Lymphatic Delivery of Pembrolizumab to Tumor Draining Lymph Nodes in Relapsed or Refractory Mycosis Fungoides

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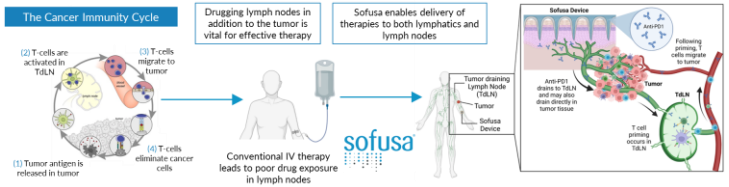
Abstract

Tumor draining lymph nodes (TDLN) have been shown to play a critical role in reactivating T cells with PD-1 checkpoint therapies[1], yet PD-1 inhibitors are dosed systemically limiting delivery to TDLNs and therapeutic efficacy. Therefore, targeting PD-1 to TDLNs could increase immune system activation to treat cutaneous T cell lymphoma. A Nanotopography-microneedle (NTM) device has recently been developed to deliver PD-1 into TDLNs through the peripheral lymphatics. Here we present an interim report on 3 patients with relapsed or refractory mycosis fungoides in a 10-patient Phase 1b, open-label, clinical trial where pembrolizumab is delivered lymphatically to TDLNs.

Background

Anti-cancer Tcells are primed and activated in tumor-draining lymph nodes (TdLNs). However, cancers suppress TdLNs while systemic IV therapy poorly delivers drug to TdLNs.[1] Re-directing immuno-oncology therapies towards TdLNs using Sofusa may improve T-cell activation leading to improved anti-tumor efficacy while reducing required dose thereby lessening adverse events.



Trial Objectives

Primary Endpoint

- T-cell exhaustion/activation markers:

Secondary Endpoints

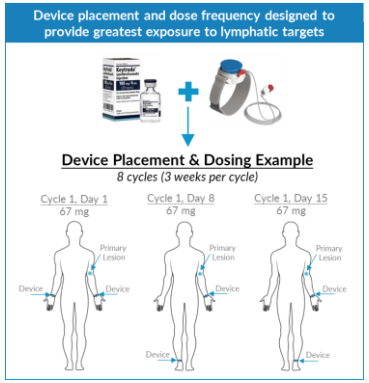
- Types, frequencies, and severities of adverse events (AEs) and the relationships of AEs to study intervention; includes serious adverse events (SAEs)
- Measurements of serum concentration of pembrolizumab

Exploratory Endpoints

- Objective Response Rate (ORR)
- Duration of Response (DOR)
- T-cell exhaustion/activations markers in blood
- Receptor occupancy of pembrolizumab in blood
- Analysis of lymphatic flow in relation to response, safety, PK

Methods

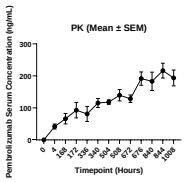
- Mycosis fungoides patients were screened for primary tumors located on upper or lower extremities to ensure that the primary TDLN was identifiable with high confidence.
- The device was then applied to the extremity either distal or proximal to the primary tumor depending on feasibility of device placement.
- Another device was then rotated each week between the other three extremities to treat all inguinal and axillary lymph nodes.
- Every week each patient was infused lymphatically with 67 mg of pembrolizumab for up to a maximum of 24 weeks.



Trial Status

- The Phase 1b, open-label, clinical trial (NCT04118868) is ongoing with the 1st patient enrolled in September 2022.
- Two grade 1 adverse events were observed (elevated ALT/ALS and diarrhea) and one serious adverse event (fever/pyrexia) that was not suspected to be due to pembrolizumab or the NTM device.

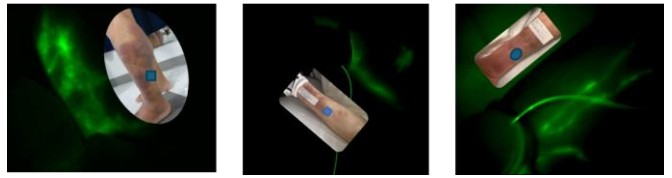
Results – PK and ADAs



ADA Assay		
Patient	Cycle	Screening Result
01-001	C1D1	Negative
	C3D1	Negative
	C5D1	Negative
	EOT	Negative
01-004	C1D1	Negative
	C3D1	Negative
	C5D1	Negative
	EOT	Negative
01-005	C1D1	Negative
	C3D1	Negative

- No ADAs were observed up to 18 weeks of treatment
- The maximum serum Concentration averaged 200 ng/mL

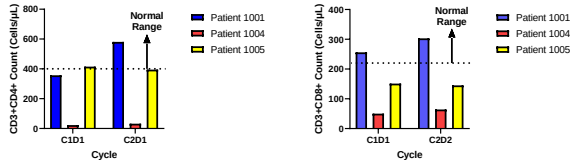
Results - Lymphatic Imaging



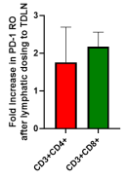
Patient 01-001 **Patient 01-004** **Patient 01-005**

Lymphatic function varied from dermal backflow to low/moderate pumping rates.

Results - CD4+ and CD8+ T cells

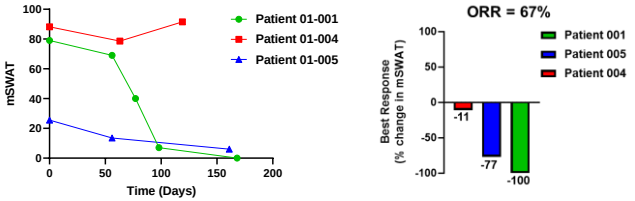


Results - PD-1 Receptor Occupancy



1.8 fold increase in PD-1 RO on CD4+ T cells and 2.2 fold increase in PD-1 RO on CD8+ T cells immediately after lymphatic treatment

Results - mSWAT



Conclusions

- The interim results are promising with an ORR of 67% for the first three patients with one complete response.
- These early results may also suggest that local-regional lymphatic delivery of PD-1 to TDLNs can produce a systemic response and may be a safer and more effective method of administration for reactivating T cells in the treatment of cutaneous T cell lymphoma.