A phase I clinical trial on intratumoral administration of autologous CD1c (BDCA-1)+ myeloid dendritic cells (myDC) plus talimogene laherparepvec (T-VEC) in patients with advanced melanoma

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INTRODUCTION

Intratumoral (IT) myDC play a pivotal role in initiating anti-tumor immune responses and "re-licensing" of anti-tumor cytotoxic T lymphocytes within the tumor microenvironment. IT injection of the oncolytic virus talimogene laherparepvec (T-VEC) leads to the release of maturation signals and tumor antigens that can be captured and processed by IT co-administered CD1c (BDCA-1)$^+$ myDC, reinvigorating the cancer immunity cycle.

In this phase I clinical trial we investigate the safety and feasibility of IT co-administration of autologous, unmanipulated CD1c (BDCA-1)$^+$ myDC plus T-VEC in patients with advanced melanoma who previously progressed on checkpoint blockade.

PATIENTS & METHODS

- Patients (n=7) with advanced melanoma with injectable non-visceral metastases who failed standard-of-care treatment are eligible to participate in this ongoing trial.
- Patients underwent a leukapheresis and were treated with IT injection of T-VEC (10^6 PFU) on day 1 followed by IT injection of autologous, non-manipulated CD1c (BDCA-1)$^+$ myDC on day 2. Administration of T-VEC (10^8 PFU) was repeated on day 21 and every 14 days thereafter.
- Isolation of CD1c (BDCA-1)$^+$ myDC was performed on a CliniMACS® Plus (Miltenyi Biotech).
- 3 dose cohorts with escalating numbers of CD1c (BDCA-1)$^+$ myDC
- Primary objective: safety (treatment-related adverse events graded according to CTCAE version 5.0)
- Secondary objectives: feasibility, antitumor responses, progression-free survival, overall survival
- Repetitive biopsies were performed, if feasible, for basic immunohistochemistry as well as multiplexed immunofluorescence (UltiMapper™ platform Ultivue). The latter was analyzed using HALO 3.0 software (Indica Labs).

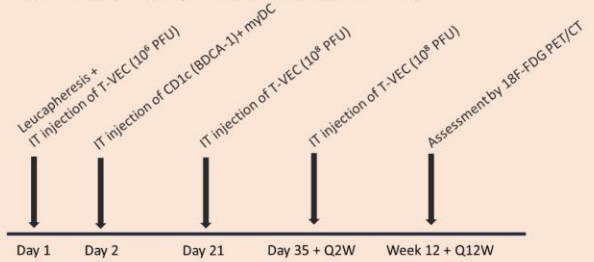

Figure 1. Treatment & Assessment Scheme

RESULTS

Patient characteristics		N = 7 (%)
Age (median, range) in years		66 (50-80)
Sex	Female	6 (86%)
	Male	1 (14%)
ECOG performance status	0	4 (57%)
	1	2 (29%)
	2	1 (14%)
Stage	IIIC	1 (14%)
	IV-M1a	2 (29%)
	IV-M1b	0 (0%)
	IV-M1c	4 (57%)
T-VEC administration	Number of injected lesions (range)	1-13
	Total amount of injections (median, range)	6 (2-10)
CD1c (BDCA-1)+ myDC administration	Cohort 1 (0,5x10^6 cells)	2
	Cohort 2 (1x10^6 cells)	2
	Cohort 3 (10x10^6 cells)	3
Previous therapies	anti-PD-1 mAb	7 (100%)
	anti-CTLA-4 mAb	6 (85%)
	Cytotoxic therapy (≥1 line)	3 (43%)
	BRAF-/MEK-inhibition	3 (43%)

Tabel 1. Baseline Characteristics & Treatment Disposition.

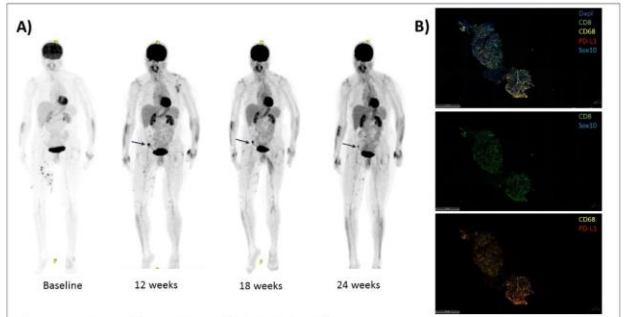

Figure 2. Case Illustration. A) 18FDG-PET/CT maximum intensity projection of a tumor response of a 68yo female patient (stage IIIC melanoma) who previously progressed on anti-PD-1 therapy. While the injected subcutaneous lesions decreased at 12 weeks, a new hypermetabolic inguinal lymph node appeared (black arrow) which decreased in volume spontaneously. **B)** Tissue biopsy (24 weeks) showing no evidence of malignancy (SOX-10 neg), but CD8$^+$ lymphocytes.

Type of AE		All grade	Grade 1	Grade 2	Grade 3	Grade 4
General	Flu-like symptoms	5 (71%)	3	2	0	0
	Fever	4 (57%)	3	1	0	0
	Chills	2 (29%)	2	0	0	0
	Fatigue	4 (57%)	1	2	1	0
Gastrointestinal	Abdominal cramps	3 (43%)	3	0	0	0
	Nausea	3 (43%)	3	0	0	0
	Constipation	1 (14%)	0	1	0	0
	Oral pain	1 (14%)	0	1	0	0
Respiratory	Dyspnea	3 (43%)	2	1	0	0
	Hemoptysis	1 (14%)	1	0	0	0
	Rhinitis	2 (29%)	2	0	0	0
Ophtalmologic	Blurry vision	1 (14%)	1	0	0	0
Musculoskeletal	Myalgia	1 (14%)	1	0	0	0
Skin	Injection-site pain	4 (57%)	3	1	0	0
	Redness at injection-site	3 (43%)	3	0	0	0
	Purpuric rash	1 (14%)	0	1	0	0
	Dermatitis	1 (14%)	0	1	0	0
Haematological	Eosinophilia	1 (14%)	0	0	1	0
	Anemia	1 (14%)	0	1	0	0
Cardiovascular/ Vascular disorders	Arterial hypertension	1 (14%)	0	0	1	0
	Hypotension	1 (14%)	0	1	0	0
	Syncope	1 (14%)	0	0	1	0
Endocrine	Hypothyroidism	1 (14%)	1	0	0	0

Tabel 2. Adverse Events of all included patients (n=7), with treatment-related adverse events highlighted in grey.

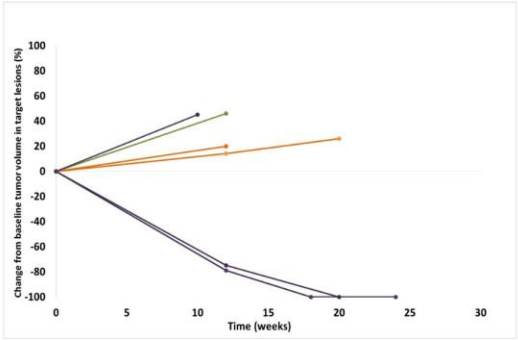

Figure 3. Tumor Responses. Spider plot showing the tumor responses of six patients (n=6). One patient had rapid clinical deterioration due to progressive disease with no imaging available to determine the tumor response. Green = cohort-1, orange = cohort-2, purple = cohort-3.

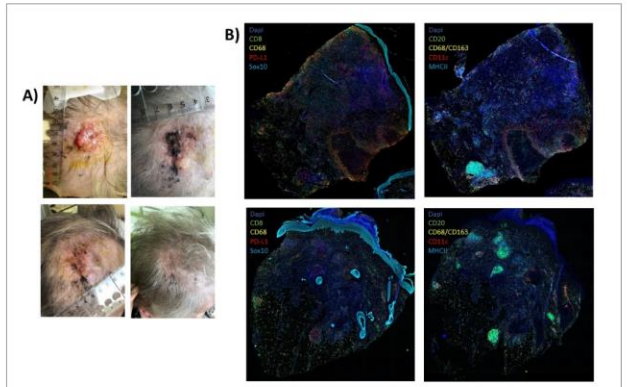

Figure 4. Case Illustration. 80yo female patient with a local melanoma recurrence who previously progressed on anti-PD-1-/anti-CTLA-4 therapy developed a durable CR. **A)** Clinical images of the subcutaneous metastasis. **B)** Multiplexed immunofluoresence images. Upper images showing the lesion on treatment (9 weeks). Lower images showing a pathological CR (19 weeks).

CONCLUSION

IT injection of autologous, non-manipulated CD1c (BDCA-1)$^+$ myDC with IT co-injection of T-VEC is feasible and tolerable.

Adverse events are low-grade and manageable (no grade 4 AE). This treatment regimen resulted in encouraging early signs of anti-tumor activity in pretreated patients. Two patients with advanced melanoma both refractory to anti-PD-1 and one patient also to anti-CTLA-4 checkpoint inhibition developed a durable pathological complete response.

Tumor response assesment by 18FDG-PET/CT may understimate tumor responses and tumor biopsies can be of added value to assess intralesional changes.

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