A Phase 1, Multi-center, Safety, Feasibility, and Preliminary Efficacy Study Evaluating a Single Dose of UNO101 in Relapsed or Refractory, Unresectable, Primary, or Metastatic Cutaneous and Subcutaneous Malignancies

BEYOND CANCER™
Next Level ImmuNO-oncology

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Background

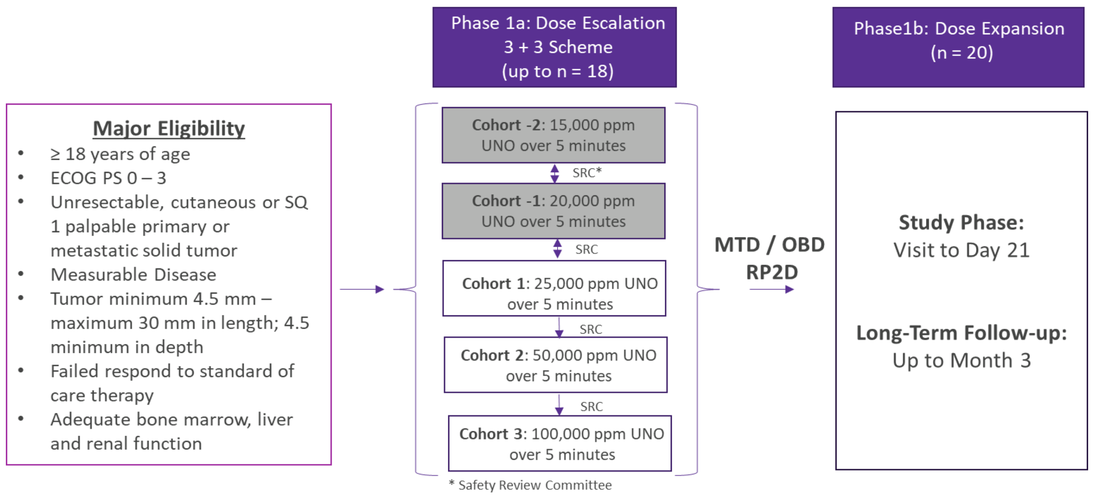
Immunomodulating agents are an accepted backbone of cancer treatment. However, they are effective only in a select group of cancers and resistance often emerges to many treatments that target single molecular mutations or cancer pathways. At elevated concentrations, the signaling molecule nitric oxide (NO) acts as an antitumor agent and has been reported to sensitize resistant tumor cells to anti-cancer therapies. Preclinical studies of Ultra-High Concentration Nitric Oxide (UNO) in solid tumor murine models such as colon carcinoma (CT26) and aggressive breast cancer (4T1) have demonstrated its ability to cause both local cell death as well as a systemic immune response. In addition, creating a memory immune response allows for the recognition and attack of subsequent primary tumors as well as distant metastases. Moreover, preclinical data of UNO in combination with immune checkpoint inhibitors has demonstrated synergistic effects resulting in significant tumor response (Confino H et al. 2023; Figure 2, p=0.0005). Survival advantages in CT-26 Balb/c tumor bearing mice were demonstrated in combination of either 5- or 10-minutes UNO and anti-mPD-1. The combination demonstrated 37.7% (29/77) survival compared to 18.5% (12/65) treated with anti-mPD-1 alone, seventy-five days post-treatment (Epshtein Y et al. 2023; Figure 4, (p=0.0038). Importantly, there were no significant toxicities associated with UNO treatment.

The initial first-in-human single agent UNO Phase 1a/Phase 1b safety and preliminary efficacy evaluation of UNO is ongoing in four centers in Israel. Cohort 1 completed without a reported DLT. Enrollment in Cohort 2 is ongoing. The Phase 1b with UNO in combination with immune checkpoint inhibitors is actively being planned given the previously published non-clinical data in support of UNO combination with immune checkpoint inhibitors.

Study Overview

BA-ONC-01 is a Phase 1 trial consisting of Dose Escalation and Dose Expansion Segments (NCT05351502). Three escalating doses of UNO: 25,000, 50,000, and 100,000 parts per million (PPM) will be delivered as a single dose intratumorally for 5 minutes in subjects with relapsed or refractory unresectable primary or metastatic cutaneous and subcutaneous solid tumors. The study was approved by Israel Ministry of Health (IMOH) as well as the four participating institution's Ethics Boards. Written ICF was obtained for all enrolled subjects.

Figure 1: Study Schematic



Primary Objectives: Determine safety profile, maximum tolerated dose (MTD) and/or optimal biological dose (OBD), and the Recommended Phase 2 dose (RP2D).

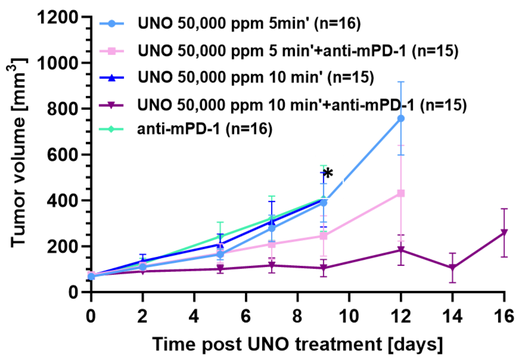
Secondary Objectives: Perform a preliminary assessment of the anti-tumor activity of a single intratumoral UNO injection, per Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 and immune RECIST (iRECIST).

Exploratory Objectives: Assess biomarkers that may predict anti-tumor activity, evaluate the feasibility and clinical utility of itRECIST to assess preliminary activity of single intratumoral UNO administration.

Study Protocol Next Steps

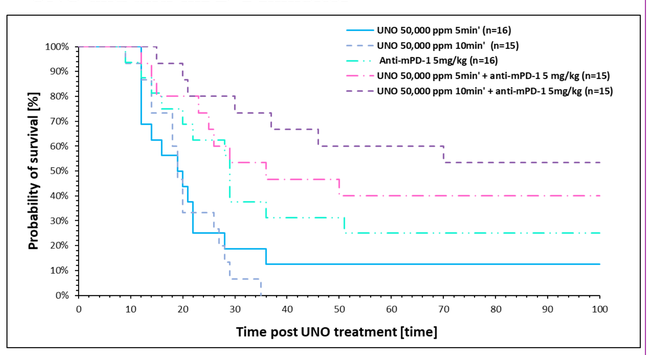
Nonclinical Data Supports Combining UNO plus anti-mPD-1 in the Clinic

Figure 2: CT26 Primary Tumor Growth in Mice Treated With Combined UNO and anti-mPD-1 Inhibitor



Tumor growth curves of CT26 tumor-bearing mice treated with 50,000 ppm UNO for 5 or 10 minutes. Analysis via mixed model repeated measures (MMRM) with fixed effects for baseline tumor volume, study day, and treatment by study day interaction, *p=0.0005 (at Day 9 post-UNO treatment). Source: Confino H. et al. 2023.

Figure 3: Survival Curves of Mice Treated with Combined UNO and anti-mPD-1 Inhibitor

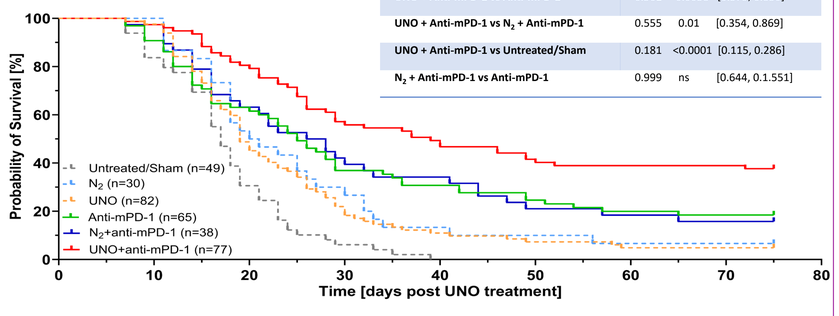


Survival curve, presented as a Kaplan–Meier curve. p=0.065 for NO + anti-mPD-1 vs. anti-mPD-1. Survival reflects not being euthanized due to tumor reaching a prespecified size. Source: Confino H. et al. 2023

Figure 4: Pooled Analysis: Effect of Single Dose UNO and anti-mPD-1 Inhibitor on Mice Survival

Pooled data across studies of 5 or 10-minutes UNO and anti-mPD-1 (5 or 10 mg/kg) treatment – survival data. [1]Hazard ratio and p-value derived from Cox proportional hazard model.

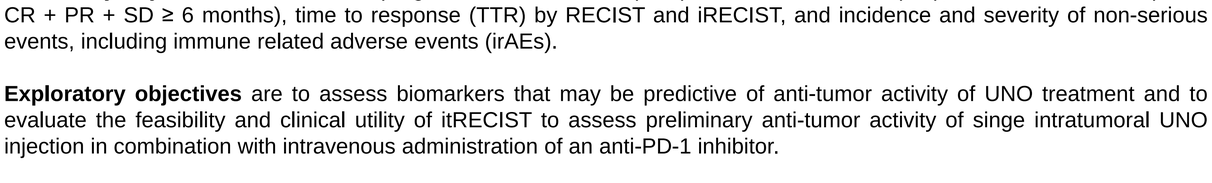
Experimental model: CT26; Mouse model: Balb/c mice. UNO treatment regimen: 50,000 or 100,000 ppm injected for 5 or 10 minutes. Anti-mPD-1 dosing started at Days (-2) to (+2). 5 or 10 mg/kg doses injected every 2-3 days, 4-5 doses in total. All studies were conducted under approved IACUC protocols. Source: Epshtein Y et al. EORTC-NCI-AACR, October 2023



Statistics – Kaplan Meier	HR[1]	p-value[1]	[95% CI]
UNO + Anti-mPD-1 vs Anti-mPD-1	0.561	0.0038	[0.379, 0.830]
UNO + Anti-mPD-1 vs N_2 + Anti-mPD-1	0.555	0.01	[0.354, 0.869]
UNO + Anti-mPD-1 vs Untreated/Sham	0.181	<0.0001	[0.115, 0.286]
N_2 + Anti-mPD-1 vs Anti-mPD-1	0.999	ns	[0.644, 0.1.551]

Proposed Revised Study Design

Figure 5: Study Schematic



Objectives:

Primary objectives are to assess preliminary efficacy by objective response rate (ORR) and duration of response (DOR) per RECIST version 1.1, and secondarily iRECIST with a single UNO dose combined with anti-PD-1 inhibitor in Cycle 1, followed by repeated cycles of single agent anti-PD-1 inhibitor until intolerable toxicity or progressive disease.

Secondary objectives are to assess progression free survival (PFS) and overall survival (OS), clinical benefit rate (CBR: CR + PR + SD ≥ 6 months), time to response (TTR) by RECIST and iRECIST, and incidence and severity of non-serious events, including immune related adverse events (irAEs).

Exploratory objectives are to assess biomarkers that may be predictive of anti-tumor activity of UNO treatment and to evaluate the feasibility and clinical utility of itRECIST to assess preliminary anti-tumor activity of singe intratumoral UNO injection in combination with intravenous administration of an anti-PD-1 inhibitor.

Eligibility:

Inclusion/exclusion criteria are amended to recruit patients with prior exposure to anti-PD-1 inhibitor with: a) a best response of progressive disease; b) a best response of complete response/partial response but developed progressive disease while on active anti-PD-1 treatment or c) prolonged stable disease on single agent anti-PD-1 inhibitor ≥ 12 weeks without radiographic evidence of continued tumor reduction.

Population:

Patients suitable for cutaneous or subcutaneous gNO (UNO) administration including, but not limited to the following anti-PD-1 approved labelled indications: Pembrolizumab labelled indications (melanoma, squamous cell carcinoma [sCC], head and neck squamous cell carcinoma [HNSCC], or triple-negative breast cancer [TNBC], merkel cell carcinoma [MCC], classical Hodgkin lymphoma [cHL], and primary mediastinal large B-cell lymphoma [PMBCL]; for nivolumab labelled indications (melanoma, cHL, and HNSCC); or cemiplimab labelled indication (cutaneous squamous cell carcinoma [cSCC]) may be recruited.

Enrolling Sites

SOROKA Medical Center feeling secure

TEL AVIV SOURASKY MEDICAL CENTER ICHILOV

Hadassah University Hospital

SHEBA Tel HaShomer City of Health

Join the BA-ONC-01 Study Team

Investigators interested in joining the BA-ONC-01 study or any future studies involving UNO, please contact the Beyond Cancer Clinical Development: Clinicaltrials@beyondcancer.com