Pomalidomide Induces T Cell Activation and Decreases Senescence in Kaposi Sarcoma

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BACKGROUND

- Kaposi sarcoma (KS) is an endothelial tumor strongly associated with HIV and CD4$^+$ lymphocytopenia but may occur in those without HIV.
- Pomalidomide (Pom) is an immunomodulatory agent recently approved by the US Food and Drug Administration for KS based on a phase 1/2 study of participants (pts) with and without HIV conducted at the National Cancer Institute (NCT01495598).
- Differences in T cell phenotypes in those with and without HIV who develop KS is not well-studied.
- The *in vivo* effect of Pom on T cell function in people with KS is unknown.

METHODS

- We prospectively evaluated CD4$^+$ and CD8$^+$ T cell phenotypes in 19 pts with KS enrolled on the NCI Pom study.
- Pts received Pom 5mg orally for 21 days of 28-day cycles for up to 1 year.
- Flow cytometry was performed on peripheral blood mononuclear cells at baseline (BL), after 2 cycles (C2), and at end-of-treatment (EOT).
- We evaluated BL differences by HIV status and the impact of Pom on lymphocyte counts and T cell subsets by Wilcoxon signed-rank and Mann-Whitney tests.
- P<0.005 was considered significant and 0.005<*p*<0.05 a strong trend.

Table 1. Participant Characteristics

Characteristic Med (IQR) or n (%)	All Participants (n=19)	HIV$^+$ Participants (n=12)	HIV$^-$ Participants (n=7)	p-value
Cisgender men	18 (95%)	11 (100%)	6 (86%)	
Transgender women	1 (5%)	—	1 (14%)	
Age (median, range)	52 (32–74)	49 (32–57)	61 (38-74)	0.021
Self-reported race/ethnicity				
White	14 (73.7%)	7 (58.3%)	7 (100%)	0.11
Black	3 (15.8%)	3 (25%)	—	0.26
Hispanic	2 (10.5%)	2 (16.7%)	—	0.51
Advanced ('T1') Disease	14 (73.7%)	7 (58.3%)	7 (100%)	0.11
Partial or complete response to Pom	14 (74%)	7 (58%)	7 (100%)	0.11
PBMC subset counts				
CD4$^+$ cells/μL	495 (349–742)	417 (339–637)	742 (501–945)	0.0068
CD8$^+$ cells/μL	506 (418–950)	782 (453–1207)	422 (321–506)	0.028
CD19$^+$ cells/μL	127 (68–197)	120 (53–142)	165 (116–235)	0.20
NK cells/μL	217 (142–283)	165 (131–245)	305 (226–432)	0.056
CRP (mg/L)	3.1 (1.3–7.9)	2.5 (1.3–6.4)	3.5 (2.0–8.1)	0.59
Detectable KSHV viral load	2 (10.5%)	2 (16.7%)	—	0.51

Pomalidomide *increased* the proportion of **central memory** (CD45RO$^+$CD27$^+$) and **activated** (CD38$^+$/HLADR$^+$) CD4$^+$ and CD8$^+$ T cells and *reduced* the proportion of **senescent** (CD57$^+$) CD4$^+$ and CD8$^+$ T cells.

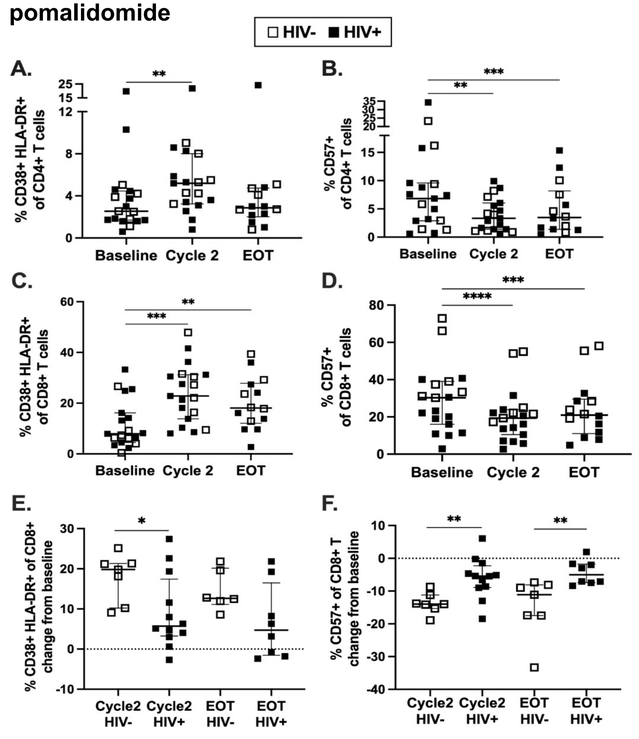
RESULTS

- At BL, HIV$^+$ pts had lower CD4$^+$ counts (median 416 vs 742 cells/μL, p=0.006) despite effective ART with HIV VL <50 copes/mL in all pts, while HIV$^-$ pts had an increased proportion of CD57$^+$ (senescent) CD8$^+$ T cells (p=0.0072).
- There were no significant changes in total CD4$^+$ and CD8$^+$ at C2, although there was a strong trend towards increased CD8$^+$ T cells at EOT (p=0.006).
- There were significant decreases in CD19$^+$ B cells at C2 and EOT (p=0.0003, p=0.0013).
- At C2, Pom led to an increased proportion of CD45RO$^+$CD27$^+$ (central memory) CD4$^+$ (p=0.002) and CD8$^+$ (p=0.0017) T cells.
- At C2, there was a decrease in CD45RO$^-$CD27$^-$ (effector) CD4$^+$ cells (p=0.0002).
- At C2, there was expansion of CD38$^+$/HLADR$^+$ (activated) CD4$^+$ (p=0.002) and CD8$^+$ (p=<0.0001) T cells. The activation of CD8$^+$ T cells persisted at EOT (p=0.0017).
- At C2 and EOT, there was reduction in the proportion of CD57$^+$ CD4$^+$ (p=0.0013, 0.0006) and CD8$^+$ (p=<0.0001, 0.0004) T cells.

CONCLUSIONS

- In pts with KS, Pom decreased the number of senescent T cells and increased the number of activated T cells.
- Our study also identified baseline differences in T cell phenotypes in HIV$^+$ and HIV$^-$ KS.
- These are important steps toward understanding the immune mechanisms of action of Pom in KS.

Figure 1. Changes in T cell phenotypes over time by HIV status in participants with Kaposi sarcoma who received pomalidomide



A, B: %CD38$^+$ HLA-DR$^+$ (activated) and %CD57$^+$ (senescent) CD4$^+$ T cells over time. C, D: %CD38$^+$ HLA-DR$^+$ (activated) and %CD57$^+$ (senescent) CD8$^+$ T cells over time. E, F: Change from BL of %CD38$^+$ HLA-DR$^+$ (activated) and %CD57$^+$ (senescent) CD8$^+$ T cells by HIV status at C2 and EOT. Symbols represent individual pts; bars represent median with interquartile range.
****p<0.0001; ***p<0.001; **p<0.01; *p<0.1

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