# SELECTED OPPORTUNITY IN HEMATO-ONCOLOGY

## Combination of Arsenic and *all trans* retinoic acid for the treatment of AML

## (BIO13408)

# COMBINATION OF ARSENIC AND *ALL TRANS* RETINOIC ACID FOR THE TREATMENT OF AML

## Product factsheet

*Preclinical*

- **Target:** Mutated Nucleophosmin-1 (NPM-1)
- **Application:** Acute Myeloid Leukemia (AML) patients with mutated NPM-1
- **Potential Product** :a combination of arsenic (ARS) and *all trans* retinoic acid (ATRA)
- **Rationale:**

- NPM-1) is the most frequently mutated gene in acute myeloid leukemia (AML).

- ATRA inhibits proliferation and induces apoptosis selectively in AML cells with mutated NPM-1. Unexpectedly, ARS had the same effects and, critically, low doses of ARS and ATRA had a major synergistic effect to initiate apoptosis, again only in *NPM-1* mutated AMLs.

- ATRA and ARS induced proteasomal degradation of NPM-1 selectively in cells where this gene is mutated

- **Patent Applications and publication** :

  - Retinoic acid and arsenic trioxide trigger degradation of mutated NPM1, resulting in apoptosis of AML cells El Hajj H. et al. *Blood* 2015 May 28;125(22):3447-54

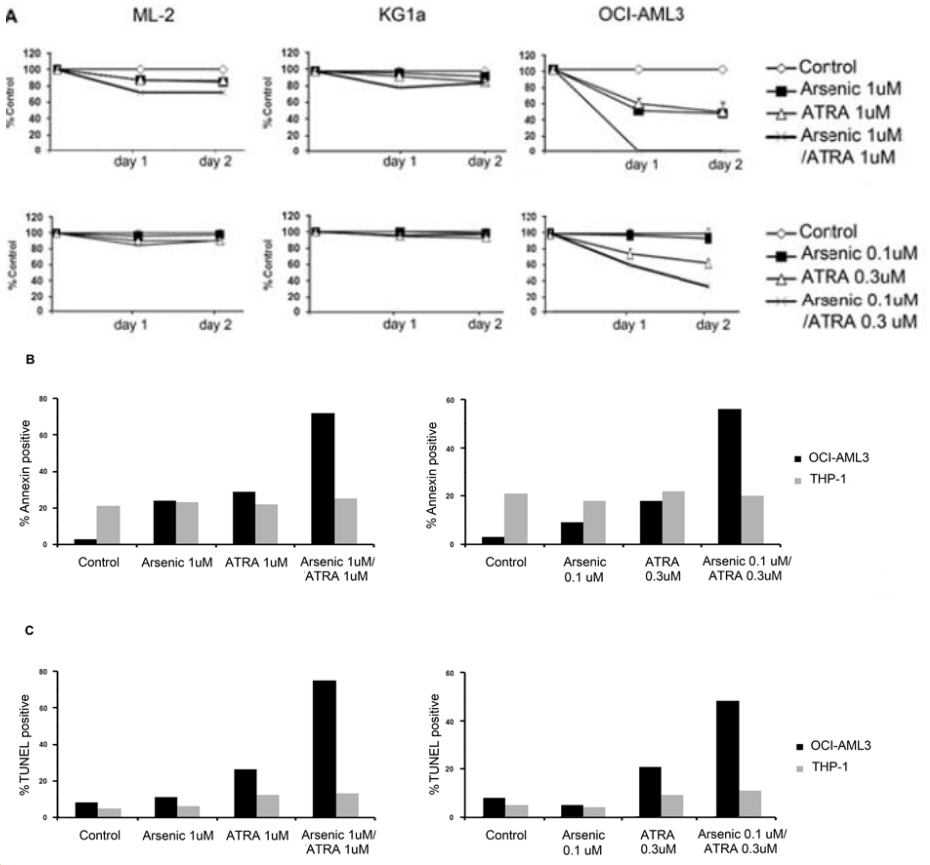
  - PCT/EP2014/079422: Methods and pharmaceutical compositions for the treatment of acute myeloid leukemia.

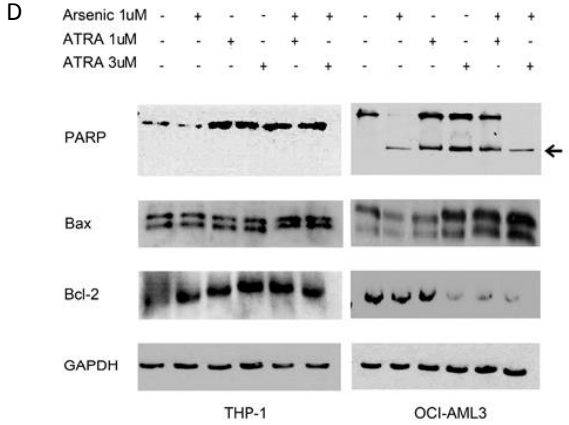
# COMBINATION OF ARSENIC AND *ALL TRANS* RETINOIC ACID FOR THE TREATMENT OF AML

## Proof of concept

*Preclinical*

### Combination of ATRA and arsenic induce cell growth inhibition and apoptosis in NPM-1 mutated AML cells



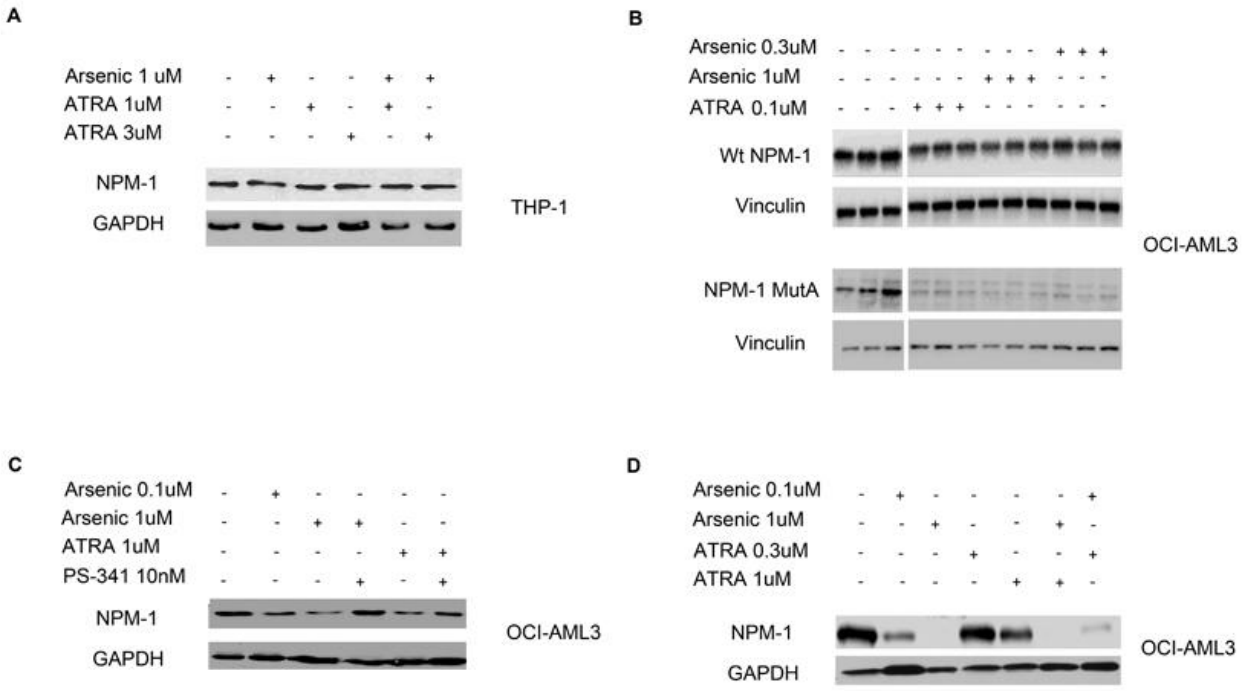




**AML cell lines with normal NPM-1 (ML-2,KG1a) or mutated NMP1 (OCI-AML3) were treated with arsenic (1µM or 0.1µM) ATRA (1µM or 0.3 µM) either alone or combined. A) Cell growth (% of control) was assayed in triplicate wells. The results represent the average of at least three independent experiments. B) Annexin V staining of THP-1 or OCI-AML3 cells treated for 48h as described. Percent of dead cells (Annexin V positive) is indicated on each graph. C) TUNEL assay of THP-1 or OCI-AML3 cells treated for 48h as described. Percent of apoptotic cells (TUNEL positive) is indicated on each graph.D) Western blot analysis for PARP, Bax, Bcl-2, and GAPDH proteins in THP-1 and OCI-AML3 treated as described for 48h.**

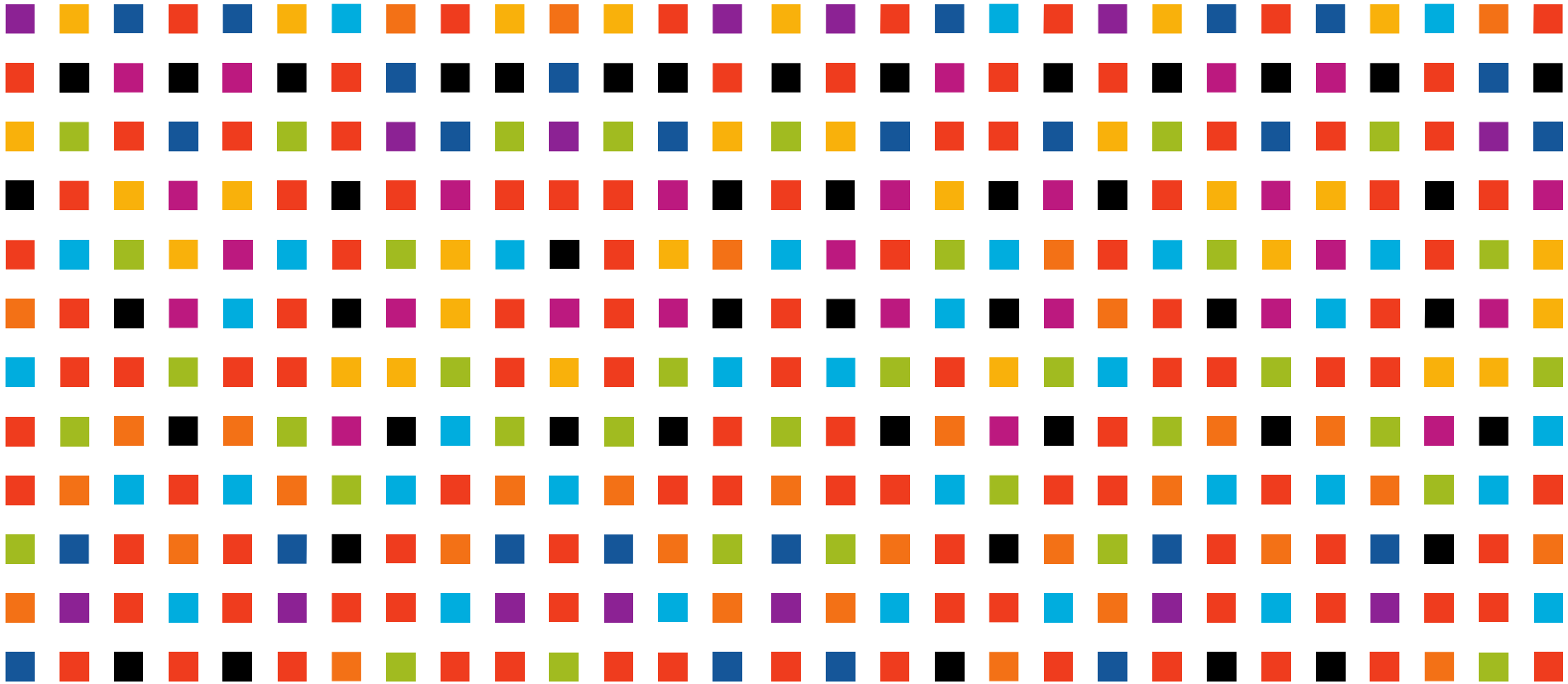
## Proof of concept

*Preclinical*

### Combination of ATRA and arsenic induce proteasomal degradation of mutated NPM-1




Western blot analysis for NPM-1 (A-D), mutated NPM-1 (B), GAPDH and vinculin proteins in THP-1 (A) and OCI-AML3 (B-D) treated as described for 24h (B) or 48h (A, C, D).



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