Improve Molecular Residual Disease monitoring by combining ctDNA molecular profiling and circulating H3K27Me3-nucleosome levels in NSCLC plasma samples

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BACKGROUND

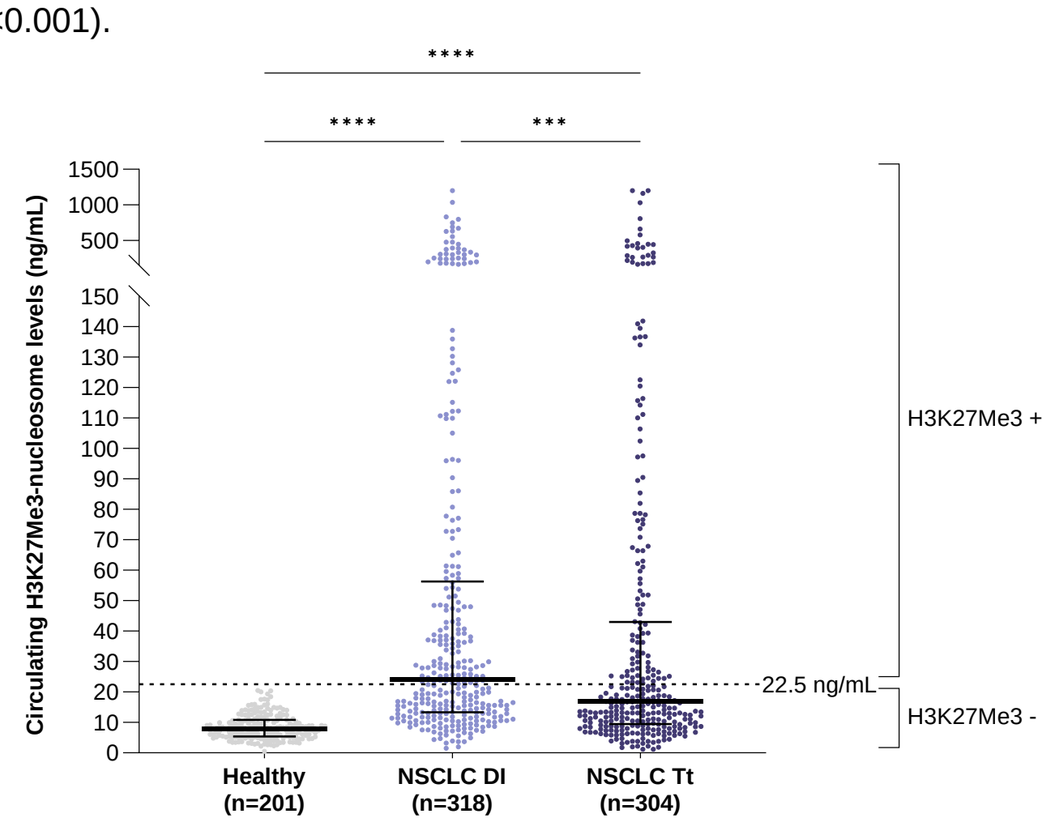
Patients diagnosed with stage IV NSCLC are treated by non-surgical therapies. The molecular profiling of circulating tumor DNA (ctDNA) is a helpful tool not only to define the most appropriate cancer treatment, but also to identify patients whose cfDNA includes residual tumor associated mutations.
However, molecular residual disease (MRD) is missed in a significant number of patients leading to a delayed treatment or suboptimal treatment selections. We propose a novel molecular profiling paradigm by combining circulating nucleosome and molecular profiling analysis and investigate its potential use in disease monitoring.

METHODS

K2-EDTA plasma samples from 318 patients with a NSCLC at diagnosis, and from 304 independent NSCLC patients under treatment were collected at Lyon University Hospital were analyzed with a custom-validated NGS panel covered 78 genes involved in cancer[1-3]. Samples from 201 healthy donors were also collected. Both NSCLC and healthy samples were analyzed for four nucleosome structures (H3K27Me3-, H3K36Me3-, H3K9Me3-, and H3K4Me2-nucleosomes) using Nu.Q® immunoassays (Belgian Volition SRL).

RESULTS

Significantly elevated concentrations of H3K27Me3-nucleosomes were found in plasmas at the diagnosis and during the treatment follow-up of NSCLC patients, compared to healthy donors (median = 24 vs 16,9 *vs*. 8 ng/ml; *p*-value <0.0001).
We can also note that H3K27Me3-nucleosomes levels is lower in patients during treatment compared to patients at diagnosis (*p*-value <0.001).



During patient follow-up, somatic mutations were still detected in 43.1% of the samples. A high H3K27Me3-nucleosome level was found in 15.1% of the samples, despite no somatic mutations being detected, allowing the identification of a potential disease progression from 43.1% to 58.2% versus molecular profiling alone.

Non-Small Cell Lung Cancer
After or during treatment

NSCLC during Treatment
Whole cohort (W) (n = 304)

ctDNA analysis
NGS

Absence of somatic alteration (ctDNA-)
W (n = 173) 56,9%

Presence of somatic alteration (ctDNA+)
W (n = 131) 43,1%

Circulating nucleosomes
Nu.Q® H3K27me3 assay

73,4% | 26,6%

ctDNA - H3K27Me3 - - / - H3K27Me3 ≤ 22,5ng/mL
W (n = 127) 41,8%

ctDNA - H3K27Me3 + - / + H3K27Me3 > 22,5ng/mL
W (n = 46) 15,1%

Circulating nucleosomes
Nu.Q® H3K27me3 assay

45,0% | 55,0%

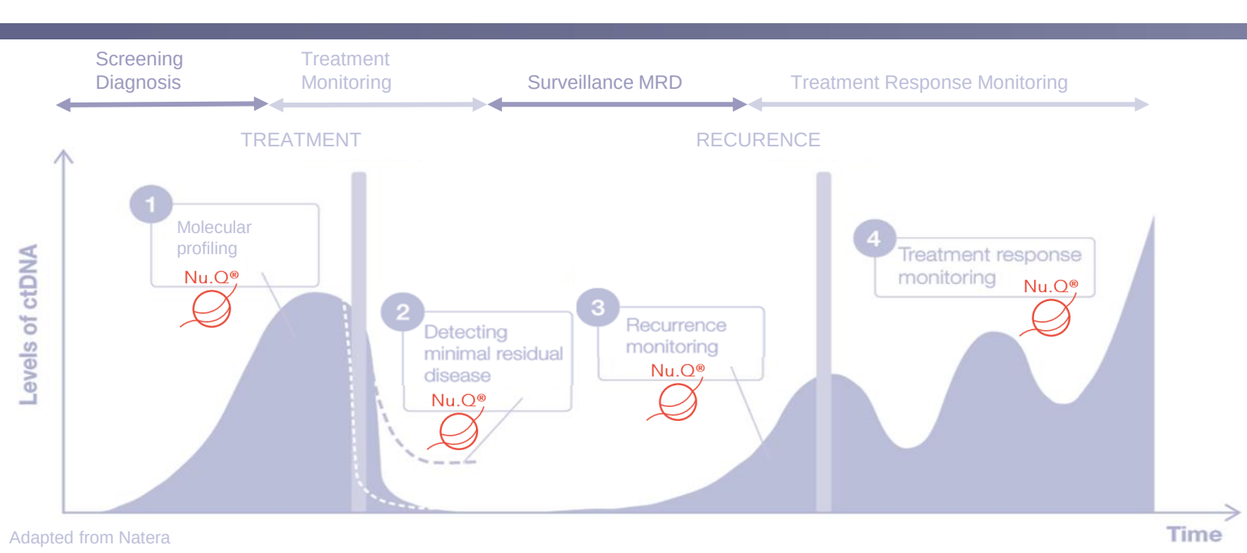
ctDNA + H3K27Me3 - + / - H3K27Me3 ≤ 22,5ng/mL
W (n = 59) 19,4%

ctDNA + H3K27Me3 + +/ + H3K27Me3 > 22,5ng/mL
W (n = 72) 23,7%

MRD detection

No circulating tumoral material detected

Combination of Nu.Q® assay and ctDNA analysis by NGS allows the detection of circulating tumoral material in **58%** of the patients



CONCLUSION

Measuring H3K27Me3-nucleosome levels in combination with ctDNA molecular profiling performed better than ctDNA molecular profiling alone.
The combination of the 2 biomarkers may be a promising new method for MRD monitoring, during and/or after treatment in patient with late-stage NSCLC.
Further clinical study would be required to prove that its use in the clinic may lead to a better patient management.

1. Bieler, J., et al., High-Throughput Nucleotide Resolution Predictions of Assay Limitations Increase the Reliability and Concordance of Clinical Tests. JCO Clin Cancer Inform, 2021. 5: p. 1085-1095.
2. Garcia, J., et al., Routine Molecular Screening of Patients with Advanced Non-Small Cell Lung Cancer in Circulating Cell-Free DNA at Diagnosis and During Progression Using OncoBEAM(TM) EGFR V2 and NGS Technologies. Mol Diagn Ther, 2021. 25(2): p. 239-250.
3. Garcia, J., et al., Sensitivity, specificity, and accuracy of a liquid biopsy approach utilizing molecular amplification pools. Sci Rep, 2021. 11(1): p. 10761.

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