



**B E Y O N D  
C A N C E R™**

Next level immuNO-oncology

**Corporate Presentation**

February 2025

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# Ultra-High Concentration Nitric Oxide (UNO) as a Potent Immunotherapy

## Upregulates Immune Activity

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Utilizing **U**ltra-high concentration **N**itric **O**xide (**UNO**) to upregulate immune activity to treat solid tumors and distant metastases

## Promising Early Phase 1a Results

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First in human, Phase 1 clinical trial ongoing in unresectable, relapsed or refractory solid tumors

## Combination Therapy

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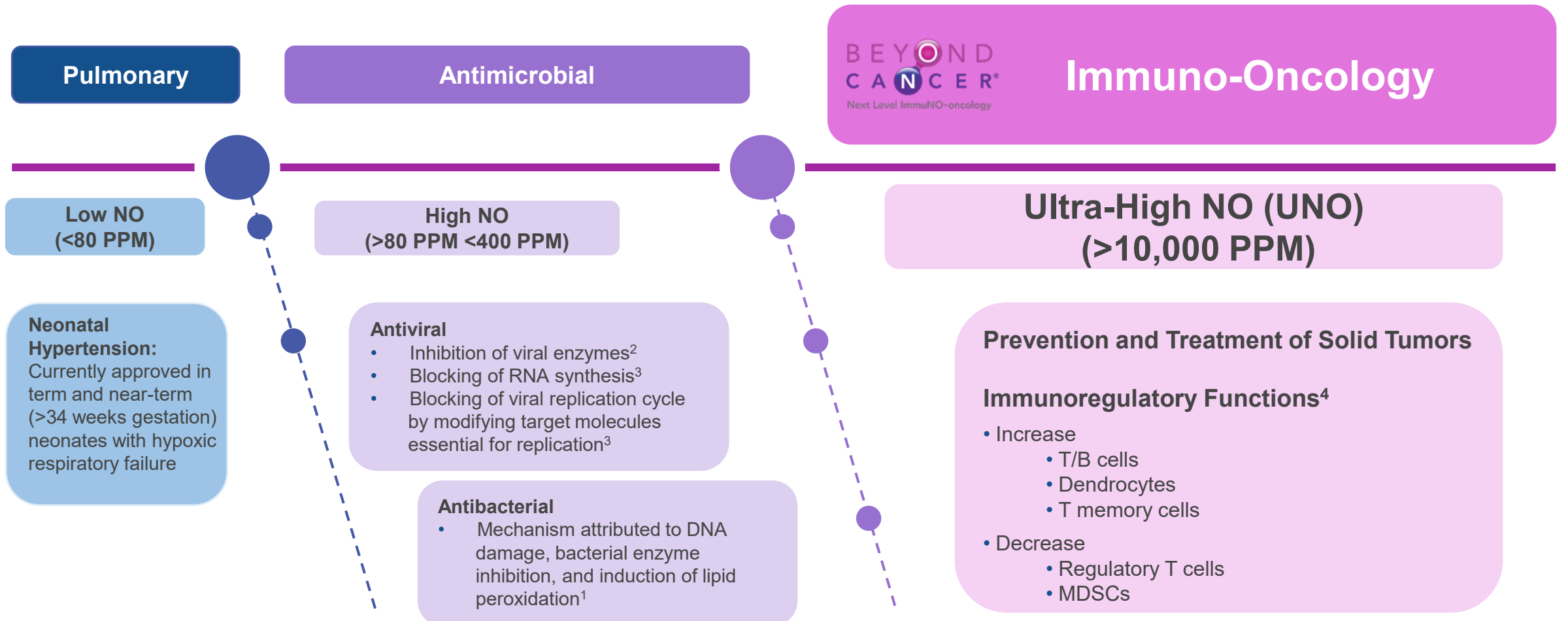
Combination therapy with immune checkpoint inhibitors (ICIs) to improve patient outcomes

## Patented Delivery Approach

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Differentiated MOA with 2 U.S. issued patents (expiry 2040) involving a novel delivery system

# Focused on UNO for the Treatment of Solid Tumors



1) Wink DA et al., Chemical biology of nitric oxide: Insights into regulatory, cytotoxic, and cytoprotective mechanisms of nitric oxide. Free Rad Biol Med 1998; (4-5): 434-56.

2) Saura, M., et al., An antiviral mechanism of nitric oxide: inhibition of a viral protease. Immunity, 1999. 10(1): p. 21-8

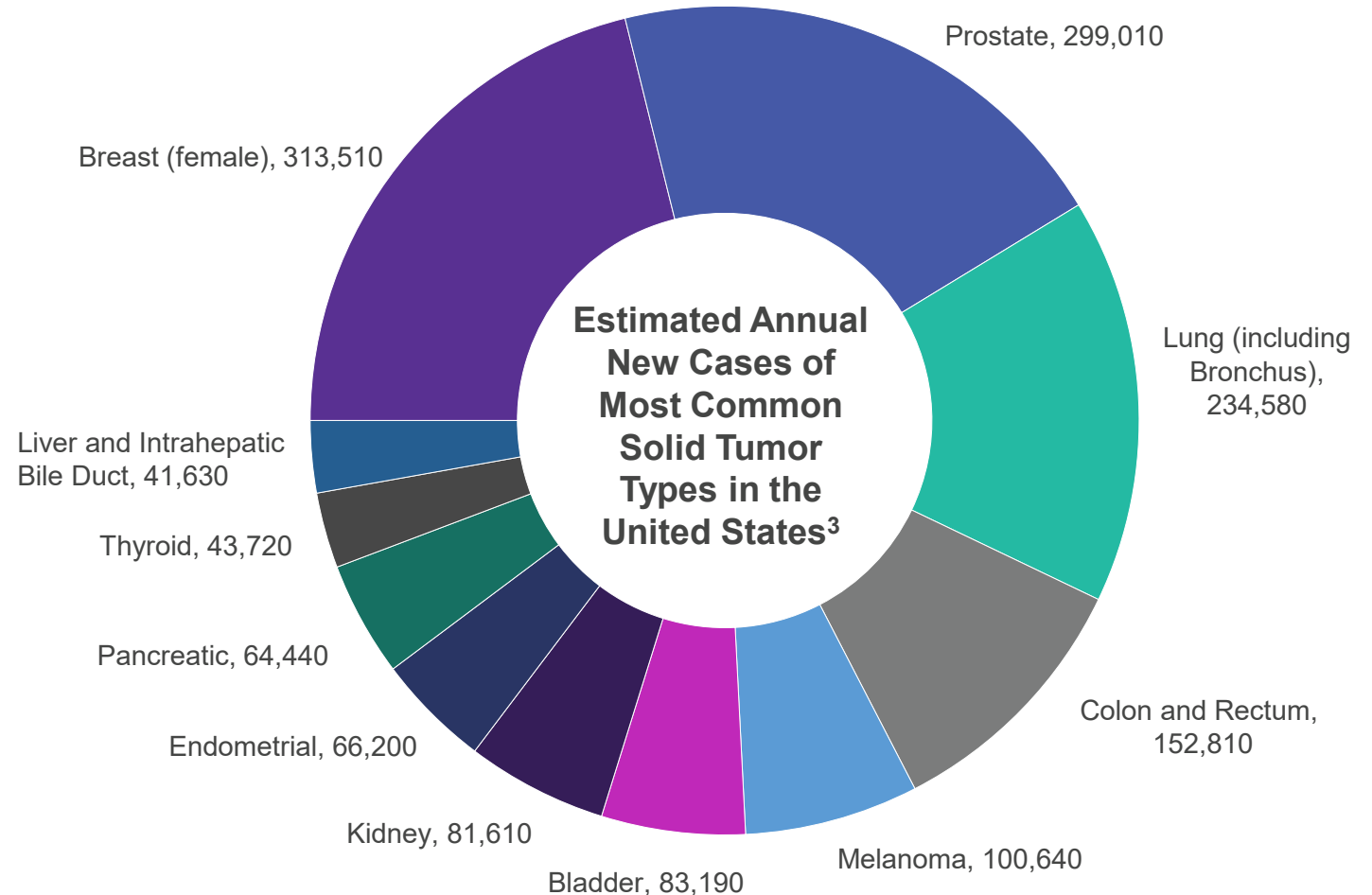
3) Akerström S et al. Nitric oxide inhibits the replication cycle of severe acute respiratory syndrome coronavirus. J Virol. 2005; 79(3):1966-9

4) 2023-10-30-SITC Poster Final.pdf (beyondcancer.com)

# Immunotherapy has Emerged as a Cornerstone Treatment for Solid Tumors

**Solid Tumors** represent approximately 90% of adult human cancers<sup>1</sup>, accounting for approximately 1.5 million annual new cases of the most common cancer types in the United States<sup>3</sup>

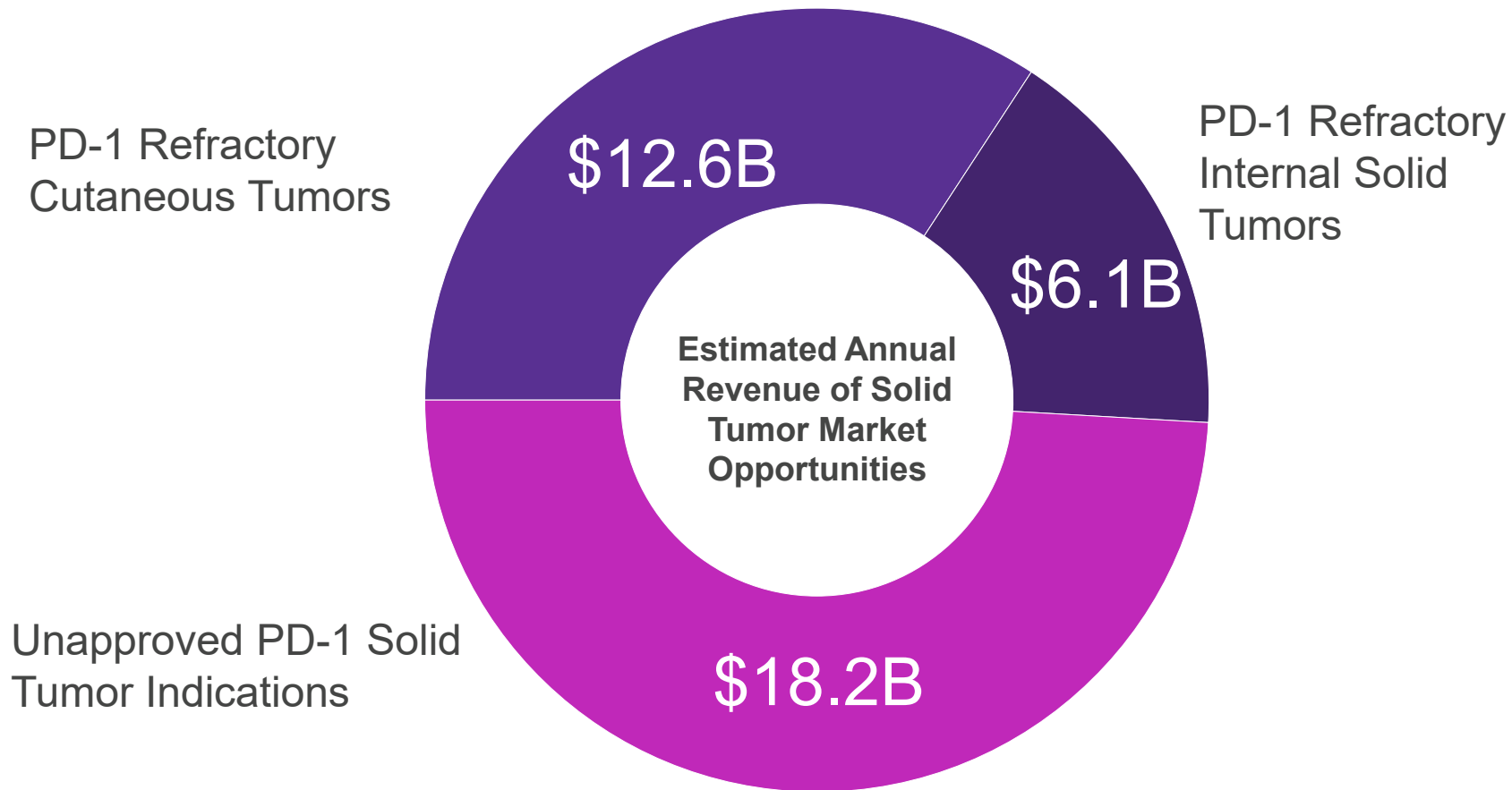
**Metastatic Disease** is responsible for 90% of solid tumor deaths<sup>2</sup>



1) Cooper GM. The Cell: A Molecular Approach. 2nd edition. Sunderland (MA): Sinauer Associates; 2000. The Development and Causes of Cancer. Available from: <https://www.ncbi.nlm.nih.gov/books/NBK9963/>  
2) Fontebasso Y, Dubinett SM. Drug Development for Metastasis Prevention. Crit Rev Oncog. 2015;20(5-6):449-473. doi: 10.1615/CritRevOncog.v20.i5-6.150  
3) According to the National Cancer Institute: <https://www.cancer.gov/types/common-cancers>. Accessed: April 15, 2024. Data as of March 7, 2023

# Commercial Opportunity

## *UNO + anti-PD-1*



# Proprietary UNO Delivery System Directly Targets the Tumor

## Novel system to deliver Ultra-high concentration Nitric Oxide (UNO)

- **Advantages**

- Ability to obtain significantly higher intra-tumoral NO concentrations than endogenous or NO donor systems
- Quick and simple procedure

- **Optimizing delivery to meaningfully improve ease of use**

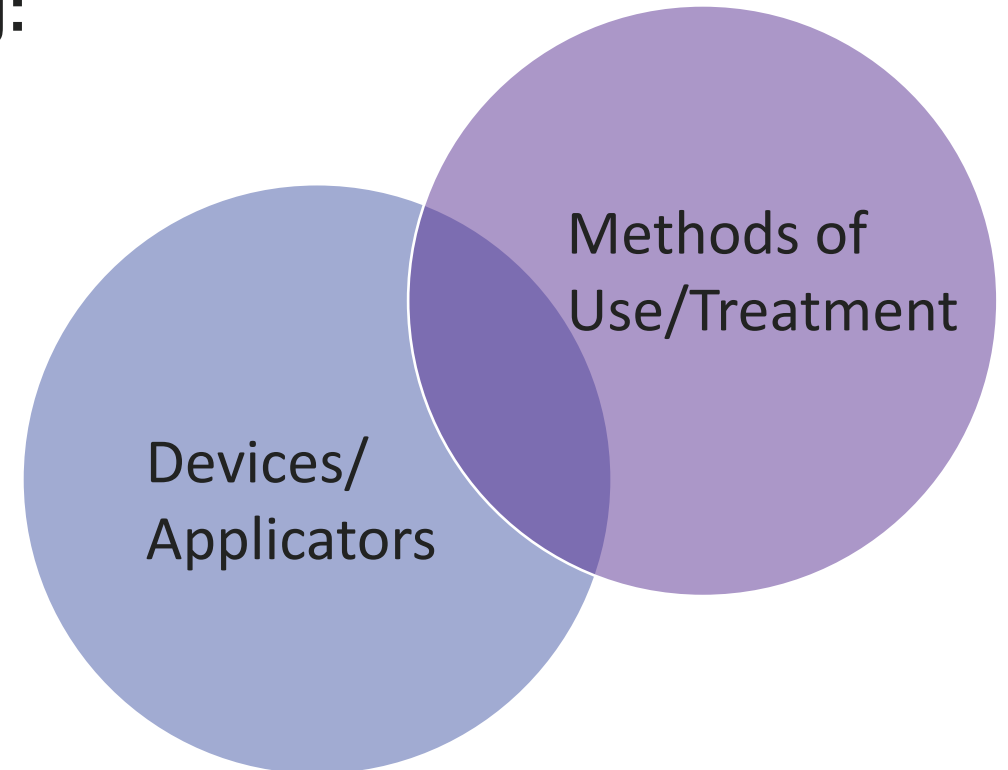
- Current high-volume system has produced promising results both preclinically and in Phase 1a
- A low-volume method has shown similar results in animals and will be introduced in the Phase 1b trial

- **Encouraging toxicity profile allows for potential combination with approved therapies to enhance clinical outcomes**



**Two issued U.S. patents (expiry 2040), with more pending from patent families including:**

- UNO monotherapy for the treatment of solid tumors
- UNO in combination with checkpoint therapies and other anti-cancer agents
- Delivery systems
- Delivery applicators





# Advancing Clinical Pipeline Using Lower UNO Volumes

Program	Initial Indication	3Q22	2024	2025	2026	2027
<b>Monotherapy</b>						
UNO101	Cutaneous / near cutaneous tumors <sup>1</sup>	Phase 1a				
<b>Combination Therapy</b>						
UNO201 + anti-PD-1	PD-1 resistant or refractory patients with cutaneous / near cutaneous tumors			Phase 1b		
UNO201 + anti-PD-1					Phase 2	

<sup>1</sup> Patients enrolled to date in Phase 1a: Melanoma, Squamous Cell Carcinoma, TNBC, mBC

UNO101: High Volume

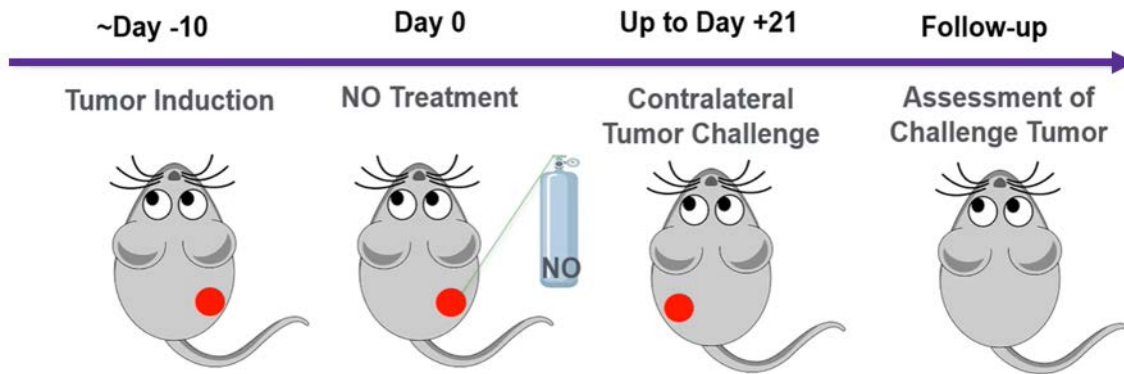
UNO201: Low Volume



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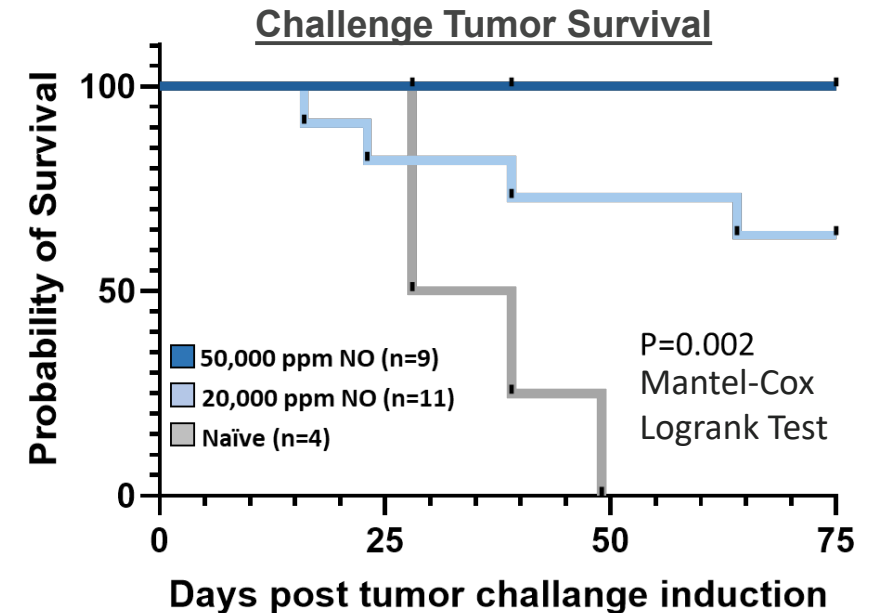
# UNO Preclinical Data Demonstrates Immune Response

# UNO in CT26 Challenge Tumors In Vivo Showed Evidence of Dose-Dependent Effects on Survival



## Challenge assay:

- CT26 study mice treated with 20,000 or 50,000 ppm NO for 5 minutes.
- Naïve mice inoculated with the same cancer cells served as an internal control.
- Up to 21 days post NO treatment, all mice were re-inoculated with colon cancer cells (CT26 cells) as a challenge tumor and survival was monitored.

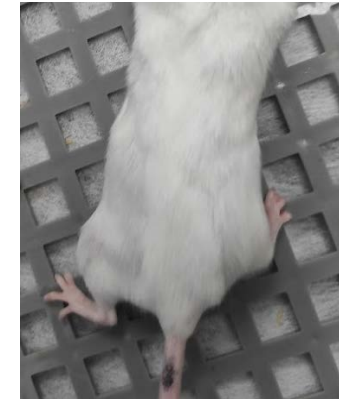
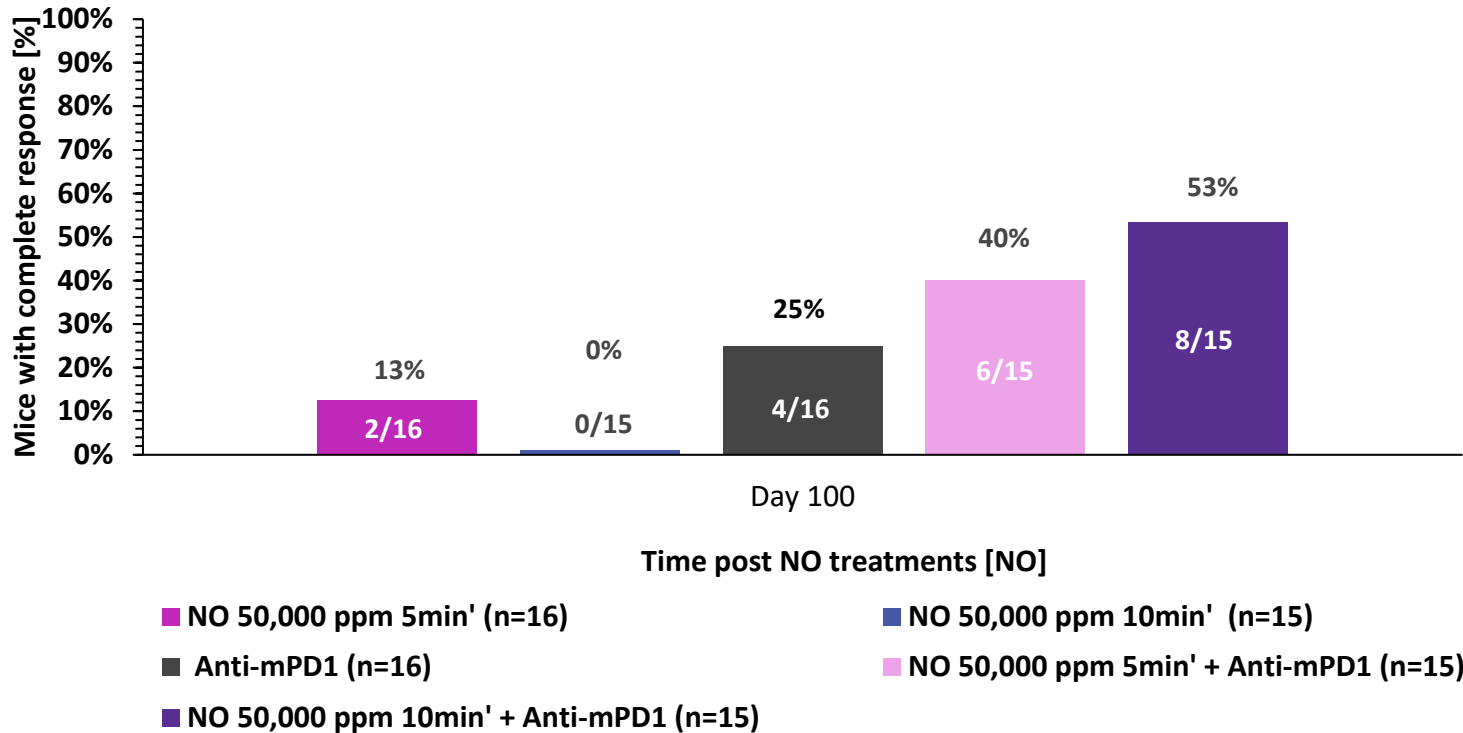


## Survival Results at Day 75:

- 100% of 50,000 ppm NO mice alive
- 64% of 20,000 ppm NO mice alive
- 0% of naïve mice alive

# UNO in Combination with Anti-mPD-1 Showed a Doubling of Tumor-Free Mice

## CT26 Primary and Secondary Tumor-free Mice



UNO+anti-PD-1  
Complete Response

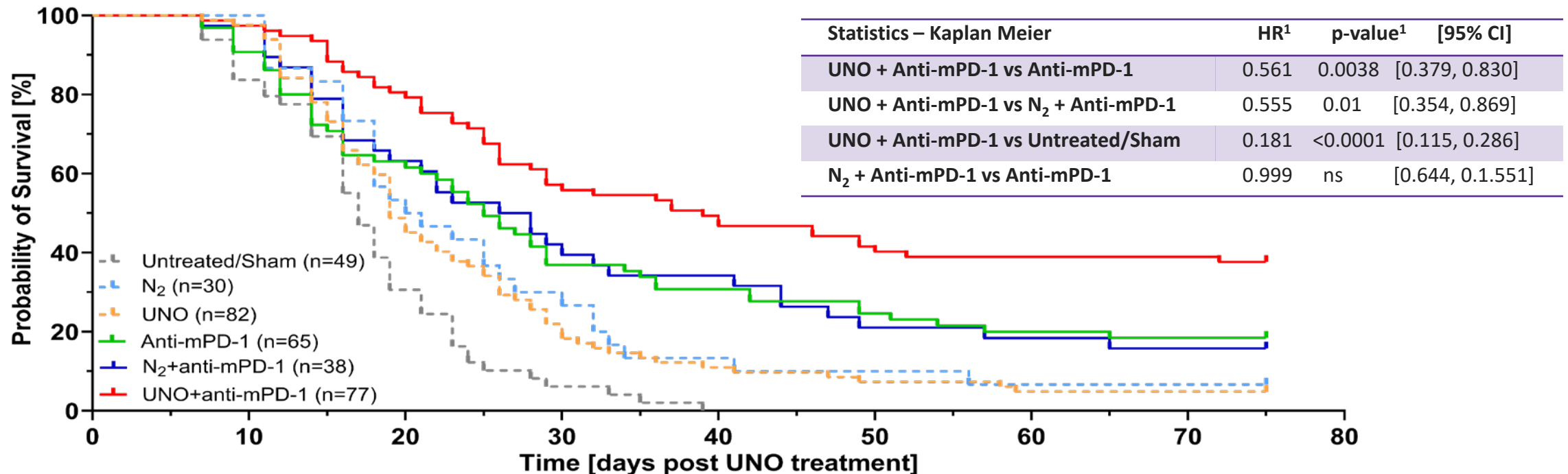


Control  
Primary &  
Secondary tumors

Statistical analysis: Fisher's Exact Test: P-value = 0.1489,  
Pairwise Treatment Group Comparison - 50,000 10 min + Anti-mPD1 vs Anti-mPD1

# Meta-Analysis: Combination of Single Dose UNO and Anti-mPD-1 Doubles Mice Survival

*The combination of Ultra-high concentration NO with anti-mPD-1 improved outcomes and mice survival compared to UNO or anti-mPD-1 alone, as UNO assists the immune system in overcoming anti-mPD-1 resistance.*



Pooled data across studies of 5 or 10-min UNO and anti-mPD-1 (5 or 10 mg/kg) treatment – survival data.

<sup>1</sup>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, at 0.2 LPM.

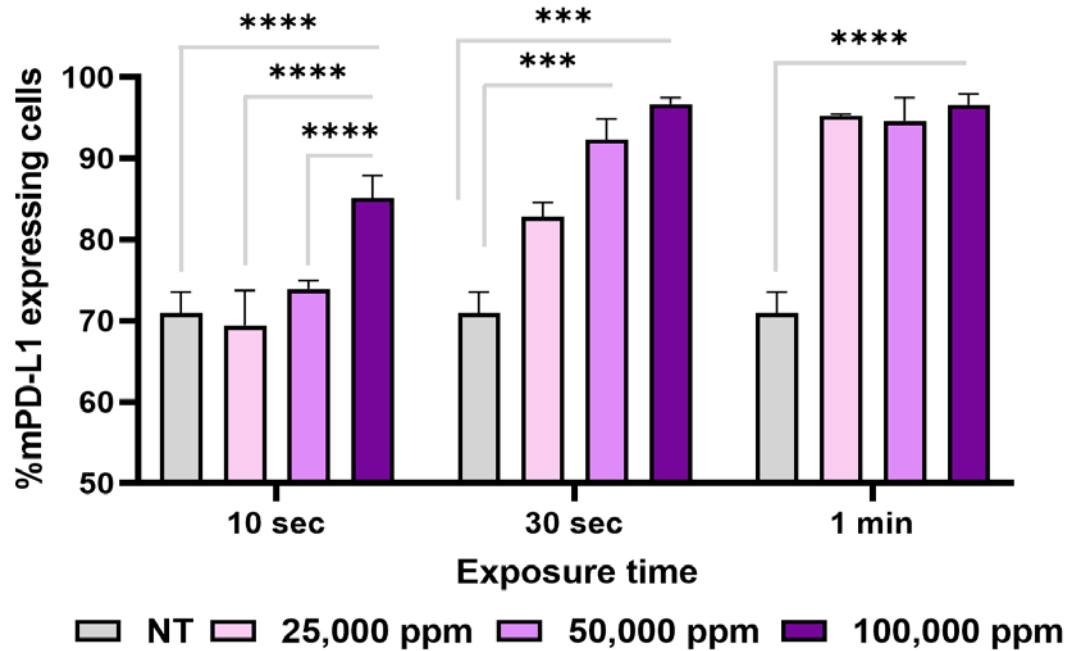
Anti-mPD-1 dosing started at days (-2) to (+2). 5 or 10 mg/kg doses injected every 2-3 days, 4-5 doses in total.

All studies were conducted under approved IACUC protocols.

Data presented at the EORTC-NCI-AACR Annual Meeting, October 2023

# UNO Upregulates mPD-L1 Expression by Day 5

## mPD-L1 expression in PI-negative CT26 tumor cells



- mPD-L1 expression 5 days after exposure to UNO
- Two-way ANOVA, multiple comparison test, \*\*\* $P < 0.001$ , \*\*\*\* $P < 0.0001$ .



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# UNO Clinical Data Corroborates Preclinical Observations

# Phase 1a Designed to Establish 3 Key Objectives

## Primary Objectives:

1. Determine safety profile
2. Determine maximum tolerated dose (MTD) and/or optimal biologically effective dose (OBD)
3. Recommend Phase 2 dose (RP2D)

**Secondary Objective:** Anti-tumor activity of single intra-tumoral escalating UNO101 dose per RECIST v1.1, iRECIST

**Exploratory Objectives:** Biomarkers predictive of response via itRECIST

## Major Eligibility Criteria

- ≥ 18 years of age
- ECOG PS 0 – 3
- **Unresectable, cutaneous or SQ primary or metastatic tumor<sup>1</sup>**
- Measurable disease
- Tumor 4.5 mm – 30 mm

**Part A: Dose Escalation**  
3 + 3 Scheme  
Follow-up to Day 21  
(Max N = 18)

**Cohort 1:** 25,000 ppm UNO101  
over 5 minutes  
(voluntary expansion to 6 patients)

**Cohort 2:** 50,000 ppm UNO101  
over 5 minutes  
(expansion to 6 patients)

**Cohort 3:** 100,000 ppm UNO101  
over 5 minutes

**MTD/OBD**



# Phase 1a Patient Characteristics

## Heavily Pre-Treated Population

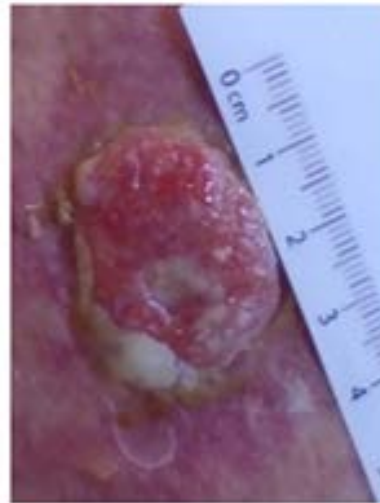
Baseline Characteristics (N=9)	N (%)	Mean	Min	Max
Age (yrs.)		60.1	34	81
<b># of All Prior Treatments (Medications, Surgeries, Radiation, etc.)</b>		<b>10.8</b>	<b>5</b>	<b>18</b>
# of Prior Medication Treatments		5.9	2	14
ECOG PS 0/1/2/3 (Day 1)	0 = 4 (44.4%) / 1 = 5 (55.6%)	--	--	--
Diagnosis				
• Squamous cell carcinoma	2 (22.2%)			
• Melanoma	2 (22.2%)	--	--	--
• Breast Cancer	3 (33.3%)			
• Triple Negative Breast	2 (22.2%)			

# Case Report: Early Response Observed with Single Dose UNO

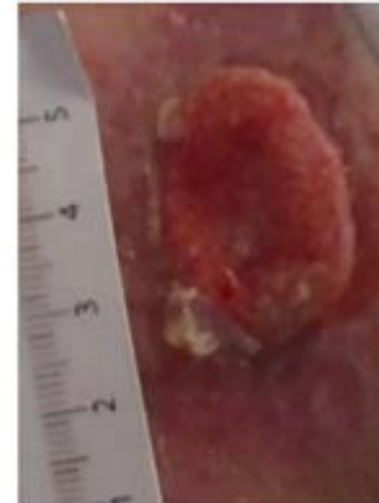
Data presented at the SITC Annual Meeting, November 2023

- 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**

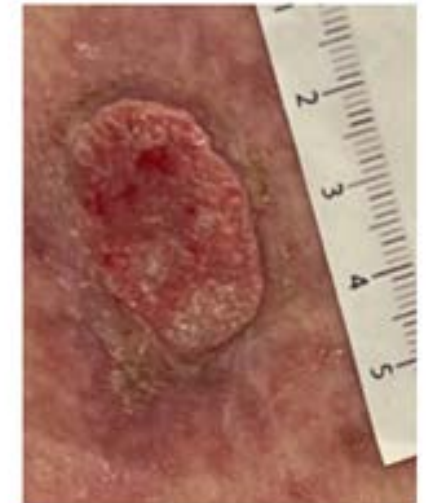
Treatment Day



Treatment Day +1



Treatment Day +7



# Case Report: Resolution of Radiation Dermatitis with Single Dose of UNO

Unpublished Data

- 34 y/o female with TNBC originally diagnosed in 2018
- Received:
  - 3 surgeries
  - 2 cycles of immunotherapy
  - 2 cycles of XRT



**Baseline**



**Day 1**



**Day 7**



**Day 21**

- Evidence of resolution of radiation dermatitis seen as early as Day 1
- Prior surgical scar is noticeably smaller by Day 21
- Biopsy of treated and adjacent lesions showed significantly lower proliferative index at Day 21 and no evidence of malignancy in the satellite lesion
- Increases in M1 macrophages and decreases in Tregs observed on Day 7

# Interim Phase 1a Biomarker Results

## Results Correlate with Preclinical Data

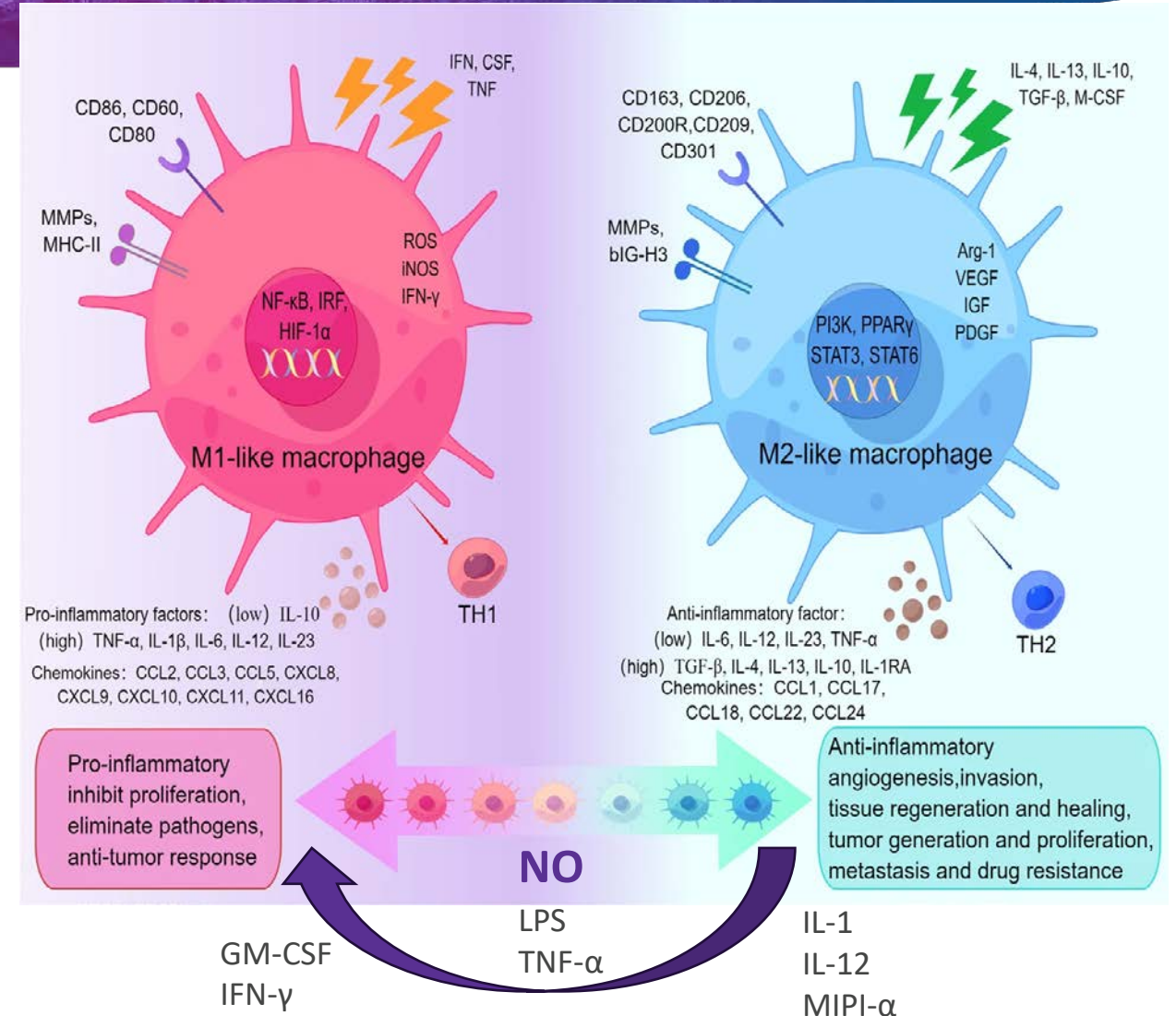
Systemic Effects	UNO Preclinical <sup>2</sup>	UNO Clinical <sup>1</sup> 25k ppm	UNO Clinical <sup>1</sup> 50k ppm
Cytotoxic T cells	↑ 14%	↑ 11%	↑ 12%
T Central Memory	↑ 161% (100k ppm NO)	↑ 241%	↑ 47%
Dendritic cells	↑ 112% (day 5)	↑ 168%	↑ 374%
MDSCs	↓ 78% (day 5)	↑ 78%	↓ 54%

UNO Clinical: 25k ppm UNO101, 5 minutes, Day 21 data  
UNO Preclinical: 50k ppm UNO101, 5 minutes, CT26 model, Day 7 data (unless otherwise noted)

1. Reported on May 31, 2024  
2. <https://beyondcancer.com/wp-content/uploads/2023/10/MOA-poster-EORTC-vFinal-5.pdf>

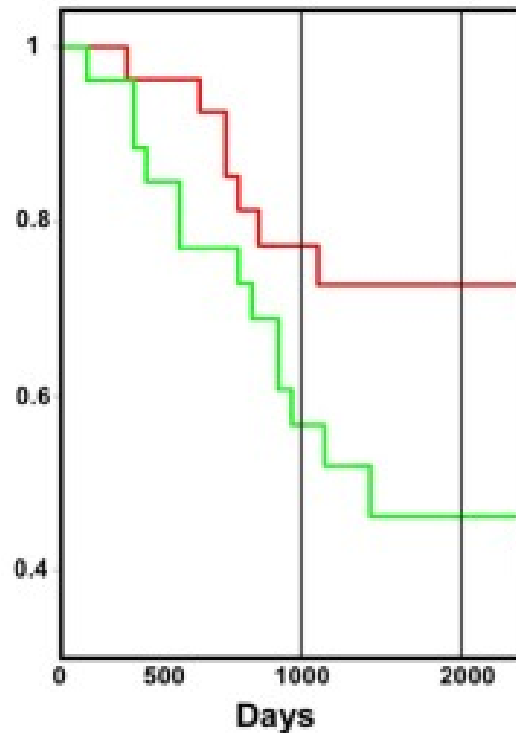
# M2→M1 Macrophage Re-Polarization

- M1 Macrophages are Anti-Tumor while M2 Macrophages are Tumorigenic
- M2 Macrophages can Re-Polarize to M1 Increasing the M1/M2 Ratio
- NO is a Potent Inflammatory Cytokine that Re-Polarizes Macrophages



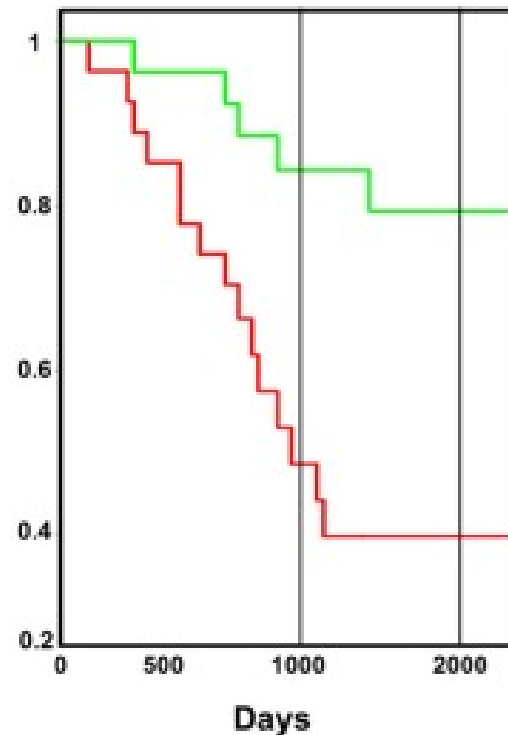
# M1/M2 Gene Expression Correlated with Survival in Many Cancers – ex. Osteosarcoma

M1 Gene Expression





HR: 0.02 (0-0.42)  
P-Value: 0.0131

M2 Gene Expression



HR: 754.07 (12.2-45515.9)  
P-Value: 0.0016

 = High Expression  
 = Low Expression

# Many Drug Targets Associated with Macrophage Re-Polarization

Phase 1	Phase 2	Phase 3
TLR3 – Ovarian	CD47 – CRC, NHL, HNSCC	TLR9 – Melanoma, NSCLC, HNSCC, Pancreatic, Prostate, HCC
TLR7 – HER2+	CXCL12/CXCR4 - Pancreatic	
TLR8 – Ovarian	CCL5/CCR5 – CRC	
CD40/CD40L – Solid Tumors	CCL2/CCR2 – NSCLC, HCC, Pancreatic	
STING – HNSCC, Melanoma, SCC,	CSF-1/1R Sarcoma, RCC, NSCLC, Pancreatic, CRC	
PI3K $\gamma$ – NSCLC, CRC, HNSCC, HCC, DLBCL		

**Bolded** indications are not currently approved for PD-1 therapy.

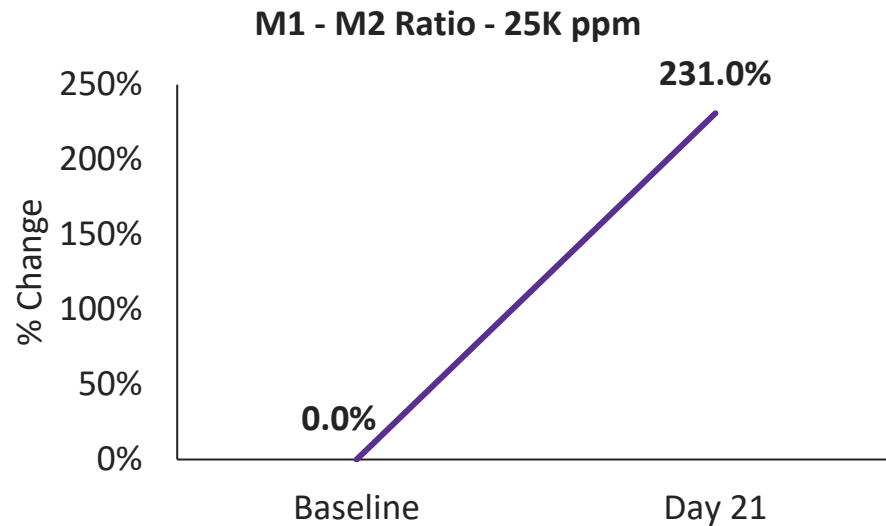
Source: Pu Y, Ji Q. Tumor-Associated Macrophages Regulate PD-1/PD-L1 Immunosuppression. Front Immunol. 2022 May 3;13:874589. doi: 10.3389/fimmu.2022.874589. PMID: 35592338; PMCID: PMC9110638.

Note: Clinical status as of 2022.

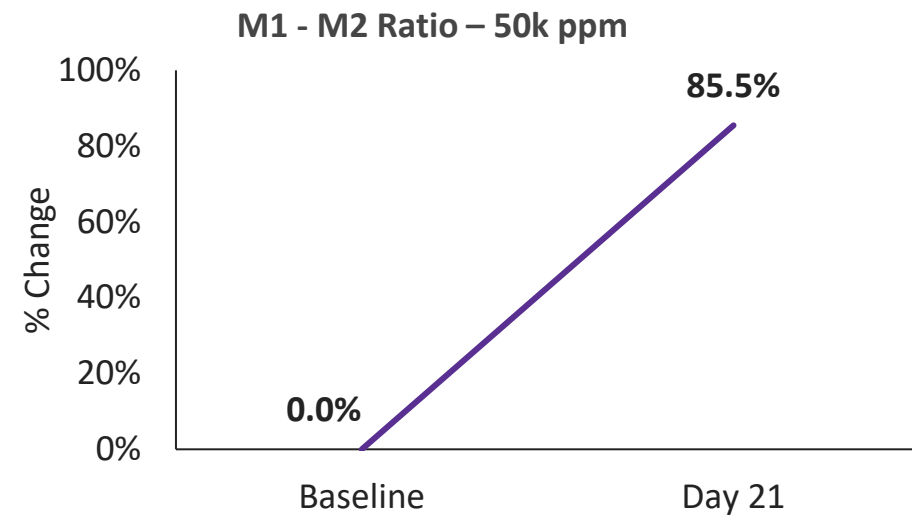
# M1-M2 Ratio

## Favorable Impact on M1/M2 Ratio in UNO Treated Patients

25,000 ppm (n=5)



50,000 ppm (n=3)



Note: n=5 in 25k ppm cohort – % change via geometric mean,  
n=3 in 50k ppm cohort average % change  
Calculated via systemic measurement of M1 and M2 reported values as a % of macrophages



# Treatment Related Adverse Events

## Mostly Grade 1

Cohort	Grade 1	Grade 3	Grade 4
25,000 ppm	Palmar-plantar erythrodysesthesia syndrome		
	Subcutaneous emphysema		
	Oxygen saturation decreased, dyspnea, nausea*		
			Hypoxia^
50,000 ppm	Hypotension, local subcutaneous emphysema		
	Fatigue, nausea, dizziness		
	Subcutaneous emphysema	Vasovagal#	

Notes:

\*Patient had 3.2L of fluid drained from lungs 1 week prior to treatment

^Declared not DLT per protocol criteria by Safety Review Committee

#Declared DLT per protocol criteria by the Safety Review Committee

# First in Human Data Support Favorable UNO Safety Profile and Demonstrate Proof of Concept

- Local administration of UNO is **well tolerated**
- **Immune biomarkers** demonstrate immunogenic response and compare favorably to previously published murine data
- **Demonstrated proof of concept with** early responses observed in a heavily pretreated patients
  
- Next Clinical Steps:
  - Advance to Phase 1b
  - **Combine with Immune Checkpoint Inhibitors (ICIs)**
  - Introduce repeat dosing

# Can we Achieve the Same Efficacy Using <1L of UNO?

## Advantages of Low Volume vs High Volume Method

- Reduce or eliminate potential risk of methemoglobinemia  
Nitric Oxide can bind to hemoglobin to produce methemoglobin
- Reduce or eliminate potential risk of air embolism
- Reduce or eliminate need for gas-related safety equipment  
Personal Protective Equipment, fume extractors, NO/NO2 gas detectors

# Low Volume Method: Pilot Study in Mouse Model

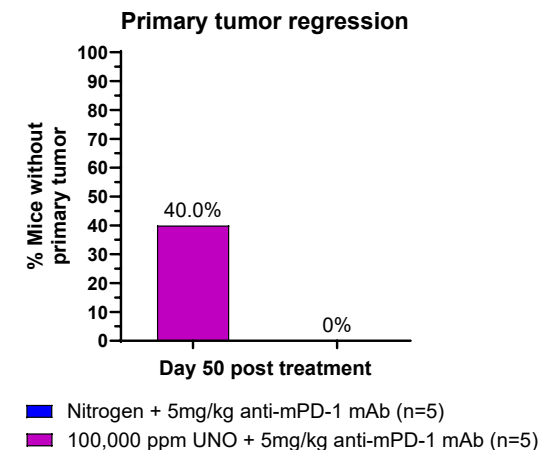
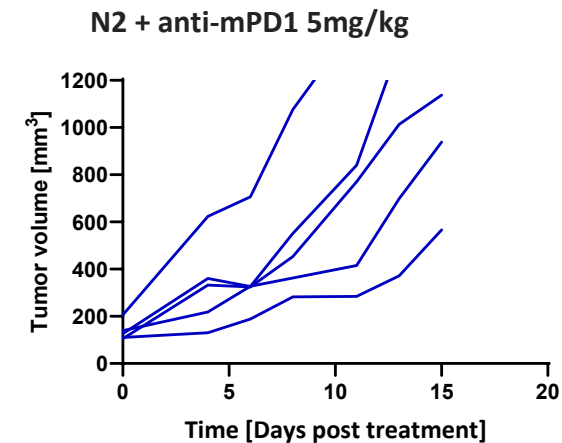
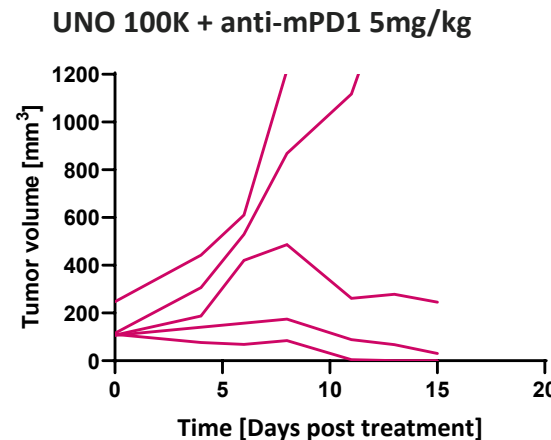
**Tumor Shrinkage is seen in 3/5 tumors in UNO vs. 0/5 in N<sub>2</sub> combo arms at Day 15**

## Experimental Conditions

- 100,000 ppm NO + anti-mPD1 vs. N<sub>2</sub> + anti-mPD-1 (5mg/kg)
- Treatment time: 2.5 min

## Results

- 60% of UNO treated tumors initially regressed
- 40% of UNO-treated tumors regressed through Day 50
- No safety events

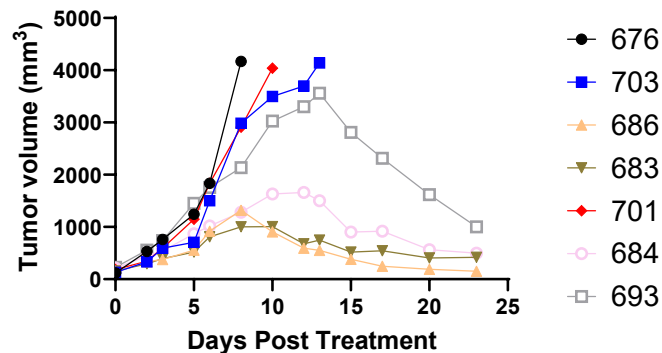


# Low Volume Method: Validated in Rat Model

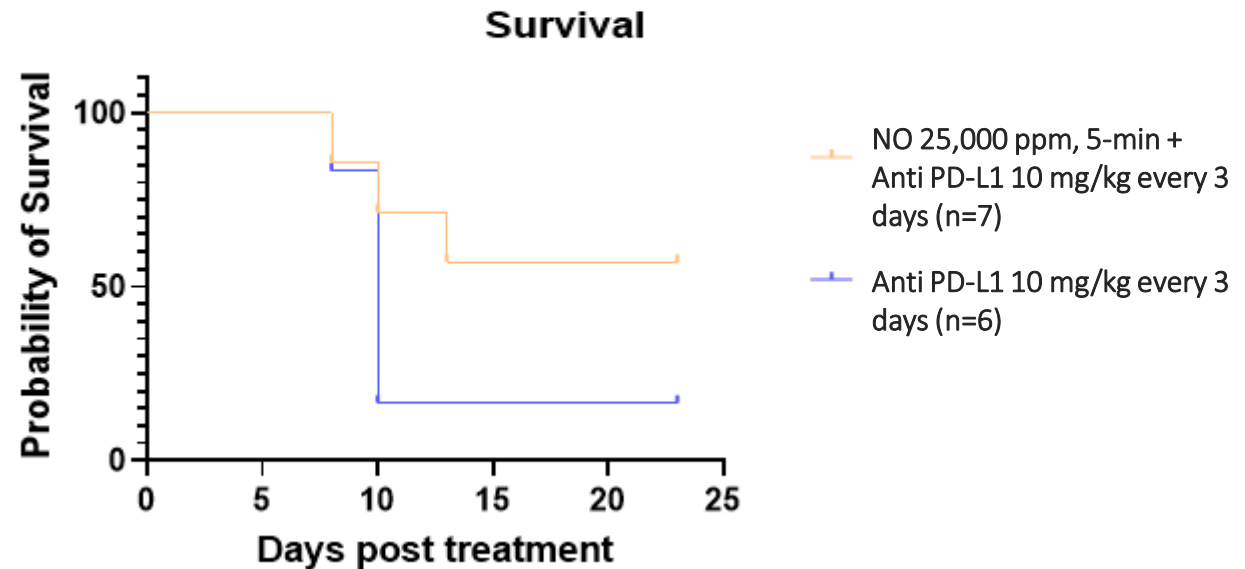
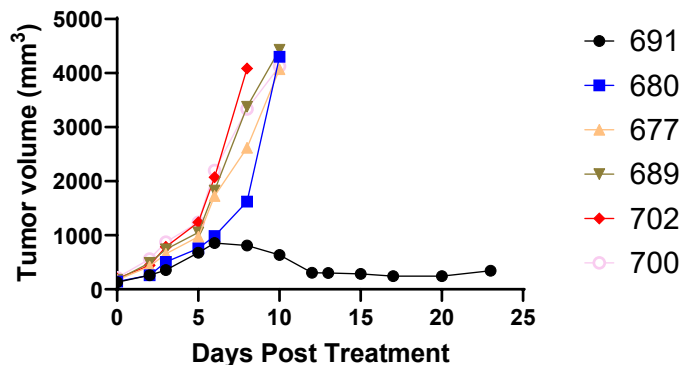
Tumor reduction in 4/7 tumors with UNO combo vs. 1/5 with Anti PD-L1

Day 23 survival advantage validates UNO's efficacy in a new animal species and tumor model

UNO + anti PD-L1 individual plots

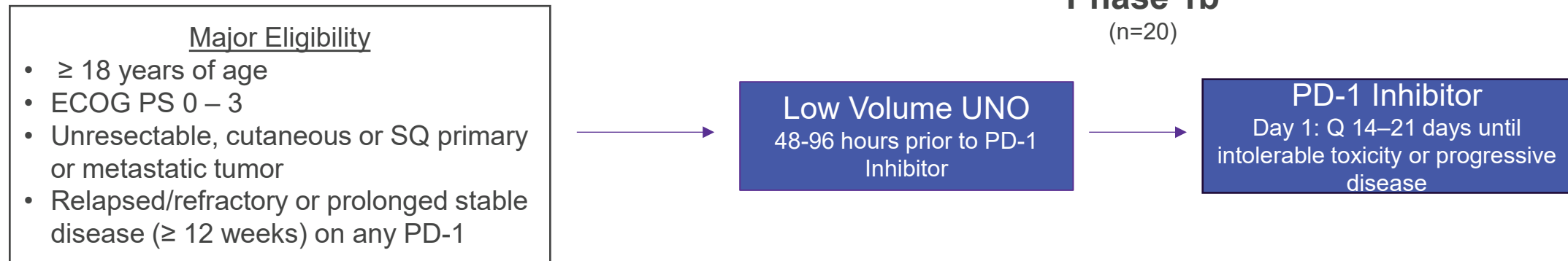


Anti PD-L1 individual plots



# Low Volume Phase 1b Protocol

**Hypothesis:** Can UNO therapy convert “cold tumor” → “hot tumor”



**Primary Objective:** To assess preliminary efficacy by objective response rate (ORR) and duration of response (DOR) per Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1, and secondarily immune-related RECIST (iRECIST).

**Secondary Objectives:** 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 adverse events, including immune related adverse events (irAEs).

**Exploratory Objectives:** To assess biomarkers that may be predictive of anti-tumor activity of an intratumoral UNO201 injection.

# Contact



Investor Relations

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