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SWISS ONCOLOGY & HEMATOLOGY CONGRESS

Phase Ib clinical trial of the hypoxia modifier Inositol trispyrophosphate (ITPP) in patients with hepato-pancreato-biliary tumors

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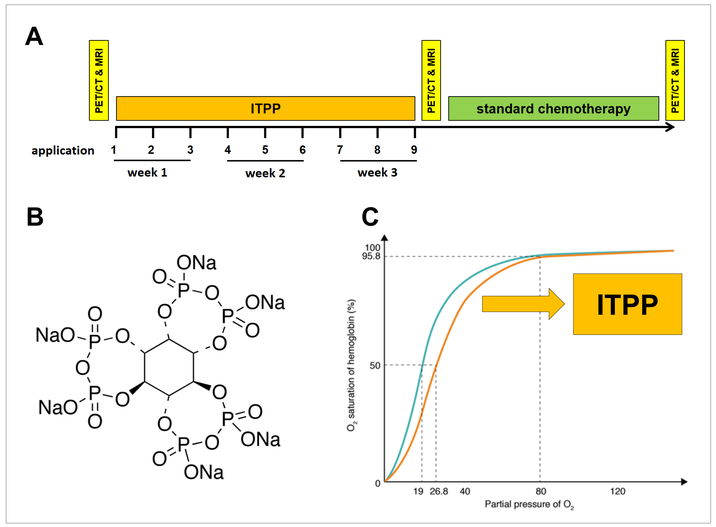
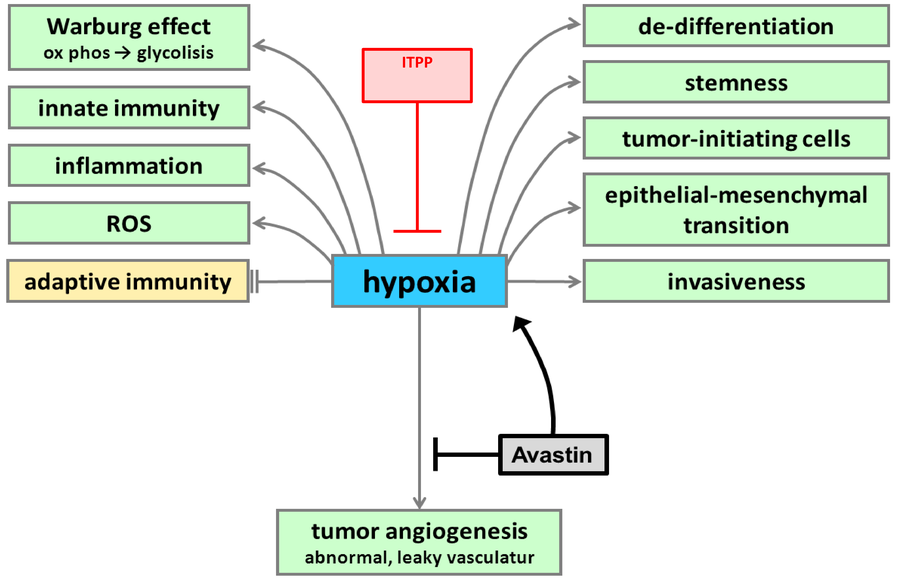
Clinical solid tumor oncology

Hypoxia is prominent in solid tumors and a recognized driver of malignancy. Thus far, targeting tumor hypoxia has remained unsuccessful. Myo-inositol trispyrophosphate (ITPP) is a re-oxygenating compound without apparent toxicity. In preclinical models, ITPP potentiates the efficacy of subsequent chemotherapy through vascular normalization.

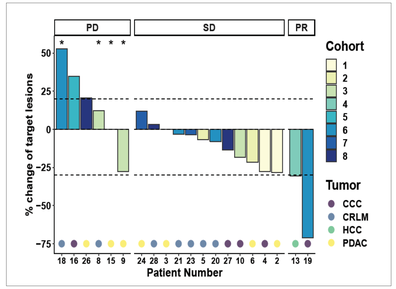
Here, we report the results of an unrandomized, open-labeled, 3 + 3 dose-escalation phase Ib study (NCT02528526) including 28 patients with advanced primary hepatopancreatobiliary malignancies and liver metastases of colorectal cancer receiving nine 8h-infusions of ITPP over three weeks across eight dose levels (1'866-14'500 mg/m2/dose), followed by standard chemotherapy.



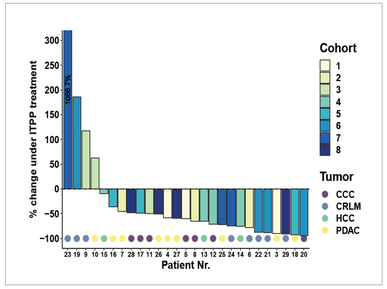
A Study schedule and experimental set up.
B chemical structure of the study drug ITPP.
C Oxygen dissociation curve shifts to the right after ITPP administration.



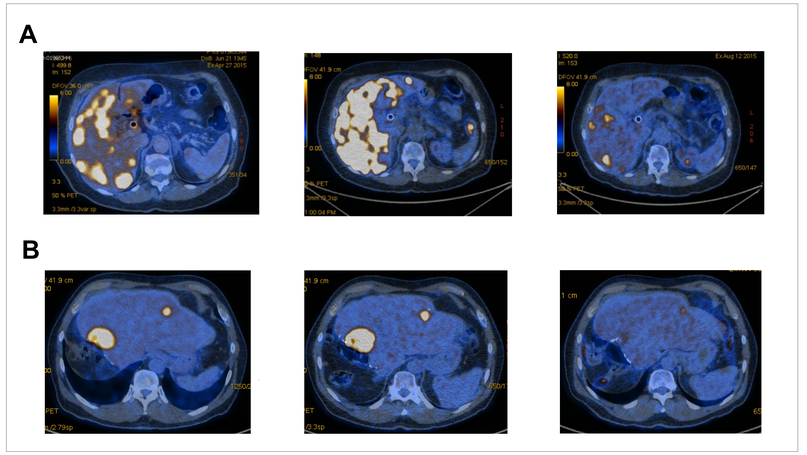
Primary objectives are assessment of the safety and tolerability and establishment of the maximum tolerated dose, while secondary objectives include assessment of pharmacokinetics, antitumor activity via radiological evaluation and assessment of circulatory tumor-specific and angiogenic markers. The **maximum tolerated dose** is 12,390 mg/m2, and ITPP treatment results in 32 treatment-related toxicities (mostly hypercalcemia) that require little or no intervention. 52% of patients have morphological disease stabilization under ITPP monotherapy. Following subsequent chemotherapy, 10% show partial responses while 60% have stable disease. Decreases in angiogenic markers are noted in ~60% of patients after ITPP and tend to correlate with responses and survival after chemotherapy. Further exploration of its anti-tumor efficacy in Phase II/III trials is highly warranted.



Tumor respone (RECIST criteria), PD progressive disease, SD stable disease, PR partial response.



Angiogenic serum markers, epidermal growth factor (EGF).



A 62 y/o F with metastasized pancreatic cancer. Before therapy, after ITPP monotherapy, after FOLFIRINOX (alive for 464 days after study start)
B 62 y/o M with metastasized biliary cancer (Bismuth II), s/p Gemcitabine/Cisplatin. Imaging as per study schedule (alive for 33 months)

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Presented at SOHC 2022 from 16 – 18 November 2022