Liquid biopsy: measuring circulating H3K27Me3-nucleosomes in Lung Cancer patients is a strong prognostic biomarker and a potential aid in treatment selection

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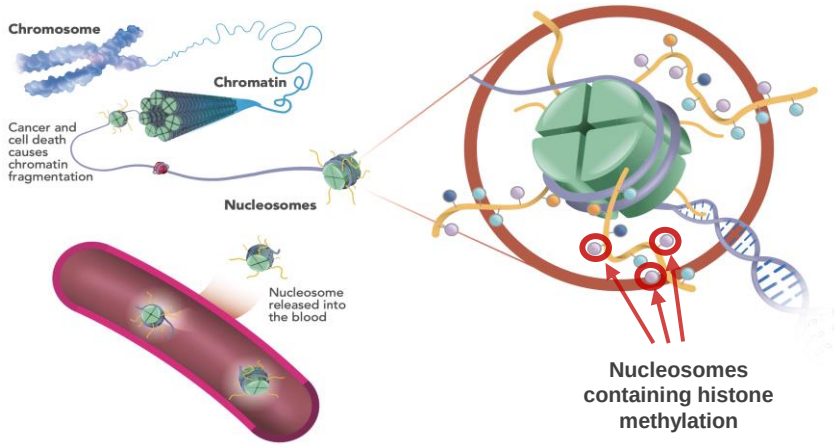
Background and Introduction

Early detection and treatment save lives, but people are often diagnosed with advanced disease when treatment options are limited. Once the disease is diagnosed, **molecular profiling** of circulating tumor DNA (ctDNA) is often used to select treatment and monitor disease. However, these techniques can **lack sensitivity**, which could lead to delays in starting more aggressive treatment. The histone post-translational modification **H3K27Me3** have been reported to play an important role in the development and progression of lung cancer.

Objectives:

To evaluate if circulating H3K27Me3-nucleosome levels could offer additional insight in patients with negative molecular profiling and help improve patient management



Nucleosomes (DNA wrapped around core histone proteins) are released by cancer cells in bloodstream after cell death. Histones are subjected to a variety of epigenetic modification at specific residue (histone post-translational modifications (PTMs)) such as methylation and can be detected in patients' plasma.

Material and Methods

H3K27Me3-nucleosomes levels were analyzed in K2EDTA plasma samples from two independent cohorts including **665 LC patients at diagnosis** and **304 LC patients under treatment** using **Nu.Q®H3K27Me3** immunoassay (Belgian Volition SRL, Belgium).

ctDNA analysis by NGS on the same samples was performed using a targeted ultra-deep technique (33 genes, 0,2% sensitivity, cohort 1 (n=201)) or Plasma SeqSensei (4 genes, 0,2% sensitivity, cohort 1 (n=260) or a comprehensive custom NGS assay (78 genes, 1% sensitivity, cohort 1 (n=204) and cohort 2 (n=304)).

The **contribution of H3K27Me3-nucleosomes to molecular profiling** and its prognostic value for overall survival (OS) were assessed (minimum 8 months follow-up, n=489).

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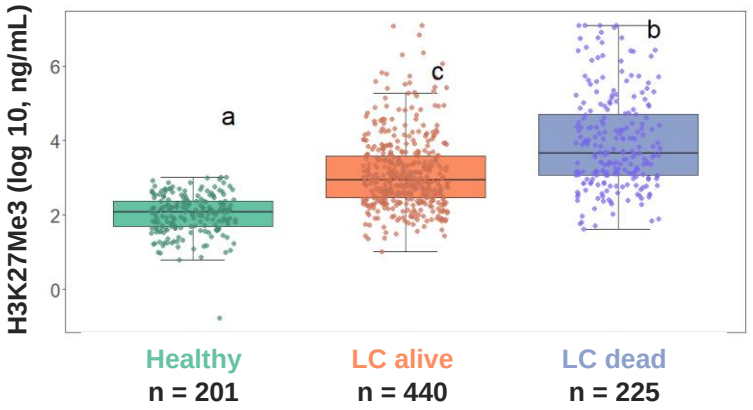
Results 1: At diagnosis, H3K27Me3-nucleosome is a *strong prognostic* biomarker in LC

A



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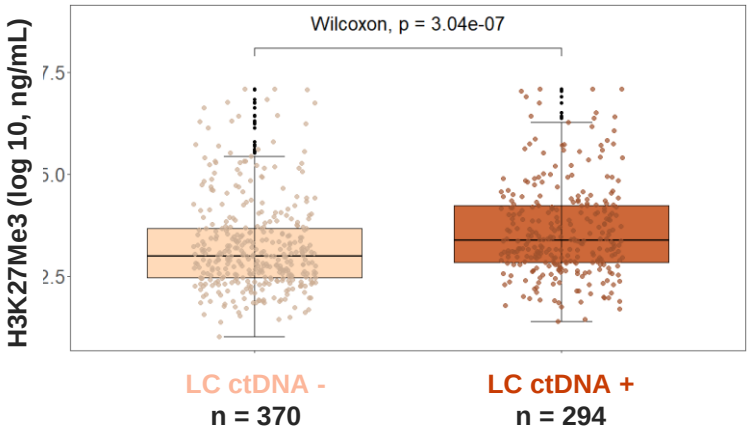


H3K27Me3-nucleosome blood levels in LC patients at diagnosis (Cohort 1)

A. According to survival (orange = alive, median 19.08 ng/mL *vs* blue = dead, median 39.00 ng/mL, p=2,47e-13) compared to a healthy cohort (green, median 8.0 ng/mL, p=3,85e-73 and p=4,48e-41, respectively)

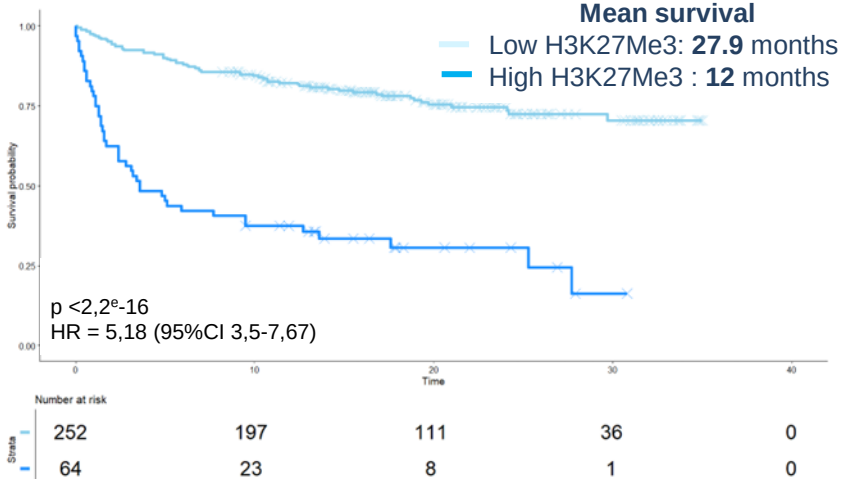
B. According to molecular profile on ctDNA *(without mutation = ctDNA-, with mutation = ctDNA+)* (median 19,83 *vs* 29,2 ng/mL)

OS analyses according to H3K27Me3-nucleosomes levels (cut-off = 54 ng/mL)

C. In patients with negative molecular profiling (ctDNA-)

D. In patients with at least one somatic mutation detected on ctDNA (ctDNA+)

C



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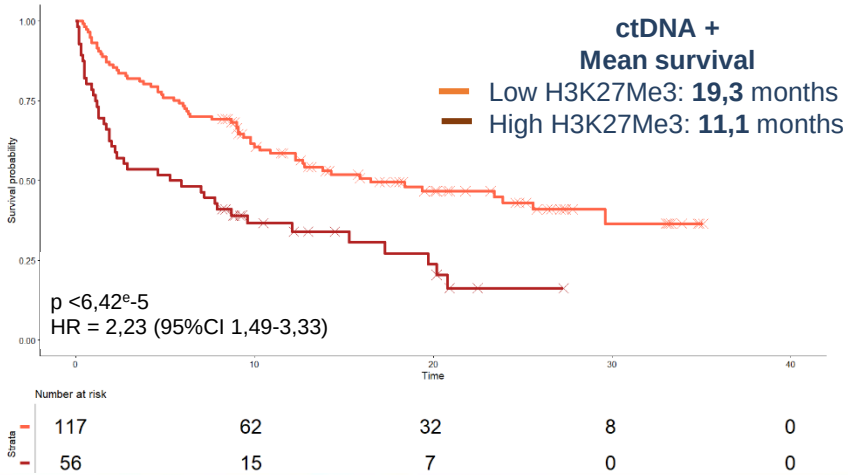

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Results 2: H3K27Me3-nucleosomes may *detect MRD* in LC patients

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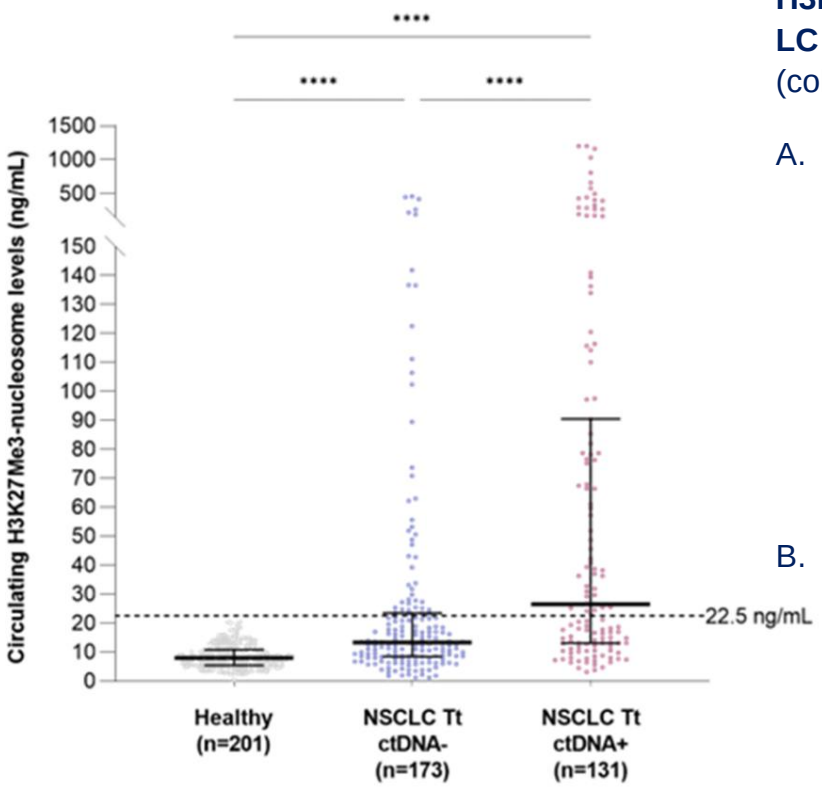
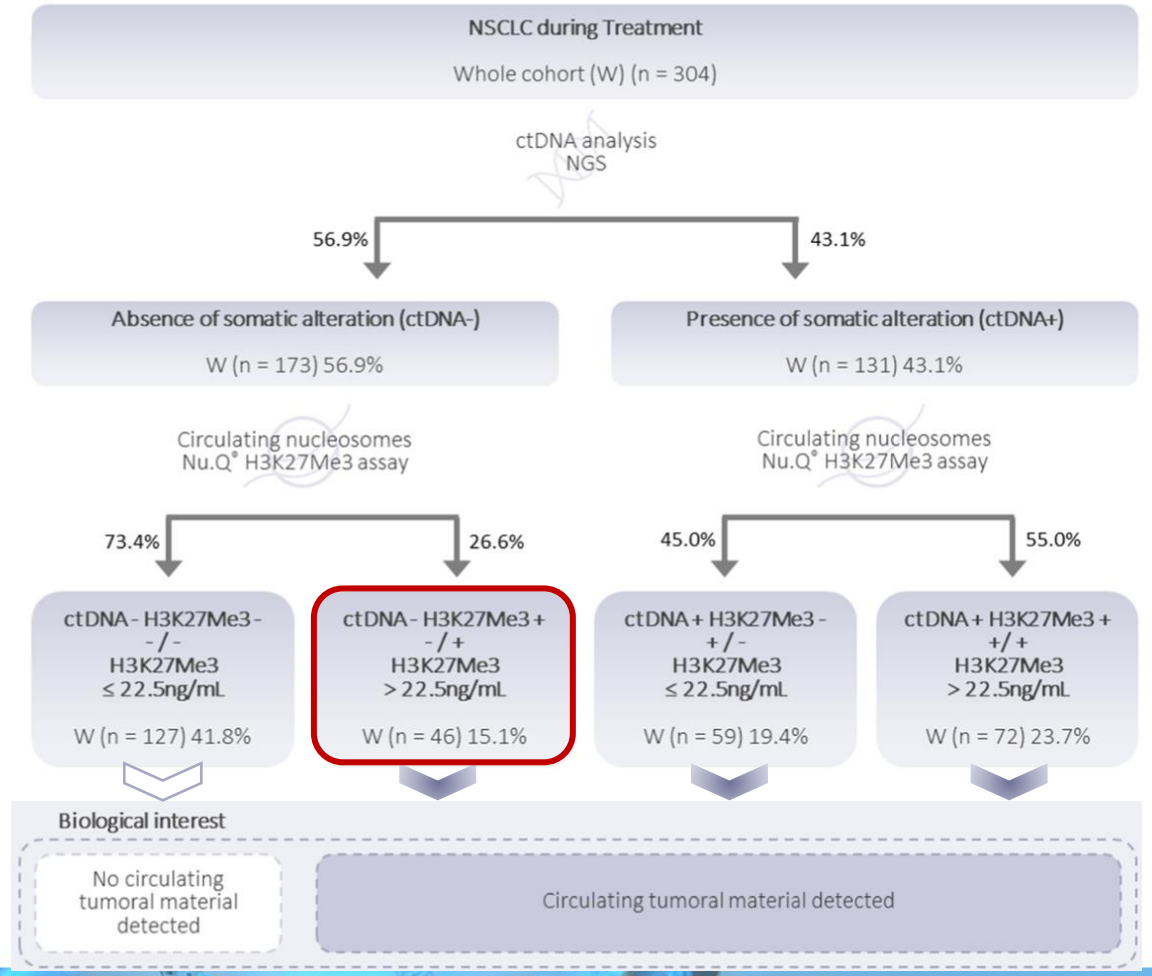


B

H3K27Me3-nucleosome levels in LC patients during treatment (cohort 2)

A. High level of H3K27Me3-nucleosomes observed in LC samples during treatment (Tt) is more pronounced in the presence of mutated ctDNA. Healthy, median: 8ng/ml; NSCLC Tt ctDNA-, median: 13,4 ng/ml; NSCLC, median: 26,1 ng/ml; **** p-value < 0.0001.

B. Decision tree proposed for the classification of NSCLC samples during patient follow-up.



Grolleau et al, Biomolecules, Aug 2023, https://doi.org/10.3390/biom13081255

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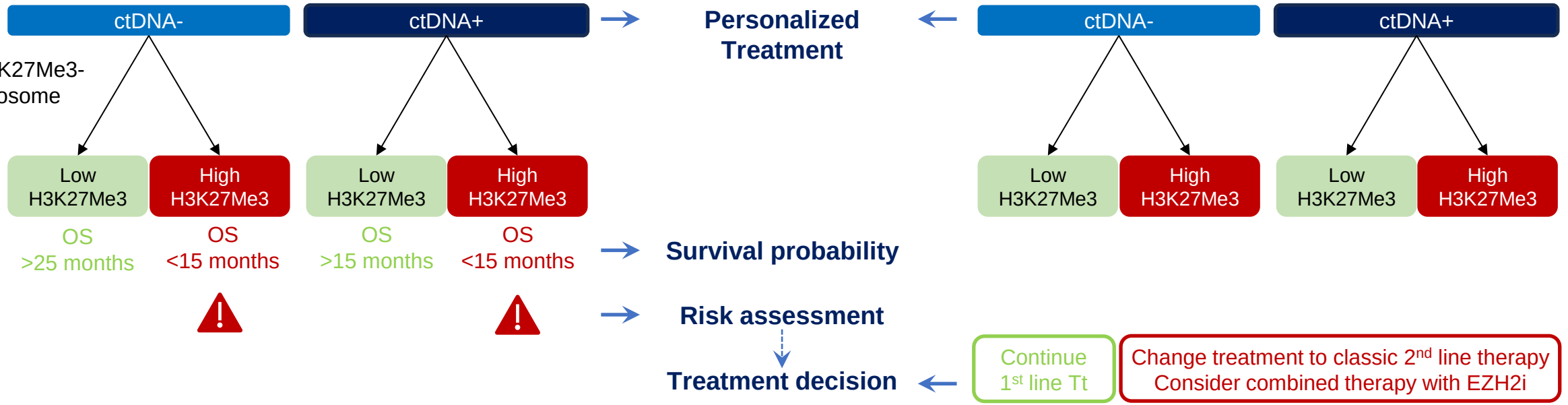
Conclusion - Discussion

At diagnosis

1) Molecular Profile

2) H3K27Me3-nucleosome levels



During Patient follow-up

Continue 1st line Tt

Change treatment to classic 2nd line therapy
Consider combined therapy with EZH2i

H3K27Me3-nucleosome levels could help in risk assessment and inform treatment decisions thereby *facilitating personalized care*

Acknowledgements

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