Can an intratumoral DNA-encoded immunotherapeutic device platform currently used in the management of cutaneous lesions be scaled in size to function in the treatment of visceral tumors through image-guided techniques?

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OBJECTIVE

The mobilization of the immune system as a therapeutic strategy has emerged as a transformative approach to the treatment of cancer. Intratumoral injection of plasmid IL-12, tavokinogene telseplasmid (TAVO), and co-localized reversible electroporation has demonstrated safe and promising results in the over 200 patients enrolled in trials for melanoma (KEYNOTE-695), breast cancer (KEYNOTE-890), and SCCHN.

This current delivery platform uses an applicator capable of reaching lesions no more than 1.5cm at or below the skin. Here, we evaluated the feasibility and performance of an applicator capable of delivering and electroporating DNA-based immunotherapy directly into the liver, lung, bone, and pancreas in a large animal model, thus paving the way for future visceral lesion treatment in humans.

INTRATUMORAL ELECTROPORATION OF IL-12 (TAVO)

IL-12 is a potent immunomodulatory cytokine that, when delivered intratumorally via electroporation (EP), 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.

1 Intratumoral injection of TAVO

2 Intratumoral electroporation delivers TAVO into the cells

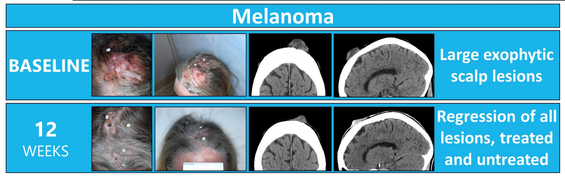
3 IL-12 is expressed and secreted

4 Local inflammation and T cell education

5 Systemic anti-tumor immune response

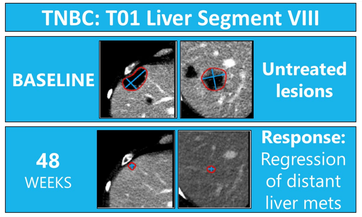
CLINICAL TRIAL EXPERIENCE -RESPONSES IN TREATED AND UNTREATED TUMORS

[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).

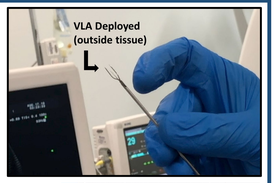
[2]KEYNOTE-890: Patient #03 (35year old female with TNBC)



- 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

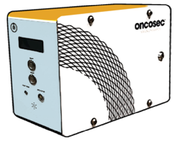
VISCERAL LESION APPLICATOR (VLA)

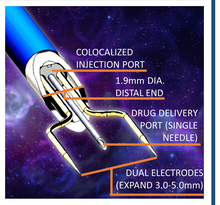
Tumors located inside the body have unique challenges. Patients are often diagnosed late when treatment options are limited. Current treatment options that change tumors from immunologically 'cold' to 'hot' do not drive strong systemic responses and ablative solutions can often lack efficacy especially when controlling metastatic tumor burden.



Rigid, trocar-based applicator

APOLLO Generator



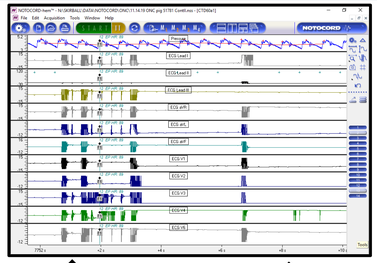


Based on encouraging and consistent data with TAVO and a clear unmet demand, we designed a platform to reach visceral lesions. In conjunction with the APOLLO generator, our rigid, trocar-based applicator allows physicians to reach liver, lung, pancreas, and bone percutaneously through CT-guidance.

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

1. Under conscious sedation or general anesthesia, insert applicator into the target lesion of a patient.
2. The distal 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 delivery of 8 rapid, low voltage pulses through the outer prongs of the applicator tip, thereby achieving a reversible EP event.
4. Within the EP area, small pores temporarily form in cell membranes, allowing the therapy to enter 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.

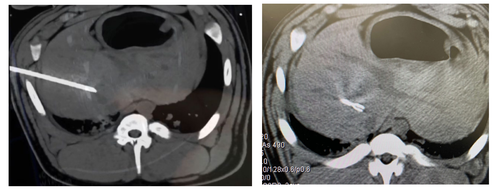
THE VOLTAGE FROM ELECTROPORATION TRANSIENTLY SATURATES THE EKG MONITOR BUT HAS NO SIGNIFICANT EFFECT ON HEMODYNAMICS, AS INDICATED BY CONSISTENT HEART RATE AND ARTERIAL BLOOD PRESSURE



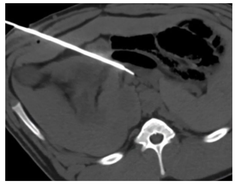
VLA IN LIVER, LUNG, PANCREAS, & BONE

Large animal simulations of CT-guided procedures were performed in the liver, lung, pancreas, and femoral medullary cavity using a Siemens Somatom Flash CT Imaging Platform. Two Yorkshire pigs were placed under general anesthesia and monitored in accordance with an approved IACUC protocol. Following rigid applicator placement and confirmation in the respective target organs, the applicator tip (injection port and electroporation tines) was deployed and electroporation commenced. CT images below show the applicator tip deployed in liver, pancreas and lung.

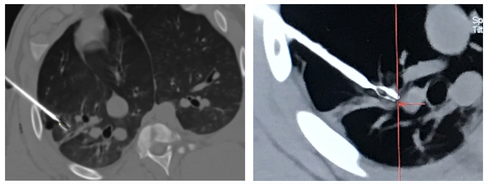
LIVER



PANCREAS



LUNG



CONCLUSION

These results demonstrate feasibility of the device to reach high value tissue targets. The ability to deliver potent and safe immunotherapy directly to a tumor presents a meaningful opportunity to drive strong clinical responses in difficult to treat malignancies and offers a potentially new solution for interventional radiologists in managing these patients. 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.

ACKNOWLEDGEMENTS &REFERENCES

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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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