Evaluation of Immune Checkpoint Inhibitors in Medically Vulnerable Populations: Challenges & Opportunities for Translational Research

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NIH NATIONAL CANCER INSTITUTE

Disclosures

- Nothing to disclose

Spectrum of PD-1/PD-L1 Antagonist Activity

Active

- Melanoma
- Renal cancer (clear cell and non-clear cell)
- NSCLC – adenocarcinoma and squamous cell
- Head and neck cancer
- Hodgkin Lymphoma
- Bladder Cancer
- Merkel Cell
- Gastric and GE junction
- Mismatch repair deficient tumors
- Hepatocellular carcinoma
- Cutaneous Squamous Cell Cancer
- Small cell lung cancer
- Triple negative breast cancer
- Primary Mediastinal B-Cell Lymphoma
- Mesothelioma
- Ovarian
- Nasopharyngeal Cancer
- Diffuse large B-cell lymphoma
- Follicular lymphoma

Minimal to no activity to single agents:

- Prostate cancer
- Microsatellite Stable Colon cancer
- Multiple Myeloma
- Pancreatic Cancer

Major PD-1/PD-L1 antagonists

- Nivolumab (anti-PD-1)
- Pembrolizumab (anti-PD-1)
- Atezolizumab (MPDL3280A, anti-PD-L1)
- Durvalumab (MEDI-4736, anti-PD-L1)
- Avelumab (anti-PD-L1)
- Cemiplimab (REGN2810, anti-PD-1)
- Other PD-1 efforts ongoing from:
  - Novartis (PDR001)
  - BeiGene (Tislelizumab)
  - INCMGA00012

Important Questions for Immuno-Oncology

- Which (often excluded) populations can receive IO Agents?
  - People Living With HIV? People with Solid Organ Transplants, Allogeneic Stem Cell Transplants?
- After an immune-related AE, can patients be re-treated with the same agent?
  - An immune-related toxicity is often different in character from a corresponding non-immune-related toxicity
  - What is the risk of recurrence of the toxicity?
  - How soon can retreatment be considered?
  - Why doesn't dose de-escalation or reduction in treatment intensity or total exposure work?
    - There has been little work on there is no guidance on package insert of approved agents for re-treatment
- Risk mitigation strategies should be tested with the intent of helping patients obtain access to beneficial therapies, even after an AE

Methods of Obtaining Answers

- Analysis of Immune Checkpoint Inhibitors in Special Populations
  - AMC-095, CITN-12: Trials of nivolumab and pembrolizumab in patients with HIV
    - Both trials have been presented; CITN-12 now being expanded to frontline patients with Kaposi Sarcoma
  - 9204: Trial of ipilimumab & nivolumab in patients following allogeneic transplant
    - Ipilimumab cohort at 10 mg/kg was published in NEJM in 2016
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- Immune-Related Adverse Event Biorepository
  - A Case Example of Tuberculosis

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Advocacy for People Living with HIV on NCI Trials

- NCI has been advocating for inclusion of PLWH for decades
- With addition of PD1/PDL1 Inhibitors, immediate effort was made to expand eligibility
- Over time, investigators and partnering companies accepted PLWH with lower CD4 thresholds and disease characteristics
- FDA, Friends of Cancer Research, and ASCO advocacy helped improve the inclusive environment
  - Based on these efforts, NCI CTEP was able to change templates to promote PLWH inclusion

JAMA Network Open

Original Investigation | Oncology

Assessment of Cancer Therapy Evaluation Program Advocacy and Inclusion Rates of People Living With HIV in Anti-PD1/PDL1 Clinical Trials

Joshua E. Reuss, MD; Diana Stern, DO; Jared C. Foster, PhD; Ramya Ramaswami, MBBS, MPH; Kathryn Lurain, MD, MPH; Helen X. Chen, MD; Howard Streicher, MD; Ravie Kem, PharmD, MPH; Richard F. Little, MD, MPH; Elad Sharon, MD, MPH

Abstract

IMPORTANCE Anti-programmed death 1 and anti-programmed death ligand 1 (anti-PD1/PDL1) immune checkpoint blockade (ICB) constitutes the therapeutic backbone for multiple malignant neoplasms. People living with HIV (PLWH) have routinely been excluded from ICB clinical trials, thus inhibiting broad implementation of ICB to PLWH with cancer.

OBJECTIVE To evaluate trends in the inclusion of PLWH in ICB cancer clinical trials that have occurred in association with ongoing efforts by the Cancer Therapy Evaluation Program (CTEP), National Cancer Institute, to promote inclusion of PLWH.

DESIGN, SETTING, AND PARTICIPANTS This quality improvement study of ICB letters of intent (LOIs) included anti-PD1/PDL1 agents (nivolumab, pembrolizumab, atezolizumab, and durvalumab) submitted to CTEP that proceeded to approved protocols between January 2014 to May 2019. The setting was ICB clinical trial development and inclusion of underrepresented populations, specifically PLWH. All 97 submitted cancer clinical trial LOIs that included the aforementioned ICB agents were eligible for inclusion. Ten proposals were excluded, of which 3 were designed specifically for PLWH and 7 were LOIs that did not advance to approved protocols within the study period. Statistical analysis was performed from April to September 2020.

EXPOSURES CTEP advocacy included the requirement for justification of exclusion of PLWH and formal discussion of inclusion criteria during conference calls between CTEP and trial investigators.

MAIN OUTCOMES AND MEASURES The frequency of inclusion of PLWH in initially submitted LOIs was compared with final approved protocols using descriptive statistics. The probability of inclusion of PLWH in submitted LOIs and approved protocols over time was assessed using logistic regression.

RESULTS Eighty-seven studies were included, of which 68 (78%) were pilot, phase 1, phase 1/2, or phase 2 studies and 19 (22%) were phase 2/3 or phase 3 studies. Thirty-nine studies (45%) included nivolumab, 23 (26%) included pembrolizumab, 19 (22%) included atezolizumab, and 6 (7%) included durvalumab. At initial LOI stage, 14 of 87 (16%) included PLWH. Following CTEP advocacy efforts, 61 of 87 protocols (70%) included PLWH. Of 36 LOIs to initially exclude PLWH, 24 (67%) included PLWH in final protocols. Among the 25 protocols to exclude PLWH, 21 (84%) were earlier phase studies (pilot to phase 2) and 4 (16%) were later phase studies (phase 2/3 to phase 3). Only 13 of 25 protocols (52%) provided justification for exclusion of PLWH, with safety being the most frequently cited concern (9 of 13 studies). The inclusion of PLWH on submitted LOIs increased over time (odds ratio, 3.38; 95% CI, 1.14-3.91), whereas inclusion on final protocols did not increase over time (odds ratio, 1.80; 95% CI, 0.81-1.59).

(continued)

Key Points

Question Has inclusion of people living with HIV in anti-programmed death 1 and anti-programmed death ligand 1 (anti-PD1/PDL1) immunotherapy trials changed during ongoing Cancer Therapy Evaluation Program advocacy efforts by the National Cancer Institute?

Findings In this quality improvement analysis of 87 anti-PD1/PDL1 trials approved by the Cancer Therapy Evaluation Program from January 2014 to May 2019, the proportion of studies including people living with HIV increased from 16% of letters of intent to 70% of approved protocols. Inclusion of people living with HIV on submitted letters of intent increased over time.

Meaning This study's findings suggest that the increasing inclusion rates of people living with HIV in anti-PD1/PDL1 clinical trials are encouraging and that advocacy for these and other underrepresented populations should continue.

+ Supplemental content

Author affiliations and article information are listed at the end of this article.

JAMA Oncology | Original Investigation

Assessment of the Safety of Pembrolizumab in Patients With HIV and Advanced Cancer—A Phase 1 Study

Thomas S. Uldrick, MD, MS; Priscila H. Gonçalves, MD; Maher Abdul-Hay, MD; Alisa J. Claeys, MSW; Brinda Emu, MD; Marc S. Ernstoff, MD; Steven P. Fling, PhD; Lawrence Fong, MD; Judith C. Kaiser, MBA, BSN, RN; Andreanne M. Lacroix, BSc; Steve Y. Lee, MD; Lisa M. Lundgren, MS, RPh; Kathryn Lurain, MD, MPH; Christopher H. Parsons, MD, PhD; Sharavi Peeramsetti, MSc; Ramya Ramaswami, MBBS; Elad Sharon, MD, MPH; Mario Sznol, MD; Chia-Ching (Jackie) Wang, MD; Robert Yarchoan, MD; Martin A. Cheever, MD; for the Cancer Immunotherapy Trials Network (CITN)-12 Study Team

Video and Supplemental content

IMPORTANCE Anti–PD-1 (anti–programmed cell death 1) and anti–PD-L1 (anti–programmed cell death ligand 1) regimens are preferred therapies for many cancers, including cancers associated with HIV. However, patients with HIV were excluded from most registered trials

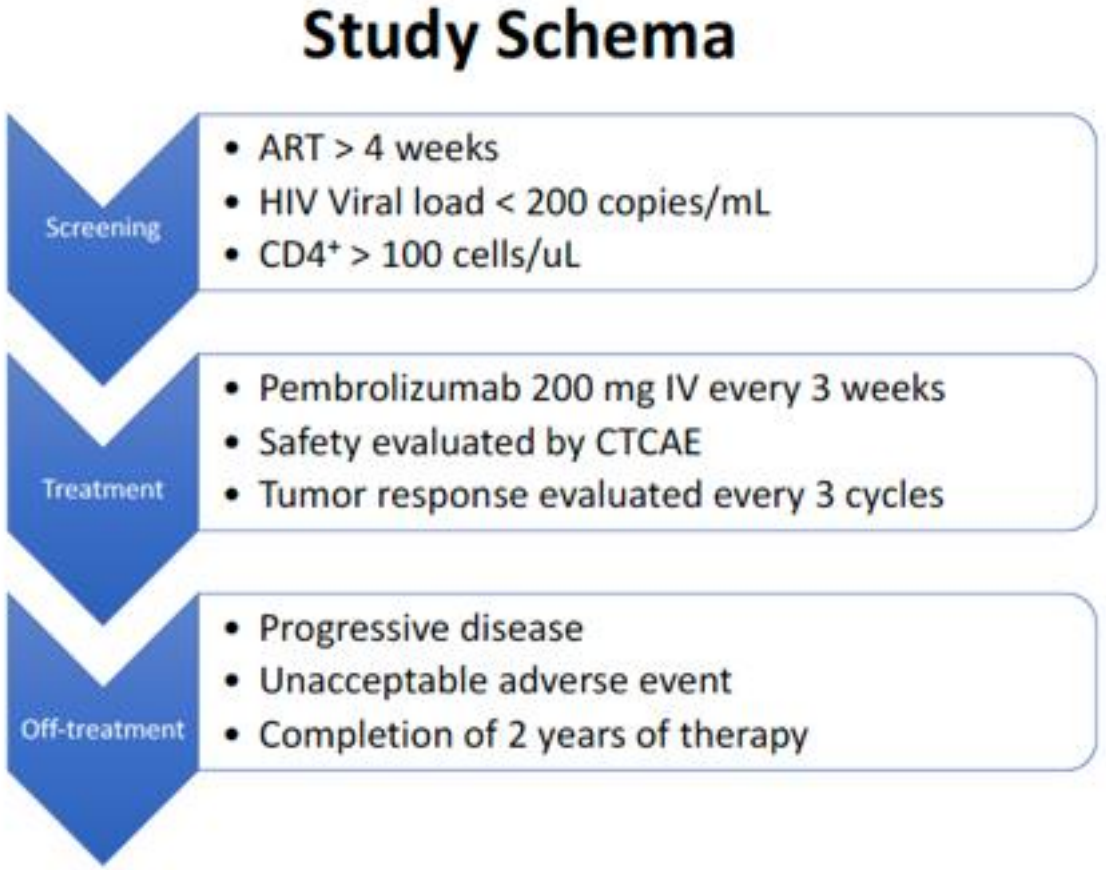
Cancer Immunotherapy Trials Network-12

Study Design

- Multicenter phase I study

Primary Objective

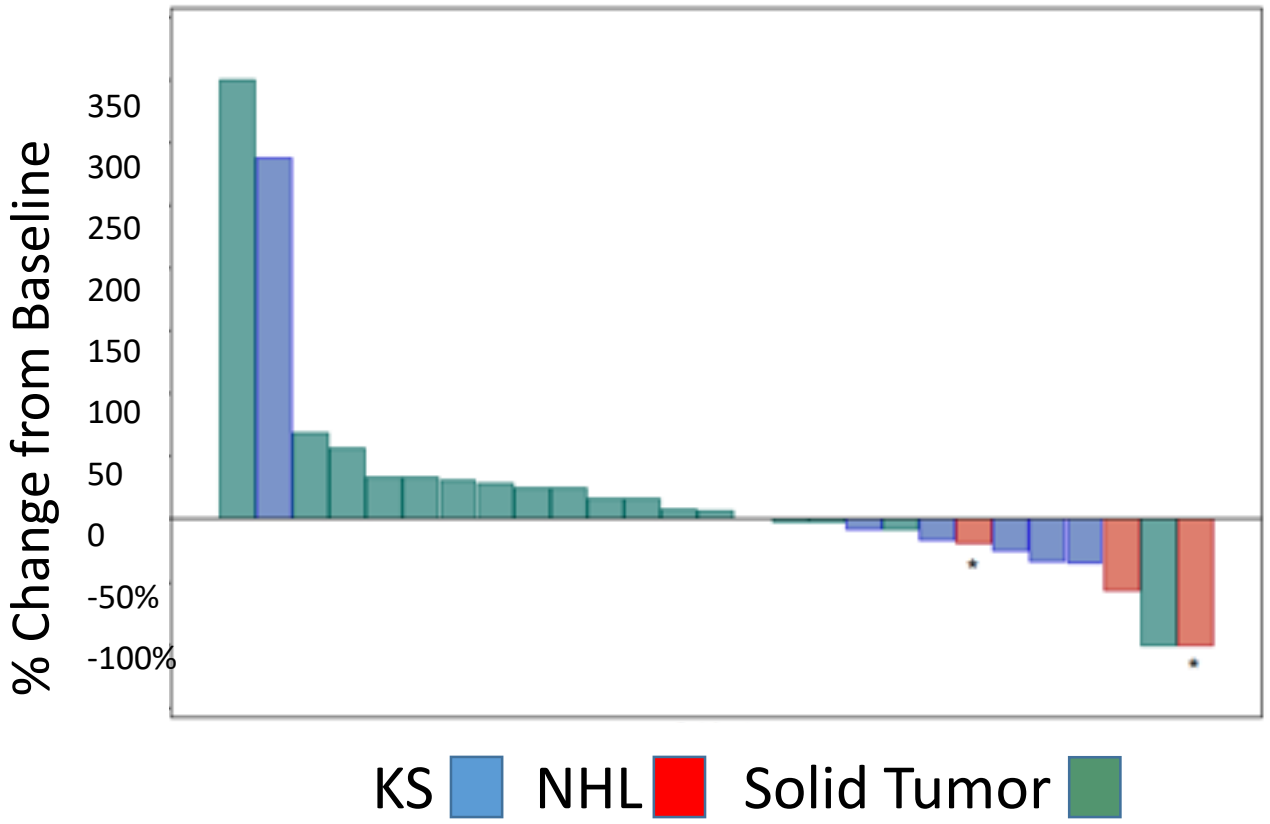
- Evaluate safety in 3 parallel cohorts
  - Cohort 1: 100-199 $CD4^+$ T cells/μL
  - Cohort 2: 200-350 $CD4^+$ T cells/μL
  - Cohort 3: >350 $CD4^+$ T cells/μL



Best Overall Response

Best Response	n
Complete	1 (Lung)
Partial	2 (NHL)
Stable >24 week	2 (KS)
Lugano Immune Response 3	2
Stable <24 week	13
Progressive Disease	8
Not evaluable	1

Waterfall Plot

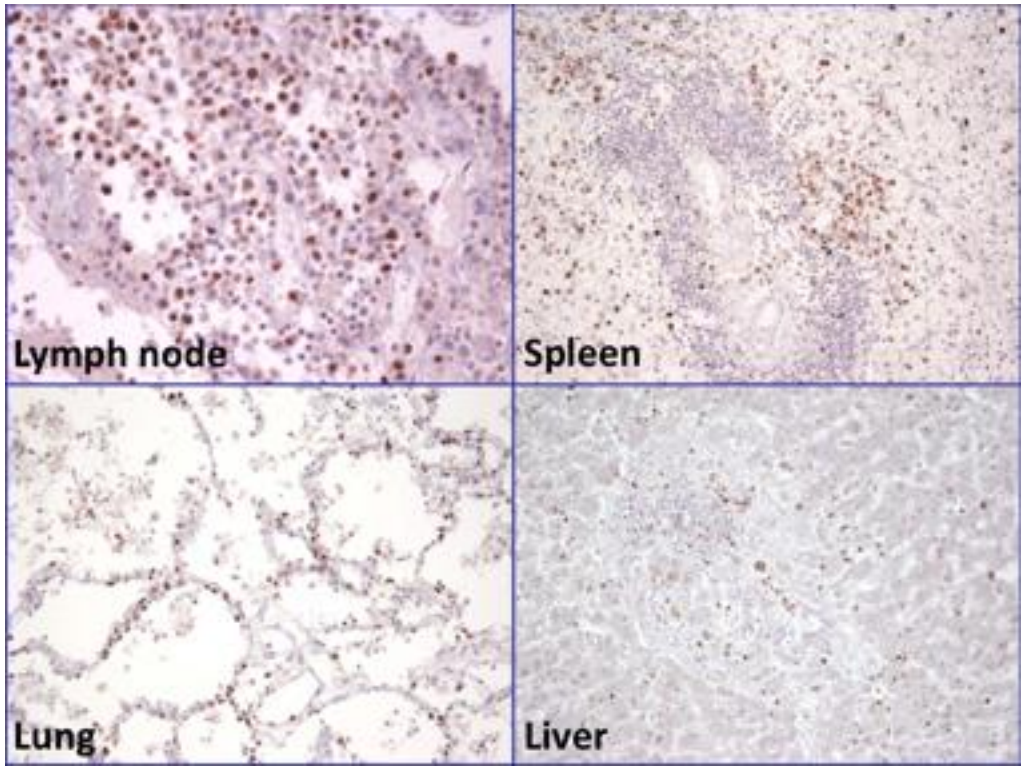


Death from polyclonal B-cell KSHV-associated lymphoproliferative disorder

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 153K copies/10^6 PBMCs
- 6/2017 Pembrolizumab,
  - $CD4^+$ T-cell count 210/uL
  - KSHV viral load 153K/10^6 PBMCs
- After second cycle,
  - edema, effusion, pulmonary infiltrate, thrombocytopenia
  - KSHV viral load 304K/10^6 PBMCs
- Rapid deterioration with anemia, thrombocytopenia, hyperbilirubinemia, volume overload progressing to death
- NOT observed in 5 other KS patients or 2 primary effusion lymphoma patients to date

KSHV Latency-Associated Nuclear Antigen



Summary

- Pembrolizumab has acceptable safety in cancer patients with HIV on ART and >100 CD4 cells/µL
- Pembrolizumab may be associated with polyclonal KSHV-associated B-cell lymphoproliferation
- Activity was noted in lung cancer, NHL, KS and liver cancer.
- Anti-PD-1 therapy is appropriate for FDA-approved indications and cancer clinical trials in this population
- Prospective evaluation of pembrolizumab as first systemic therapy in Kaposi sarcoma ongoing

Methods of Obtaining Answers

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- Immune-Related Adverse Event Biorepository
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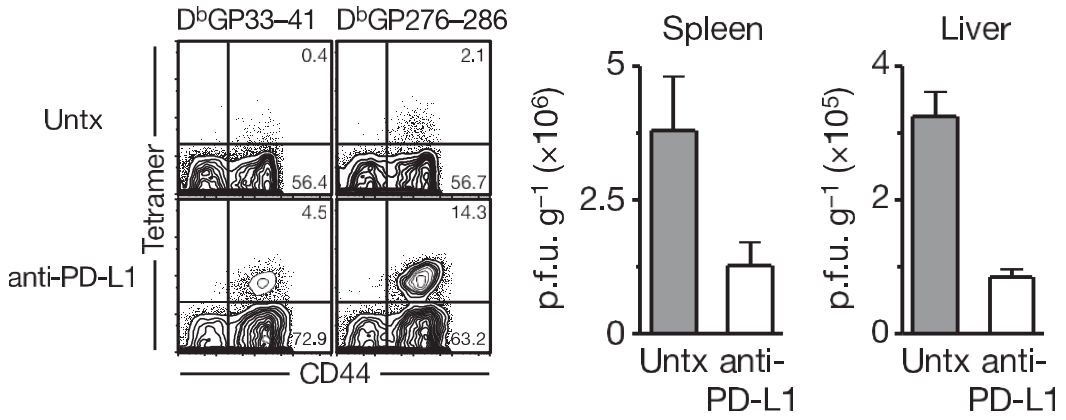
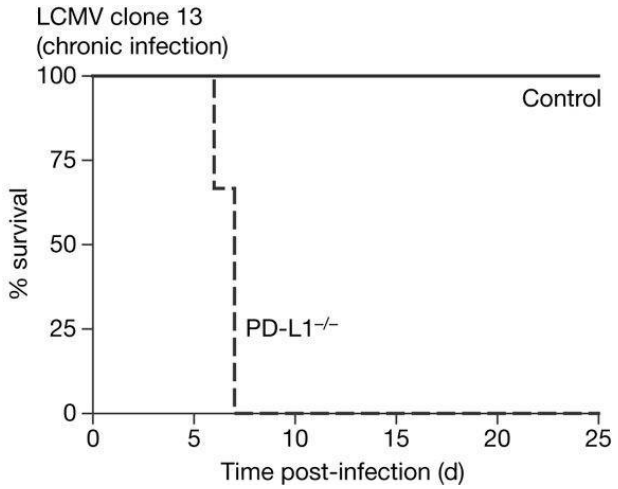
In the setting of infectious disease PD-1 pathway blockade can be either beneficial or detrimental

PD-L1 blockade late during chronic viral infection boosts the function of exhausted CD8 T cells

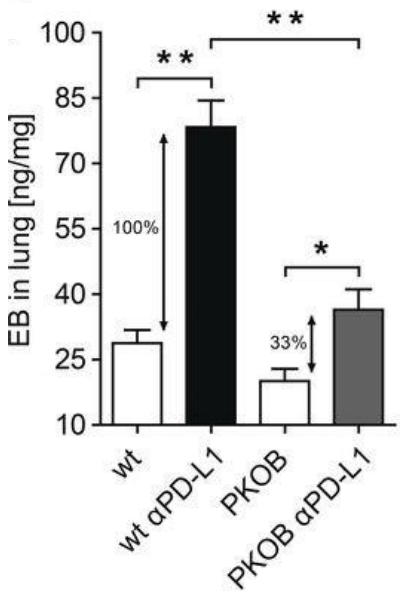


Barber et al *Nature* 2006

PD-L1 KO mice die early after chronic LCMV infection



perforin driven cytolysis drives loss of vascular integrity after PD-L1 blockade in chronic LCMV infection



Frebel et al *JEM 2012*

WHO GLOBAL TB REPORT 2016

Actions and investments to End TB fall far short

Tuberculosis among top 10 causes of death worldwide last year

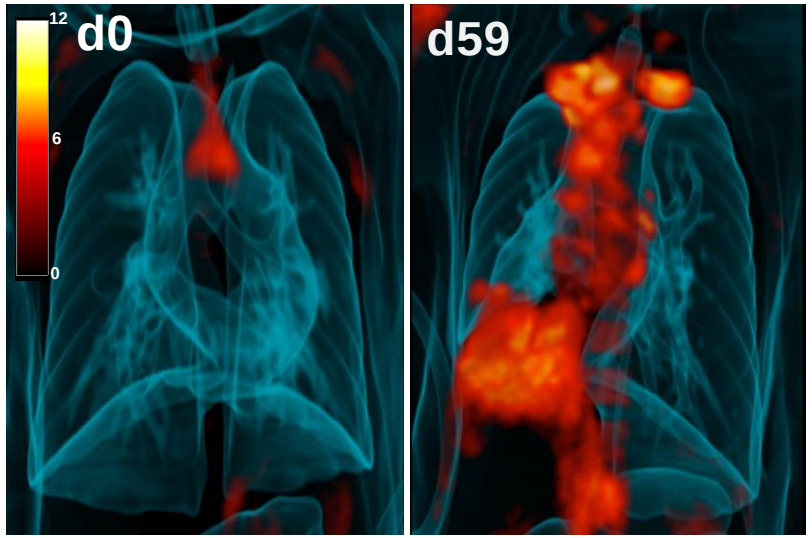
Here are the statistics from 2015

10.4 million people
FELL ILL FROM TB

1.8 million people
DIED FROM TB
including 400,000
WITH HIV + TB

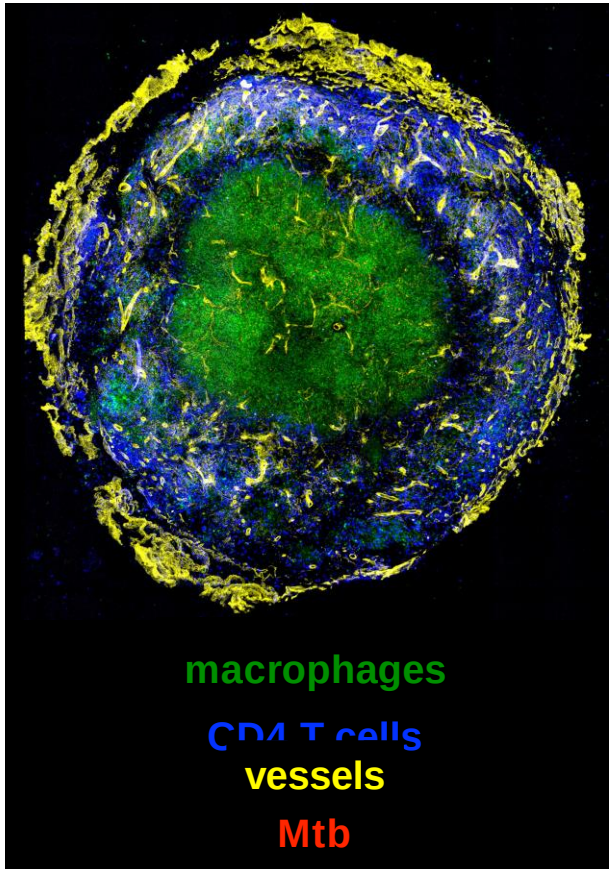
Key immunological features of tuberculosis

tuberculosis is primarily a lung infection

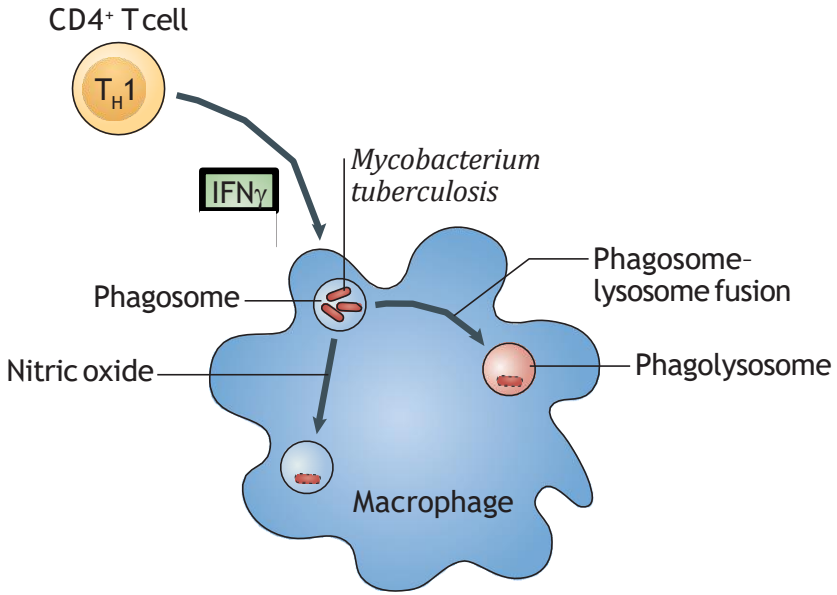


PET-CT scan of Mtb infected rhesus macaque

organized, complex immune structures called granulomas

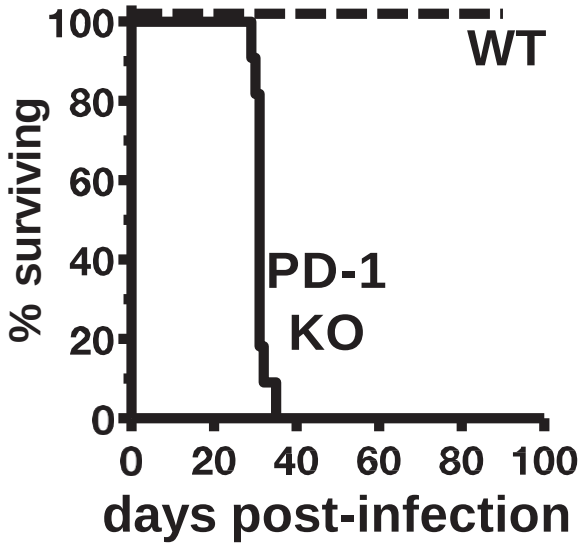


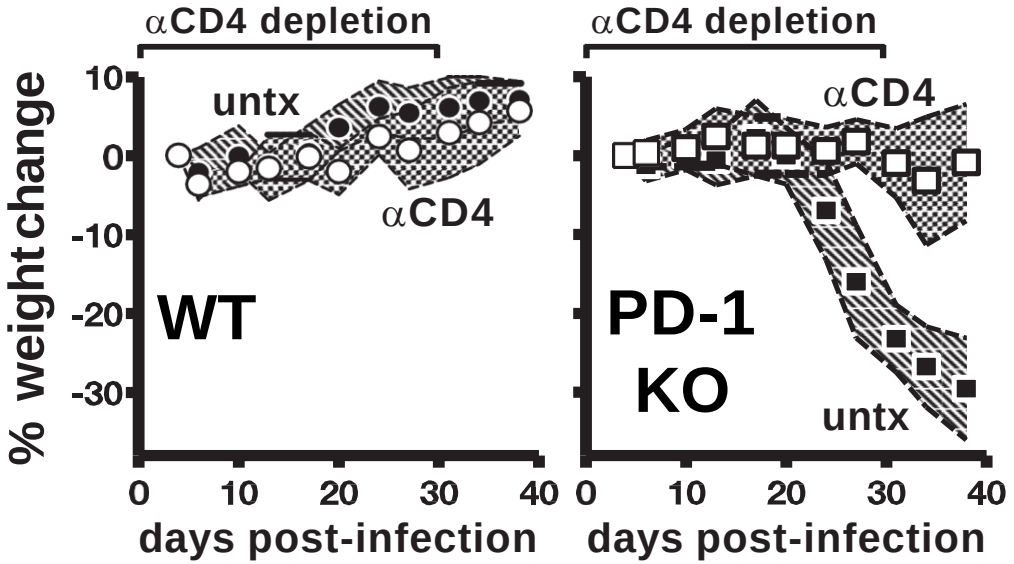
CD4 T cells and IFNγ are critical for control of Mtb infection

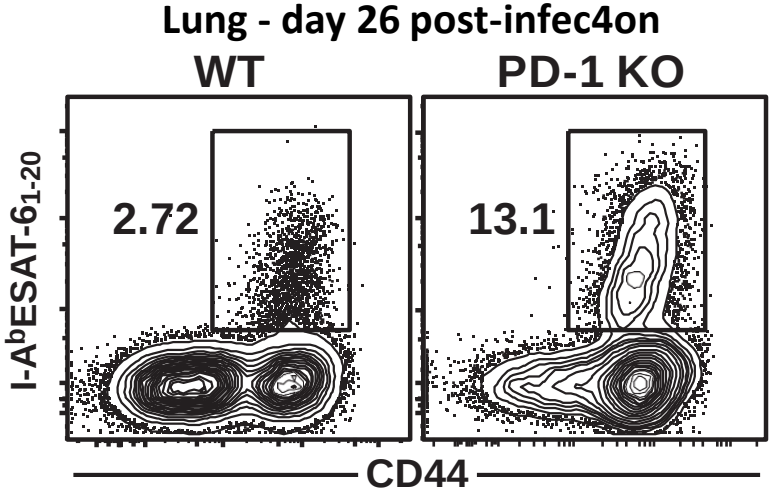


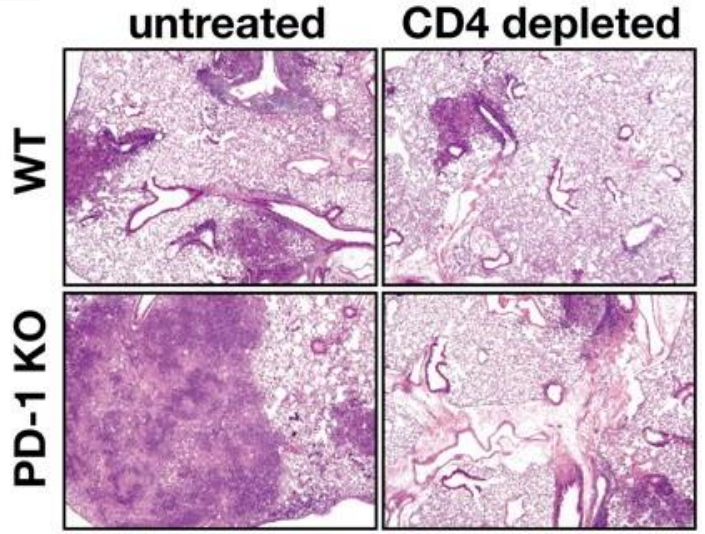
Adapted from Nunes-Alves et al Nature Reviews Microbiology 12, 289–299 (2014)

CD4 T cells drive early mortality in *Mycobacterium tuberculosis* infected PD-1$^{-/-}$ mice



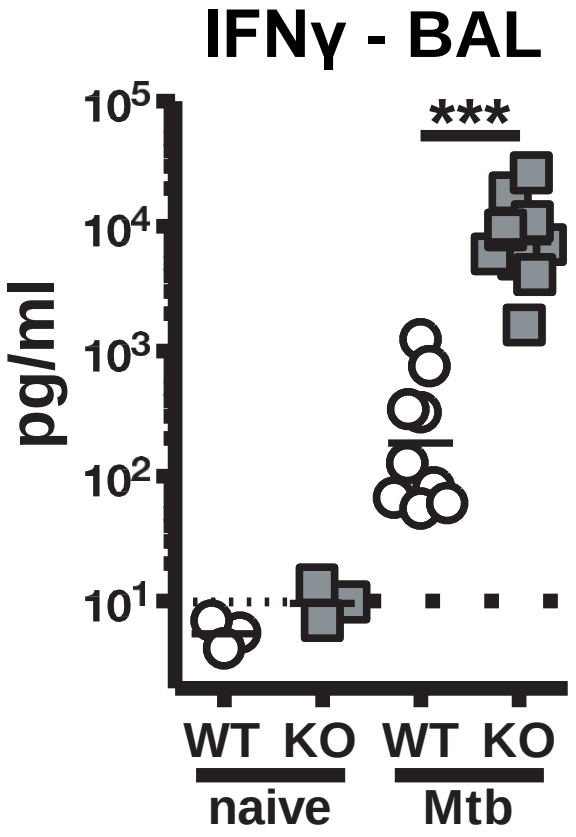


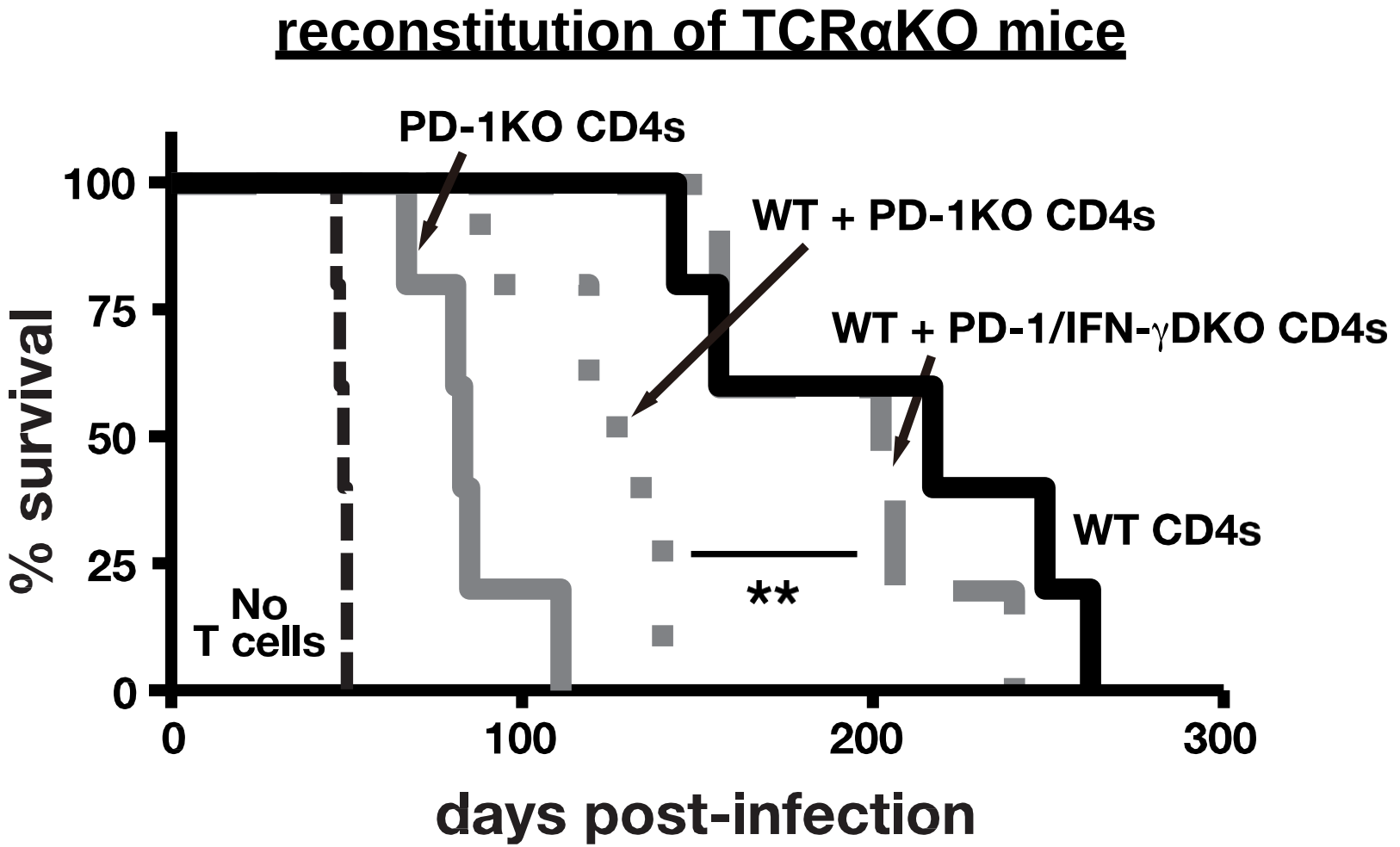




Barber et al *J. Immunol* 2011

CD4 T cell-derived IFNγ must be limited by PD-1 to prevent immunopathology in Mtb infected mice





Sakai et al *PLOS PATH* 2016

Based on the successes in cancer, PD-1 blockade is often proposed as a host-directed therapy for tuberculosis

International Journal of Infectious Diseases 56 (2017) 221–228

Contents lists available at ScienceDirect

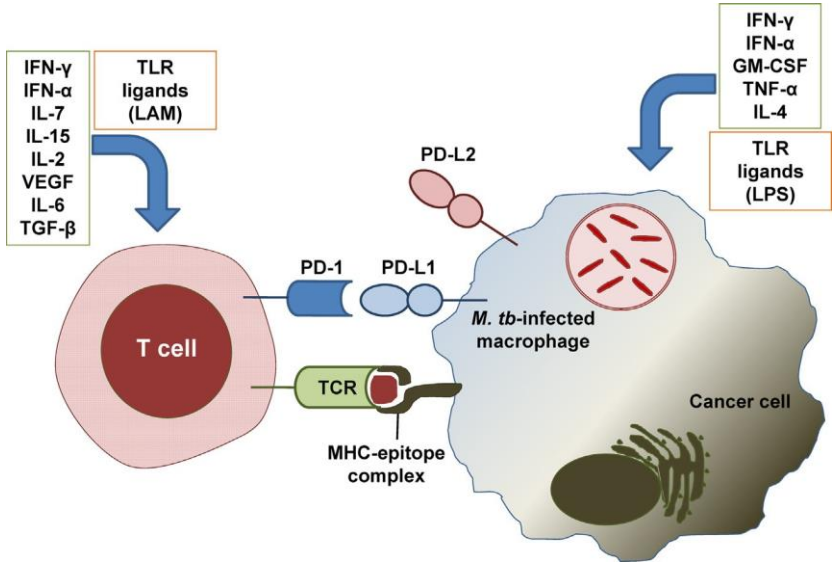
International Journal of Infectious Diseases

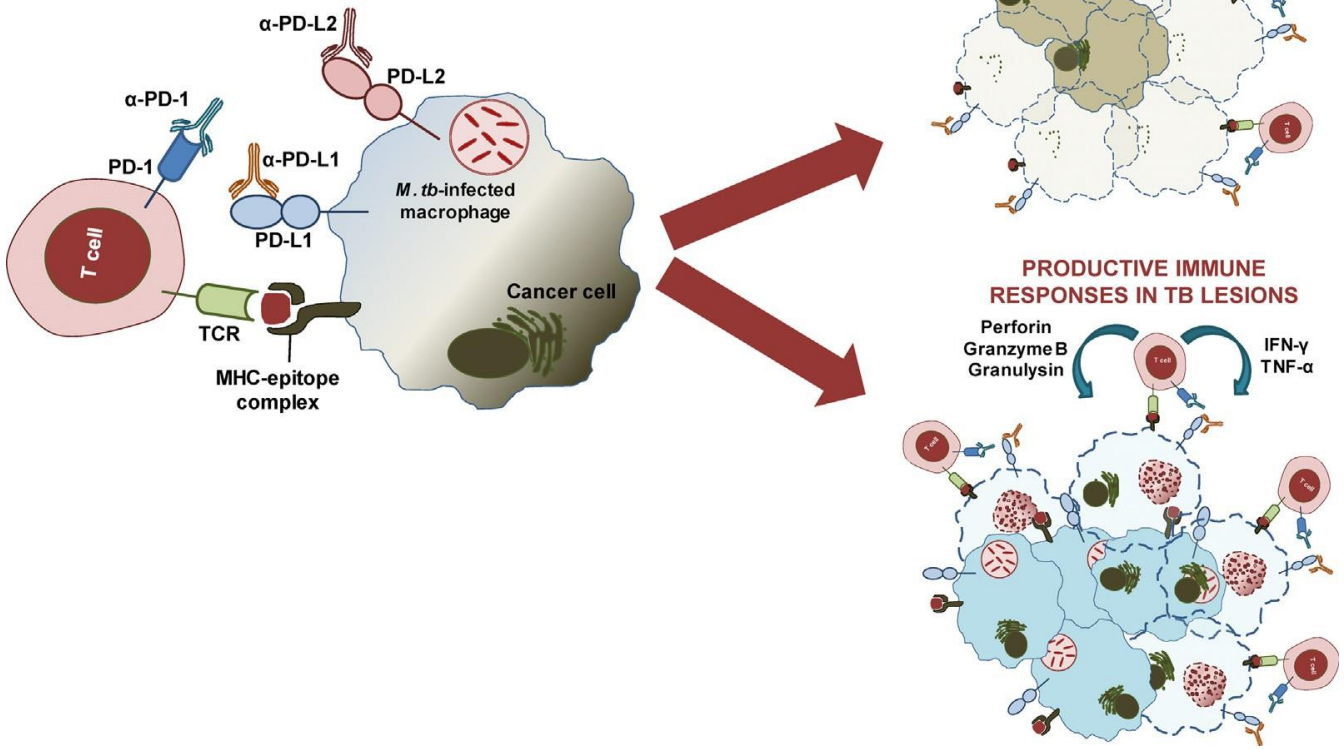
journal home page: www.elsevier.com/locate/ijid

Review

Anti-PD-1/PD-L1 therapy for infectious diseases: learning from the cancer paradigm

Martin Rao[a], Davide Valentini[a,b], Ernest Dodoo[a,c], Alimuddin Zumla[d], Markus Maeurer[a,b,*]





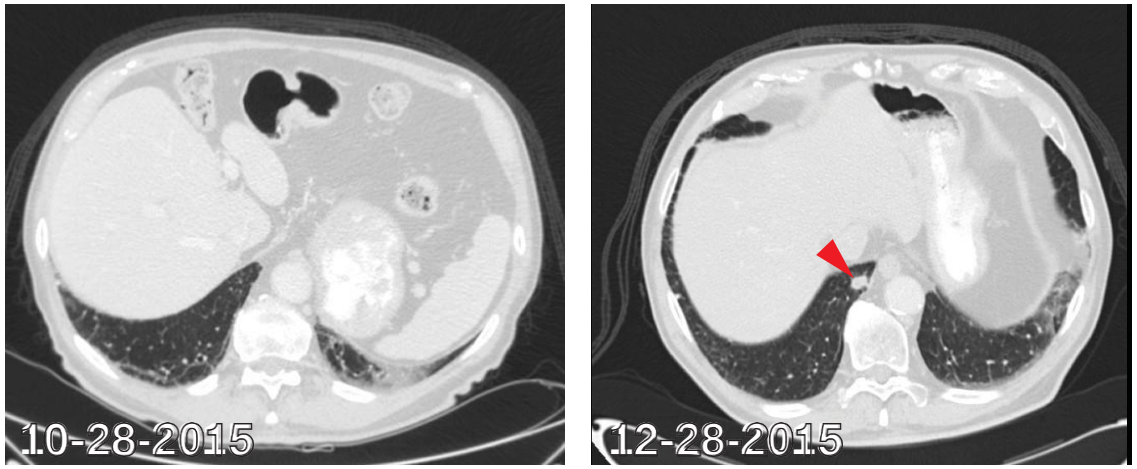
Case reports documenting tuberculosis after PD-1 blockade for cancer

- Tuberculosis reactivation in a patient receiving anti-programmed death-1 (PD-1) inhibitor for relapsed Hodgkin's lymphoma. Acta Oncol 2016;55:519-20.
- Anti-PD1 Antibody Treatment and the Development of Acute Pulmonary Tuberculosis. J Thorac Oncol 2016;11:2238-40.
- Pericardial Tamponade Caused by a Hypersensitivity Response to Tuberculosis Reactivation after Anti-PD-1 Treatment in a Patient with Advanced Pulmonary Adenocarcinoma. J Thorac Oncol 2017;12:e111-e4.
- Development of pulmonary tuberculosis following treatment with anti-PD-1 for non-small cell lung cancer. Acta Oncol. 2018 Jan 31:1-2.
- Two other cases reported to REISAMIC, the French irAE registry, were described in a review article. Clinical Microbiology and Infection 24 (2018) 216e218
- Product label of Atezolizumab indicates that mycobacterial infections were observed.

Tuberculosis after PD-1 blockade for Merkel cell carcinoma

- 83 year old individual treated with pembrolizumab for Merkel cell carcinoma.
- Developed lung lesion at cycle 11.

~4 months after αPD-1 **~6 months after αPD-1**



Collaboration with Dan Barber, NIAID and teams at Emory U., Fred Hutchinson CRC, U. W., U. Florida College of Medicine and IDRI

Barber DL *et al. Sci Trans Med*. 2019

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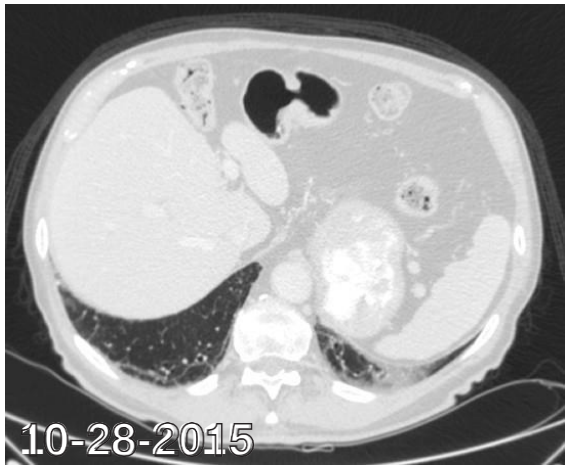

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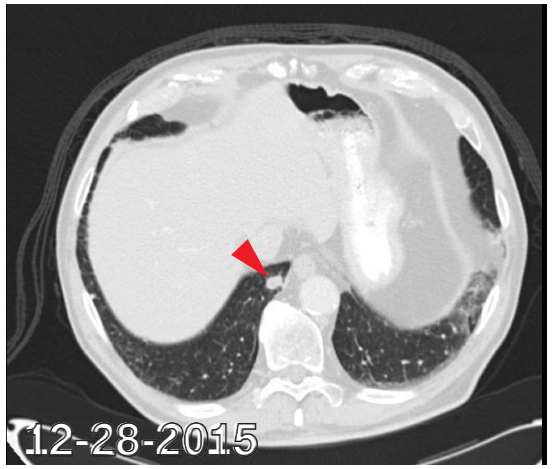
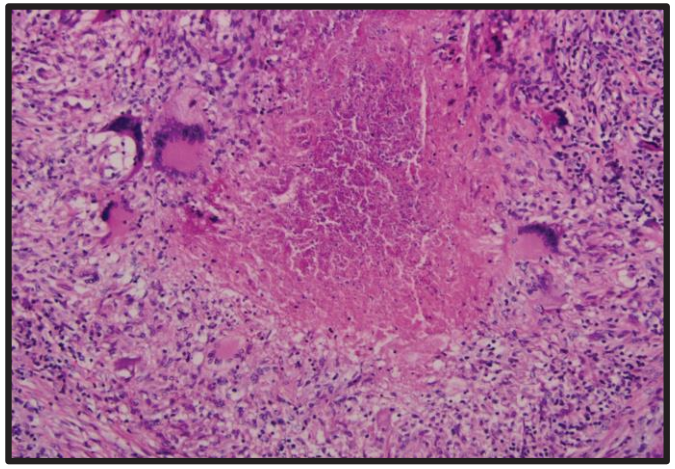


necrotic granuloma



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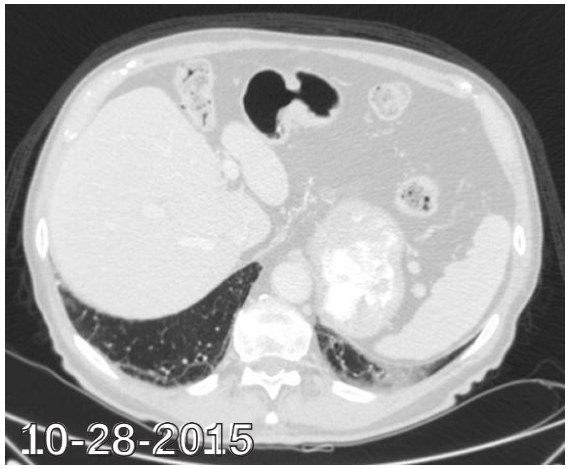

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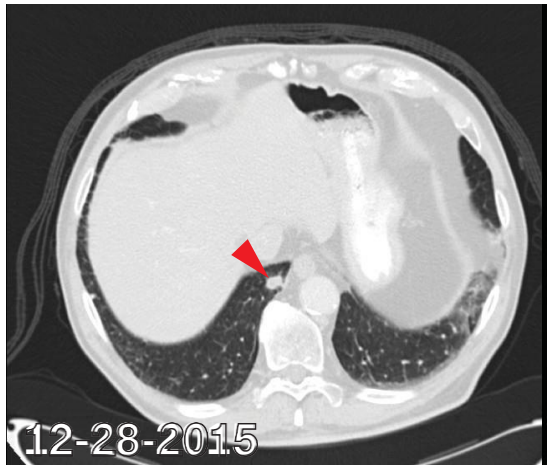

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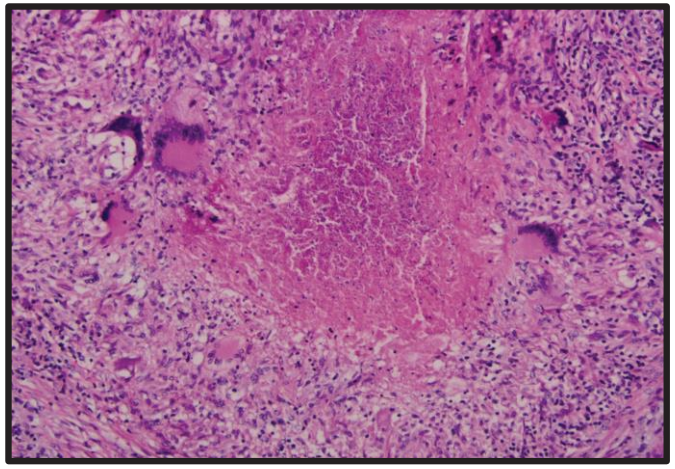
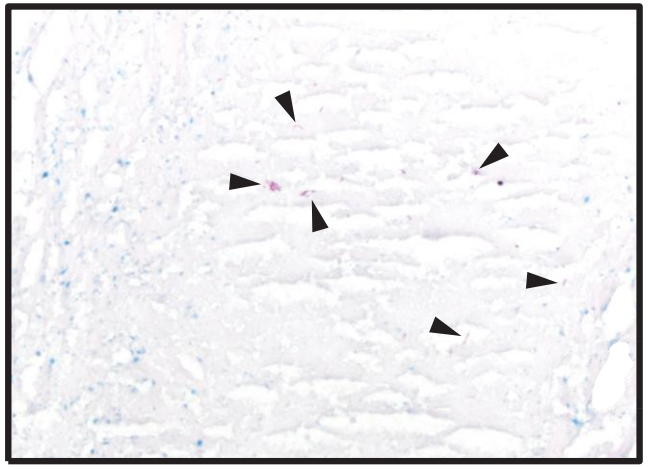


acid fact bacilli



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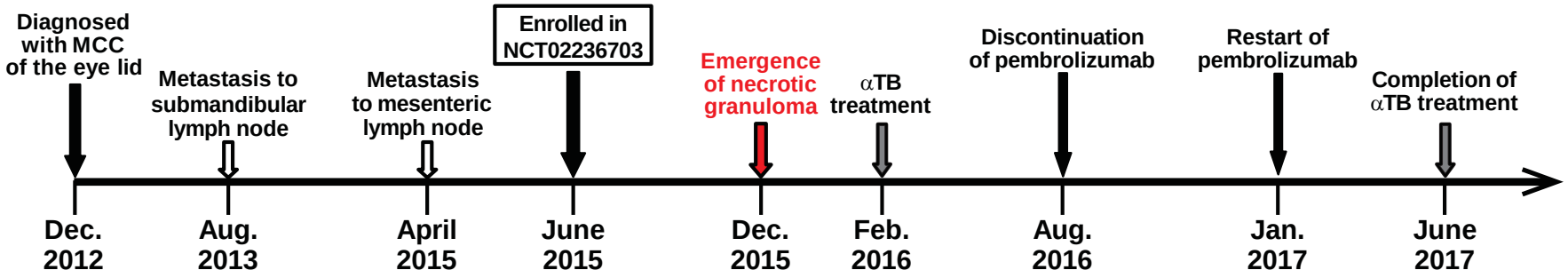

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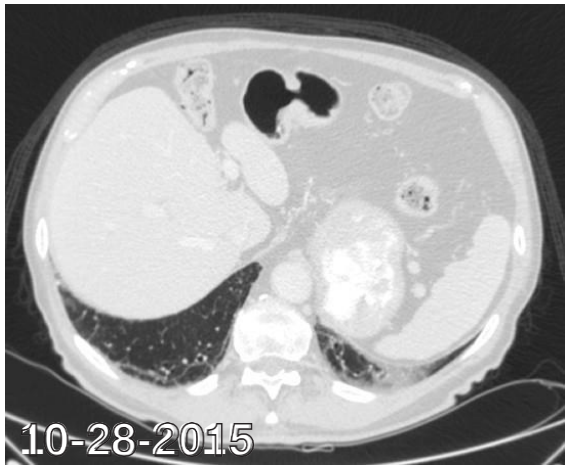

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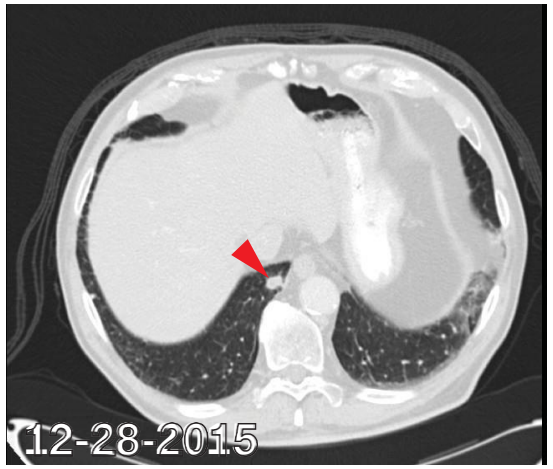
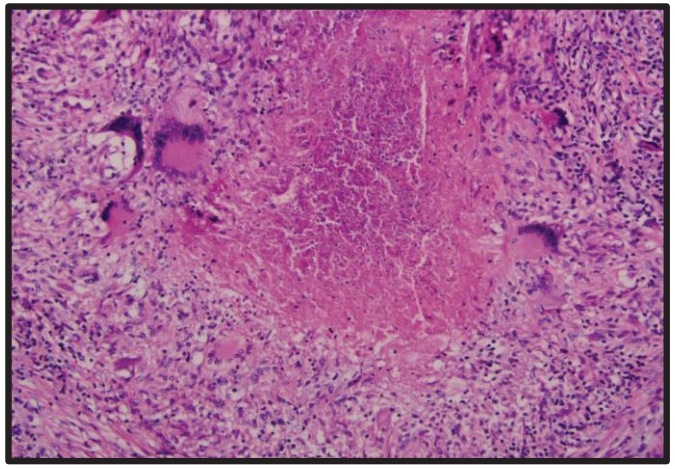
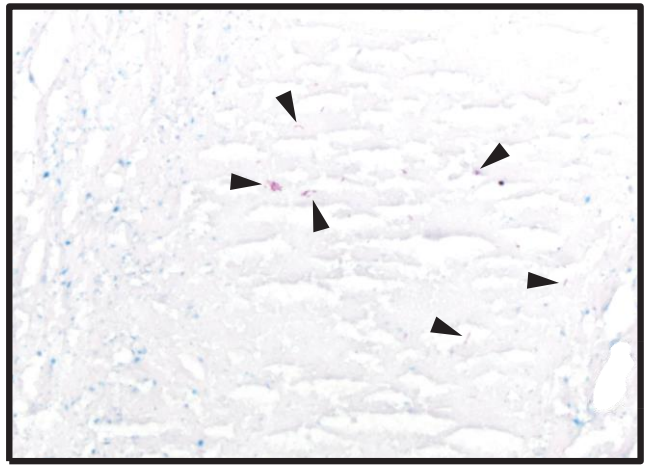


necrotic granuloma



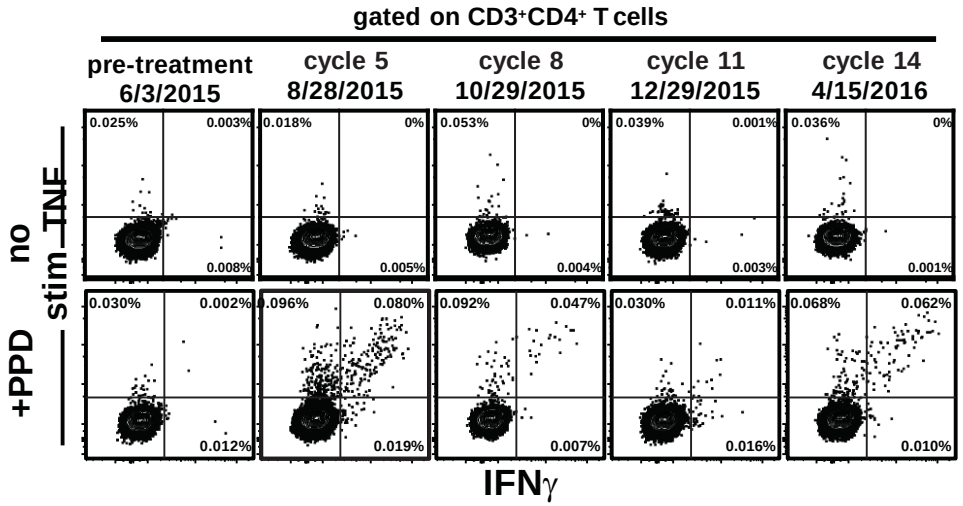
acid fact bacilli

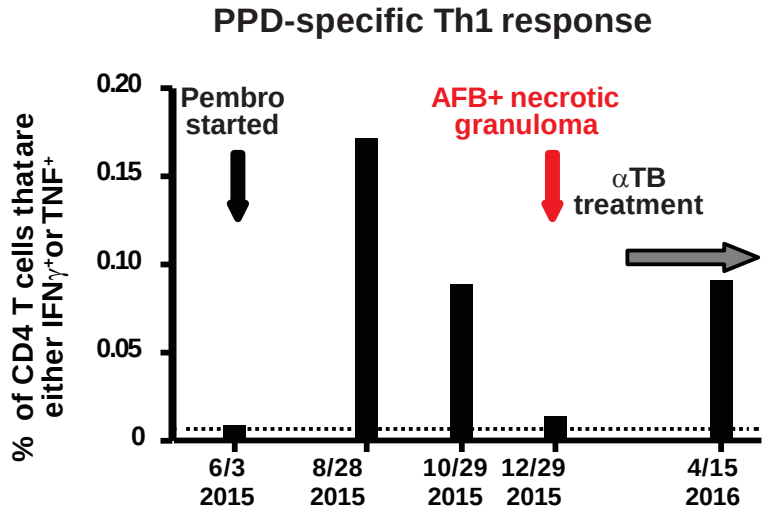


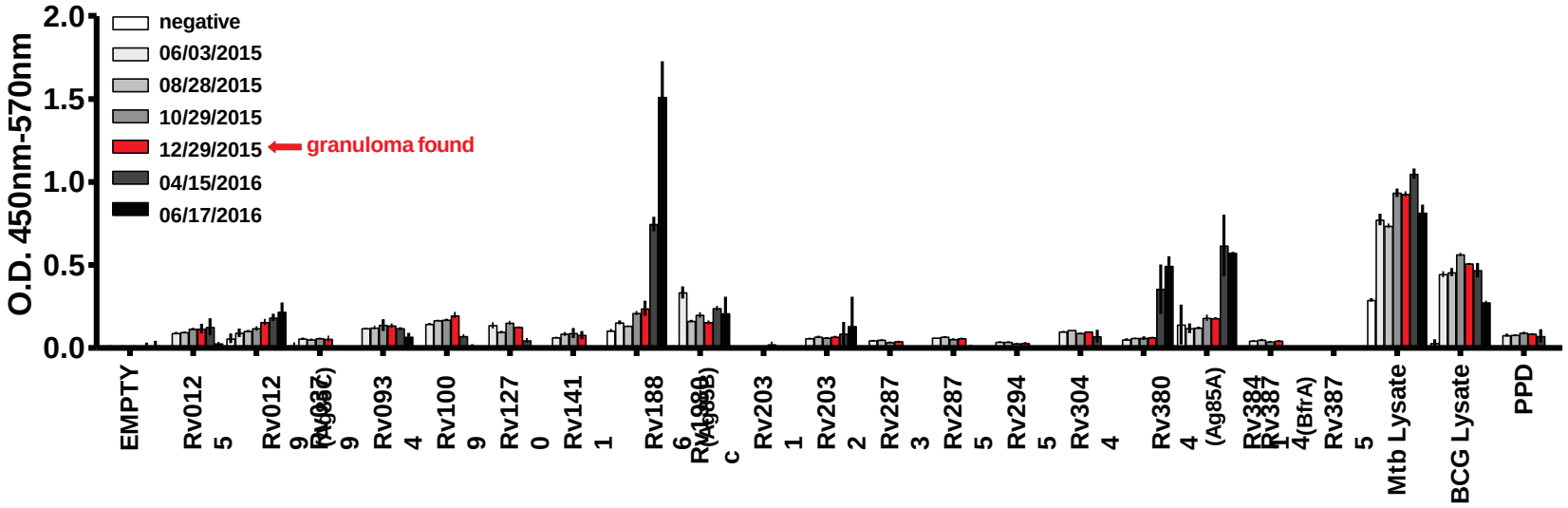
Collaboration with Dan Barber, NIAID and teams at Emory U., Fred Hutchinson CRC, U. W., U. Florida College of Medicine and IDRI

Barber DL *et al. Sci Trans Med*. 2019

Increased mycobacteria-specific Th1 cells prior to development of necrotic granuloma after PD-1 blockade



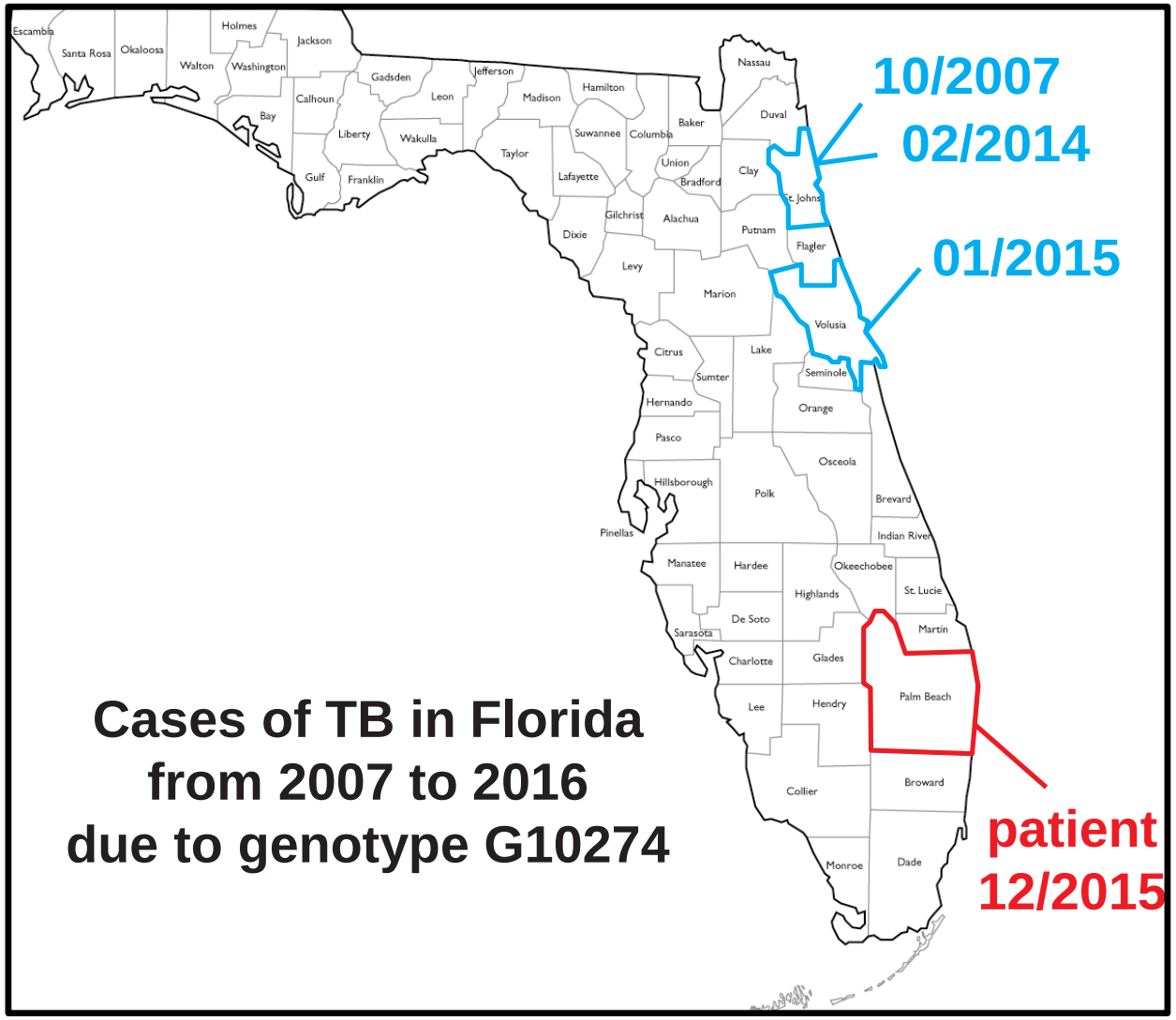




Barber DL… Sharon E *Sci Trans Med*. 2019

TB in this individual was most likely due to reactivation

- No skin test or IGRA was done before entering trial
- The patient had never been diagnosed with Mtb
- No recent travel to TB endemic regions or known exposures
- Mtb isolated from the patient was sub lineage 4 Euro-American strain
- This Mtb strain was not associated with any local transmission



Alliance-NCI irAE biorepository

Development of an irAE Biorepository: Tissue & Data Procurement Project from Patients with irAEs on Clinical Trials or Standard of Care with Immune Checkpoint Inhibitors

Protocol PI: David Kozono, DFCI

Summary

- During tuberculosis, PD-1 is required to limit the pathogenic overproduction of IFNγ by CD4 T cells.
- There is an increasing number of case reports showing tuberculosis after PD-1 blockade immunotherapy for cancer, although it is still not clear if there is a direct link.
- Future studies of tuberculosis (and other infections) during PD-1 blockade cancer immunotherapy are needed.
- Building a mechanism to rapidly evaluate rare irAEs can help facilitate translational research and improve safety for patients

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www.cancer.gov www.cancer.gov/espanol