Baseline KSHV T Cell Responses Are Associated With Pre-Treatment Clinical Presentation in KS

Poster 00750

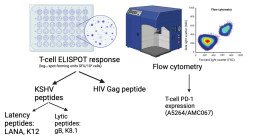
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INTRODUCTION

- T-cell immunity is important in controlling KS herpesvirus (KSHV) disease progression.
- We evaluated T-cell responses to KSHV and associations with pre-treatment clinical characteristics and outcomes in 2 ACTG/AMC studies (A5263/AMC066; A5264/AMC067) of KS treatment in resource-limited settings.

METHODS





A5263/AMC066

Phase II, prospective, randomized, multi-step open-label trial
(Total N = 446)

Comparison of the safety and efficacy of three regimens of chemotherapy with compatible ART for treatment of advanced AIDS-KS in resource-limited settings

Secondary immunology analysis
Classification: Good responder, stable, progressor, none
Analysis population: Receipt of Bleomycin +Vincristine+ART or Paclitaxel+ART, meeting of KS responder criteria
PBMC: Week 0 + week 12

A5264/AMC067

Phase II, prospective, randomized, multi-step open-label trial
(Total N = 190)

Evaluation of ART alone or with delayed chemotherapy vs. ART with immediate adjunctive chemotherapy for treatment of limited stage AIDS-KS in resource-limited settings

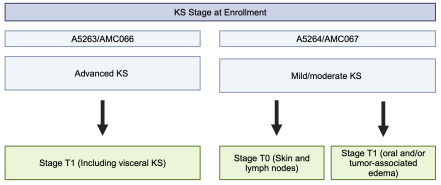
Secondary immunology analysis
Analysis population: Receipt of ART alone or with delayed ET upon KS progression
Outcome groups: KS-IRIS, Non KS-IRIS early progressive disease (PD), Late PD by week 48, No PD by week 48
PBMC: Week 0 + week 12 + week 48

Statistical analyses:
Comparison of dichotomous or categorical measures between groups: Fisher's exact test

Comparison of continuous measures between groups: Wilcoxon ran-sum tests

Immune response measures:
(Performed on subset of participants)
T-cell ELISpot responses
KSHV peptides: Latency (LANA, K12) + Lytic (gB, K8.1), HIV Gag peptide

Flow cytometry (A5264/AMC067 only)
CD4+PD-1+, CD8+PD-1+



RESULTS

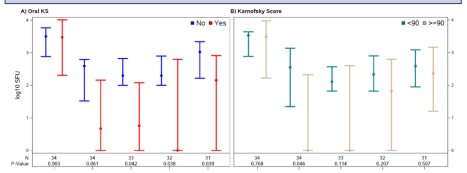
- **Higher baseline KSHV-specific T-cell immune responses were associated with the absence of oral KS lesions and lower Karnofsky scores pre-treatment.**
- **These immune responses were not associated with treatment outcomes.**

Table 1 - Baseline demographics and health-related characteristics

	Advanced KS (A5263/AMC066)	Mild/moderate KS (A5264/AMC067)
Baseline demographics		
Median age (years) *(Q1,Q3)*	34 *(30,41)*	34 *(28,41)*
Male (%)	83	70
Black African (%)	98	95
Baseline health-related characteristics		
Median CD4 count (cells/cmm³) *(Q1,Q3)**	250 *(134,384)*	190 *(88,325)*
Median plasma HIV-1 RNA (Log_{10}copies/mL)* *(Q1,Q3)*	3.5 *(2.50,5.14)*	5.11 *(4.48,5.62)*

**Longer average exposure to ART in A5263/AMC066 vs. A5264/AMC067*

Figure 1 - Correlation between median baseline immune responses to KSHV and HIV and pre-treatment clinical characteristics in advanced KS (A5263/AMC066)



Oral KS
Advanced KS
Lower median baseline responses to K12, K8.1 and LANA in oral KS vs. No oral KS

Mild/moderate KS
Immune response to LANA in more participants without oral KS vs. oral KS (65% vs. 19%; p=0.013)

Karnofsky score
Advanced KS
Higher median baseline responses to gB in KPS < 90 vs. > 90

Mild/moderate KS
Immune response to gB in more participants with KPS < 90 vs. > 90 (63% vs. 21%; p=0.040)

Immune response to Gag not associated with oral KS or KPS despite strong median responses in all groups

Table 2 - Baseline immune responses and screening KS stage in mild/moderate KS (A5264/AMC067)

Baseline Immune Responses and Screening KS Stage in Mild/moderate KS (A5264/AMC067) Number of participants with positive Log10-fold SFU / Total number of available samples (percentage)				
	Total	T0	T1	P-value
Gag	30/38 (79%)	10/15 (67%)	20/23 (87%)	0.223
gB	11/36 (31%)	7/13 (54%)	4/23 (17%)	0.056
K12	18/38 (47%)	8/14 (57%)	10/24 (42%)	0.503
K8.1	11/33 (33%)	5/11 (45%)	6/22 (27%)	0.437
LANA	14/33 (42%)	6/11 (55%)	8/22 (36%)	0.459

Trend for mild/moderate KS participants with screening T0 KS stage to respond to gB vs. screening T1 stage (54% vs. 17%, p-value=0.056). No difference observed with other immune markers

Table 3 - BaselineELISpot responses and clinical outcomes in advanced and mild/moderate KS

Baseline ELISpot Responses and Clinical Outcomes in Advanced and Mild/moderate KS Number of participants with positive Log10-fold SFU/mcl number of available samples (%)									
	A5263/AMC066				A5264/AMC067				
	Total	Non-progressor	Progressor	P-value	Total	Failure	Stable	Response	P-value
Gag	32/34 (94%)	15/17 (88%)	17/17 (100%)	0.48	22/27 (81%)	10/14 (71%)	5/5 (100%)	7/8 (88%)	0.536
gB	21/34 (62%)	10/17 (59%)	11/17 (65%)	> 0.99	8/26 (31%)	4/11 (36%)	2/4 (50%)	2/11 (18%)	0.617
K12	20/33 (61%)	10/16 (63%)	10/17 (59%)	> 0.99	14/26 (54%)	7/14 (50%)	2/5 (40%)	5/7 (71%)	1.000
K8.1	20/32 (63%)	11/15 (73%)	9/17 (53%)	0.29	10/27 (37%)	4/13 (31%)	2/4 (50%)	4/10 (40%)	0.762
LANA	25/31 (81%)	11/15 (73%)	14/16 (88%)	0.39	10/25 (40%)	8/13 (46%)	1/4 (25%)	3/8 (38%)	0.868

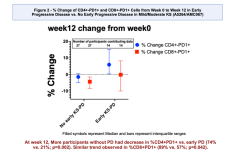
No association between KSHV T-cell responses and clinical outcomes in either study

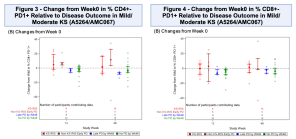
Table 4 - Baseline ELISpot Responses and Presence of Tumor-associated Edema

Baseline ELISpot Responses and Tumor-associated Edema in Advanced and Mild/moderate KS Number of participants with positive Log10-fold SFU/mcl number of available samples (%)								
	A5263/AMC066				A5264/AMC067			
	Total	Yes	No	P-value	Total	Yes	No	P-value
Gag	32/34 (94%)	30/32 (94%)	2/2 (100%)	N/A	30/38 (79%)	21/24 (88%)	9/14 (64%)	0.117
gB	21/34 (62%)	20/32 (63%)	1/2 (50%)	N/A	11/36 (31%)	5/14 (21%)	6/12 (50%)	0.124
K12	20/33 (61%)	19/31 (61%)	1/2 (50%)	N/A	18/38 (47%)	10/26 (38%)	8/12 (67%)	0.164
K8.1	20/32 (63%)	18/30 (63%)	1/2 (50%)	N/A	11/33 (33%)	7/23 (30%)	4/10 (40%)	0.696
LANA	25/31 (81%)	24/29 (83%)	1/2 (50%)	N/A	14/33 (42%)	8/23 (35%)	6/10 (60%)	0.257

No significant correlation between baseline ELISpot assay results and presence vs absence of tumor associated edema at study entry despite strong responses to HIV Gag peptides

RESULTS





- Week 12: Median changes in %CD4+PD1+ cells positive in KS-IRIS and early PD and negative in late PD and no PD.
- Week 48: higher proportions of participants with late PD and no PD had decreased %CD4+PD1+ vs. KS-IRIS and early PD.
- Week 12: Changes in %CD8+PD1+ from week 0 more negative in late PD and no PD groups vs KS-IRIS and early PD.
- Week 48: higher proportions of participants with late PD and no PD had decreased %CD8+PD1+ vs. KS-IRIS and early PD.

CONCLUSION

- **In advanced and mild/moderate KS, pre-treatment KSHV-specific T-cell responses were associated with several pre-treatment clinical characteristics including absence of oral KS and screening KPS < 90**
- **In mild/moderate KS, decreased T-cell exhaustion was associated with less early KS disease progression supporting T-cell immunity's importance in controlling KS**
- **Samples analyzed were from a subset of participants in each study, which constitutes a potential limitation of the study**

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