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CADTH Health Technology Review

NovoTTF-200A (Optune)

Sponsor: Novocure Canada Inc.
Therapeutic area: Supratentorial glioblastoma (GBM)

Supplemental Materials

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Abbreviations

AE	adverse event
BIA	budget impact analysis
CI	confidence interval
EORTC QLQ-C30	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30
GBM	glioblastoma
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 score
LY	life years
MGMT	Methyl-guanine methyl transferase
MID	minimal important difference
MRI	magnetic resonance imaging
ndGBM	newly diagnosed glioblastoma multiformae
OS	overall survival
PD	progressed disease
PF	progression-free
PFS	progression free survival
PFS6	progression-free survival at 6 months
PP	per protocol
QALY	quality-adjusted life years
RCT	randomized controlled trial
RT	radiotherapy
SAE	serious adverse event
SD	standard deviation
ToT	time on treatment
TTFields	tumour treating fields

Clinical Review Appendices

Note that this appendix has not been copy-edited.

Appendix 1: Methods of the Systematic Review Conducted by the Sponsor

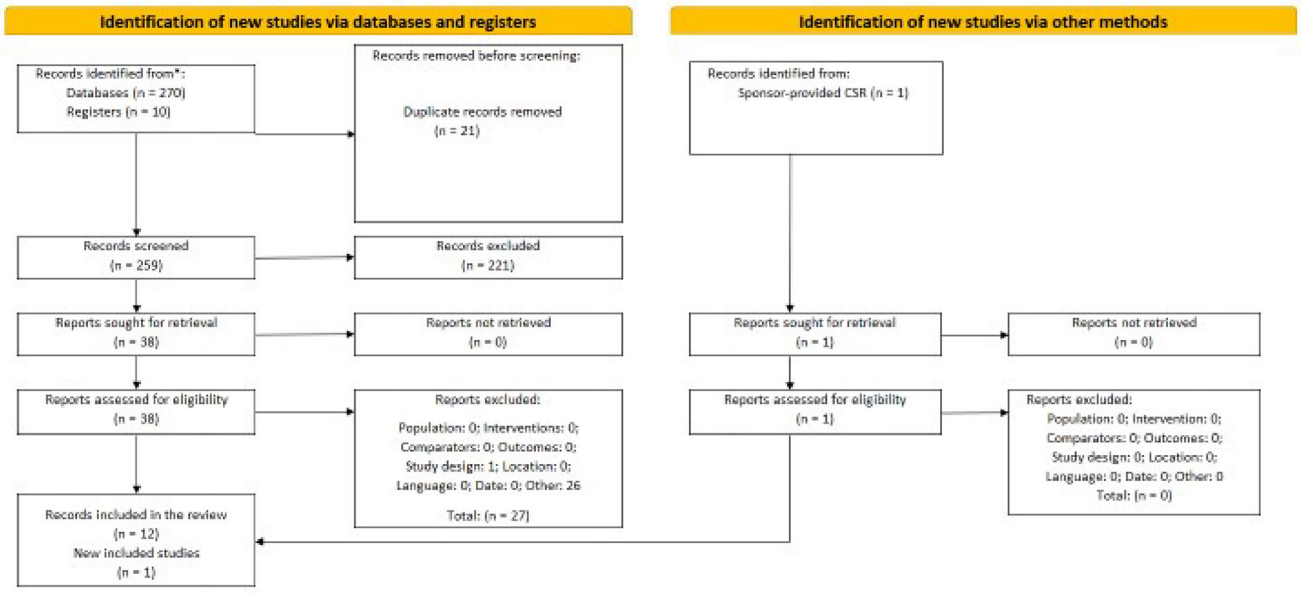
Table 1: Inclusion Criteria for the Systematic Review

Criteria	Description
Population	Adult patients with newly diagnosed, supratentorial glioblastoma following maximal debulking surgery and completion of radiation therapy
Intervention	TTFields, delivered through OPTUNE, together with and after standard of care maintenance chemotherapy
Comparator	Temozolomide as standard of care maintenance chemotherapy
Outcomes	**Efficacy outcomes:** OS (continuous, rates at 1 year and 2 years, and survival from first progression), PFS, PFS6, KPS, cognitive function, HRQoL (EORTC QLQ C30 + BN20 scores), and radiological response **Harms outcomes:** AEs, SAEs, WDAEs, Mortality (no AESIs were specified in the pivotal trial protocol)
Study Designs	Pivotal trials, phase 3 to 4 randomized controlled trials

AE = adverse event; AESI = adverse event of special interest; BN20 = a brain tumour-specific questionnaire; EORTC QLQ C30 = European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire; HRQoL = health-related quality of life; KPS = Karnofsky performance status; OS = overall survival; PFS = progression-free survival; PFS6 = progression-free survival at 6 months; SAE = serious adverse event; TTFields = tumour-treating fields; WDAE = withdrawal due to adverse event.

Source: Sponsor's Summary of Clinical Evidence.[1]

Figure 1: PRISMA Flow Chart



* Searched databases were Ovid MEDLINE Epub Ahead of Print, In-Process, In-Data-Review and Other Non-Indexed Citations and Daily; Ovid Embase; EBM Reviews - Cochrane Central Register of Controlled Trials; and EBM Reviews - Cochrane Database of Systematic Reviews.

Source: Sponsor's Summary of Clinical Evidence.[1]

Appendix 2: Methods of EF-14 Trial

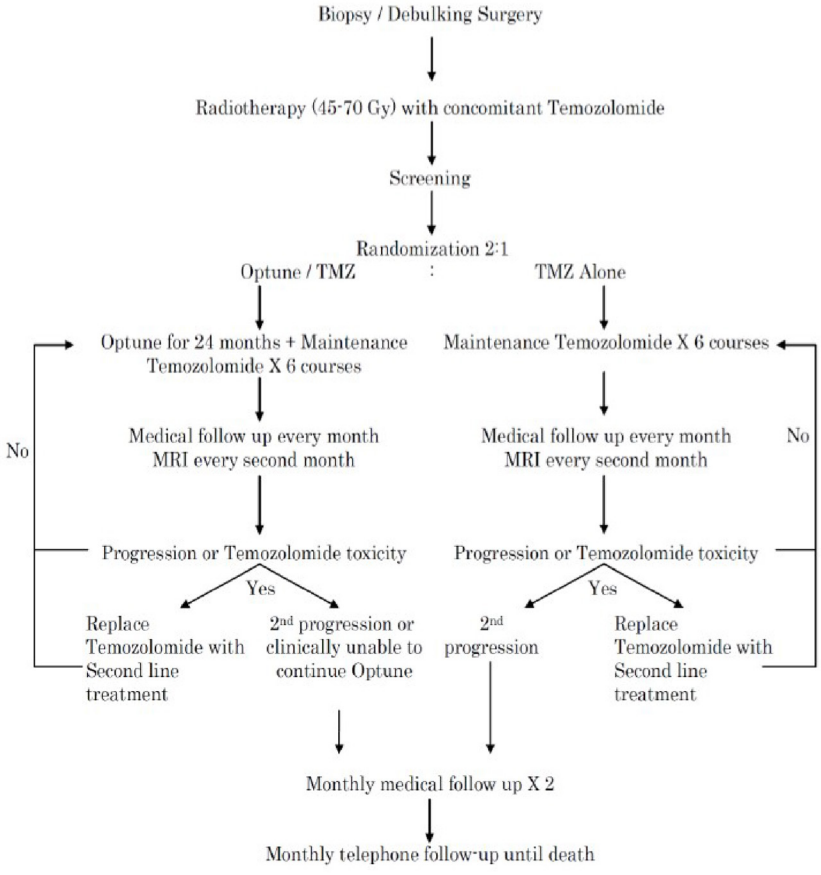
Study Schema

Outcomes

Progression Free Survival (PFS)

The primary outcome in Study EF-14 was PFS, which was defined as the number of months patients experienced no disease progression or death following treatment. 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 (see below). Progression was identified using the Macdonald criteria when an MRI (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 glioblastoma [GBM]) or based on a clinical diagnosis if MRI was not available (decline in functional status based on Karnofsky Performance score [KPS] decrease > 10 plus decline in neurologic function based on Medical Research Counsel Clinical Scale decrease of ≥ 2 points plus a ≥ 50% increase in steroid use). Based on the trial supporting the Stupp regimen, a clinically meaningful

Figure 2: Study Schema



Source: Study EF-14 Clinical Study Report.[2]

improvement in PFS was 1.9 months with radiotherapy (RT) + temozolomide versus RT alone (6.9 months versus 5.0 months).[3]

Events were adjudicated by a blinded central committee consisting of an independent neuro-oncologist and independent neuro-radiologist using the following guidelines:

If progression was identified using MRI measurements, then the PFS date was set to the MRI date unless treatment was changed before the MRI date, in which case PFS was censored at the date of the treatment change.

Progression based on an MRI measurement in a patient that continued temozolomide and subsequently had MRI-determined tumour stabilization or shrinkage was classified as pseudoprogression and not real progression. In these cases, the next MRI date showing tumour progression was used for the PFS date.

In the absence of MRI-determined progression:

If the patient fulfilled all 3 clinical criteria for progression (KPS decline, Medical Research Counsel Clinical Scale decline, and increased steroid use), the date of the clinical assessment was set as the PFS date.

If the patient died, the PFS date was set to the date of death or censored at the last MRI or withdrawal of consent (whichever came first).

If there was no date of death, then the PFS date was censored at the date of the last MRI before withdrawal of consent or at the date of the withdrawal of consent.

Overall survival (OS)

In Study EF-14, OS was a powered secondary outcome that was defined as the number of months patients lived following treatment. In the current trial, non-progressive patients were randomized only after temozolomide /RT. This trial was powered to achieve a hazard ratio (HR) of 0.76 for OS, this would translate to a 6-month increase in median survival to 24 months, a difference that would be considered clinically meaningful (versus the 2.5-month improvement in median OS observed in the trial evaluating the Stupp regimen).[3] 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). Events were adjudicated by the blinded central committee.

PFS at 6 months

Progression-free survival at 6 months (PFS6) was a secondary outcome that was calculated based on the number of patients in each treatment arm that were still progression-free at 6 months after treatment initiation. Events were adjudicated by the blinded central committee.

One- and Two-year Survival Rates

One- and two-year survival rates were secondary outcomes that were determined based on the number of patients still alive 1 year (12 months) and 2 years (24 months) after treatment initiation. Events were adjudicated by the blinded central committee. The sponsor is not aware of any reports regarding a minimal

important difference (MID) for 1-year and 2-year OS rates in patients with newly diagnosed glioblastoma multiformae (ndGBM).

Health Related Quality of Life (HRQoL)

The HRQoL of patients was a secondary outcome and 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 indicates increased life quality, and higher scores in symptom subscales indicates heightened disease burden.[4] Change in score was determined by comparing scores at baseline to scores taken at 3, 6, 9, and 12 months. The sponsor is not aware of any published reports regarding the MID in the EORTC QLQ C-30 scores among patients with ndGBM, although MID values based on 1,687 glioma patients in 3 randomized controlled trials were generally between 4 and 11 points for within-group mean changes and between-group mean differences in changes.[5]

Radiological Response Rate

Radiological response was a secondary outcome and was evaluated based on the Macdonald criteria for each response level (progressive disease, stable disease, partial response, complete response).[6] The clinical benefit rate was derived by calculating the proportion of patients with stable disease, partial response, or complete response following treatment.[2] The sponsor is not aware of any reports regarding an MID for radiological response rate in patients with ndGBM.

Safety and Tolerability

The frequency of specific treatment-emergent adverse events and serious adverse events (SAEs) was recorded for each treatment group.[2] No adverse events of special interest were pre-specified in the study protocol.

Table 2: Summary of Outcome Measures and Their Measurement Properties

Outcome measure	Type	Conclusions about measurement properties	MID
EORTC QLQ-C30	A patient self-administered questionnaire consisting of 9 multi-item scales (i.e., 5 functional scales, 3 symptom scales, and 1 a global health and quality-of-life scale) and 6 single-item symptom measures to assess HRQoL of patients with cancer[4]	**Validity** • Scales assessed distinct components of the HRQoL construct. • Scales were found to distinguish between patients with different performance status and degrees of weight loss. **Reliability** • Test-retest reliability: Pearson's correlation coefficient ranged from 0.63 to 0.91 for all scales and 0.72 to 0.84 for single-item	MID in the EORTC QLQ C-30 scores among patients with ndGBM is unknown. MID values based on 1,687 patients with glioma in 3 RCTs were generally between 4 and 11 points for within-group mean changes and between-group mean differences in changes.[5]

Outcome measure	Type	Conclusions about measurement properties	MID
		measures in patients with cancer.[7] • Internal consistency: Cronbach's alpha coefficient for the multi-item scales ranged from 0.54 to 0.86 before treatment and from 0.52 to 0.89 during treatment in patients with lung cancer.[8] **Responsiveness** • Scales detected significant change over time in physical and role functioning, global quality of life, fatigue, and nausea and vomiting.[8]	

BN20 = a brain tumour-specific questionnaire; EORTC QLQ-C30 = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30; HRQoL = health related quality of life; MID = minimal important difference; ndGBM = newly diagnosed glioblastoma multiforme; RCT = randomized controlled trial.
Source: Details included in the table are from the sponsor's Summary of Clinical Evidence.[1]

Statistical analysis

Clinical Trial End points

PFS

This summary covers the final pre-specified long-term analysis of all enrolled patients after the last patient reached 24 months of follow-up (data cut-off: December 28, 2016).

The primary end point would be achieved if PFS was significantly greater in the Optune + temozolomide arm than in the temozolomide alone arm, based on a log-rank test stratified according to methyl-guanine methyl transferase (MGMT) status (a potential predictor of response to temozolomide) and the extent of resection at randomization. Because an interim analysis was planned in addition to the final analysis, the alpha level for each time point was calculated according to the Lan-DeMets method using the O'Brien and Fleming spending function at the final analysis (interim: alpha = 0.01394, final: alpha = 0.04574). Patients were censored at the last follow-up date that they were last known to be alive and recurrence-free (if withdrawn or lost to follow-up) or at study closeout.[2] The primary analysis was conducted in the intent-to-treat population (ITT, all randomized patients according to their assigned treatment).

Risk of progression was also analyzed using a Cox regression model to determine the relative HR and 95% confidence interval (CI) between groups. The Cox regression model was adjusted for KPS, age, region, *MGMT* methylation status, *IDH1R132H* status, *EGFR* status, *1p19q* status, and prior resection status.[2] The impact of missing data was assessed using a tipping point analysis to determine how extreme missing parameters would need to be to overturn the original conclusion, as well as whether the extreme shift in those parameters would be clinically plausible.[9] Additional sensitivity analyses included a best/worst case scenario analysis, interval analysis, and *MGMT* status subgroup analysis (Table 3).

OS

A hierarchical approach was used to first test PFS and then OS to avoid issues with statistical multiplicity. While the original protocol specified that secondary analyses would be conducted based on the per-protocol (PP) population, these analyses were ultimately performed in the ITT population because patients who had crossed-over would be excluded from the PP because this was a major protocol deviation under the original protocol. This approach is considered conservative and might underestimate the efficacy of Optune + temozolomide, as cross-over patients might have better outcomes than control patients who did not cross-over. Additional analyses using the PP population were also conducted to identify any discrepancy.

Any difference in OS was analyzed using a log-rank test. To account for the interim and final analyses, the alpha for each time point was derived using the Lan-DeMets method and O'Brien and Fleming spending function (interim: alpha = 0.00598, final: alpha = 0.0481). As with PFS, the risk of death was analyzed using a OS Cox regression model that was adjusted for KPS, age, region, *MGMT* methylation status, *IDH1R132H* status, *EGFR* status, *1p19q* status, and prior resection status.[2] No tests/procedures were carried out to address missing data. A sensitivity analysis focusing on *MGMT* status was performed to expand on the conclusions of the main analysis.

PFS6

Analyses of PFS6 were performed using a one-sided chi-square test in the ITT population that assumed patients receiving Optune + temozolomide would experience a lower rate of progression at 6 months than patients receiving temozolomide alone. No sensitivity analyses were performed, although an identical analysis was performed using the PP population. Tests and procedures to address missing data were not carried out.

One- and Two-year Survival Rates

The analyses of 1- and 2-year survival rates were performed in the same manner as the analyses of PFS6 (Optune + temozolomide assumed to be superior in the ITT population), with an additional analysis using the PP population. Additional analyses up to 5 years were performed based on the available data. The impacts of missing data were not assessed, and sensitivity analyses were not performed.

Radiological Response Rate

The analyses of radiological response were performed in the same manner as the analyses of PFS6 (optune + temozolomide assumed to be superior in the ITT population), with an additional analysis using the PP population. The impacts of missing data were not assessed, and sensitivity analyses were not performed.

HRQoL

Descriptive results (ratio of change from baseline) up to 12 months were reported for HRQoL in each treatment arm based on the EORTC QLQ-C30 and BN20 questionnaire (Tab H).

Safety and Tolerability

Descriptive results (incidences and severities) were reported for the safety population (all patients who received at least 1 dose of temozolomide or tumour treating fields [TTFields]) up to the data cut-off.

Table 3: Statistical Analysis of Efficacy End points in Study EF-14

End point	Statistical model	Adjustment factors	Handling of missing data	Sensitivity analyses
PFS	Log-rank test (stratified by MGMT status and the extent of resection at randomization). Alpha levels for interim and final analyses were calculated according to the Lan-DeMets method using the O'Brien and Fleming spending function. Hazard ratios were calculated using a Cox regression model.	Cox regression model was adjusted for KPS, age, region (US vs. other regions), MGMT methylation status, other genetic markers (IDH1, 1p19q, EGFR), and resection status	Tipping point analysis was performed for participants with missing MGMT status.	• best/worse case censoring • interval censoring • *MGMT* status subgroups • tipping point analysis on MGMT status • treatment compliance subgroups
OS	As above (provided a significant improvement in PFS was detected).	As above	None	*MGMT* status subgroups
EORTC QLQ-C30	Ratio of change from baseline in each arm	None	None	None
Safety and tolerability	Numbers and frequencies	None	None	None

BN20 = a brain tumour-specific questionnaire; EORTC QLQ-C30 = EORTC Core Quality of Life questionnaire; KPS = Karnofsky performance status; MMSE = Mini Mental State Exam; OS = overall survival; PFS = progression-free survival; PFS6 = progression-free survival rate at 6 months.

Source: Study EF-14 Clinical Study Report.[2]

Sample Size and Power Calculation

In the revised protocol, the final analysis was planned with a sample size of 700 patients (210 temozolomide patients + 420 Optune + temozolomide patients + 10% loss to follow-up), which was determined for analysis of time to progression or death (PFS and OS) based on the log-rank test. In that scenario, the null hypothesis was that there would be identical recurrence rates in each group (HR = 1), with an expected median time to progression of 7 months in the control group[3] and 9 months in the treatment group. That sample size was determined to provide 80% power to detect a 2-month difference in PFS at a two-sided alpha of 0.05 based on expected accrual time of 48 months and additional follow-up of 18 months after the end of recruitment. In addition, that sample was determined to provide 80% power to detect a ≥ 4.5-month difference in OS at a two-sided alpha of 0.05 (median OS of 14.6 months expected for control patients).

In the initial protocol, a sample size of 283 patients (temozolomide alone: 80 patients, Optune + temozolomide: 160 patients, plus 15% for loss to follow-up) was determined for analysis of time to recurrence based on the log-rank test. In that scenario, the null hypothesis was that the 2 groups would have the same recurrence rate (HR = 1), with expected median time to progression of 7 months in the control group[3] and 10.7 months in the treatment group. That sample size was determined to provide 80% power at a two-sided alpha of 0.05 based on 2:1 randomization with expected accrual time of 24 months, follow-up of 12 months for time to progression, and an additional 18 months for OS after the end of recruitment. In

addition, that sample size was determined to have adequate power (80%) to detect a ≥ 8.9-month increased in median OS with Optune + temozolomide versus temozolomide alone, which is consistent with the results observed in the pilot study (median OS of 26 months in patients who received Optune + temozolomide versus 14.6 months in historical controls).

Statistical Testing

A hierarchical approach was used to first test PFS and then OS, which were analyzed as time to event outcomes using a log-rank test that was stratified according to *MGMT* status and the extent of resection at randomization. To handle testing at the interim and final analyses, alpha levels were calculated according to the Lan-DeMets method and O'Brien and Fleming spending function for both PFS (interim: 0.01394, final: 0.04574) and OS (interim: 0.00598, final: 0.0481).[2] Calculations of HRs and 95% CIs were performed using a Cox regression model adjusted for key prognostic factors (KPS, age, region, *MGMT* methylation status, *IDH1R132H* status, *EGFR* status, *1p19q* status, prior resection status).[2]

Only descriptive results were reported for the non-powered secondary and exploratory end points.

Subgroup Analyses

Several subgroup analyses were performed using the ITT population for the different end points:[2]

- PFS: *MGMT* methylation status (unmethylated, methylated), resection status (biopsy, partial, gross total), age (< 65 years, ≥ 65 years), KPS (90 to 100, ≤ 80), sex (male, female), TTField treatment compliance (10% groups), and overall treatment compliance (≥ 75%, < 75%).
- OS: as for PFS.
- Annual survival rates: based on the 3 highest compliance subgroups (90% to 100%, 80% to 90%, 70% to 80%).

Analysis populations

The main analysis populations used in Study EF-14 are shown in Table 4. The ITT population was used in the main efficacy analyses presented in the Results section; the PP population was initially planned for the secondary analyses but would have confounded the analyses based on the presence of both approved and unapproved crossover from the temozolomide alone arm to the Optune + temozolomide arm. Results from the PP analyses are available to demonstrate the robustness of the findings in the ITT population.

Table 4: Analysis Populations of EF-14

Study	Population	Definition	Application
EF-14	ITT	All participants included in the randomization process according to their assigned treatments	All efficacy analyses.
	PP	Excludes participants who never started treatment, patients who did not receive adequate therapy, and patients with major protocol violations (e.g., cross-over).	Additional efficacy analyses of OS and QoL (EORTC QLQ-C30 + BN20 Questionnaire; TAB H) as described in the original protocol.
	As-treated population	Patients with any exposure to TTFields (including patients originally randomized to temozolomide alone who crossed over to receive TTFields) vs. patients with only exposure to temozolomide.	An exploratory analysis of OS after first progression.
	Safety	All participants who received at least one dose of temozolomide or who started TTField therapy.	All safety analyses.

BN20 = a brain tumour-specific questionnaire; EORTC QLQ-C30 = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30; ITT = intention to treat; OS = overall survival; PP = per protocol; QoL = quality of life; TTFields = tumour treating fields.

Source: Study EF-14 Clinical Study Report.[2] Details included in the table are from the sponsor's Summary of Clinical Evidence.[1]

Appendix 3: Results of EF-14 Trial

Table 5: Summary of Patient Disposition - EF-14, Final Analysis

Patient disposition	EF-14	
	Optune+ temozolomide (N = 466)	Temozolomide (N = 229)
Screened, N		
Reason for screening failure, n (%)		
Randomized, N	695	
ITT, N	466	229
PP, N		
Safety, N		
Disposition at 24 months, n (%)		
Alive		
Dead		
Discontinued from study, n (%)		
Reason for discontinuation, n (%)		
Adverse events		
Non-compliance with study protocol		
Lost to follow-up		

Patient disposition	EF-14	
	Optune+ temozolomide (N = 466)	Temozolomide (N = 229)
Withdrawal of consent	[redacted]	[redacted]
Investigator's decision	[redacted]	[redacted]
Disease progression[a]	[redacted]	[redacted]

ITT = intention to treat; NR = not reported; PP = per protocol; TTFields = tumour treating fields.

[a]Indicates patients who were lost to follow-up because of disease progression, not all patients in the study who experienced disease progression.

Source: Study EF-14 Clinical Study Report.[2] Details included in the table are from the sponsor's Summary of Clinical Evidence.[1]

Table 6: Summary of Baseline Characteristics – Study EF-14, Final Analysis, ITT Population

Characteristic	EF-14	
	Optune+ temozolomide (N = 466)	Temozolomide (N = 229)
Age, Mean (SD)	[redacted]	[redacted]
Race, n (%)		
Caucasian	416 (89.3)	201 (87.8)
African American	3 (0.6)	1 (0.4)
Asian	27 (5.8)	19 (8.3)
Hispanic	18 (3.9)	7 (3.1)
Native American	1 (0.2)	1 (0.4)
Sex, n (%)		
Female	150 (32.2)	72 (31.4)
Male	316 (67.8)	157 (68.6)
Antiepileptic medication, n (%)	185 (39.7)	89 (38.9)
Corticosteroid therapy, n (%)	135 (29.0)	64 (27.9)
Region, n (%)		
United States	221 (47.4)	118 (51.5)
Canada	32 (6.9)	14 (6.1)
Rest of World	213 (45.7)	97 (42.4)
Extent of Resection		
Biopsy, n (%)	60 (12.9)	29 (12.7)
Partial Resection, n (%)	157 (33.7)	77 (33.6)
Gross Total Resection, n (%)	249 (53.4)	123 (53.7)
MGMT Tissue Available/Tested, n (%)	384 (82.4)	185 (80.8)

Characteristic	EF-14	
	Optune+ temozolomide (N = 466)	Temozolomide (N = 229)
Methylated, n (%)	136 (35.4)	77 (41.6)
Unmethylated, n (%)	208 (54.2)	95 (51.4)
Invalid, n (%)	40 (10.4)	13 (7.0)
IDH1R132H Tissue Available/Tested, n (%)	259 (55.6)	119 (52.0)
Positive	19 (7.3)	6 (5.0)
Negative	239 (92.3)	113 (95.0)
Invalid	1 (0.2)	0 (0.0)
EGFR Tissue Available/Tested, n (%)	252 (54.1)	112 (48.9)
Positive	102 (40.5)	43 (38.4)
Negative	147 (58.3)	68 (60.7)
Invalid	3 (1.2)	1 (0.9)
1p19q Tissue Available/Tested, n (%)	258 (55.4)	112 (48.9)
Co-deletion	2 (0.8)	0 (0.0)
Loss 1p only	4 (1.6)	1 (0.9)
Loss 19q only	3 (1.2)	3 (2.7)
Retained	238 (92.2)	102 (91.1)
Invalid	11 (4.3)	6 (5.4)
Tumor Position, n (%)		
Corpus Callosum	25 (5.4)	12 (5.2)
Frontal Lobe	190 (40.8)	84 (36.7)
Occipital Lobe	58 (12.4)	27 (11.8)
Parietal Lobe	146 (31.3)	89 (38.9)
Temporal Lobe	191 (41.0)	90 (39.3)
Missing	3 (0.6)	3 (1.3)
Tumor Location, n (%)		
Left	214 (45.9)	99 (43.2)
Right	249 (53.4)	127 (55.5)
Both	4 (0.9)	2 (0.9)
Corpus Callosum	15 (3.2)	9 (3.9)
Missing	1 (0.2)	1 (0.4)
Completed RT, n (%)		
< 57 Gy	21 (4.5)	11 (4.8)

Characteristic	EF-14	
	Optune+ temozolomide (N = 466)	Temozolomide (N = 229)
60 Gy (standard ± 5%)	422 (90.6)	212 (92.6)
> 63 Gy	18 (3.9)	3 (1.3)
Previous Use of RT with Concomitant Temozolomide, n (%)		
Yes	433 (92.9)	212 (92.6)
Unknown	33 (7.1)	17 (7.4)
Karnofsky Performance Status, Mean (SD)	87.7 (10.27)	88.2 (9.67)
Mini-Mental State Examination Score Available, n (%)	444 (95.3)	208 (90.8)
≤ 26	88 (19.8)	48 (23.1)
27 to 30	356 (80.2)	160 (76.9)
Time from Last Day of RT to Randomization (Days), Mean (SD)	[redacted]	[redacted]
Time from Diagnosis to Randomization (Days), Mean (SD)	[redacted]	[redacted]

EGFR = Epidermal growth factor receptor; IDH = isocitrate dehydrogenase; MGMT = O(6)-methylguanine-DNA methyltransferase; RT = radiotherapy/radiation therapy; SD = standard deviation; TTFields = tumour treating fields.

[a]TTFields/temozolomide = [redacted], temozolomide = [redacted]

[b]TTFields/temozolomide = [redacted] temozolomide = [redacted]

Source: Study EF-14 Clinical Study Report.[2] Details included in the table are from the sponsor's Summary of Clinical Evidence.[1]

Table 7: Summary of Patient Exposure – Study EF-14

Exposure	EF-14	
	Optune+ temozolomide (N = 448)	Temozolomide (N = 216)
Months of Optune treatment, mean (SD)	[redacted]	NA
Months of Optune treatment, median (range)	8.2 (0 to 82)	NA
Cycles of Optune treatment, mean (SD)	[redacted]	NA
Adherent to Optune treatment (≥ 18 hour per day during first 3 months), n (%)	347 (74.5)	NA
Cycles of temozolomide treatment, mean (SD)	6.4 (4.65)[b]	6.0 (4.44)[b]

NA = not applicable; SD = standard deviation

[a]Adherence to Optune therapy ≥ 75% during first 3 months of treatment.

[b]Optune/temozolomide = 454, temozolomide = 216

Source: Study EF-14 Clinical Study Report.[2] Details included in the table are from the sponsor's Summary of Clinical Evidence.[1]

Table 8: Summary of Subsequent Treatment – Study EF-14

Exposure	EF-14	
	Optune+ temozolomide (N = [redacted])	Temozolomide (N = [redacted])
Other chemotherapy, n (%)	[redacted]	[redacted]
Bevacizumab, n (%)	[redacted]	[redacted]
Resection, n (%)	[redacted]	[redacted]
Radiosurgery, n (%)	[redacted]	[redacted]
RT, n (%)	[redacted]	[redacted]
Resection with carmustine wafers, n (%)	[redacted]	[redacted]
Optune monotherapy, n (%)	[redacted]	[redacted]

NA = not applicable; RT = radiotherapy/radiation therapy

Note: the study protocol was amended to allow for crossover from the temozolomide alone arm to the Optune+ temozolomide arm in November 2014. Before this amendment, some patients in the temozolomide alone arm received Optune through prescription at non-study centers (a major protocol violation), which was considered unapproved crossover.

Source: Study EF-14 Clinical Study Report.[2] Details included in the table are from the sponsor's Summary of Clinical Evidence.[1]

Table 9: Summary of Key Efficacy Results of EF-14, Final analysis, ITT

Variable	EF-14	
	Optune + temozolomide (N = 466)	Temozolomide alone (N = 229)
OS		
Events, n	341	187
Censored, n	125	42
Median follow-up time	40 months	
HR (95% CI)[a]	0.63 (0.53 to 0.76)	
Log-rank test P value	0.00004	
Median OS, months (95% CI)	20.9 (19.1 to 22.6)	16.0 (13.9 to 18.2)
Treatment group difference vs. control	4.9	
OS rates at 6 months (95% CI), %	92.8 (90.0 to 94.8)	87.3 (82.1 to 91.1)
Treatment group difference vs. control	5.5 (0.5 to 10.5)	
P value	0.015	
OS rates at 24 months (95% CI), %	43.1 (38.5 to 47.7)	30.7 (24.6 to 36.9)
Treatment group difference vs. control	12.5 (4.7 to 20.2)	
P value	0.001	
PFS		
Events, n (%)	342	168

Variable	EF-14	
	Optune + temozolomide (N = 466)	Temozolomide alone (N = 229)
Censored, n(%)	124	61
Median follow-up time	40 months	
HR (95% CI)[b]	0.63 (0.52 to 0.76)	
Log-rank test P value	0.00004	
Median PFS, months (95% CI)	6.7 (6.1 to 8.1)	4.0 (3.8 to 4.3)
Treatment group difference vs. control	2.7	
PFS rates at 6 months (95% CI), %	55.6 (50.6 to 60.2)	36.5 (29.7 to 43.4)
Treatment group difference vs. control	19.1 (10.6 to 27.4)	
P value	0.0000	
PFS rates at 24 months (95% CI), %	14.2 (10.7 to 18.3)	9.5 (5.4 to 14.9)
Treatment group difference vs. control	4.7 (−1.4 to 10.8)	
P value	0.06402	
Radiological Response Rates		
Time point of assessment	24 months	
Progressive disease, n (%)	75 (17.9)	53 (28.2)
Stable disease, n (%)	313 (74.7)	110 (58.5)
Partial response, n (%)	30 (7.2)	21 (11.2)
Complete response, n (%)	1 (0.2)	4 (2.1)
Clinical benefit (stable disease or better),[c] n (%)	344 (82.1) P = 0.004	135 (71.8) *Ref*
Central best response[d], n (%)	[redacted]	[redacted]
Treatment group difference vs. control (95% CI)	[redacted]	
HRQoL (EORTC QLQ-C30)		
Participants completing the questionnaire		
Baseline, n (%)	639 patients (91.9% of randomized)	
12-months, n (%)	197 (41.7% of patients alive)	
Cognitive Functioning		
Baseline score, mean (SD)	76.7 (23.4)	76.5 (23.9)
12-month score, mean (SD)	76.2 (23.1)	77.6 (24.9)
Emotional Functioning		
Baseline score, mean (SD)	77.4 (21.4)	79.7 (18.6)
12-month score, mean (SD)	80.2 (20.4)	77.3 (23.1)

Variable	EF-14	
	Optune + temozolomide (N = 466)	Temozolomide alone (N = 229)
Physical Functioning		
Baseline score, mean (SD)	83.5 (20.1)	82.3 (20.7)
12-month score, mean (SD)	82.5 (22.7)	81.4 (21.2)
Role Functioning		
Baseline score, mean (SD)	74.5 (28.9)	72.8 (31.6)
12-month score, mean (SD)	75.9 (28.1)	70.1 (29.6)
Social Functioning		
Baseline score, mean (SD)	73.9 (27.6)	72.4 (28.9)
12-month score, mean (SD)	75.8 (25.2)	75.0 (27.6)
Global Health Status		
Baseline score, mean (SD)	69.0 (21.0)	66.4 (22.0)
12-month score, mean (SD)	69.8 (22.5)	67.8 (22.2)
Insomnia		
Baseline score, mean (SD)	18.3 (25.0)	18.9 (26.0)
12-month score, mean (SD)	18.0 (25.1)	19.9 (27.4)
Pain		
Baseline score, mean (SD)	10.0 (16.8)	11.2 (17.4)
12-month score, mean (SD)	11.8 (19.9)	14.0 (21.1)
Hair Loss		
Baseline score, mean (SD)	16.0 (25.8)	15.5 (26.2)
12-month score, mean (SD)	6.6 (18.9)	9.2 (22.3)
Headaches		
Baseline score, mean (SD)	15.4 (22.1)	14.6 (21.3)
12-month score, mean (SD)	13.9 (23.8)	18.4 (28.7)
Itchy Skin		
Baseline score, mean (SD)	14.8 (24.8)	16.7 (24.5)
12-month score, mean (SD)	18.0 (26.5)	19.3 (25.9)
Motor Dysfunction		
Baseline score, mean (SD)	14.5 (20.5)	17.2 (21.5)
12-month score, mean (SD)	13.5 (20.2)	17.4 (21.2)
Seizures		

Variable	EF-14	
	Optune + temozolomide (N = 466)	Temozolomide alone (N = 229)
Baseline score, mean (SD)	3.5 (12.5)	4.6 (16.1)
12-month score, mean (SD)	2.9 (13.7)	6.3 (21.1)
Visual Disorder		
Baseline score, mean (SD)	11.4 (17.7)	11.1 (16.4)
12-month score, mean (SD)	8.5 (13.2)	9.8 (17.9)
Weakness Of Legs		
Baseline score, mean (SD)	15.8 (25.5)	14.6 (25.7)
12-month score, mean (SD)	11.5 (22.0)	15.5 (23.5)

CI = confidence interval; EORTC QLQ-C30 = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30; HR = hazard ratio; HRQoL = health related quality of life; OS = overall survival; PFS = progression-free survival; SD = standard deviation.

[a]Based on a log-rank test stratified according to *MGMT* status (a potential predictor of response to temozolomide) and the extent of resection at randomization.

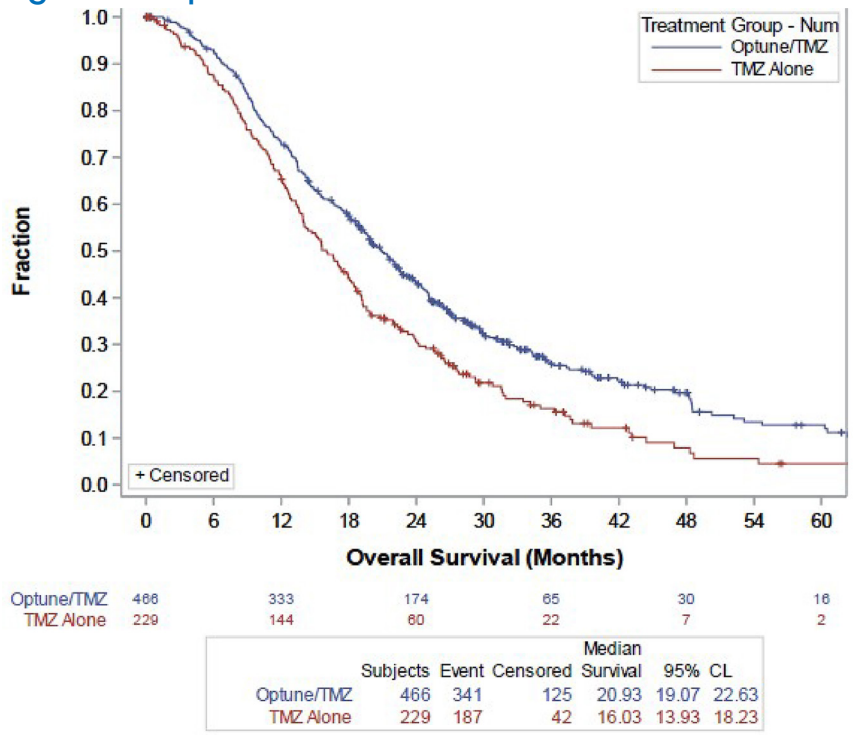
[b]based on a log-rank test stratified according to *MGMT* status (a potential predictor of response to temozolomide) and the extent of resection at randomization

[c]clinical benefit was defined in the trial as the proportion of patients with stable disease, partial response, or complete response.

[d]Clinical best response data was provided by the sponsor. It is the proportion of patients with either partial or complete response.

Source: Study EF-14 Clinical Study Report,[2] Taphoorn et al. (2018)[10] Details included in the table are from the sponsor's Summary of Clinical Evidence[1] or provided by the sponsor.

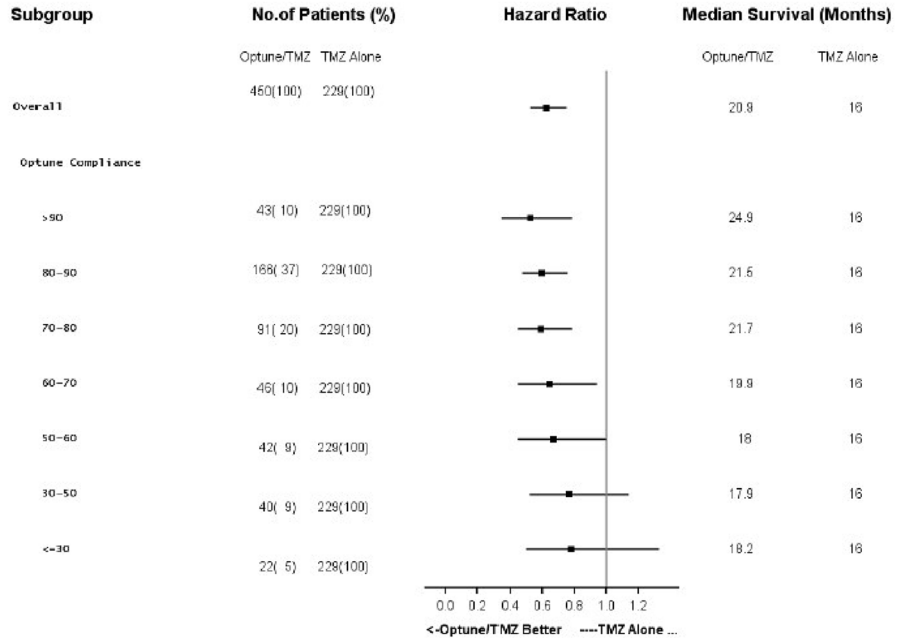
Figure 3: Kaplan-Meier Curve of OS From the Final Analysis, ITT



TMZ = temozolomide.

Source: Study EF-14 Clinical Study Report.[2]

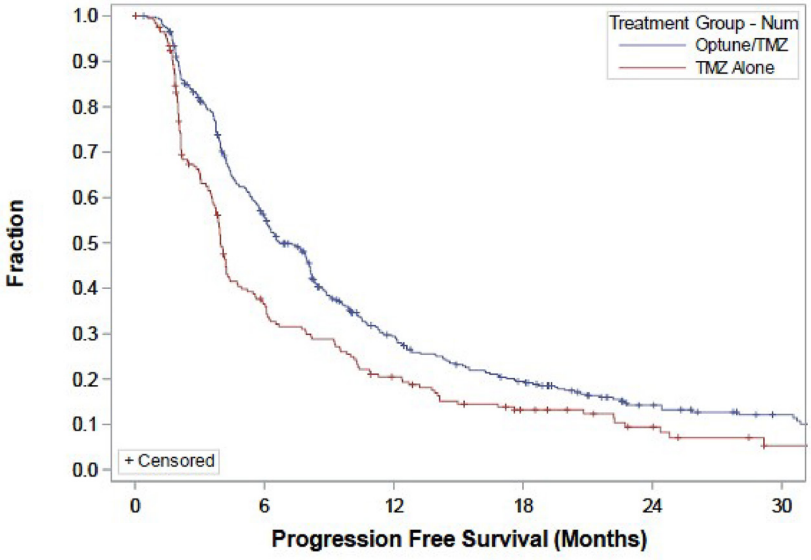
Figure 4: OS Stratified by Treatment Adherence From the Final Analysis, ITT



TMZ = temozolomide.

Source: Study EF-14 Clinical Study Report.[2]

Figure 5: Kaplan-Meier curve of PFS From the Final Analysis, ITT

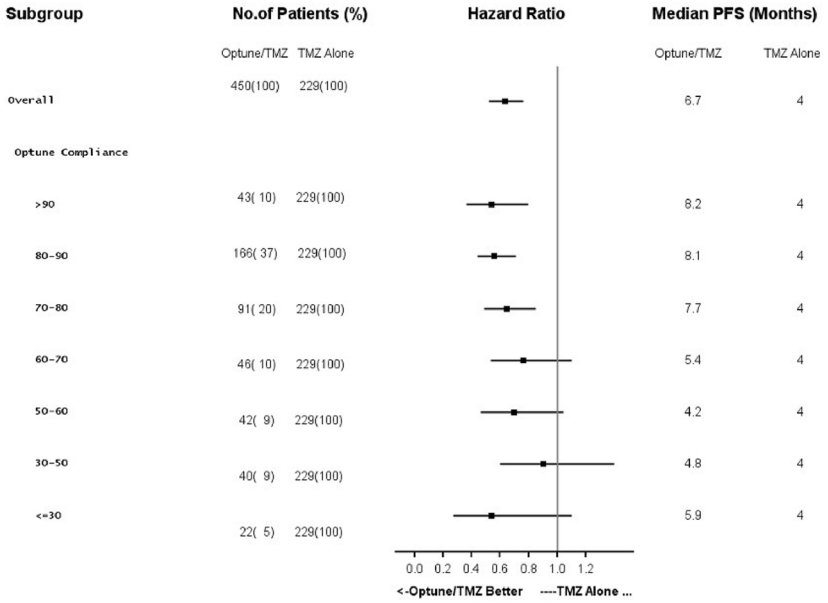


	Subjects	Event	Censored	Median Survival	95% CL	
Optune/TMZ	466	342	124	6.700	6.100	8.100
TMZ Alone	229	168	61	3.967	3.767	4.300

TMZ = temozolomide.

Source: Study EF-14 Clinical Study Report.[2]

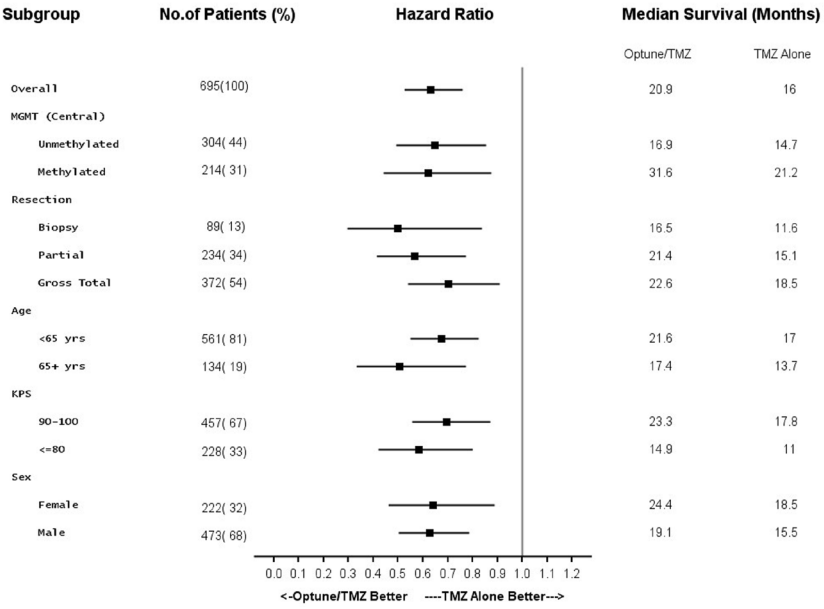
Figure 6: PFS Stratified by Treatment Adherence From the Final Analysis, ITT



PFS = progression free survival; TMZ = temozolomide.

Source: Study EF-14 Clinical Study Report.[2]

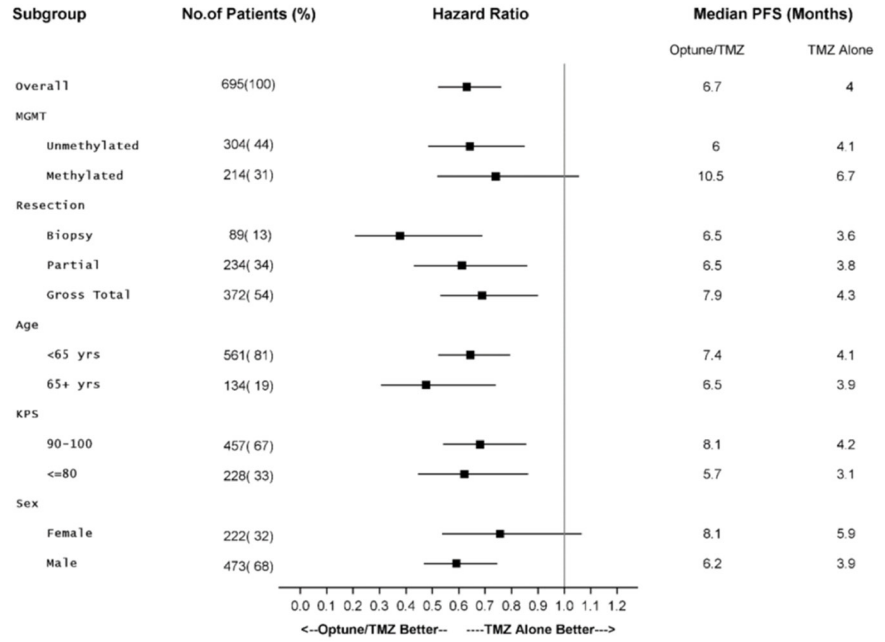
Figure 7: Subgroup Analyses of OS from the Final Analysis, ITT



KPS = Karnofsky performance status score; MGMT = O(6)-methylguanine-DNA methyltransferase; TMZ = temozolomide.

Source: Study EF-14 Clinical Study Report.[2]

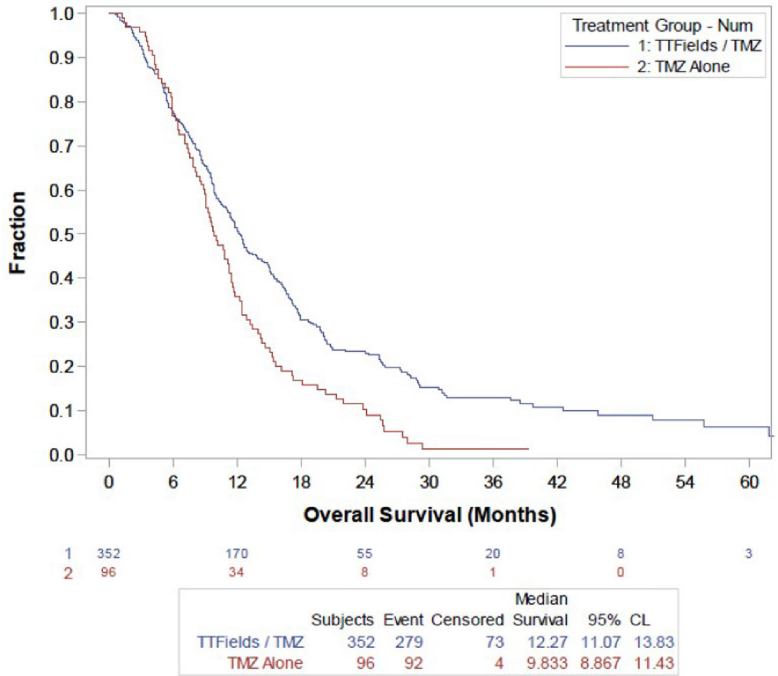
Figure 8: Subgroup Analyses of PFS from the Final Analysis, ITT



KPS = Karnofsky performance status score; MGMT = O(6)-methylguanine-DNA methyltransferase; TMZ = temozolomide.

Source: Study EF-14 Clinical Study Report.[2]

Figure 9: Kaplan-Meier Curve of OS from First Progression, As-treated Population



TMZ = temozolomide; TTFields = tumour treating fields.

Source: Study EF-14 Clinical Study Report.[2]

Table 10: Summary of Harms Results From the EF-14 Trial, Safety Population

Adverse events	EF-14	
	Optune+ temozolomide (N = 456)	Temozolomide (N = 216)
≥ 1 adverse event, n (%)	438 (96)	197 (91)
Most common adverse events, System organ class and preferred term, n (%)		
Blood and lymphatic system disorders	156 (34)	73 (34)
Leukopenia	38 (8)	18 (8)
Lymphopenia	43 (9)	13 (6)
Neutropenia	33 (7)	12 (6)
Thrombocytopenia	108 (24)	50 (23)
General disorders and administration site conditions	257 (56)	103 (48)
Injury, poisoning, and procedural complications	279 (61)	44 (20)
Contusion	17 (4)	5 (2)
Fall	37 (8)	7 (3)
Medical device site reaction	242 (53)	23 (11)
Musculoskeletal and connective tissue disorders	148 (32)	66 (31)
Neoplasms benign, malignant and unspecified (including cysts and polyps)	115 (25)	40 (19)
Nervous system disorders	330 (72)	141 (65)
Aphasia	50 (11)	17 (8)
Cognitive disorder	46 (10)	17 (8)
Convulsion	100 (22)	45 (21)
Headache	127 (28)	44 (20)
Hemiparesis	65 (14)	21 (10)
Psychiatric disorders	165 (36)	57 (26)
Anxiety	44 (10)	9 (4)
Confusional state	35 (8)	11 (5)
Depression	55 (12)	22 (10)
Insomnia	51 (11)	15 (7)
Serious adverse events, n (%)[a]		
Patients with ≥ 1 SAE, System organ class	156 (34)	67 (31)
Blood and lymphatic system disorders	9 (2)	4 (2)
Injury, poisoning, and procedural complications	17 (4)	5 (2)
Metabolism and nutrition disorders	6 (1)	1 (0.5)

Adverse events	EF-14	
	Optune+ temozolomide (N = 456)	Temozolomide (N = 216)
Musculoskeletal and connective tissue disorders	9 (2)	3 (1)
Nervous system disorders	64 (14)	26 (12)
Psychiatric disorders	10 (2)	4 (2)
Patients who stopped treatment due to adverse events, n (%)		
Patients who stopped	0 (0)	0 (0)
Deaths, n (%)		
Patients who died	253 (54)[a]	150 (66)[a]
SAE-related deaths[b]	1 (< 1)	1 (< 1)
Sudden SAE-related deaths[c]	1 (< 1)	0 (0)

AE = adverse event; SAE = serious adverse event.

[a]Deaths in FAS (Optune/temozolomide = 466, temozolomide = 229) through 24 months.

[b]As determined by the investigators

[c]As determined by the investigators

Source: Study EF-14 Clinical Study Report.[2] Details included in the table are from the sponsor's Summary of Clinical Evidence.[1]

Economic Review Appendices

Note that this appendix has not been copy-edited.

The current review is for Optune (tumour treating fields; OPTUNE® (NovoTTF-200A)) with maintenance temozolomide for the treatment of newly diagnosed GBM patients, after surgery and radiotherapy with adjuvant temozolomide.

Appendix 4: Economic Evaluation

Summary of Sponsor's Economic Evaluation

The sponsor submitted a cost-utility analysis to assess the cost-effectiveness of Optune + temozolomide against temozolomide alone for the treatment of patients with newly diagnosed GBM, after surgery and radiotherapy based on the population in the EF-14 trial. The analysis was conducted from the perspective of the Canadian publicly funded health care payer perspective over a lifetime time horizon (i.e., 30 years). The modelled population is aligned with the reimbursement request and Health Canada indication.[11]

Optune is available as a treatment kit consisting of the rented portable field generator and consumable transducer arrays.[11] The recommended frequency for GBM is 200 kHz for at least 18 hours a day.[12] 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.[11] Additional services covered as part of the monthly subscription cost include: individual planning of the INE Transducer Array treatment layout specific to each tumour per patient by trained radiologists, on-site 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 once a patient discontinues treatment. The comparator for this analysis was temozolomide alone which has a 28-day cost of $559 in Cycle 1 and $743 in Cycles 2 and beyond.

The sponsor submitted a partitioned survival model to track a cohort of newly diagnosed GBM patients. The model consisted of 3 health states including: progression free (PF; on- or off-treatment), progressed disease (PD), and death. The proportion of patients who were PF, experience disease progression, or death at any time, was derived from independent survival curves informed by the EF-14 trial.[11] All patients entered the model in the PF health state. The proportion of patients in the PF state was estimated based on extrapolated data from the respective PFS curves obtained from the EF-15 trial. The proportion of patients in the progressed disease state was calculated as the proportion alive (based on the OS curve) minus the proportion of patients alive and progression free (based on the PFS curve).[11]

A summary of key model inputs and data sources can be found in Table 11.

Table 11: Summary of Key Inputs in the Sponsor's Economic Evaluation

Parameter	Estimate/Assumption
Time horizon	30 years[11]
Cycle Length	1 month (28 days)[11]
Discount rate	1.5%[11]
Baseline characteristics	Age: 56 years Female: 32%
PFS, median (95% CI), months	Optune + TMZ: 6.7 (6.1 to 8.1) TMZ alone: 4.0 (3.8 to 4.4) HR: 0.63 (0.52 to 0.76)
PFS Extrapolations	Generalized gamma curve for both treatments[11]
OS, median (95% CI), months	Optune + TMZ: 20.9 (19.3 to 22.7) TMZ alone: 16.0 (14.0 to 18.4) HR: 0.63 (0.53 to 0.76)
OS Extrapolations	0 to 5 years: log-logistic curve for both treatments 5 to 15 years: conditional survival weights for GBM were used based on literature[13] Beyond 15 years: assumed survival was the same as the general Canadian population[14]
Time on treatment[a], median, months	Optune + TMZ: 8.2 TMZ alone: 7.2 (assumed to align with median PFS for Optune + TMZ)
Utility values	PF: 0.8474[15] PD: 0.7314[15]
Treatment costs	Optune: $27,000 per month[11] TMZ: $546 in Cycle 1 and $722 in Cycles 2+[11]

CI = confidence interval; GBM = glioblastoma; HR = hazard ratio; OS = overall survival; PD = progressed disease; TMZ = temozolomide; PF = progression free; PFS = progression free survival; PFS = progression free survival.

Inputs are informed by the EF-14 trial (data cut December 2016, minimum follow-up of 24 months and median follow-up of 40 months), unless otherwise stated.
[a]used to inform drug and device costs only

Summary of Sponsor's Economic Evaluation Results

All analyses were run probabilistically with 500 iterations. The deterministic results were aligned with the probabilistic results. The probabilistic findings are presented below.

The results of the sponsor's probabilistic base case analysis demonstrated that Optune + temozolomide was associated with an additional 0.64 quality-adjusted life-years (QALYs) at an additional cost of $228,507. Therefore, the incremental cost-effectiveness ratio (ICER) of Optune + temozolomide was $354,960 per QALY gained compared to temozolomide alone (Table 12). Based on the deterministic results, the majority (approximately 74%) of the incremental QALYs for Optune + temozolomide were found to be accrued during the extrapolation period (i.e., after the 2.5-year follow-up time from the TF-14 trial data).

Table 12: Summary of the Sponsor's Economic Evaluation Results

Drug	Total costs ($)	Incremental costs ($)	Total LYs	Incremental LYs	Total QALYs	Incremental QALYs	ICER vs. TMZ alone ($/QALY)
TMZ alone	63,507	Reference	2.04	Reference	1.91	Reference	Reference
Optune + TMZ	292,014	228,507	2.53	0.49	2.54	0.64	354,960

ICER = incremental cost-effectiveness ratio; LY = life years; QALY = quality-adjusted life-year; vs. = versus; TMZ = temozolomide.
Source: Sponsor's Pharmacoeconomic Evaluation[11]

In addition to the base case analysis, the sponsor conducted several scenario analyses. Analyses conducted included those that examined the impact of alternative time horizon, alternative discount rates, informing long-term survival with parametric curves for the entire time horizon, selecting alternative curves to inform PFS and OS, excluding supportive care and end of life costs, and excluding adverse event. ICERs from the scenario analyses ranged from $591,922 per QALY gained to $298,932 per QALY gained. However, no scenario had a significant impact on the relative cost-effectiveness of Optune + temozolomide versus temozolomide alone.

The sponsor also conducted a scenario analysis from a societal perspective. This analysis included additional costs associated with productivity loss for patients due to the inability to work or death. In this analysis, relative to temozolomide alone, the ICER was $350,321 per QALY gained. The results from this analysis were similar to the sponsor's base case analysis using a health care payer perspective.

CADTH Appraisal of the Sponsor's Economic Evaluation

CADTH identified several key limitations to the sponsor's analysis that have notable implications on the economic analysis:

- **Long-term efficacy of Optune + temozolomide for patients with GBM is highly uncertain.** OS in the sponsor's submitted pharmacoeconomic analysis was derived via a three-phased approach. Years 0 to 5 were informed by extrapolated OS data from the EF-14 trial (loglogistic curve for temozolomide alone, adjusted with a HR of 0.63 [95% CI, 0.53 to 0.76, P < 0.001] for Optune + temozolomide).

Patients who survived the first 5 years had conditional survival probabilities informed from Porter et al., 2011 for years 5 to 15, and general Canadian population mortality data from Statistics Canada was used to inform years 16 and beyond. As noted in the CADTH clinical review, while OS rates for Optune + temozolomide were considered clinically meaningful by 24 months, the assumption that survival probabilities match the general population after 16 years suggests that Optune is curative; however, there is no robust evidence to support this. This aligns with clinical expert feedback that patients with GBM have an increased risk of death compared to the general population even when progression free, and with prior health technology assessment reviews of Optune.[16] Thus using general population mortality may overestimate OS.

The sponsor conducted an exploratory analysis to determine if Optune + temozolomide had a post-progression benefit given the observation of no meaningful PFS benefit at 24 months yet a potential OS benefit. Due to limitations with the exploratory analysis (i.e., hypothesis generating, allowance of crossover from temozolomide alone to the Optune arm in the EF-14 trial, usage of the as-treated population), a causal inference for treatment with Optune and post-progression survival benefit should not be made.

  - In the CADTH reanalysis, the Weibull parametric curve was used to inform OS of both treatment arms over the 30-year time horizon (i.e., no cure assumption) based on clincial expert feedback received by CADTH. However, based on data from real world studies of patients with GBM such as Porter et al., OS may be higher than suggested from the Weibull curve (2.9% at 10 years based on Porter et al. compared with 2.2% at 10 years based on the Weibull curve; for reference, the sponsor's modelling approach suggested the proportion of patients alive at 10 years was 4.9%).

- **Comparative clinical efficacy of Optune + temozolomide compared to temozolomide alone is uncertain.** Comparative clinical efficacy used to inform the sponsor's submitted pharmacoeconomic model was informed by the EF-14 trial where PFS curves for Optune + temozolomide and temozolomide alone were generated using data from the EF-14 trial (data cut December 2016, median follow-up of 40 months). As noted in the CADTH clinical review, the sponsor conducted a subgroup analysis by treatment adherence to Optune. While the subgroup analyses suggested that higher treatment adherence (> 70%, or wearing the device for at least 18 hours per day) was associated with an increase in survival compared to temozolomide alone, the results are difficult to interpret due to the post-hoc nature of the analysis. Clinical expert feedback received by CADTH noted that there appears to be a dose response consideration with Optune, but treatment compliance in clinical practice remains a concern. As such the true efficacy of Optune in Canadian practice is uncertain.
  - CADTH was unable to address this limitation.
- **Uncertainty in the time on treatment (ToT) for Optune + temozolomide treatment.** ToT for both comparator arms were based on data from the EF-14 trial. A median time of 8.2 months was used to inform the time on Optune and temozolomide for the Optune + temozolomide arm. As the EF-14 trial did not report the median ToT for maintenance temozolomide, the sponsor used the median PFS time for Optune + temozolomide (7.2 months) to inform time on maintenance temozolomide alone.

Clinical expert feedback received by CADTH noted that ToT with Optune + temozolomide is highly uncertain as some patients in the EF-14 trial continued beyond progression and use may be impacted by factors such as patient motivation. As ToT was only used to inform drug and device costing in the model, underestimation in treatment duration may result in underestimated costs in the analysis biasing results in favour of Optune + temozolomide.

  - While modelling ToT based on PFS was considered, it was deemed inappropriate as patients in the EF-14 trial could continue treatment beyond progression. Although the median ToT is [redacted] than the mean ToT indicating most patients on Optune + temozolomide used the therapy for [redacted] than [redacted] months, due to limitations in the model structure, unavailability of ToT KM data and the large range of ToT during the EF-14 trial, mean ToT ([redacted] months) was used as a proxy to inform the duration of Optune + temozolomide in the CADTH reanalysis.

- **Utility value estimates used to inform the model are uncertain.** In the sponsor's submitted base case analysis, health state utility values were informed by Garside et al., 2007 which is a National Institute for Health and Care Excellence (NICE UK) commissioned review to assess the cost-effectiveness of carmustine implants and temozolomide for the treatment of newly diagnosed high-grade glioma in the UK.[15] The adjusted values were used where patients in the PF and PD health states had utility values of 0.8474 and 0.7314, respectively.[15] Based on the mean Canadian utility norms from Yan et al., 2023, the reported utility for individuals aged 55 to 64 is 0.839.[17] Therefore, by applying a utility value of 0.8474 to patients, the sponsor is implying that patients with newly diagnosed GBM while on Optune + temozolomide or temozolomide alone have a higher wellbeing compared to the general Canadian population. Clinical expert feedback received by CADTH noted that while the utility difference between patients who are in the PF health state and those in the PD health state was considered reasonable, the absolute values used did not meet face validity. Specifically, a value of 0.7314 is likely not representative of patient's experiencing continued progression as quality of life decreases rapidly with progression.

  - Due to the lack of robust alternate estimates, CADTH was unable to address this limitation.

CADTH Reanalyses of the Economic Evaluation

The CADTH base case was derived by making changes in model parameter values and assumptions, in consultation with clinical experts. These changes, summarized in Table 13, involved removal of the 3-phase approach to inform OS and using an alternative input to inform ToT of Optune.

Table 13: CADTH Revisions to the Submitted Economic Evaluation

Stepped analysis	Sponsor's value or assumption	CADTH value or assumption
Changes to derive the CADTH base case		
1. OS	3 phase approach (0 to 5 years = loglogistic curve for both treatments; 5 to 15 years = conditional survival weights based on literature; beyond 15 years = assumed same as the general Canadian population)	Weibull parametric curve
2. Optune ToT	8.2 months	[redacted] months
CADTH base case	reanalysis 1 + 2	

OS = overall survival; ToT = time on treatment.

Note: Results are based on the probabilistic analysis

The results of the CADTH base case analysis demonstrated that Optune + temozolomide was associated with an additional 0.37 QALYs at an additional cost of $336,902 versus temozolomide alone. Therefore, the ICER of Optune + temozolomide was $899,470 per QALY gained compared to temozolomide alone. The probability of cost-effectiveness at a $50,000 per QALY willingness-to-pay threshold was 0%. A summary of the CADTH base case reanalysis results can be found in Table 14 and Table 15.

Table 14: Summary of the Stepped Analysis of the CADTH Reanalysis Results

Stepped analysis	Medical device or intervention	Total costs ($)	Total QALYs	ICER ($/QALY)
Sponsor's base case (probabilistic)	TMZ	$63,507	1.91	Ref.
	Optune + TMZ	$292,014	2.56	$354,960
CADTH reanalysis 1	TMZ	$58,493	1.54	Ref.
	Optune + TMZ	$285,112	1.91	$604,311
CADTH reanalysis 2	TMZ	$64,045	1.92	Ref.
	Optune + TMZ	$405,486	2.58	$521,983
CADTH base case (reanalysis 1 + 2; probabilistic)	TMZ	$58,435	1.54	Ref.
	Optune + TMZ	$395,336	1.92	$899,470

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

Note: Results are based on the probabilistic analysis

Table 15: Disaggregated Summary of CADTH's Economic Evaluation Results

Parameter	Optune + TMZ	TMZ alone	Incremental
Discounted LYs			
Total LYs	**2.53**	**2.04**	**0.49**
PF	1.45	1.12	0.33
PD	1.08	0.92	0.16
Discounted QALYs			
Total QALYs	**1.92**	**1.54**	**0.37**
PF	1.23	0.95	0.28
PD	0.79	0.67	0.12
AE disutility	0.10	0.08	0.02
Discounted costs			
Total Cost	**$395,336**	**$58,435**	**$336,902**
Drug and device costs	$337,682	$5,243	$332,439
PF follow-up	$11,496	$8,891	$2,605
PD follow-up	$12,487	$10,653	$1,834
End of life	$32,238	$32,464	-$226
AE	$1,433	$1,184	$249
Indirect costs	$0	$0	$0
ICER ($/QALY)	$899,470		

AE = disutility; ICER = incremental cost-effectiveness ratio; LY = life-year; PD = progressed disease; PF = progression free; QALY = quality-adjusted life-year; TMZ = temozolomide.

Note: Results are based on the probabilistic analysis

CADTH undertook price reduction analyses based on the sponsor's and CADTH's base case (Table 16). The CADTH base case suggested a price reduction of 91% to 97% (i.e., month cost of $864 to $2,403) would be required to achieve cost-effectiveness of Optune + temozolomide at willingness-to-pay thresholds ranging from $50,000 per QALY gained to $100,000 per QALY gained.

If the utility values were considered too uncertain to use, when considering the cost per life year gained, a price reduction of 88% to 95% would be required to achieve cost-effectiveness of Optune + temozolomide at willingness-to-pay thresholds ranging from $50,000 to $100,000 per QALY gained.

Table 16: CADTH Price Reduction Analyses

Analysis	Cost per QALY for Optune plus TMZ vs. TMZ alone		Cost per Life Year for Optune plus TMZ vs. TMZ alone	
Price reduction (monthly fee)	Sponsor base case	CADTH reanalysis	Sponsor base case	CADTH reanalysis
No price reduction ($27,000)	$352,459	$900,012	$265,222	$692,105
10% ($24,300)	$318,613	$812,193	$239,752	$624,573
20% ($21,600)	$284,766	$724,375	$214,283	$557,041
30% ($18,900)	$250,919	$636,556	$188,813	$489,509
40% ($16,200)	$217,072	$548,738	$163,344	$421,977
50% ($13,500)	$183,225	$460,919	$137,875	$354,445
60% ($10,800)	$149,378	$373,101	$112,405	$286,913
70% ($8,100)	$115,531	$285,282	$86,936	$219,381
80% ($5,400)	$81,685	$197,464	$61,467	$151,849
90% ($2,700)	$13,991	$109,645	$35,997	$84,317

ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life-year; TMZ = temozolomide; vs. = versus.
Note: Results are based on the deterministic analysis.

Appendix 5: Submitted BIA and CADTH Appraisal

Table 17: Summary of Key Take-aways

Key Take-aways of the BIA

• CADTH identified the following key limitations with the sponsor's BIA:
  ◦ Uncertainty in the estimated number of newly diagnosed GBM eligible for treatment.
  ◦ Uncertainty in the duration of Optune + temozolomide treatment.
  ◦ Drug plan payer perspective is inappropriate.
• The CADTH reanalysis reduced the proportion of patients who undergo external beam radiation therapy with adjuvant temozolomide and increased the ToT for Optune + temozolomide by using the mean ToT for patients receiving Optune + temozolomide from the EF-14 trial. Based on the CADTH base case, an estimated 1,352 patients would be eligible for treatment over the initial 3-year period, of whom 232 were assumed to receive Optune. The estimated incremental budget impact of reimbursing Optune + temozolomide is $12,153,567 in Year 1, $27,689,944 in Year 2, and $35,951,813 in Year 3. Therefore, the estimated budget impact is $75,795,323 for the first three years of availability.

Summary of Sponsor's BIA

The sponsor submitted a budget impact analysis (BIA) to estimate the three-year budget impact of reimbursing Optune + temozolomide for the treatment of newly diagnosed GBM after surgery and radiotherapy with adjuvant temozolomide. The analysis was taken from the perspective of the Canadian public drug plan. A three-year time horizon was used from 2024 to 2026, with 2023 as the base year. The target population size was derived with an epidemiological approach. Key inputs to the BIA are documented in Table 18.

The BIA compared 2 scenarios to determine the incremental budget impact of reimbursing Optune + temozolomide. The reference case scenario assumed that all eligible patients would be on temozolomide. The new drug scenario included Optune + temozolomide. In the sponsor's base case, costs related to drug acquisition were considered.

The following key assumptions were included in the BIA:

- The payer for Optune is CADTH-participating drug plans.
- 100% of adult patients with GBM undergo surgery.
- 75% of patients who underwent surgery receive external beam radiation therapy with adjuvant temozolomide.
- Treatment duration of Optune + temozolomide is 8.2 months, as informed by the EF-14 trial.
- US data informing proportion of GBM out of malignant central nervous system tumours is generalizable to Canada.

Table 18: Summary of Key Parameters in the Budget Impact Analysis

Parameter	Sponsor's estimate (reported as Year 1 / Year 2 / Year 3 where appropriate)
Target Population	
Malignant central nervous system incidence (per 100,000 person years)	7.9[18,19]
Proportion GBM out of malignant tumours	50.1%[19]
Proportion adult patients	95%[20]
Proportion that undergo surgery	100%
Proportion that undergo external beam radiation therapy with adjuvant TMZ	75%
Proportion with stable disease/no progression	85%[3]
Number of patients eligible	759 / 768 / 777
Market Uptake (3 years)	
Uptake (reference scenario) TMZ	 100% / 100% / 100%
Uptake (new drug scenario) Optune + TMZ TMZ	 8.42% / 18.82% / 24.02% 91.58% / 81.18% / 75.98%
Cost of treatment (per patient)	
Optune + TMZ TMZ	$225,368[a] $3,968

GBM = glioblastoma; TMZ = temozolomide.

[a]assuming treatment duration is 8.2 months, as informed by the EF-14 trial. TMZ was costed assuming 6 cycles.

[b]calculated assuming patient body surface area of 1.91 m^2 estimated from the 2008 Canadian Community Health Survey[21]

Summary of the Sponsor's BIA Results

In the sponsor's base case analysis, the estimated incremental budget impact of funding Optune + temozolomide for the treatment of newly diagnosed adult GBM patients, after surgery and radiotherapy with adjuvant temozolomide was $14,156,143 in Year 1, $32,016,556 in Year 2, and $41,342,082 in Year 3. Therefore, the three-year incremental budget impact was $87,514,781.

CADTH Appraisal of the Sponsor's BIA

CADTH identified several key limitations to the sponsor's analysis that have notable implications on the results of the BIA:

- **Estimated number of patients with newly diagnosed GBM eligible for treatment is uncertain.** The incidence of malignant central nervous system tumours, the proportion of GBM out of malignant tumours, and the proportion of adult patients with GBM were informed by published literature. The sponsor further assumed that 100% of patients receive surgery and 75% undergo external beam radiation therapy with adjuvant temozolomide based on feedback from clinicians they had consulted. Clinical expert feedback received by CADTH noted that while 100% of patients receive a tissue diagnosis, there are patients with GBM who are deemed ineligible for surgery based on imaging. Thus, the proportion of patients who undergo external beam radiation therapy with adjuvant temozolomide is likely overestimated. This was supported by published literature from a Canadian hospital which suggested approximately 44% of patients underwent external beam radiation therapy with adjuvant temozolomide.[22]
    - In the CADTH reanalysis, the proportion of patients who undergo external beam radiation therapy with adjuvant temozolomide was revised to 44% based on Canadian published literature.
- **Uncertainty in the duration of Optune + temozolomide treatment.** The annual cost of Optune was calculated using the median ToT for Optune + temozolomide informed by the EF-14 trial (i.e., 8.2 months). Clinical expert feedback received by CADTH noted that the amount of time on Optune for newly diagnosed GBM patients after surgery and radiotherapy with adjuvant temozolomide remains uncertain as some patients in the EF-14 trial continued treatment beyond progression and factors such as patient motivation need to be carefully considered when determining suitability for Optune. As a result, the actual duration of therapy in clinical practice is unknown. In the trial, ToT ranged from 0 to 82 months, as such the budget impact of Optune + temozolomide may be over or underestimated should patients utilize Optune for more or less time, respectively.
    - In the CADTH reanalysis, the time on treatment for Optune was set equal to the mean ToT from the EF-14 trial ([redacted] months).
- **Drug plan payer perspective is inappropriate.** The sponsor's submitted budget impact analysis was conducted from the perspective of the CADTH-participating public drug plans as the sponsor considered they would be the payers for Optune. Optune is a device, therefore it is unclear whether paying for a device would be under the remit of the CADTH-participating public drug plans. As the primary payers of Optune remains uncertain, the perspective submitted by the sponsor may fail to

represent the true budget impact of reimbursing Optune in Canada. A broader perspective health system perspective should have been considered by the sponsor.

- CADTH was unable to address this limitation.

CADTH Reanalyses of the BIA

Table 19: CADTH Revisions to the Submitted Budget Impact Analysis

Stepped analysis	Sponsor's value or assumption	CADTH value or assumption
Corrections to sponsor's base case		
None	—	—
Changes to derive the CADTH base case		
1. Proportion of patients who undergo external beam radiation therapy with adjuvant TMZ	75%	44%
2. Optune ToT	8.2	[redacted]
CADTH base case	Reanalysis 1 + 2	

TMZ = temozolomide; ToT = time on treatment.

The results of the CADTH step-wise re-analysis are presented in summary format in Table 20 and a more detailed breakdown is presented in Table 21.

Based on the CADTH base case, 1,352 patients would be eligible for treatment where an estimated 232 were assumed to receive Optune. Therefore, the estimated incremental budget impact of reimbursing Optune + temozolomide is $12,153,567 in Year 1, $27,689,944 in Year 2, and $35,951,813 in Year 3. Therefore, the three-year total budget impact is $75,795,323.

Table 20: Summary of the CADTH Reanalyses of the BIA

Stepped analysis	Three-year total
Submitted base case	$87,514,781
CADTH reanalysis 1	$51,342,005
CADTH reanalysis 2	$129,196,574
CADTH base case	$75,795,323

BIA = budget impact analysis.

Table 21: Detailed Breakdown of the CADTH Reanalyses of the BIA

Stepped analysis	Scenario	Year 0 (current situation)	Year 1	Year 2	Year 3	Three-year total
Submitted base case	Reference	$2,977,071	$3,012,832	$3,048,593	$3,084,354	$9,145,779
	New medical device	$2,977,071	$17,168,975	$35,065,149	$44,426,436	$96,660,560

Stepped analysis	Scenario	Year 0 (current situation)	Year 1	Year 2	Year 3	Three-year total
	Budget impact	$0	$14,156,143	$32,016,556	$41,342,082	$87,514,781
CADTH base case	Reference	$1,746,548	$1,767,528	$1,788,508	$1,809,488	$5,365,524
	New medical device	$1,746,548	$13,921,095	$29,478,452	$37,761,300	$81,160,847
	Budget impact	$0	$12,153,567	$27,689,944	$35,951,813	$75,795,323
CADTH scenario analysis: 91% price reduction	Reference	$1,746,548	$1,767,528	$1,788,508	$1,809,488	$5,365,524
	New medical device	$1,746,548	$2,861,349	$4,280,603	$5,045,151	$12,187,103
	Budget impact	$0	$1,093,821	$2,492,095	$3,235,663	$6,821,579
CADTH scenario analysis: 97% price reduction	Reference	$1,746,548	$1,767,528	$1,788,508	$1,809,488	$5,365,524
	New medical device	$1,746,548	$2,132,135	$2,619,206	$2,888,042	$7,639,383
	Budget impact	$0	$364,607	$830,698	$1,078,554	$2,273,860

BIA = budget impact analysis.

Ethics Review Appendix

Note that this appendix has not been copy-edited.

Appendix 6: Methods for the Ethics Review

Research Questions

This report addresses the following research questions:

What ethical considerations arise in the context of newly diagnosed supratentorial glioblastoma?

What ethical considerations arise related to the evidence (e.g., clinical and economic data) used to evaluate Optune?

What ethical considerations arise in the use of Optune for patients, their caregivers, and clinicians in Canada?

What ethical considerations for health systems are involved in the context of implementing Optune in Canada?

To identify ethical considerations relevant to the use of Optune in the treatment of for newly diagnosed supratentorial glioblastoma following maximal debulking surgery and completion of radiation therapy together with and after standard of care maintenance chemotherapy, this ethics report was driven by relevant questions identified in the EUnetHTA Core Model 3.0, Ethics Analysis Domain,[23] and supplemented by

relevant questions from the Equity Checklist for HTA (ECHTA).[24] These guiding questions were organized to respond to the research questions posed.

Data Collection: Review of Project Inputs and Literature

Data to inform this ethics report drew from an identification of ethical considerations (e.g., values, norms, or implications related to the harms, benefits, and implications for equity, justice, resource allocation, and ethical considerations in the evidentiary basis) in the patient and clinician group, and clinical expert and caregiver input collected by CADTH to inform this review, a complementary search of the published literature, and ongoing collaboration with CADTH reviewers working on the clinical and economic reviews for this submission.

Review of Project Inputs

During this CADTH review, a single reviewer collected and considered input from 5 main sources for content related to ethical considerations relevant to addressing the research questions guiding this ethics report. In addition to published literature, this report considered the following sources:

1. The sponsor submission, including noting relevant information and external references or sources relevant to each of the research questions driving this report;
2. Clinician group input received by CADTH from a group of Canadian oncologists who treat patients with newly diagnosed glioblastoma;
3. Patient input received by CADTH from the Brain Tumour Foundation of Canada (BTFC);
4. Discussion with clinical experts (n = 5 of clinical experts) and caregivers (n = 1) directly engaged by CADTH over the course of this reimbursement review, including through 1 clinical consultation meetings involving 1 experts, and 1 expert panel meeting involving 5 clinical experts and 1 caregiver. During these meetings, clinical experts and caregivers were asked targeted questions related to ethical considerations corresponding to the research questions driving this report. All clinical experts were practicing oncologists with experience treating patients with newly diagnosed glioblastoma and some had experience treating patients with Optune. The caregiver had experience providing care for a person with glioblastoma.
5. Engagement with CADTH clinical and economic reviewers to identify domains of ethical interest arising from their respective reviews as well as relevant questions and sources to further pursue in this report.

Literature Search Methods

An information specialist conducted a literature search on key resources including MEDLINE via Ovid and Philosopher's Index via Ovid. Google Scholar was searched to find additional materials not captured in the major bibliographic databases. The search strategy comprised both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts were tumour-treating fields and glioblastoma.

CADTH-developed search filters were applied to the searches conducted in MEDLINE to limit retrieval. The concept of tumour-treating fields was limited to citations related to ethical concepts or considerations, equity

concepts or considerations, or qualitative studies; and the concept of glioblastoma was limited to citations related to ethical concepts or considerations or equity concepts or considerations. Due to limited number of results, no filters were applied to the searches conducted in Philosopher's Index to limit the retrieval by study type. Duplicates were removed by manual deduplication in EndNote. The search was completed on September 20, 2023.

Literature Screening and Selection

Literature retrieved according to the search and selection methods detailed above was screened in 2 stages. First, titles and abstracts of citations retrieved were screened for relevance by a single reviewer. Articles were identified and retrieved for full-text review by a single reviewer if their titles or abstracts identified ethical considerations, or provided normative analysis (i.e., focusing on 'what ought to be' through argumentation), or presented empirical research (i.e., focusing on 'what is' through observation) of ethical considerations related to: the experiences, incidence, diagnosis, treatment, or outcomes of newly diagnosed supratentorial glioblastoma; or the evidence on, use of, or implications of Optune for patients with newly diagnosed supratentorial glioblastoma. In the second stage, full-text publications categorized as 'retrieve' were reviewed by the same reviewer. Texts that included substantive information meeting the aforementioned criteria were included in the review, and reports that did not meet these criteria were excluded. As a parallel process, other sources drawn from relevant bibliographies, relevant key concepts, in consultation with experts, or other CADTH reviewers were retrieved and reviewed using the selection criteria listed above.

Data Analysis

Data analysis was driven by the 4 research questions guiding this report and included the collection, coding, and thematic analysis of data drawn from the literature and project inputs. The reviewer conducted 2 iterative cycles of coding and analysis to abstract, identify, and synthesize relevant ethical considerations in the literature and from relevant project inputs.

In the initial coding phase, publications and input sources were reviewed for ethical content (e.g., claims related to potential harms, benefits, equity, justice, resource allocation and ethical issues in the evidentiary basis). Once identified, claims related to ethical content were coded using methods of qualitative description.[25] In the second coding phase, major themes and sub-codes were identified through repeated readings of the data,[25] and summarized into thematic categories within each guiding domain or research question. Where ethical content did not fit into these categories or domains outlined in the research questions, this was noted, as were discrepancies or conflicts between ethical considerations or values identified between project sources or within thematic categories. Data analysis was iterative, and themes identified in the literature, in project inputs, and during consultations with clinical experts were used to further refine and re-interpret ethical considerations identified. Data collected and analyzed from these sources were thematically organized and described according to the 4 research questions and domains driving this report.

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