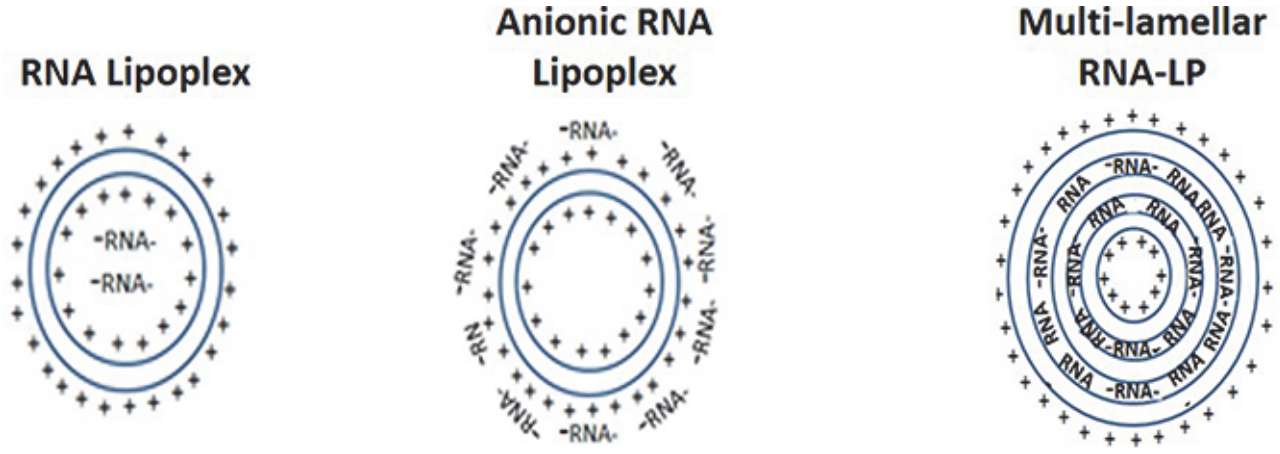
772 NOVEL RNA-NANOPARTICLE VACCINE FOR THE TREATMENT OF EARLY MELANOMA RECURRENCE FOLLOWING ADJUVANT ANTI-PD-1 ANTIBODY THERAPY

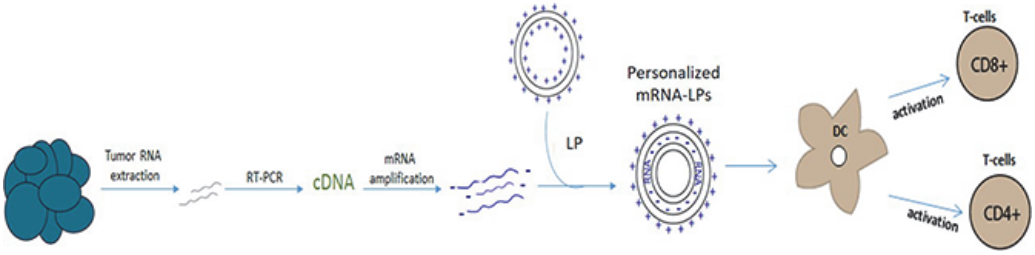
[1]Bently Doonan*, [1]Christiana Shaw, [2]Ji-Hyun Lee, [1]Eugenio Manso, [1]Hector Mendez-Gomez, [1]Christina Von Roemeling, [1]Duane A Mitchell, [1]Elias Sayour. [1]*University of Florida, Gainesville, FL, USA*; [2]*University of Florida Health Cancer Center, Gainesville, FL, USA*

Background Melanoma is an increasing public health concern. Immune checkpoint inhibitors (ICI) has revolutionized the treatment of advanced melanoma. Unfortunately, in the adjuvant setting, up to 30% of subjects have disease recurrence within 1 year of treatment. Previous studies have shown that subjects who progress while on adjuvant ICI, or soon after completion, have a more aggressive course of disease that responds poorly to subsequent immunotherapy. One reason for the failure of ICI in the post adjuvant setting is the immune suppressive nature of the tumor microenvironment (TME) and lack of professional APC activation. These APCs remain in an inert state unable to present tumor antigens for immune detection due to lack of innate immune activation and inhibition from myeloid derived suppressor cells (MDSCs). We have developed a novel RNA-lipid particle (RNA-LP) vaccine that simultaneously penetrates and reprograms the TME while inducing a tumor specific adaptive response (figure 2). This vaccine utilizes novel engineering design that layers tumor derived mRNA into a lipid-nanoparticle 'onion-like' package along with pp65 full length lysosomal associated membrane protein (LAMP1) mRNA (figure 2). These RNA-LPs localize to the TME and activate multiple innate pathways thereby activating APCs and suppressing the function of MDSCs (figure 3). In this study we propose the use of subject derived RNA-LP vaccine in patients who progress on, or soon after completion of adjuvant ICI. We propose that through re-priming of the antitumor immune response and alteration of the TME we can restore the efficacy of ICI therapy. If effective, this treatment will revolutionize the management of this aggressive subset of melanoma. This study will also gather information into the mechanisms of early ICI resistance, identify novel biomarkers of innate resistance and response to treatment, and provides a cutting edge, personalized immunology approach to melanoma treatment.

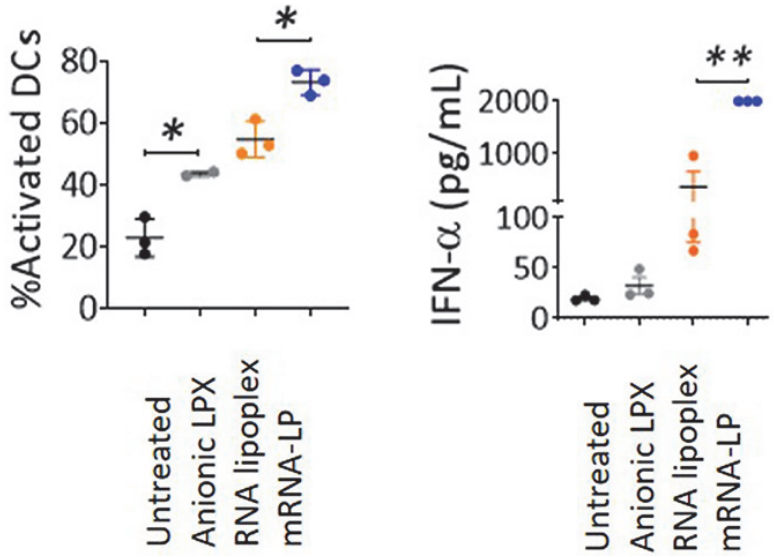
Methods We have designed a 3+3 design phase I clinical trial (NCT05264974) assessing the manufacturing feasibility, safety, and maximum tolerated dose of RNA-LP vaccines in melanoma patients with early adjuvant ICI failure. Patients will receive a 3-part vaccine series, 2 weeks apart at time of progression then resume ICI therapy (figure 4). Major eligibility criteria include progression on ICI therapy or within 6 months of completion of adjuvant therapy. A minimum of 6 and maximum of 18 subjects will be treated. Secondary endpoints include overall response rate (ORR) and progression free survival rate (figure 5). Exploratory analysis will investi-



Abstract 772 Figure 1 Different RNA loaded lipid-particle formulations. LPs or liposomes have been developed to protect nucleic acid delivery in vivo. (Left) RNA lipoplexes were first developed with mRNA persevered in the lipid core and a net positive charge located on the outer surface. (Middle) Alternatively, anionic lipoplexes have been developed with an excess of RNA tethered to the surface of bi-lamellar liposomes. (Right) Our lab has developed multi-lamellar RNA-LPs with several layers of mRNA contained inside a tightly coiled liposome with alternating layers of positive/negative charge. This design maximizes the amount of mRNA that can be loaded into each particle.

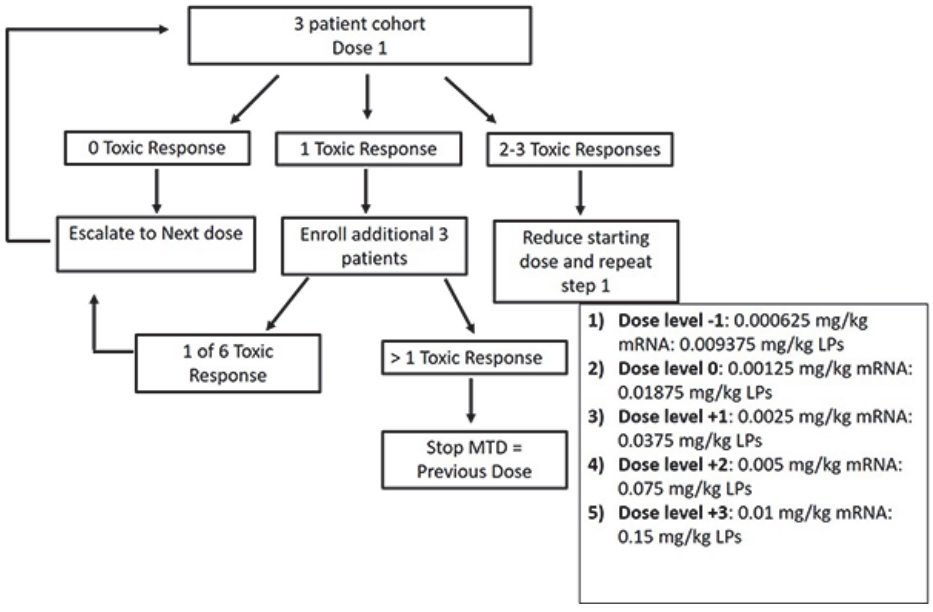


Abstract 772 Figure 2 Generation of personalized tumor mRNA loaded LPs: From as few as 100–500 biopsied tumor cells, total RNA is extracted and a cDNA library is generated from which copious amounts of mRNA (representing a personalized tumor specific transcriptome) can be amplified. Negatively charged tumor mRNA is then encapsulated into multi-lamellar LPs. LPs encapsulate and coil RNA through electrostatic interactions before intravenous delivery for uptake by DCs in lungs and in reticuloendothelial organs (i.e. liver, spleen and lymph nodes). The RNA is then translated and processed by a DC's intracellular machinery for presentation of peptides onto MHC Class I and II molecules, which activate CD4 and CD8+ T cells.

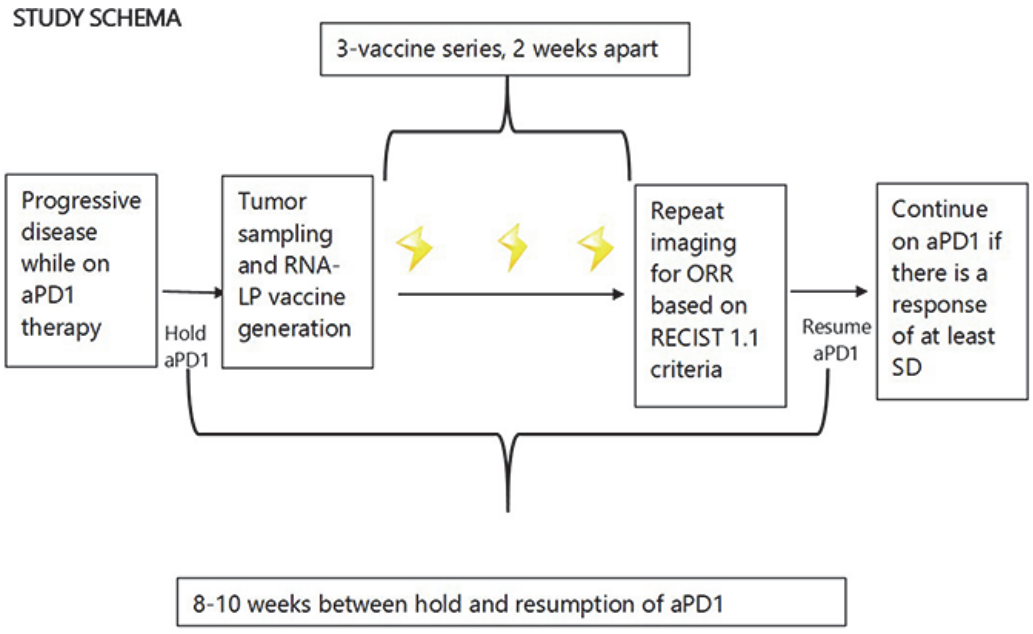


Abstract 772 Figure 3 Multi-lamellar RNA-LP mediate increased DC activation and IFN-α release. RNA/anionic lipoplex (LPX) or RNA-LPs were administered once weekly (x3) and spleens were harvested one week later for assessment of activated DCs (left). Serum was drawn 6h after the first vaccine for IFN-α assessment by ELISA (right) (*p<0.05, Mann-Whitney test).

Fig. 12



Abstract 772 Figure 4



Abstract 772 Figure 5

gate the TME through single cell analysis pre and post vaccine series.

Trial Registration Novel RNA-nanoparticle Vaccine for the Treatment of Early Melanoma Recurrence Following Adjuvant Anti-PD-1 Antibody Therapy ClinicalTrials.gov Identifier: NCT05264974

Ethics Approval This trial has been approved by the University of Florida Institutional Review Board IRB202200462 Novel RNA-nanoparticle vaccine for the treatment of early melanoma recurrence following adjuvant anti-PD-1 antibody therapy- UF-CUT-001.

http://dx.doi.org/10.1136/jitc-2023-SITC2023.0772