The Impact of Tumor Treating Fields (TTFields) Usage on Cost-Effectiveness: An Analysis of the Incremental Cost-Effectiveness Ratio (ICER)

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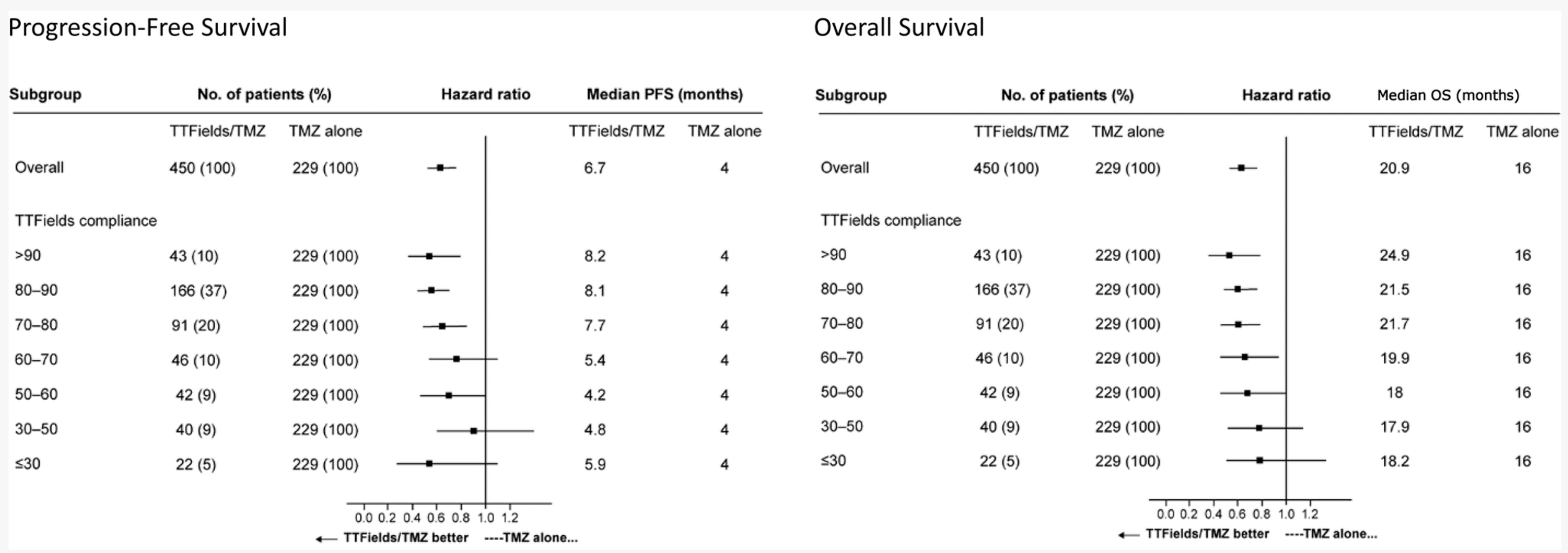
Objective

- Glioblastoma multiforme (GBM) is the most common and aggressive primary brain malignancy. It typically rapidly progresses and has a very poor prognosis[1].
- OPTUNE® is a medical device that uses **Tumor-Treating Fields (TTFields)** technology to treat GBM. The **phase III EF-14-trial**[1] compared the efficacy and safety of TTFields plus maintenance Temozolomide (TMZ) to TMZ 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 **progression-free survival (PFS)**, and the powered secondary endpoint was **overall survival (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)[1].
- 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+TMZ and 5% for patients treated with maintenance TMZ alone (p=0.004)[1].
- Toms et al.[2] conducted an analysis within the EF-14 study, examining the relationship between compliance with TTFields+TMZ treatment and, **PFS and OS**.
- Their findings revealed that a compliance rate of at least **50%** with TTFields+TMZ treatment improved **PFS and OS**. Higher compliance resulted in better outcomes, with patients exceeding **90%** compliance experiencing a median survival of **24.9 months** and a **5-year survival rate of 29.3%**. Notably, compliance was not influenced by factors such as gender, extent of resection, MGMT methylation, age, region, and performance status (p = **0.031** for OS at compliance ≥ **75%** vs. < **75%**).
- Our objective was to estimate the impact of more significant daily TTFields usage on cost-effectiveness, as measured by incremental cost-effectiveness ratios (ICERs).



Progression-Free Survival

Subgroup	No. of patients (%) TTFields/TMZ	TMZ alone	Median PFS (months) TTFields/TMZ	TMZ alone
Overall	450 (100)	229 (100)	6.7	4
TTFields compliance				
>90	43 (10)	229 (100)	8.2	4
80–90	166 (37)	229 (100)	8.1	4
70–80	91 (20)	229 (100)	7.7	4
60–70	46 (10)	229 (100)	5.4	4
50–60	42 (9)	229 (100)	4.2	4
30–50	40 (9)	229 (100)	4.8	4
≤30	22 (5)	229 (100)	5.9	4

Overall Survival

Subgroup	No. of patients (%) TTFields/TMZ	TMZ alone	Median OS (months) TTFields/TMZ	TMZ alone
Overall	450 (100)	229 (100)	20.9	16
TTFields compliance				
>90	43 (10)	229 (100)	24.9	16
80–90	166 (37)	229 (100)	21.5	16
70–80	91 (20)	229 (100)	21.7	16
60–70	46 (10)	229 (100)	19.9	16
50–60	42 (9)	229 (100)	18	16
30–50	40 (9)	229 (100)	17.9	16
≤30	22 (5)	229 (100)	18.2	16

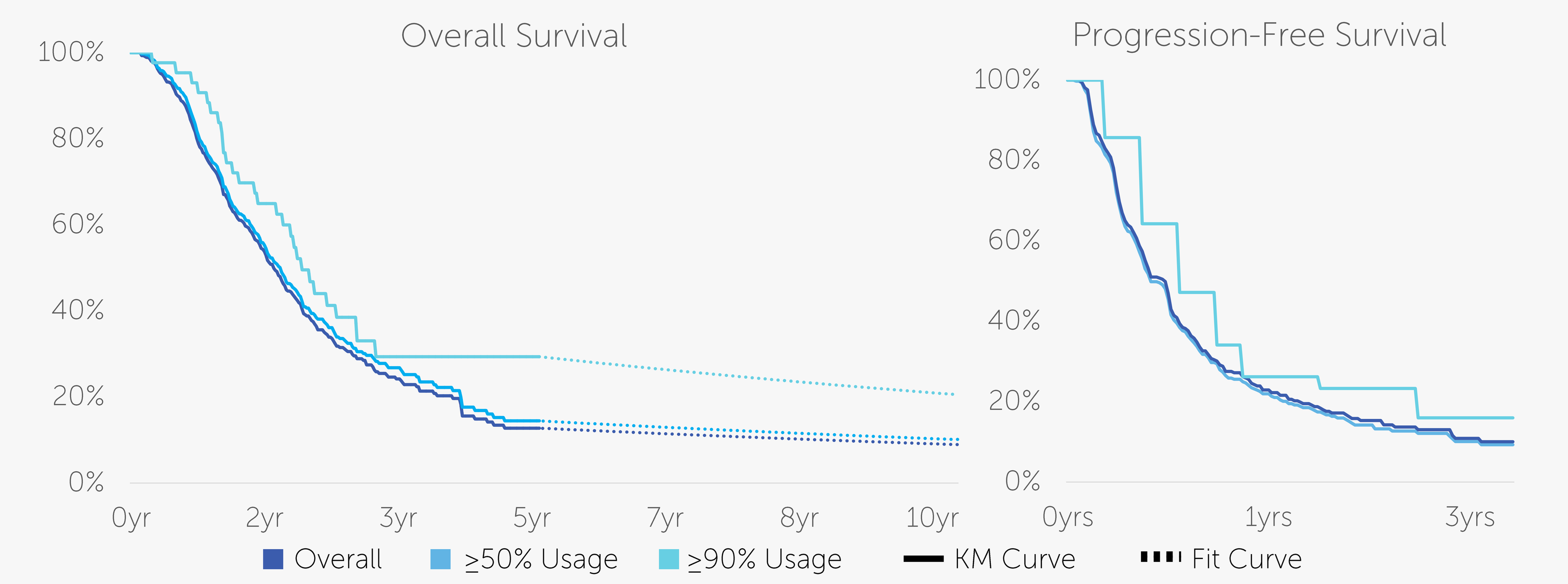
Table 1: Effect of compliance on TTFields on PFS and OS: Results show that at least 50% compliance provides a significant extension of OS compared to TMZ alone. Higher compliance levels show further improvement in PFS and OS.

Methods

- **The TTFields Cost-effectiveness Analysis (CEA) model**, described by Guzauskas et al[3], was initially tailored to the Spanish healthcare system. This adaptation included crucial elements such as **mortality rates**, **adverse events (AE)**, and **treatment costs**.
- A **partitioned survival model** was developed to evaluate the impact of adding **TTFields+TMZ** versus TMZ treatment alone. This model partitioned the patients into three distinct health states: **PFS**, **progressed disease (PD)**, and **death**. This partitioned approach allowed for a detailed comparison of the treatment strategies.
- The analysis projected costs and health outcomes over a 40-year time horizon, utilizing a monthly cycle and applying a **discount rate of 3% per year** to account for the time value of money. To assess the effectiveness, **OS** and **PFS** were estimated following the methodology outlined in Guzauskas et al[4]. The OS analysis employed a three-phase approach:
  - First, it incorporated **Kaplan-Meier data** from the first five years of the **EF-14 trial**. This trial assessed the combination of TTFields with maintenance TMZ compared to TMZ alone in newly diagnosed GBM patients, comprising 695 patients with a median 40-month follow-up.
  - Then, **epidemiological conditional survival** data were incorporated for the long-term outlook for GBM survival from **year 5 to year 15**. This integrates Porter et al. epidemiological data, which was chosen for its consistent patient population treated before TMZ introduction. Covering cases from 1985 to 2005, including 5991 GBM patients, the study provides **10-year (70.4%, 95% CI: 55.6–81.2%)** and **15-year (84.0%, 95% CI: 38.9–96.8%) GBM survival probabilities**[5].
  - Finally, background mortality data was considered for the period beyond year 15.
- PFS was modeled using parametric extrapolation, specifically employing the **Weibull distribution**.
- The data for OS and PFS were derived from specific patient subgroups of the pivotal EF-14 study. These subgroups were segmented based on the daily usage of TTFields, measured as a percentage of the day (e.g., **18 hours per day, representing 75% usage**). The segments included in the analysis were: 50-60% Usage, 60-70% Usage, 70-80% Usage, 80-90% Usage, Above 50% Usage, and Above 90% Usage.

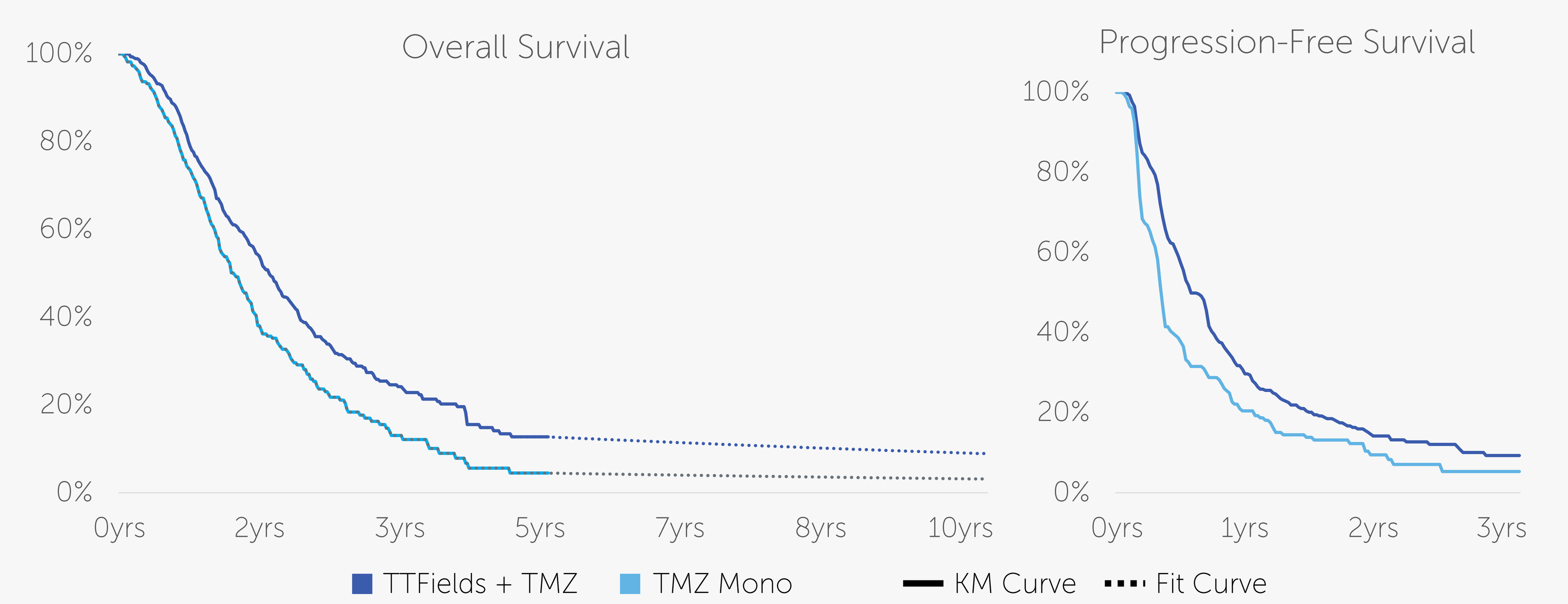
Methods .- cont.

TTFields+TMZ Usage curves comparison



Graphs 2: OS and PFS Curves – Usage TTFields: compare OS and PFS based on TTFields usage (overall, >50%, and >90%), clearly indicate that higher TTFields compliance levels lead to improved outcomes, with the >90% compliance group showing the most favorable results. This underscores the importance of adherence to TTFields therapy for enhanced patient outcomes

TMZ Mono vs. TTFields+TMZ



Graphs 1: OS and PFS Curves – TTFields+TMZ vs. TMZ Mono: compare OS and PFS between the TTFields + TMZ and TMZ alone arms, distinctly demonstrate superior results in the TTFields + TMZ arm, emphasizing the efficacy of this combination treatment.

Results

Higher Daily Usage and ICER Reduction:

- We segmented the patient population into cohorts based on their daily utilization, highlighting the percentage reduction in ICER compared to the overall trial population for each cohort.
- Daily usage of at least 50% resulted in a significant **15% decrease in the ICER**, highlighting substantial cost-saving benefits.
- Patients with daily usage of at least 90% experienced an impressive **56% reduction in ICER** compared to the overall trial population, demonstrating substantial cost-effectiveness gains.
- This approach effectively illustrates the **compelling cost-effectiveness benefits** associated with higher TTFields usage rates, emphasizing the importance of patient adherence to this treatment.

ICER %Δ vs. Overall Population	
50-60 Usag.	-11.8%
60-70 Usag.	-2.3%
70-80 Usag.	-4.6%
80-90 Usag.	-11.7%
>50 Usag.	-14.8%
>90 Usag.	-56.3%

Table 2: Impact of TTFields Usage on ICER: displaying ICER deltas between TTFields usage categories highlights variations in cost-effectiveness.

Sensitivity Analyses for Reliability:

- Our analysis went beyond these observations to include **sensitivity analyses** to ensure the robustness of our findings. These analyses examined how our conclusions held up when making adjustments to assumptions about costs and health outcomes related to TTFields.
- The results remained consistent, affirming the **reliability and relevance** of our findings

Conclusion

- Higher daily TTFields usage significantly reduced the ICER.
- A daily usage rate of at least 90% led to an impressive 56% reduction in ICER compared to the entire trial population. Even with a 50% daily usage rate, a 15% ICER reduction was observed, emphasizing the importance of adherence.
- We conducted sensitivity analyses to ensure the reliability of our findings. These findings were robust to sensitivity analyses, demonstrating the importance of greater TTFields usage on clinical and cost-effectiveness outcomes.

References
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