ACTIVATE
The tribulations of a panobinostat/interferon-α cure trial

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Background

- HDACi are effective in reversing viral latency in 4 studies (Panobinostat, Vorinostat x2, Romidepsin)
- No significant HIV-1 DNA decline in any study
- Failure to reduce HIV-1 DNA attributed to insufficient immune-mediated clearance
- Two studies ongoing to test combinations of HDACi and CTL vaccines
  - Denmark: Romidepsin + Vacc4x (see CROI 2016)
  - Oxford: Vorinostat + ChAdV63/MVA vaccine
Panobinostat
Study Hypotheses

- Panobinostat reverses HIV-1 latency
- IFN-α activates innate effector cells and induces ISG expression
- Combined use of both agents leads to innate immunity-dependent elimination of cells in which viral reactivation is induced by panobinostat
Rationale

- Panobinostat increases HIV-1 RNA in CD4 T cell in prior study (Rasmussen et al, Lancet HIV 2014)
- Some patients experienced 70-80% decline of HIV-1 DNA
- HIV-1 DNA decline during panobinostat treatment associated with delayed viral rebound kinetics during ATI
- Decline of HIV-1 DNA during panobinostat treatment associated with
  - Higher numbers of activated NK cells
  - Higher frequencies of pDC
  - Distinct ISG expression patterns
  - IL28B “CC” genotype
Design

- Prospective, randomized, single-center, open-label phase II clinical trial
- Treatment arm A: panobinostat
- Treatment arm B: panobinostat + PEG-IFN-α2a
- 1:2 randomization
Participants

- N=30 total
- All patients on suppressive ART for at least 24 months
- Participants with early and late initiation of ART eligible
- No major pre-existing comorbidities
- Pregnant or breastfeeding patients not eligible
- All participants must use effective contraception
- Cannot take medication known to prolong QTc or strong/moderately strong CYP3A4 inhibitors
Study scheme

Randomization

PEG-IFNa 2a

PBT

Arm B only

PBT

Arm A and B

Screening Baseline assessments

Treatment Cycle I

Study day
-80d
-30d
-10d
0d
6h
2d
4d
6h
14d
28d

Blood draws

Visit number

Arm B only

PEG-IFNa 2a

PBT

Arm A and B

Treatment Cycle II-IV

post-treatment observation

Study day
Cycle II 29d 6h
Cycle III 57d 6h
Cycle IV 85d 6h
observation

Blood draws

Visit number

Cycle II 8
Cycle III 12
Cycle IV 16
observation

Cycle II 9
Cycle III 13
Cycle IV 17
observation

Cycle II 10
Cycle III 14
Cycle IV 18
observation

Cycle II 11
Cycle III 15
Cycle IV 19
observation

Cycle II 12
Cycle III 16
Cycle IV 20
observation

Cycle II 13
Cycle III 17
Cycle IV 21
observation
Treatment regimen

- Panobinostat 20mg po QOD (M, W, F) p. o.
- PEG-IFN-α2a one s. c. shot during each treatment week (Arm B only)
- Each treatment week interrupted by three weeks off-treatment
- Four treatment cycles in total
- ART continued for entire study; only NRTI, NNRTI and Integrase Inhibitors permitted
Endpoints and Statistics

- Primary efficacy: HIV-1 DNA levels in CD4 T cells at end-of-study in comparison to baseline, in Arm A vs Arm B.
- Primary efficacy endpoint will be met if $p<0.05$ between treatment arm A vs B (Wilcoxon test)
- Primary safety: Number of AEs and SAEs; study not powered for safety comparisons between Arm A and B.
- Secondary: QVOA, innate immunity, adaptive immunity, ISG expression profile, T cell subset reservoirs, immunogenetic studies, immune activation
- Secondary analysis of virologic and immunologic parameters between carriers of specific HLA and IL-28B genotypes
Safety and Toxicity

- Investigator Safety Review Committee: Kuritzkes, Lichterfeld, Gandhi, Lu
- Non-investigator Safety Monitoring Committee: Hirsch (MGH), Gallant (JHU), Bosch (HSPH)
- All AEs and SAEs recorded at each visit
- Possible side effects: Fatigue, N/V, CBC changes, LFT increases, QTc prolongation – all expected to be minor (<or equal to grade 2) based on prior experience
- Toxicity further minimized by three week off-treatment between each treatment week
- General: tolerate grade 1/2 toxicity; d/c treatment in case of grade 3/4 toxicity unless limited to laboratory abnormalities
FDA Discussions

- **Initial input from FDA (9/12/14)**
  - Concern re: panobinostat toxicities
    - Mutagenicity
    - Hematological toxicity
    - Cardiac toxicity
    - GI toxicity
  - Participants should have alternative ART regimens available
  - More conservative management of AEs
FDA response to IND application

- Full clinical hold (7/31/15)
  - Black box warning in panobinostat label
    - Cardiovascular toxicity
    - Severe diarrhea
  - Hemorrhage, myelosuppression, infection
  - CLEAR study too small to provide reassurance
  - Lack of equipoise
  - Require *new data* regarding panobinostat safety
Teleconference (10/23/15)
- FDA, investigators, DAIDS, Novartis
- Primary concern is potential for cardiac toxicity
- Secondary concern is mutagenicity
- Suggest starting with lower doses, shorter courses
Protocol modifications

- Three graded steps with increasing panobinostat dosages
  - 5 mg (6 participants)
  - 10 mg (6 participants)
  - 15 mg (15 participants)

- First two cohorts are for safety (randomized 2:1 to receive IFN-α or control)

- Third cohort is for activity (randomized 2:1 to receive IFN-α or control)

- Additional screening tests required
  - Stress-ECHO
Resolution

- Full clinical hold removed (2/12/16)