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CADTH Health Technology Review

Optune (NovoTTF-200A)

Sponsor: Novocure Canada Inc.

Therapeutic area: Supratentorial glioblastoma multiforme

Summary

What Is the Indication Under Review?

The indication under review is for the treatment of adult patients with newly diagnosed glioblastoma multiforme (ndGBM) following maximal debulking surgery and completion of radiotherapy (RT) together with and after standard of care maintenance chemotherapy. Glioblastoma is the development of cancer among glial cells in the central nervous system and is the most common form of brain cancer in Canada.

What Is Optune?

Optune is a medical device that produces alternating electrical fields called tumour-treating fields (TTFields) to target growth of cancerous cells in addition to chemotherapy. Current treatment for glioblastoma consists of a combination of surgery, radiotherapy, and chemotherapy.

How Did CADTH Evaluate This Device?

To examine the value of Optune for the treatment of ndGBM, CADTH:

- **reviewed and critically appraised the following evidence submitted by the sponsor:**
 - clinical evidence on efficacy and safety
 - economic evidence on cost-effectiveness and budget impact
- **reviewed the literature to:**
 - assess the validity of the sponsor's modelling approaches, assumptions, and estimates regarding Optune
 - identify and describe ethical considerations relevant to the use of Optune for the treatment of ndGBM in Canada
- **sought input from patient and clinician groups and consulted an expert panel to:**
 - identify unmet needs, place in therapy, and implementation considerations regarding Optune
 - assess the validity of the sponsor's modelling approaches and assumptions regarding Optune
 - identify and describe ethical considerations relevant to the use of Optune for the treatment of ndGBM in Canada.

What Did CADTH Find?

Clinical Evidence

This review included the EF-14 trial, a pivotal, multicentre, open-label randomized controlled trial, which assessed the efficacy and safety of Optune plus temozolomide in adult patients with ndGBM following maximal

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debulking surgery and completion of radiotherapy (RT), together with and after standard-of-care maintenance chemotherapy.

Based on the single trial, there is evidence of low to moderate certainty that Optune plus temozolomide likely increases progression-free survival at 6 months of treatment, and overall survival at 24 months of treatment, compared to temozolomide alone. The treatment effect of Optune plus temozolomide on progression and survival may be dose-dependent, with at least 18 hours of daily use required for the most benefit.

Optune plus temozolomide may result in little to no difference in health-related quality of life (HRQoL) (very low certainty) when compared to temozolomide alone. There was little to no difference in serious adverse events between Optune plus temozolomide and temozolomide alone, which suggests that the addition of Optune did not add safety concerns to temozolomide alone. More than half of the patients who received Optune reported skin irritation (2% severe), likely due to the transducer patches placed on the scalp.

Overall, evidence was of very low to moderate certainty due to concerns regarding selection bias and low generalizability of results to real-world settings. No longer-term studies or indirect comparisons were identified by the sponsor for the review.

Economic Evidence

The submitted fee for Optune is \$27,000 per month, which is added to the cost of temozolomide based on its public list price. Using this pricing information; the available clinical evidence; and input from clinicians, patients, and caregivers who have experience with GBM; the incremental cost-effectiveness ratio (ICER) for Optune plus temozolomide versus temozolomide alone was \$899,470 per quality-adjusted life-year (QALY) gained (incremental costs = \$336,902; incremental QALYs = 0.37). Optune plus temozolomide was not considered cost-effective relative to temozolomide alone at conventional willingness-to pay thresholds (i.e., \$50,000 per QALY gained and \$100,000 per QALY gained). Consequently, a price reduction of between 91% and 97% would be required for Optune plus temozolomide to be considered cost-effective at a willingness to pay threshold between \$50,000 and \$100,000 per QALY gained.

The budget impact of reimbursing Optune through the federal, provincial, and territorial public drug plans (excluding Quebec) is estimated to be \$75,795,323 to cover 232 patients over the initial 3 years of funding.

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Ethical Considerations

GBM is physically, psychosocially, and economically burdensome for patients and their caregivers. The extent to which Optune meets patients' needs for effective, accessible, and easily usable treatment may depend on an individual patient's values and caregiver support network, especially as Optune requires managing an additional treatment modality and may require additional caregiver support. Due to generalizability limitations with pivotal trial data, further study on how – or if – factors such as functional status, race, sex, age, socioeconomic status, and availability of caregiver support have implications for device uptake and ability to adhere to treatment would be helpful to inform patient-centred and equitable use, given the diverse patient population in Canada. Careful attention must be paid to the quality of clinical consent conversations, including considerations of disease progression potentially impairing capacity to consent and requiring a substitute decision-maker. Consent conversations require ensuring that patients and caregivers understand that Optune is not curative and is proposed as an addition to standard of care maintenance chemotherapy, so that Optune is considered within a full range of therapeutic and care options. Equity-enhancing strategies for implementation will need to be explored if Optune is to be accessible in a fair and effective manner for patients in Canada, including those who do not fit the profile of participants enrolled in the pivotal trial or who are otherwise underserved.

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Abbreviations

AE	adverse event
BTFC	Brain Tumour Foundation of Canada
CI	confidence interval
EORTC QLQ-C30	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30
GBM	glioblastoma multiforme
GRADE	Grading of Recommendations Assessment, Development and Evaluation
HR	hazard ratio
HRQoL	health-related quality of life
ICER	incremental cost-effectiveness ratio
ITT	intention-to-treat
KPS	Karnofsky performance status
MID	minimal important difference
ndGBM	newly diagnosed glioblastoma multiforme
OS	overall survival
PFS	progression-free survival
QALY	quality-adjusted life-year
RCT	randomized controlled trial
RT	radiotherapy
SAE	serious adverse event
SD	standard deviation
TTField	tumour-treating field

What Is Glioblastoma?

Contents within this section have been informed by materials submitted by the sponsor and clinical expert input. The following has been summarized and validated by the CADTH review team.

Overview of the Condition

Glioblastoma multiforme (GBM) is an aggressive malignant tumour of the brain and spinal cord. It is the most common primary malignant tumour of the central nervous system, accounting for about 48.6% of cases.¹ Data from the Brain Tumour Registry of Canada (2010 to 2017) indicated that there were approximately 1,850 prevalent cases of GBM during that period, which mainly involved patients aged 40 to 64 years (1,020 patients) and 65 years or older (625 patients).² Registry studies have found that the incidence of GBM is comparable in the US, England, and Canada, and has been increasing in recent decades across all age groups.^{3,4}

GBM is a grade IV, diffusely infiltrating, highly cellular, and pleomorphic glioma arising from the astrocyte glial cells.⁵ In the 2021 WHO classification of central nervous system tumours,⁶ 4 types of glioblastoma were recognized, of which GBM with *IDH* wild type accounted for about 90% of the cases.¹ Most GBM tumours occur in parts of the brain above the brainstem (supratentorial), namely the hemispheres and corpus callosum.⁷ Symptoms associated with glioblastoma depend more on the location of the tumour than its pathological properties.⁸ Depending on the location, symptoms may appear quickly or occur later when the tumour reaches a larger size. Intracranial hypertension is responsible for 30% of clinical signs and symptoms, followed by motor deficit (20%), loss of body weight and condition (17%), confusion (15%), and visual or speech deficit (13%).⁹ Other symptoms include nausea, seizures, and progressive deterioration of neurologic function.⁸

Despite aggressive treatment, the prognosis for patients with GBM is poor, with an overall median survival of 15 months.^{10,11} If untreated, the median survival is around 3 months.¹¹ In Canada, findings from the survival analysis by the Brain Tumour Registry of Canada (2010 to 2017) showed that the median survival was 8 months for glioblastoma.¹²

Several key factors that may impact GBM prognosis have been identified, as follows:

- age (worse prognosis with advancing age)¹³
- performance status before surgery
 - WHO performance status (lower score [greater well-being] correlates with improved survival)¹³
 - Karnofsky performance status (KPS), which is a measure of overall health status, with scores ranging from 0 to 100; higher KPS scores before surgery are associated with better survival¹⁴⁻¹⁶
- *MGMT*-promoter methylation status (survival was longer in patients who had *MGMT*-promoter methylation);^{17,18} roughly 40% of *IDH* wild-type GBM tumours are *MGMT*-promoter methylated¹⁹
- *IDH* mutations are associated with a better prognosis than tumours with unmutated (wild-type) *IDH*; however, in the new classification, *IDH* mutant gliomas are considered as a separate condition¹

- male sex is associated with some survival advantage in the first year after treatment but none thereafter¹¹
- tumours that are amenable to more complete resection generally carry a more favourable prognosis.²⁰

Diagnosis of the Condition

The diagnostic workup for GBM includes MRI, and may also involve functional MRI, diffusion-weighted imaging, diffusion tensor imaging, dynamic contrast-enhanced MRI, perfusion imaging, protein magnetic resonance spectroscopy, and PET.²¹ However, MRI is not sufficient for definitively diagnosing GBM;²² tissue biopsy, which may include surgical debulking, is essential in the differential diagnosis of brain tumours.²³ Postoperative imaging (using MRI) is recommended within 72 hours of surgery to evaluate the extent of resection.²⁴

What Is the Current Treatment Paradigm?

Current Treatment Paradigm

There is no curative treatment for GBM.²⁵ In Canada, the initial treatment for newly diagnosed GBM (ndGBM) involves maximal resection of the tumour, which aims to reduce tumour size without compromising quality of life and neurologic function.²³ After maximal resection, the current standard of care is the Stupp regimen,¹³ as outlined by the recommendations for the treatment of GBM by the Canadian GBM Recommendations Committee.²⁴

The Stupp regimen includes 60 Gy (in 30 fractions) of targeted radiotherapy (RT) with concomitant temozolomide, followed by 6 months of adjuvant temozolomide.¹³ The Stupp regimen was established in 2005 based on a large randomized controlled trial (RCT) that demonstrated a significant and clinically meaningful improvement in overall survival (OS) among patients with ndGBM (14.6 months for RT plus temozolomide, versus 12.1 months for RT alone; $P < 0.001$).¹³

Temozolomide is a DNA alkylating agent; it acts by methylating DNA strands at specific positions, including the O6 position of guanine.²⁶ These changes result in unrepairable mutations, leading to cell-cycle arrest and apoptosis of the cancer cells. *MGMT* is an enzyme that repairs DNA damage by removing the methylation of O-6-methylguanine. Methylation of *MGMT* gene promoter reduces the expression of *MGMT* enzyme, leading to increased sensitivity of tumour tissues to temozolomide. GBM patients with an unmethylated *MGMT* promoter do not respond to temozolomide therapy as well as those with a methylated *MGMT* promoter.^{11,26} This means that in up to 60% of GBM tumours,¹⁹ the currently available chemotherapeutic drug may not be as effective in improving survival.²⁷

Unmet Needs

There have been no new treatment options that improve survival of GBM patients since the early 2000s. Evidence suggests that the current chemotherapeutic drug temozolomide is considerably less effective

in patients with *MGMT* unmethylated tumours,²⁷ constituting up to 60% of ndGBM patients.¹⁹ None of the available treatments are curative and the disease has a poor prognosis. Thus, there are several needs that are not being met by current standard of care for newly diagnosed patients with GBM.

What Is Optune?

Overview of the Device

Optune (NovoTTF-200A) is a portable and noninvasive device that treats GBM by providing continuous, locoregional treatment with tumour-treating fields (TTFields). It is indicated together with and after standard of care maintenance chemotherapy using temozolomide.

The Optune system consists of an electric field generator, a connection cable and box, transducer arrays, a shoulder bag and strap, 4 portable batteries, a charger for portable batteries, a plug-in power supply, and power cords (Figure 1).²⁸⁻³⁰ The electric field generator is the portable Optune device that delivers TTFields.³⁰ TTFields are applied to the patient by electrically insulated surface transducer arrays,²⁸ which are adhesive bandages that hold the insulated ceramic disks needed to deliver treatment, along with wiring that connects the disks to the field generator and allows the device to monitor and regulate treatment.^{28,31} The effects of TTFields on cancer cells are frequency-specific. The optimal frequency for the treatment of GBM is 200 kHz.^{8,28} Optune uses 1 battery at a time and each battery lasts 2 to 3 hours.²⁸ When the patient is stationary, they may use the plug-in power supply instead of batteries.^{28,30}

Figure 1: The OPTUNE System



Source: Sponsor's Summary of Clinical Evidence.³⁰

Mechanism of Action

TFields have been shown to inhibit the proliferation of cancer cells by interfering with the process of mitosis, or cell division. Typically, biological processes such as cell division and motility are subject to electric forces.^{32,33} Cells contain polar cellular components (e.g., molecules and organelles that contain charges) that can be influenced by electric fields.³⁴ Electric field distribution can be uniform or nonuniform, depending on the geometry of the cell, and has consequences for the localization and organization of polar molecules within cancer cells.^{35,36}

According to the information provided by the sponsor,³⁰ the electrical field frequencies delivered by Optune disrupt the localization and orientation of polar molecules, such as tubulin and septin, which play a critical role in cell division and movement.^{35,37,38} Optune delivers alternating TFields that disrupt cancer cell division at a frequency (100 to 300 kHz) that specifically targets cancerous cells through the transducer arrays placed on the scalp.²⁹

Stakeholder Perspectives

CADTH sought input from patient and clinician groups who responded to CADTH's call for input, and consulted clinical experts for the purpose of this review. Detailed input provided by stakeholders is published separately.³⁹

Patient Input

The Brain Tumour Foundation of Canada (BTFC) submitted the patient input for this review. BTFC is a registered Canadian charitable organization working to help people in Canada who are affected by brain tumours through advocacy, support, education, information, and funding of research. Information from this input was gathered by BTFC through an online survey and videoconference interviews. A total of 80 patients and 259 caregivers responded to the online survey (227 in English and 112 in French) from May 10, 2023, to May 24, 2023, with more than 94% of responses from Canada and others from France, the US, Germany, Algeria, and the Republic of Guinea. Six patients and 4 caregivers sharing their experiences with Optune highlighted its potential to prolong survival. While most patients experienced only skin-related side effects, they noted the need for lifestyle adjustments when using the Optune device.

Clinician Input

Input From Clinical Experts Consulted by CADTH

CADTH consulted a clinical specialist with expertise in the diagnosis and management of GBM. The expert pointed out that the standard treatment only offers a median survival of approximately 15 months. Patients with *IDH* wild-type tumours and those with *MGMT* unmethylated tumours respond poorly to current standard treatment (radiation and chemotherapy). There is no standard second-line treatment at present. The expert mentioned that because there is no influence of *MGMT* methylation status on the effectiveness of Optune, it could be a promising option for patients with *MGMT* unmethylated tumours and therefore addresses an unmet need. The expert suggested that the Optune device is expected to shift the standard care for patients

with ndGBM. According to the expert, patients who are younger, have better performance status at baseline, have better cognitive and physical function, and have supports at home may be more adherent to treatment and therefore respond better. Clinician judgment plays an important role in determining patient eligibility. The expert suggested that Optune treatment could be discontinued if disease progression is detected along with symptom progression.

Clinician Group Input

Clinician group input was received from a group of oncologists in Canada who treat patients with ndGBM and share the goals of improving the outcomes and quality of life of patients. A total of 20 clinicians provided input for this review. They mentioned the unmet needs for effective treatment options, noting that the median survival of patients with GBM undergoing current treatments (i.e., surgery followed by chemoradiotherapy and maintenance temozolomide) is 15 months. The group noted that, per the EF-14 trial, all subgroups of patients, regardless of *MGMT*-promoter methylation status, can benefit from Optune treatment. The group suggested considering quality of life, neurocognitive functioning, and treatment-related cytotoxicity when deciding to discontinue Optune treatment.

Sponsor Submission

An overview of the submission details for the device under review is provided in [Table 1](#).

Table 1: Background Information of Application Submitted for Review

Item	Description
Brief product description	Optune (NovoTTF-200A) is a portable and noninvasive device that delivers TTFIELDS at 100 to 300 kHz via transducer arrays worn on the scalp.
Sponsor	Novocure Canada Inc.
Indication	Optune with temozolomide is indicated for the treatment of adult patients with newly diagnosed, supratentorial glioblastoma following maximal debulking surgery and completion of radiation therapy together with and after standard of care maintenance chemotherapy.
Reimbursement request	Novocure Canada Inc. requests that Optune with temozolomide be reimbursed for the treatment of adult patients with newly diagnosed, supratentorial glioblastoma following maximal debulking surgery and completion of radiation therapy together with and after standard of care maintenance chemotherapy.
Health Canada approval status	Health Canada Class III MDL: November 8, 2022
Health Canada review pathway	Standard review
MDL date	Licence date: November 8, 2022
Recommended dose	100 to 300 kHz via transducer arrays worn on the scalp

MDL = Medical Device Licence; TTFIELDS = tumour-treating fields.

Clinical Evidence

Clinical Review Objective

The objective of CADTH's Clinical Review is to review and critically appraise the evidence submitted by the sponsor on the beneficial and harmful effects of Optune with temozolomide for the treatment of adult patients with newly diagnosed, supratentorial glioblastoma following maximal debulking surgery and completion of RT, together with and after standard of care maintenance chemotherapy.

Contents within this section have been informed by materials submitted by the sponsor and clinical expert input. The following have been summarized and validated by the CADTH review team.

Summary of Sponsor's Systematic Review

The sponsor conducted a systematic review of the beneficial and harmful effects of TTFIELDS, delivered through Optune, together with and after standard of care maintenance chemotherapy for adult patients with ndGBM following maximal debulking surgery and completion of RT. The methods and results of the systematic review are provided in the [Supplemental Materials](#) document.

Description of the Evidence

One randomized, open-label, active-controlled trial (the EF-14 trial, N = 695) met the inclusion criteria for the systematic review conducted by the sponsor.³⁰

The EF-14 trial evaluated the effectiveness of Optune plus temozolomide compared to temozolomide alone in patients with adult patients with newly diagnosed, supratentorial glioblastoma following maximal debulking surgery and completion of radiation therapy, together with and after standard of care maintenance chemotherapy. The primary analyses were performed using the intention-to-treat (ITT) population.⁴¹ The final data cut-off was in December 2016, when the last enrolled patient had their 24-month follow-up visit.⁴¹

[Table 2](#) presents the characteristics of the EF-14 trial.

Patients were screened while undergoing treatment with radiotherapy and temozolomide and, if eligible, were randomized 2:1 to receive either Optune plus temozolomide or temozolomide alone.⁴⁰ Randomization was stratified based on the extent of resection (biopsy only, partial resection, or gross total resection), and *MGMT* methylation status (positive, negative, or unknown).⁴⁰

The study enrolled 695 patients (Optune plus temozolomide, n = 466; temozolomide alone, n = 229) across 83 sites. After baseline evaluations during the screening period, patients received interventions no later than 7 weeks from the last dose of RT or temozolomide. Patients randomized to receive Optune plus temozolomide (NovoTTF-100A) were treated for up to 24 months with Optune; in cases of temozolomide toxicity, temozolomide treatment was to be replaced with the best available second-line therapy (reoperation, RT, and/or chemotherapy).⁴⁰

Patients were provided training on how to use the device, battery replacements and recharging, and troubleshooting errors, and were advised on possible adverse events (AEs). Patients randomized to receive

temozolomide alone were also followed up and, in cases of radiological progression or unacceptable toxicity, were to be switched to the best available second-line therapy.⁴⁰ After second progression, all patients were followed via telephone until death.⁴⁰ The study schema is provided in Appendix 2 in the [Supplemental Materials](#) document.

The data monitoring committee recommended that the study be closed early for success in 2014 (based on a statistically significant increase in progression-free survival [PFS] with Optune plus temozolomide) and that patients from the temozolomide-alone arm be offered the option to cross over to the Optune plus temozolomide arm before disease progression, which was subsequently approved by the FDA in November 2014.⁴⁰

The primary analyses were performed using the ITT population.⁴⁰ The final data cut-off was in December 2016 when the last enrolled patient had their 24-month follow-up visit.⁴⁰

Table 2: Details of the EF-14 Trial Included in the Systematic Review

Detail	EF-14 trial
Study design	Multicentre, open-label RCT
Locations	83 sites in the US, Europe, South Korea, Israel, and Canada (46 patients at 7 Canadian sites)
Key dates	Study initiation: July 2009 Last patient enrolled: December 2014 Final long-term analysis: December 2016
Randomized (N)	695 patients (466 receiving Optune plus temozolomide; 229 receiving temozolomide alone)
Population	Patients with newly diagnosed and histologically confirmed GBM after initial treatment with maximal debulking surgery and concomitant chemoradiotherapy
Inclusion criteria	<ul style="list-style-type: none"> • Pathological evidence of GBM using WHO classification criteria • ≥ 18 years of age • Received maximal debulking surgery and RT concomitant with temozolomide (45 to 70 Gy) • Karnofsky performance status score ≥ 70% • Life expectancy at least 3 months • Treatment start date ≥ 4 weeks after surgery and ≥ 4 to 7 weeks from the later instance of the last dose of concomitant temozolomide or RT
Exclusion criteria	<ul style="list-style-type: none"> • Progressive disease (according to Macdonald criteria); if pseudoprogression is suspected, additional imaging studies must be performed to rule out true progression • Actively participating in another clinical treatment trial • Pregnant • Significant comorbidities at baseline that would prevent maintenance temozolomide treatment • Implanted pacemaker, programmable shunts, defibrillator, deep brain stimulator, other implanted electronic devices in the brain, or documented clinically significant arrhythmias • Infratentorial tumour • Evidence of increased intracranial pressure (midline shift > 5 mm, clinically significant papilledema, vomiting and nausea, or reduced level of consciousness) • History of hypersensitivity reaction to temozolomide or a history of hypersensitivity to DTIC

Detail	EF-14 trial
Intervention	Optune (NovoTTF-100A) (200 kHz, 707 mA RMS TTFields, 1 second per field direction) in combination with temozolomide (150 to 200 mg/m ² /day for 5 days every 28 days for 6 cycles; extension beyond 6 cycles allowed per local practice) Note: In the experimental group, Optune could be continued until the second radiological progression or for a maximum of 24 months (whichever was earlier).
Comparator	Maintenance temozolomide (150 to 200 mg/m ² /day for 5 days every 28 days for 6 cycles; extension beyond 6 cycles was allowed per local practice)
Study duration	
Screening phase	1 week before treatment initiation
Treatment phase	24 months (18-month interim analysis)
Follow-up phase	2 medical follow-ups then monthly telephone follow-ups until death
Outcomes	
Primary end point	PFS, powered to detect a 2-month increase in PFS in the Optune plus temozolomide arm (80% power; 2-sided alpha = 0.05)
Secondary and exploratory end points	Powered secondary: OS, powered to detect a 4.5-month increase in OS in the Optune plus temozolomide arm (80% power; 2-sided alpha = 0.05) Other secondary (not powered): PFS6, proportion surviving to 1 and 2 years, radiological response, EORTC QLQ-C30, KPS, MMSE score, AE severity and frequency Exploratory: OS from first progression
Publications	Stupp et al., 2017 ¹³

AE = adverse event; DTIC = dacarbazine; EORTC QLQ-C30 = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30; GBM = glioblastoma multiforme; KPS = Karnofsky performance status; MMSE = Mini-Mental State Examination; NA = not applicable; OS = overall survival; PFS = progression-free survival; PFS6 = progression-free survival at 6 months; RCT = randomized controlled trial; TTFields = tumour-treating fields; .

Source: Study EF-14 Clinical Study Report.⁴⁰ Details included in the table are from the sponsor's Summary of Clinical Evidence.³⁰

Results

Patient Disposition

The trial investigators screened 1,019 patients for eligibility.⁴¹ Among them, 324 patients were excluded, including 52 patients who did not meet the inclusion criteria. Other reasons for exclusion were disease progression before randomization (n = 82), refusal to participate (n = 53), refusal to use the Optune device (n = 46), participation in another clinical trial (n = 20), and residing far from the study centre (n = 18).⁴¹ Thus, 695 patients were randomized 2:1 to receive Optune plus temozolomide (n = 466) or temozolomide alone (n = 229).

At the data cut-off date (December 28, 2016), ■ patients had more than 24 months of follow-up and ■ patients died before 24 months. The median follow-up duration was 40 months (interquartile range, 34 months to 66 months).¹³ Refer to Appendix 3 in the [Supplemental Materials](#) document for patient disposition details in the trial.

Baseline Characteristics

The baseline characteristics outlined in Appendix 3 in the [Supplemental Materials](#) document are limited to those that are most relevant to this review, as determined by CADTH staff and based on the literature and clinician input that were deemed to affect the outcomes or interpretation of the study results.

Overall, key baseline characteristics were generally balanced between treatment groups. Patients were predominantly male (68.2%) and white (88.5%), with a mean age of 54.9 years (standard deviation [SD] = 11.46). Approximately 39.4% of patients had frontal-lobe GBM, and 53.5% of patients underwent a gross total resection. The median KPS score among patients was 90 (range, 60 to 100).

More than half of patients had an *MGMT* unmethylated tumour (53.3%). *IDH* mutations were not detected in 93.3% of patients, indicating predominantly *IDH* wild-type tumours.

The mean duration from diagnosis to randomization was 115.8 days (SD ■■■). The mean duration from last day of RT to randomization was ■■■ days (SD ■■■).

Exposure to Study Treatments

Details of exposure to study treatments are provided in Appendix 3 in the [Supplemental Materials](#) document. Patients receiving Optune plus temozolomide were exposed to Optune for a median duration of 8.2 months (range, 0 to 82 months; 8 cycles) and, on average, received ■■■ (SD: ■■■) cycles of temozolomide. Patients receiving temozolomide alone were exposed for an average of ■■■ (SD: ■■■) cycles.⁴⁰

Three-quarters (74.5%) of the participants in the Optune plus temozolomide arm used Optune for more than 18 hours per day (i.e., more than 75% of the time) during the first 3 months of treatment.

At baseline, similar proportions of patients in the Optune plus temozolomide and temozolomide-alone arms were receiving antiepileptic medications (39.7% versus 38.9%, respectively) or corticosteroids (29.0% versus 27.9%, respectively). The dose and duration of these concomitant treatments were not reported. No other concomitant medications or co-interventions were reported.

■■■ patients from the temozolomide-alone arm received Optune treatment, either before the FDA approval for crossover (unapproved use of Optune via prescription from a nonstudy centre, n = ■■■) or after (based on a protocol amendment, n = 26). The baseline characteristics of patients who crossed over (n = ■■■) and those who did not cross over (n = ■■■) were not balanced. Patients who crossed over were slightly ■■■ (mean age ■■■ years versus ■■■ years) and had ■■■ mean KPS scores (■■■ versus ■■■). A ■■■ proportion of them had an *MGMT*-promoter methylated tumour (■■■ versus ■■■). They also received ■■■ cycles of temozolomide treatment (mean ■■■ cycles) compared to patients who did not cross over (mean ■■■ cycles).

Patients who experienced disease progression were given subsequent treatments. While there was no discontinuation of treatment due to AEs in either group, ■■■ patients in the Optune plus temozolomide arm and ■■■ patients in the temozolomide-alone arm received subsequent treatments after progression. Compared to the temozolomide-alone arm, ■■■ proportions of patients in the Optune plus temozolomide arm received second-line treatment using other chemotherapy (■■■■■ respectively), bevacizumab (■■■■■ respectively), or re-resection (■■■■■ respectively). Approximately one-quarter (26%) of patients in the Optune plus

temozolomide arm continued Optune monotherapy after progression.⁴⁰ Details of subsequent treatments received by patients are provided in Appendix 3 in the [Supplemental Materials](#) document.

Efficacy Results

Summarized end points are based on outcomes included in the sponsor's Summary of Clinical Evidence,³⁰ as well as any outcomes identified as important to this review according to the clinical expert consulted by CADTH and stakeholder input from patient and clinician groups. Using the same considerations, the CADTH review team selected end points that were considered to be most relevant to inform CADTH's expert committee deliberations.

The following list of outcomes was finalized in consultation with the clinical expert. Definitions and measurement of these key outcomes along with statistical analysis methods are provided in the [Supplemental Materials](#) document.

- **OS:** OS was a powered secondary outcome. It was defined as the number of months patients lived following treatment initiation. Patients were censored at the date they were last known to be alive if they withdrew consent, were lost to follow-up, or were still under observation at the time of the final analysis (administrative censoring). OS rates at 6 months and 24 months were determined based on the number of patients still alive at these time points after treatment initiation. Events were adjudicated by the blinded central committee. The minimal important difference (MID) for OS rates at 6 months and 24 months was not established.
- **PFS:** PFS was the primary outcome in the trial. It was defined as the number of months patients experienced no disease progression or death following treatment initiation. Patients were censored at the date of their last known progression-free visit if they changed treatments, withdrew consent, or were lost to follow-up (refer to sections that follow). Progression was identified using the Macdonald criteria when MRI was available (tumour growth > 25% compared to smallest tumour area measured for that patient during the trial, or appearance of ≥ 1 new brain tumour radiologically diagnosed as GBM), or based on a clinical diagnosis if MRI was not available (decline in functional status based on KPS decrease > 10, plus decline in neurologic function based on a Medical Research Council Clinical Scale decrease of ≥ 2 points, plus a $\geq 50\%$ increase in corticosteroid dose). Events were adjudicated by the blinded central committee. PFS rates at 6 months and 24 months were determined based on the number of patients in each treatment arm that were still progression-free at the corresponding time points after treatment initiation. Events were adjudicated by the blinded central committee. The MID for PFS rates at 6 months and 24 months was not established.
- **Radiological response rate:** This secondary outcome was evaluated based on the Macdonald criteria for each response level (progressive disease, stable disease, partial response, and complete response).⁴² The clinical benefit rate was derived by calculating the proportion of patients with stable disease, partial response, or complete response following treatment.⁴⁰ The central best response rates were derived by calculating the proportion of patients with either complete or partial response following treatment. The MID for radiological response rate in patients with ndGBM was not established.

- **HRQoL:** This secondary outcome was assessed using the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ C-30), which measures physical, psychological, and social functioning in cancer patients. The questionnaire consists of several subscales, where higher scores in general quality-of-life subscales indicate increased life quality, and higher scores in symptom subscales indicate heightened disease burden.⁴³ Descriptive results for all of the items of the EORTC QLQ C-30 were prespecified and reported in the Clinical Study Report for the EF-14 trial with statistical comparisons between groups. The study protocol for the EF-14 trial stated that no efficacy claims would be made for the HRQoL data. A published exploratory analysis reported the mean change from baseline of 9 selected scales and items from the EORTC QLQ C-30 (global health status, physical functioning, cognitive functioning, role functioning, social functioning, emotional functioning, itchy skin, pain, and weakness of legs). Among various analyses, a 10-point difference from baseline was considered clinically meaningful; a difference of less than 10 points was considered “stable” and an increase of 10 or more points was considered “improved.”
- **Safety:** Descriptive results (incidences and severities) were reported for the safety population (all patients who received at least 1 dose of temozolomide or TTFields) up to the data cut-off.

The subgroups identified as important to this review included age (< 65 years, ≥ 65 years), *MGMT* methylation status (unmethylated, methylated), extent of resection (biopsy, partial, or gross total), and treatment adherence (≥ 75%, < 75%).

Detailed results of efficacy and harms outcomes are presented in Appendix 3 of the [Supplemental Materials](#) document.

Overall Survival

The median follow-up time in the EF-14 trial was 40 months (interquartile range, 34 to 66 months),⁴¹ and all participants had at least 24 months of follow-up data. At the final analysis of the ITT population, the median OS in the Optune plus temozolomide arm (20.9 months; 95% confidence interval [CI], 19.1 to 22.6 months) was 4.9 months longer than that in the temozolomide arm (16.0 months; 95% CI, 13.9 to 18.2 months). The between-group hazard ratio (HR) was 0.63 (95% CI, 0.53 to 0.76; $P < 0.001$), favouring Optune plus temozolomide over temozolomide alone.

At 6 months, the OS rate in the Optune plus temozolomide arm was 5.5% more than that in the temozolomide-alone arm (92.8% versus 87.3%; $P = 0.015$). By 24 months, 12.5% more patients who received Optune plus temozolomide were alive than those who received temozolomide alone (43.1% versus 30.7%; $P = 0.001$)

Results of the subgroup analysis were consistent with the results of the main analysis. Optune therapy was associated with increased survival across the subgroups of interest such as age (< 65 years versus ≥ 65 years), *MGMT*-promoter methylation status (methylated versus unmethylated), and extent of resection (biopsy versus partial versus gross total).

Stratified analysis of OS outcomes based on treatment adherence suggests a dose response, in that patients who were exposed to Optune for a greater proportion of time appeared to have greater improvements in

OS compared to those who used Optune for shorter durations. Patients who used Optune for more than 18 hours a day (75% adherence) showed an increase in median OS compared to those who used the device for less than 18 hours a day, on average (22.6 months versus 19.1 months; $P = 0.0001$). There was a between-group survival benefit favouring Optune treatment when the treatment adherence with Optune was more than 50%, and the benefit increased with increased device adherence. The results of OS outcomes stratified by treatment adherence are provided in Appendix 3 in the [Supplemental Materials](#) document.

Progression-Free Survival

The median PFS was 6.7 months (95% CI, 6.1 to 8.1 months) in the Optune plus temozolomide arm and 4.0 months (95% CI, 3.8 to 4.3 months) in the temozolomide-only arm. Thus, patients in the Optune plus temozolomide arm remained progression-free for a median 2.7 months longer. The between-group HR was 0.63 (95% CI, 0.52 to 0.76; $P < 0.001$), favouring Optune plus temozolomide over temozolomide alone.

At 6 months, 19.1% more patients who received Optune plus temozolomide were progression-free than those who received temozolomide alone (55.6% versus 36.5%, $P < 0.001$). However, at 24 months, there were no between-group differences in the proportion of patients who were progression-free (14.2% versus 9.5%; $P = 0.06402$)

Results of the subgroup analysis were consistent with the main analysis. They showed consistently higher PFS with Optune therapy across the subgroups of interest such as age (< 65 years versus ≥ 65 years), *MGMT*-promoter methylation status (methylated versus unmethylated), and extent of resection, compared to temozolomide alone.

Patients who used Optune for more than 18 hours a day (75% adherence) showed an increase of 3.8 months in median PFS compared to those who used the device for less than 18 hours a day, on average ($P = 0.0001$). Similar to OS, an analysis of PFS outcomes based on treatment adherence showed that, at approximately 70% to 80% adherence, a significant progression-free survival benefit was observed in the Optune plus temozolomide group compared to the temozolomide-alone group. Lower HRs were observed with higher adherence, indicating a dose response to Optune treatment with adherence to device use.

Radiological Response Rate

The results showed that a [redacted] proportion of patients in the Optune plus temozolomide arm experienced a trial-defined clinical benefit (either stable disease, partial response, or complete response) compared to the temozolomide arm ([redacted] versus [redacted]). The sponsors reported that [redacted] of patients in the Optune plus temozolomide group and [redacted] in the temozolomide arm showed either complete or partial response to treatment, categorized as trial-defined [redacted] (absolute difference = [redacted] (95% CI, [redacted] to [redacted])).

Health-Related Quality of Life

Self-reported HRQoL was measured using the EORTC QLQ C-30 questionnaire with BN-20 (brain symptom) supplement at baseline, and every 3 months until 12 months. HRQoL assessments were completed by 639 patients (91.9% of those randomized) at baseline and 197 (41.7% of patients alive) at 12 months.⁴⁴ Descriptive analysis of the final assessment suggested that the mean scores for all domains and subscales were generally similar between the treatment arms at baseline and all time points up to 12 months.

Results of published exploratory analyses⁴⁴ suggested that there were no differences between the treatment groups in any of the 9 selected scales and items considered by the investigators to be relevant to patients with ndGBM after 12 months of treatment. Compared to temozolomide alone group, more patients in the Optune plus temozolomide group were found to have stable or improved scores in several of the selected scales and items, such as global health status (53.5% versus 38%), physical functioning (54.0% versus 37%), pain (56.8% versus 35.9%), and weakness of legs (58.7% versus 42%). It was reported that there was no significant difference in the rest of the preselected scales and items. Taphoorn et al.(2018)⁴⁴ reported that there were no differences between treatment arms on the EORTC QLQ C30 items over 12 months, except for localized itchy skin.⁴⁴

Harms Results

Summary of harms results are provided in Appendix 3 in the [Supplemental Materials](#) document.

Adverse Events

In the safety population of the EF-14 trial, 438 (96%) of the 456 patients in the Optune plus temozolomide arm and 197 (91%) of the 216 patients in the temozolomide arm experienced at least 1 AE.

The most common type of AE was nervous system disorders (Optune plus temozolomide 72% versus temozolomide 65%), most frequently including headaches (28% versus 20%), convulsions (22% versus 21%), hemiparesis (14% versus 10%), and aphasia (11% versus 8%). Injuries and procedural complications were also common (61% versus 20%), with patients experiencing falls (8% versus 3%), contusions (4% versus 2%), and medical device site reactions (53% versus 11%).

Serious Adverse Events

Serious adverse events (SAEs) were also reported for Study EF-14, occurring in 156 (34%) of patients receiving Optune plus temozolomide and 67 (31%) of patients receiving temozolomide alone. The most common SAEs were nervous system disorders (14% versus 12%) (most frequently including convulsions [7% versus 6%]), followed by infections (9% versus 5%). All other types of SAEs occurred in less than or equal to 5% of patients.

Withdrawals Due to Adverse Events

No patients discontinued treatment due to AEs or SAEs. Among patients that died during the study, 2 patient deaths (< 1%) in the Optune plus temozolomide group and 1 patient death (< 1%) in the temozolomide group were related to SAEs.

CADTH Appraisal of the Clinical Evidence

Internal Validity

The EF-14 trial was a multicentre, open-label RCT. The patients' knowledge of the treatment allocation could have biased outcomes such as HRQoL, functioning, and AEs in favour of Optune. In addition, the open-label design appeared to influence patient adherence to treatment assignment (discussed in more detail later in this section). The trial did not use a sham device in the temozolomide-alone group. It is acknowledged that, considering the nature of the intervention and potential ethical issues with using a sham device (e.g.,

risk of injury such as skin irritation or burns, need for shaving the head), a sham controlled trial is more challenging to conduct. Nonetheless, these aspects of the study design created uncertainty in interpreting the patient-reported outcomes depending on patients' perceptions about effects of the treatments used in the study; the presence and magnitude of the potential bias could not be determined based on the available information. OS and PFS events as well as radiographic response events were mostly conducted by a blinded independent review, which helped mitigate the open-label study design for these outcomes. The percentage of tumour assessments that were not by independent radiology review (i.e., when MRI was not available) was not reported. The degree of variability in determination of response and progression could not be determined based on the available information.

Randomization was reported to have been done using a centralized web-based system that concealed patient allocation to treatment groups. Randomization was stratified by *MGMT* methylation status and the extent of resection. According to the clinical expert consulted by CADTH, these stratification factors were clinically appropriate because they are well known to affect outcomes of patients with GBM. The baseline characteristics of patients were generally similar between both treatment arms, indicating that randomization was successful.

The patient inclusion criteria for the EF-14 trial were skewed toward enrolling patients with better functional and disease status, and better prognosis at baseline. A KPS score of 70 or more, indicating ability of patients to care for themselves and perform normal activities, was required for trial eligibility. Although this is perhaps a practical consideration in the design of an RCT, this inclusion criterion, for example, would likely lead to an overestimation of the treatment effect of both Optune plus temozolomide and temozolomide alone, given that – in clinical settings – the general health and functioning of newly diagnosed patients with GBM are more diverse, according to the consulted clinical expert. It is noted that the treatment groups were similar at baseline for KPS score.

Similarly, during the screening phase of the EF-14 trial, more than 1,000 patients were screened, and 82 were excluded due to disease progression before randomization. While disease progression was an exclusion criterion per the study protocol, this could introduce a selection bias by including patients with a better prognosis. Additionally, the average time from diagnosis to randomization was 3 months, indicating that only those patients who survived (without progression) until randomization were included in the study. The selection bias due to these reasons could result in higher survival outcomes in both groups.

Following the interim analysis, 26 patients in the temozolomide-alone arm received Optune after the initial analysis (following an approval from FDA to cross over). Another 22 patients in the temozolomide arm received Optune without investigator or sponsor consent (through prescription from outside of the study) when interim results were released and before FDA approval. The latter was noted as a protocol deviation. The survival analyses used for OS and PFS rely on the assumption of noninformative censoring to be valid; however, informative crossover happened for up to 20% of patients assigned to temozolomide alone. The analysis plan was revised after the FDA's approval based on the interim analysis to perform the secondary analyses in the ITT population, in which all patients were analyzed as randomized, including the 48 patients who crossed over. The ITT analysis approach may provide unbiased estimates in the scenario

of nonadherence to assigned treatment and no study withdrawals, but the latter is not the case in the EF-14 trial, in which more than 8% of patients in both treatment groups discontinued the study, primarily for reasons of loss to follow-up and withdrawn consent. This suggests that at least some missing data were missing not at random. Thus, the underlying assumptions of the ITT analysis would not necessarily have been met, and there is potential for selection bias related to the reasons for study discontinuation.

Additionally, the sponsor examined the baseline characteristics of the patients in the temozolomide group who crossed over ($n = 48$) versus the rest of the temozolomide group ($n = 181$). Differences were noted for baseline KPS score, *MGMT* methylation, completion of radiation therapy before randomization, and median number of temozolomide cycles completed. The sponsor highlighted (and the CADTH reviewers agreed) that the observed differences in these characteristics signal that the crossover patients had more favourable prognostic characteristics than those in the temozolomide-alone group who did not cross over. Several sensitivity analyses were conducted for PFS – including tipping point analyses, worst and best case scenarios, and interval censoring – which are considered appropriate but do not represent an exhaustive approach to assessing the potential impacts of the aforementioned issues. Nevertheless, the available sensitivity analyses suggest that the results for PFS were not invalidated by the nonadherence to treatment assignment and discontinuations, yet there remains the potential for bias from untestable assumptions. No such sensitivity analyses were conducted for OS, and combined with the allowance for subsequent therapies, the impact of crossover on OS is unclear.

The study protocol allowed for patients in the Optune plus temozolomide group to continue Optune if they had to discontinue temozolomide for toxicity. The number of patients who experienced temozolomide toxicity and discontinued or switched treatment before progression was unclear. It was reported in the Patient Disposition section that there were no treatment discontinuations due to adverse effects in either treatment group; therefore, it is unlikely that this allowance in the protocol for early discontinuation of temozolomide for toxicity did in fact have an impact on the study results.

The trial allowed for patients who experienced disease progression to continue Optune with or without second-line treatments (until the earlier of second progression or 24 months). It is possible that these subsequent treatments affected the OS outcomes in both groups. The direction of this potential bias depends on the effectiveness of second-line treatments and the proportion of patients in each arm who received them. The clinical expert pointed out that, in real-world settings, second-line therapy after progression would result in a median OS of 6 to 8 months (< 3 months with best supportive care alone) compared to any other treatment. Among the 352 patients in the Optune plus temozolomide arm (including those who crossed over) and the 96 patients in the temozolomide-alone arm, the majority of patients received subsequent treatments including bevacizumab, other chemotherapy, surgical resection, or other second-line treatments. As mentioned previously, the impact of the subsequent treatments on OS estimates is unclear.

At baseline, 28.6% of study participants were reported as receiving concomitant corticosteroids. Duration and dose of concomitant steroids by study participants in each treatment group through the study period were not reported. Additionally, a 50% or greater increase in corticosteroid dose was part of the criteria

for determining clinical progression when MRI was not available. Therefore, the possible impact of corticosteroid use and regimen changes on survival and quality-of-life outcomes in the study could not be ascertained based on the available information.

While the sponsors conducted several subgroup analyses for the survival outcomes (OS and PFS), the study was not designed or powered to detect differences between the groups. There were limitations in the analysis as well, such as the lack of tests for interaction and multiplicity adjustment. Due to these reasons, the certainty in the results of subgroup analyses is low.

While 92% of randomized patients completed an HRQoL questionnaire at baseline, at 12 months, less than half (41.7%) of the patients who were alive at the time provided responses. This large amount of missing data and the descriptive nature of the analysis lower the interpretability of the results. While the impact of missing data on this outcome was not assessed with sensitivity analyses, it is likely that the missing data were not missing completely at random or missing at random; therefore, the validity of the results was considered by CADTH to be very low.

External Validity

The population requested for the reimbursement aligns with the Health Canada indication. The clinical expert consulted by CADTH considered the trial population generalizable to the those with ndGBM in Canadian settings, with a few caveats. The CADTH review team also identified some limitations to the external validity of the trial.

The clinical expert consulted by CADTH estimated that the average age of ndGBM patients in their practice is 65 years; the patients in the trial were slightly younger (mean age 54.9 years). The mean KPS score of patients in the EF-14 trial was 87.8, indicating that on average, the study participants were able to carry on normal daily activities while experiencing some signs and symptoms of the disease. According to the expert, the mean KPS score of patients in Canadian settings is lower. This could limit the generalizability of the results. Furthermore, more than half of the study participants in the trial underwent a total resection of the tumour (53.5%). In real-world settings, approximately 20% to 30% of ndGBM tumours are amenable to gross total resection, according to the clinical expert. Because high KPS scores and resectable tumours are associated with higher survival rates, it is possible that the study enrolled patients with a relatively better prognosis that might not be generalizable to the real-world setting. The sponsor provided a meta-analysis published in 2023⁴⁵ that compared the survival of patients with ndGBM who received treatment with TTFIELDS with those who received standard of care. In addition to the EF-14 trial, the authors identified 8 retrospective cohort studies, 5 of which were conducted in a “real-world setting” according to the authors. The results of the meta-analysis were consistent with the findings of the EF-14 trial, in that treatment with TTFIELDS plus standard of care was associated with an increased OS compared to standard of care alone (HR = 0.63; 95% CI, 0.53 to 0.75). However, CADTH did not formally appraise the publication because it was not provided as a data source in the sponsor’s submission but as supportive information. Nonetheless, the analysis appears to have made several assumptions about the similarity of the pooled study data that were not easily verifiable based on the provided information. CADTH reviewers also noted that, as with the population in the EF-14 trial, the population included in the meta-analysis had a better prognosis than would typically be expected;

namely with higher proportions of total resection (47% to 79% across the studies) and higher KPS scores (80 to 90). Therefore, the generalizability to Canadian settings remains low.

The expert panel consulted by CADTH suggested that Optune treatment would be continued after progression, while acknowledging that patient preferences may change after progression. In the trial, 51% of the patients (per the Stupp et al. [2017]⁴¹ publication) continued Optune treatment (with or without other treatments) after experiencing progression. It is unclear whether this is consistent with the proportion of patients who would continue Optune use in real-world clinical settings.

Both OS and PFS were considered the powered end points of the trial. Radiologic response rate was considered a clinically important efficacy outcome. However, the clinical evidence and rationale for using PFS and radiologic response rates as surrogate outcomes for OS in patients with ndGBM were unclear. While evidence suggests a strong correlation of median PFS with OS in patients with glioblastoma, objective response rates were found to be poorly correlated with survival.⁴⁶ Results of the trial should be interpreted in the light of this limitation.

GRADE Summary of Findings and Certainty of the Evidence

The selection of outcomes for Grading of Recommendations Assessment, Development and Evaluation (GRADE) assessment was based on the sponsor's Summary of Clinical Evidence,³⁰ consultation with clinical experts, and input received from patient and clinician groups and public drug plans.

Table 3: Summary of Findings for Optune Plus Temozolomide Versus Temozolomide for Patients With Newly Diagnosed GBM – OS, PFS, and Radiological Response Rates

Outcome and follow-up	Patients (studies), N	Relative effect (95% CI)	Absolute effects (95% CI)			Certainty	What happens
			Temozolomide	Optune and temozolomide	Difference		
Overall survival - ITT analysis set							
OS rates at 6 months Median follow-up time: 40 months	695 (1 RCT)	NR	873 per 1,000 (821 to 910)	928 per 1,000 (900 to 948)	55 more per 1,000 (5 more to 105 more)	Low ^a	Optune plus temozolomide may result in little to no clinically important difference in OS at 6 months when compared to temozolomide alone.
OS rates at 24 months Median follow-up time: 40 months	695 (1 RCT)	NR	307 per 1,000 (246 to 369)	431 per 1,000 (385 to 477)	125 more per 1,000 (47 more to 202 more)	Low ^b	Optune plus temozolomide may result in a clinically important increase in OS rates at 24 months compared with temozolomide alone. There is uncertainty in the treatment effect because the difference may include little to no clinically important difference in OS.
PFS – ITT analysis set							
Proportion of patients without progression at 6 months Median follow-up time: 40 months	695 (1 RCT)	NR	365 per 1,000 (297 to 434)	556 per 1,000 (506 to 602)	190 more per 1,000 (106 more to 274 more)	Moderate ^c	Optune plus temozolomide likely results in an increase of PFS rates at 6 months compared to temozolomide alone. This increase in PFS rates is considered clinically important.
Proportion of patients without progression at 24 months Median follow-up time: 40 months	695 (1 RCT)	NR	95 per 1,000 (54 to 149)	142 per 1,000 (107 to 183)	47 more per 1,000 (14 fewer to 108 more)	Low ^d	Optune plus temozolomide may result in little to no clinically important difference in PFS at 24 months when compared with temozolomide alone.

Outcome and follow-up	Patients (studies), N	Relative effect (95% CI)	Absolute effects (95% CI)			Certainty	What happens
			Temozolomide	Optune and temozolomide	Difference		
Radiological response rates – ITT analysis set							
Proportion of patients with best response at final analysis, n (%) Follow-up: 40 months	695 (1 RCT)	NR	133 per 1,000 (NR) (n = 31)	74 per 1,000 (NR) (n = 25)	55 fewer per 1,000 (2 fewer to 121 fewer)	Very low ^e	The evidence is very uncertain about the effect of Optune plus temozolomide on radiological response rates when compared with temozolomide alone.

CI = confidence interval; GBM = glioblastoma multiforme; HR = hazard ratio; ITT = intention-to-treat; MID = minimal important difference; NR = not reported; OS = overall survival; PFS = progression-free survival; RCT = randomized controlled trial.

Note: Study limitations (which refer to internal validity or risk of bias), inconsistency across studies, indirectness, and imprecision of effects were considered when assessing the certainty of the evidence. All serious concerns in these domains that led to the rating down of the level of certainty are documented in the table footnotes.

^aRated down 1 level for risk of bias (selection bias, open-label study design, crossover from the temozolomide-alone arm). Rated down 1 level for serious imprecision. The treatment effect estimate and the lower bound of the 95% CI for difference between groups includes possibility of a trivial effect (little to no difference) when compared with temozolomide alone. In the absence of an empirically derived MID, a between-group difference of 10 percentage points was used as the clinically meaningful threshold according to clinical expert input.

^bRated down 1 level for risk of bias (selection bias, open-label study design, crossover from the temozolomide-alone arm). Rated down 1 level for imprecision. The lower bound of the 95% CI for difference between groups includes possibility of a trivial effect (little to no difference) when compared with temozolomide alone. In the absence of an empirically derived MID, a between-group difference of 10 percentage points was used as the clinically meaningful threshold according to clinical expert input.

^cRated down 1 level for risk of bias (e.g., selection bias, open-label study design, crossover from the temozolomide-alone arm). Certainty of evidence was not rated down 1 level for indirectness related to PFS as a surrogate outcome for OS. The best available evidence from one meta-analysis suggests a correlation between PFS and OS in patients with GBM; however, there are numerous limitations with the evidence including important weaknesses in the source studies, such as heterogeneity in patient characteristics, outcome definitions and assessments, incomplete reporting of important patient information especially post progression, and study designs (particularly shorter durations of follow-up), PFS does not appear to be well correlated at 6 month time points and of unclear correlation with longer-term OS beyond the follow-up reported in the source studies for the correlation analysis. The clinical expert consulted indicated PFS seems to predict OS in clinical settings. In the absence of an empirically derived MID, a between-group difference of 10 percentage points was used as the clinically meaningful threshold according to clinical expert input. The certainty of evidence was not rated down for imprecision even though the lower 95% CI for the absolute difference between groups was close to the 10 percentage-point threshold (10.6%).

^dRated down 1 level for risk of bias (e.g., selection bias, open-label study design, crossover from the temozolomide alone arm). Rated down 1 level for serious imprecision. The treatment effect estimate and the lower bound of the 95% CI for difference between groups includes possibility of a trivial effect (little to no difference) when compared with temozolomide alone. In the absence of an empirically derived MID, a between-group difference of 10 percentage points was used as the clinically meaningful threshold according to clinical expert input. Rated down 1 level for serious imprecision. The upper bound of the 95% CI was only slightly greater (10.8%) than the threshold. Certainty of evidence was not rated down 1 level for indirectness related to PFS as a surrogate outcome for OS, per footnote b.

^eRated down 1 level for risk of bias (e.g., selection bias, open-label study design, crossover from the temozolomide alone arm). Rated down 1 level for indirectness. The association of radiological response rate as a surrogate outcome for OS has not been established. Predicting OS using radiological response rate outcomes remain uncertain. Rated down 1 level for imprecision. The 95% CI for difference between groups includes possibility of a trivial effect (little to no difference). In the absence of an empirically derived MID, a between-group difference of 10 percentage points was used as the clinically meaningful threshold according to clinical expert input.

Details included in the table are from the sponsor's Summary of Clinical Evidence,³⁰ or obtained from the sponsor.

Sources: Study EF-14 Clinical Study Report;⁴⁰ Stupp et al. (2017).¹³

Table 4: Summary of Findings for Optune Plus Temozolomide Versus Temozolomide for Patients With Newly Diagnosed GBM – HRQoL and Harms Outcomes

Outcome and follow-up	Patients (studies), N	Effect	Certainty	What happens
Change from baseline of HRQoL domains as measured by EORTC QLQ C30 (including the BN20 supplement) MID ranged from 4 to 11 points ⁴⁷ Time point: Baseline and at 12 months	N = 695 (1 RCT) At baseline: n = 639 ⁴⁴ At 12 months, n = 197 ⁴⁴	The results were reported descriptively. The mean scores for all domains and subscales were generally similar between the treatment arms at baseline and all time points up to 12 months.	Very low ^a	Optune plus temozolomide may result in little to no difference in HRQoL when compared to temozolomide alone.
Harms				
SAEs	672 (1 RCT)	In the total population, there were 156 patients (34%) in Optune plus temozolomide group versus 67 patients (31%) in the temozolomide-alone group with at least 1 SAE.	Moderate ^b	Optune plus temozolomide may result in little to no difference in SAEs when compared to temozolomide alone.

BN20= brain cancer module; EORTC QLQ C30 = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30; GBM = glioblastoma multiforme; HRQoL = health-related quality of life; MID = minimal important difference; RCT = randomized controlled trial; SAE = serious adverse event.

Note: Study limitations (which refer to internal validity or risk of bias), inconsistency across studies, indirectness, imprecision of effects, and publication bias were considered when assessing the certainty of the evidence. All serious concerns in these domains that led to the rating down of the level of certainty are documented in the table footnotes.

^aRated down 1 level for risk of bias in measurement of outcome because the trial was open-label and the tool requires subjective responses. Rated down 2 levels for very serious imprecision because there is a possibility of little to no difference between the groups (descriptive results only).

^bRated down 1 level for risk of bias (e.g., selection bias, open-label study design, crossover from the temozolomide alone arm).

Details included in the table are from the sponsor's Summary of Clinical Evidence.³⁰

Source: Sources: Study EF-14 Clinical Study Report;⁴⁰ Stupp et al. (2017);¹³ Taphoorn et al. (2018).⁴⁴

How Did CADTH Interpret the Clinical Evidence?

The evidence included in this Clinical Review consisted of 1 pivotal trial (the EF-14 trial) that met the inclusion criteria conducted by the sponsor. The sponsor did not identify any long-term extension studies, indirect comparisons, or studies filling gaps in the RCT evidence for this review.³⁰

The EF-14 trial (N = 695) was a multicentre, open-label RCT designed to assess the efficacy and safety of Optune in adult patients with ndGBM following maximal debulking surgery and completion of RT, together with and after standard of care maintenance chemotherapy. Eligible patients were randomized (2:1) to either receive Optune plus temozolomide or temozolomide alone for 24 months. The powered end points of the trial were PFS and OS. The other study outcomes pertinent to this review were survival rates at various time points, radiologic response rates, and HRQoL (measured using the EORTC QLQ-C30 questionnaire), along with safety and tolerance.

The baseline characteristics were generally balanced between the treatment groups. The patients were predominantly male (68.2%) and white (88.5%), with a mean age of 54.9 years. The trial participants had high KPS scores indicating the ability to perform normal activities. More than half of the participants (53.3%) had an *MGMT*-promotor unmethylated tumour, and 53.5% of patients had undergone a gross total resection of the tumour. The mean duration from diagnosis to randomization was 115.8 days.

CADTH identified some potential sources of bias arising from the open-label design, possible selection bias due to enrolling patients with a better prognosis, and due to deviation from intended intervention (crossover). Additionally, only those patients who survived (without progression) from diagnosis to randomization were included in the study, further affecting the internal validity of the results. According to the clinical expert consulted by CADTH, the study participants were slightly younger and had better health status and degree of independent functioning than what is typically observed in clinical practice. These factors lowered the generalizability of the results for both treatment arms. The certainty of the evidence from the single RCT was generally rated as low, ranging from very low to moderate, depending on the outcome.

Efficacy

The current treatment options for GBM are not curative and most patients experience disease recurrence. The main goal of treatment of ndGBM is prolonging life. Evidence from the included trial suggested that Optune plus temozolomide may result in a clinically meaningful increase in the probability of OS at 24 months (OS absolute difference = 12.5%; 95% CI, 4.7% to 20.2%) when compared with temozolomide alone; however, the 95% CI for the estimate includes the possibility that Optune plus temozolomide has little to no effect on OS at 24 months based on a clinically meaningful threshold of a 10% difference between groups. Compared to temozolomide alone, the median OS was 4.9 months longer in the Optune plus temozolomide arm. The certainty of the evidence was graded as low based on the aforementioned limitations of the evidence, including the potentially high risk of bias from informative treatment crossover from control to active treatment, subsequent treatments post progression, and data missing not at random. CADTH reviewers determined there were insufficient analyses performed to evaluate the impact of the potential biases on the OS results.

Results of the subgroup analysis were generally consistent with the overall OS findings, with HRs indicating Optune plus temozolomide was favoured over temozolomide alone in the analyzed subgroups, including those identified as clinically relevant for this review (age, *MGMT* methylation status, and treatment adherence). Subgroup analysis by treatment adherence suggested a dose response to Optune. Higher treatment adherence (> 75%, or wearing the device for at least 18 hours daily) to Optune treatment appeared to be associated with an increase in survival compared to temozolomide alone. *MGMT*-promoter methylation status is a key prognostic factor^{17,18} and an indicator of improved response to alkylating agents, such as temozolomide.²⁷ In the EF-14 trial, the proportions of patients with *MGMT*-methylated tumours were consistent with existing literature (approximately 40%).¹⁹ The HRs for OS favoured Optune plus temozolomide treatment over temozolomide alone, regardless of *MGMT* methylation status. The subgroup results are difficult to interpret with certainty because the EF-14 study was not designed or analyzed for causal inferences in the subgroups, with several subgroups having relatively small sample sizes, not tested

for interaction, and no adjustments for multiplicity. For the *MGMT* methylation status subgroups, the status was unknown in 25% of patients. These limitations also make it difficult to identify patients who are most likely to derive clinically meaningful benefit in OS with Optune plus temozolomide treatment. Of note, the clinical expert consulted by CADTH indicated that the OS results in the temozolomide group at 24 months were higher than what would be expected in clinical settings, which is likely due to the selection bias in the population, resulting in better outcomes in both groups. Thus, it is difficult to determine how well the magnitude of the OS treatment effect with Optune plus temozolomide will be replicated in clinical practice, particularly in a more diverse patient population that has, for example, poorer health status and worse prognostic traits at treatment initiation.

Delaying disease progression is another important goal of treatment of ndGBM and was an outcome considered important to patients and clinicians, as indicated in the stakeholder input. In the EF-14 trial, evidence suggested with moderate certainty that the proportion of patients who were progression-free at 6 months was clinically meaningful, based on a threshold of a 10% difference between groups (absolute difference = 19.1%; 95% CI, 10.6% to 27.4%). At 24 months, evidence suggested that Optune plus temozolomide provided little to no meaningful improvement in PFS versus temozolomide (low certainty). The median PFS in the Optune plus temozolomide group was 2.7 months longer than that in the temozolomide-alone group. Unlike with the OS analyses, several sensitivity analyses were performed for PFS that indicated the results were robust to the various potential sources of bias and assumptions made in the primary analysis. While there is some evidence suggesting that PFS is correlated with OS in patients with glioblastoma,⁴⁶ many uncertainties remain in the strength of the association between PFS and longer-term OS. Therefore, it is unknown based on the current evidence how well the results will translate to OS benefit beyond what was observed in the EF-14 trial. Results of subgroup analyses were generally consistent with the results of the primary analysis. However, the same limitations with the subgroup analyses for OS apply to the PFS results.

The sponsor conducted an exploratory analysis to try to determine whether Optune plus temozolomide has a postprogression survival benefit, given the observation of no meaningful PFS benefit at 24 months yet a potential OS benefit. Results were that median OS time from first progression was longer in patients who were initially randomized to Optune compared to those who were not (12.3 months versus 9.8 months), with an HR of 0.67 (95% CI, 0.52 to 0.85) favouring the Optune group (refer to Appendix 3 in the [Supplemental Materials](#) document). However, these results are considered by CADTH to be hypothesis-generating, given the exploratory nature of the analysis. In addition, because 48 patients in the study crossed over from temozolomide alone to receive Optune, the exploratory analysis was done in the as-treated population and not in the ITT population (for the analysis: n = 352 in the Optune group; n = 96 in the temozolomide-alone group). The trial allowed participants to continue using Optune after first progression (until the earlier of second progression or 24 months); 26% of patients randomized to Optune plus temozolomide continued Optune monotherapy after first progression. The clinical expert consulted by CADTH pointed out that no second-line therapy has been shown to increase OS in ndGBM patients when compared to any other treatment. In real-world settings, the expert estimated that a second-line therapy after progression would result in a median OS of 6 to 8 months (< 3 months with best supportive care alone). Given these limitations,

a causal inference for initial treatment with Optune plus temozolomide and postprogression survival benefit should not be made.

Radiologic response rate was identified as an important outcome by the clinical expert consulted by CADTH. The sponsors reported that in the EF-14 trial, a higher proportion of patients in the temozolomide-alone group (13.3%) showed trial-defined central best response (complete or partial response) compared to those in the Optune plus temozolomide group (7.1%), with an absolute difference of 5.1% (95% CI, 0.2 to 1.1) between the groups. In the absence of an empirical MID, the clinical expert indicated that a 10% difference can be considered clinically meaningful. Thus, the findings indicate that there was no clinically meaningful difference between the groups. Furthermore, evidence from the literature suggests that radiological response rates are not correlated with OS in GBM patients.⁴⁶

Quality of life was highlighted as an important outcome and treatment goal for patients. In the EF-14 trial, self-reported HRQoL scores were generally similar between the treatment groups at baseline and at 12 months. This suggests that the use of Optune does not pose an additional burden on patients' HRQoL and function. In a published analysis of the HRQoL data from Study EF-14, treatment with Optune plus temozolomide was reported as leading to stable or improved HRQoL in 4 out of 9 preselected domains on the EORTC QLQ C30 compared with temozolomide alone.⁴⁴ The analysis also identified that any deterioration in HRQoL with Optune treatment was likely related to increased local skin itching from the placement of the transducer arrays on the patient's scalp. However, the evidence was graded as very low because the study was open-label, and it is possible that the results of this self-reported outcome were biased in favour of Optune, lowering the certainty of the evidence. In addition, the descriptive analysis and missing data mean there is likely serious imprecision in the between-group difference. The efficacy analyses suggest that the benefit of Optune plus temozolomide increases with the number of hours wearing the device, with perhaps at least 18 hours as an important threshold. How this will affect HRQoL and how the level of adherence and suggested stable HRQoL during the progression-free period will translate to real-world clinical settings is unknown based on the existing evidence.

Harms

Evidence from the EF-14 trial suggest that Optune plus temozolomide may result in little to no difference in SAEs when compared to temozolomide alone. Optune treatment did not clearly add safety concerns to temozolomide alone. More than half of the patients receiving Optune reported skin irritation (with 2% experiencing severe skin irritation), likely due to the transducer patches. Psychiatric symptoms like anxiety, insomnia, and confusion were noted in similar proportions (36%, with 2% experiencing serious symptoms) to the temozolomide-alone arm. The other frequently reported AEs included thrombocytopenia due to temozolomide (24% with Optune plus temozolomide versus 23% with temozolomide alone), fatigue (32% versus 25%), headaches (28% versus 20%), and convulsions (22% versus 21%). Other safety concerns included possible falls due to the device wires (tripping hazard), reported in less than 10% of patients who received Optune. SAEs were reported in approximately 30% of participants, and were generally similar between the groups.

Key findings and uncertainties of the clinical evidence are summarized in [Table 6](#).

Economic Evidence

Economic Review Objective

The objective of CADTH's Economic Review is to review and critically appraise the pharmacoeconomic evidence submitted by the sponsor on the cost-effectiveness of Optune (NovoTTF-200A) plus temozolomide compared to temozolomide alone for the treatment of adult patients with newly diagnosed glioblastoma, after surgery and RT with adjuvant temozolomide.

Summary of the Sponsor's Economic Evaluation

Optune is available as a treatment kit consisting of the rented portable field generator and consumable transducer arrays.⁴⁸ The device should be worn for at least 18 hours a day. Optune is available at a \$27,000 monthly fee (as provided by the sponsor), which includes rental of the treatment kit containing the electric field generator, INE transducer arrays (unlimited 1 month supply), plug-in power supply connection cable and other related accessories, services associated with the use of the product, and data tracking. The subscription stops the month after the patient discontinues treatment. Patients are to use Optune in addition to their current chemotherapy regimen (temozolomide).²⁹ Temozolomide costs between \$559 and \$743 per 28-day treatment cycle, when used according to the product monograph–recommended dosing.⁴⁸

The sponsor submitted a cost-utility analysis to assess the cost-effectiveness of Optune in combination with temozolomide compared with temozolomide alone for the treatment of patients with newly diagnosed GBM, after surgery and RT, based on the population in the EF-14 trial. The modelled population is aligned with the Health Canada indication under review by CADTH. The analysis was undertaken using a lifetime time horizon (30 years) from the public payer perspective, with life-years and QALYs as the key clinical outcomes measured.⁴⁸

The sponsor used a partitioned survival model to track a cohort of patients with ndGBM, consisting of 3 health states (progression-free, progressed disease, and death).⁴⁸ PFS curves were generated using extrapolated data from the EF-14 trial for each arm. OS curves were informed by the EF-14 trial for the first 5 years, conditional survival probabilities from published literature for years 5 to 15, and general Canadian population mortality data to inform years 16 and beyond.^{41,48-50} Duration of treatment was informed from the median time on treatment from the EF-14 trial and other data from the EF-14 trial.^{41,48} HRQoL was informed from published literature.⁵¹ Costs considered in the economic analysis included those associated with drug and device acquisition, supportive care (routine patient monitoring), and AE management costs.⁴⁸

CADTH Appraisal

CADTH identified several key limitations with the sponsor's analysis:

- While the clinical data used to inform the sponsor's submitted pharmacoeconomic model from the EF-14 trial (data cut-off December 2016; median follow-up of 40 months) indicated likely increases in PFS and OS associated with Optune plus temozolomide, the treatment effect appeared to be dependent on the frequency and duration of use of Optune. That is, if patients do not wear Optune for at least 60% of the day, the effect of Optune plus temozolomide may not be different

from temozolomide alone. Clinical experts consulted by CADTH during this review suggested that treatment compliance is expected to be lower in Canadian clinical practice than in the EF-14 trial, and thus the true efficacy of Optune is uncertain.

- The predicted long-term OS for Optune may be overestimated due to the sponsor's assumption that patients would be functionally cured after 15 years. Patients who survived beyond the first 5 years were assumed to have a lower risk of death based on published literature on patients with GBM; patients who survived beyond 15 years were then assumed to have rates of mortality based on the general Canadian population. These assumptions suggest that Optune is curative; there is no robust evidence to suggest this will occur in Canadian clinical practice.
- Time on treatment for both Optune plus temozolomide and temozolomide alone were based on median data from the EF-14 trial (Optune plus temozolomide: 8.2 months; temozolomide alone: 7.2 months). There is uncertainty in the expected time on treatment in clinical practice. CADTH noted the median time on treatment for Optune differed from the mean (■ months). While the median is ■ than the mean, indicating most patients on Optune plus temozolomide used the therapy for ■ than ■ months there was a ■ time on treatment during the EF-14 trial.⁴¹ Although time on treatment was only used to inform drug and device costing in the model, the use of median values may underestimate treatment duration and result in underestimated costs in the sponsor's analysis.
- Health-state utility values were informed by Garside et al., 2007.⁵¹ These values did not meet face validity, as the values implied that patients with ndGBM have greater well-being compared to the general Canadian population. Alternate utility values from robust sources could not be identified. However, CADTH obtained clinical expert feedback that noted that the difference between the utility values for the progression-free and progressed disease health states may be considered reasonable. As the difference between health states is instrumental in determining relative cost-effectiveness, CADTH maintained the sponsor-submitted values despite the limitations with the values.
- The sponsor-submitted fee for Optune is a monthly rental payment model that includes the components of the device (portable field generator and consumable transducer arrays) and support features. It is unknown whether the payer will be able to implement the payment model suggested by the sponsor, and whether there are relevant cost components that have not been captured within the sponsor's costing model for which the cost may be borne by the health system or patients.

CADTH revised the sponsor's OS curves and altered the duration of treatment to inform the base-case analysis. CADTH was unable to address the uncertainty associated with comparative clinical effectiveness, payment model, and concerns relating to the utility estimates used.

CADTH Assessment of Cost-Effectiveness

The results of the CADTH base-case analysis demonstrate that use of Optune plus temozolomide is associated with an additional 0.37 QALYs at an additional cost of \$336,902 compared with temozolomide alone (Table 5). This results in an incremental cost-effectiveness ratio (ICER) of \$899,470 per QALY gained for Optune plus temozolomide compared to temozolomide alone. CADTH observed that these results were

highly sensitive to duration of treatment with Optune, the relative efficacy of Optune, and the monthly fee of Optune.

Table 5: Summary of the CADTH Cost-Effectiveness Results

Medical device or intervention	Total costs (\$)	Incremental costs (\$)	Total QALYs	Incremental QALYs	ICER vs. TMZ alone (\$ per QALY)
TMZ alone	58,435	Reference	1.54	Reference	Reference
Optune plus TMZ	395,336	336,902	1.92	0.37	899,470

ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life-year; TMZ = temozolomide; vs. = versus.

Based on the CADTH reanalysis results, Optune plus temozolomide is not considered cost-effective relative to temozolomide alone, based on conventional willingness-to-pay thresholds at the submitted monthly fee of \$27,000 for Optune. A reduction of 91% to 97% in the monthly fee of Optune (i.e., monthly fee of \$864 to \$2,403) is required for Optune plus temozolomide to be considered cost-effective at a willingness-to-pay threshold of between \$50,000 and \$100,000 per QALY gained. Given the uncertainty associated with the utility values, CADTH undertook a scenario analysis focusing on an incremental cost per life-year gained outcome. This analysis suggested that a slightly lower price reduction range may be considered (88% to 95%).

The sponsor also conducted a scenario analysis from a societal perspective, in which additional costs associated with productivity loss for patients, due to the inability to work or death, were included. The ICER from this analysis was similar to the ICER from the health care payer perspective.

Additional information regarding the sponsor's Pharmacoeconomic Evaluation and CADTH appraisal is located in the [Supplemental Materials](#) document (Appendix 4).

Summary of the Budget Impact

The sponsor submitted a budget impact analysis to estimate the 3-year (2024 to 2026) budget impact of reimbursing Optune plus temozolomide for the treatment of newly diagnosed GBM after surgery and RT with adjuvant temozolomide. The sponsor assumed the payer would be CADTH-participating public drug plans and the population size was derived using an epidemiological approach. The monthly fee for Optune aligned with the sponsor's economic evaluation. Using data from published literature and clinical expert feedback received by the sponsor, the sponsor estimated that approximately 759 to 777 patients would be eligible for treatment in years 1 to 3, respectively.

CADTH identified uncertainty in the estimated number of newly diagnosed patients with GBM eligible for treatment, uncertainty in the duration of Optune plus temozolomide treatment, and indicated that the drug plan payer perspective was inappropriate.

CADTH reduced the proportion of patients who undergo external beam radiation therapy with adjuvant temozolomide and increased the time on treatment for Optune plus temozolomide by using the mean time on treatment for patients receiving Optune plus temozolomide from the EF-14 trial to align with clinical expert feedback and published evidence. Based on these revisions, CADTH estimated that 1,352

patients would be eligible for treatment over the initial 3-year period, of whom 232 were assumed to receive Optune based on the sponsor's market uptake assumptions. The estimated incremental budget impact of reimbursing Optune plus temozolomide is \$12,153,567 in Year 1, \$27,689,944 in Year 2, and \$35,951,813 in Year 3, resulting in a 3-year budget impact of \$75,795,323.

Additional information regarding the sponsor's budget impact analysis and CADTH appraisal is located in the [Supplemental Materials](#) document (Appendix 5).

Key findings and uncertainties of the economic evidence are summarized in [Table 6](#).

Ethics Review

Ethics Review Objective

To identify and describe ethical considerations associated with the use of Optune (NovoTTF-200A) for newly diagnosed supratentorial glioblastoma following maximal debulking surgery and completion of RT together with and after standard of care maintenance chemotherapy. These include ethical considerations related to the context of supratentorial glioblastoma; the evidence used to evaluate Optune; the use of Optune for patients, their caregivers, and clinicians in Canada; and the implementation of Optune for health systems in Canada.

Methods

Information on methods for the Ethics Review is available in the [Supplemental Materials](#) document (Appendix 6).

Results

Treatment and Experiences of GBM

The current standard of care treatment for patients with ndGBM is maximal safe surgical resection of tumour tissue followed by the Stupp protocol, which consists of a combination of targeted RT and chemotherapy with temozolomide, followed by standard of care maintenance chemotherapy using temozolomide.¹³ There have been no significant advances in treatment for GBM since the introduction of the Stupp protocol in 2005, so the prospect of a new treatment modality is of great interest to patients, their caregivers, and their treating clinicians. The clinician group input noted the current goals of treatment for ndGBM include the prolongation of life and PFS, paired with the minimization of AEs due to treatment-related toxicity, and the maximization of quality of life. The patient group input reported that patients seek improvements over existing treatments, including: making the tumour smaller or slowing its growth, making their day-to-day living easier, being easy for them to access and use, and having no or minimal cost.

The patient group input and clinical experts reported that the patient experience of GBM varies significantly depending on tumour type, size, and location; response to standard of care treatment; and access to personal and formal support networks. As an almost universally fatal condition with a high symptom burden,

GBM is physically, emotionally, and psychologically burdensome for patients.^{9,52-54} Symptoms vary, but can include headaches, seizures, nausea, vomiting, dizziness, fatigue, memory loss, mood and personality changes, and concentration and cognitive difficulties.⁹ Symptoms can be alleviated somewhat with standard of care treatment but will recur with tumour regrowth, as is common in GBM. Standard of care treatment, including a combination of surgery, radiation, and chemotherapy, is aggressive and physically burdensome.⁵² The patient group input noted that patients experience increasing challenges with maintaining autonomy, including activities of daily living (ADLs), speech, and cognitive functioning as the disease progresses. Patients become progressively more dependent on caregiver support with disease progression. As a result, GBM is also physically, psychologically, and economically burdensome for caregivers.⁵⁵ Caregiver burdens include managing patients' mood, personality, and cognitive changes; difficulties in coping with finances (including managing work obligations or time away from work); efforts to juggle obligations to other dependent family members; and struggles with their own physical and emotional well-being.

Ethics of Evidence and Evaluation of Optune

The effectiveness of Optune plus temozolomide compared to temozolomide alone in adult patients with ndGBM who had already undergone maximal debulking surgery and completed RT concomitant with temozolomide was evaluated in the pivotal open-label EF-14 trial (N = 695). Treatment goals regarding safe and tolerable treatment appear to have been met, as Optune-related AEs included skin irritation, falls, headaches, and psychiatric symptoms, but no notable SAEs. The use of Optune plus temozolomide for a minimum of 18 hours per day on average appeared to prolong PFS and OS, which are both considered clinically meaningful by the clinical experts consulted by CADTH in the course of this Reimbursement Review. However, as detailed in the Clinical Review, the trial evidence is of moderate to very low certainty, due to concerns regarding a selection bias and low generalizability of results to real-world settings. Additionally, although HRQoL results were reported as being generally similar between the treatment arms, completion of the questionnaires at the 1-year follow-up was poor. Clinical experts acknowledged that patients with GBM may face challenges with reporting HRQoL as the disease progresses, which may make it challenging to assess whether Optune offers differential HRQoL benefits within a heterogeneous patient population in the real world. For example, it may be important to understand whether requirements to wear Optune 18 hours a day and manage technical issues would disproportionately impact the HRQoL of older adults.⁵⁶ As detailed in the Clinical Review, the overall lack of representativeness of clinical trial participants raises potential concerns regarding the generalizability of the study findings for the broader patient population in Canada. This has potential ethical implications for consent conversations, the acceptability and uptake of the device, and the supports required to facilitate equitable access in a diverse patient population. The clinical experts noted that participants in the EF-14 trial were not reflective of patients with ndGBM in Canada. Rather, participants were younger (median age of 54.9 years) and had a higher mean KPS score of 87.8 at initiation (and so were able to perform ADLs independently), both of which are associated with better clinical outcomes in patients with GBM in Canada.⁵⁷ Additionally, participants were predominantly white (88.5%) and male (68.2%). The clinical experts noted that they did not expect a patient's race, sex, or socioeconomic status to have any direct bearing on the efficacy of Optune; however, the lack of diversity in the trial, and the lack of information on barriers that may be faced by patients in equity-deserving groups

— including those who may be less comfortable with technology, those who are less able to navigate the complexities of the patient journey, those who face socioeconomic or geographic disadvantages, and those who lack adequate caregiver support — present uncertainty about disparities in efficacy and access in real-life settings. Additionally, clinical experts noted that it is uncertain whether the high level of adherence (75% within the first 3 months) reported in the clinical trial is generalizable to the broader patient population, due to differences in patient motivation and support outside the trial context. The degree of adherence may impact efficacy, as treatment effect is believed to be dose-dependent (requiring the device to be worn for at least 18 hours per day). Further study on how, or if, these factors have implications for device uptake and treatment adherence would be helpful to support patient-centred and equitable use, given the diversity of the population in Canada.

Ethical Considerations in the Use of Optune

Benefits and Harms

Ethical considerations related to the use of Optune by patients, caregivers, and clinicians require considering the balance of potential benefits, risks, and burdens related to its safety, efficacy, and use requirements. Optune (administered for at least 18 hours per day) in conjunction with adjuvant temozolomide likely prolongs PFS and OS for patients with ndGBM. The clinical expert noted that tumour methylation status does not appear to impact the efficacy of Optune, and there seem to be no clinically notable concerns with respect to toxicity, so this is a treatment modality that may be especially helpful to patients with unmethylated tumours who do not benefit from existing therapeutic options. Optune is proposed as an addition to, rather than a replacement for, existing treatment options, so there is no prima facie reason to suppose that expanded access to Optune will have significant negative effects on the population of patients with GBM, beyond the generally manageable skin breakdown reported in the EF-14 trial. Additionally, advances in device design may offer opportunities to increase patient satisfaction with and ease of use of the device.³¹

Patient group input drew on the experiences of patients and caregivers who had direct experience with Optune, and noted, “Almost all patients using Optune and caregivers of people on the treatment would recommend that it be made accessible to people living with glioblastoma.” Clinical experts consulted by CADTH similarly noted that they would offer Optune plus temozolomide to patients with ndGBM owing to the clinically significant treatment benefit, which is important to patients and their caregivers, and unmet need for additional treatment options for this patient population. However, it will be important to emphasize during consent and treatment conversations that Optune is offered in conjunction with temozolomide, and that the observed treatment effect is not achieved by Optune alone. As a result, clinicians will need to communicate clearly that any burdens patients have experienced or continue to experience with standard of care maintenance chemotherapy will not be lifted with the addition of Optune. Instead, patients and their caregivers will be required to manage an additional treatment modality (including frequent shaving of the scalp, wearing the device for at least 18 hours per day, and managing any skin breakdown that may occur) even as the disease progresses. As a self-administered treatment, Optune has high educational needs for patients and caregivers at treatment initiation.⁵⁸

The use of Optune need not preclude the use of other valuable tools for managing the course of GBM. However, there may be opportunity costs associated with a focus on a treatment modality that is not curative.⁵⁹ The promise of an increase in OS and PFS of a few months comes at the cost of an excess of 18 hours per day of adherence to device use that requires significant commitment from patients and caregivers. As noted by clinical experts, some patients will wish to maintain a sense of control over their illness by pursuing interventions that may extend life (a value that may have been a high priority for those who elected to enter Optune trials).⁵⁸ Similarly, patient group input described Optune as providing “people hope and a quality of life, because if you are wearing this device, you feel like you’re a part of the process of healing and extending your life.” However, the importance of managing expectations well during consent conversations to support informed decision-making and respect for autonomy, and the benefits of timely palliative care, should not be overlooked.^{60,61} There is a risk that a focus on the hope that may be engendered by this treatment modality may shift attention from other management strategies that may have a greater prospect of meeting patients’ end-of-life needs. A qualitative study examining patient, caregiver, and provider experiences and preferences around GBM treatment communication noted that “[t]reatment was often presented or understood as ‘the only option,’” which was in tension with caregivers’ and patients’ desires for enhanced communication about available support services and preparation for life’s end.⁶⁰ Palliative care services are often postponed until the last days or weeks of life, despite benefits of supportive and palliative care (such as longer survival, improved quality of life, and a reduction of caregivers’ depressive symptoms and burden).⁶⁰ It is important to recognize that hope can be both beneficial and potentially limiting in the case of false hope,⁶¹ and that clinicians continue to refer patients and families to a full range of treatment and care options, including available palliative care supports.⁶⁰ Technical supports provided by the sponsor to facilitate the use of Optune should not be expected to take the place of the comprehensive advance care planning and comfort care that a palliative care team is able to provide. Nonetheless, patient group input and the clinical expert panel consulted by CADTH noted that hope may outweigh the challenges associated with using the device for some patients and caregivers, which was similarly noted by the Institut national d’excellence en santé et en services sociaux (INESSS).⁶¹

Eligibility

As reported in the product user manual, listed contraindications to the use of Optune include additional neurologic diseases (e.g., epilepsy, encephalitis or hydrocephalus, and allergy), intolerance to components of the hydrogels, presence of other medical devices such as brain stimulators or pacemakers, and presence of a skull bone defect. Optune has not been tested in people who are pregnant and is advised not to be used in this patient population or in those who intend to become pregnant. The clinical experts noted that these contraindications were reasonable in the context of an early trial as well as general clinical practice. Nonetheless, if patient-centred care is a goal of treatment, clinician judgment and patient or substitute decision-maker preferences may prompt reconsideration of certain contraindications, as risk tolerance and individual circumstances vary.⁶² Case reports describing ongoing treatment for pregnant women with GBM illustrates the possibility of fulfilling a patient and family’s preferences for continuing the pregnancy to viability despite a grim prognosis.⁶³⁻⁶⁵ Although this may be a rare occurrence, given the toxicity of chemotherapy and radiation, and their possible effects on fertility and a developing fetus, it illustrates that

patients in clinical practice may differ significantly from trial participants, and there may be additional applications for Optune that are clinically supportable.

Acceptability

Given the requirements for using Optune (e.g., shaving one's head every 3 days to allow adequate conductivity, wearing the device for at least 18 hours per day, having access to a reliable power source to recharge batteries, and support with placing electrodes), it is important to consider the acceptability of the device by patients and caregivers when considering how to support patient and caregiver use and uptake within Canada.

A retrospective study assessing the acceptance of and compliance with Optune in patients (n = 58) with high-grade GBM reported that 36% of eligible patients accepted the offer of this treatment, and more than 75% complied with using the device for a minimum of 18 hours per day.⁶⁶ Reasons given for declining the device include: head shaving, visibility of the device, impairment of mobility, independence in daily life, noncompatibility with work (50%), lack of social or family support (17%), technical challenges (8%), and unknown (25%). The study investigators suggest that high compliance with Optune may require careful patient education and a staged approach to introducing Optune to patients. They also stress the importance of informing patients about logistics and possible side effects, and note that patients and caregivers may need up to 4 weeks to adjust to the everyday challenges of the therapy.

INESSS reports that, although difficult to predict, Optune has an expected maximum acceptability rate of 50% of patients offered treatment in Quebec, with patients declining treatment due to the device's appearance and demands of use.⁶¹ The clinical expert panel consulted by CADTH similarly noted that the acceptability of Optune by patients in the pan-Canadian context, were it reimbursed, would be variable. They suggested that acceptability would likely depend in part on a patient's disposition (e.g., the extent to which use of the device provided them with a sense of control over the disease versus visibly reminded them of the disease and illness) and in part on patients' caregiver support networks, as they would require assistance with using the device. Although Optune is visible even with headwear, and users will have their mobility constrained with use, the expert panel suggested that some users will accept losses with respect to privacy, comfort, and convenience as reasonable tradeoffs for the prospect of an enhanced sense of control over the progression of their disease. As an equity-related consideration, however, it would be helpful to have reliable data as to whether patients who identify as women are less inclined to accept head shaving, or if those who belong to communities in which hair has an important spiritual or cultural significance would find this device unacceptable, even with the promise of clinical benefit. Overall, however, patient and clinician group input and the expert panel consulted by CADTH expressed interest in making Optune available as an additional treatment option for patients in Canada.

Informed Consent

As patients with ndGBM can be described as "vulnerable," owing to their incurable and progressive condition and reliance on clinician recommendations and referrals as well as caregiver support, careful attention must be paid to the quality of consent conversations and shared decision-making.^{67,68} This includes efforts to ensure that patients' values are elicited and understandings assessed and reconfirmed over time to

ensure that they have an appreciation of the likely risks, benefits, burdens, and uncertainty associated with treatment, given evolving evidence available over time for this new treatment option. Ascertaining a patient's values and treatment goals is additionally important, as disease progression may impair cognitive function and capacity to consent and thus require the involvement of a substitute decision-maker.⁶⁷⁻⁷⁰ A systematic review focused on communication, information, and supports for patients with GBM reported that patients may be unaware of their prognosis, and noted the importance of tailoring information about prognosis to individuals' coping abilities, as well as maintaining hope despite a poor prognosis.⁵⁵ Consent conversations will also require ensuring that patients and/or substitute decision-makers understand that Optune is neither curative nor a replacement to temozolomide and challenges experienced with temozolomide may persist, so that they can weigh the potential benefits, risks, and burdens of use accordingly. Patients should also be informed that the use of the device will require transmitting MRI scans to the sponsor for the development of a treatment plan before treatment initiation. Consent conversations should include information on the measures that the sponsor will take to ensure that data are stored, transmitted, and disposed of in accordance with applicable provincial privacy standards. Additional consent should be obtained if nonclinical use of patient data is anticipated.

Health Systems Considerations

Barriers to Equitable Access

Equity-enhancing strategies will need to be explored if Optune is to be accessed in a fair and effective manner by patients in Canada, including those who may have been unrepresented or underrepresented in the EF-14 trial. As reported by INESSS in Quebec, and confirmed by experts consulted by CADTH in the pan-Canadian context, the trial population overall was younger, had a higher median KPS score, and had greater *MGMT* methylation status than what would typically be found in Canadian practice.⁶¹ INESSS reports that certain social determinants (e.g., geographic, linguistic, or cultural factors) could present barriers to access for some patients.⁶¹ Experts consulted by CADTH similarly noted that such factors also apply to the pan-Canadian context, in which patients' circumstances are very heterogeneous and access to specialty cancer care varies widely across the country. Understanding potential barriers to access or effective use of Optune, as discussed in the Ethics of Evidence and Evaluation of Optune section, is important for equitable implementation in real-world contexts. This is particularly important given existing disparities in access to treatment, care, and outcomes reported for GBM associated with lower socioeconomic status, geography (including rurality, greater distance travelled, and lower hospital volume), and other social determinants of health in Canada and internationally.⁷¹⁻⁷⁶ The sponsor offers a patient support program for patients currently accessing Optune and their caregivers in Canada, which it intends to continue if Optune is reimbursed. The sponsor has also reported a willingness to work with patients, caregivers, clinicians, and payers to support equitable access in Canada. Additionally, as noted by clinical experts, Optune is administered in patients' homes, and does not require frequent clinical visits, so it is possible that this treatment modality could also enhance access to care for patients who live at a distance from specialized cancer centres when paired with adequate patient education and support.

Equity concerns also arise with respect to patients' variable access to caregiver support. Although the expert panel maintained that good support structures, including help from informal caregivers, are important for

patients with cancer to be able to access many of the treatment options that may benefit them, this remains an equity-related barrier for accessing and effectively using Optune. This is notable as the patient group input reported that caregivers describe themselves as feeling anxious, overwhelmed, depressed, unsupported, and unprepared to assume the responsibilities of caregiving. A number had become full-time caregivers who found themselves unable to continue with their regular paid employment, and several stated that they had become unable to attend to their own well-being or that of other family members. Even if caregivers declare a willingness to assume these onerous caring responsibilities, including with the addition of the use of Optune, many will not be able to forego employment for the many months that treatment is needed. Patients who lack caregiver support, or whose caregivers have limited availability to offer support due to employment or other obligations, may face disproportionately greater challenges with accessing, using, and benefiting from Optune. If the use of Optune is to be accessible to patients with limited financial means or without an extended network of community support, consideration should be given to resources that could be provided to lighten the caregiver load.

An additional equity-related consideration is that temozolomide, an oral chemotherapeutic drug, is not reimbursed by all public drug programs across Canada. As a result, inconsistencies in reimbursement of oral temozolomide across jurisdictions may present a barrier to equitable access owing to high-out-of-pocket costs. As Optune works synergistically with temozolomide, it is necessary to consider the variable access that patients in Canada may have to this chemotherapeutic drug. If oral temozolomide is inaccessible to patients in jurisdictions where it is not reimbursed, the benefits of Optune (even if reimbursed) may remain inaccessible to patients who have limited financial means or lack adequate private insurance coverage.

Limitations

There is little published literature discussing ethical considerations related to the use of Optune for the treatment of ndGBM, given both the heterogeneity of the disease and the novelty of the device under review. Nonetheless, this does not imply that ethical considerations in the context of Optune for GBM are absent, and this review of ethical considerations was augmented by drawing from additional resources collected in the course of this Reimbursement Review. Although this review drew on patient group, clinician group, and caregiver and clinical expert input, it is possible that more direct engagement with additional groups (e.g., interviews with a more representative group of patients, caregivers, family members, and decision-makers) on their specific experiences with GBM and/or Optune could have offered additional relevant ethical considerations.

Key findings and uncertainties of the Ethics Review are summarized in [Table 6](#).

Issues for Consideration

- Results from other health technology assessments are consistent with our findings.^{61,77,78} INESSS concluded that the use of Optune for the treatment of ndGBM is clinically beneficial in prolonging OS with minimal safety issues and quality-of-life burden, but is not cost-effective when combined with temozolomide versus temozolomide alone.⁶¹ The report also highlighted the limitations of the

evidence, such as possible selection bias, and the uncertainty in the generalizability of findings to real-world settings.

- The sponsor considered that the payer for Optune would be public drug plans, based on sponsor-conducted consultations with provincial jurisdictions and cancer agencies advocating for pan-Canadian health technology assessment (HTA) reviews. Thus, public drug plans informed the perspective for the submitted economic evaluation and budget impact analysis. As Optune is a device, it is unclear whether the CADTH-participating drug plans are the appropriate payer for Optune. An alternate approach in which other payers were considered may have been more appropriate.
- Based on the sponsor's submitted materials, the submitted fee for Optune is \$27,000 per month, which includes rental of the treatment kit containing the electric field generator, batteries and charger, plug-in power supply connection cable and box, INE transducer arrays (unlimited 1-month supply), power cords, battery case, and shoulder bag and strap. Additional services covered by the monthly fee include: individual planning of the INE transducer array treatment layout specific to each tumour per patient by trained radiologists, onsite and 24/7 technical phone support from Novocure throughout the duration of the therapy, regular meetings with the Novocure device support specialist, ongoing maintenance of the electric field generator with device replacement (if needed), and transmission of usage data to the attending physician. The monthly subscription stops the month after a patient discontinues treatment. Clinician feedback received by CADTH raised concerns regarding the feasibility of implementing a subscription model, including cases where patients discontinue treatment early in a subscription cycle or the definition of "per month" (i.e., 30 days versus the first day of each month). Thus, the actual implementation of a subscription model by the primary payer is uncertain. Additionally, should the sponsor decide to no longer cover item(s) or support within their monthly fee, then additional costs are likely to be borne by other government payers or patients.
- The lifespan of Optune and its components is uncertain. The sponsor assumed that the monthly rental fee of Optune would cover repair, replacement, maintenance, technical support, and clinical support associated with the device; however, the responsiveness of the sponsor to deliver the suggested services within the monthly fee is unknown. Furthermore, it is unclear if new versions of Optune will be covered under the submitted agreement, or associated with changes to the sponsor's fee structure.
- An earlier version of the device (NovoTTF-100A) was used in the clinical trial. While it had the same functionality, the NovoTTF-100A was heavier (weighing approximately 2.7 kg). The newer generation Optune (NovoTTF-200A) includes a redesigned electric field generator and smaller battery, making the device lighter (weighing approximately 1.2 kg) and more user-friendly, according to the manufacturer.³¹ The lighter weight and reduced noise of the NovoTTF-200A could impact HRQoL; however, the degree of the impact is unknown.

Key Findings and Uncertainties

Table 6: Summary of Key Findings and Uncertainties

Domains	Key findings	Uncertainties
<p>Need</p>	<ul style="list-style-type: none"> • GBM is a high-grade brain tumour with poor prognosis and no curative treatment. It is the most common primary malignant tumour of the CNS. • There are approximately 1,850 patients with GBM in Canada (data from 2010 to 2017).¹² • The current treatment strategy is the Stupp regimen, which includes surgical resection followed by chemoradiation and adjuvant chemotherapy with temozolomide. • GBM is physically, psychosocially, and economically burdensome for patients and their caregivers. • Optune (NovoTTF-200A) is a portable and noninvasive device that treats GBM by providing continuous, locoregional treatment with TTFIELDS. 	<ul style="list-style-type: none"> • There have been no new treatment options that improve survival of patients with GBM since the early 2000s. • The current chemotherapeutic drug temozolomide is considerably less effective in patients with <i>MGMT</i> unmethylated tumours,²⁷ which constitute up to 60% of patients with ndGBM.¹⁹ • None of the available treatments (including Optune) are curative, and the disease has a poor prognosis.
<p>Clinical benefits</p>	<ul style="list-style-type: none"> • CADTH reviewed evidence from a multicentre, open-label RCT that compared the efficacy and safety of Optune with temozolomide in adult patients with ndGBM following maximal debulking surgery and completion of RT, together with and after standard of care maintenance chemotherapy. • Optune plus temozolomide likely increases PFS at 6 months of treatment and OS at 24 months of treatment compared to temozolomide alone (moderate to low certainty). • The treatment effect of Optune plus temozolomide on PFS and OS may be dose-dependent, with at least 18 hours of daily Optune use required for the most benefit. • Optune plus temozolomide may result in little to no difference in HRQoL (very low certainty) when compared to temozolomide alone. 	<ul style="list-style-type: none"> • CADTH identified weaknesses of the study that could affect the internal validity of the results. • The patient inclusion criteria were skewed toward enrolling patients with a better functional and disease status, and better prognosis at baseline. Only those patients who survived (without progression) from diagnosis to randomization were included in the study. • The open-label design of the trial created uncertainty in interpreting the patient-reported outcomes. • There were concerns regarding the crossover of some patients from the temozolomide-alone arm. • The study participants were slightly younger and had better health status and degree of independent functioning than what is typically observed in clinical practice. These factors lowered the generalizability of the results. • Overall, evidence was of moderate to very low certainty due to concerns regarding selection bias and low generalizability of results to real-world settings. • No longer-term studies or indirect comparisons were identified by the sponsor for the review.

Domains	Key findings	Uncertainties
Clinical harms	<ul style="list-style-type: none"> CADTH found little to no difference in serious adverse events between Optune plus temozolomide and temozolomide alone (moderate certainty). Optune treatment did not clearly add safety concerns to temozolomide alone. 	<ul style="list-style-type: none"> There were some adverse events related to the device, such as skin irritation or itching from the transducer arrays, but they were mostly not severe.
Patient preferences	<ul style="list-style-type: none"> Patients receiving Optune with temozolomide may benefit from clear MRI results, prolonged survival, and some resumption of daily activities. Nonetheless, they may also experience side effects, particularly scalp irritation and dermatitis. Most patients with lived experience using Optune recommended making the treatment more accessible to people living with GBM. 	<ul style="list-style-type: none"> Patients using Optune need to manage lifestyle adjustments, such as wearing it for 18 hours daily, maintaining regular head shaving, and applying the transducer arrays to the head, which may require caregiver assistance.
Economic impact	<ul style="list-style-type: none"> The submitted fee for Optune is \$27,000 per month, which includes the treatment kit and support features. This cost is added to the cost of temozolomide. At the submitted monthly fee for Optune and public list price for temozolomide, the ICER for Optune plus temozolomide vs. temozolomide alone was \$899,470 per QALY gained (incremental costs = \$336,902; incremental QALYs = 0.37). At this ICER, Optune plus temozolomide was not considered cost-effective relative to temozolomide alone at conventional willingness-to-pay thresholds (i.e., \$50,000 per QALY gained or \$100,000 per QALY gained). A price reduction of between 91% and 97% is required for Optune plus temozolomide to be considered cost-effective at a willingness-to-pay threshold between \$50,000 and \$100,000 per QALY gained. The budget impact of reimbursing Optune through the federal, provincial, and territorial public drug plans (excluding Quebec) is estimated to be \$75,795,323 over 3 years. Optune is estimated to be used by 232 patients over 3 years. 	<ul style="list-style-type: none"> The long-term efficacy of Optune is uncertain and may be dependent on the frequency and duration of the use of Optune by patients. The sponsor assumed that patients would be functionally cured after 15 years. There is no robust evidence to support the validity of this assumption. Time on treatment for Optune plus temozolomide and temozolomide alone were based on data from the EF-14 trial. There were wide ranges in time on treatment in the trial and differences in median and mean time on treatment. It is unclear how time on treatment data from the EF-14 trial will translate to Canadian clinical practice. Health-state utility values did not meet face validity.
Implementation	<ul style="list-style-type: none"> Following surgical resection and RT with concomitant temozolomide, patients would receive Optune during the adjuvant temozolomide treatment phase. The sponsor assumed the payer for Optune would be drug plans. The sponsor assumed that the monthly rental fee would cover repair, replacement, 	<ul style="list-style-type: none"> It is unclear whether the CADTH-participating drug plans, as suggested by the sponsor, are the appropriate payer for Optune. It is unclear whether the subscription model and full set of included services indicated by the sponsor will be implementable by the payer. The lifespan of Optune and its components is uncertain. The responsiveness of the sponsor

Domains	Key findings	Uncertainties
	<p>maintenance, technical support, and clinical support.</p> <ul style="list-style-type: none"> • A clinician must undergo a training course provided by the sponsor and obtain certification to prescribe Optune. • It is suggested that there are no additional costs to the health care payer associated with training physicians, patients, and caregivers to be familiar with the technology. • Clinical experts consulted by CADTH commented that it may be reasonable for patients to continue treatment beyond initial disease progression. 	<p>to deliver the suggested services within the monthly fee cost is unclear. It is also unclear whether any new versions will be associated with changes to the sponsor's fee structure.</p> <ul style="list-style-type: none"> • It is unclear whether the same standard of device repair and maintenance support observed in clinical trials could be maintained as the customer base of Optune expands in the real-world health system environment. • Effectiveness of Optune appears to be dependent on treatment adherence (e.g., time wearing the device); thus, patient motivation may be important in determining device uptake. Family and caregiver support may be important in increasing the treatment adherence. • It is unclear whether any suggested discontinuation criteria can be implemented.
<p>Ethics</p>	<ul style="list-style-type: none"> • The balance of benefits, risks, and burdens associated with Optune is understood within the context of an individual patient's values and situation. Some patients may consider Optune as providing hope and an opportunity to gain a sense of control over the disease, while others may consider it as burdensome or a visible reminder of the disease. • To mitigate false hope, clinicians will need to convey that burdens experienced with maintenance chemotherapy will not be lifted with the addition of Optune, and instead, patients and caregivers will be required to manage an additional treatment modality. • As patients with ndGBM can be described as "vulnerable," careful attention must be paid to the quality of consent conversations to support informed decision-making and respect for patient autonomy. Eliciting a patient's values with respect to treatment is also important, as disease progression may impair capacity to consent and require the involvement of a substitute decision-maker. • Consent conversations require ensuring that patients and caregivers understand that Optune is not curative and is proposed as an addition to maintenance chemotherapy, and that Optune is considered within a full range of treatment and care options, including available palliative care supports. Consent should also cover privacy considerations, as the use of Optune requires transmitting patient data to the sponsor. • Equity-enhancing strategies will need to be 	<ul style="list-style-type: none"> • Acceptability of the device, and the extent to which Optune meets patients' needs for effective, accessible, and easily usable treatment, remain uncertain and will likely depend on an individual patient's values and caregiver support network. • Limitations in HRQoL data and the generalizability of the trial findings have implications for consent conversations and the ability to adhere to and benefit from treatment in a diverse patient population in the real world. • Further study on how, or if, factors such as functional status, race, sex, age, socioeconomic status, and availability of caregiver support have implications for acceptability and ability to adhere to treatment would be helpful to support patient-centred care and equitable access, given the diversity of the population in Canada. • There are no data for pregnant patients, and neither Optune nor temozolomide are recommended for use in this population. Patient or substitute decision-maker preferences may prompt reconsideration as risk tolerance and individual circumstances vary.

Domains	Key findings	Uncertainties
	<p>explored if Optune is to be accessible in a fair and effective manner for patients in Canada. Special attention is required to address barriers to accessing Optune due to geography, socioeconomic status, language barriers, requirements for additional caregiver support, and barriers to accessing oral temozolomide in jurisdictions where it is not reimbursed.</p>	

CNS = central nervous system; GBM = glioblastoma multiforme; HRQoL = health-related quality of life; ICER = incremental cost-effectiveness ratio; ndGBM = newly diagnosed glioblastoma multiforme; OS = overall survival; PFS = progression-free survival; QALY = quality-adjusted life-year; RCT = randomized controlled trial; RT = radiotherapy; TTFields = tumour treating fields; vs. = versus.

References

1. Grochans S, Cybulska AM, Simińska D, et al. Epidemiology of Glioblastoma Multiforme-Literature Review. *Cancers (Basel)*. 2022;14(10). [PubMed](#)
2. Walker EV, Zhou Y, Wu Y, et al. The Incidence and Prevalence of Primary Central Nervous System (CNS) Tumours in Canada (2010-2017), and the Survival of Patients Diagnosed with CNS Tumours (2008-2017). *Curr Oncol*. 2023;30(4):4311-4328. [PubMed](#)
3. Davis FG, Smith TR, Gittleman HR, Ostrom QT, Kruchko C, Barnholtz-Sloan JS. Glioblastoma incidence rate trends in Canada and the United States compared with England, 1995-2015. *Neuro Oncol*. 2020;22(2):301-302. [PubMed](#)
4. Philips A, Henshaw DL, Lamburn G, O'Carroll MJ. Brain Tumours: Rise in Glioblastoma Multiforme Incidence in England 1995-2015 Suggests an Adverse Environmental or Lifestyle Factor. *J Environ Public Health*. 2018;2018:7910754. [PubMed](#)
5. D'Alessio A, Proietti G, Sica G, Scicchitano BM. Pathological and Molecular Features of Glioblastoma and Its Peritumoral Tissue. *Cancers (Basel)*. 2019;11(4). [PubMed](#)
6. Louis DN, Perry A, Wesseling P, et al. The 2021 WHO Classification of Tumors of the Central Nervous System: a summary. *Neuro Oncol*. 2021;23(8):1231-1251. [PubMed](#)
7. Hanif F, Muzaffar K, Perveen K, Malhi SM, Simjee Sh U. Glioblastoma Multiforme: A Review of its Epidemiology and Pathogenesis through Clinical Presentation and Treatment. *Asian Pac J Cancer Prev*. 2017;18(1):3-9. [PubMed](#)
8. Mvasi - Glioblastome. Avis transmis au ministre en octobre 2022. Québec (QC): Institut national d'excellence en santé et en services sociaux (INESSS); 2022: https://www.inesss.qc.ca/fileadmin/doc/INESSS/Inscription_medicaments/Avis_au_ministre/Novembre_2022/Novembre_2022_avis_31_octobre_/Mvasi_2022_10.pdf. Accessed 2023 Jan 3.
9. Gilard V, Tebani A, Dabaj I, et al. Diagnosis and Management of Glioblastoma: A Comprehensive Perspective. *J Pers Med*. 2021;11(4). [PubMed](#)
10. Chahal M, Thiessen B, Mariano C. Treatment of Older Adult Patients with Glioblastoma: Moving towards the Inclusion of a Comprehensive Geriatric Assessment for Guiding Management. *Curr Oncol*. 2022;29(1):360-376. [PubMed](#)
11. Thakkar JP, Dolecek TA, Horbinski C, et al. Epidemiologic and molecular prognostic review of glioblastoma. *Cancer Epidemiol Biomarkers Prev*. 2014;23(10):1985-1996. [PubMed](#)
12. Walker EV, Liu JL, Davids FG, Climans S, Yuan Y. Brain Tumour Registry of Canada (BTRC): Survival and Prevalence Report 2010–2017. Edmonton (AB): University of Alberta School of Public Health and Brain Tumour Foundation of Canada; 2022: <https://braintumourregistry.ca/2022-survival-and-prevalence-report/>. Accessed 2023 May 12.
13. Stupp R, Mason WP, van den Bent MJ, et al. Radiotherapy plus Concomitant and Adjuvant Temozolomide for Glioblastoma. *N Engl J Med*. 2005;352(10):987-996. [PubMed](#)
14. Alvarez de Eulate-Beramendi S, Alvarez-Vega MA, Balbin M, Sanchez-Pitiot A, Vallina-Alvarez A, Martino-Gonzalez J. Prognostic factors and survival study in high-grade glioma in the elderly. *Br J Neurosurg*. 2016:1-7. [PubMed](#)
15. Witteler J, Schild SE, Rades D. Prognostic Factors of Local Control and Survival in Patients Irradiated for Glioblastoma Multiforme (GBM). *Anticancer Res*. 2020;40(12):7025-7030. [PubMed](#)
16. Rulesh AM, Keller J, Klener J, Sroubek J, Dbalý V. Long-term survival of patients suffering from glioblastoma multiforme treated with tumor-treating fields. *World J Surg Oncol*. 2012;10:220. [PubMed](#)
17. Gilbert MR, Dignam JJ, Armstrong TS, et al. A randomized trial of bevacizumab for newly diagnosed glioblastoma. *N Engl J Med*. 2014;370(8):699-708. [PubMed](#)
18. Stupp R, Hegi ME, Mason WP, et al. Effects of radiotherapy with concomitant and adjuvant temozolomide versus radiotherapy alone on survival in glioblastoma in a randomised phase III study: 5-year analysis of the EORTC-NCIC trial. *Lancet Oncol*. 2009;10:459-466. [PubMed](#)
19. Iorgulescu JB, Sun C, Neff C, et al. Molecular biomarker-defined brain tumors: Epidemiology, validity, and completeness in the United States. *Neuro Oncol*. 2022;24(11):1989-2000. [PubMed](#)
20. Walid MS. Prognostic factors for long-term survival after glioblastoma. *Perm J*. 2008;12(4):45-48. [PubMed](#)

21. Aliferis C, Trafalis DT. Glioblastoma multiforme: Pathogenesis and treatment. *Pharmacol Ther.* 2015;152:63-82. [PubMed](#)
22. Fine HA. New strategies in glioblastoma: exploiting the new biology. *Clin Cancer Res.* 2015;21(9):1984-1988. [PubMed](#)
23. Wilson TA, Karajannis MA, Harter DH. Glioblastoma multiforme: State of the art and future therapeutics. *Surg Neurol Int.* 2014;5:64. [PubMed](#)
24. Mason W, Maestro R, Eisenstat D, et al. Canadian recommendations for the treatment of glioblastoma multiforme. *Curr Oncol.* 2007;14(3):110-117. [PubMed](#)
25. Tran B, Rosenthal MA. Survival comparison between glioblastoma multiforme and other incurable cancers. *J Clin Neurosci.* 2010;17(4):417-421. [PubMed](#)
26. Torre M, Wen PY, Iorgulescu JB. The predictive value of partial MGMT promoter methylation for IDH-wild-type glioblastoma patients. *Neurooncol Pract.* 2023;10(2):126-131. [PubMed](#)
27. Hegi ME, Diserens AC, Gorlia T, et al. MGMT gene silencing and benefit from temozolomide in glioblastoma. *N Engl J Med.* 2005;352(10):997-1003. [PubMed](#)
28. *Optune User Manual* [internal sponsor's report]. Montreal (QC): Novocure Canada Inc; 2022.
29. Optune Model #- TFH9100. Instructions for use [internal sponsor's report]. Root (CH): Novocure GmbH; 2022.
30. Clinical Evidence Template: Tumour Treating Fields: OPTUNE (NovoTTF-200A) [internal sponsor's report]. In: *CADTH Reimbursement Review sponsor submission: Optune (NovoTTF 200A)*. Montreal (QC): Novocure Canada Inc; 2023 Aug.
31. Kinzel A, Ambrogio M, Varshaver M, Kirson ED. Tumor Treating Fields for Glioblastoma Treatment: Patient Satisfaction and Compliance With the Second-Generation Optune((R)) System. *Clin Med Insights Oncol.* 2019;13:1179554918825449. [PubMed](#)
32. Zhao Y, Zhan Q. Electric fields generated by synchronized oscillations of microtubules, centrosomes and chromosomes regulate the dynamics of mitosis and meiosis. *Theor Biol Med Model.* 2012;9:26. [PubMed](#)
33. McCaig CD, Rajniecek AM, Song B, Zhao M. Controlling cell behavior electrically: current views and future potential. *Physiol Rev.* 2005;85(3):943-978. [PubMed](#)
34. Kirson ED, Dbalý V, Tovarys F, et al. Alternating electric fields arrest cell proliferation in animal tumor models and human brain tumors. *Proc Natl Acad Sci U S A.* 2007;104(24):10152-10157. [PubMed](#)
35. Mun EJ, Babiker HM, Weinberg U, Kirson ED, Von Hoff DD. Tumor-Treating Fields: A Fourth Modality in Cancer Treatment. *Clin Cancer Res.* 2018;24(2):266-275. [PubMed](#)
36. Gutin PH, Wong ET. Noninvasive application of alternating electric fields in glioblastoma: a fourth cancer treatment modality. *Am Soc Clin Oncol Educ Book.* 2012(32):126-131. [PubMed](#)
37. Gera N, Yang A, Holtzman TS, Lee SX, Wong ET, Swanson KD. Tumor treating fields perturb the localization of septins and cause aberrant mitotic exit. *PLoS One.* 2015;10(5):e0125269. [PubMed](#)
38. Voloshin T, Schneiderman RS, Volodin A, et al. Tumor Treating Fields (TTFields) Hinder Cancer Cell Motility through Regulation of Microtubule and Actin Dynamics. *Cancers (Basel).* 2020;12(10). [PubMed](#)
39. CADTH Reimbursement Review stakeholder input: NovoTTF-200A (Optune) for supratentorial glioblastoma (GBM) [in-progress]. Ottawa (ON): CADTH; [2024]: <https://www.cadth.ca/novottf-200a>.
40. *Clinical Study Report: EF-14. A Prospective, Multicenter Trial of Optune Together With Temozolomide Compared to Temozolomide Alone in Patients with Newly Diagnosed GBM* [internal sponsor's report]. Haifa (IL): NovoCure Ltd.; 2018.
41. Stupp R, Taillibert S, Kanner A, Read W, D S. Effect of Tumor-Treating Fields Plus Maintenance Temozolomide vs Maintenance Temozolomide Alone on Survival in Patients With Glioblastoma: A Randomized Clinical Trial. *JAMA.* 2017;318(23):2306-2316. [PubMed](#)
42. Chinot OL, Macdonald DR, Abrey LE, Zahlmann G, Kerloeguen Y, Cloughesy TF. Response assessment criteria for glioblastoma: practical adaptation and implementation in clinical trials of antiangiogenic therapy. *Curr Neurol Neurosci Rep.* 2013;13(5):347. [PubMed](#)

43. Kasper B. The EORTC QLQ-C30 Summary Score as a Prognostic Factor for Survival of Patients with Cancer: A Commentary. *Oncologist*. 2020;25(4):e610-e611. [PubMed](#)
44. Taphoorn MJB, Dirven L, Kanner AA, et al. Influence of Treatment With Tumor-Treating Fields on Health-Related Quality of Life of Patients With Newly Diagnosed Glioblastoma: A Secondary Analysis of a Randomized Clinical Trial. *JAMA Oncol*. 2018;4(4):495-504. [PubMed](#)
45. Ballo MT, Conlon P, Lavy-Shahaf G, Kinzel A, Vymazal J, Rulseh AM. Association of Tumor Treating Fields (TTFields) therapy with survival in newly diagnosed glioblastoma: a systematic review and meta-analysis. *J Neurooncol*. 2023;164(1):1-9. [PubMed](#)
46. Han K, Ren M, Wick W, et al. Progression-free survival as a surrogate endpoint for overall survival in glioblastoma: a literature-based meta-analysis from 91 trials. *Neuro Oncol*. 2014;16(5):696-706. [PubMed](#)
47. Dirven L, Musoro JZ, Coens C, et al. Establishing anchor-based minimally important differences for the EORTC QLQ-C30 in glioma patients. *Neuro Oncol*. 2021;23(8):1327-1336. [PubMed](#)
48. Pharmacoeconomic evaluation [internal sponsor's report]. In: *CADTH Reimbursement Review sponsor submission: Optune (NovoTTF 200A)*. Montreal (QC): Novocure Canada Inc; 2023 August 18.
49. Porter KR, McCarthy BJ, Berbaum ML, Davis FG. Conditional Survival of All Primary Brain Tumor Patients by Age, Behavior, and Histology. *Neuroepidemiology*. 2011;36(4):230-239. [PubMed](#)
50. Table: 17-10-0057-01 Projected population, by projection scenario, age and sex, as of July 1 (x 1,000). Ottawa (ON): Statistics Canada; 2022: <https://www150.statcan.gc.ca/t1/tbl1/en/tv.action?pid=1710005701>. Accessed 2023 Sep 13.
51. Garside R, Pitt M, Anderson R, et al. The effectiveness and cost-effectiveness of carmustine implants and temozolomide for the treatment of newly diagnosed high-grade glioma: a systematic review and economic evaluation. *Health Technol Assess*. 2007;11(45):iii-iv, ix-221.
52. Ellor SV, Pagano-Young TA, Avgeropoulos NG. Glioblastoma: background, standard treatment paradigms, and supportive care considerations. *J Law Med Ethics*. 2014;42(2):171-182. [PubMed](#)
53. Bennett SR, Cruickshank G, Lindenmeyer A, Morris SR. Investigating the impact of headaches on the quality of life of patients with glioblastoma multiforme: a qualitative study. *BMJ Open*. 2016;6(11):e011616. [PubMed](#)
54. Edelstein K, Coate L, Massey C, Jewitt NC, Mason WP, Devins GM. Illness intrusiveness and subjective well-being in patients with glioblastoma. *J Neurooncol*. 2016;126(1):127-135. [PubMed](#)
55. Catt S, Chalmers A, Fallowfield L. Psychosocial and supportive-care needs in high-grade glioma. *Lancet Oncol*. 2008;9(9):884-891. [PubMed](#)
56. Hanna C, Lawrie TA, Rogozinska E, et al. Treatment of newly diagnosed glioblastoma in the elderly: a network meta-analysis. *Cochrane Database Syst Rev*. 2020;3(3):CD013261. [PubMed](#)
57. Fatehi M, Hunt C, Ma R, Toyota BD. Persistent Disparities in Survival for Patients with Glioblastoma. *World Neurosurg*. 2018;120:e511-e516. [PubMed](#)
58. Schwartz MA, Onuselegu L. Rationale and Background on Tumor-Treating Fields for Glioblastoma. *Clin J Oncol Nurs*. 2016;20(5 Suppl):S20-24. [PubMed](#)
59. Wenger NS, Vespa PM. Ethical issues in patient-physician communication about therapy for cancer: professional responsibilities of the oncologist. *Oncologist*. 2010;15 Suppl 1:43-48. [PubMed](#)
60. Boele FW, Butler S, Nicklin E, et al. Communication in the context of glioblastoma treatment: A qualitative study of what matters most to patients, caregivers and health care professionals. *Palliat Med*. 2023;37(6):834-843. [PubMed](#)
61. Mailhot B, Allard B, Rousseau A, Corbin D. Dispositif OptuneMC pour le traitement des patients adultes atteints d'un glioblastome nouvellement diagnostiqué. Québec (QC): Institut national d'excellence en santé et en services sociaux (INESSS); 2023: https://www.inesss.qc.ca/fileadmin/doc/INESSS/Rapports/Innov_non_pharma/INESSS_Optune_Avis.pdf. Accessed 2023 Oct 21.
62. Hasnain-Wynia R. Is evidence-based medicine patient-centered and is patient-centered care evidence-based? *Health Serv Res*. 2006;41(1):1-8. [PubMed](#)

63. Al-Rasheedy IM, Al-Hameed FM. Advanced case of glioblastoma multiforme and pregnancy. An ethical dilemma. *Neurosciences*. 2015;20(4):388-391. [PubMed](#)
64. Policicchio D, Doda A, Muggianu G, Dipellegrini G, Boccaletti R. Ethical and therapeutic dilemmas in glioblastoma management during pregnancy: Two case reports and review of the literature. *Surg Neurol Int*. 2019;10:41. [PubMed](#)
65. Marakovic J, Chudy D, Muller D, et al. Malignant transformation of pleomorphic xanthoastrocytoma in pregnant patient: Clinical case and ethical dilemma. *Surg Neurol Int*. 2021;12:469. [PubMed](#)
66. Onken J, Staub-Bartelt F, Vajkoczy P, Misch M. Acceptance and compliance of TTFIELDS treatment among high grade glioma patients. *J Neurooncol*. 2018;139(1):177-184. [PubMed](#)
67. Cote DJ, Balak N, Brennum J, et al. Ethical difficulties in the innovative surgical treatment of patients with recurrent glioblastoma multiforme. *J Neurosurg*. 2017;126(6):2045-2050. [PubMed](#)
68. Musella A, DeVitto R, Anthony M, Elliott Mydland D. The Importance of Shared Decision-Making for Patients with Glioblastoma. *Patient Prefer Adherence*. 2021;15:2009-2016. [PubMed](#)
69. Triebel KL, Martin RC, Nabors LB, Marson DC. Medical decision-making capacity in patients with malignant glioma. *Neurology*. 2009;73(24):2086-2092. [PubMed](#)
70. Harrison RA, de Groot JF. Treatment of Glioblastoma in the Elderly. *Drugs Aging*. 2018;35(8):707-718. [PubMed](#)
71. Lawrence YR, Mishra MV, Werner-Wasik M, et al. Improving prognosis of glioblastoma in the 21st century: who has benefited most? *Cancer*. 2012;118(17):4228-4234. [PubMed](#)
72. Walker EV, Ross J, Yuan Y, Smith TR, Davis FG. Brain cancer survival in Canada 1996-2008: effects of sociodemographic characteristics. *Curr Oncol*. 2019;26(3):e292-e299. [PubMed](#)
73. Lopez Ramos C, Brandel MG, Steinberg JA, et al. The impact of traveling distance and hospital volume on post-surgical outcomes for patients with glioblastoma. *J Neurooncol*. 2019;141(1):159-166. [PubMed](#)
74. Gorenflo MP, Shen A, Murphy ES, Cullen J, Yu JS. Area-level socioeconomic status is positively correlated with glioblastoma incidence and prognosis in the United States. *Front Oncol*. 2023;13:1110473. [PubMed](#)
75. Bird CE, Traylor JI, Youssef M, Abdullah KG. Distance traveled to glioblastoma treatment: A measure of the impact of socioeconomic status on survival. *Clin Neurol Neurosurg*. 2021;209:106909. [PubMed](#)
76. Ostrom QT, Krebs HL, Patil N, Cioffi G, Barnholtz-Sloan JS. Racial/ethnic disparities in treatment pattern and time to treatment for adults with glioblastoma in the US. *J Neurooncol*. 2021;152(3):603-615. [PubMed](#)
77. Tumor treating fields, (Optune®) - re-review. Final evidence report. Olympia (WA): Washington State Health Care Authority; 2018: <https://www.hca.wa.gov/assets/program/tumor-treating-fields-final-report-20181016.pdf>. Accessed 2023 Oct 21.
78. Optune for the Treatment of Newly Diagnosed and Recurrent Glioblastoma. Singapore (SG): Agency for Care Effectiveness; 2023: <https://www.ace-hta.gov.sg/docs/default-source/default-library/optune-for-the-treatment-of-newly-diagnosed-and-recurrent-glioblastoma.pdf>. Accessed 2023 Oct 21.

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