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# H3K27Me3-nucleosome is a strong prognostic biomarker in Non-Small Cell Lung Cancer: interim results from the analysis of up to 832 patients at baseline


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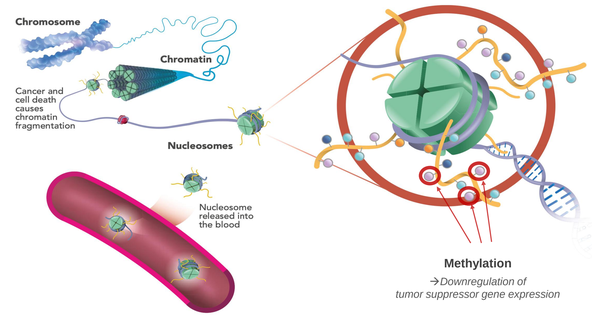
## CONTEXT

- Molecular profiling of somatic tissue and circulating tumor DNA (**ctDNA**) is critical for personalizing **lung cancer** treatment. Yet, all tumors do not harbor targetable mutations.
- Epigenetic modifications of nucleosomes play a crucial role in gene expression and are commonly dysregulated in tumors *(Scheme 1)*. **Aberrant levels of methylated nucleosomes in plasma** have already been reported in lung cancer *(Grolleau et al., 2023)*




***Scheme 1:*** *Methylated nucleosomes (DNA wound around histone proteins carrying methylation marks) are released by cancer cells in bloodstream after cell death and can be detected in patients' plasma (figure from Volition©).*

**OBJECTIVE:**

To evaluate the **complementarity of ctDNA molecular profiling and H3K27Me3-nucleosome titers** in the prediction of NSCLC patients' outcome at diagnosis.

## MATERIALS & METHODS

- Interim analysis relies on plasma samples from **832 patients with NSCLC (from cohort n=1050)** collected at diagnosis in the University Hospital of Lyon in between 2022-2024.
- **ctDNA molecular profiling by NGS** was performed using either PlasmaSeqSensei (4 genes, 0.2% sensitivity – Sysmex, Japan), a custom comprehensive panel (77 genes, 1% sensitivity – SOPHiA Genetics, Switzerland), or a custom targeted ultra-deep technique (33 genes, 0.2% sensitivity – SOPHiA Genetics, Switzerland).
- **H3K27Me3-nucleosome** titers were measured by the Nu.Q® immunoassay (Volition SRL, Belgium) on IDS i10 automated immunoanalyzer (Immunodiagnostic Systems Ltd, UK) .
- Statistical analyses were performed using R software (version 4.4.1). Associations with survival and relapse were quantified using Hazard Ratios (HR) using "survival" package.

## RESULTS

### 1 H3K27Me3-nucleosome titers are increased in ctDNA positive samples

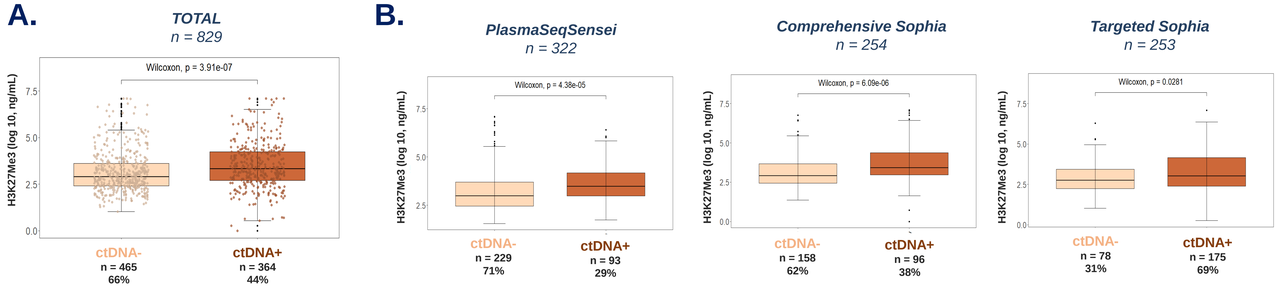



**Figure 1**
H3K27Me3-nucleosome titers at diagnosis according to molecular profile on ctDNA *(without mutation = ctDNA-, with mutation = ctDNA+)* (A) in the global cohort (median 18,2 vs 27,8 ng/mL) and (B) according to NGS techniques *(median PlasmaSeqSensei 19.8 vs 32.1, Comprehensive Sophia 18.2 vs 30.4 Targeted Sophia 15.6 vs 20.6ng/mL)*.

### 2 H3K27Me3-nucleosome titers are increased in patients with low survival probability, independently of molecular profiling results on ctDNA

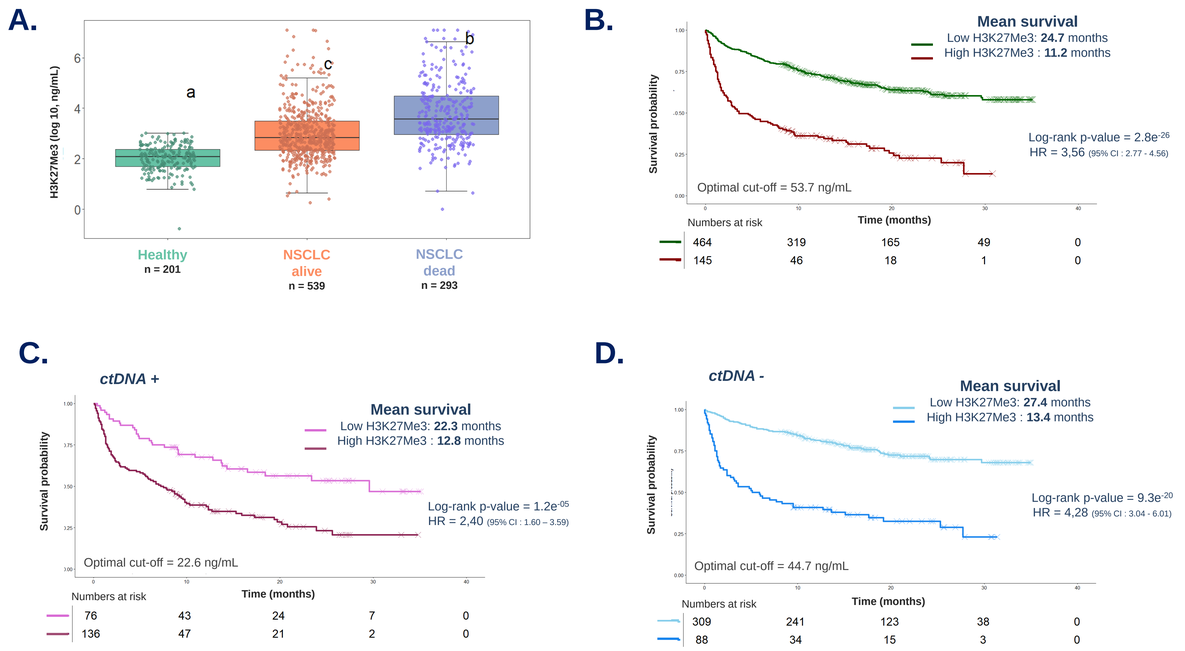


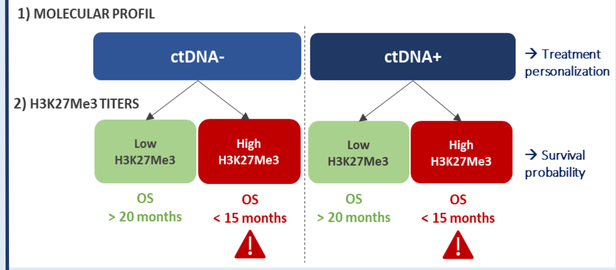

**Figure 2**
(A) H3K27Me3-nucleosome blood titers in cancer patients at diagnosis according to survival status (orange = alive, median 17.03 ng/mL vs blue = dead, median 35.49 ng/mL) compared to a healthy cohort (green, median 8.0 ng/mL). (B) Survival analysis according H3K27Me3-nucleosomes titers at diagnosis (optimal cut-off 53.7 ng/mL). (C) Overall survival according to H3K27Me3-nucleosomes titers in patients with at least one somatic mutation detected on ctDNA (ctDNA+, optimal cut-off = 22.6 ng/mL). (D) Overall survival of patients with negative molecular profiling (ctDNA-) according to H3K27Me3-nucleosomes titers (optimal cut-off = 44.7 ng/mL).

## CONCLUSION

H3K27Me3-nucleosome is a **non-invasive biomarker,** that **complements ctDNA** and **predicts survival** regardless of mutation status

## PERSPECTIVES

**H3K27Me3-nucleosome titers at diagnosis could help inform treatment decisions and patients' monitoring thereby facilitating *personalized care.***




- Prognostic value of H3K27Me3-nucleosomes titers was assessed across different **cancer stages.**
- Evaluating the predictive value of H3K27Me3-nucleosomes titers for **treatment response** and disease progression may be valuable for patients undergoing treatment.

## NEXT STEPS

- Survival analysis to be reviewed according to the **cut-off of 22,5 ng/mL** previously determined in Grolleau et al,2023.
- The H3K27Me3-nucleosomes titers according to the **type of somatic mutation detected on ctDNA** to be investigated.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