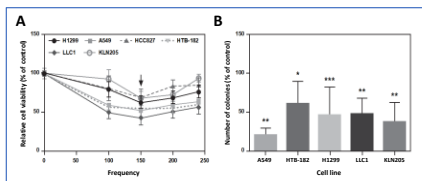


## Background

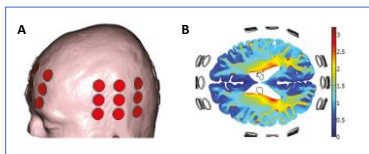
- Tumor Treating Fields (TTFields) are a non-invasive, locoregional, antimetabolic treatment modality<sup>1</sup> that induces DNA damage and replication stress in cancer cells.<sup>2</sup> TTFields utilize low-intensity alternating electric fields delivered via a portable, home-use device (Optune<sup>®</sup>).
- TTFields (200 kHz) are FDA approved for treating glioblastoma and are recommended in NCCN guidelines as a category 1 adjuvant therapy for patients with newly diagnosed disease.<sup>3</sup>
- TTFields have shown activity in multiple *in vitro* and *in vivo* lung cancer models<sup>4,5</sup> (Figure 1) and in a phase 1/2 clinical trial in non-small cell lung cancer (NSCLC).<sup>6</sup>
- The FDA recently approved TTFields (150 kHz) plus chemotherapy for first-line unresectable malignant pleural mesothelioma.



**Figure 1. Effect of TTFields on lung cancer cell lines.** (A) TTFields treatment frequency effects on cell line viability (arrow indicates optimal frequency of 150 kHz). (B) TTFields (150 kHz) treatment effects on clonogenic potential in different cell lines. \* $P < 0.05$ , \*\* $P < 0.01$ , and \*\*\* $P < 0.001$  vs control group. H1299, A549, HCC827 (human adenocarcinoma); HTB-182 (human squamous cell carcinoma); LLC1 (murine Lewis lung carcinoma); HLN205 (murine squamous cell carcinoma).

## Objectives

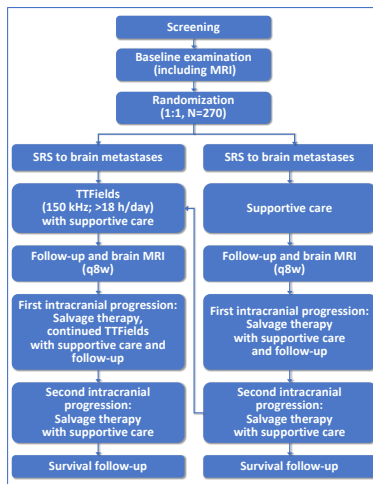
- Secondary brain metastases are a serious complication of NSCLC. The phase 3 METIS study (NCT02831959) is designed to test the efficacy, safety, and neurocognitive outcomes of TTFields in patients with 1–10 brain metastases secondary to NSCLC.
- TTFields (150 kHz) are delivered via 2 pairs of transducer arrays placed on the scalp (Figure 2).



**Figure 2. TTFields distribution in the brain.** Computer model showing (A) transducer array layout on scalp, and (B) electric field distribution in the brain using segmentation of magnetic resonance imaging (MRI) and finite element method.<sup>7</sup>

## The METIS trial (NCT02831959)

- Patients (N=270) with 1–10 brain metastases secondary to NSCLC will be randomized 1:1 to stereotactic radiosurgery (SRS) followed by either TTFields or supportive care alone (Figure 3).
- Patients will be followed bimonthly until their second intracranial progression.
- Patients in the control arm may cross over to receive TTFields at the time of second intracranial progression.
- The trial is enrolling patients in the US, Canada, and the EU.



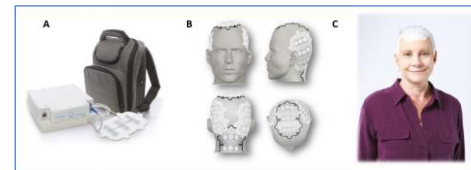
**Figure 3. Design of the phase 3 METIS study.**

## Key eligibility criteria

- Inclusion:** New diagnosis of 1 inoperable or 2–10 supratentorial and/or infratentorial brain metastases from confirmed NSCLC, amenable to SRS; Karnofsky Performance Status  $\geq 70$ ; optimal therapy for the extracranial disease; prior surgical resection of metastases is allowed.
- Exclusion:** A single resectable lesion or recurrent brain metastases; prior whole brain radiation therapy; mutations in ALK, EGFR, ROS-1 or B-RAF.

## Treatment

- Continuous TTFields (150 kHz) will be applied to the brain using the portable NovoTTFields-100M device (Figure 4) within 7 days of SRS. Patients will receive the best standard of care for their systemic disease.



**Figure 4. TTFields (150 kHz) delivery.** (A) The NovoTTFields-100M System is a portable, battery-operated, home-use medical device. (B) Positioning of the 4 transducer arrays on the scalp. (C) Model wearing transducer arrays on the scalp. The model presented is an actor and not a patient.

## Endpoints

- Primary:** Time to first intracranial progression.
- Secondary:** Overall survival; time to neurocognitive failure using Hopkins Verbal Learning Test, Controlled Oral Word Association Test, and Trail Making Test (if available in patient's language); radiological response rate (Response Assessment in Neuro-Oncology Brain Metastases and Response Evaluation Criteria In Solid Tumors version 1.1); time to first and second intracranial progression evaluated in 2 cohorts (1–4 and 5–10 brain metastases); bimonthly intracranial progression rate from 2–12 months; time to second intracranial and distant progression; neurocognitive failure-free survival; cognitive decline rate; quality of life; and adverse events (severity and frequency).

## Statistical considerations

- A sample size of 270 patients is estimated to detect an increase in time to intracranial progression from 7.7 to 13.4 months (hazard ratio 0.57) with 80% power using a 2-sided alpha level of 0.05. Sample size was calculated using a log-rank test with the competing risk taken as loss to follow-up.
- Patients will be censored at time of death if it occurs prior to intracranial progression or neurological death.

## DMC recommendation

- On September 26<sup>th</sup> 2019, an independent Data Monitoring Committee (DMC) reviewed METIS trial data collected to that point.
- The DMC concluded that no unexpected safety issues have emerged, and recommended study continuation.

**References:** 1. Kirson ED, et al. *Proc Natl Acad Sci U S A* 2007;104(24):10152–10157. 2. Karanam NK, et al. *Transl Res* 2019;DOI: <https://doi.org/10.1016/j.trsl.2019.10.003>. 3. NCCN. Central Nervous System Cancers (v3.2019). <https://www.nccn.org>. Accessed July 27<sup>th</sup>, 2020. 4. Giladi M, et al. *Semin Oncol* 2014;41(suppl 6):S35–S41. 5. Karanam NK, et al. *Cell Death Dis* 2017;8(3):e2711. 6. Pless M, et al. *Lung Cancer* 2013;81(3):445–450. 7. Wenger C, et al. *Phys Med Biol* 2015;60(18):7339–7357.