Effectiveness of Tumor Treating Fields (TTFields) together with gemcitabine and nab-paclitaxel in pancreatic ductal adenocarcinoma (PDAC) preclinical models

Janin Knop[1], Hila Ene[2],Tal Kan[2], Tharwat Haj Khalil[2], Yiftah Barsheshet[2], Tali Voloshin[2], Avital Vorontsov[2], Boris Brant[2], Simona Zisman-Rozen[2], Lilach Koren[2], Roni Blatt[2], Shay Cahal[2], Catherine Tempel Brami[2], Sara Jacobovitch[2], Adi Haber[2], Moshe Giladi[2], Uri Weinberg[1], and Yoram Palti[2]

[1]*Novocure GmbH, Baar, Switzerland;* [2]*Novocure Ltd, Haifa, Israel*

Poster 311P

Introduction

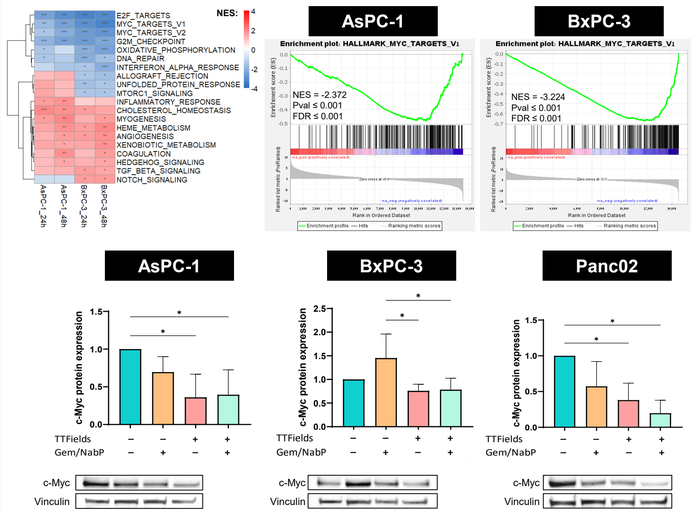
- Tumor Treating Fields (TTFields) are low-intensity electric fields that disrupt cellular processes critical for cancer cell division and tumor progression.[1,2]
- TTFields have been shown to induce immunogenic cell death (ICD) in cancer cells and elicit a systemic anti-cancer immune response. [3-4]
- TTFields are approved for treatment of glioblastoma and pleural mesothelioma together with standard chemotherapy, and as second line treatment for metastatic non-small cell lung cancer together with immune checkpoint inhibitors (ICIs) or docetaxel.[1,2,5]
- Pancreatic ductal adenocarcinoma (PDAC) is a deadly malignancy with few therapeutic options. A phase 3 clinical trial has demonstrated increase overall survival when TTFields therapy was applied concomitant with standard-of-care gemcitabine and nab-paclitaxel (Gem/NabP) as a front-line treatment of locally advanced PDAC.[6]
- The current study aimed to investigate TTFields-induce immune responses and the possible benefit of TTFields treatment together with Gem/NabP in PDAC preclinical models .

Methods

- **In vitro:** Human AsPC-1, BxPC-3, and mouse Panc02 cell lines were treated with TTFields (150 kHz, 1.62 V/cm RMS). Cell treated for 48 hours were examined by RNA sequencing. Cell treated for 72 hours were analyzed by western blot for c-Myc and by flow cytometry for cell count, apoptosis (7AAD/annexin V staining), ATP depletion (quinacrine staining), and surface calreticulin exposure. HMGB1 was measured with Homogeneous Time Resolved Fluorescence (HTRF) technique.
- In vivo: An orthotopic PDAC tumor model was established by inoculating 4X10^5 Panc02-luc pancreatic cancer cells with stable luciferase expression into the pancreas tail of immune-competent C57BL/6 mice. The mice were randomized into four groups following bioluminescence measurements: control, TTFields (150 kHz, 10 days), Gem/NabP (50 mg/kg each, i.p. injected once a week for a total of two administrations), and Gem/NabP + TTFields. Control groups received sham-heat and saline injections. At the end of treatment, tumor volume was measured using a caliper. Tumor single cell suspensions and peripheral blood were collected for spectral flow cytometry-based immunophenotyping.
- **Immunophenotyping:** Tumor single cell suspensions were stained with Zombie NIR, then stained for the following markers and acquired by floow cytometry: CD45, CD11b, CD3e, CD4, CD8a, Ly6G, Ly6C, CD11c, CD44, CD62L, and MHC class II (MHC-II).

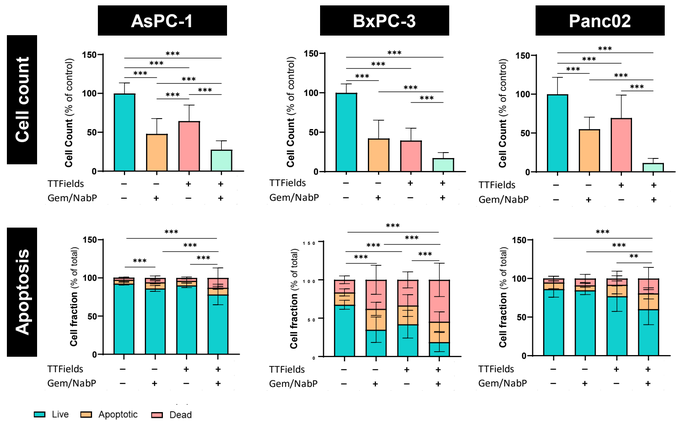
Results

FIGURE 1. TTFields downregulated the expression of c-Myc and associated downstream pathways , alone and when applied concomitant with Gem/NabP



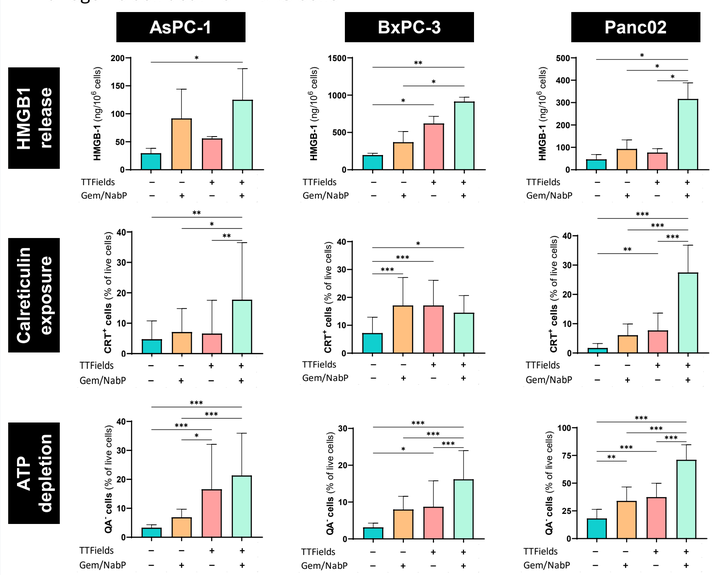
One-way ANOVA with Tuckey's multiple comparisons; *p < 0.05

FIGURE 2. Concomitant treatment with TTFields and Gem/NabP enhanced cytotoxicity to PDAC cells



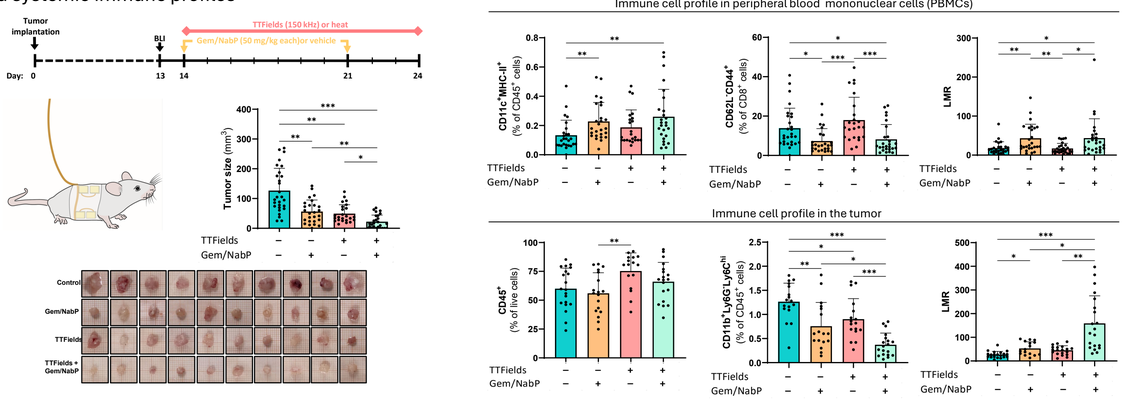
One-way ANOVA with Tuckey's multiple comparisons; **p < 0.01, ***p < 0.001

FIGURE 3. Concomitant treatment with TTFields and Gem/NabP promoted immunogenic cell death of PDAC cells



One-way ANOVA with Tuckey's multiple comparisons; *p < 0.05, **p < 0.01, ***p < 0.001

FIGURE 4. Concomitant TTFields and Gem/NabP treatment significantly reduces tumor volume and modulates tumor-associated and systemic immune profiles



One-way ANOVA with Tuckey's multiple comparisons; *p < 0.05, **p < 0.01, ***p < 0.001

Conclusions

This study demonstrates that TTFields have the potential to enhance the therapeutic efficacy of standard-of-care chemotherapy for PDAC by downregulating c-Myc expression, inducing immunogenic cell death, and reshaping the tumor immune microenvironment towards a more immune-inflamed phenotype. These findings provide a strong rationale for future investigations into the integration of TTFields with chemotherapy and immunotherapy strategies in PDAC.

References: **1.** Moser, J. C., et al. (2022). Cancer Res 82(20): 3650-3658. **2.** Karanam, N. K. and M. D. Story (2021). Int J Radiat Biol 97(8): 1044-1054. **3.** Voloshin, T., et al. (2020). Cancer Immunol Immunother 69(7): 1191-1204. **4.** Barsheshet, Y., et al. (2022). Int J Molec Sci 23(22): 14073. **5.** Leal, T., et al. (2023). The Lancet Oncology 24(9): 1002-1017. **6.** H. M. Babiker et al. (2023) *J. Clin. Oncol.* 41(16_suppl): p. TPS4199-TPS4199

For further information, please contact Dr Moshe Giladi (mosheg@novocure.com)

Presented at the ESMO Gastrointestinal Cancers Congress, July 2-5, 2025