TTFields with maintenance temozolomide (TMZ) and pembrolizumab versus TTFields with maintenance TMZ and placebo for newly diagnosed glioblastoma: the phase 3 EF-41/KEYNOTE D58 trial

David D. Tran[1], Ashley P. Ghiaseddin[2], Michael Lim[3], Michael Weller[4], Motoo Nagane[5], Jacob C. Easaw[6], Elizabeth Cohen-Jonathan Moyal[7]

[1]Department of Neurological Surgery, Norris Comprehensive Cancer Center, University of Southern California, Los Angeles, CA, USA; [2]University of Florida Department of Neurosurgery, Gainesville, FL, USA; [3]Department of Neurosurgery, Stanford University School of Medicine, Palo Alto, CA, USA; [4]University Hospital and University of Zurich, Zurich, Switzerland; [5]Kyorin University School of Medicine, Tokyo, Japan; [6]Alberta Health Services, Edmonton, Alberta, Canada; [7]Université de Toulouse, Oncopole Claudius Regaud, IUCT-Oncopole, Toulouse, France

Poster TPS2096

BACKGROUND

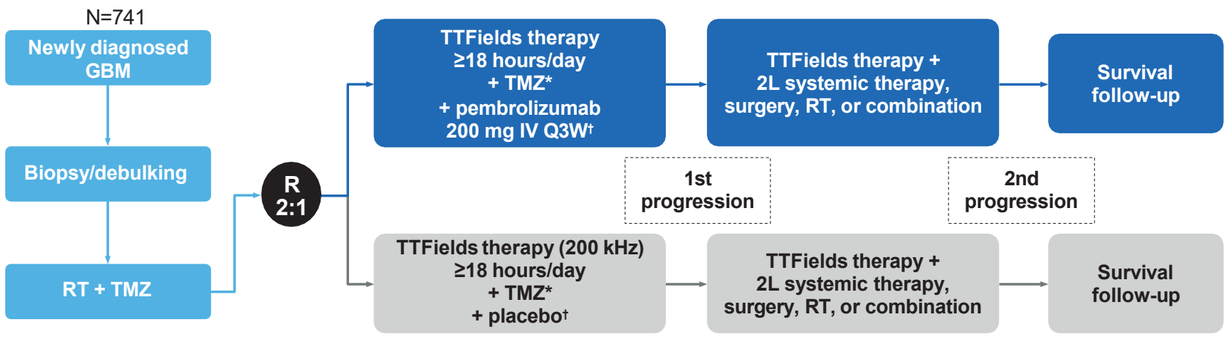
- Glioblastoma (GBM) is the most aggressive and common primary brain tumor in adults: it grows rapidly, invades surrounding tissue, and is resistant to therapy[1]
- Current standard of care for newly diagnosed GBM consists of maximal safe resection followed by radiotherapy with concurrent temozolomide (TMZ), then maintenance TMZ with Tumor Treating Fields (TTFields) therapy[2]
  - In the pivotal EF-14 trial, median overall survival (OS) using this approach was 20.9 months[3]
- While immune checkpoint inhibitors (ICIs) have improved outcomes in multiple malignancies,[4] they have not demonstrated meaningful clinical benefit in GBM, in part because the GBM tumor microenvironment (TME) is typically profoundly immunosuppressive[5]
- Strategies that reprogram the TME toward immune activation may therefore enable ICIs to elicit more effective antitumor immunity in GBM[6]
- In addition to their antimitotic effects, TTFields have shown preclinical evidence of inducing immunogenic cell death and activating type 1 interferon signaling via DNA sensor inflammasomes, with downstream increases in dendritic cell activation and cytotoxic T cell infiltration[7,8]
- In a single-arm phase 2 study in patients with newly diagnosed GBM (NCT03405792), TTFields therapy plus TMZ and pembrolizumab was associated with improved progressionfree survival (PFS) and OS compared to historical controls[9]
- The EF-41/KEYNOTE D58 trial is a phase 3 trial designed to evaluate the efficacy and safety of TTFields therapy concomitant with TMZ and pembrolizumab in patients with newly diagnosed GBM who have completed radiochemotherapy

TTFields device and array placement. Image shows an actor, not a patient

STUDY DESIGN

- EF-41/KEYNOTE D58 (NCT06556563) is a randomized, doubleblind, placebo-controlled, phase 3 study
- Patients are randomized 2:1 to TTFields therapy (200 kHz for ≥18 hours/day) plus maintenance TMZ (150–200 mg/m²/day PO, days 1–5 of each 28-day cycle for 6–12 cycles) with either pembrolizumab 200 mg IV Q3W (up to 35 cycles) or matching placebo (Figure 2)
  - Patients are stratified by extent of resection (biopsy only, partial resection, gross total resection [defined as removal of ≥95% of enhancing tumor per MRI]) and MGMT promoter methylation status (positive, negative, indeterminate/unknown)
- TTFields therapy is continued until second progression
  - At first progression, TTFields therapy is maintained and patients may receive standard salvage therapy, including re-resection and/or radiotherapy as well as systemic therapy
- Target enrollment is 741 patients, providing 85% power to detect an OS improvement at a two-sided alpha of 0.05 using a 2-sided log-rank test

KEYNOTED-58 Study Design (NCT06556563)



*On days 1–5 of each 28-day cycle; cycle 1 given at a dose of 150 mg/m² and escalated to 200 mg/m² for subsequent cycles in the absence of toxicity; †Up to 35 cycles
2L, second line; GBM, glioblastoma; Q3W, every 3 weeks; R, randomization; RT, radiotherapy; TMZ, temozolomide

Selected Inclusion Criteria

- New diagnosis of GBM (WHO 2021 Classification)
- Recovered from maximal debulking surgery (gross total resection, partial resection and biopsy-only are all acceptable)
- Completed standard adjuvant chemoradiotherapy of radiotherapy according to local practice (56–64 Gy) and concomitant TMZ chemotherapy
- Age ≥18 years
- Tissue available for MGMT promoter methylation status analysis
- ECOG performance status 0/1, assessed within 7 days before randomization
- Able to have MRI of the brain with contrast

ECOG, Eastern Cooperative Oncology Group; GBM, glioblastoma; MGMT, O⁶-methylguanine-DNA-methyltransferase; MRI, magnetic resonance imaging; TMZ, temozolomide; WHO, World Health Organization

Selected Exclusion Criteria

- Progressive disease after end of chemoradiotherapy
- Infratentorial or leptomeningeal disease
- Ongoing requirement for >2 mg dexamethasone (or equivalent) due to intracranial mass effect
- Prior therapy with an anti-PD(L)-1 agent, anti-PD-L2 agent, or an agent directed to another stimulatory or co-inhibitory T-cell receptor
- Known allergy to medical adhesive or hydrogel
- Implanted active medical devices
- Skull defect

PD-1, programmed cell death protein 1; PD-L1/2, programmed cell death ligand 1/2

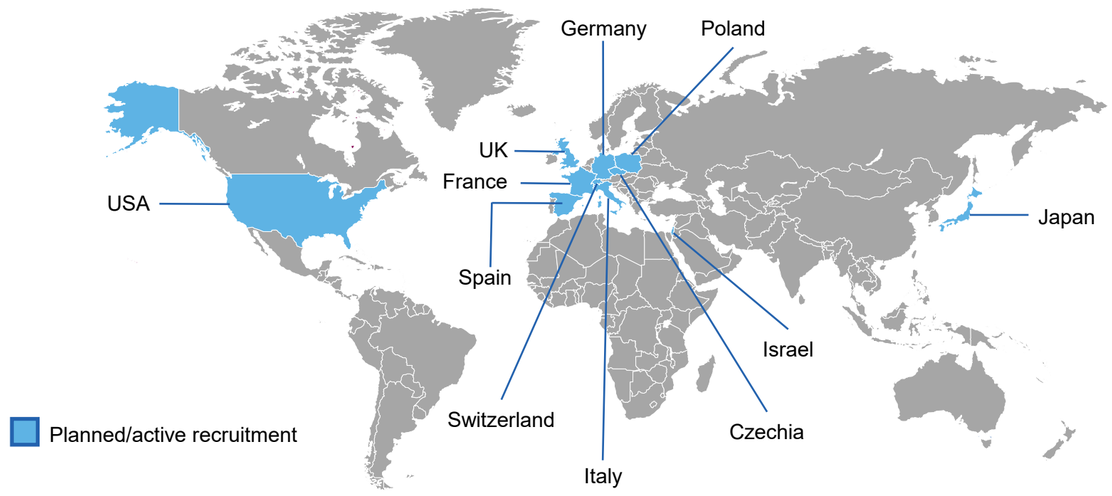
Study Endpoints

1° Overall survival

2°
- Progression-free survival (PFS), PFS at 6 (PFS6) and 12 months (PFS12), and next PFS (PFS2) per mRANO and RANO 2.0 criteria, as assessed by investigator
- 1- and 2-year survival
- Health-related quality of life
- Safety

STUDY STATUS

- Recruitment began in February 2025 and is ongoing
- As of April 2026, recruitment has started at >80 sites in the countries shown



ACKNOWLEDGEMENTS This study is sponsored by Novocure Inc. in collaboration with Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA. Medical writing assistance was provided by Andy Noble of Bioscript Group Ltd, Macclesfield, UK, funded by Novocure GmbH.

REFERENCES 1. Gaiaschi L, et al. Curr Issues Mol Biol 2024;46:14324–50; 2. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines): Central Nervous System Cancers, Version 2.2025 - August 28, 2025. https://www.nccn.org/professionals/physician_gls/pdf/cns.pdf; 3. Stupp R, et al. JAMA 2017;18:2306–16; 4. Zhang M, et al. Mol Cancer 2025;24:136; 5. Kordyukova MY, et al. Int Mol Sci 2026;27:2207; 6. White J, et al. J Transl Med 2024;22:540; 7. Voloshin T, et al. Cancer Immunol Immunother 2020;69:1191–1204; 8. Chen D, et al. J Clin Ivest 2022;132:e149258; 9. Chen D, et al. Med 2025;6:100708

DISCLOSURES **David D. Tran** has no disclosures. Ashley P. Ghiaseddin has consultancy roles with Alexion, Deciphera, Geosoma, Monteris, Novocure, Nuvation Bio, Servier, and Telix; stocks with crispr therapeutics and Prime Medicine; research funding from Novocure and Nuvation Bio.

CONTACT Ashley P. Ghiaseddin (Ashley.Ghiaseddin@neurosurgery.ufl.edu)