

Interim Analysis of the EF-14 Trial: A Prospective, Multi-center Trial of NovoTTF-100A Together With Temozolomide Compared to Temozolomide Alone in Patients with Newly Diagnosed GBM

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BACKGROUND: Tumor Treating Fields (TTFields) are an anti-mitotic, physical treatment modality that acts in metaphase, anaphase and telophase. The NovoTTF-100A System (NovoTTF), a home-use medical device that delivers TTFields to the brain, is an established monotherapy for recurrent glioblastoma (GBM).

METHODS: We conducted an international, multicenter, prospective, randomized phase III trial in newly diagnosed GBM patients. After completion of radiotherapy (RT) with concomitant temozolomide (TMZ), patients were randomized (2:1) to adjuvant TMZ with NovoTTF or adjuvant TMZ alone. The primary endpoint was progression-free survival (PFS), with overall survival (OS) an important secondary endpoint. Here we report on a pre-specified interim analysis of the first 315 patients randomized, after a minimum follow-up of 18 months (range 18-60 months).

RESULTS (intent-to-treat): 210 pts were randomized to NovoTTF/TMZ and 105 to TMZ alone. Patient characteristics were balanced: median age 57 and 58 years, tumor resection in 89 and 90%, KPS 90%, for the NovoTTF and the control arms, respectively. *MGMT* promoter methylation status was assessable centrally in 60% of patients; of these 39% and 41% were methylated. Adverse events (AE) were comparable between treatment arms. The most common device-related AE was skin irritation in 45% of patients (all grades, severe 2%). Severe seizures were observed at a frequency of 7% in both arms. Median PFS was 7.1 months [mo] (95% confidence interval [CI] 5.9-8.2) and 4.0 mo (CI 3.0-4.3; Hazard ratio 0.63, $p=0.001$), OS was 19.6 mo (CI 16.5-24.1) and 16.6 mo (CI 13.5-19.1) (HR 0.75, $p=0.034$), both favoring NovoTTF. This translates into a 24-mo survival rate of 43% (CI 36-50%) and 29% (CI 21-39%) for the NovoTTF/TMZ and the TMZ alone arm, respectively.

CONCLUSIONS: The trial met its primary and main secondary endpoints, and was closed to accrual after this interim analysis. Adjuvant TMZ chemotherapy and NovoTTF provides a clinically and statistically significant improvement in progression-free and overall survival, and should become the new standard of care against GBM.

Top 10 recruiters – absolute numbers – global:

Country	PI Last Name	Site #	Visit Date	Number of Months open	Number of Patients Enrolled	Average Patients per Month
FRANCE	Taillibert-Idbaih/Paris	29	16-Oct-09	55	44	0.80
ISRAEL	Kanner/TLV	27	27-May-09	60	38	0.63
USA	Kesari/UCSD	64	17-Jul-09	58	25	0.43
USA	Barnett/CCF	21	6-May-11	37	19	0.51
USA	Toms/Geisinger	60	21-Jul-09	58	19	0.33
USA	Lieberman/UPMC	15	1-Jul-09	59	16	0.27
ITALY	Silvani/Besta	50	19-May-09	60	16	0.27
USA	Fink/Baylor	63	24-Jun-09	59	16	0.27
USA	Taylor/Tufts	66	13-Jul-09	58	16	0.28
CHECK REP	Sroubek/Prague	4	13-Jan-11	40	15	0.38

Top 10 recruiters – patients/month – global:

Country	PI Last Name	Site #	Visit Date	Number of Months open	Number of Patients Enrolled	Average Patients per Month
FRANCE	Taillibert-Idbaih/Paris	29	16-Oct-09	55	44	0.80
Canada	Hirte/Hamilton(Canada)	22	10-May-13	12	9	0.75
ISRAEL	Kanner/TLV	27	27-May-09	60	38	0.63
USA	Fathallah-Shaykh/Alabama	87	18-Sep-13	8	5	0.63
Canada	Easaw/Calgary	37	1-May-13	13	8	0.62
Canada	Muanza/McGill Univ.	26	23-Jul-13	10	6	0.60
USA	Tran, D./St. Louis	81	3-Jul-12	23	13	0.57
USA	Barnett/Cleveland	21	6-May-11	37	19	0.51
SWEDEN	Stragliotto/Karolinska	59	15-Feb-13	15	7	0.47
USA	Kesari/UCSD	64	17-Jul-09	58	25	0.43