Cost-Effectiveness of Tumor-Treating Fields in Combination with Temozolomide for Glioblastoma Patients: An Italian Healthcare System Perspective

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BACKGROUND

- Glioblastoma (GBM) is an aggressive brain tumor with a poor prognosis despite standard-of-care treatment. Tumor-Treating Fields (TTFields) therapy, when added to temozolomide (TMZ) during the maintenance phase, has shown improved clinical outcomes.
- In the EF-14 trial (Stupp et al., 2017), patients receiving TTFields + TMZ achieved a median overall survival (OS) of 20.9 months compared to 16.0 months with TMZ alone, and a progression-free survival (PFS) of 6.7 vs. 4.0 months. This study assesses the cost-effectiveness of TTFields + TMZ versus TMZ alone in newly diagnosed GBM patients from the perspective of the Italian National Healthcare System.

OBJECTIVE

- To evaluate the cost-effectiveness of adding Tumor-Treating Fields (TTFields) therapy to maintenance temozolomide (TMZ) in patients with newly diagnosed glioblastoma (GBM), using clinical outcomes from the EF-14 trial. The analysis was conducted from the perspective of the Italian National Healthcare System, considering both survival benefits and healthcare costs to determine the value of this treatment combination in routine clinical practice.

METHODS

A **partitioned survival model** with three health states—**progression-free survival (PFS), post-progression survival (PPS),** and **death**—was developed to assess the cost-effectiveness of TTFields + temozolomide (TMZ) versus TMZ alone in newly diagnosed glioblastoma (GBM) patients.

The model adopted a **30-year time** horizon with monthly cycles, from the perspective of the **Italian national healthcare payer**, in line with local economic guidelines. **Costs and outcomes were discounted at 3%** annually following the French HAS methodology, which informed this adaptation. The modeled population reflected the intent-to-treat cohort of the **EF-14 trial**, considered generalizable to Italian patients eligible for TTFields.

Clinical Data and Extrapolation

PFS and OS inputs were derived from **EF-14 Kaplan-Meier curves.**

- **PFS** was extrapolated independently by treatment arm using a **generalized gamma distribution**, as the proportional hazards assumption was violated.
- **OS** was modeled using a **hybrid approach**: Kaplan-Meier data were used for the first 5 years, followed by extrapolation based on **conditional survival probabilities from Porter et al**. and general population mortality thereafter. This method avoided implausible long-term projections observed in parametric models and was previously validated by the Swedish TLV.

Utilities

- Utility values for PFS and PPS were sourced from Garside et al., a published economic evaluation in high-grade glioma. Utilities were applied by health state and assumed independent of treatment arm (see Table 1):

Costs

- All costs reflect the Italian public payer perspective, expressed in **2023 EUR**. Monthly costs included: **TTFields therapy, TMZ, monitoring, adverse events, progression, and end-of-life care**
- Cost estimates were based on the Lombardy Region inpatient tariff schedule (2015) and inflated as needed (see Table 1).
- Only grade ≥3 adverse events and grade 1–2 TTFields-related skin reactions were included.

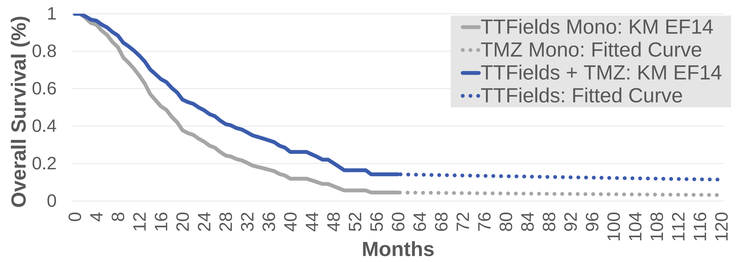
Analyses

- Base case: Estimated incremental cost per QALY and per life-year (LY) gained.
- Deterministic and probabilistic sensitivity analyses explored parameter uncertainty.

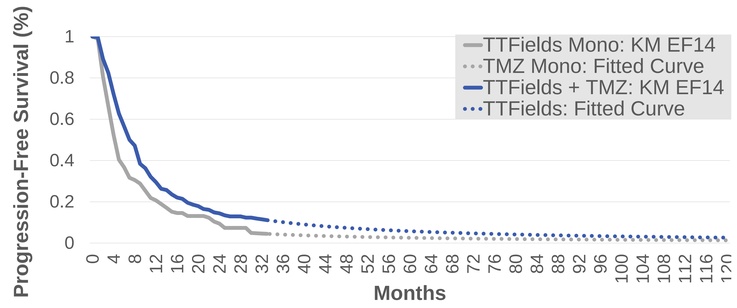
Scenario analyses evaluated alternative extrapolation methods, utility sources, time horizons, and TTFields pricing variations (±10–20%).

Variable	Base Case	Source
General Inputs		
Age	56	Stupp et al.
Horizon	30	Stupp et al.
Discount	3%	Fattore et al. 2009
Utility Inputs		
Utility: PFS	0.85	Garside et al.
Utility: Progressed Disease	0.73	Garside et al.
Costs		
TTFields + TMZ		
Cost of Optune per month	21,000 €	Novocure
Time on Treatment - TTFields	8.2 months	Stupp et al. 2017
TMZ Monotherapy		
Cost, per mg	0.59 €	Novocure
TMZ dose/day per mg/m²	150 mg	Novocure
Time on Treatment - TMZ	7.2 months	Stupp et al. 2017
Adverse Events		
Pulmonary Embolism	4,466 €	Inpatient tariffs 2015 (Lombardy)
Seizure	1,507 €	Inpatient tariffs 2015 (Lombardy)
Infections	3,221 €	Inpatient tariffs 2015 (Lombardy)
Leukopenia or Lymphopenia	2,891 €	Inpatient tariffs 2015 (Lombardy)
General Disorders*	934 €	Inpatient tariffs 2015 (Lombardy)
Thrombocytopenia	2,891 €	Inpatient tariffs 2015 (Lombardy)

Table 1: Key Model Inputs



Graph 1: Overall Survival



Graph 2: Progression-Free Survival

RESULTS

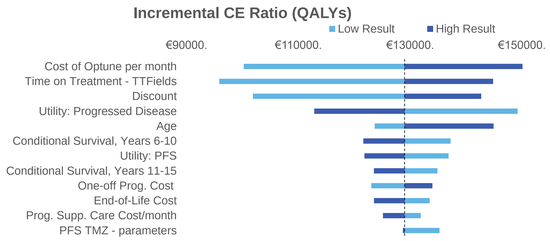
- The base-case analysis showed that **TTFields + TMZ** resulted in a **total cost of €254,778**, compared to **€51,217** for TMZ monotherapy, representing an **incremental cost of €203,561** (Table 2). Most of the cost difference was driven by the TTFields therapy, while **end-of-life costs were €1,404 lower** in the TTFields arm due to prolonged survival.
- In terms of clinical outcomes, patients receiving TTFields + TMZ gained **3.87 life-years (LYs)** and **2.99 quality-adjusted life-years (QALYs)**, compared to **2.12 LYs** and **1.65 QALYs** with TMZ alone. This corresponds to **incremental gains of 1.75 LYs and 1.34 QALYs**.
- The resulting **incremental cost-effectiveness ratio (ICER)** was **€116,316 per LY gained** and **€152,382 per QALY gained**, indicating improved survival and quality of life at an increased cost.

	TTFields + TMZ	TMZ Monotherapy	Δ
Total Cost	**254,778 €**	**51,217 €**	**203,561 €**
Drug Costs	196,472 €	6,642 €	189,830 €
PFS & AE	4,072 €	2,871 €	1,202 €
Prog	37,758 €	23,825 €	13,933 €
EoL	16,475 €	17,879 €	-1,404 €
Life Years	**3.87**	**2.12**	**1.75**
Cost/LY Gained	--	--	116,316 €
QALYs	**2.99**	**1.65**	**1.34**
ICER	--	--	152,382 €

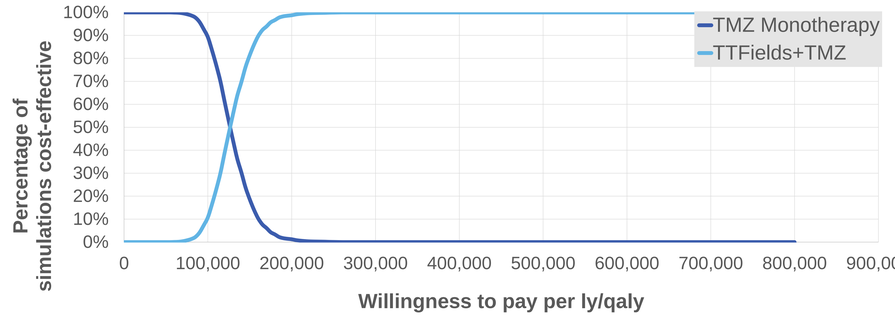
Table 2: Deterministic Results

Sensitivity Analyses:

In the **probabilistic sensitivity analysis (PSA)**, TTFields + TMZ costs ranged from **€527,862 to €717,132**, and TMZ monotherapy from **€365,725 to €541,239**. Incremental QALYs ranged from **1.09 to 1.52**, resulting in ICERs between **€116,048 and €148,699**, with a **mean of €127,423/QALY**.
TTFields + TMZ remained cost-effective across a range of inputs, with limited ICER variability.



Graph 3: Tornado Diagram



CONCLUSION

From an Italian healthcare system perspective, adding TTFields to temozolomide improves survival and quality-adjusted life expectancy in newly diagnosed GBM patients. Although associated with higher costs, the clinical benefit supports consideration for reimbursement and adoption.

References

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