SITC
2017
November 8-12
NATIONAL HARBOR
MARYLAND
Gaylord National Hotel
& Convention Center
sitc
Society for Immunotherapy of Cancer

November 8-12 • NATIONAL HARBOR, MD

SITC 2017

Interim Safety Analysis of Cancer Immunotherapy Trials Network – 12 (CITN-12):

A Phase 1 Study of Pembrolizumab in Patients with HIV and Relapsed, Refractory or Disseminated Malignancies

Thomas S. Uldrick, MD, MS

HIV & AIDS Malignancy Branch

Center for Cancer Research, NCI

NIH NATIONAL CANCER INSTITUTE

sitc Society for Immunotherapy of Cancer

cancer immunotherapy trials network

#SITC2017

Presenter Disclosure Information

Thomas S. Uldrick

The following relationships exist related to this presentation:

Merck & Co, Research Support through CRADA with NCI
Celgene, Research Support through CRADA with NCI
Celgene, I am named on an employee invention report for the use of IMIDs for the treatment of KSHV-associated malignancies
Roche, Research Support through CRADA with NCI

Background: Checkpoint Inhibitors in People with HIV

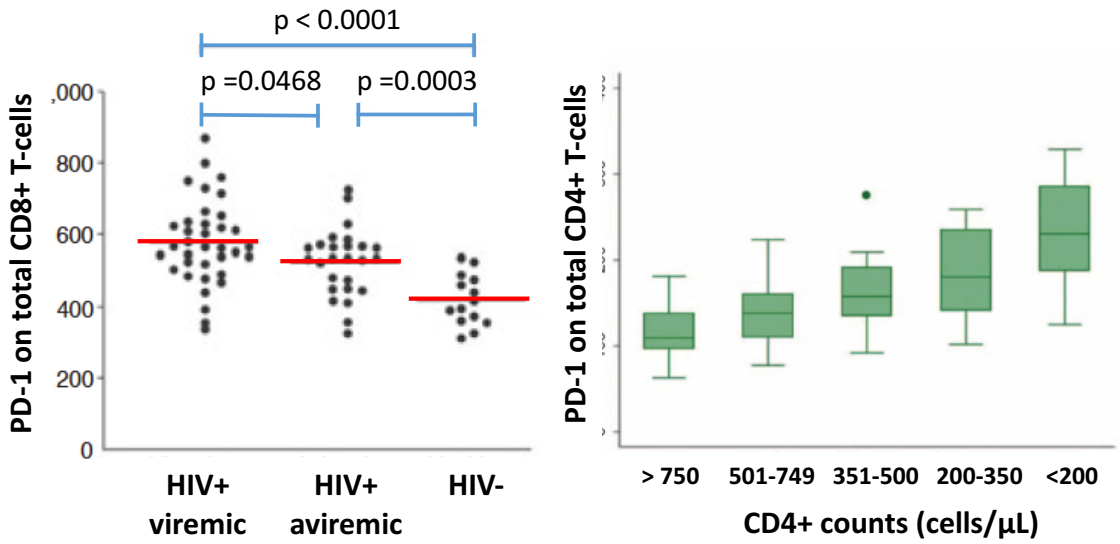
- Anti-PD-1 and anti-PD-L1 antibodies are approved for multiple indications
- Cancer is the leading cause of morbidity and mortality in the >35 million people worldwide living with HIV
- Many cancers occurring in people with HIV are known to respond to checkpoint inhibition
- Patients with HIV have been excluded from FDA approval trials for pembrolizumab, nivolumab, atezolizumab and avelumab
- Safety data in this patient population is imperative for treating physicians and clinical investigators

Background: Safety Considerations

Safety concerns in part due to:

- Immune dysregulation of unknown clinical significance
  - PD-1 upregulation on $CD4^+/CD8^+$
  - Perturbed TCR repertoire
- Potential concern related to concurrent infections
- Unexpected toxicities from anti-PD1 therapy and ART
- Unexpected effects of anti-PD-1 therapy on virus biology

T-cell PD-1 Expression Associated with HIV Viremia and Immunosuppression



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

Methods: Study Design

Study Design

- Multicenter Phase I Study

Primary Objective

- Evaluate safety and tolerability of pembrolizumab in HIV-infected patients with relapsed/refractory cancers on antiretroviral therapy
- Parallel cohorts:
  - Cohort 1: 100-199 $CD4^+$ T cells/µL
  - Cohort 2: 200-350 $CD4^+$ T cells/µL
  - Cohort 3: >350 $CD4^+$ T cells/µL

Methods: Key Eligibility Criteria

Inclusion

- Adults with biopsy proven cancers
  - Relapsed/Refractory
  - Ineligible for standard therapies
  - Anti-PD-1 therapy indicated in HIV-uninfected patients
- On tolerable antiretroviral regimen ≥4 weeks with suppressed HIV viral load
- Adequate organ function
- ECOG performance status 0 or 1

Exclusion

- On immunosuppressive therapy
- Hepatitis B or C by PCR
- Prior allogeneic transplant
- Uncontrolled CNS disease
- Other cancer therapy

Methods: Study Schema

- Antiretroviral therapy starting at least 4 weeks prior to enrollment
- Pembrolizumab 200 mg IV every 3 weeks for up to 2 years
- AEs assessed by CTCAEv4 each cycle
- Standard management of immune-related AEs
- Response criteria:
  - RECIST (Solid tumors)
  - Lugano (Lymphoma)
  - ACTG (Kaposi sarcoma)
- Off-treatment criteria:
  - Progressive disease
  - Unacceptable AE
  - Patient preference
  - Completion of therapy

Results: Patient population

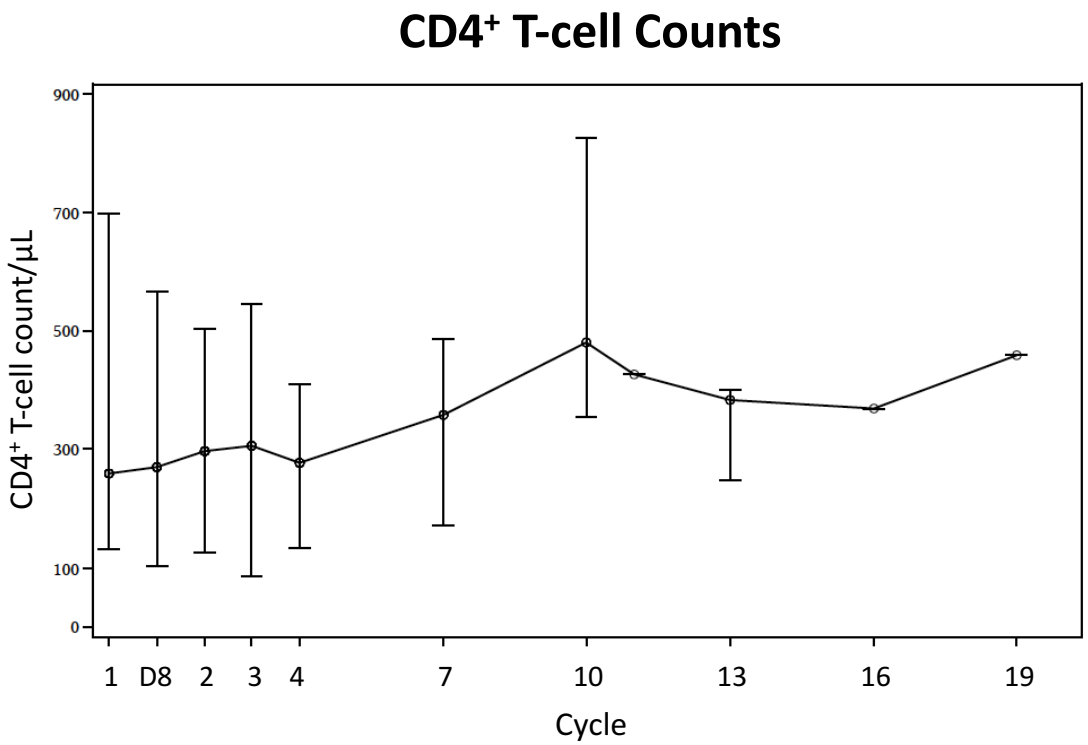
Characteristic	All	Cohort 1 CD4+ 100-199 cells/µL	Cohort 2 CD4+ 200-350 cells/µL	Cohort 3 CD4+ >350 cells/µL
Number	17	4	9	4
Age, years (median, range)	56 (43-77)	56.5 (47,68)	53 (43, 77)	60 (53,71)
Sex				
Men	16 (94%)	4	8	4
Women	1 (6%)		1	
Race				
White	13 (76%)	4	7	2
African American	3 (18%)	0	2	1
Hispanic	1 (6%)		1	
CD4+ T-cells/uL, median (range)	249 (103-698)	148 (103,184)	249 (204,343)	538 (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

Results: Cancers

Cancer	All	Cohort 1 CD4+ 100-199 cells/µL	Cohort 2 CD4+ 200-350 cells/µL	Cohort 3 CD4+ >350 cells/µL
AIDS Defining	**4**			
Primary Effusion Lymphoma	2	1	1	
Kaposi sarcoma	1			1
Diffuse Large B-cell Lymphoma	1	1		
Non-AIDS Defining	**13**			
Anal Cancer	5	3	2	
Head and Neck Cancer	1		1	
Metastatic Skin, Squamous Cell Carcinoma	1		1	
Non-Small Cell Lung Cancer	1		1	
Hepatocellular Carcinoma	1		1	
Sarcomatoid Lung Cancer	1			1
Transitional Cell Carcinoma	1			1
Pancreatic Cancer	1			1
Cholangiocarcinoma	1		1	

Results: CD4+ T-cells and HIV viral load

- Median CD4+ T-cell counts tended to increase over time
- HIV remained suppressed on antiretroviral therapy in all patients



Results: Treatment Emergent AEs

- Safety observed over 100 cycles
- Median 4 cycles (range 1-20)
- 82 treatment emergent AEs ≥ possibly related to pembrolizumab
- 93% grade 1-2 AEs
- No difference in rates of Grade 3-4 AEs between cohorts

TEAEs 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 TEAEs

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

Results: Immune-related AEs

Immune-related AEs requiring therapy

- Levothyroxine (6)
- Steroids (4)

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: Serious AEs

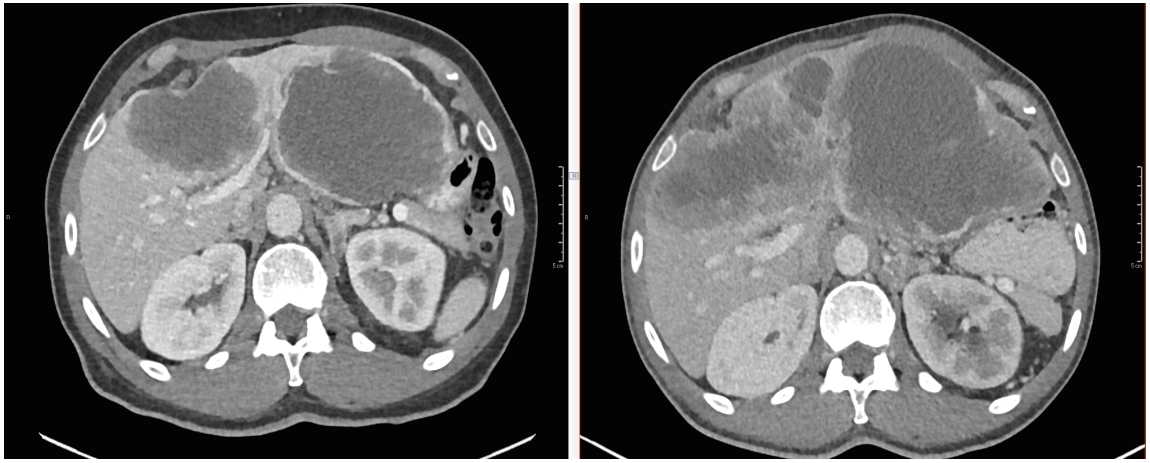
Cohort	Disease	Serious AEs	Cycle	Grade	Intervention	At least possibly attributed to IND	Unacceptable AE
1	Anal cancer	Febrile neutropenia/ Lung Infection	2	3	Antibiotics	Yes	No
1	Anal cancer	Urinary obstruction	3	3	Catheter, IVF	No	No
1	Anal cancer	Hypercalcemia	1	4	IVF, bisphosphonate	No	No
2	Anal cancer	Urinary retention	1	2	Catheter	No	No
		Hypercalcemia	1	3	IVF, bisphosphonate	No	No
2	Anal cancer	Hypercalcemia	1	3	IVF, bisphosphonate	No	No
2	SCC tongue	Dyspnea	2	2	Trach adjustment	No	No
		Hypercalcemia	1	4	IVF, bisphosphonate	No	No
2	SCC skin	Hypercalcemia	4	4	IVF, bisphosphonate	No	No
2	Cholangiocarcinoma	Retinal detachment	2	4	Surgery	No	No
3	Pancreatic cancer	Pulmonary embolism	3	3	Anticoagulation	No	No
3	Sarcomatoid lung cancer, liver mets	AST/ALT elevations	2	3	Steroids, MMF	Yes	Yes

Results: Unacceptable AE Case

53-year-old man

- 20 year history of HIV on ART
- Sarcomatoid lung cancer
  - Primary tumor resected
  - Liver metastases 7 months later
- $CD4^+$ T-cell count 382 cells/uL
- Grade 1 AST/ALT elevations at baseline
- After 2 cycles, Grade 3 AST/ALT
- Started on steroids

CT Abdomen

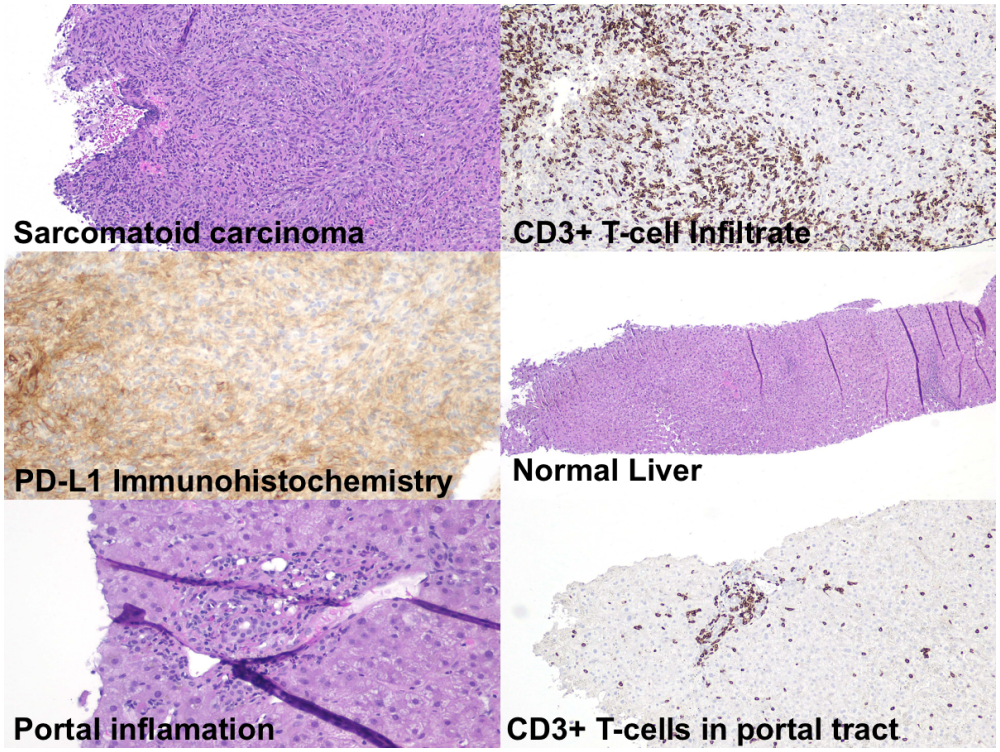


Baseline | After Cycle 2

Results: Unacceptable AE Case (cont)

- T-cell infiltrates in viable tumor
- Immunostaining confirmed strong PD-L1 expression
- T-cell infiltrates and inflammation in portal tract

Pathology of Liver Metastasis and Normal Liver



Lessons and Take Home Messages: Pembrolizumab in HIV

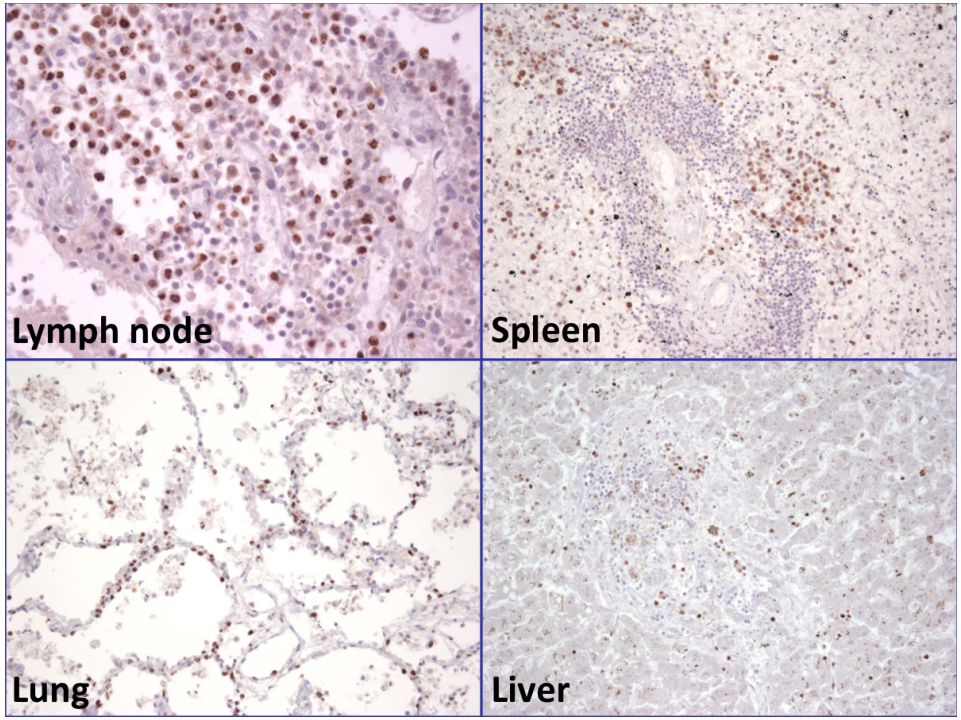
- To date, pembrolizumab has an acceptable safety profile in patients with HIV
- $CD4^+$ T-cells counts may increase on pembrolizumab and HIV control is maintained on antiretroviral therapy
- Anti-PD1 therapy should be considered in patients with HIV and malignancies with FDA-approved indications
- Patients with HIV who meet appropriate eligibility criteria for a given cancer should be included in immunotherapy studies
- Studies evaluating strategies to treat HIV that incorporate checkpoint inhibitors are warranted

Subsequent unanticipated problem: Disseminated Kaposi Sarcoma Herpesvirus (KSHV)

61-year-old man

- 1995 HIV on ART
- 1999 Classical Hodgkin lymphoma
- 2009 Kaposi sarcoma
- 2013 KSHV-inflammatory cytokine syndrome
  KSHV viral load range 1 to 6268 copies/10^6 PBMCs
- 6/2017 Pembrolizumab,
  - $CD4^+$ T-cell count 210/uL
  - KSHV viral load 1/10^6 PBMCs
- After second cycle, edema, effusion, pulmonary infiltrate, thrombocytopenia
  - KSHV viral load 304K/10^6 PBMCs
- Initially improved with steroids, antibiotics
- Subsequent rapid deterioration with anemia, thrombocytopenia, hyperbilirubinemia, volume overload progressing to death
- **NOT observed in 4 other KS patients or 2 primary effusion lymphoma patients to date**

KSHV Latency-Associated Nuclear Antigen



Lessons and Take Home Messages: KSHV-associated Diseases

- Additional studies in patients with Kaposi sarcoma and primary effusion lymphoma are warranted
- Patients with KSHV-associated multicentric Castleman disease or unexplained KSHV viremia require special consideration and should probably be excluded
- Physicians should be aware of the possibility of emergent KSHV-associated multicentric Castleman disease and early treatment is advised

Acknowledgements

NIH/ NCI - Frederick
- Bob Yarchoan
- Priscila Goncalves
- Kate Lurain
- Karen Aleman
- Anna Widell
- Kirsta Waldon
- Matt Lindsley
- Kathleen Wyvill
- Ramya Ramaswami

CITN
- Mac Cheever
- Holbrook Kohrt
- Steve Fling
- Lisa Lundgren
- Betty Bertoli
- Judy Kaiser
- Andreanne Lacroix

Axio Research
- Sharavi Peeramsetti

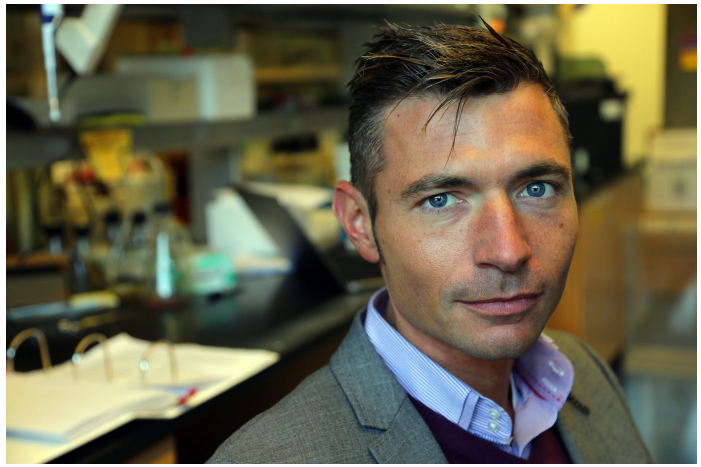
CTEP
- Elad Sharon
- Sherry Ansher
- Richard Little
- William Merritt

LSU
- Chris Parsons
- James Outland

Roswell Park
- Marc Ernstoff
- Ashley Jackson

Yale
- Brinda Emu
- Matthew Madura

Study Participants and their families



Holbrook Kohrt

cancer immunotherapy trials network

NIH NATIONAL CANCER INSTITUTE

Delaney AIDS Research Enterprise DARE to find a cure