Novel Controlled Delivery of Potent Anti-Cancer Immunotherapy Directly to Deep Visceral Lesions

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Background

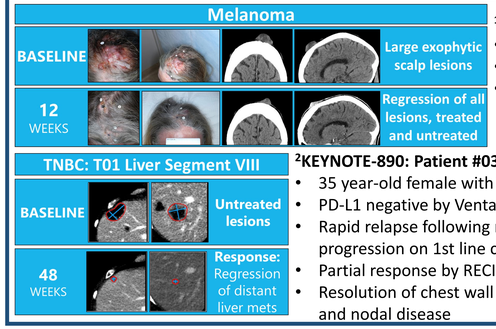
Intratumoral immunotherapies continue to demonstrate clinical utility in treating various cancers. In particular, intratumoral electroporation of plasmid IL-12, tavokinogene telseplasmid (TAVO™), has been administered in clinical trials to over 200 patients to safely treat metastatic melanoma, Merkel cell carcinoma, triple-negative breast cancer (TNBC), and squamous cell carcinoma of the head and neck (SCCHN) with longitudinal biomarker data supporting immunological and clinical responses in treated and untreated tumors. Notably, responses in untreated tumors of visceral organs such as liver and lung have been observed. While the current delivery platform is restricted to treating these cutaneous and subcutaneous lesions, here we describe a next-generation intratumoral delivery platform that provides treatment of internal or visceral lesions. This platform comprises novel access applicators, both rigid and flexible catheter-based, as well as an advanced reversible low-voltage electroporation generator (APOLLO), capable of detecting differences in tissue impedance and providing the physician validation of applicator placement in the appropriate target. The applicator options will enable the ability to use a variety of interventional and surgical approaches to access a wide variety of lesions, such as distal lung metastases (flexible catheter-based) and primary and metastatic liver tumors (rigid-based). This is clinically significant because many of these cancers are difficult to reach and directly deliver immunotherapy.

Intratumoral Electroporation of IL-12 (TAVO)

IL-12 is a potent immunomodulatory cytokine that, when delivered intratumorally via electroporation, can generate local and systemic immune responses that effectively convert immunologically cold tumors to hot tumors. Providing IL-12 intratumorally avoids the toxicities associated with systemic IL-12 delivery while still enabling the regression of both treated and untreated lesions throughout the body. Our electroporation device, currently involved in several clinical trials (e.g. KEYNOTE-695: melanoma and KEYNOTE-890: TNBC), consists of a generator and an applicator capable of reaching lesions no more than 1.5cm from the surface of the skin.

1 Intratumoral injection of TAVO
2 Intratumoral electroporation delivers TAVO into the cells
3 IL-12 is expressed and secreted
4 Local inflammation and T cell education
5 Systemic anti-tumor immune response

Clinical Trial Experience -Responses in Treated and Untreated Tumors



[1]KEYNOTE-695: Patient 2

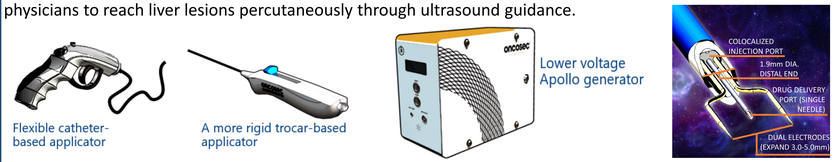
- 71 year old female with stage IVA melanoma
- Complete response (no longer being treated)
- Prior treatment with checkpoint therapies single agent and combination (17 cycles).

[2]KEYNOTE-890: Patient #03

- 35 year-old female with TNBC
- PD-L1 negative by Ventana SP-142 and Dako 22C3
- Rapid relapse following neoadjuvant chemotherapy and rapid progression on 1st line chemotherapy
- Partial response by RECIST v1.1 with a 66% reduction in SLD
- Resolution of chest wall disease and regression of distant hepatic and nodal disease

Visceral Lesion Applicator (VLA)

Tumors located inside the body, including liver (e.g. hepatocellular carcinoma) and lung, have unique challenges. Patients are often diagnosed late when treatment options are limited. Current treatment options that change tumors from immunologically 'cold' to 'hot' do not drive strong systemic responses and ablative solutions can often lack efficacy especially when controlling metastatic tumor burden. Based on encouraging and consistent data with TAVO and a clear unmet demand, we designed a platform to reach visceral lesions. In conjunction with the APOLLO generator, the flexible, catheter-based applicator can be fed through a bronchoscope to enable physicians to reach lung lesions in a less invasive manner; whereas the rigid, trocar-based applicator allows physicians to reach liver lesions percutaneously through ultrasound guidance.

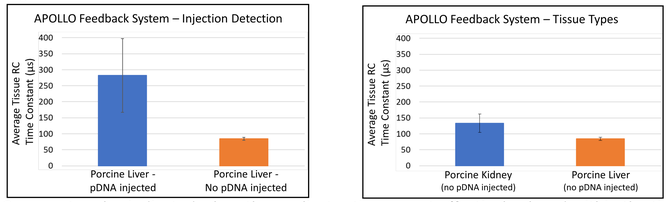


The drug delivery and electroporation process with the VLA works through the following steps:

1. Under conscious sedation or general anesthesia, the applicator is inserted into the target lesion of a patient.
2. The three-pronged end of the applicator is extended, and therapy is given through the central needle portal.
3. A foot pedal connected to the generator is used to initiate the delivery of 8 rapid, low voltage pulses through the outer prongs of the applicator tip. This step achieves a reversible electroporation (EP) event.
4. Within the EP area, small pores temporarily form in cell membranes, which allow the therapy to enter the cells. The small pores then automatically close without cellular damage, keeping the therapy inside.
5. Concurrently with the above biological response in Step 4, the applicator prongs are retracted, and the applicator is removed from the patient.

APOLLO Generator Feedback System

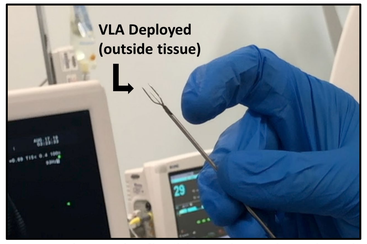
In these feasibility studies at the CRF Skirball Center for Innovation, our surgeons successfully and safely reached the target organs, deployed the applicator tip, and performed EP events. Utilizing a proprietary algorithm and porcine tissue impedance properties, the APOLLO generator was able to output the RC time constant of any given tissue. The RC time constant is a complex measurement used to optimize the transfection efficiency of EP and is theoretically related to the optimal electrical energy required by the target treatment site to experience EP. Preliminary data highlighted in the left graph, suggests that the APOLLO generator can distinguish RC time constants associated with the presence or absence of pDNA during electroporation of the liver. Additionally, the right graph focuses on RC time constant trends between tissue types, highlighting the possibility of differentiating between porcine kidney and liver and ultimately between healthy tissue and a local tumor.

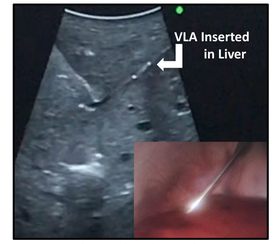


The APOLLO generator also indicated when the applicator tip was not effectively placed within the tissue. This safety feature allowed the physician to adjust the surgical placement and, in conjunction with imaging, confirm correct applicator placement in the target tissue. Collectively, these results demonstrate a promising treatment modality for delivering immunotherapy in a targeted, tissue-specific manner.

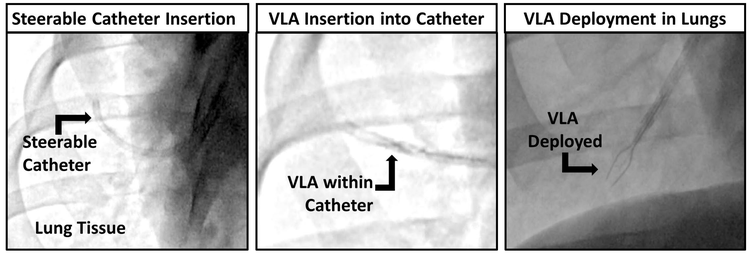
VLA in Lung and Liver of Live Porcine Model

Three device feasibility studies were performed at the CRF Skirball Center for Innovation using healthy, live, female Yorkshire domestic pigs. For all studies, subjects were placed under general anesthesia and monitored in accordance with an approved IUCAC protocol. Liver parenchyma was accessed via laparoscopy and rigid-based applicator placement confirmed via ultrasound. Following confirmation of placement, the applicator tip (injection port and electroporation tines) was deployed and electroporation was performed using the APOLLO generator. No adverse effects were seen on the pig during or after electroporation.





During lung procedures, the flexible, catheter-based applicator was inserted through a bronchoscope and a steerable catheter. The steerable catheter was directed towards peripheral lung parenchyma utilizing fluoroscopy. Following confirmation of applicator placement in lung, the applicator tip (injection port and electroporation tines) was deployed.



Conclusions/Acknowledgements/References

These studies successfully demonstrated the ability of both applicator types (flexible, catheter based and rigid, trocar based) to access target organs, while initial data from the feedback system embedded within the platform detected and recorded trends in impedance values between the different tissue types. We will next look to commence a safety study in an appropriate animal model to obtain the necessary data for filing with the FDA, allowing for initiation of a phase 1 human trial using this platform in combination with TAVO to target liver tumors. Based on the findings in this feasibility study, we will also explore the use of a flexible catheter-based applicator in conjunction with cone beam CT-guided bronchoscopy to treat lung cancer.

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References: [1] Society for Immunotherapy of Cancer 2018 poster (Atkinson *et al*); [2]San Antonio Breast Cancer Symposium 2019 poster (Telli *et al*)
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