Cost-effectiveness analysis of adding tumor-treating fields therapy to temozolomide versus temozolomide only in patients with glioblastoma in France

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BACKGROUND AND OBJECTIVE

- Glioblastoma multiforme (GBM) is the most common and aggressive primary brain malignancy. It typically rapidly progresses and has a very poor prognosis[1,2].
- OPTUNE® is a medical device that uses **Tumor-Treating Fields (TTFields) technology** to treat GBM. The **phase III EF-14-trial[3]** compared the efficacy and safety of TTFields plus maintenance temozolomide (TMZ) to temozolomide alone for newly diagnosed GBM patients. A total of 695 patients were included for a median follow-up time of 40 months
- The primary endpoint was PFS, and the powered secondary endpoint was OS. Median PFS for TTFields+TMZ was **6.7 months vs 4.0 months** in the TMZ-alone group (hazard ratio [HR] = 0.63; 95% confidence interval [CI] = 0.52–0.76]; $p < 0.001$). Median OS for TTFields+TMZ was **20.9 months vs 16.0 months** in the TMZ-alone group (HR = 0.63; 95% CI = 0.53–0.76, $p < 0.001$).
- The EF-14 trial demonstrated that the **OS benefit of adding TTFields was maintained through 5 years** after starting treatment. The reported survival at 5-years was **13%** for patients treated with TTFields and maintenance TMZ and **5%** for patients treated with maintenance TMZ alone ($p = 0.004$).
- This study assesses the cost-effectiveness of adding TTFields therapy to TMZ versus TMZ only for patients with newly diagnosed GBM from the French healthcare system perspective

METHOD

Economic model

- A **partitioned survival model** composed of three health states (progression-free survival (PFS), progressed disease (PD), and death), was developed to compare adding TTFields therapy to TMZ versus TMZ only
- Costs and health outcomes were projected over a **20-year time horizon,** with a monthly cycle, and were discounted at 2.5% per year

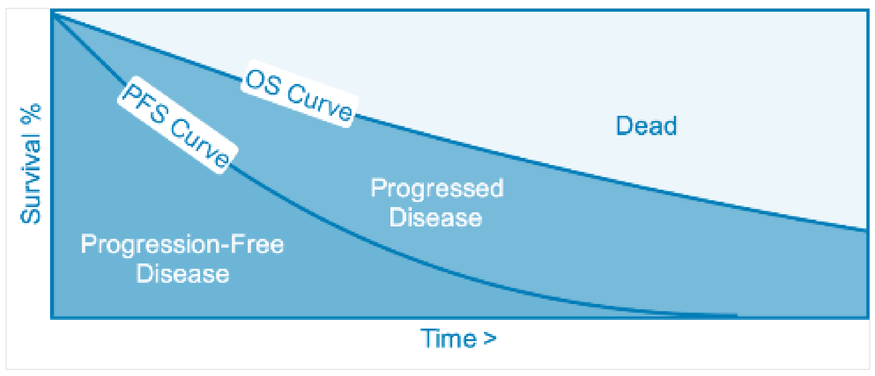

Figure 1 : Model structure

Integration of clinical data

- The model used **Kaplan Meier (KM) estimates of progression-free survival, overall survival, and treatment duration** from EF-14 clinical trial. An **independent extrapolation** of PFS for both the TTFields+TMZ arm and TMZ-alone arm was performed using a generalized gamma function
- For OS, KM curves from EF-14 were directly used for simulating the 5 first years. Epidemiological GBM survival data from the registry study by Porter et al.[4] were then used for the simulation of year 6 to year 15 for both arms, followed by general population French mortality data to model the mortality from 15 years to the end of the time horizon

Efficacy criteria	Data source	Model type	Distribution
PFS	EF-14	Independent	Generalized gamma for both arms
OS	EF-14, Porter et al., French general mortality	Conditional probability	1. KM the first 5 years 2. Conditional probabilities from Porter et al.[4] between 5 and 15 years 3. French general population mortality from year 15

Table 1 : Summary of extrapolation choices in base case analysis

Adverse events

- Grade 3-4 adverse events (AEs) with a frequency ≥ 5% and grade 1-2 AEs due to TTFields (skin reaction) were considered in terms of costs and utility.
- Treatment durations were integrated based on the KM curves from the EF-14 trial. In line with NICE DSU TSD 14[5], extrapolation of the TTFields + TMZ arm led to the selection of the generalized gamma distribution for the base case model.

Utility data

- EQ-5D-5L data were collected from 853 patients using TTFields therapy in a real-world setting in the US and Europe[6]. The EQ-5D-5L responses were converted into health state utility values using a EuroQol-endorsed French value set provided by Andrade et al.[7]

Health states	Data source	Inputs
PFS	Chavez et al.[6], Andrade et al.[7]	0.882
PD		0.748

Table 2 : Summary of utility values in base case analysis

Costs data

- Direct medical and non-medical costs (in 2020) were considered, including acquisition and administration, transportation, follow-up, adverse events, subsequent treatments and end-of-life care costs.

RESULTS

Base case analysis

- Model simulations demonstrated that adding TTFields therapy to TMZ versus TMZ only in France is associated with **1,13 additional Life Years** (LY) and **0,90 additional Quality adjusted Life Years** (QALY) as well as incremental costs of €210,2. **ICERs were €186,4/LY and €232,7/QALY.**
- Compared to TMZ only, TTFields+TMZ generated savings of €1,063 in post-progression costs and savings of €301 in death costs due to greater survival in the TTFields+TMZ arm.

Therapeutic strategy	Costs (€)	LYs	QALYs	ICER (€/LY)	ICER (€/QALY)
TTFields + TMZ	226 752	2,55	2,05	186 432	232 739
TMZ	16 561	3,18	1,65		

Table 3 : Base case analysis results

- Patients treated with TTFields+TMZ experienced an average of 16.2 months with progression-free disease compared to 10.5 months for patients treated with TMZ alone, and experienced 21.9 months with progressed disease compared to 14.1 months for patients with TMZ alone. Thus patients treated with TTFields+TMZ had a total survival gain of 13.5 months compared to patients treated with TMZ alone.

Health states	Mean PFS (months)	Mean PD (months)	Mean OS (months)
TTFields + TMZ	16.2	21.9	38.1
TMZ	10.5	14.1	24.6

Table 4 : Average time spent in health states for reference analysis

Sensitivity analysis

- According to the deterministic sensitivity analysis, treatment cost of TTFields and discount rate were the two parameters with an impact higher than 10% on the results.
- Probabilistic sensitivity analysis estimated a mean ICER of TTFields+TMZ vs TMZ only at **€238,951/QALY (+2%).** With a willingness-to-pay (WTP) threshold up to €280,000/QALY, TTFields+TMZ has at least an 85.4% probability of being cost-effective relative to TMZ only.
- As shown in the Figure 2, **TTFields + TMZ is both more expensive and more effective** than the TMZ arm alone. The dispersion was found to be higher for incremental costs than for incremental QALY (with 16% and 5% variations respectively).

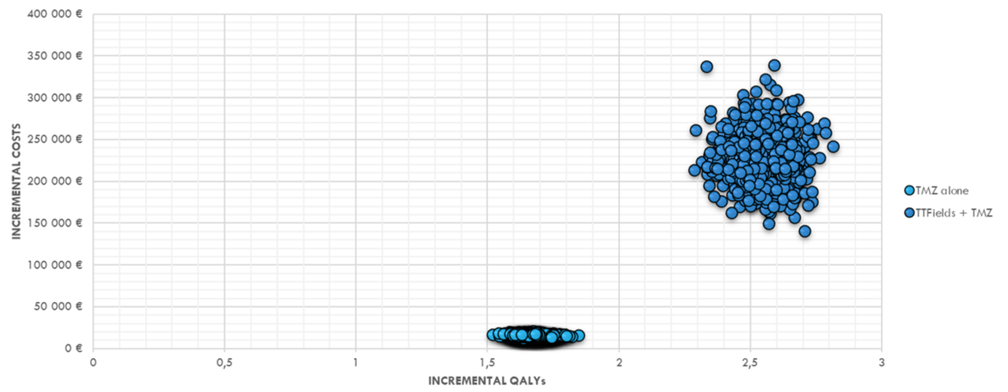

Figure 2 : Cost-effectiveness scatterplot

CONCLUSION

Compared to TMZ only, the strategy combining TTFields with TMZ is associated with a substantial gain in clinical efficacy along with additional cost. The result is considered robust due to low uncertainty. TTFields+TMZ provided sufficient additional clinical value to achieve national reimbursement.

Acronyms : AE: Adverse Events; EQ-5D-5L : EuroQol-5 Dimensions-5 Levels; GBM : Glioblastoma multiforme; HTA : Health Technology Assessment; ICER : Incremental Cost-Effectiveness Ratio; KM: Kaplan-Meier; LY: Life Years; OS: Overall Survival; PFS : Progression Free Survival; PD: Progressed Disease; QALY: Quality Adjusted Life Years; TMZ: Temozolomide; TTFields: Tumor-Treating Fields; WTP : Willingness To Pay

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