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Phase 1 Study of Ultra-High Concentration Nitric Oxide (UNO) in Relapsed or Refractory, Unresectable, Primary, or Metastatic Cutaneous and Subcutaneous Malignancies

BEYOND CANCER™
Next Level ImmuNO-oncology

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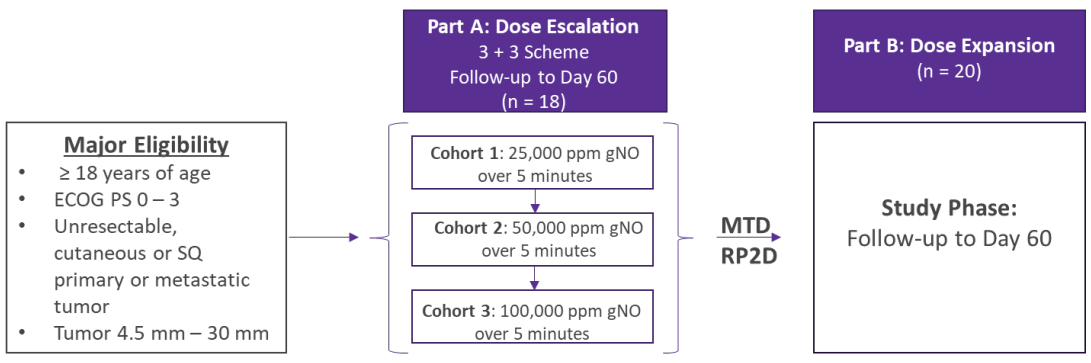
Background

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 and survival advantages. Here, we present the initial first-in-human Phase 1 safety and preliminary efficacy data of UNO.

Study Overview

BA-ONC-01 is a Phase 1 trial consisting of Dose Escalation and Dose Expansion Segments (NCT05351502). Three single escalating doses of UNO: 25,000, 50,000, and 100,000 ppm will be delivered intratumorally over 5 minutes in subjects with relapsed or refractory unresectable primary or metastatic cutaneous and subcutaneous solid tumors.

Study Schematic:



Enrolled subjects are followed through Day 60. Upon determination of the Maximum Tolerated Dose (MTD), the Recommended Phase 2 Dose (RP2D) will be further evaluated in the Dose Expansion portion of the study. RECIST version 1.1 will be utilized to assess response. Safety and toxicity will be graded per NCI CTCAE version 5.0. The study was approved by Israel Ministry of Health (IMOH) as well as the participating institution's Ethics Board. Written ICF was obtained for all enrolled subjects.

Objectives

Primary Objective:
Determine safety profile, MTD and the RP2D.

Secondary Objective:
Perform a preliminary assessment of the anti-tumor activity of a single intratumoral UNO injection at all administered doses, per RECIST version 1.1.

Exploratory Objective:
Assess biomarkers that may predict anti-tumor activity of a single intratumoral UNO injection.

Major Eligibility

- 18 years of age or older with ECOG Performance Status of 0–3.
- Confirmed diagnosis of at least 1 palpable unresectable cutaneous or subcutaneous histologically confirmed primary or metastatic solid tumor.
- Superficial tumor axis of 4.5 mm minimum/30 mm maximum length.
- No therapy of proven efficacy exists, not amenable to standard therapies, has failed to respond to standard therapy or has progressed despite standard therapy.
- Adequate bone marrow, liver and renal function.
- Tumor is not situated in the lymph node, not situated in the thyroid, close to the trachea or in a facial or other region which, in the Investigator's opinion, can pose extra risk.
- Tumor vascularity, as determined by central radiologist, does not pose risks to the subject.

Results

Table 1: Baseline Demographics

Baseline Characteristics	N (%)	Mean	Min	Max
Age (yrs.) (n=5)	5* (100%)	64.4	43	81
Male/Female	2 (40%) / 3 (60%)	--	--	--
ECOG PS 0/1/2/3 (Day 1)	0 = 2 (40%) / 1 = 3 (60%) / -- / --	--	--	--
# of Prior Treatment Regimens	5 (100%)	5.8	2	12
Diagnosis •Squamous cell carcinoma •Melanoma •Breast	 2 1 2	--	--	--
Time from Diagnosis to First UNO Treatment (yrs.)	5 (100%)	4.7	1.4	9.5

**All subjects received NO 25,000 ppm*

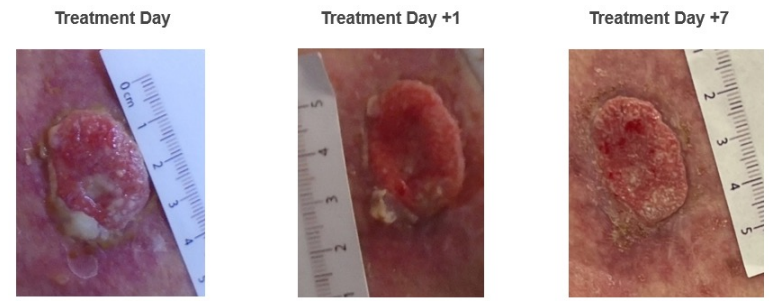
Table 2: Treatment Emergent Adverse Events

System Organ Class	Adverse Event (Preferred Term)	Grade 1	Grade 2	Grade 3	Grade 4
Respiratory, thoracic and Mediastinal disorders	Dyspnea (Certainly related)	✓			
	Hypoxia* (Possibly related)				✓
Skin and subcutaneous tissue disorders	Palmar-plantar erythrodysesthesia syndrome (Certainly related)	✓			
Gastrointestinal disorders	Nausea (Possibly related)	✓			

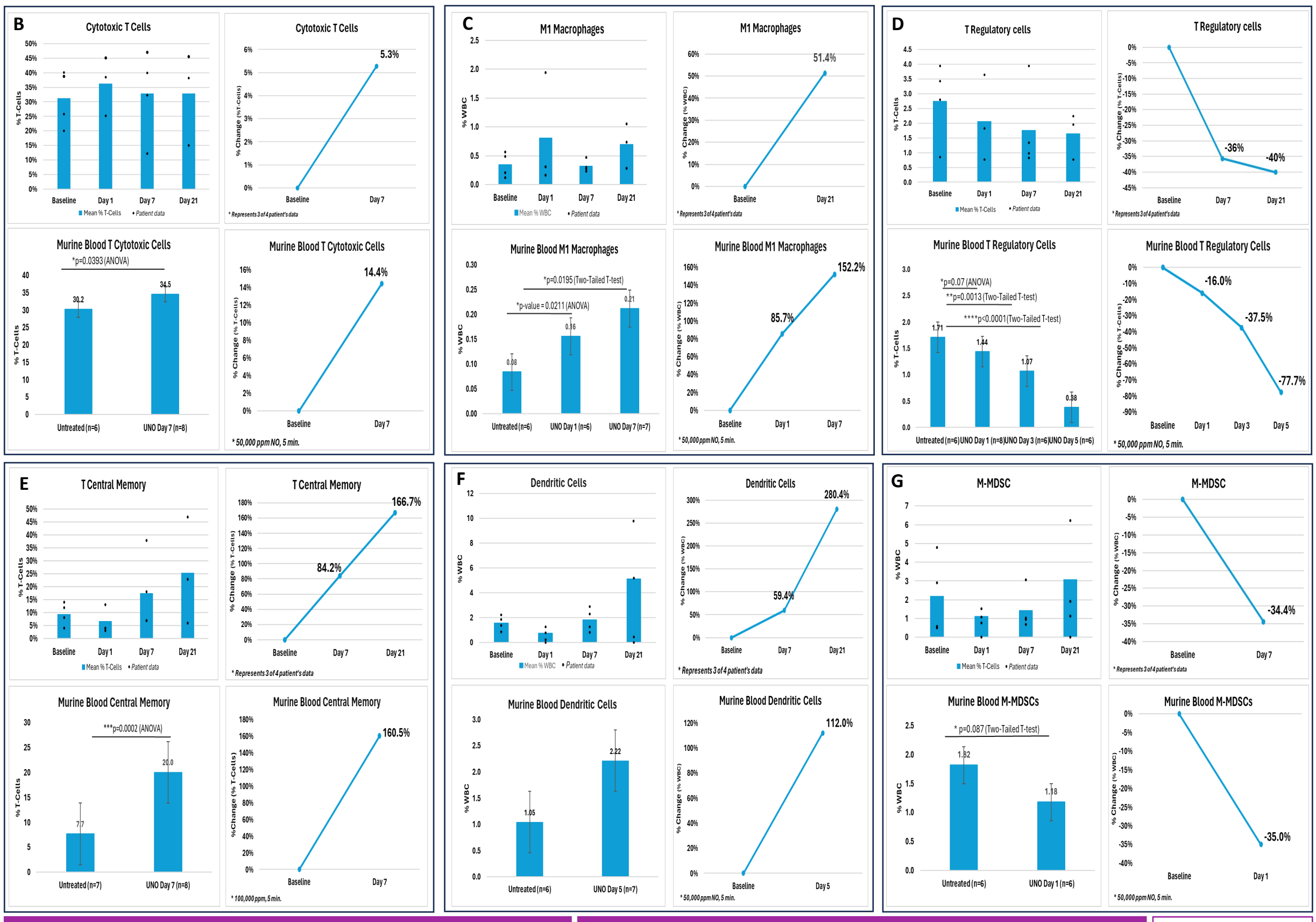
** IMOH causality assessment. Final Sponsor causality assessment & SRC adjudication pending.*

Figure A: Case Report Early Response (Subject #3)

- 82 y/o male with history of squamous cell carcinoma. 2017 metastases to neck and back.
- Received 2 prior surgeries, 2 prior lines of immunotherapy, 2 prior lines of chemotherapy/targeted therapy, and 5 prior cycles of XRT.
- Early response observed by Day 7 post UNO treatment.



Figures B–G: Clinical Immune Biomarkers Post UNO Treatment and Corresponding Murine Immune Biomarkers



Conclusions

BA-ONC-01 is currently active and enrolling subjects. Initial results in five subjects with highly relapsed/refractory cutaneous or subcutaneous malignancies demonstrated that a single dose of 25,000 ppm was well tolerated, with immune biomarkers trending in a favorable direction on Day 7 and Day 21. These results compare favorably to previously shown murine data. Additional dose levels, including repeat dosing, are expected to be further evaluated.

Acknowledgements

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