Circulating H3K27me3 modified nucleosomes as a biomarker to monitor anti EZH2-based treatment in advanced solid tumour patients: translational analyses from CAIRE trial

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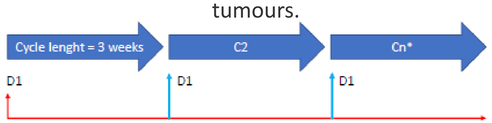
Background

CAIRE (NCT04705818)

Phase 2 multi-cohort study which assessed activity of combined anti-EZH2 **tazemetostat**(T, 800mgx 2/day) and anti-PDL1 **durvalumab** (D, 1120 mg q3 weeks) (**T+D**) across different pretreated solid tumours.



Tazemetostat: 800 mg twice a day (p.o)
Durvalumab: 1120 mg (i.v)

** Treatment can continue until disease progression or unacceptable toxicity*

EZH2 catalyses tri-methylation of Lysine 27 (**K27me3**) on histone 3 (**H3, H3K27me3**).

Circulating, cell-free H3K27me3 (**cfH3K27me3**) modified nucleosomes are thus a **potential pharmacodynamic biomarker** for Tazometostat activity.

We aimed to test if **Nu.Q ®-H3K27me3** levels normalised to total H3.1 variant nucleosomes served as a pharmacodynamic biomarker for anti-EZH2 treatment

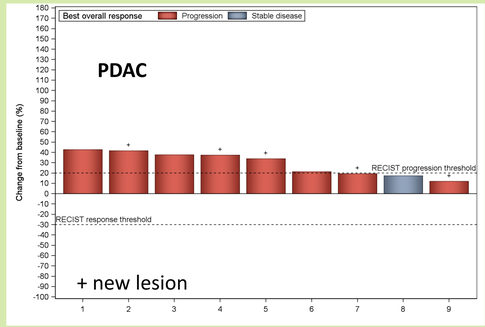
Methods

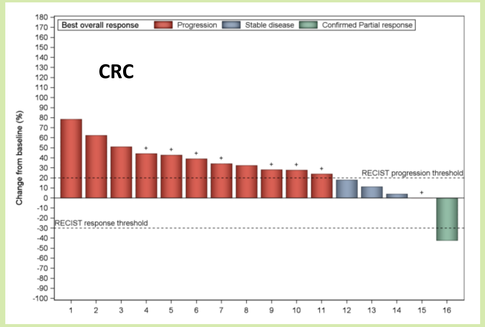
Circulating **cfH3K27me3 modified, and histone H3.1 variant, nucleosomes** were quantified in patients with pancreatic adenocarcinoma (PDAC), colorectal cancer (CRC) and soft-tissue sarcomas (STS) T+D treated patients using **Nu.Q®-H3K27me3** and **Nu.Q®-H3.1** chemiluminescent immunoassays (Belgian Volition SPRL).

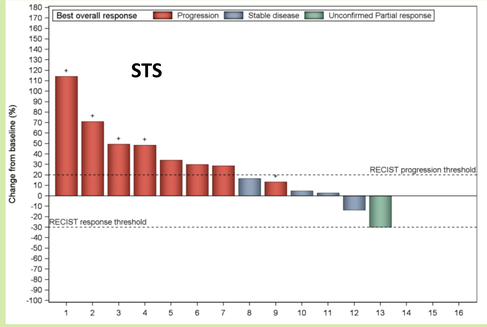
K2EDTA Plasma was collected at baseline (cycle 1 day 1, C1D1), cycle 2 day 1 (C2D1), cycle 3 day 1 (C3D1) and end of treatment (EOT).

Results

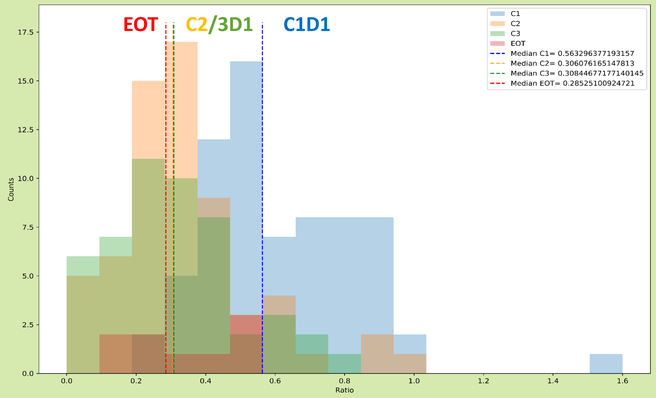
CAIRE safety and activity stage-1 cohort: 9 PDAC, 16 CRC, 13 STS assessed for activity.
Signs of activity have been seen for each cohort, thus the study has proceeded to stage-2







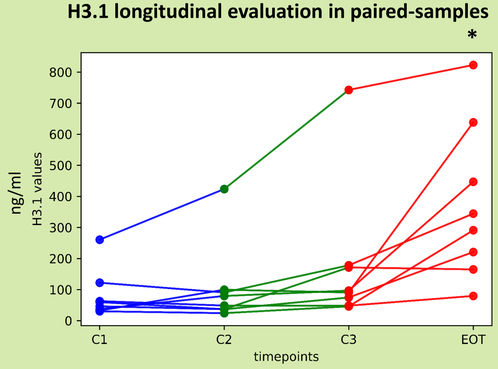
Normalised Nu.Q ®-H3K27me3 on T+D treatment



191/197 patients were evaluable for normalised Nu.Q®-H3K27me3; [range]: 0.025 - 1.541.

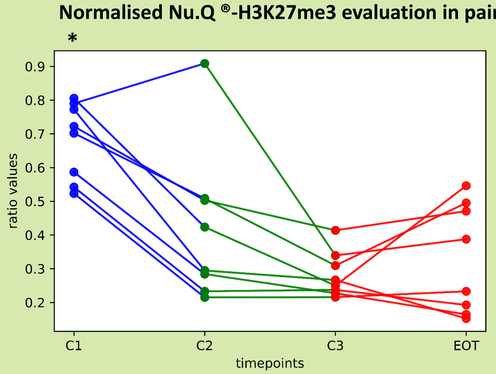
The normalised Nu.Q®-H3K27me3 C1D1 median value (0.56 +/- 0.22) was **significantly higher** than C2D1 (0.31 +/- 0.19, p: e -12), C3D1 (0.31 +/- 0.18, p: e -12) and EOT ones (0.28 +/- 0.14, p: 0.001).

H3.1 longitudinal evaluation in paired-samples



Nucleosomal [H3.1] was significantly (*) higher at **EOT** than any previous timepoint

Normalised Nu.Q ®-H3K27me3 evaluation in paired-samples



normalised Nu.Q®-H3K27me3 was significantly (*) higher at C1 than later timepoints

Conclusions

Total nucleosomal **H3.1** represents a surrogate of **disease burden** in metastatic PDAC, MSS-CRC and STS, as noted previously in haematological malignancies.

We show for the first time that the proportion of **circulating nucleosomal H3K27me3** significantly **decreases** during Tazametostat treatment in metastatic solid tumour patients, irrespective of the primary disease site, supporting its potential role as a pharmacodynamic biomarker for EZH2 inhibition.

Acknowledgements

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Project's partners

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