A5370

Safety and Immunotherapeutic Activity of an Anti-PD-1 Antibody (Cemiplimab) in HIV-1-Diagnosed Participants on Suppressive cART: A Phase I/II, Double-blind, Placebo-controlled, Ascending Multiple Dose Study

Pre-CROI Community HIV Cure Research Workshop Saturday
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ACTG
AIDS CLINICAL TRIALS GROUP

Background

- ART effectively suppresses HIV RNA to undetectable levels in most PLWH.

- Why persistent viremia fails to stimulate effective HIV-specific T cell responses and virus-producing cells are not cleared is not understood.

- Chronic low level viremia suppresses HIV-specific cellular immune responses.

- The resulting T cell "exhaustion" is characterized by impaired T cell function and cell survival

- In PLWH receiving suppressive ART, CD4+ T cells express high levels of PD-1 (programmed cell death-1) markers and other immune checkpoint molecules.

- <u>Anti-PD-1 antibodies may reverse immune exhaustion and boost the immune system to target the latent viral reservoir.</u>

Rationale
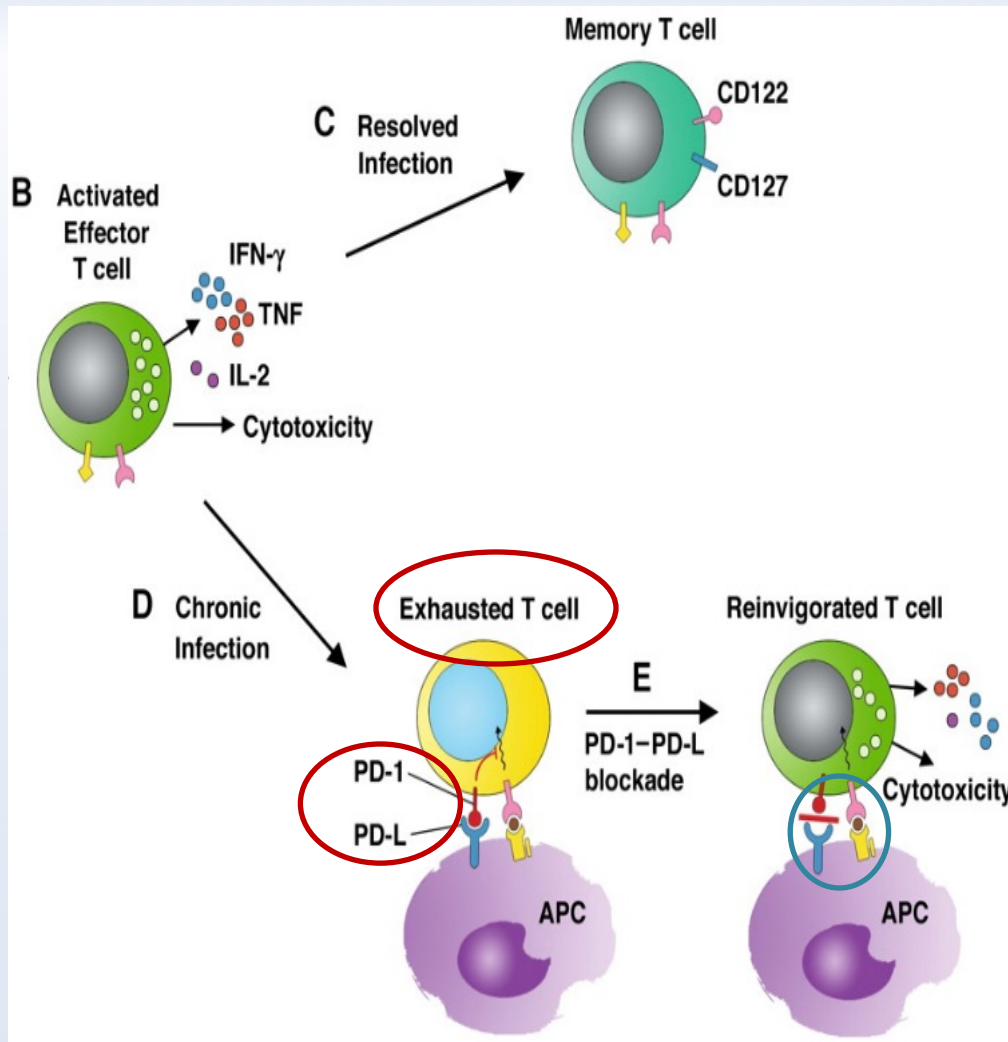
PD-1 is an **immune checkpoint marker** expressed on activated T cells and involved with immune tolerance.

When PD-1 binds to its inhibitory receptor PDL-1, it dampens T-cell responses and is a marker of immune exhaustion seen in chronic HIV, other viral infections and cancer.

Figure adapted from: Freeman, G, Wherry, J, Ahmed R. et al. JEM 2006, 203 (10): 2223;

Rationale

- Immune checkpoint inhibitors (ICIs) have revolutionized cancer treatment with several FDA- approved agents now available for a variety of tumor types.

- T cell exhaustion mediated by PD-1/PD-L1 may be a barrier to HIV eradication.

- Prior study showed CD8^{+} T cells from patients suppressed on ART were unable to kill infected resting CD4^{+} cells after HIV reactivation, suggesting impaired CTL function.[1]

- *In vitro* or *in vivo* blockade of PD-1/PD-L1 in NHP studies of SIV
  - Reduced viremia[2,3], prolonged survival[2], increased Ag-specific T cell function[2,3,4]

- Data suggests CD4^{+} T cells expressing PD-1 are enriched for latent HIV
  - making anti-PD-1 antibodies a relevant, targeted strategy.[6]

[1]Shan et al. Immunity 2012, 36(3):491-501; [2]Velu V, et al. Nature. 2009; [3]Whitney et al. 6th International Workshop on HIV Persistence, 2013; [4]Fuller MJ et al. Proc Natl Acad Sci USA 2013; [5]Margolis DM et al. Science, 2016; [6]Fromentin R et al. *PLoS Pathog.* Jul 2016.

Background

Cemiplimab is an antibody to PD-1 which has been given to 534 cancer patients in multiple doses. FDA-approved 2018 (Libtayo®) for treatment of metastatic, advanced skin cancer (squamous cell carcinoma).

- **R2810-ONC-1423 (n=26)** and **R2810-ONC-1540 (n=82):**
  - 3mg/kg <u>every 2 weeks</u> for up to 48 or 96 wks, respectively with other anti-cancer therapies (surgery/radiation)
  - Objective response (disease control) - 47%
    - 44% - partial response,
    - 4% - complete response
  - Duration of response
    - Range - 1 to 15 months
    - >6 months – 61%

Libtayo® FDA Package Insert (9/2018); accessed January 23, 2019
https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/761097s000lbl.pdf

Risk vs Benefit

- Although participants will receive no direct benefit and ICIs are associated with immune-related adverse events (irAEs), and potentially irreversible irAEs, there remains a strong desire in PLWH and the HIV community at large, to pursue HIV cure and remission strategies.

- Widely accepted that therapies which improve HIV-1-specific immune responses will be necessary with any HIV remission or eradication strategy.

- There is sufficient expectation this study will show an improvement in HIV-1-specific immune responses (e.g., A5326 [Anti-PD-L1 Antibody in HIV-1]) and the potential for latency reversal such that results would advance the field.

Study Design

Phase I/II, placebo-controlled study of 2 IV infusions of cemiplimab at weeks 0 and 6, among 3 sequential dose-escalating cohorts

- Cohort 1 will receive 0.3 mg/kg IV or placebo
- Cohort 2 will receive 1 mg/kg IV or placebo
- Cohort 3 will receive 3 mg/kg IV or placebo

Each cohort will have 15 participants

- 12 active and 3 placebo = 45 total participants

Accrual: Require ≥ 9 wks of safety follow-up of each cohort prior to dose escalation (total enrollment ~20 mo)
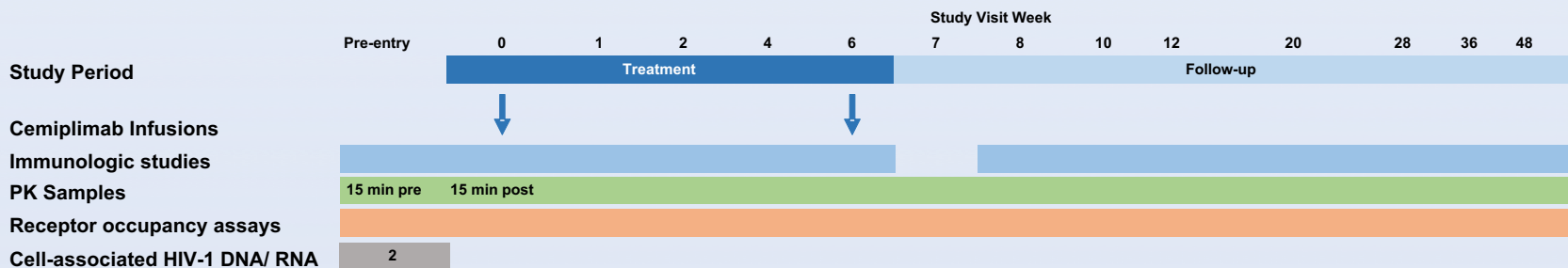
PRIMARY OBJECTIVES / ENDPOINTS

Hypothesis

Two doses of an anti-PD-1 antibody (cemiplimab) will be safe in PLWH on ART and enhance HIV-specific immune responses.

Safety

Assess safety of 2 infusions of 0.3, 1, and 3 mg/kg dose levels of cemiplimab vs placebo

- Occurrence of a Grade ≥ 3 AE or
- Grade ≥ 1 immune-related AE, possibly related to study treatment any time from study treatment administration through week 48.

Immunologic

Evaluate change in T cell immune response from baseline to several time points after 2 doses of cemiplimab (average of responses from weeks 2, 4, 6, 8, 10 and 12) vs placebo

Risk Mitigation

- Focus on PLWH with well-controlled viremia on ART and high CD4+ counts without acute infection or malignancy

- Thoughtfully designed dose-escalation protocol with close clinical and laboratory monitoring to minimize risk
  - SAEs and irAEs reported w/in 24 hrs and to FDA and IRBs, Safety Monitoring Committee, stopping rules

- Limit to 2 doses separated by 6 weeks for extended safety monitoring prior to the second dose, vs every 2 week dosing in cancer studies

Risk Mitigation

- <u>Exclude</u> individuals at increased risk for irAEs: prior autoimmune disorder, pneumonitis, pre-existing conditions that could make detection/attribution of potential irAEs difficult (COPD, heart failure), pre-existing specific auto-antibodies or current/history of endocrine disorders

- Adapted guidelines for toxicity management of irAEs to ensure prompt detection and appropriate management (pausing criteria for SMC review)

- Participants could not have end-organ disease present- in cancer patients that may increase toxicity risk or hinder early recognition of an irAE

STUDY POPULATION

- PLWH, age $\geq$18 and <65 on stable cART ≥2 years

- Undetectable HIV-1 RNA x 2 in 18 months

- CD4+ cell count $\geq$350 cells/mm^3 *

- No active HCV or HBV infection; cured HCV infection OK

- No history of or active autoimmune disorder, adrenal insufficiency, pre-/diabetes, thyroid disorder, inflammatory eye disease*

- Normal AST, ALT, bilirubin; morning cortisol >10 mcg/dL and < ULN; normal thyroid hormone levels, normal HgbA1c and fasting blood sugar*

- Negative antibody test results for: thyroid peroxidase (TPO), glutamic acid decarboxylase 65 (GAD65/GAD), and islet cell antigen*

- Antinuclear antibody (ANA) <1:80 at screening*

- No prior radiation therapy; no history of cancer or AIDS-OI w/in 5 years*

- Negative IGRA for TB unless completed prophylaxis treatment

* Exclusion criteria not used in previous cancer studies

Safety Data

- Toxicities observed with cemiplimab are similar to those seen with other FDA-approved anti-PD-1 mABs (nivolumab and pembrolizumab).

- Immune-related AEs (irAEs) with no clear trend in frequency or ≥Grade 3 AEs with higher or multiple doses.

- Due to increased experience in cancer field, there are clinical algorithms for the management of more common irAEs.

- **High suspicion and prompt management of new symptoms is critical** and has resulted in decreased severity of irAEs and improved clinical outcomes.

Toxicity Management

- Detailed instructions for recognition, grading and management of infusion-related, immune-related and other local and systemic adverse effects derived from sponsor's (Regeneron) collective clinical trial experience with cemiplimab, recently published review of AEs seen with ICIs, consultation with oncology investigators and experience from A5326.

- All A5370 participants with any grade irAE will not receive additional cemiplimab dosing.

[1]Michot, et al., Eur J. Cancer 2016; [2]DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Events, Version 2.1, March 2017, http://rsc.tech-res.com/clinical-research-sites/safety-reporting/daids-grading-tables; [3]NCI's Table for Common Terminology Criteria for Adverse Events (CTCAE), version 4.0, https://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-0614_QuickReference_8.5x11.pdf.

STUDY PAUSE CRITERIA

- Enrollment suspended and SMC review if:
  - Three or more participants have Grade ≥3 event definitely, probably, or possibly related to treatment (per team assessment); or

  - Two or more participants experience an immune-related AE that is definitely, probably, or possibly related to study treatment:
    - Grade ≥1 pneumonitis (lung inflammation), adrenal insufficiency, myocarditis (heart inflammation), diabetes or uveitis (eye inflammation)
    - Grade ≥2 colitis (colon inflammation), myositis (muscle inflammation), rash, hyper- or hypothyroidism, or elevated AST or ALT

  - One or more participants experience a Grade 4 AE that is definitely, probably, or possibly related to study treatment.

- If enrollment safety pause criteria are met, participants already enrolled will not receive the second infusion pending SMC review.

INFORMED CONSENT

- Informed Consent Form (ICF) explicitly states that the risks of irAEs, as well as their <u>potential irreversibility</u>, which may necessitate lifelong treatment.

- The study physician investigator will directly participate in the informed consent process to support participants' understanding of all study related activities.

Assessment of Understanding

- The informed consent process includes an Assessment of Understanding tool to evaluate participants' comprehension of the risks and lack of direct benefits of study participation.

Study Results

Five participants enrolled and received 0.3 mg/kg cemiplimab (n=4) or placebo (n=1).

- Participant #1: 50-yo male with protocol-acceptable baseline labs, CD4+ count of 1957/mm^3 and normal TSH/free T4 revealed hyperthyroidism on routine safety labs at 4 weeks after 1st infusion.

- Mild fatigue was the only symptom and attributed to chronic depression and recent change in anti-depressant medications.

- Per protocol for possible irAEs, 2nd infusion was held; one week later repeat labs confirmed thyroiditis judged probably related to study drug.

Participant #2

- 57-yo male with protocol-acceptable baseline labs including CD4+ count 911/mm^3 and normal baseline AST/ALT, but Grade 1 elevations in AST/ALT pre-infusion, had asymptomatic Grade 3 AST and ALT elevations 2 weeks after 1st infusion.

- He reported one dose of acetaminophen and alcohol consumption (6 beers and 2 whiskey drinks) 12 hours before week 2 labs were drawn. Per protocol for irAEs, 2nd infusion held.

- AST/ALT elevations resolved 35 days after the 1st infusion without intervention. Consultation with local hepatology service found no autoimmune etiology or hepatic synthetic dysfunction but did elicited undisclosed chronic alcohol use.

- Transaminase enzyme elevation pattern (AST=ALT) and slow resolution were deemed inconsistent with acute alcohol toxicity and therefore were judged possibly related to study drug.

Study Results (con't)

- Safety Monitoring Committee recommended halting accrual and further infusions.

- Two participants received both infusions without report of adverse events or laboratory abnormalities.

- All 4 treated participants remain in follow-up.

Topics for Discussion

- Risk tolerance in HIV cure studies
  - What level of risk is acceptable in quest for cure?
  - How high should we place the bar?
- Risk assessment/tolerance
  - From perspective of PLWH
  - From perspectives of investigators, IRB, FDA
- Translating successful therapies from cancer or immunotherapy research to HIV cure research
  - Is curing HIV comparable to curing cancer or autoimmune diseases?

Topics for Discussion

- Were study participants adequately screened to predict risk of developing irAEs?

- What additional screening studies could have been done?

- Is irAE thyroid disease predictable?

- "Natural history" of irAE thyroid disease?

- Long-term outcome of irAE disease

Topics for Discussion

- Adequate socio-behavioral screening of study participants

- Pursuing etiology of irAEs or AEs in general in HIV cure studies (e.g., liver biopsy)
  - Value to field of HIV cure developmental research?

- Criteria for thorough and adequate evaluation of new agents for HIV cure.

Questions?