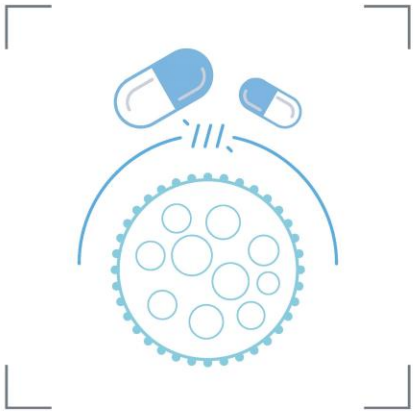
TTFIELDS

TUMOR TREATING FIELDS THERAPY

Understanding the science behind the versatile modality

Patients with aggressive solid tumors often face suboptimal survival outcomes,* despite advancements in treatment modalities[1-4]

These outcomes are due to diverse treatment challenges, including[2,4,5]:



Therapeutic tumor resistance

Drug-to-drug interactions

Additive systemic toxicities

With a poor survival outlook, physicians and patients need additional treatment strategies[2-4]

*Relative survival = net measure representing cancer survival in the absence of other causes of death.

References: 1. Siegel RL, Miller KD, Fuchs HE, Jemal A. Cancer statistics, 2021. *CA Cancer J Clin*. 2021;71(1):7-33. doi:10.3322/caac.21654 **2.** Dagogo-Jack I, Shaw AT. Tumour heterogeneity and resistance to cancer therapies. *Nat Rev Clin Oncol*. 2018;15(2):81-94. doi:10.1038/nrclinonc.2017.166 **3.** Gotwals P, Cameron S, Cipolletta D, et al. Prospects for combining targeted and conventional cancer therapy with immunotherapy. *Nat Rev Cancer*. 2017;17(5):286-301. doi:10.1038/nrc.2017.17 **4.** Lopez JS, Banerji U. Combine and conquer: challenges for targeted therapy combinations in early phase trials. *Nat Rev Clin Oncol*. 2017;14(1):57-66. doi:10.1038/nrclinonc.2016.96 **5.** Bashraheel SS, Domling A, Goda SK. Update on targeted cancer therapies, single or in combination, and their fine tuning for precision medicine. *Biomed Pharmacother*. 2020;125:1-16. doi:10.1016/j.biopha.2020.110009

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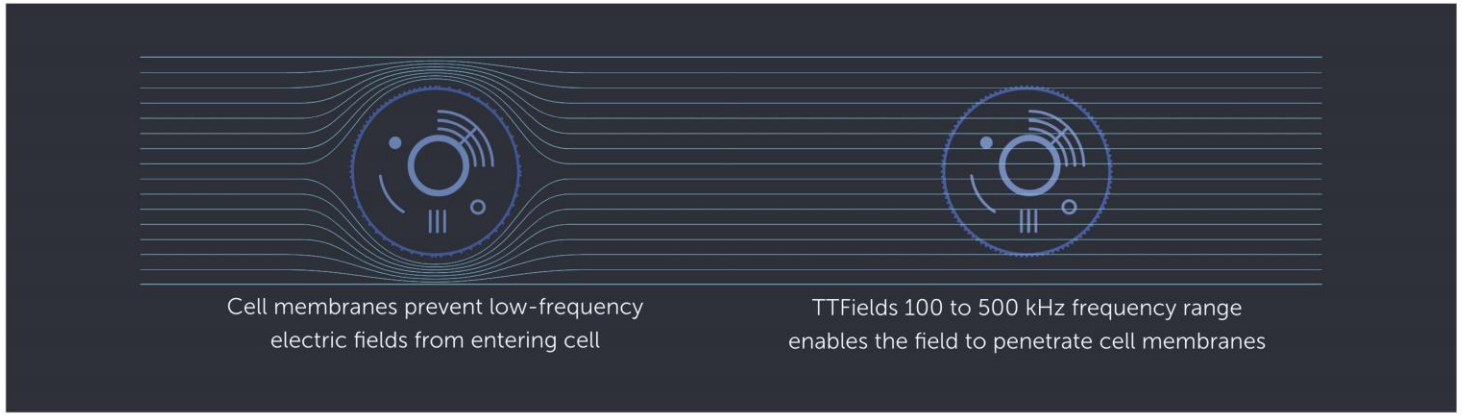
TTFields are electric fields that exert physical forces to kill cancer cells via a variety of mechanisms[1-7]

- Tumor Treating Fields (TTFields) employ electric fields at a frequency range of 100 kHz to 500 kHz[4,8]
- This allows TTFields to enter cells more effectively without stimulating or significantly heating the surrounding tissue[4,8]
- The unique frequency range of TTFields allows the electric fields to be generated through the cancer cell membrane, while a lower frequency would not[4,8]



- TTFields therapy can be customized via frequencies based on cell type to target a diverse range of solid tumors[2]

References: 1. Giladi M, Schneiderman RS, Voloshin T, et al. Mitotic spindle disruption by alternating electric fields leads to improper chromosome segregation and mitotic catastrophe in cancer cells. *Sci Rep*. 2015;5:1-16. doi:10.1038/srep18046 **2.** Kirson ED, Dbalý V, Tovaryš F, et al. Alternating electric fields arrest cell proliferation in animal tumor models and human brain tumors. *Proc Natl Acad Sci U S A*. 2007;104(24):10152-10157. doi:10.1073/pnas.0702916104 **3.** Mun EJ, Babiker HM, Weinberg U, Kirson ED, Von Hoff DD. Tumor-treating fields: a fourth modality in cancer treatment. *Clin Cancer Res*. 2018;24(2):266-275. doi:10.1158/1078-0432.CCR-17-1117 **4.** Karanam NK, Story MD. An overview of potential novel mechanisms of action underlying tumor treating fields-induced cancer cell death and their clinical implications. *Int J Radiat Biol*. 2021;97(8):1044-1054. doi:10.1080/09553002.2020.1837984 **5.** Cooper GM. The development and causes of cancer. In: *The Cell: A Molecular Approach*. 2nd ed. Sinauer Associates; 2000:chap 15. Accessed June 21, 2022. https://www.ncbi.nlm.nih.gov/books/NBK9963/ **6.** Baba AI, Cătoi C. Tumor cell morphology. In: *Comparative Oncology*. The Publishing House of the Romanian Academy; 2007:chap 3. Accessed June 21, 2022. https://www.ncbi.nlm.nih.gov/books/NBK9553/ **7.** Voloshin T, Schneiderman RS, Volodin A, et al. Tumor treating fields (TTFields) hinder cancer cell motility through regulation of microtubule and actin dynamics. *Cancers (Basel)*. 2020;12(10):1-18. doi:10.3390/cancers12103016 **8.** Wenger C, Giladi M, Bomzon Z, Salvador R, Basser PJ, Miranda PC. Modeling Tumor Treating Fields (TTFields) application in single cells during metaphase and telophase. *Annu Int Conf IEEE Eng Med Biol Soc*. 2015;2015:6892-6895. doi:10.1109/EMBC.2015.7319977

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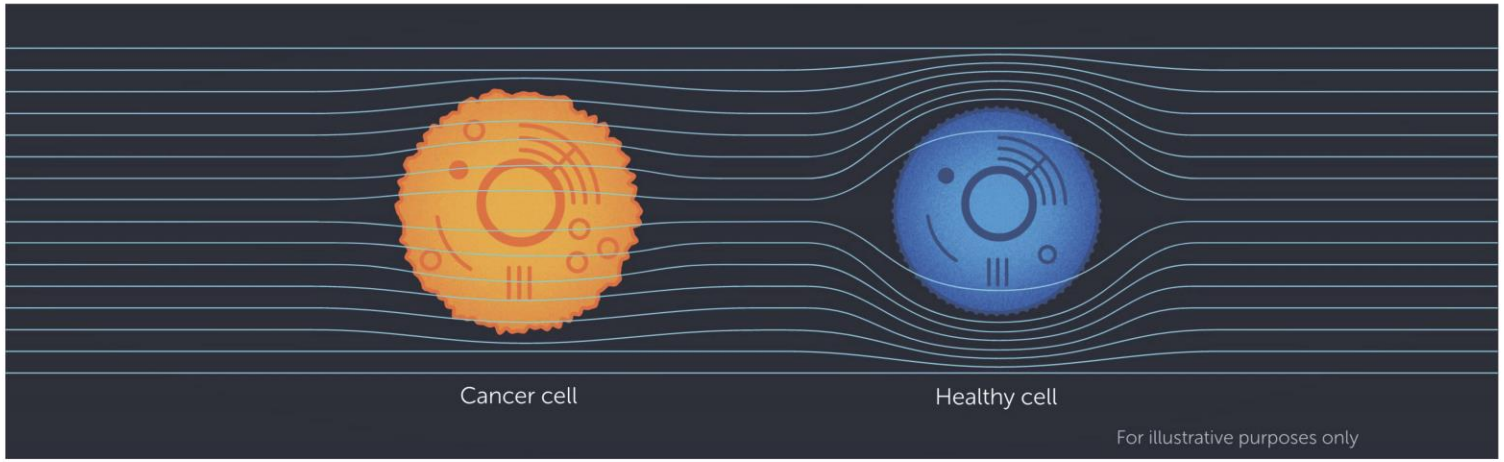
TTFields spare healthy cells because they have different properties—including division rate, morphology, and electrical properties—than cancer cells[1-6]



References: 1. Karanam NK, Story MD. An overview of potential novel mechanisms of action underlying tumor treating fields-induced cancer cell death and their clinical implications. *Int J Radiat Biol*. 2021;97(8):1044-1054. doi:10.1080/09553002.2020.1837984 **2.** Cooper GM. The development and causes of cancer. In: *The Cell: A Molecular Approach*. 2nd ed. Sinauer Associates; 2000:chap 15. Accessed June 21, 2022. https://www.ncbi.nlm.nih.gov/books/NBK9963/ **3.** Baba AI, Cătoi C. Tumor cell morphology. In: *Comparative Oncology*. The Publishing House of the Romanian Academy; 2007:chap 3. Accessed June 21, 2022. https://www.ncbi.nlm.nih.gov/books/NBK9553/ **4.** Trainito CI, Sweeney DC, Čemažar J, et al. Characterization of sequentially-staged cancer cells using electrorotation. *PLoS One*. 2019;14(9):1-18. doi:10.1371/journal.pone.0222289 **5.** Haemmerich D, Schutt DJ, Wright AW, Webster JG, Mahvi DM. Electrical conductivity measurement of excised human metastatic liver tumours before and after thermal ablation. *Physiol Meas*. 2009;30(5):459-466. doi:10.1088/0967-3334/30/5/003 **6.** Ahmad MA, (IEEE SM), Al Natour Z, Mustafa F, Rizvi TA. Electrical characterization of normaland cancer cells. *IEEE Access*. 2018;6:25979-25986. doi:10.1109/ACCESS.2018.2830883

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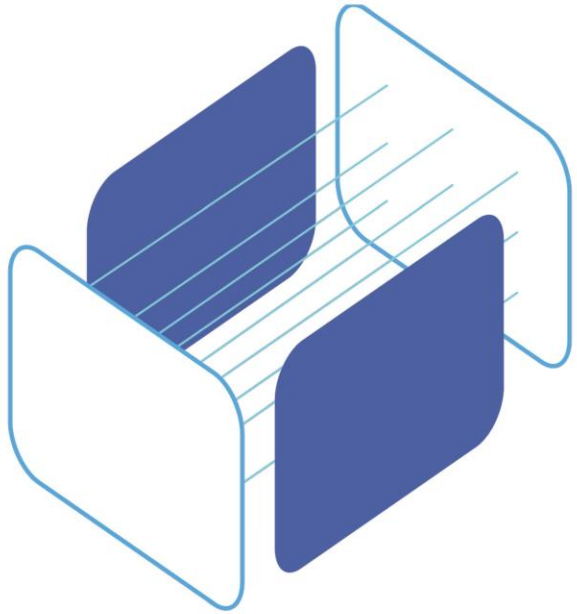
TTFields therapy can be delivered noninvasively and locoregionally via a portable device[1]



Reference: 1. Mun EJ, Babiker HM, Weinberg U, Kirson ED, Von Hoff DD. Tumor-treating fields: a fourth modality in cancer treatment. *Clin Cancer Res.* 2018;24(2):266-275. doi:10.1158/1078-0432.CCR-17-1117

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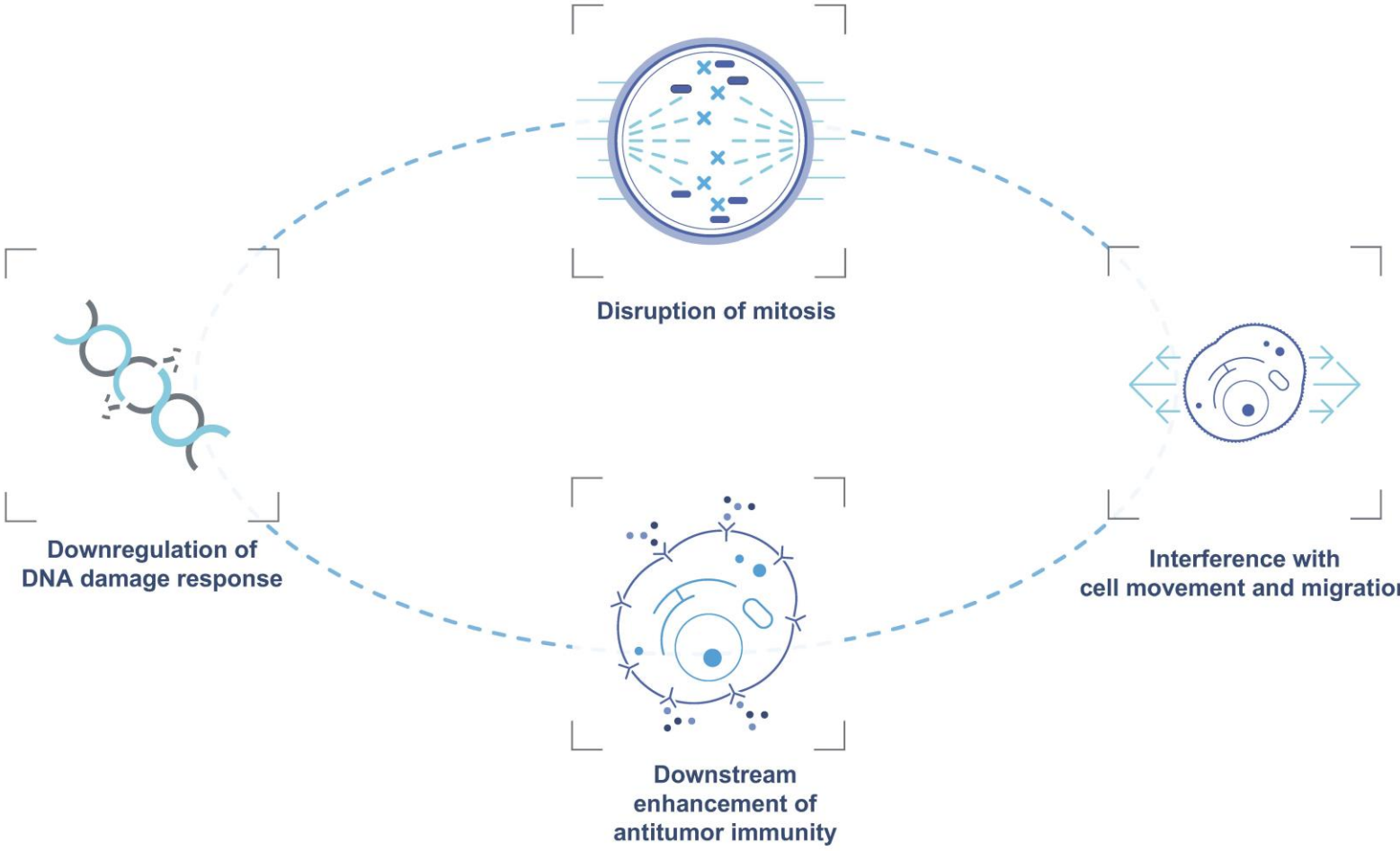
BASED ON PRECLINICAL DATA

The multiple, distinct mechanisms of TTFields therapy work together to selectively target and kill cancer cells[1-5]



References: 1. Karanam NK, Story MD. An overview of potential novel mechanisms of action underlying tumor treating fields-induced cancer cell death and their clinical implications. *Int J Radiat Biol*. 2021;97(8):1044-1054. doi:10.1080/09553002.2020.1837984 **2.** Voloshin T, Schneiderman RS, Volodin A, et al. Tumor treating fields (TTFields) hinder cancer cell motility through regulation of microtubule and actin dynamics. *Cancers (Basel)*. 2020;12(10):1-18. doi:10.3390/cancers12103016 **3.** Hall A. The cytoskeleton and cancer. *Cancer Metastasis Rev*. 2009;28(1-2):5-14. doi:10.1007/s10555-008-9166-3 **4.** Giladi M, Schneiderman RS, Voloshin T, et al. Mitotic spindle disruption by alternating electric fields leads to improper chromosome segregation and mitotic catastrophe in cancer cells. *Sci Rep*. 2015;5:1-16. doi:10.1038/srep18046 **5.** Kirson ED, Dbalý V, Tovaryš F, et al. Alternating electric fields arrest cell proliferation in animal tumor models and human brain tumors. Proc Natl Acad Sci U S A. 2007;104(24):10152-10157. doi:10.1073/pnas.0702916104

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BASED ON PRECLINICAL DATA

TTFields have been shown to **disrupt mitosis** in cancer cells by exerting physical forces on their polar components[1-3,*]

Metaphase[2,4]

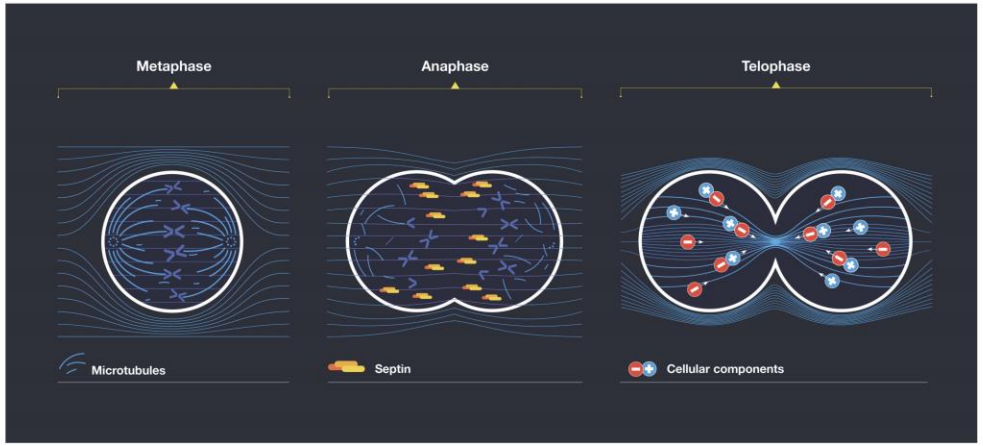
- TTFields impair microtubule assembly in cancer cells, leading to aberrant mitotic spindle formation

Anaphase[1,5]

- TTFields disrupt the arrangement of septin at the anaphase cleavage furrow in cancer cells, inducing cytoplasmic membrane blebbing, mitotic failure, and asymmetric chromosome segregation

Telophase[4,5]

- Polar organelles and macromolecules in cancer cells are pushed toward the area of higher TTFields intensity when cancer cells assume an hourglass shape during telophase and cytokinesis in a process known as dielectrophoresis



Adapted from Mun et al. 2018.

*Eg, microtubule spindle formation during mitosis.

References: 1. Gera N, Yang A, Holtzman TS, Lee SX, Wong ET, Swanson KD. Tumor treating fields perturb the localization of septins and cause aberrant mitotic exit. *PLoS One*. 2015;10(5):1-20. doi:10.1371/journal.pone.0125269 **2.** Giladi M, Schneiderman RS, Voloshin T, et al. Mitotic spindle disruption by alternating electric fields leads to improper chromosome segregation and mitotic catastrophe in cancer cells. *Sci Rep*. 2015;5:1-16. doi:10.1038/srep18046 **3.** 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;69(7):1191-1204. doi:10.1007/s00262-020-02534-7 **4.** Gutin PH, Wong ET. Noninvasive application of alternating electric fields in glioblastoma: a fourth cancer treatment modality. *Am Soc Clin Oncol Educ Book*. 2012:126-131. doi:10.14694/EdBook_AM.2012.32.122 **5.** Mun EJ, Babiker HM, Weinberg U, Kirson ED, Von Hoff DD. Tumor-treating fields: a fourth modality in cancer treatment. *Clin Cancer Res*. 2018;24(2):266-275. doi:10.1158/1078-0432.CCR-17-1117

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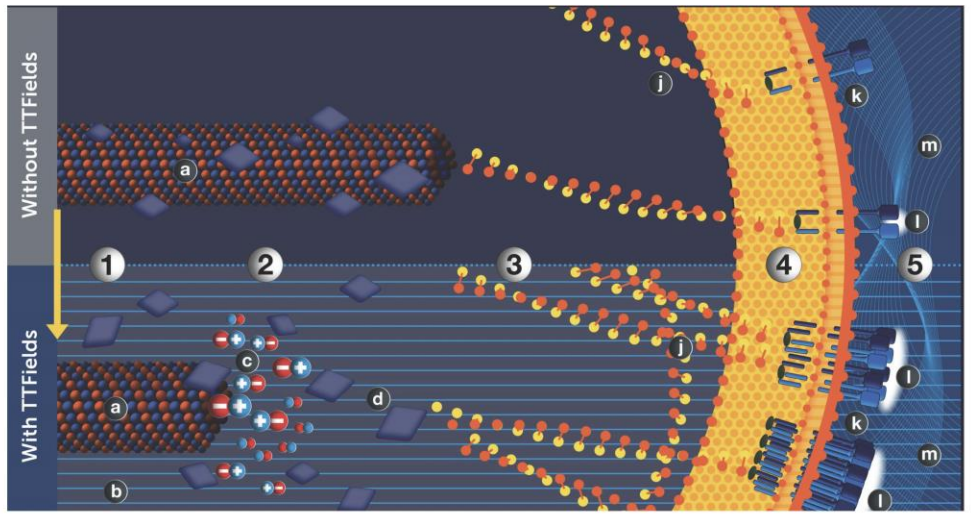
BASED ON PRECLINICAL DATA

In preclinical models, TTFields have been shown to alter the organization and dynamics of the cytoskeleton, **disrupting cancer cell motility and migration**, which are essential for metastasis[1]

TTFields disrupt the direction and diminish the abundance of the microtubule network, interfering with cancer cell migration[1]



A model illustrating the mechanism by which TTFields modulates cancer cell motility.

(1) Microtubules are required to specify the direction of cell movement. GEF-H1 catalytic activity is downregulated through microtubule binding.

(2) TTFields exert directional forces on polar tubulins leading to their alignment in the direction of the field. This, in turn, leads to the reorganization of the microtubule network resulting in changes in the abundance of microtubules and initiation of the GEF-H1/RhoA/ROCK signaling pathway

(3) to increase actin bundling

(4) and formation of focal adhesions,

(5) which disrupt cell polarity and migration directionality.

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a) microtubule; **b)** TTFields; **c)** tubulin aligned with field; **d)** active GEF-H1
j) actin fiber; **k)** integrin; **l)** focal adhesion; **m)** extracellular matrix.

Adapted from Voloshin et al. 2020.

GEF-H1=a microtubule-associated protein that couples microtubule dynamics to cell contractility.
RhoA/ROCK=a pathway that regulates cell morphology, polarity, and cytoskeletal remodeling by regulating actin and cell migration.

Reference: 1. Voloshin T, Schneiderman RS, Volodin A, et al. Tumor treating fields (TTFields) hinder cancer cell motility through regulation of microtubule and actin dynamics. *Cancers (Basel)*. 2020;12(10):1-18. doi:10.3390/cancers12103016

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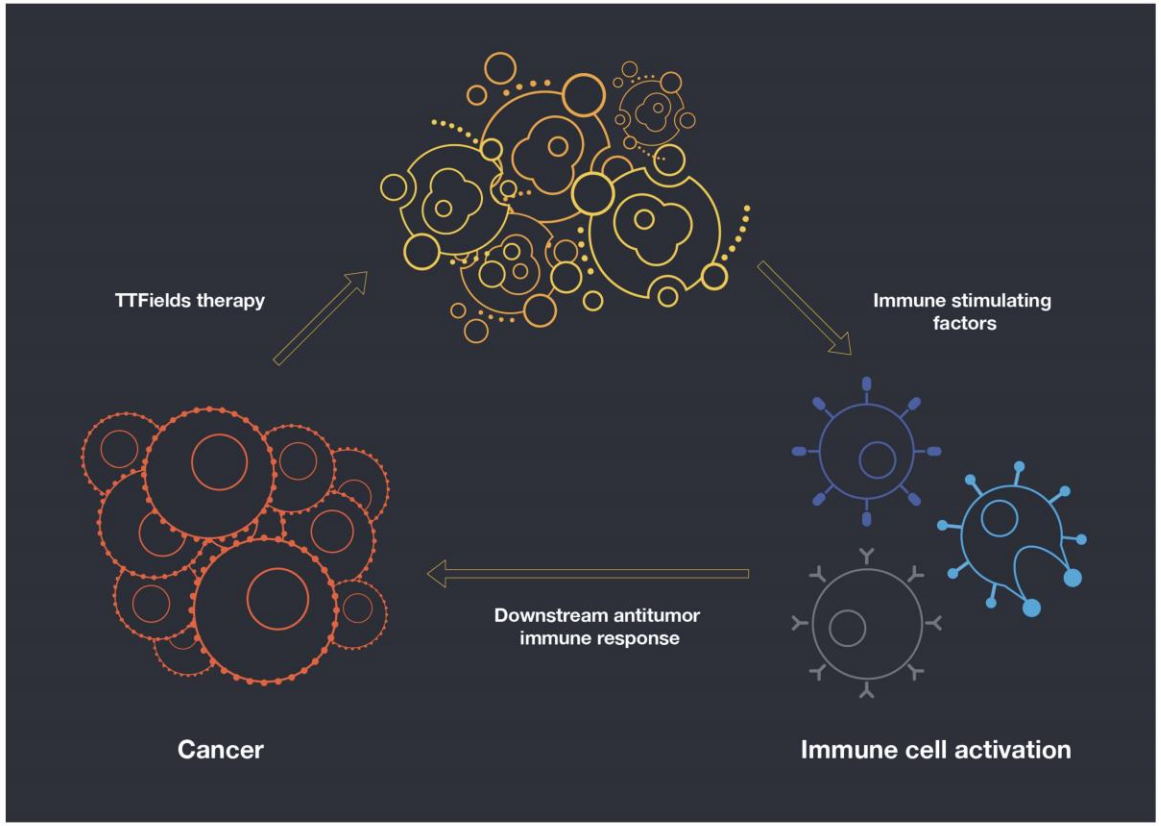
BASED ON PRECLINICAL DATA

TTFields-mediated cell disruption activates the immune system and **triggers a downstream antitumor cell response**[1]



TTFields induces downstream immunogenic cell death, including release of DAMPs (damage-associated molecular patterns)

Adapted from Ahmed et al. 2020.

Reference: 1. 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;69(7):1191-1204. doi:10.1007/s00262-020-02534-7

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TTFields **downregulate genes** important for DNA damage repair[1,2]

Continuous TTFields application leads to disruption of DNA damage responses in cancer cells, **leading to cell death[1-4]**

- TTFields downregulate genes important for DNA replication and DNA damage response pathways in cancer cells[1,2]
- Evidence has proven TTFields' ability to disrupt DNA damage repair by downregulating genes that are part of the well-known FA-BRCA pathway[1,2]

Adapted from Karanam et al. 2020.

References: 1. Karanam NK, Srinivasan K, Ding L, Sishc B, Saha D, Story MD. Tumor-treating fields elicit a conditional vulnerability to ionizing radiation via the downregulation of BRCA1 signaling and reduced DNA double-strand break repair capacity in non-small cell lung cancer cell lines. *Cell Death Dis.* 2017;8(3):1-10. doi:10.1038/cddis.2017.136 **2.** Karanam NK, Ding L, Aroumougame A, Story MD. Tumor treating fields cause replication stress and interfere with DNA replication fork maintenance: implications for cancer therapy. *Transl Res.* 2020;217:33-46. doi:10.1016/j.trsl.2019.10.003 **3.** Giladi M, Munster M, Schneiderman RS, et al. Tumor treating fields (TTFields) delay DNA damage repair following radiation treatment of glioma cells. *Radiat Oncol.* 2017;12(1):1-13. doi:10.1186/s13014-017-0941-6 **4.** Kim EH, Kim YJ, Song HS, et al. Biological effect of an alternating electric field on cell proliferation and synergistic antimitotic effect in combination with ionizing radiation. *Oncotarget.* 2016;7(38):62267-62279. doi:10.18632/oncotarget.11407

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TTFields is a highly versatile first-in-class treatment modality[1-3]

TTFields therapy has significant potential for broad applicability across solid tumor types and lines of therapy[1-3]

- Investigation of TTFields therapy is ongoing across clinical trials in multiple tumor types[4-9]
- In approved indications, TTFields therapy is well tolerated, suggesting a low risk of additive systemic toxicity when used with other cancer treatment modalities[2,10]

References: 1. Karanam NK, Story MD. An overview of potential novel mechanisms of action underlying tumor treating fields-induced cancer cell death and their clinical implications. *Int J Radiat Biol*. 2021;97(8):1044-1054. doi:10.1080/09553002.2020.1837984 **2.** Mun EJ, Babiker HM, Weinberg U, Kirson ED, Von Hoff DD. Tumor-treating fields: a fourth modality in cancer treatment. *Clin Cancer Res*. 2018;24(2):266-275. doi:10.1158/1078-0432.CCR-17-1117 **3.** Rominiyi O, Vanderlinden A, Clenton SJ, Bridgewater C, Al-Tamimi Y, Collis SJ. Tumour treating fields therapy for glioblastoma: current advances and future directions. *Br J Cancer*. 2021;124(4):697-709. doi:10.1038/s41416-020-01136-5 **4.** Pless M, Droege C, von Moos R, Salzberg M, Betticher D. A phase I/II trial of tumor treating fields (TTFields) therapy in combination with pemetrexed for advanced non-small cell lung cancer. *Lung Cancer*. 2013;81(3):445-450. doi:10.1016/j.lungcan.2013.06.025 **5.** Novocure. Pivotal, open-label, randomized study of radiosurgery with or without tumor treating fields (TTFields) for 1-10 brain metastases from non-small cell lung cancer (NSCLC). Clinical Trials. Accessed June 21, 2022. https://clinicaltrials.gov/ct2/show/NCT02831959 **6.** Rivera F, Benavides M, Gallego J, Guillen-Ponce C, Lopez-Martin J, Küng M. Tumor treating fields in combination with gemcitabine or gemcitabine plus nab-paclitaxel in pancreatic cancer: results of the PANOVA phase 2 study. *Pancreatology*. 2019;19(1):64-72. doi:10.1016/j.pan.2018.10.004 **7.** Novocure. Effect of tumor treating fields (TTFields, 150 kHz) as front-line treatment of locally-advanced pancreatic adenocarcinoma concomitant with gemcitabine and nab-paclitaxel (PANOVA-3). Clinical Trials. Accessed June 21, 2022. https://clinicaltrials.gov/ct2/show/NCT03377491 **8.** Vergote I, von Moos R, Manso L, Van Nieuwenhuysen E, Concin N, Sessa C. Tumor treating fields in combination with paclitaxel in recurrent ovarian carcinoma: results of the INNOVATE pilot study. *Gynecol Oncol*. 2018;150(3):471-477. doi:10.1016/j.ygyno.2018.07.018 **9.** Novocure. Effect of tumor treating fields (TTFields, 200 kHz) concomitant with weekly paclitaxel for the treatment of recurrent ovarian cancer (ENGOT-ov50 / GOG-3029 / INNOVATE-3). Clinical Trials. Accessed June 21, 2022. https://clinicaltrials.gov/ct2/show/NCT03940196 **10.** 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

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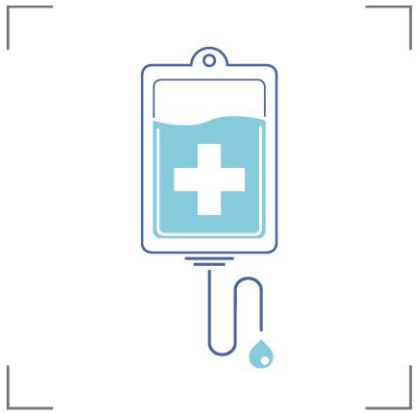
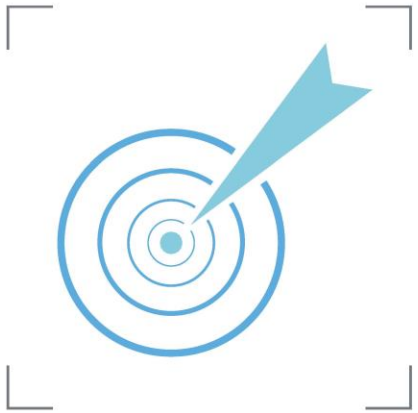
Due to its multimechanistic actions, TTFields therapy can be added to cancer treatment modalities in approved indications[1-6]

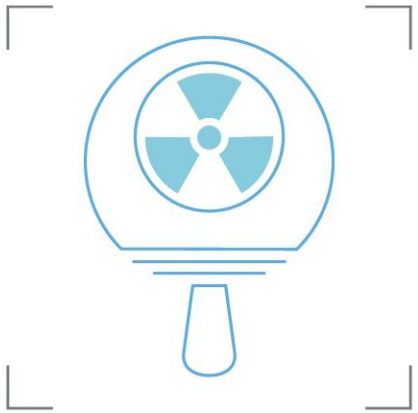
TTFields **demonstrate enhanced effects** across multiple solid tumor types, when used concomitantly with each of the following (based on preclinical data):



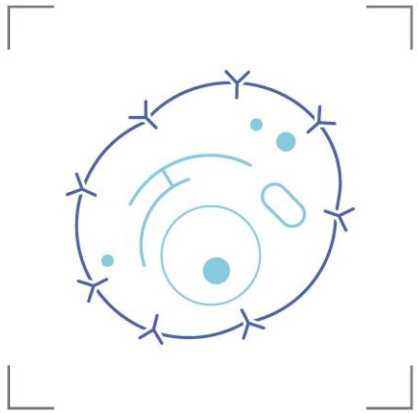
Chemotherapy



Targeted therapies



Radiation therapy (RT)



Immuno-oncologic (IO) agents

Adapted from Karanam et al. 2020.

References: 1. Pless M, Droege C, von Moos R, Salzberg M, Betticher D. A phase I/II trial of tumor treating fields (TTFields) therapy in combination with pemetrexed for advanced non-small cell lung cancer. *Lung Cancer*. 2013;81(3):445-450. doi:10.1016/j.lungcan.2013.06.025 **2.** Novocure. Pivotal, open-label, randomized study of radiosurgery with or without tumor treating fields (TTFields) for 1-10 brain metastases from non-small cell lung cancer (NSCLC). Clinical Trials. Accessed June 21, 2022. https://clinicaltrials.gov/ct2/show/NCT02831959 **3.** Rivera F, Benavides M, Gallego J, Guillen-Ponce C, Lopez-Martin J, Küng M. Tumor treating fields in combination with gemcitabine or gemcitabine plus nab-paclitaxel in pancreatic cancer: results of the PANOVA phase 2 study. *Pancreatology*. 2019;19(1):64-72. doi:10.1016/j.pan.2018.10.004 **4.** Novocure. Effect of tumor treating fields (TTFields, 150 kHz) as front-line treatment of locally-advanced pancreatic adenocarcinoma concomitant with gemcitabine and nab-paclitaxel (PANOVA-3). Clinical Trials. Accessed June 21, 2022. https://clinicaltrials.gov/ct2/show/NCT03377491 **5.** Vergote I, von Moos R, Manso L, Van Nieuwenhuysen E, Concin N, Sessa C. Tumor treating fields in combination with paclitaxel in recurrent ovarian carcinoma: results of the INNOVATE pilot study. *Gynecol Oncol*. 2018;150(3):471-477. doi:10.1016/j.ygyno.2018.07.018 **6.** Novocure. Effect of tumor treating fields (TTFields, 200 kHz) concomitant with weekly paclitaxel for the treatment of recurrent ovarian cancer (ENGOT-ov50 / GOG-3029 / INNOVATE-3). Clinical Trials. Accessed June 21, 2022. https://clinicaltrials.gov/ct2/show/NCT03940196

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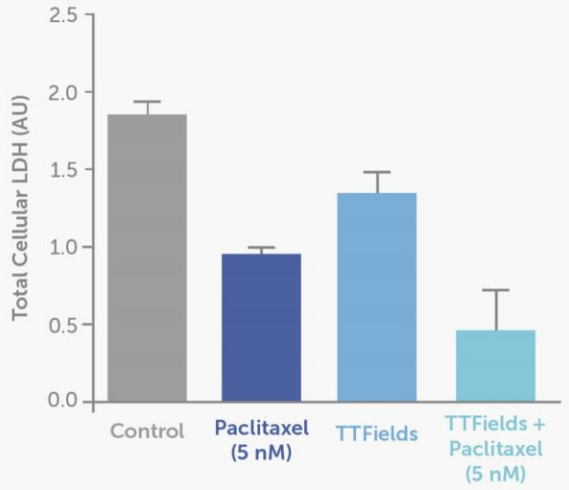
BASED ON PRECLINICAL DATA

TTFields used with a **chemotherapeutic microtubule stabilizing agent** (paclitaxel) has demonstrated enhanced effects, in multiple tumor models[1-3]

TTFields + paclitaxel resulted in additive reductions in cell proliferation*



Adapted from Michelhaugh et al. 2020.

*Changes in proliferation induced by TTFields application in vitro were examined and measured by LDH (lactose dehydrogenase).

References: 1. Michelhaugh SK, Mittal S. Combined *in vitro* TTFields and paclitaxel reduce proliferation and clonogenicity in non-small cell lung cancer (NSCLC) cells from a patient previously treated with standard-of-care. Poster presented at: AACR Annual Meeting 2020; April 27-28 and June 22-24, 2020; Philadelphia, PA **2.** Karanam NK, Story MD. An overview of potential novel mechanisms of action underlying tumor treating fields-induced cancer cell death and their clinical implications. *Int J Radiat Biol*. 2021;97(8):1044-1054. doi:10.1080/09553002.2020.1837984 **3.** 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;139(12):2850-2858. doi:10.1002/ijc.30406

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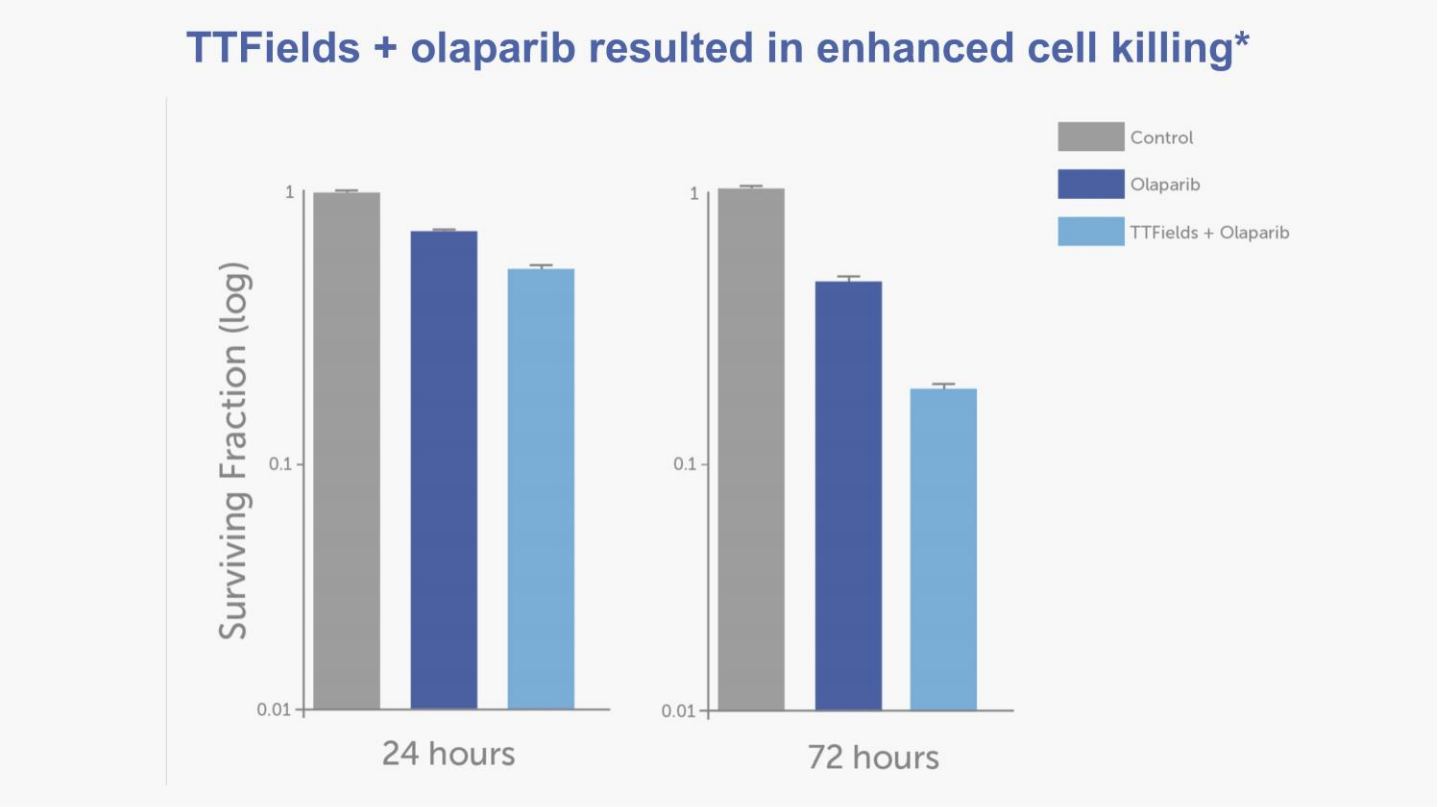
BASED ON PRECLINICAL DATA

TTFields used with a PARP inhibitor that inhibits DNA damage repair (olaparib) has demonstrated enhanced cytotoxic effects in tumor models[1,2]



Adapted from Karanam et al. 2020.

PARP=poly-ADP ribose polymerase.

*Clonogenic survival assays of olaparib together with TTFields were performed.

References: 1. Karanam NK, Story MD. An overview of potential novel mechanisms of action underlying tumor treating fields-induced cancer cell death and their clinical implications. *Int J Radiat Biol*. 2021;97(8):1044-1054. doi:10.1080/09553002.2020.1837984 **2.** Karanam NK, Ding L, Aroumougame A, Story MD. Tumor treating fields cause replication stress and interfere with DNA replication fork maintenance: implications for cancer therapy. *Transl Res*. 2020;217:33-46. doi:10.1016/j.trsl.2019.10.003

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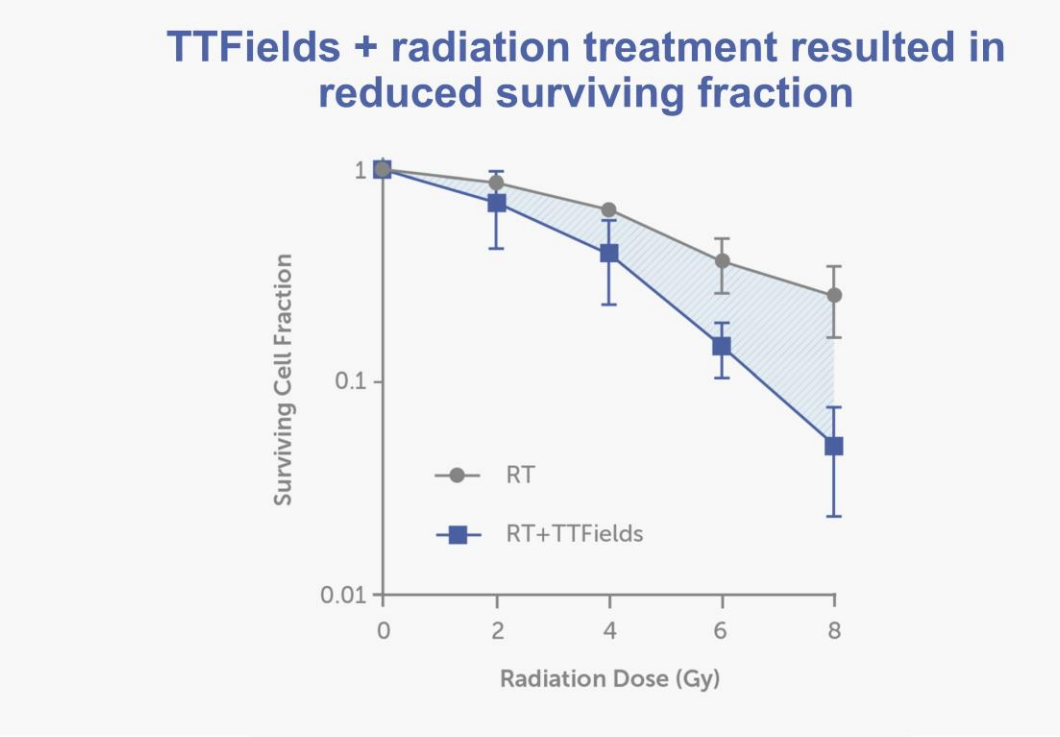
BASED ON PRECLINICAL DATA

TTFields **used with RT**, a therapy that induces DNA damage, has **demonstrated enhanced cytotoxic effects** in tumor models, particularly when TTFields precede RT[1-8,*]



Adapted from Giladi et al. 2017.

RT=radiation therapy.

*The efficacy of the concomitant application of TTFields and varying doses of ionizing radiation were tested when 72-hour TTFields treatment was applied immediately after RT in U-118 MG cells.

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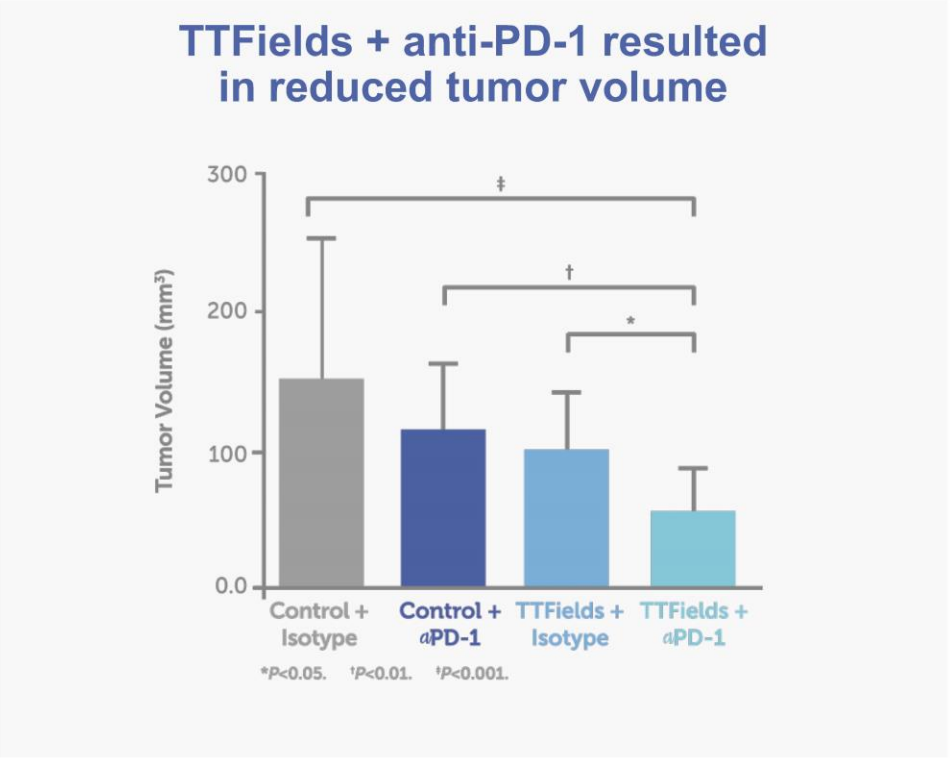
TTFIELDS
TUMOR TREATING FIELDS THERAPY

BASED ON PRECLINICAL DATA

TTFields **used with PD-1 inhibition** has demonstrated **decreased tumor size**, increased immune cell infiltration, and increased cytokine production in tumor models[1,*]



Adapted from Voloshin et al. 2020.

PD-1=programmed cell death protein 1.

*Tumor volume (LLC-1 cells) following TTFields application and an intraperitoneal (IP) injection of anti-PD-1 (αPD-1) was measured using Vernier calipers.[1]

Reference: 1. 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;69(7):1191-1204. doi:10.1007/s00262-020-02534-7

TTFIELDS TUMOR TREATING FIELDS THERAPY

SUMMARY

TTFields therapy provides clinical versatility that has potential to help address treatment challenges across a range of solid tumors[1-5]

With a poor survival outlook, physicians and patients need additional treatment strategies

- TTFields are electric fields that exert physical forces to kill cancer cells via a variety of mechanisms, while sparing healthy cells
- The multiple, distinct mechanisms of TTFields therapy work together to selectively target and kill cancer cells
- Due to its multimechanistic actions, TTFields therapy can be added to cancer treatment modalities in approved indications
- As a highly versatile first-in-class modality, TTFields therapy has significant potential for broad applicability across solid tumor types and lines of therapy

References: 1. Karanam NK, Story MD. An overview of potential novel mechanisms of action underlying tumor treating fields-induced cancer cell death and their clinical implications. *Int J Radiat Biol*. 2021;97(8):1044-1054. doi:10.1080/09553002.2020.1837984 **2.** Mun EJ, Babiker HM, Weinberg U, Kirson ED, Von Hoff DD. Tumor-treating fields: a fourth modality in cancer treatment. *Clin Cancer Res*. 2018;24(2):266-275. doi:10.1158/1078-0432.CCR-17-1117 **3.** Rominiyi O, Vanderlinden A, Clenton SJ, Bridgewater C, Al-Tamimi Y, Collis SJ. Tumour treating fields therapy for glioblastoma: current advances and future directions. *Br J Cancer*. 2021;124(4):697-709. doi:10.1038/s41416-020-01136-5 **4.** Giladi M, Schneiderman RS, Voloshin T, et al. Mitotic spindle disruption by alternating electric fields leads to improper chromosome segregation and mitotic catastrophe in cancer cells. *Sci Rep*. 2015;5:1-16. doi:10.1038/srep18046 **5.** Kirson ED, Dbalý V, Tovaryš F, et al. Alternating electric fields arrest cell proliferation in animal tumor models and human brain tumors. *Proc Natl Acad Sci U S A*. 2007;104(24):10152-10157. doi:10.1073/pnas.0702916104

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