Baseline values of circulating nucleosomes in Lung Cancer: NUCLEO-LUNG study

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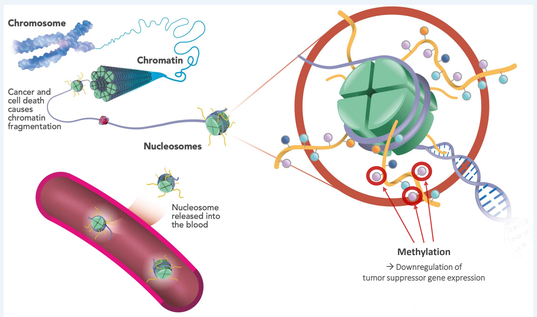
CONTEXT

Nucleosomes (DNA wound around histone proteins) are released in bloodstream after cell death. Lysine residues on histone proteins carry epigenetic modifications, such as methylation, participating in the control of gene repression *(Scheme 1)*. Deregulation of such post-translational modifications in lung cancer (LC) results in **aberrant levels of circulating methylated nucleosomes**, already reported as putative cancer biomarkers *(Grolleau et al., 2023)*.



Scheme 1: *Nucleosomes released by cancer cells carry methylated histones that can be detected in bloodstream of patients (figure from Volition)*

ONCOPRO (NCT03787056) is a prospective case-control study led in Lyon University Hospital that collected plasma at diagnosis and along disease management of 420 patients with 16 newly cancers.

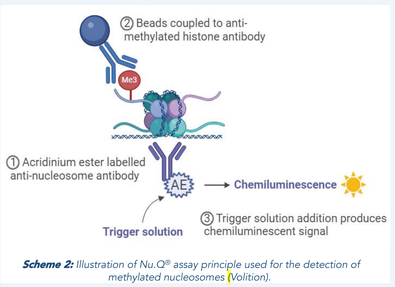
This study was perfectly designed to assess the diagnostic and prognostic values of circulating nucleosomes in lung cancer.

Results of a preliminary analysis are presented here.

MATERIALS & METHODS

To asses their prognostic values regarding overall survival and lung cancer progression, 2 forms of circulating methylated nucleosomes (**H3K27Me3- and H3K36Me3-nucleosome**) were measured in K2EDTA plasma samples of **179 healthy** subjects and **69 patients with lung cancer** of the ONCOPRO study.

Cancer patients were separated in two cohorts according to treatment: curative (surgery, n=19) or palliative (immunotherapy, n=20, or chemotherapy, n=30).



Scheme 2: *Illustration of Nu.Q® assay principle used for the detection of methylated nucleosomes (Volition).*

Immunoassays (*Scheme 2*) were performed on IDS i10 automated immunoanalyzer (Immunodiagnostic Systems Ltd, UK) using Nu.Q® prototypes (Volition SRL, Belgium).

Statistics were performed on R software (version 4.2.1). Association with survivals was quantified by Hazard ratios (HR). Diagnostic accuracy (or ability to predict event) was quantified by the area under the ROC curve.

RESULTS

1 Circulating levels of H3K27Me3- and H3K36Me3-nucleosomes are higher in LC patients compared to healthy individuals

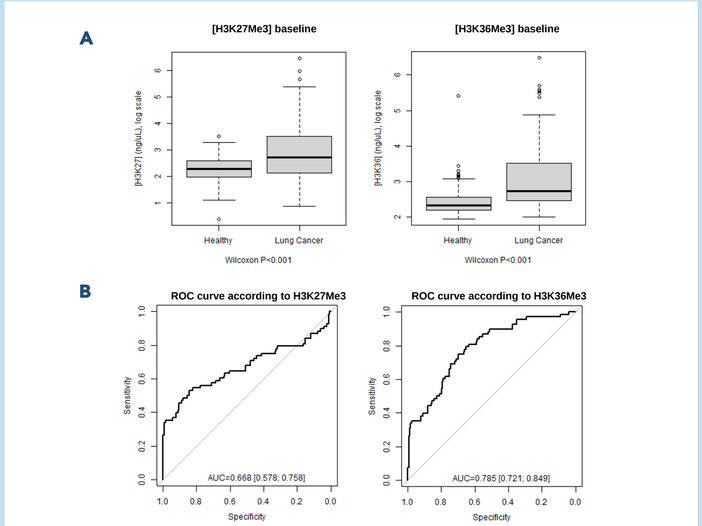


Figure 1
(A) Plasma levels of H3K27Me3- (left) and H3K36Me3-nucleosome (right) measured in cancer-free subjects (healthy) or lung cancer patients.
(B) ROC curve analysis determining the diagnostic performance of H3K27Me3 (left) and H3K36Me3 (right) baseline levels.

2 Curative cohort have lower levels of H3K27Me3- and H3K36Me3-nucleosome at diagnosis than the palliative one

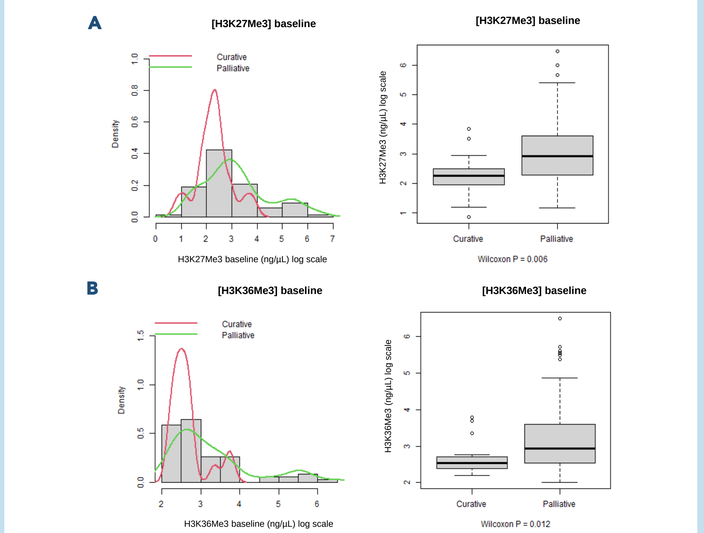
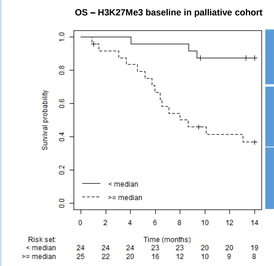


Figure 2
(A) Plasma levels of H3K27Me3-nucleosome measured at diagnosis in the curative and palliative cohorts.
(B) Plasma levels of H3K36Me3-nucleosome measured at diagnosis in the curative and palliative cohorts.

3 Baseline levels of H3K27Me3- and H3K36Me3-nucleosome are predictive of overall survival and progression in the palliative cohort

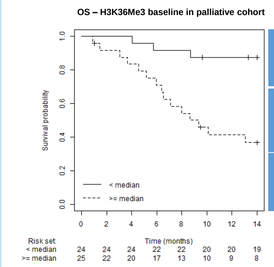
A Overall Survival (OS)

OS – H3K27Me3 baseline in palliative cohort



H3K27Me3 baseline (ng/µL)	Median [95% CI]	HR [95% CI]
< median palliative H3K27Me3	NR [NR; NR]	-
≥ median palliative H3K27Me3	10.09 [7.1; NR]	4.86 [1.41; 16.78] p = 0.012

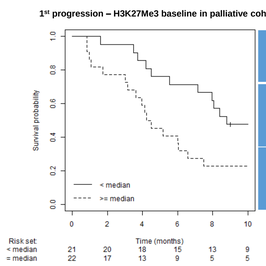
OS – H3K36Me3 baseline in palliative cohort



H3K36Me3 baseline (ng/µL)	Median [95% CI]	HR [95% CI]
< median palliative H3K36Me3	NR [NR; NR]	-
≥ median palliative H3K36	10.09 [7.1; NR]	7.22 [1.66; 31.45] p = 0.008

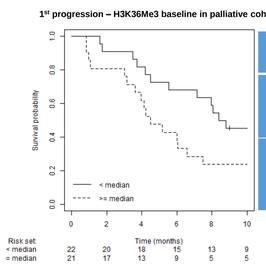
B Recurrence prediction

1st progression – H3K27Me3 baseline in palliative cohort



H3K27Me3 baseline (ng/µL)	Median [95% CI]	HR [95% CI]
< median palliative H3K27Me3	8.8 [7.95; NR]	-
≥ median palliative H3K27Me3	4.37 [3.61; 10.32]	2.33 [1.13; 4.81] p = 0.022

1st progression – H3K36Me3 baseline in palliative cohort



H3K36Me3 baseline (ng/µL)	Median [95% CI]	HR [95% CI]
< median palliative H3K36Me3	13.73 [8.05; NR]	-
≥ median palliative H3K36Me3	4.22 [3.61; 7.49]	2.68 [1.29; 5.55] p = 0.008

C Progression in palliative cohort without immunotherapy

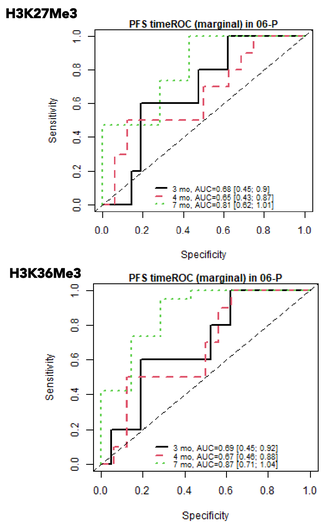


Figure 3
(A) Survival analysis in palliative cohort according to H3K27Me3- (up) and H3K36Me3-nucleosome (down) blood levels at diagnosis. **(B)** Progression-free survival in palliative cohort according to H3K27Me3- (up) and H3K36Me3-nucleosome (down) blood titers at diagnosis. **(C)** Time-dependent ROC curve for prediction of progression at 3, 4 and 7 months based on baseline concentrations of H3K27Me3 (up) and H3K36Me3 (down) in the palliative cohort without immunotherapy
Medians blood levels considered for threshold are 18.46 and 18.88 ng/µL for H3K27Me3- and H3K36Me3-nucleosome, respectively. (NR: Not reach)

CONCLUSION

Plasmatic levels of Nu.Q® H3K36Me3 and Nu.Q® H3K27Me3 at diagnosis could represent a **non-invasive biomarker in lung cancer** with potential relevant prognostic tumor burden value and progression-risk value in newly diagnosed patients.

PERSPECTIVES

- Circulating methylated nucleosomes concentrations during follow-up of patients will be assessed as potential biomarkers of cancer progression.
- Nucleosomes contain and protect released-tumor DNA, thus, the association between nucleosomes blood levels and molecular profiling on circulating DNA will be studied, at baseline and during progression.

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