Circulating tumor DNA to detect minimal residual disease, response to adjuvant therapy and identify patients at high risk of recurrence in stage I-III CRC.

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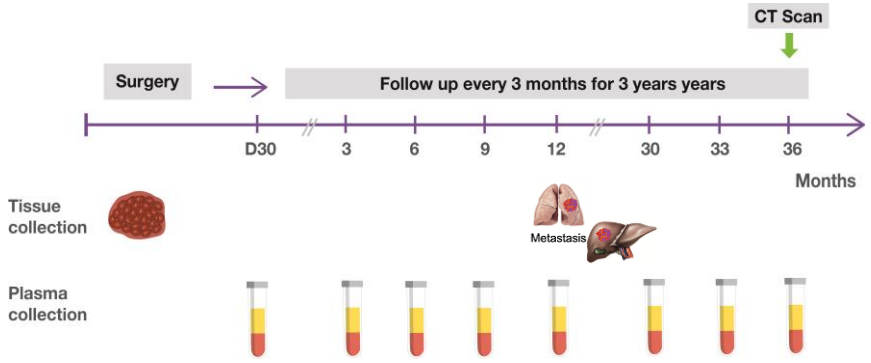
Aims and Study Design

1. To detect MRD and stratify patients based on risk of relapse using Signatera™ ctDNA (bespoke, mPCR NGS) assay.
2. To assess post-therapy relapse risk in ctDNA-positive patients.
3. To determine molecular lead time of recurrence between ctDNA and CT imaging.

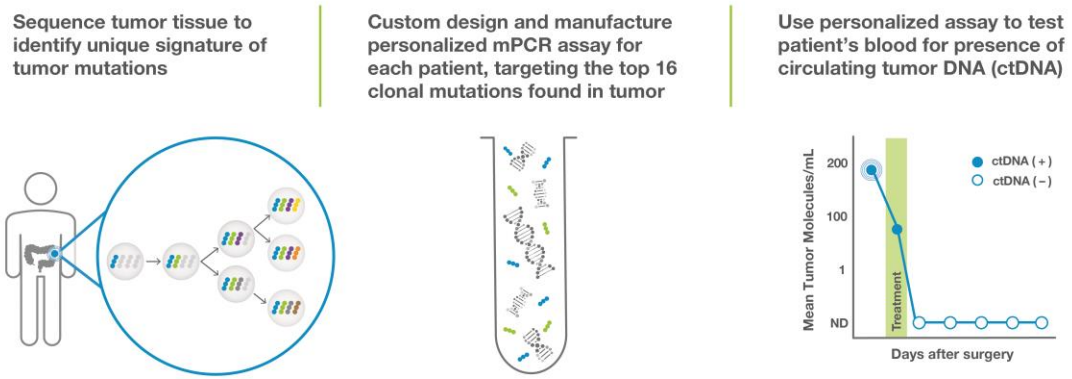
Patient Characteristics

- Patients enrolled = 198
- Patients analyzed = 193
- Median follow-up: 21.9 (1.4-41.9) months
- Stage I: (n=5), Stage II: (n=85), Stage III: (n=103)
- Adjuvant treated: (n=105)

INCLIVA and Aarhus University - Clinical Protocol

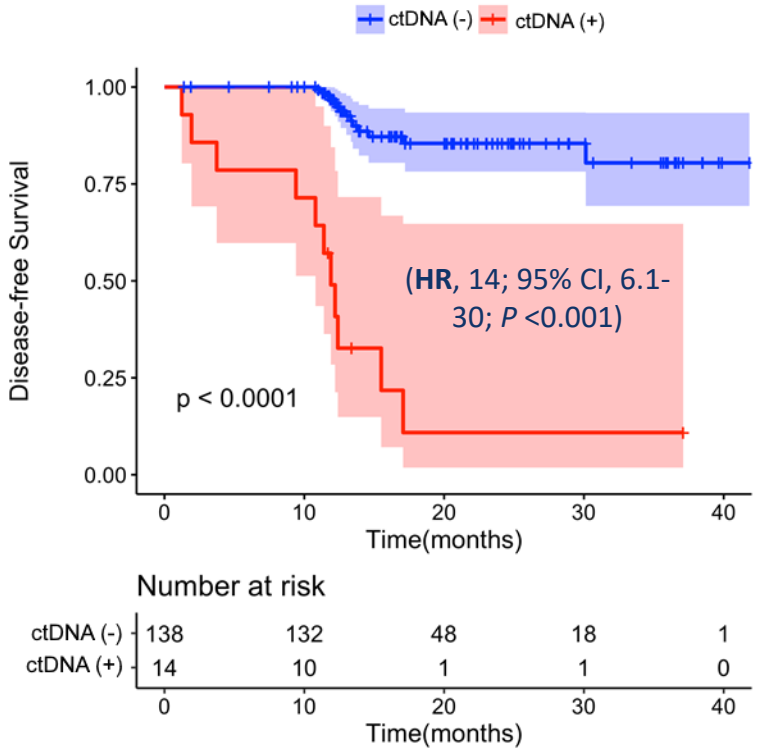


Signatera's Molecular Protocol



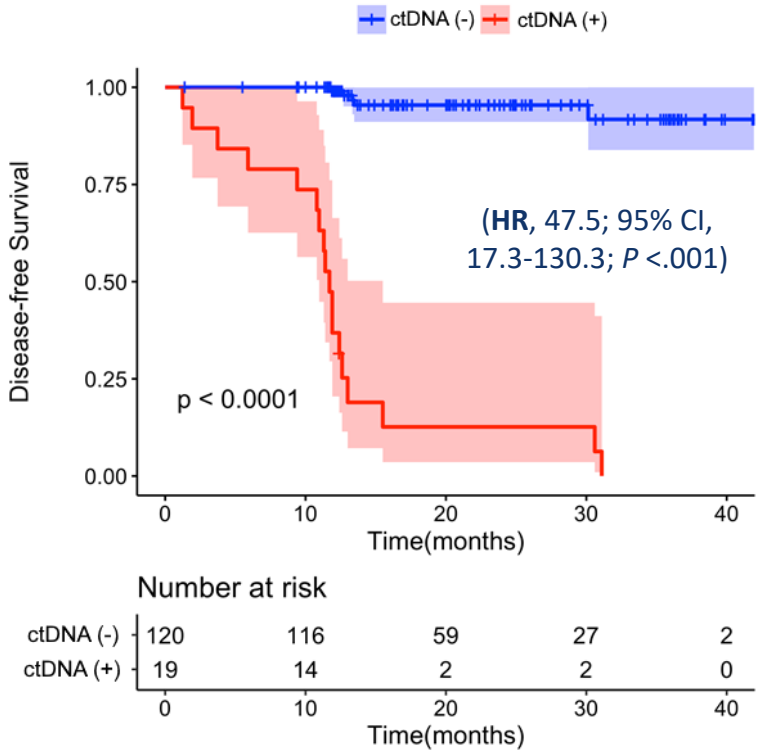
Results| Relapse-Risk Stratification by ctDNA Status

Post-operative setting (single timepoint)



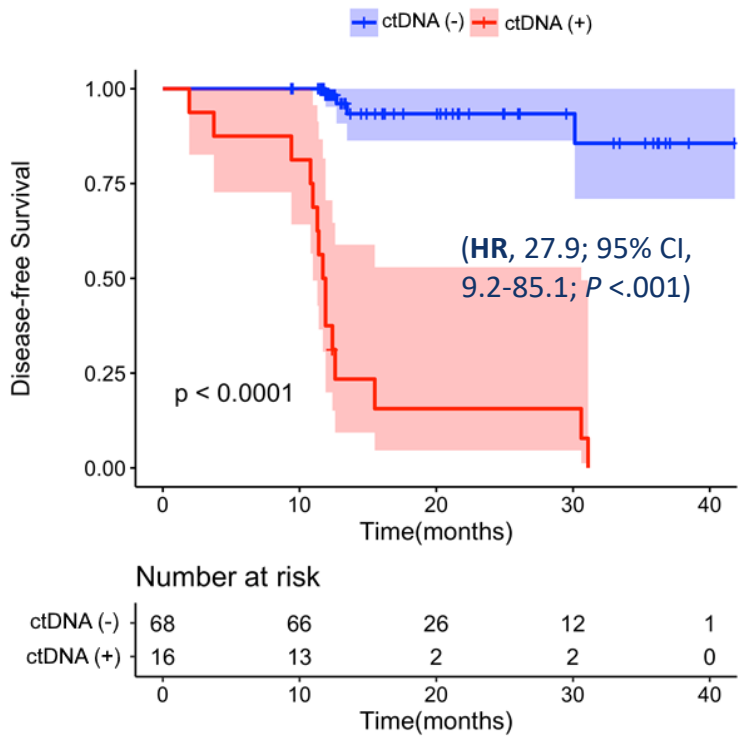
MRD-Positive: 9.2% (14/152)
Patients relapsed: 78.5% (11/14)

Post-definitive treatment setting



ctDNA positivity in longitudinal follow-up was associated with significantly worse DFS

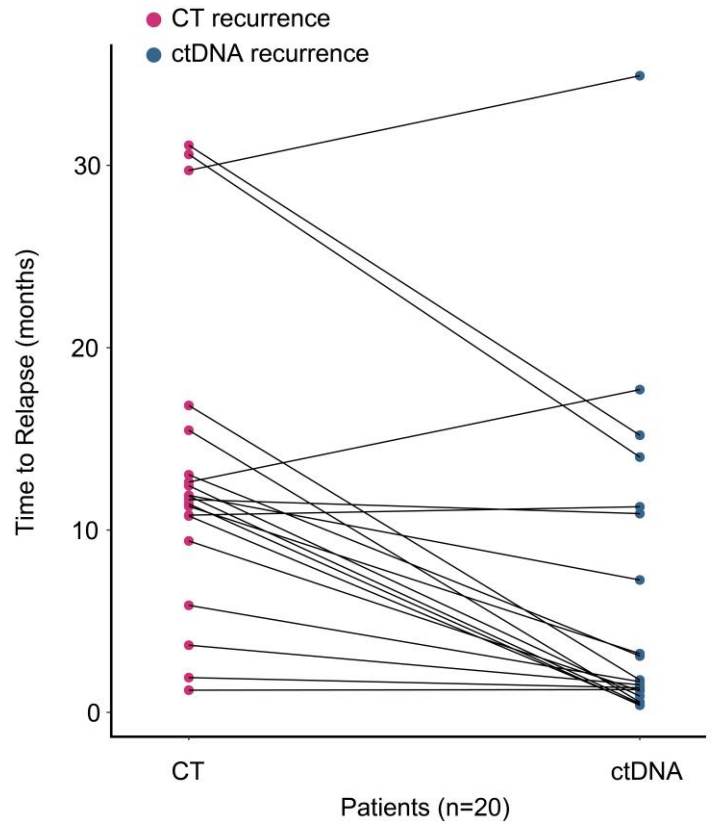
Post-ACT setting



Post-ACT longitudinal ctDNA positivity was strongly associated with significantly worse DFS

Results| Molecular Lead Time and Multivariate Analysis

Molecular Lead Time



Median lead time over radiological recurrence was 8.15 (IQR 0.56-16.6) months, *P* < 0.001.

Multivariable Cox Proportional-Hazards Model

Multivariable analysis included: ctDNA status, age, sex, stage, ACT, MSI, perineural invasion and number of resected lymph nodes

Akaike Information Criterion statistics suggests that the best model includes ctDNA status and age.

N = 137 Events = 23	HR	CI	Pr(>|z|)
Longitudinal ctDNA status (ref.negative)	53.19	(18.87-149.90)	<0.001
Age (ref. <70 years)	1.99	(0.81-4.86)	0.13

ctDNA was the only significant risk factor

Conclusions

1. Signatera ctDNA assay showed a sample level specificity of over 99.8% in a multi-institutional study.

2. Post-operative ctDNA status was the only significant predictor of DFS than all other risk factors combined.

3. ctDNA-positive status at the end of adjuvant treatment may potentially indicate resistance to standard therapy.

4. Longitudinal ctDNA tracking enables identification of patients at higher risk of relapse with a median lead time of 8.15 months over radiologic identification.

5. ctDNA analysis can help guide treatment decisions both in the adjuvant and post-adjuvant setting.

Disclosures

Prof. Andrés Cervantes

Employment: None; Stock Ownership: None.

Consultant or Advisory Role: Merck Serono, Roche, Beigene, Bayer, Servier, Lilly, Novartis, Takeda, Astelas.

Research Funding: Genentech, Merck Serono, Roche, Beigene, Bayer, Servier, Lilly, Novartis, Takeda, Astelas, Pierre Fabre, Fibrogen, Amcure, Sierra Oncology, Astra Zeneca, Medimmune, BMS, MSD.

Speaking: Merck Serono, Roche, Angem, Bayer, Servier, Foundation Medicine. Grant support: Merck Serono, Roche.

Others: Executive Board member of ESMO, Chair of Education ESMO, ESMO Education Director, INCLIVA General and Scientific Director, Associate Editor: Annals of Oncology and ESMO Open, Editor in chief: Cancer Treatment Reviews.

Shruti Sharma, Svetlana Shchegrova, Derrick Renner, Himanshu Sethi, Bernhard Zimmermann, Alexey Aleshin are employees at Natera and own stock/options to own stock in the company .

All other authors declare no conflicts of interest.