In vivo PD-1 blockade in a series of 12 HIV-infected patients with lung cancer

IAS - Abstract A-854-0121-02601

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Anti-PD1 usage in HIV+ patients with cancer

- Monoclonal antibodies against the PD-1 axis:
  - Antagonize the negative signals induced by PD-1 in exhausted T cells
  - The new standard of care for NSCLC (Brahmer 2015, Herbst 2016) by enhancing anti-tumor T cell activity
    but no published data on anti-tumor efficacy in PLWHAs (excluded from clinical trials)

- Restore exhausted anti-HIV T cell activity:
  - *in vitro* (Trautmann, 2006; Day 2006)
  - *in vivo*: one case report (Le Garff, AIDS 2017) but still few data available

- Proposed as a strategy to purge latent HIV reservoirs (Katlama, 2013)
  - enriched in PD1+ CD4+ T cells (Fromentin 2016)
  - although CD4+CD32+ cells not enriched in PD1+ cells
data from a 37markers Mass cytometry comparison of CD4+ CD32a+ and CD32a- cells:
while enriched in Tim3+ cells (Corneau et al. Ms in prep.)
A 1st series of anti-PD1 usage in HIV+ patients from the CANCERVIH network

• Non small cell lung cancers (NSCLC) in HIV+ patients:
  – The most common non-AIDS-related malignancy;
  – Chemotherapy: poor efficacy and higher toxicity than in the general population
  – Leading cause of cancer-related death in PLWHA (Spano Ann Oncol 2016)

• CANCERVIH: A national French multidisciplinary network dedicated to PLWHA with cancer
  – Coordinated by Pr JP Spano, Pitié-Salpêtrière, Paris, France
  – Funded by the French national cancer institute (Inca)
  – CANCERVIH recommendation: to discuss all new cases of PLWHAs with cancer

• Data from 12 HIV+ patients treated for NSCLC by anti-PD1 mAb (Nivolumab)
  – extracted from a prospective CANCERVIH cohort of 270 HIV+ patients with cancer
  – allow evaluating:
    • Immunological and Immune Tolerance of anti-PD1 in HIV-infected patients
    • In vivo effects on anti-HIV immunity and HIV reservoirs
## Anti-PD-1 (Nivolumab) treated Patients Characteristics

<table>
<thead>
<tr>
<th>Patients Nb</th>
<th>Sex</th>
<th>Age</th>
<th>HIV diagnosis</th>
<th>CD4</th>
<th>VL</th>
<th>ART</th>
<th>Pathology</th>
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**Median**: 61,5 | 313 | <20

**SCC**: squamous cell carcinoma; **ADC**: adenocarcinoma; **CIS**: cisplatin; **GEM**: gemcitabin; **DOC**: docetaxel; **CARBO**: carboplatin; **PEM**: pemetrexeld; **ERLO**: erlotinib; **BEVA**: bevacizumab
## Evolution after 4 injections of anti-PD1 (Nivolumab)

<table>
<thead>
<tr>
<th>Patients Nb</th>
<th>baseline CD4 counts</th>
<th>CD4 counts after 4 infusions</th>
<th>pVL after 4 infusions</th>
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S: stability; DP: disease progression; PR: partial response;
Transient restoration of HIV-specific T cells and peak of inflammation after anti-PD-1 therapy in Patient #1 (G. Le Garff et al., AIDS 2017)

A. Increased inflammation, mobilised HIV-DNA levels

- IL-6 (pg/ml)
- USVL (copies/ml)
- CD4/mm\(^3\)
- CD8/mm\(^3\)
- HIV-DNA (copies/10\(^6\) cells)

B. Few changes in Immune activation

- CD38+/CD8+
- HLA-DR+/CD8+
- DR+CD38+/CD8+
- HLA-DR+/CD4+

C. Decreased Immune check-points expression

- PD-1+CD8+/mm\(^3\)
- LAG-3+CD8+/mm\(^3\)
- Tim-3+CD8+/mm\(^3\)
- PD-1 MFI/CD8+IFN\(\gamma^+\) (gag)
- PD-1 MFI/CD8+IFN\(\gamma^+\) (RT, nef)

D. Increased HIV-specific CD8 T cells

- HIV pool Gag
- HIV pool RT, Nef
- EBV pool

Few changes in Immune activation

Decreased Immune check-points expression

Increased HIV-specific CD8 T cells
Major decrease in HIV-DNA levels and restoration of HIV-specific T cells after anti-PD-1 therapy in Patient #11

A 3-fold decrease in HIV-DNA levels

B Increased immune activation

C Decreased immune check-points expression

D Enhanced HIV-specific CD8 T cells

Time since start of treatment (days)
Conclusion: Effects of anti-PD1 in a series of 12 PLWHA treated for NSCLC

- Clinical outcome: some efficacy in 6/12 patients, as in the general population

- Tolerance:
  - Few clinical side effects except 1 neurosyphilis and 1 hepatitis re-activation
  - Transient increase of Inflammation or immune activation after 1 injection
  - No changes of plasma HIV viral load nor CD4 or CD8 cell counts

- Comprehensive Immuno-virological analysis in 2 patients:
  - Transient increase in HIV-specific CD8 T cells after 1 or 2 injections, with decrease in immune check points expression on CD4 & CD8 T cells
  - Effects on HIV Reservoirs?
    - Transient weak mobilisation of HIV-DNA levels in PBMcs from one patient,
    - Drastic decrease of the total HIV-DNA levels for another patient (more investigations in progress)

- open the way for future HIV cure therapeutic strategies
Acknowledgements

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- Launching of the ANRS OncoVIHAC cohort
  Coordinators: JP Spano & O Lambotte