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Title: Phase 1 study of ultra-high concentration nitric oxide (UNO) in relapsed or refractory, unresectable, primary, or metastatic cutaneous and subcutaneous malignancies

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Abstract:

Background: Tumor ablation is a minimally invasive technique commonly used to treat solid tumors in the liver, kidney, bone, and lung and is based on thermal and nonthermal approaches. Local and *in-situ* tumor ablation methods demonstrated enhance anti-tumor immune responses resulting in the destruction of residual malignant cells in primary tumors and distant metastases. Nitric oxide (NO) is a colorless gas and is a short-lived free radical. It is a ubiquitous, endogenously generated gas implicated in the homeostatic regulation of physiological processes, as well as in numerous pathological conditions. Preclinical studies evaluating the effect of high concentration exogenously administered NO demonstrated its anti-cancer properties and suggested that it may serve as a potent tumoricidal agent. We have previously shown that treating mouse colon carcinoma (CT26) tumor-bearing mice with ultra-high concentrations of nitric oxide (UNO) upregulates innate and adaptive immune cells both locally and systemically. Beyond Air and Beyond Cancer is currently conducting a first-in-human, first-in-class Phase 1 safety and preliminary efficacy clinical study of UNO at multiple institutions in Israel.

Methods: The study is a 2-part Phase 1 trial with a Dose Escalation and a Dose Expansion portion (NCT05351502). A conventional 3+3 dose escalation will evaluate three single escalating doses of UNO: 25,000, 50,000 and 100,000 ppm delivered intratumorally over 5 minutes at a flow rate of 0.2 liters-per-minute in subjects with relapsed or refractory unresectable primary or metastatic cutaneous and subcutaneous solid tumors. Upon determination of the maximum tolerated dose or biological effective dose, the recommended Phase 2 dose will be further evaluated in the Dose Expansion portion of the study. RECIST version 1.1 will be utilized to assess the rate of malignant tumor response after UNO administration and toxicity will be graded per NCI CTCAE version 5.0. Up to thirty-eight enrolled subjects are anticipated. This study was approved by Israel Ministry of Health (Form 8; 202124820) as well as the participating institution's Ethics Board. Written informed consent was obtained for all enrolled subjects and a copy of the written consent is available for review.