SELECTED OPPORTUNITIES IN ONCOLOGY

A Checkpoint kinase 1 inhibitor sensitises cancer cells to dihydroorotate dehydrogenase inhibition (BIO17261)

A CHECKPOINT KINASE 1 INHIBITOR SENSITISES CANCER CELLS TO DIHYDROOROTATE DEHYDROGENASE INHIBITION (BIO 17261)

Product factsheet

Preclinical

Targets:

- Checkpoint kinase 1 (Chk1) and dihydroorotate dehydrogenase (DHODH)

Product:

- A combination of a Chk1 inhibitor and a DHODH inhibitor

Application:

- Cancer in particular triple negative breast cancer.

Rational / POC:

- Reduction in nucleotide pools through the inhibition of mitochondrial enzyme dihydroorotate dehydrogenase (DHODH) has been demonstrated to effectively reduce cancer cell proliferation and tumour growth.
- The pharmacological activity of a DHODH inhibitor (teriflunomide) was more selective towards transformed mouse embryonic fibroblasts than their primary or immortalised counterparts, and this effect was amplified when cells were subsequently exposed to a Chk1 inhibitor (PF477736).
- Flow cytometry analyses revealed substantial accumulations of cells in S and G2/M phases, followed by increased cytotoxicity which was characterised by caspase 3-dependent induction of cell death.
- Associating PF477736 with teriflunomide (TFN) significantly sensitised two human triple negative breast cancer cell lines (SUM159 and HCC1937) to dihydroorotate dehydrogenase inhibition.

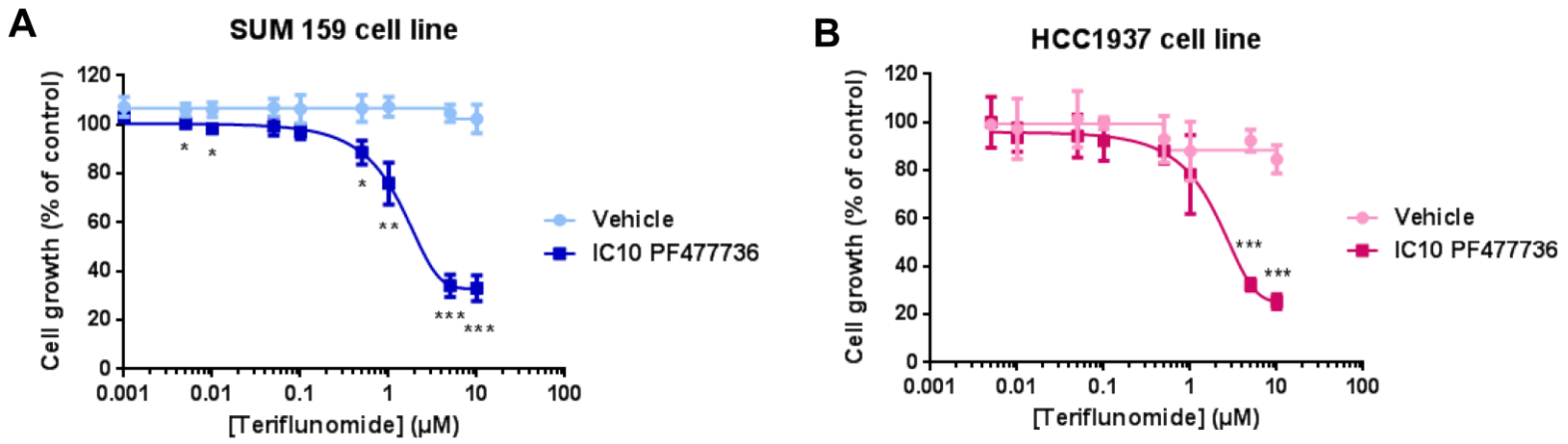
Patent and publication:

- **Checkpoint kinase 1 inhibitor sensitises cancer cells to dihydroorotate dehydrogenase inhibition** Arnould S. et al. Oncotarget 2017 Jul12;8(56):95206-95222.
- **Patent:** EP17306028.6 METHOD FOR TREATING CANCER

A Checkpoint kinase 1 inhibitor sensitises cancer cells to dihydroorotate dehydrogenase inhibition (BIO 17261)

Proof of concept

The combination of teriflunomide and PF477736 reduces proliferation of SUM159 and HCC1937 triple negative breast cancer cell lines.

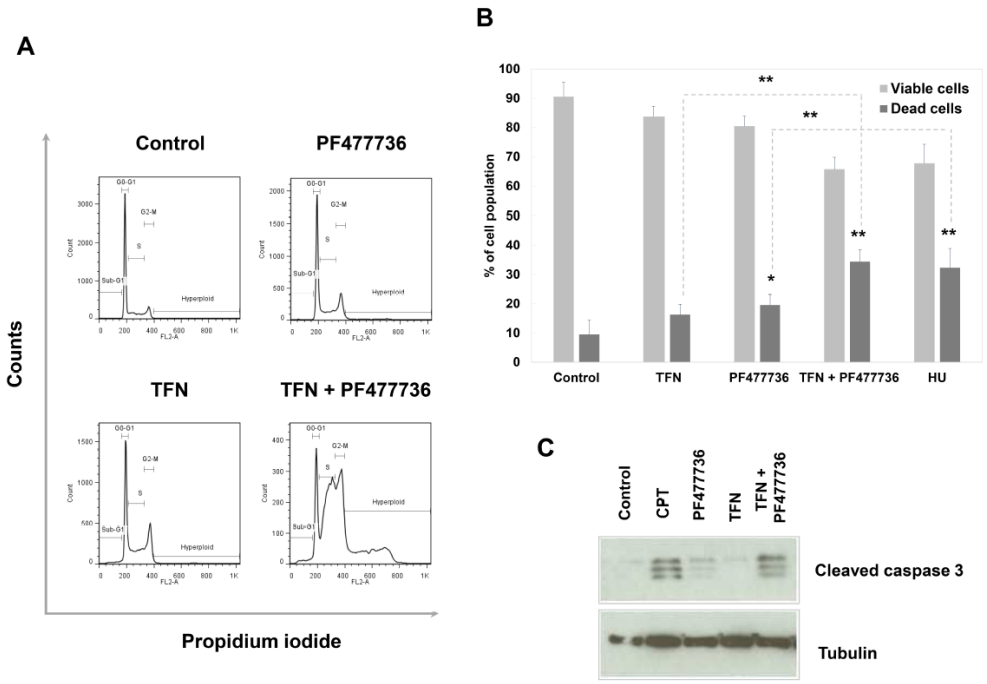


(A) SUM159 and (B) HCC1937 cells were exposed for 24 hours to increasing concentrations of teriflunomide ± IC10 PF477736 (0.29 µM) and grown in drug-free medium for three doubling times. Mean ± SD, n=3 independent experiments. * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$ as determined by two-tailed unpaired t-test. IC10 PF477736 is the concentration of the Chek1 inhibitor required to achieve 10% of inhibition.

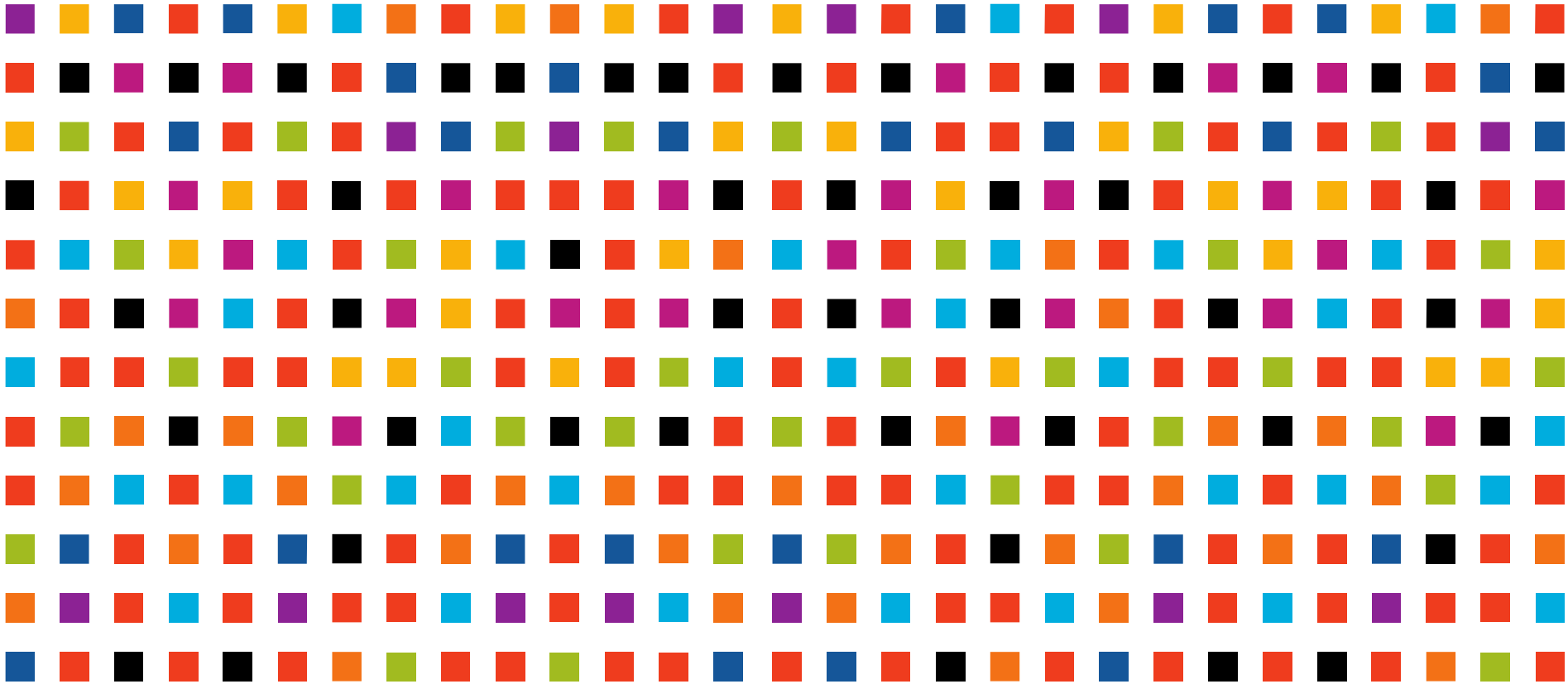
A CHECKPOINT KINASE 1 INHIBITOR SENSITISES CANCER CELLS TO DIHYDROOROTATE DEHYDROGENASE INHIBITION (BIO 17261)

Proof of concept

The combination of teriflunomide (TFN) and PF477736 is cytotoxic in SUM159 triple negative breast cancer cell line



A) Representative flow cytometry analysis of cell cycle distribution in SUM159 cells collected 48 hours after the beginning of exposure to vehicle, 25 µM teriflunomide (TFN), IC10 PF477736 (2.5 µM), or their combination at the same concentrations. (B) Flow cytometry analysis for apoptosis / necrosis. Cells were exposed to vehicle, 5 mM hydroxyurea (HU) as a positive control, 25 µM TFN, IC10 PF477736 or their combination, collected and stained with annexin V/7-AAD. Quantitation was performed with FlowJo software. Results are expressed as mean values ± SD of three independent experiments. * $p < 0.05$ and ** $p < 0.01$ as determined by two-tailed unpaired t-test. (C) Western blotting analysis of caspase 3 cleavage in cell lysates prepared 72 hours after the beginning of the exposure to either compound, their combination or 0.1 µM positive control camptothecin (CPT).



ANNE.COCHI@INSERM-TRANSFERT.FR

Inserm Transfert - Paris Biopark
7 Rue Watt - 75013 Paris
Tel: +33 1 55 03 01 00 / Fax: +33 55 03 01 60
www.inserm-transfert.fr