Impact of Low-Dose Intra-lesional Nivolumab for Kaposi Sarcoma on T Cell Proliferation and Function

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BACKGROUND

- Infection with Kaposi sarcoma herpesvirus (KSHV, human herpesvirus-8) causes Kaposi sarcoma (KS). These virally associated diseases occur more frequently in HIV-infected individuals, but can also be found in HIV-uninfected population.
- Immunosuppressive mechanisms presumably plays a permissive role in the development, progression and recurrence of these virus-associated cancers.
- Currently, available treatment options for these lesions are imperfect.
- The goal of this study is to determine whether intra-lesional injections of nivolumab can enhance specific T cell responses in vitro and enhance activity against these virus-associated lesions.

METHODS

- This is a prospective, single center, non-randomized, single arm phase 1 study to evaluate the safety and feasibility of intra-lesional injections of nivolumab to treated limited cutaneous KS (NCT 03316274).
- Participants must have fewer than 25 cutaneous lesions with KS+ screening skin biopsy. Participants with HIV (PWH) must have CD4 ≥ 350 cells/mm^3. All have ECOG performance status ≤ 1 or Karnofsky ≥ 70% .
- Those with visceral KS, history of autoimmune disease in past 2 years or OI in the past 3 months excluded.
- Participants can not have received prior anti-PD-1, anti-PD-L1 or anti-PD-L2 therapy

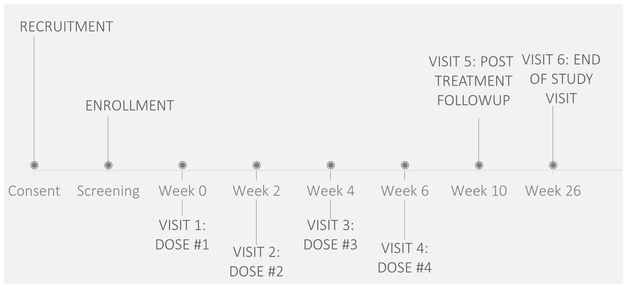
We recruited participants with and without HIV. For participants whose injected lesions achieve PR or CR by week 26 and who did not experience any SAE, we will inject up to 4 residual KS lesions (total volume 10 mg in 1 mL) every 2 weeks for up to 4 additional doses.

- **Treatment:** 10 mg of nivolumab (volume 1 mL, concentration 10 mg/mL), every 2 weeks x 4 doses.
- High-dimensional spectral flow cytometry was used to assess circulating T cell phenotypes, PD1 expression/receptor occupancy, and HIV and HHV8-specific immune responses prior to nivolumab therapy, following the 2nd dose and 26 weeks after the last of a total of 4-8 injections. HIV-1 reservoirs were measured in participants with HIV.

ADDITIONAL KEY INFORMATION

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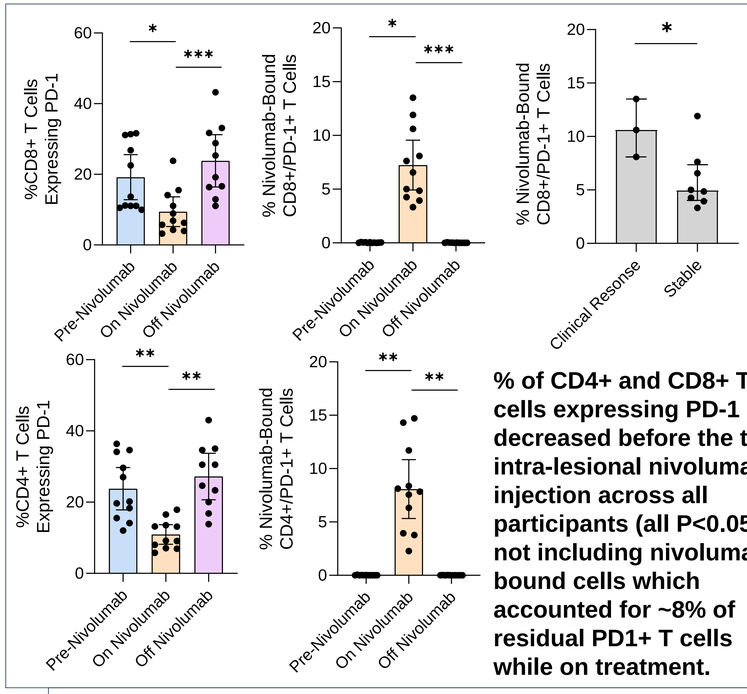
Low dose locally delivered nivolumab was safe for participants with Kaposi sarcoma; and it led to marked PD-1 downregulation and increases in T cell cycling and memory expansion in participants with and without HIV while receiving treatment.





Week 0

Week 28

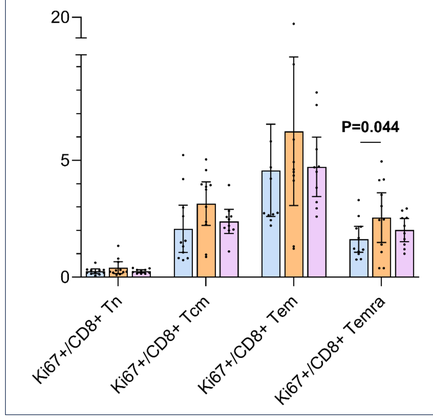


% of CD4+ and CD8+ T cells expressing PD-1 decreased before the third intra-lesional nivolumab injection across all participants (all P<0.05), not including nivolumab-bound cells which accounted for ~8% of residual PD1+ T cells while on treatment.

RESULTS

	Age	Sex	Race Ethnicity	Doses of Nivo received	HIV	Baseline CD4 (cells/mm^3)	Prior KS tx	Number of KS Lesions	KS Status
1	64	M	HW	4	Neg	868	Alitretinoin, Radiation	8	SD
2	69	M	NHW	8	Neg	1024	Vinblastine , Excision	1	CCR
3	55	M	HW	4	Pos	510	Vinblastine, Cryotherapy, PLD	3	SD
4	53	M	A	8	Neg	459	Alitretinoin, PLD	4	CR
5	73	M	NHW	8	Pos	496	Vinblastine, Maraviroc*	5	SD
6	53	M	NHW	8	Pos	945	Alitretinoin, Vinblastine	1	SD
7	58	M	NHW	8	Neg	708	Vinblastine	12	CR
8	72	M	NHW	8	Neg	704	Alitretinoin, PLD	9	SD
9	68	M	NHB	8	Pos	1056	Radiation	10	SD
10	81	M	NHW	8	Neg	457	Vinblastine	13	SD
11	61	M	NHW	8	Pos	544	None	3	SD
12	57	M	A	7	Pos	555	None	9	SD

- **Participant #4 had abscopal effect on 8 lesions that resolved without treatment.**
- 2 participants were HCV Ab+
- 9 participants were either immune to Hep B or had prior hep B infection.



A significant increase in the frequency of Ki67+ (cell cycling) terminally differential CD8+ T cells was observed from baseline to on therapy and trend which was observed across all other memory CD8$^+$ T cell subsets.

- **HIV serostatus did not impact PD-1 expression or T cell proliferation.**
- **The frequency of CD4$^+$ and CD8$^+$ central memory and effector phenotypes also significantly increased on therapy compared to baseline.**
- **No changes in HIV-1 or HHV8-specific CD4$^+$ or CD8$^+$ T cell frequencies or in cell-associated HIV-1 DNA or RNA were observed prior to, during and after treatment.**
- **Given these promising data, larger studies will be needed to assess the impact on HIV-1 persistence and virus-specific immune responses.**