15*	*51*	*97*	*137*	*157*
TMZ alone					
Number of patients year 1	98	64	20	3	0
Number of patients year 2	0	74	49	15	2
Number of patients year 3	0	0	51	33	10
Number of patients year 4	0	0	0	38	25
Number of patients year 5	0	0	0	0	39
Total	*98*	*138*	*129*	*90*	*77*
Total patient population	**113**	**189**	**226**	**227**	**234**

Table 8.17 The size of the patient population WITH the recommendation to use Optune and the distribution across the two alternatives. TMZ, temozolomide.

	Year 1	Year 2	Year 3	Year 4	Year 5
Optune plus TMZ					
Number of patients year 1	0	0	0	0	0
Number of patients year 2	0	0	0	0	0
Number of patients year 3	0	0	0	0	0
Number of patients year 4	0	0	0	0	0
Number of patients year 5	0	0	0	0	0
Total	*0*	*0*	*0*	*0*	*0*
TMZ alone					
Number of patients year 1	113	74	23	4	0
Number of patients year 2	0	114	75	23	4
Number of patients year 3	0	0	114	75	23
Number of patients year 4	0	0	0	114	75
Number of patients year 5	0	0	0	0	115
Total	*113*	*188*	*212*	*216*	*217*
Total patient population	**113**	**188**	**212**	**216**	**217**

Table 8.18 The size of the patient population WITHOUT the recommendation to use Optune and the distribution across the two alternatives. TMZ, temozolomide.

8.4.2 Results of the BIA

The total expected cost for a scenario where Optune is recommended as standard treatment is presented in Table 8.18. The BIA demonstrates an additional cost of approximately DKK 17.9 million in year on, with 113 patients eligible for Optune treatment and up to DKK 96 million in year five with 234 patients eligible for Optune treatment (see Table 8.19).

Budget impacts of recommendation	Year 1	Year 2	Year 3	Year 4	Year 5	Total
Total costs without Optune	40.163.901	59.232.320	62.388.132	62.754.405	62.944.523	287.483.282

Treatment cost	3.728.489	3.760.588	3.757.688	3.766.349	3.779.211	18.792.326
Routine monitoring & AEs	34.129.444	51.445.532	54.364.365	54.693.900	54.858.568	249.491.809
Death	2.305.968	4.026.199	4.266.079	4.294.156	4.306.744	19.199.146
Total costs with Optune	57.993.420	107.107.356	139.597.732	157.018.768	158.993.294	620.710.570
Treatment cost	22.456.393	53.308.241	82.450.108	98.356.703	98.692.568	355.264.013
Routine monitoring & AEs	33.333.32	49.995.299	53.204.229	54.726.443	56.324.212	247.583.505
Death	2.241.005	3.841.116	3.980.695	3.972.922	4.013.814	18.049.552
Budget impact of recommendation to use	17.829.519	47.875.037	77.209.600	94.264.363	96.048.771	333.227.289

Table 8.19 Overview of budget impact of a recommendation to use Optune over a five-year time horizon.
AEs, adverse events; DKK, Danish Kroner.

8.4.2.1 Sensitivity analysis

A sensitivity analysis on the BIA was performed where the duration of treatment with Optune of 8.2 months was varied with -30% and +30% (5.7 months and 10.7 months). These sensitivity analyses change the total net budget impact from DKK 333.227.289 to DKK 204.076.159 by adjusting the treatment duration by -30%, and to DKK 419.370.249 by adjusting the treatment duration by +30%.

Budget impacts of recommendation	Year 1	Year 2	Year 3	Year 4	Year 5	Total
Total costs without Optune	40.017.010	59.084.164	62.240.091	62.606.022	62.795.634	286.742.921
Treatment cost	3.728.489	3.760.588	3.757.688	3.766.349	3.779.211	18.792.326
Routine monitoring & AEs	33.982.553	51.297.377	54.216.324	54.545.517	54.709.679	248.751.449
Death	2.305.968	4.026.199	4.266.079	4.294.156	4.306.744	19.199.146
Total costs with Optune	50.658.019	87.940.854	109.244.430	120.562.870	122.412.907	490.819.080
Treatment cost	15.248.450	34.238.479	52.163.190	61.951.032	62.162.581	225.763.732
Routine monitoring & AEs	33.205.865	49.898.558	53.137.845	54.676.215	56.273.813	247.192.296
Death	2.241.005	3.841.116	3.980.695	3.972.922	4.013.814	18.049.552
Budget impact of recommendation to use	10.641.009	28.856.690	47.004.339	57.956.847	59.617.273	204.076.159

Table 8.20 Overview of budget impact of a sensitivity analysis varying the duration of the treatment with Optune with -30% (to 5,7 months) over a five-year time horizon.
AEs, adverse events; DKK, Danish Kroner.

Budget impacts of recommendation	Year 1	Year 2	Year 3	Year 4	Year 5	Total
Total costs without Optune	40.244.072	59.313.181	62.468.931	62.835.390	63.025.784	287.887.358
Treatment cost	3.728.489	3.760.588	3.757.688	3.766.349	3.779.211	18.792.326
Routine monitoring & AEs	34.209.615	51.526.393	54.445.164	54.774.885	54.989.830	249.895.886
Death	2.305.968	4.026.199	4.266.079	4.294.156	4.306.744	19.199.146
Total costs with Optune	62.868.280	119.873.331	159.825.242	181.316.629	183.374.126	707.257.607
Treatment cost	27.261.688	66.021.415	102.641.387	122.627.150	123.045.893	441.597.534
Routine monitoring & AEs	33.402.886	50.048.099	53.240.460	54.753.856	56.351.719	247.797.020
Death	2.241.005	3.841.116	3.980.695	3.972.922	4.013.814	18.049.552

Budget impact of recommendation to use	22.624.207	60.560.150	97.356.311	118.481.239	120.348.341	419.370.249

Table 8.21 Overview of budget impact of a sensitivity analysis varying the duration of the treatment with Optune with +30% (to 10,7 months) over a five-year time horizon.
AEs, adverse events; DKK, Danish Kroner.

9 Discussion on the documentation submitted

GBM is rapidly fatal if left untreated, with a poor prognosis and a low survival rate. It has a particularly poor survival with a five-year survival rate of just 5%. Patients experience a significant decline in quality of life due to GBM symptoms, intracranial hypertension, motor deficit, and visual or speech impairment, as well as the burden of treatment requiring prolonged hospitalization. Current treatment options for patients with ndGBM have poor response rates leading to a high likelihood of relapse after initial remission. This means survival outcomes are poor and the median OS is low.

In this context, there is a high need for new treatment approaches that offer durable responses and improve survival while maintaining HRQoL and contributing to patients' convenience for GBM patients. One promising treatment option is the combination of Optune plus TMZ which has shown significant improvement compared to TMZ alone, the current stand of care in Danish clinical practice, in an open-labeled, phase three RCT by Stupp et al. (2017) (2). The median OS was 20.9 months in patients to receive Optune plus TMZ compared with 16.0 months in the TMZ alone arm. A meta-analysis of studies conducted in a real-world showed a median survival difference between Optune plus TMZ compared to TMZ alone of 10.8 months, a 12-month survival of 12.3% points, and a 24-month survival of 18.7% points. No new risks associated with Optune plus TMZ were identified. The Optune combination provides an alternative treatment option with a distinct mechanism of action, addressing the high unmet medical need of adult patients with ndGBM – an important step forward for the treatment of GBM. Furthermore, the safety profile of Optune in combination with TMZ is acceptable and manageable in this patient population. Compared with TMZ alone, the combination therapy with Optune was well tolerated. No new risks apart from dAEs associated with Optune plus TMZ at the proposed treatment duration and frequency were identified.

Assumptions on long-term survivors in line with this are common in GBM and have been discussed and accepted by several HTA agencies, such as TLV, Agency for care effectiveness in France, Canada's Drug and Health Technology Agency, and Washington State Health Care Authority, among others supported by clinical expertise (14–17). This analysis shows that Optune plus TMZ is an effective treatment option for patients with ndGBM following prior radiotherapy and complete resection. Compared to TMZ alone, Optune is expected to yield improved LY and QALY gain of 1.2 and 0.85 per patient, respectively. The cost for this is DKK 156,000 per month using Optune public purchase price resulting in an ICER of DKK 2.4 million per QALY gained and DKK 1.7 million per LY gained. All the analyses presented for the base-case and the sensitivity analyses are based on list prices for the acquisition cost of Optune.

The analysis is based on best practices in accordance with the guidance provided by the DHTC methods guidelines. The standard three-health state model structure is consistent with the approaches adopted in economic evaluations and technology appraisals with Optune. The findings from the CUA are supported by the results from the PSA and OWSAs. Subsequent device acquisition costs are the biggest driver of cost-effectiveness. The utility values applied to the pre-progression and post-progression health states also impact the results. In this evaluation we used Danish utility values are based upon data from Palmer et al. (2021) and Jensen et al. (2021). Sensitivity analysis shows that the findings from the evaluation are most sensitive towards the cost of Optune, treatment duration, and time horizon. However, clinical expert feedback suggests that long-term survival beyond five years is likely. Therefore, it also makes sense that the time horizon of the analysis is important and that any time horizon shorter than the full lifetime (40 years in the base-case) essentially cuts short the expected survival benefits for otherwise healthy patients.

In summary, Optune in combination with TMZ presents a beneficial treatment option to address the urgent unmet medical need in a disease with very high severity of illness. The CUA has several strengths: direct comparative data from the pivotal Stupp et al. study (2), Danish utility weights using EQ-5D-5L data from the Palmer et al. (2021) study (68), a comprehensive model, and OS from several studies and trials. The data and

input from clinicians highlight that Optune is an important evolution of the treatment of GBM patients, with significant benefits and well-tolerated AEs as well as a cost-effectiveness and manageable cost to society in terms of budget impact leading to the conclusion that Optune should be made available to Danish clinicians and patients for the treatment of GBM.

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