Preclinical evaluation of Tumor Treating Fields (TTFields) with FOLFIRINOX or KRAS inhibition in pancreatic Cancer

Hila Fishman[1], Yara Eid Mutlak[1], Sewar Zbidat[1], Hila Ene[1], Kerem Ben Meir[1], Zeina Drawshy[1], Helena Mumblat[1], Mariell Sellevoll[1], Hila Gabay[1], Eyal Dor-On[1], Itai Tzchori[1], Adi Haber[1], Moshe Giladi[1], Uri Weinberg[2]

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

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Introduction

- Pancreatic ductal adenocarcinoma (PDAC) remains lethal despite systemic therapies including gemcitabine/nab-paclitaxel and FOLFIRINOX.[1]
- Tumor Treating Fields (TTFields) therapy was recently approved in the US together with gemcitabine/nab-paclitaxel for locally advanced, unresectable pancreatic adenocarcinoma.[2]
- TTFields are electric fields that disrupt cancer cell viability via antimitotic effects, with downstream induction of antitumor immunity and downregulation of DNA damage response pathways and of c-Myc, a downstream effector associated with KRAS-driven growth programs.[3,4]
- This study examined in preclinical models the potential concomitant use of TTFields with FOLFIRINOX or the pan-KRAS inhibitor (KRASi), daraxonrasib.

Methods

- **TTFields in vitro:** TTFields were applied to pancreatic cell lines for 72 h (150 kHz, 0.7-1 V/cm RMS). BxPC3 and AsPC1 cells received TTFields via inovitro with escalating FOLFIRINOX. KPC and PANC-1 cells (bearing the KRAS G12D mutation) received TTFields with increasing dose of daraxonrasib.
- **Cell count:** Cells were counted by flow cytometry. Expected value for an additive effect was calculated by multiplying the observed effects of corresponding individual treatments. Synergy was defined when the observed value was lower than that predicted for an additive effect.
- **Apoptosis:** Treated cells were double-stained with FITC-conjugated annexin V (AnnV) and 7-aminoactinomycin D (7AAD), and data acquisition was performed with a flow cytometer.

Experimental setup of the inovitro system

Cells are seeded into inovitro treatment dishes, and the dishes positioned on the baseplate. The baseplate is connected to the generator, enabling transmission of TTFields to each dish.



- **TTFields in vivo:** Male C57BL/6 mice were orthotopically inoculated with either 400,000 murine Panc02-luc cells or 50,000 murine KPC-mCherry cells, and tumor localization was verified by in vivo imaging system (IVIS). Mice were then treated with TTFields or sham heat using the inovivo device. In the Panc02-luc model, TTFields/heat treatment was initiated on day 14 and applied continuously for 10 days, with FOLFIRINOX/5-FU or vehicle administered i.p. according to the timeline in Figure 2. In the KPC-mCherry model, TTFields/heat treatment was initiated on day 8 and applied for 9 days, with daraxonrasib or vehicle administered by oral gavage according to the timeline in Figure 4. At the end of treatment, tumors were excised and weighed.

References: 1. Rosen MN, et al. (2021) *World J Gastroenterol.* 27(17): 1943-1958. 2. Babiker HM, et al. (2023) *J. Clin. Oncol.* 41(16_suppl): TPS4199. 3. Giladi, M, et al. (2014). *Pancreatology.* 14(1): 54-63. 4. Kan T, et al. (2026) *Int J Cancer*. 158: 3091-3100.

Disclosures: Hila Fisman is an employee of Novocure and holds Novocure stocks. This study was funded by Novocure.

Results

FIGURE 1. TTFields augmented the cytotoxic effects of FOLFIRINOX in pancreatic cancer cells

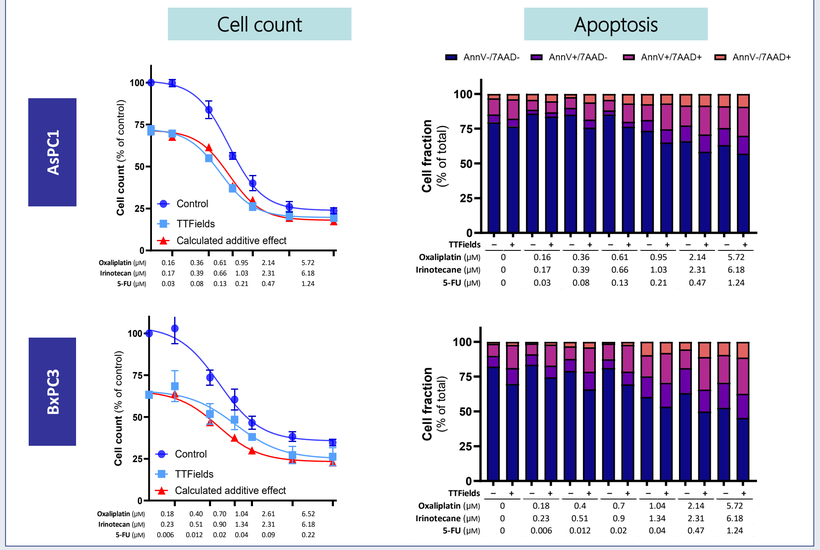
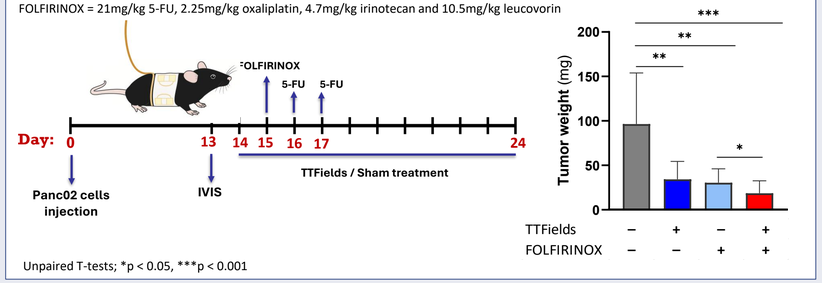


FIGURE 2. TTFields augmented the antitumor effect of FOLFIRINOX in a pancreatic cancer animal model

FOLFIRINOX = 21mg/kg 5-FU, 2.25mg/kg oxaliplatin, 4.7mg/kg irinotecan and 10.5mg/kg leucovorin



Unpaired T-tests; *p < 0.05, ***p < 0.001

FIGURE 3. TTFields augmented the cytotoxic effects of daraxonrasib in pancreatic cancer cells

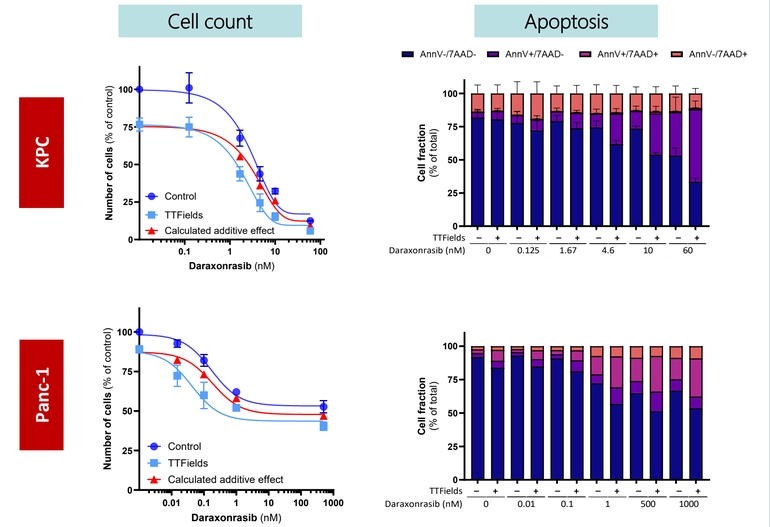
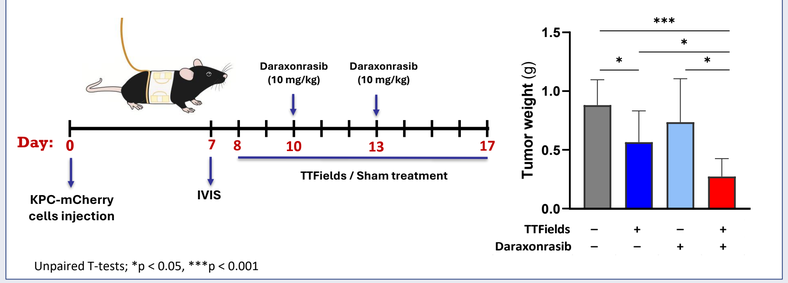


FIGURE 4. TTFields augmented the antitumor effect of daraxonrasib in a pancreatic cancer animal model



Unpaired T-tests; *p < 0.05, ***p < 0.001

Conclusions

- Concomitant application of TTFields with FOLFIRINOX or the pan-KRAS inhibitor daraxonrasib produced an antitumor effect, in vitro and in vivo.
- These effects are potentially related to the effect of TTFields on DNA repair pathways and c-Myc expression and warrant further evaluation and translation into clinical studies.

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

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