EPA0068

LONG-TERM PROTECTION AGAINST HIV INFECTION AFTER DISCONTINUATION TREATMENT WITH PONATINIB FOR 1 YEAR

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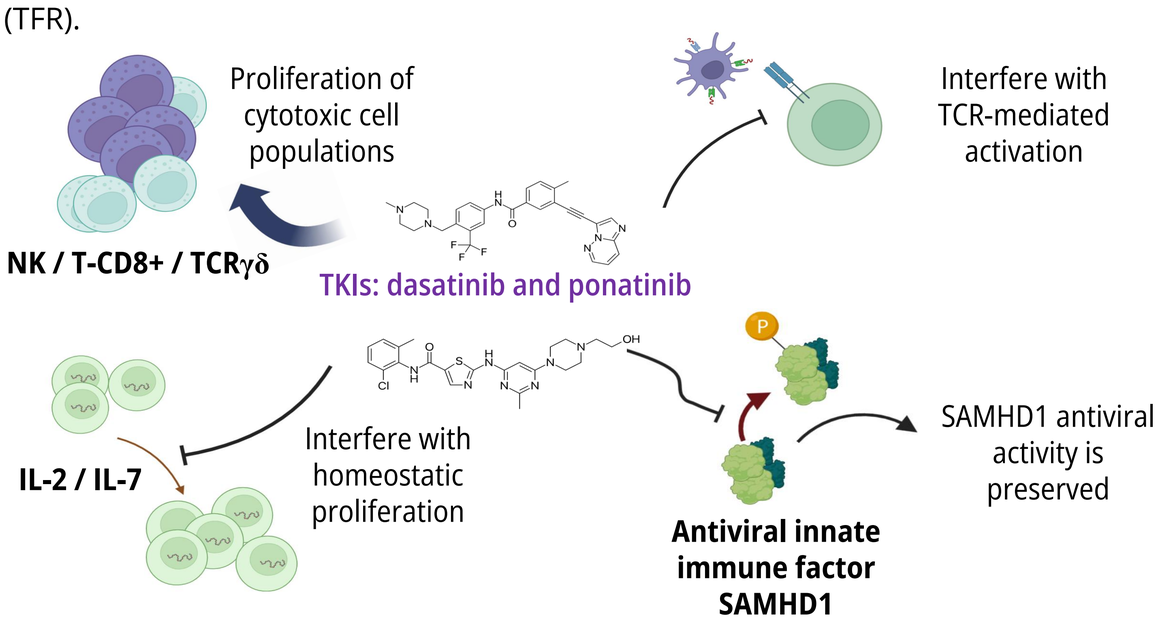
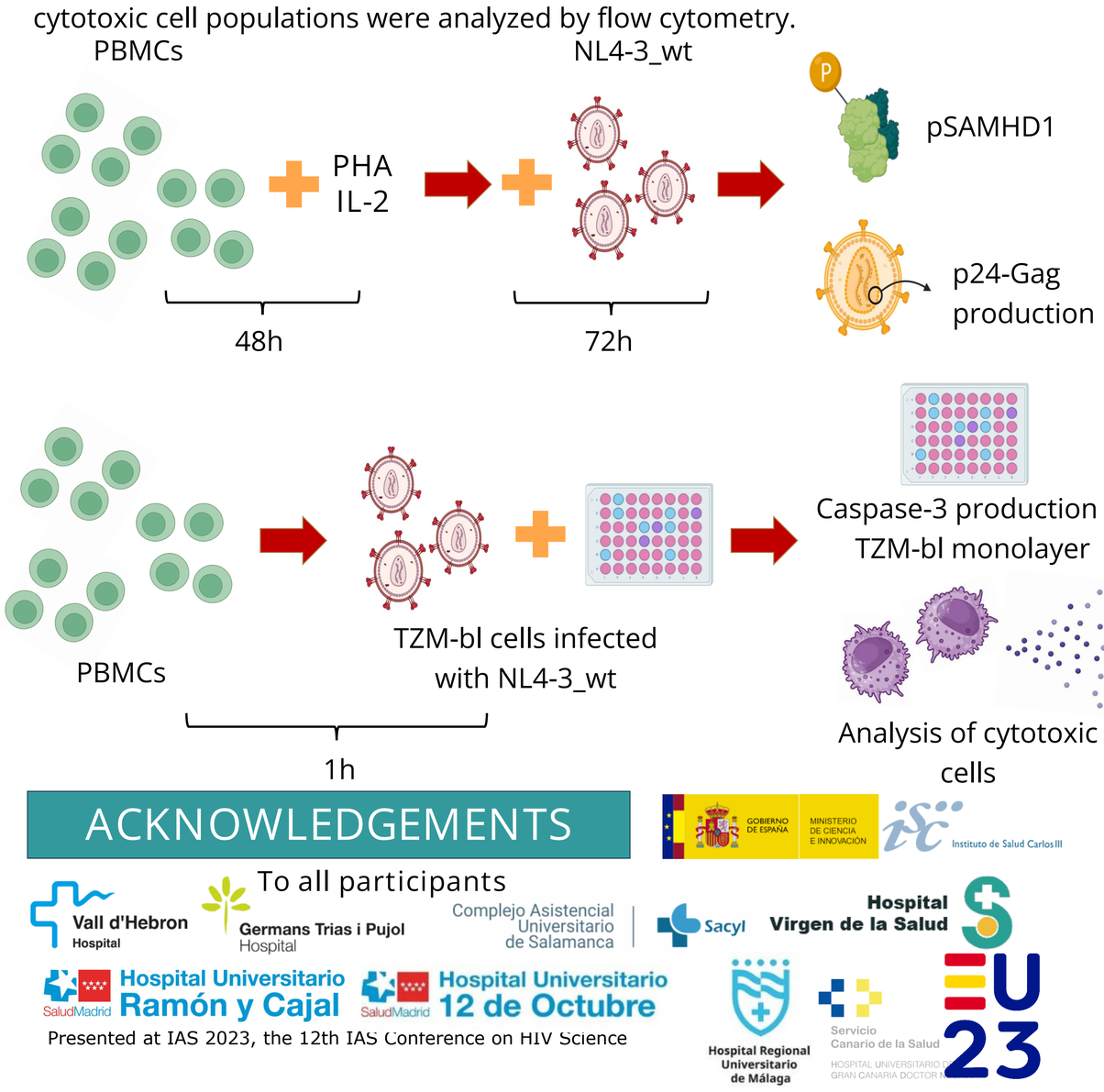
BACKGROUND

- Tyrosine Kinase Inhibitors (TKIs) interfere with formation and replenishment of HIV reservoir by preserving SAMHD1 antiviral activity in CD4+ T cells, inducing the proliferation of cytotoxic cells populations and interfering with homeostatic proliferation and TCR-mediated activation
- People Living with HIV (PLWH) on ART and dasatinib show reduced reservoir size resistant to reactivation.
- We evaluated if treatment with ponatinib for 1 year may protect CD4 from HIV infection and if this protection was maintained during treatment-free remission (TFR).



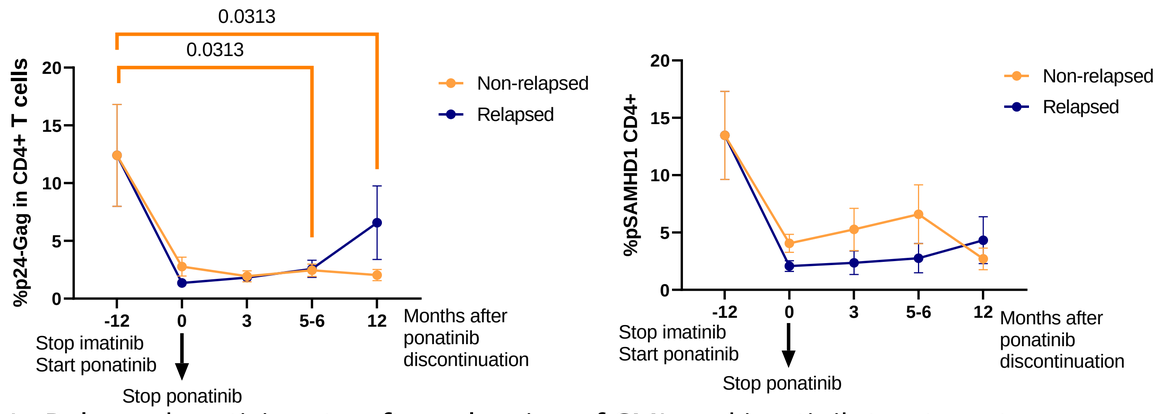
METHODS

- 12 participants with chronic myeloid leukemia (CML) of Phase II Clinical Trial NCT04043676 were recruited. Imatinib treatment was interrupted, and they received 1 year consolidation treatment with ponatinib 15 mg/day. Primary endpoint of this trial was to evaluate relapse to CML after ponatinib treatment interruption.
- Blood samples were collected before starting ponatinib, after 1-year treatment, and 3,6 and 12 months after discontinuation. In case of relapsing of CML, two more samples were obtained: after relapsing of CML and 3 months after imatinib treatment reintroduction.
- PBMCs were activated with PHA/IL-2 for 48h and then infected with NL4-3_wt for 72h. HIV-p24, pSAMHD1 and CD4 memory subpopulations were analyzed by flow cytometry: T naïve (TN), T central memory (TCM), T effector memory (TEM) and terminally differentiated effector memory cells (TEMRA).
- PBMCs were cocultured with TZM-bl cells that were previously infected with NL4-3_wt for 48h. Antiviral activity was evaluated by measuring caspase-3 activity and cytotoxic cell populations were analyzed by flow cytometry.

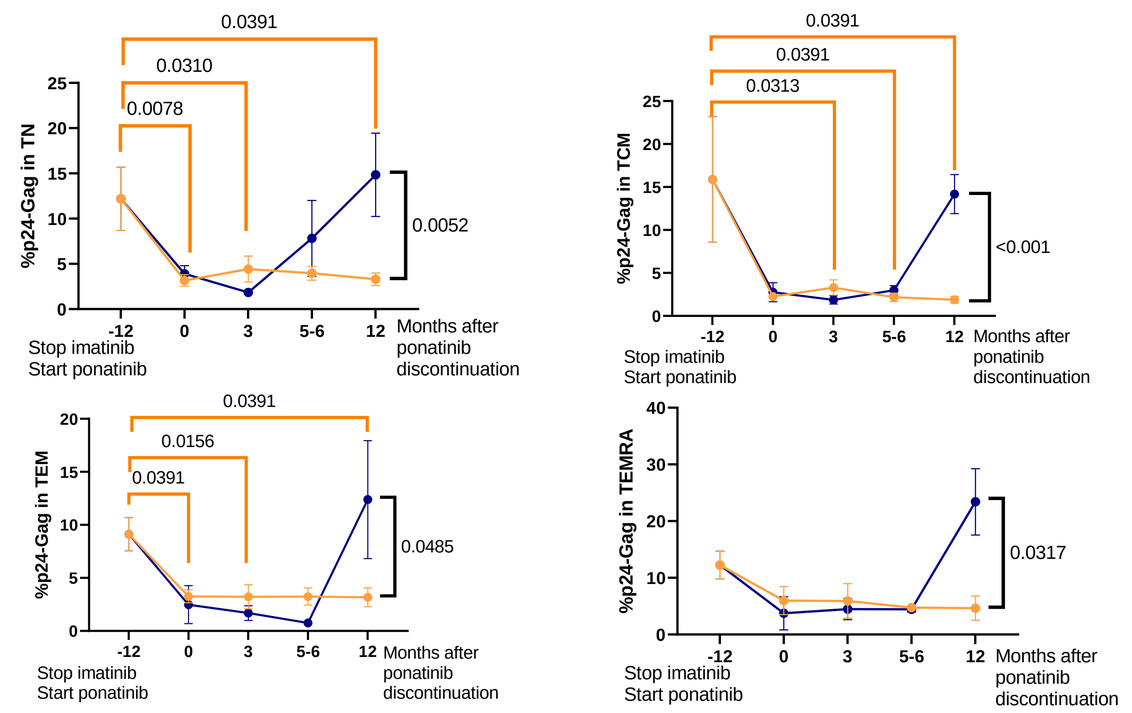


RESULTS

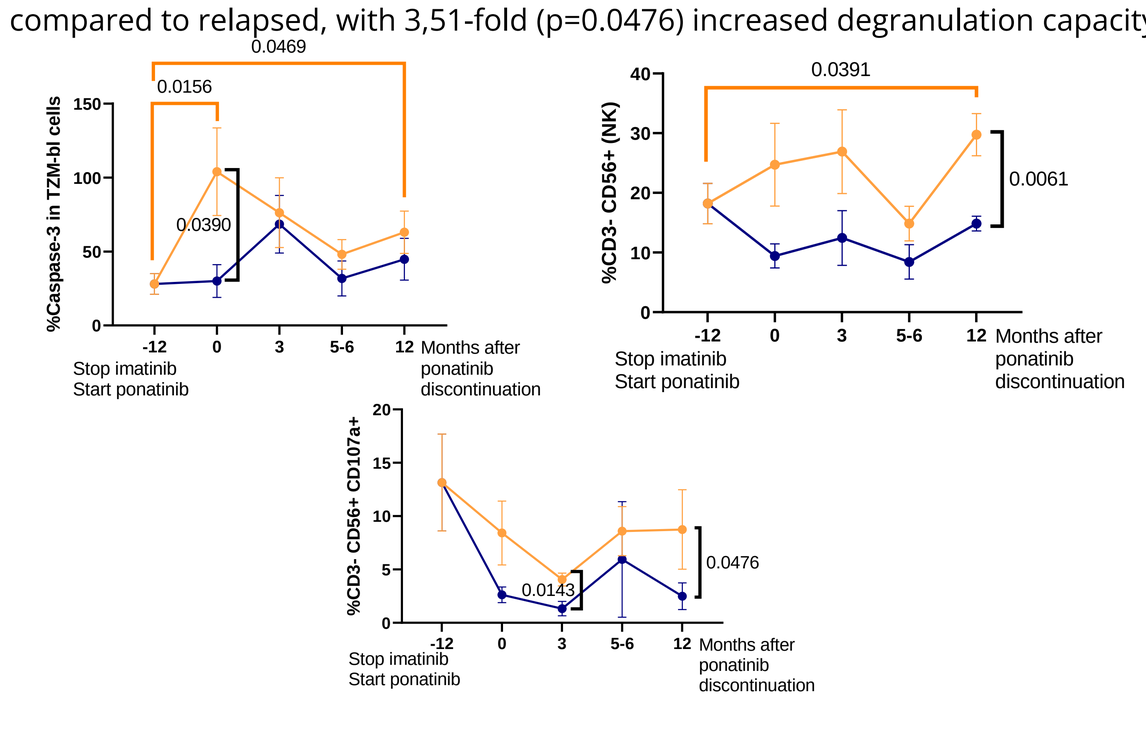
- 8 participants (66,6%) did not relapse from CML 12 months after ponatinib interruption (Non-relapsed participants). 4 participants (33,3%) relapsed after 5,5 months (IQR 4,25-6,75) of ponatinib interruption (Relapsed).
- CD4+ T cells were susceptible to HIV infection in all participants while treatment with imatinib, but 1-year treatment with ponatinib reduced 5,75-fold p24-Gag production in CD4. This protection was maintained 6 (p=0.0313) and 12 months (p=0.0313) during TFR in Non-relapsed participants. SAMHD1 phosphorylation was reduced after ponatinib treatment in both Non-relapsed and Relapsed participants, and this effect was maintained during all TFR.



- In Relapsed participants, after relapsing of CML and imatinib treatment reintroduction, all CD4 memory subpopulations regained susceptibility to HIV replication compared to Non-relapsed, including in TN (3.19-fold; p=0.0052), TCM (7.53-fold; p<0.001), TEM (3,79-fold; p=0.0485) and TEMRA (4,93-fold; p=0.0317).



- Antiviral cytotoxicity increased 4.22-fold (p=0.0156) in PBMCs from Non-relapsed participants after 1-year of ponatinib and remained enhanced for 12 months of TFR.
- NK cells increased 1.86-fold (p=0.0061) after 1-year on TFR in Non-relapsed compared to relapsed, with 3,51-fold (p=0.0476) increased degranulation capacity



CONCLUSIONS

- One-year treatment with ponatinib preserved SAMHD1 in CD4 and induced sustained cytotoxic effect, impeding HV infection and reservoir formation.,
- Antiviral protection was maintained 12 months during TFR in correlation with sustained antileukemic response.
- Short-term intensification with TKIs such as dasatinib and ponatinib could be used for HIV cure strategies.

ACKNOWLEDGEMENTS

To all participants

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