SELECTED OPPORTUNITY IN HEMATO-ONCOLOGY

Combination of Arsenic and Interferon alpha for the treatment of Myeloproliferative Disorders

(BIO16455)

COMBINATION OF ARSENIC AND INTERFERON ALPHA FOR THE TREATMENT OF MYELOPROLIFERATIVE DISORDERS

Product factsheet

Preclinical

- **Application:** Myeloproliferative disorder in a patient presenting a dysregulation of the JAK2-STAT signalling pathway

- **Potential Product** :Combination of Arsenic (ARS) and Interferon α (IFN)

- **Rationale:**

Combining ARS with IFN improves most of the benefits provided by IFN alone during MPN treatment (mouse model). This was evidenced on:

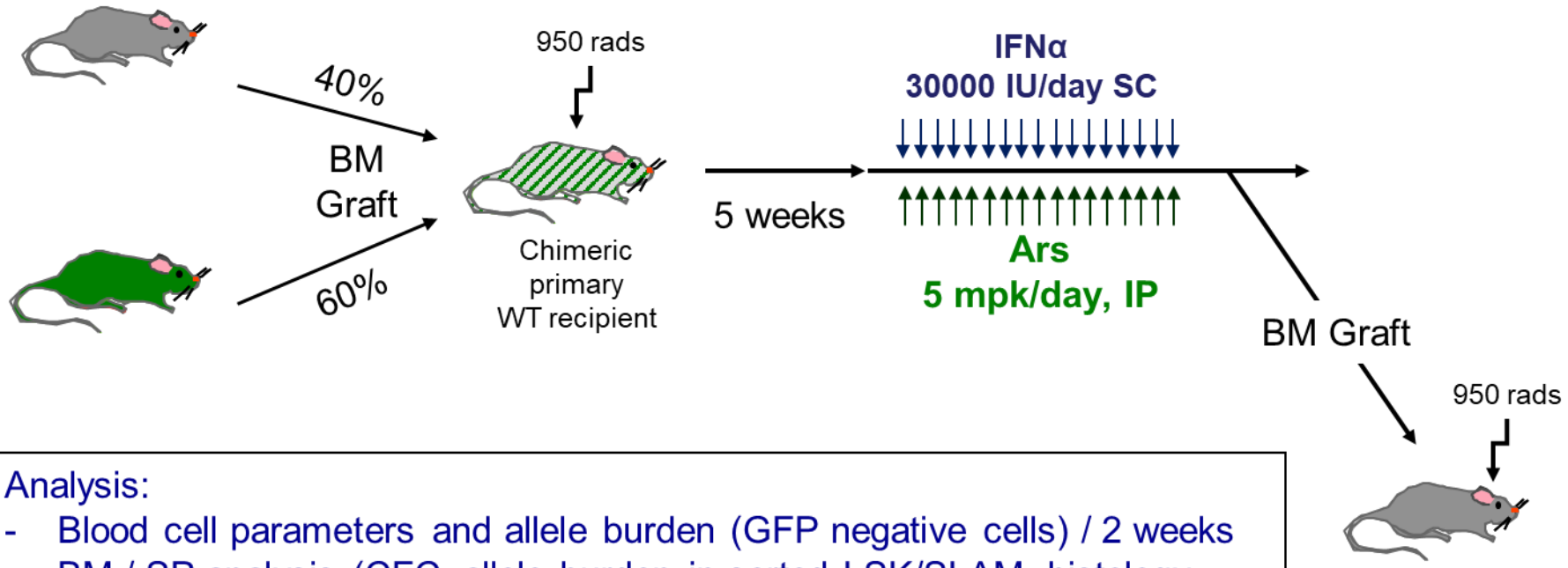
- Correction of polycythemia
- Correction of leukocytosis
- Correction of thrombocytopenia induced by IFN
- Reduction of circulating granulocytes, platelet and red blood cells derived from the neoplastic JAK2V617F clones
- Reduction of bone marrow and spleen neoplastic JAK2V617F progenitor and stem cells
- Suppression of JAK2V617F-positive disease initiating cells
- Prevention of disease relapse after treatment cessation
- ARS and IFN synergistically reduced the clonogenic activity of primary bone marrow cells derived from CML patients

- **Patent Applications and publication:**
  - Effective targeting of chronic myeloid leukemia initiating activity with the combination of arsenic trioxide and interferon alpha El Eit R.M. et al. *Int J Cancer* 2014 Feb 15;134(4):988-96.
  - PCT/EP2018/051118: Methods and pharmaceutical compositions for the treatment of myeloproliferative disorders

Combination of Arsenic and Interferon alpha for the treatment of Myeloproliferative Disorders

Preclinical mouse model and protocol

chimeric recipients mice were generated by transplanting a mixture of 60% Ubi-GFP TG mice (JAK2WT) and 40% KI JAK2^{V617F} bone marrow (BM) cells. The JAK2^{V617F} cells are here GFP negative



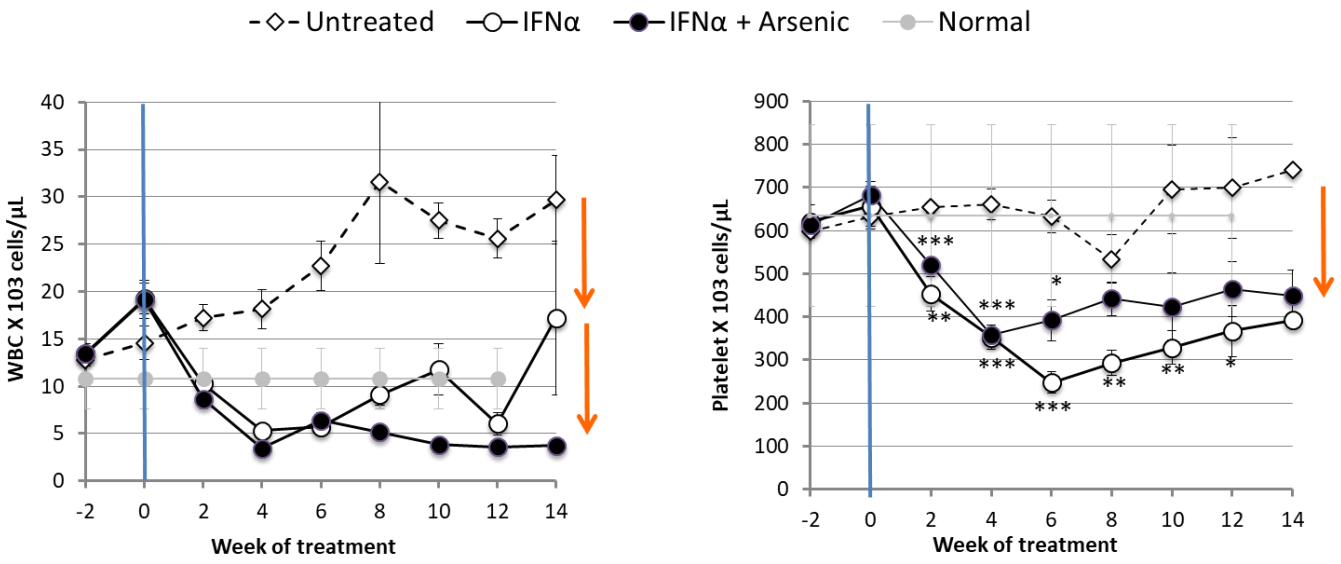
Analysis:
- Blood cell parameters and allele burden (GFP negative cells) / 2 weeks
- BM / SP analysis (CFC, allele burden in sorted LSK/SLAM, histology
- Evaluation of disease-initiating cells in secondary recipients
- Evaluation of cure or relapse in treated mice after cessation of treatment

Combination of Arsenic and Interferon alpha for the treatment of Myeloproliferative Disorders

Proof of concept

Preclinical

White blood cells and platelets in mice treated with IFN or IFN + Arsenic



WBC: IFN alone or IFN + ARS significantly decreased ($p<0.005$) the leucocytosis to normal or below normal values. The combination tend to slightly increase the effect of IFN alone

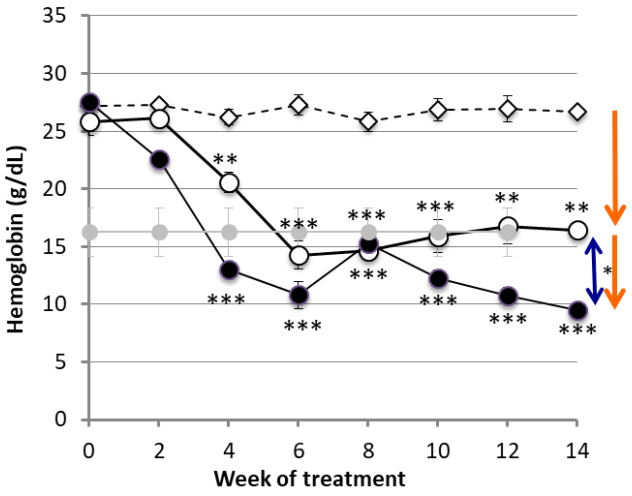
Platelets: IFN alone decreased the platelet counts ($p<0,0005$) to thrombocytopenia or IFN + ARS on platelet counts improved by the combination)

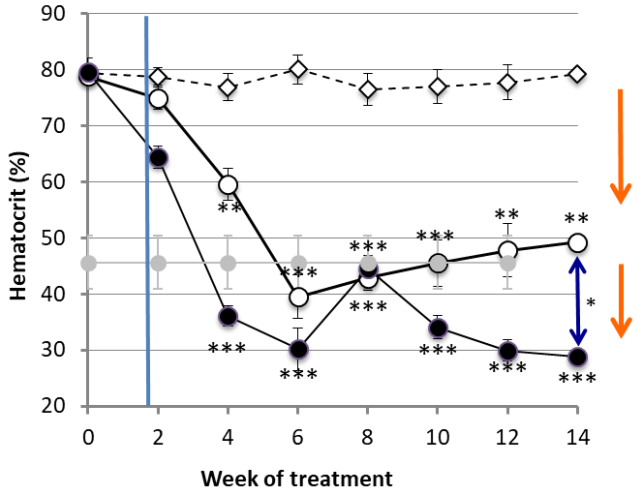
Combination of Arsenic and Interferon alpha for the treatment of Myeloproliferative Disorders

Proof of concept

Preclinical

Red blood cells in mice treated with IFN and Arsenic or the combination





IFN or IFN + ARS decreased polycythemia to normal levels with IFN (P<0001) or to anemia with the combination (P<0,0001).

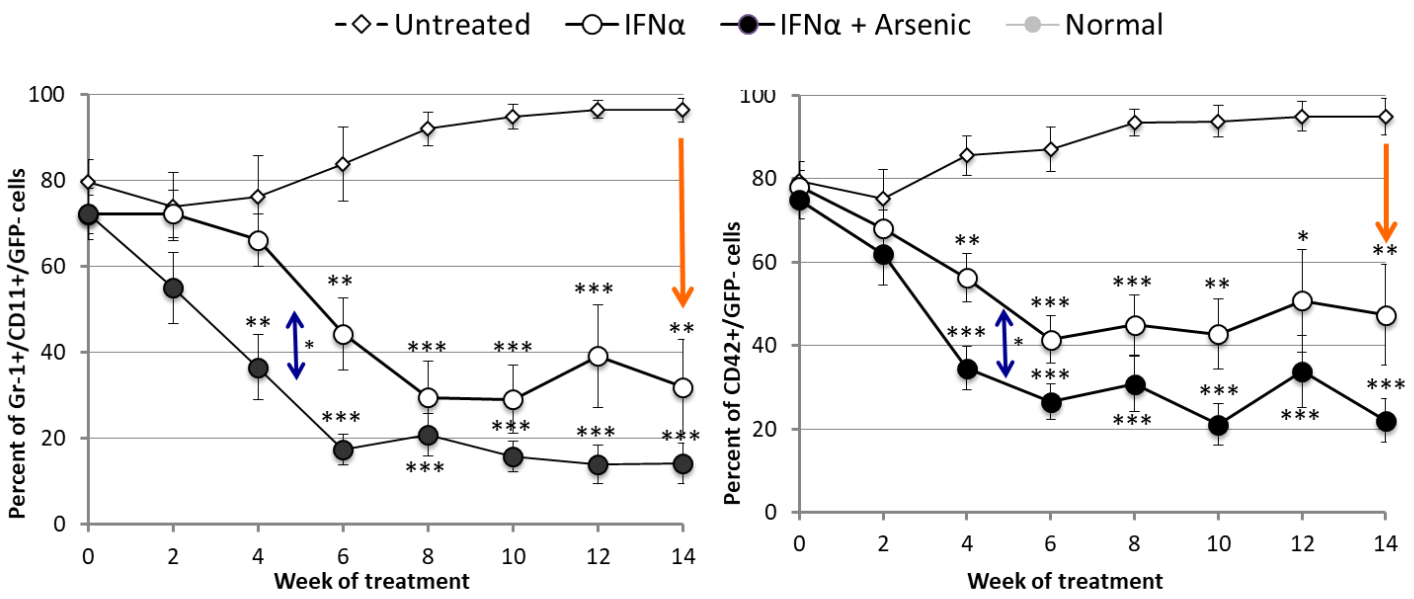
The combination did better than IFN alone (p<0.05) on hemoglobin or hematocrit levels. Similar results were obtained with RBC counts.

Combination of Arsenic and Interferon alpha for the treatment of Myeloproliferative Disorders

Proof of concept

Preclinical

Allele burden in granulocytes and platelets



IFN decreased the WBC (≈ 30% of NT) and platelet (≈ 50% of NT) allele burdens ($p<0.005$)

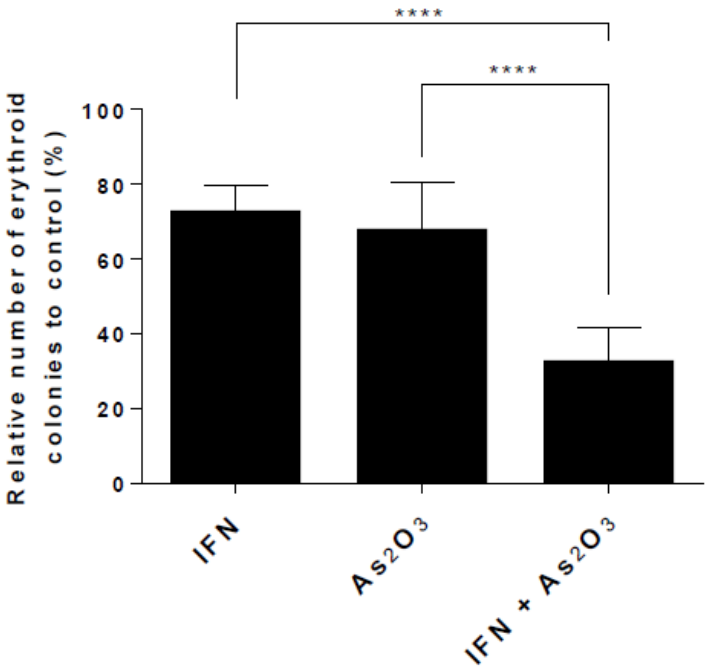
The combination IFN + ARS improved the effect of IFN alone on the WBC (≈ 15% of NT) and platelet (≈ 20% of NT) allele burdens ($p<0.0001$). The effect is significantly more elevated than with IFN alone at early time (day 4).

Combination of Arsenic and Interferon alpha for the treatment of Myeloproliferative Disorders

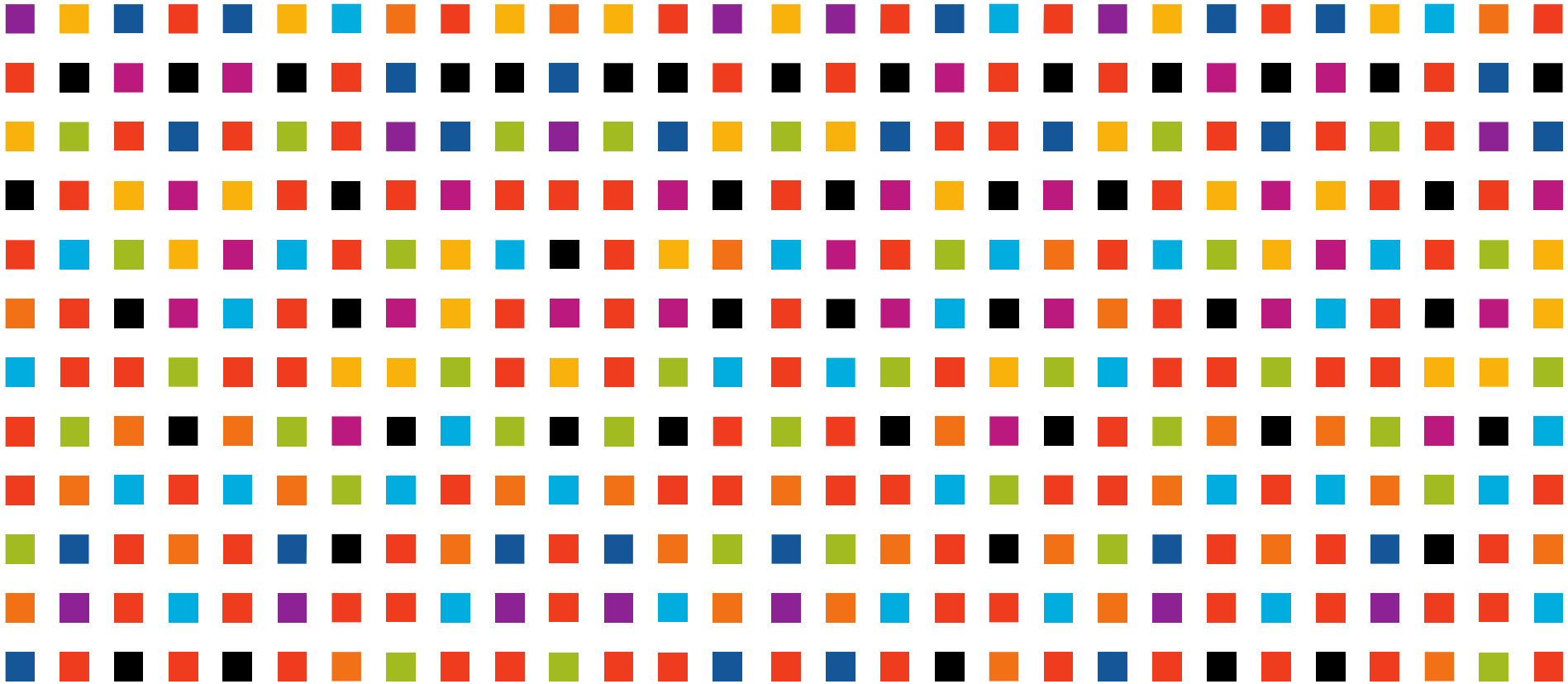
Proof of concept

Preclinical

Selective and Synergistic impairment of the growth of mutant erythroid colonies is observed with the combination of IFN and ARS in clonogenic methyl-cellulose cultures of patient progenitors.



ARS or IFN did not modify the total number of myeloid progenitor cells
The combination IFN+ARS decreases the total number of progenitors



ANNE.COCHI@INSERM-TRANSFERT.FR

Inserm Transfert - Paris Biopark
7 Rue Watt - 75013 Paris
Tel: +33 1 55 03 01 00 / Fax: +33 55 03 01 60
www.inserm-transfert.fr