656LB - Interim Safety Analysis of CITN–12: Pembrolizumab in Patients with HIV and Cancer

Thomas S Uldrick[1], Priscila H Gonçalves[2], Steven Fling[1], Brinda Emu[3], Marc S Ernstoff[4], Robert Gorelick[6], Judith Kaiser[1], Matthew Lindsley[2], Lisa M Lundgren[1], Kathryn Lurain[2], Frank Maldarelli[6], Chris Parsons[7], Elad Sharon[8], Robert Yarchoan[2], and Martin A "Mac" Cheever[1]

1. Cancer Immunotherapy Trials Network/Fred Hutchinson Cancer Res Center, Seattle, USA; 2. National Institutes of Health Clinical Center, HIV and AIDS Malignancy Branch, Bethesda, USA
3. Yale University, Medicine/Oncology, New Haven, USA; 4. Roswell Park Cancer Institute, Buffalo, USA; 5. National Cancer Institute at Frederick, AIDS and Cancer Virus Program, Frederick MD
6. National Cancer Institute, HIV Dynamics and Replication Program, Frederick, MD; 7. Louisiana State University Health Science Center, New Orleans, USA
8. National Cancer Institute, Cancer Therapy and Evaluation Program, Bethesda, USA

Background

Checkpoint inhibitors and Cancer

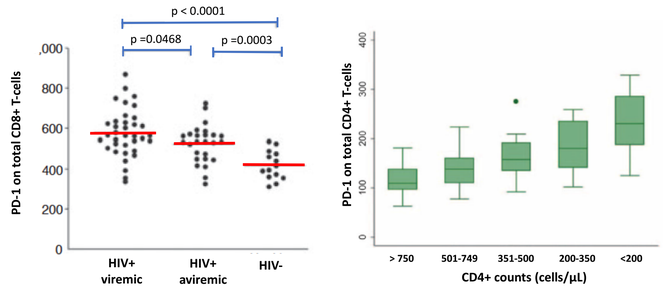
- Anti-PD-1 and anti-PD-L1 antibodies are becoming mainstays of cancer therapy
- The safety of pembrolizumab, an anti-PD-1 humanized monoclonal antibody, is being evaluated in patients with HIV and cancer
- The effect of anti-PD-1 therapy on HIV reservoirs is unknown

Safety concerns in people with HIV in part due to:

- Immune dysregulation of unknown clinical significance
  - PD-1 upregulation
  - Perturbed TCR repertoire
- Potential concern related to concurrent infections

Trautmann L. Nature Medicine 2006;
Cockerman LR. AIDS 2014

T-cell PD-1 Expression by HIV and CD4 Status



Methods

- Cancer Immunotherapy Trials Network (CITN)-12 is a multicenter study of pembrolizumab in patients with HIV and advanced cancers
- Three CD4 defined cohorts (C) are accruing; C1: 100-199, C2: 200-350, and C3: >350 cells/uL
- Eligibility: >4 weeks antiretroviral therapy (ART), HIV viral load <200 copies/mL, ECOG 0-1, no HBV or HCV detectable in blood by PCR (seropositive not excluded)
- Treatment: pembrolizumab 200mg intravenously every 3 weeks for up to 2 years
- Primary objective: assess safety and tolerability by summarizing CTCAEv4 graded adverse events (AEs) and evaluating HIV viral load (VL) and CD4 counts
- Immune mediated AEs are managed using standard guidelines
- We performed an interim analysis of treatment emergent adverse events at least possibly related to pembrolizumab (rTEAEs), serious AEs, and CD4 counts on therapy
- Plasma HIV VL was measured by an HIV gag single copy assay (SCA)
- One Serious Unexpected Adverse Event occurring after locking of the data for the interim analysis

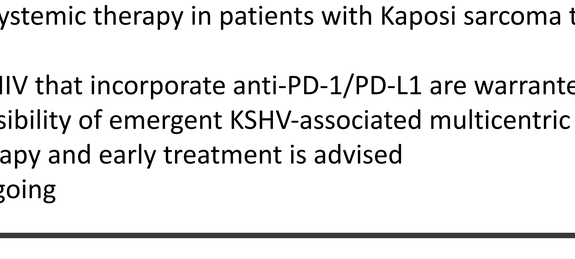
Study Schema

Screening
- ART > 4 weeks
- HIV Viral load < 200 copies/mL
- CD4⁺ > 100 cells/uL

Treatment
- Pembrolizumab 200 mg IV every 3 weeks
- Safety evaluated by CTCAE
- Tumor response evaluated every 3 cycles

Off-treatment
- Progressive disease
- Unacceptable adverse event
- Completion of 2 years of therapy

HIV Correlatives



Results

- 17 patients were accrued starting April 2016 and followed through May 2017
- Safety was observed over 100 total cycles, median 4 (range 1-20)

Patient Characteristics

Patient Characteristic	All	Cohort 1 CD4⁺ 100-199 cells/µL	Cohort 2 CD4⁺ 200-350 cells/µL	Cohort 3 CD4⁺ >350 cells/µL
Number	17	4	9	4
Age, years (median, range)	56 (43-77)	56.5 (47,68)	53 (43, 77)	60 (53,71)
Sex				
Men	16 (94%)	4	8	4
Women	1 (6%)		1	
Race				
White	13 (76%)	4	7	2
African American	3 (18%)	0	2	1
Hispanic	1 (6%)		1	
CD4⁺ T-cells/uL	249	148	249	538
(median, range)	(103-698)	(103,184)	(204,343)	(382,698)
HIV viral load, < 20 copies/mL	16 (94%)	4	8	4
ECOG Performance Status				
0	8 (47%)	1 (25%)	5 (56%)	2 (50%)
1	9 (53%)	3 (75%)	4 (44%)	2 (50%)
Prior systemic therapy, median (range)	1 (0-4)			
Prior radiation	12 (71%)	4	8	0

Cancers	All	Cohort 1 CD4⁺ 100-199 cells/µL	Cohort 2 CD4⁺ 200-350 cells/µL	Cohort 3 CD4⁺ >350 cells/µL
AIDS Defining	**4**			
PEL	2	1	1	
Kaposi sarcoma	1			1
DLBCL	1	1		
Non-AIDS Defining	**13**			
Cancers				
Anal	5	3	2	
Head and Neck	1		1	
Metastatic Skin, Squamous Cell	1		1	
Non-Small Cell Lung	1		1	
Hepatocellular	1		1	
Sarcomatoid Lung	1			1
Transitional Cell	1			1
Pancreatic	1			1
Cholangiocarcinoma	1		1	

PEL: Primary effusion lymphoma; DLBCL, diffuse large B-cell lymphoma

Adverse Events

- 82 rTEAEs were observed and comparable between cohorts
- 93% were grade 1-2
- Subsequent Unanticipated problem: *Death from KSHV-associated lymphoproliferation in patient with likely undiagnosed multicentric Castleman disease.*
- ***NOT*** observed in 4 other KS and 2 primary effusion patients

Treatment emergent adverse events at least possibly related to pembrolizumab

Occurring in > 20% of Participants

Adverse Event	Grade 1	Grade 2	Grade 3	Total (%)
Anemia	4	4	3	11 (64.7)
Hypothyroidism	2	4		6 (35.3)
Abdominal pain	4			4 (23.5)
Nausea	5			5 (29.4)
Fatigue	6	1		7 (41.2)
Alk Phos increased	3	1		4(23.5)
Lymphocytes decreased	2	2		4 (23.5)
Pruritus	4			4 (23.5)

Grade 3-4

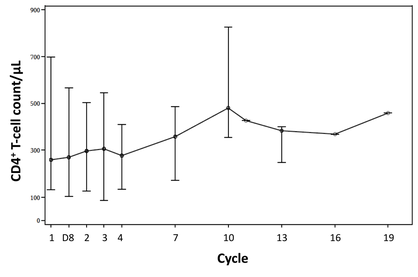
Adverse Event	Grade 3
Anemia	3
ALT increased	1
AST increased	1
Neutrophil decreased	1
TOTAL	6

Immune Related

Adverse Event	Grade 1	Grade 2	Grade 3	Total N (%)
Hypothyroidism	2	4		6 (35.3)
ALT increased	1		1	2 (17.6)
Joint stiffness	1			1 (5.9)
Pneumonitis	1	2		3 (11.8)

Results

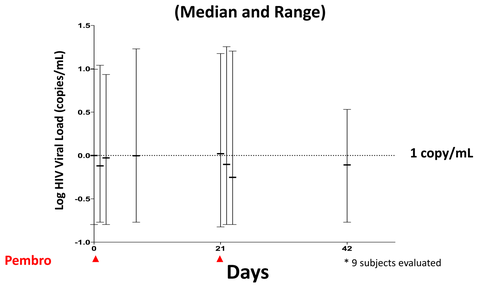
CD4+ T-cell Dynamics



- Median CD4 increased over time, changes did not reach statistical significance
- HIV remained suppressed on ART in all patients.

HIV Viral Load

(Median and Range)



- In a subset of 14 patients, baseline median HIV VL by SCA was 0.8 copies/mL (range: <0.3-9.9)
- In an evaluation of plasma HIV kinetics over the first two cycles, no significant increases from baseline were noted

Conclusions

- Pembrolizumab has an acceptable safety profile to date in patients with HIV and cancer
- CD4⁺ T-cells counts may increase on pembrolizumab and HIV control is maintained on ART
- Anti-PD1 therapy is appropriate in patients with HIV for FDA-approved indications
- Evaluation of pembrolizumab as first systemic therapy in patients with Kaposi sarcoma to start Spring 2018
- Studies evaluating strategies to treat HIV that incorporate anti-PD-1/PD-L1 are warranted
- Physicians should be aware of the possibility of emergent KSHV-associated multicentric Castleman disease with anti-PD-1 therapy and early treatment is advised
- Accrual and correlative studies are ongoing