#723 Intratumoral Administration of Low Volume Ultra High-Concentration Nitric Oxide and Anti-rPD-L1 Treatment Leads to Prolonged Survival in MAT B III Tumor-Bearing Rats

BEYOND CANCER™ Next level immuNO-oncology

Hila Confino[1], Mark Rimkus[2], Selena Chaisson[1], Mark D. Pegram[3]

[1]Beyond Cancer, Rehovot, Israel and Atlanta GA, USA; [2]Beyond Air, Garden City NY, USA; [3]Stanford University School of Medicine, Stanford CA, USA

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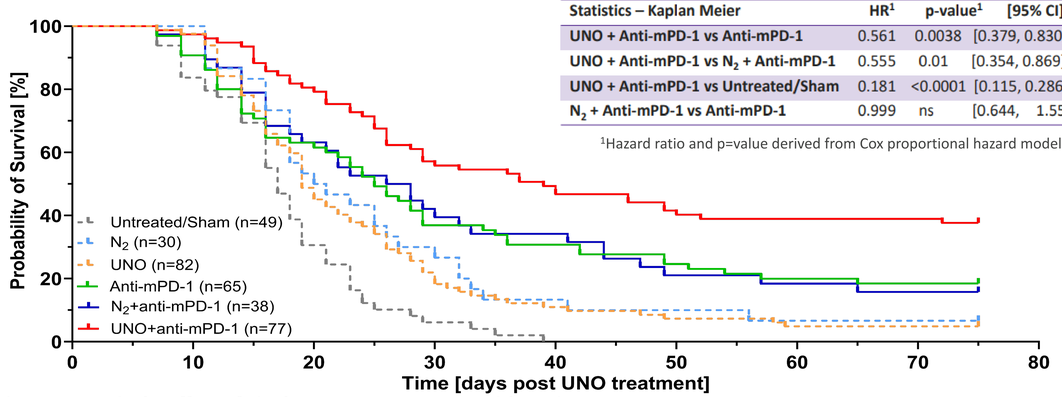
Background and Study Aims: In prior studies, we have used the mouse colon and breast tumor models, CT26 (Confino H 2023) and 4T1 (Confino H 2022) respectively, to assess the effect of ultra-high concentration nitric oxide (UNO) administered in high volumes (HV, 1 liter). The effects of UNO + immune check point inhibitors (ICIs) have also been evaluated in these mouse models and have demonstrated the combination increased survival (Epshtein Y 2023).



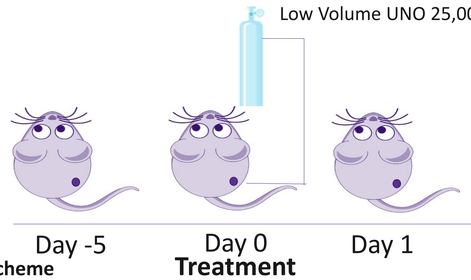
Statistics – Kaplan Meier	HR[1]	p-value[1]	[95% CI]
UNO + Anti-mPD-1 vs Anti-mPD-1	0.561	0.0038	[0.379, 0.830]
UNO + Anti-mPD-1 vs N_2 + Anti-mPD-1	0.555	0.01	[0.354, 0.869]
UNO + Anti-mPD-1 vs Untreated/Sham	0.181	<0.0001	[0.115, 0.286]
N_2 + Anti-mPD-1 vs Anti-mPD-1	0.999	ns	[0.644, 1.551]

[1]Hazard ratio and p=value derived from Cox proportional hazard model

Figure 1: Survival – Effect of Single HV UNO Treatment with Anti-mPD-1

In this pilot study, we evaluated whether low volume UNO (LV, < 100 mL) is effective in a rat breast tumor model. Fischer Rats, bearing a subcutaneous MAT B III breast tumor, were treated with LV UNO in combination with anti-rat Programmed Death-Ligand 1 monoclonal antibody (rPD-L1).

Methods: The combination of LV UNO and anti-rPD-L1 was assessed in MAT B III tumor-bearing rats.



Follow-up:
- Primary tumor volume
- Survival

Anti-rPD-L1 10 mg/kg dosed every third day, beginning on either Day –5 or Day 1 for a total of up to six doses.

Figure 2: Assay Scheme

Results: LV UNO and Anti-rPD-L1 Doubled Survival by Day 37 versus Anti-rPD-L1 Alone

Anti-rPD-L1 mAb in combination with either 25,000 ppm or 100,000 ppm UNO resulted in prolonged survival.

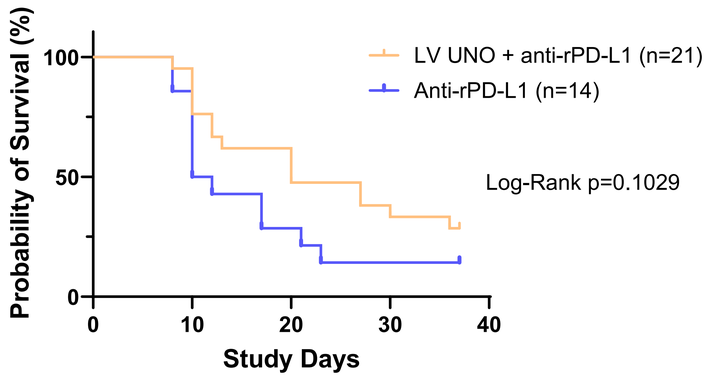


Figure 3: Survival Post UNO and Anti-rPD-L1 Treatment

Results: LV UNO and Anti-rPD-L1 Slowed Tumor Growth versus Anti-rPD-L1 Alone

Anti-rPD-L1 mAb in combination with either 25,000 ppm or 100,000 ppm UNO resulted in inhibition of MAT B III tumor growth.

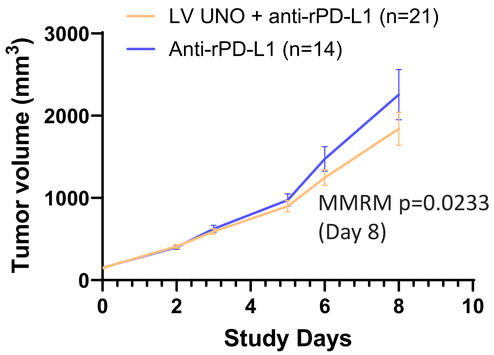


Figure 4: Tumor Growth Curve Until First Death

Conclusions: The combination of UNO with anti-rPD-L1 doubled survival by Day 37 compared with anti-rPD-L1 alone in MAT B III tumor bearing rates. Moreover, low volume UNO increases the efficacy of immune checkpoint inhibitors (anti-rPD-L1) as demonstrated by improved tumor inhibition. LV UNO may confer an improved safety profile compared to HV UNO given the marked reduction of gas delivered. The optimal LV UNO dose and administration schedule relative anti-rPD-L1 administration remains under investigation.

References: Confino H et al. Cells 2023, 12: 2439; Confino H et al. Cancer Cell International 2022, 22:405; Epshtein Y 2023 AACR-NCI-EORTC.