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National Comprehensive Cancer Network
Malignant Pleural Mesothelioma Panel
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Via E-mail: submissions@nccn.org

NCCN Guidelines Panel: Malignant Pleural Mesothelioma

On behalf of Novocure Inc., I respectfully request that the NCCN Malignant Pleural Mesothelioma panel review the enclosed data supporting the use of Tumor Treating Fields (TTFields) in combination with pemetrexed and platinum-based chemotherapy as a first-line treatment option for adult patients with malignant pleural mesothelioma.

Specific Changes: Recommend TTFields as a treatment option for appropriate patients with malignant pleural mesothelioma in combination with pemetrexed and platinum-based chemotherapy.

FDA Approval: Optune Lua™ is indicated for the treatment of adult patients with unresectable, locally advanced or metastatic, malignant pleural mesothelioma (MPM) to be used concurrently with pemetrexed and platinum-based chemotherapy.

Rationale: Optune Lua is the first treatment for MPM approved by the FDA in more than 15 years. Optune Lua for MPM is classified as a Humanitarian Use Device (HUD) and was approved under Humanitarian Device Exemption (HDE). The HDE pathway was created to encourage companies to innovate in rare diseases with underserved patient populations who have few approved treatment options. The FDA approved Optune®, another Tumor Treating Fields delivery system, under the Premarket Authorization (PMA) pathway in 2011 for the treatment of glioblastoma (GBM). Since 2011, more than 15,000 patients with GBM have been treated with Tumor Treating Fields worldwide. The use of Optune in newly diagnosed GBM is included in the NCCN guidelines with a Category 1 level of evidence and consensus.

In the STELLAR trial, 80 unresectable MPM patients treated with TTFields plus platinum-based chemotherapy experienced a median overall survival of 18.2 months (95% CI 12.1-25.8). The STELLAR trial was a prospective, single-arm trial including 80 patients that studied the use of Tumor Treating Fields, delivered via Optune Lua, in combination with pemetrexed plus cisplatin/carboplatin as a first-line treatment for patients with unresectable, locally advanced or MPM.

Data showed a median overall survival of 18.2 months (95 percent CI, 12.1 months-25.8 months) for patients treated with Optune Lua and pemetrexed plus cisplatin or carboplatin. One- and two-year survival rates were 62.2 percent (95 percent CI, 50.3 percent-72.0 percent) and 41.9 percent (95 percent CI, 28.0 percent-55.2 percent), respectively. Additionally, despite the lower rate of epithelioid histology (66%), OS was better than the control arm in the MAPS trial (81% epithelioid, OS 16.1m) which assessed the addition of bevacizumab to pemetrexed/cisplatin. No serious systemic adverse events were considered to be related to the use of Optune Lua. The most common mild to moderate adverse event was skin irritation beneath the transducer arrays.

Additionally, a retrospective analysis of post-market safety surveillance data in more than 11,000 patients treated with TTFields in glioblastoma/high grade glioma confirms this favorable safety profile with the only device related adverse events recorded as localized, mild-to-moderate skin reactions that are often resoluble with over-the-counter topical ointments or by temporarily withholding TTFields treatment.

The following articles are submitted in support of this proposed change. We would like to thank the NCCN Guidelines Panel for their consideration of the attached information.

1. Ceresoli GL, Aerts JG, Dziadziuszko R, Ramlau R, Cedres S, van Meerbeeck JP et al. Tumour Treating Fields in combination with pemetrexed and cisplatin or carboplatin as first-line treatment for unresectable malignant pleural mesothelioma (STELLAR): a multicentre, single-arm phase 2 trial. Lancet Oncol. 2019 Dec;20(12)1702-1709. doi: 10.1016/S1470-2045(19)30532-7. Epub 2019 Oct 15.
2. Stupp R, Taillibert S , Kanner A, et al. Effect of Tumor-Treating Fields Plus Maintenance Temozolomide vs Maintenance Temozolomide Alone on Survival in Patients With Glioblastoma A Randomized Clinical Trial. JAMA. 2017;318(23):2306-2316. doi:10.1001/jama.2017.18718
3. Stupp R, Taillibert S, Kanner AA, et al. Maintenance therapy with tumor-treating fields plus temozolomide vs temozolomide alone for glioblastoma: a randomized clinical trial. JAMA. 2015;314(23):2535-2543.
4. Shi W, Blumenthal DT, Oberheim Bush NA, Kebir S, Lukas RV, Muragaki Y, Zhu JJ, Glas M. Global post-marketing safety surveillance of Tumor Treating Fields (TTFields) in patients with high-grade glioma in clinical practice. J Neurooncol. 2020 Jun 13. https://doi.org/10.1007/s11060-020-03540-6 [Epub ahead of print]
5. Voloshin T, Munster M, Blatt R, et al. Alternating Electric Fields (TTFields) in Combination With Paclitaxel Are Therapeutically Effective Against Ovarian Cancer Cells in Vitro and in Vivo. Int J Cancer. 2016 Dec 15;139(12):2850-2858. doi: 10.1002/ijc.30406. Epub 2016 Sep 19.
6. Giladi M, Munster M, Schneiderman R, et al. Tumor Treating Fields (TTFields) Delay DNA Damage Repair Following Radiation Treatment of Glioma Cells. Radiat Oncol. 2017 Dec 29;12(1):206. doi: 10.1186/s13014-017-0941-6.
7. Voloshin T. Kaynan N, Davidi S, et al. Tumor-treating Fields (TTFields) Induce Immunogenic Cell Death Resulting in Enhanced Antitumor Efficacy When Combined With anti-PD-1 Therapy. Cancer Immunol Immunother. 2020 Jul;69(7):1191-1204. doi: 10.1007/s00262-020-02534-7. Epub 2020 Mar 6.

Sincerely,

Ely Benaim, MD
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