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National Comprehensive Cancer Network
Central Nervous System Cancers Committee
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VIA E-Mail: submissions@nccn.org

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NCCN Guidelines Panel: Central Nervous System Cancers

On behalf of Novocure Inc., I respectfully request the NCCN Central Nervous System Cancers committee to review and discuss the enclosed data for a consensus recommendation of Tumor Treating Fields (TTFields) delivered by the NovoTTF™-100A System in appropriate patients with recurrent glioblastoma who have exhausted surgical and radiation options.

Specific Changes: Recommend the inclusion of TTFields delivered by the NovoTTF-100A System in the Central Nervous System Cancer guidelines as a FDA approved option for adult patients (22 years of age or older) with histologically-confirmed glioblastoma (GBM), following radiologically confirmed recurrence in the supra-tentorial region of the brain.

Rationale: The NovoTTF-100A System received PMA approval by the United States Food and Drug Administration in April 2011 for the treatment of recurrent glioblastoma multiforme; this approval was based upon a phase III randomized controlled trial (EF-11) showing comparable outcomes to chemotherapy regimens, including bevacizumab with reduced toxicity and improved quality of life scores when compared to chemotherapy alone. The pivotal study also showed durable long-term survival in a subset of patients receiving treatment with the NovoTTF-100A System..

Additional research has been performed to date including the Mrugala et al (2014) report on PRiDe, a post-marketing registry of every recurrent GBM patient who received NovoTTF Therapy in the U.S. between the commercial launch in October 2011 and November 2013. Analysis of this real-world data provides additional information about the efficacy and safety of the NovoTTF-100A System. Data was collected from all 457 recurrent GBM patients who began commercial treatment at one of 91 oncology centers during the study period. Age and gender characteristics were similar in the PRiDe and EF-11 trial. Overall survival was collected using the Social Security Death Date Registry and obituaries. Patients who were treated with the NovoTTF-100A System were not restricted to the number of recurrences or types of prior therapies. Information was not collected on combination therapy; some patients may have received chemotherapy or anti-VEGF agents in addition to the NovoTTF-100A System. Subgroup analyses were performed on patient/clinical characteristics found to be significantly correlated with OS. A monthly compliance assessment was performed for each patient using a computer download of an internal log file from the NovoTTF-100A System. Collection of these data began mid-way through the study so these data are available for under two thirds of registry patients. Overall survival in PRiDe compares favorably to the reported median OS for the EF-11 trial (9.6 vs 6.6 months), demonstrating effectiveness of the NovoTTF-100A System in the real-world setting. The safety profile in the registry dataset was also consistent with the EF-11 study, with the most common treatment-related adverse event being mild to moderate skin irritation.

Combined, the EF-11 and PRiDe datasets represent approximately 600 patients with recurrent GBM treated with the NovoTTF-100A System. The efficacy results are comparable to other published datasets for recurrent GBM therapies. The safety profile for NovoTTF-100A System remains favorable to systemic therapies with fewer treatment-related adverse events.

The following articles and supporting materials are submitted in support of this proposed change. We would like to acknowledge the contributions of NCCN panel members who are also co-authors or contributors of some of these publications.

Stupp R, Wong ET, et al. NovoTTF-100A versus physician's choice chemotherapy in recurrent glioblastoma: a randomized phase III trial of a novel treatment modality. *Eur J Cancer* 2012; 48(14): 2192-2202. doi: 10.1016/j.ejca.2012.04.011

Mrugala MM, Engelhard HH, et al. Clinical practice experience with NovoTTF-100A™ system for glioblastoma: the patient registry dataset (PRiDe). *Semin Oncol* 2014; Sep 11, pii: S0093-7754(14)00203-6 (Epub ahead of print). doi: 10.1053/j.seminoncol.2014.09.010

Kanner AA, Wong E, et al. Post hoc analysis of intention-to-treat population in phase 3 comparison of NovoTTF-100A™ system versus best physician's choice chemotherapy. *Semin Oncol* 2014; Sep 11, pii: S0093-7754(14)00201-2 (Epub ahead of print). doi: 10.1053/j.seminoncol.2014.09.008

Vymazal J, Wong E. Response patterns of recurrent glioblastomas treated with tumor treating fields (TTFields). *Semin Oncol* 2014; Sep 11, pii: S0093-7754(14)00202-4 (Epub ahead of print). doi: 10.1053/j.seminoncol.2014.09.009.

Wong ET, Lok E, et al. Response Assessment of NovoTTF-100A versus best physician's choice chemotherapy in recurrent glioblastoma. *Cancer Med* 2014; 3(3): 592-602. doi: 10.1002/cam4.210

Miranda, PC, Mekonnen, A, et al. Predicting the electric field distribution in the brain for the treatment of glioblastoma. *Physics in Medicine and Biology* 2014; Aug 7;59(15):4137-47. doi: 10.1088/0031-9155/59/15/4137.

Lacouture ME, Davis ME, et al. Characterization and management of dermatologic adverse events with the NovoTTF-100A system, a novel anti-mitotic electric field device for the treatment of recurrent glioblastoma. *Semin Oncol* 2014; 41(suppl 4): S1-S14. doi: http://dx.doi.org/10.1053/j.seminoncol.2014.03.011

U.S. Food and Drug Administration, Center for Drug Evaluation and Research. Novo-TTF-100A P10034 approval letter, April 8, 2011. Retrieved July 9, 2012, from http://www.accessdata.fda.gov/cdrh_docs/pdf10/p100034a.pdf

We appreciate the consideration of the attached information by the Central Nervous System Cancer committee in its review of the NCCN Guidelines for Central Nervous System Cancers. Should you require additional information or have any questions, please feel free to contact me.

Sincerely,

Eilon Kirson, MD, PhD
Novocure Inc.