Minimal Residual Disease in Solid Cancers: Perspective of Industry

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Disclaimer

Darren Hodgson

I have the following financial relationships to disclose:

Stockholder in: *AstraZeneca*

Employee of: *AstraZeneca*

I will discuss the following off label use and/or investigational use in my presentation:

Immune checkpoint inhibitors in patients with MRD+ lung cancer

Overview

- **ctDNA biology and potential utility in drug development**
- Minimal Residual Disease – patient selection
- Minimal Residual Disease - endpoint
- Summary

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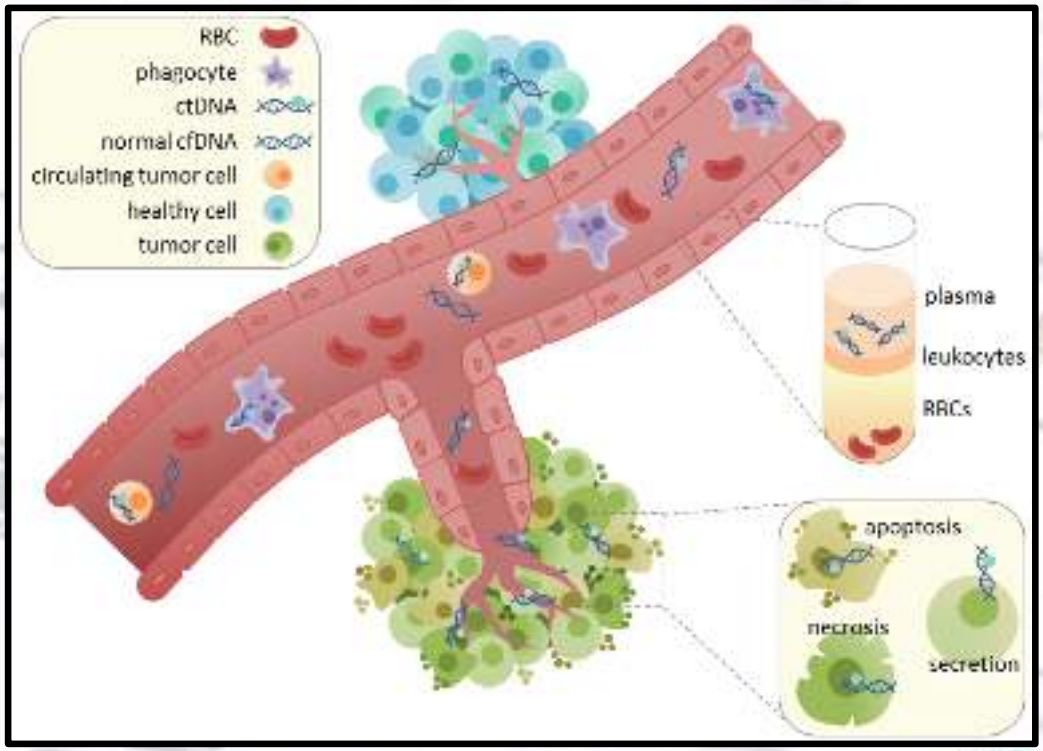
Measurable Residual Disease (MRD) and Circulating Tumour Nucleotides (ct DNA) in cancer drug development

ctDNA can provide critical information about a tumour through non-invasive techniques



- Genetic & epigenetic markers **characteristic** of disease
- **Patient friendly** sampling that can be used in place of tissue for some selection markers and changes can be monitored time with longitudinal analyses
- Can represent a **small fraction** of total circulating free (cf) DNA
- Very short t1/2 ~2hrs, **quantity** influenced by tumor volume, location, aggressiveness
- **Absolute units:** mutation copies, genome equivalents (GE) /ml. **Relative units:** mutant allele fraction (MAF)

https://acsjournals.onlinelibrary.wiley.com/doi/full/10.3322/caac.21650

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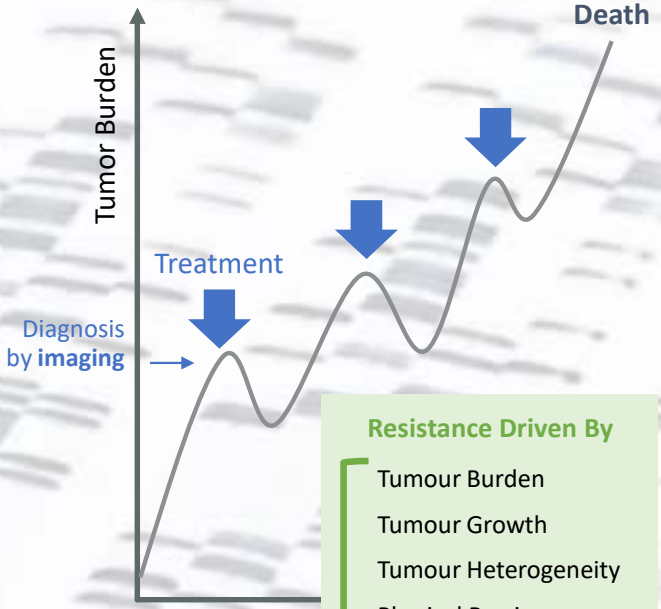
How to cure cancer: Hit *Earlier*, *Harder*, *Smarter*

Today



Resistance Driven By

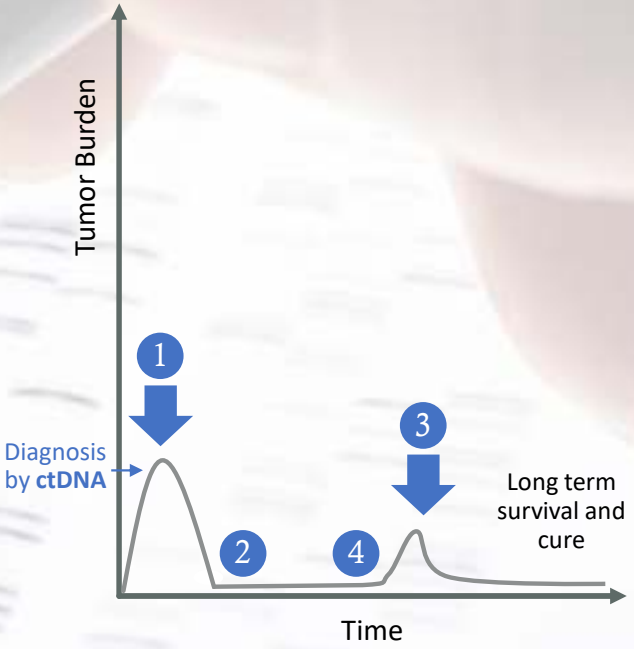
- Tumour Burden
- Tumour Growth
- Tumour Heterogeneity
- Physical Barriers
- Immune system/TME
- Undruggable genome
- Therapeutic Pressure

Potential Solutions

1. Earlier Detection and Cancer Interception
2. Deeper Response
3. Therapeutic Monitoring and Adaptive Interventions
4. Mapping Cancer Dependencies

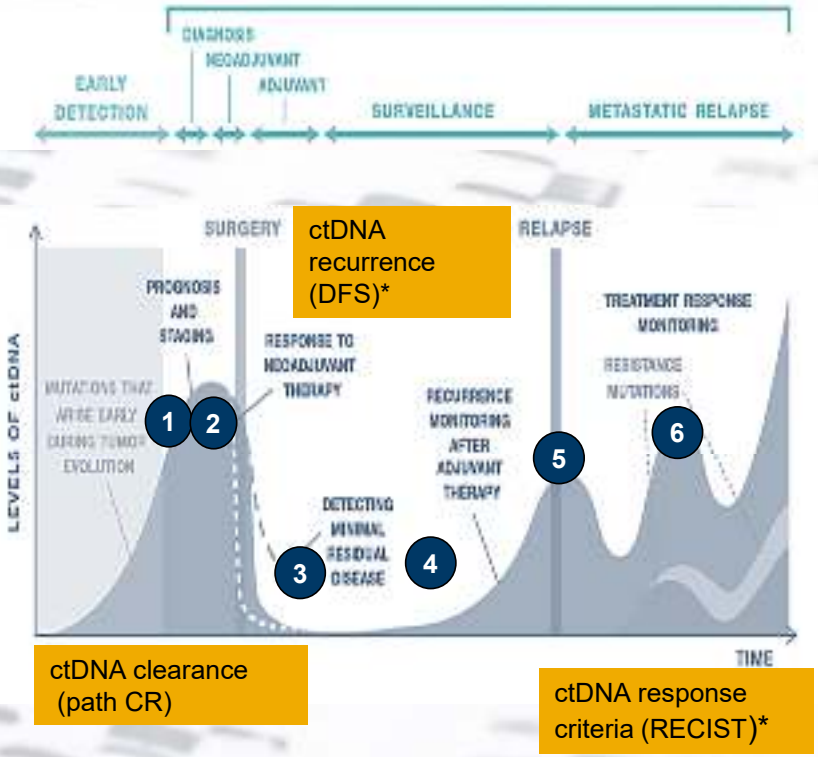
OR

Tomorrow



Adapted from https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8008476/

ctDNA: New Points of Intervention and Endpoints



Intervention ?	
1*	Diagnosis with tissue of origin: possible change in stage distributions
2*	Prognosis: possible upstaging
3*	Landmark MRD
4*	Surveillance MRD (ctDNA recurrence)
2, 5, 6	Treatment selection
6*	Treatment switch on ctDNA progression or detecting resistance mechanism

Adapted from product brochure (Natera, https://www.natera.com/wpcontent/uploads/2020/11/Oncology-Clinical-Seeingbeyond-the-limit-Detect-residual-disease-andassess- treatment-response-SGN_AV_WP.pdf accessed on Sep 17 2021)

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***sensitivity/comparison to imaging essential**

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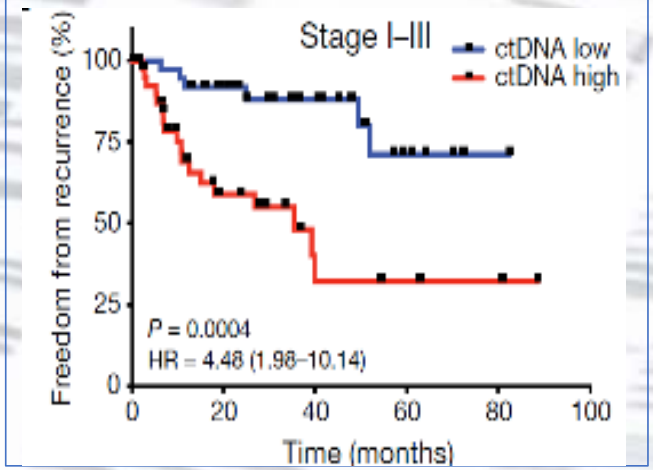
ctDNA can identify patients whose cancer will recur

Pre-Treatment

NSCLC



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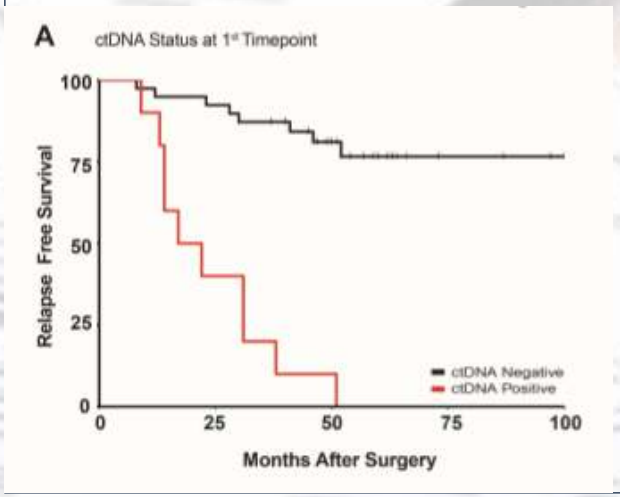
Post-Surgical Landmark

Breast Cancer



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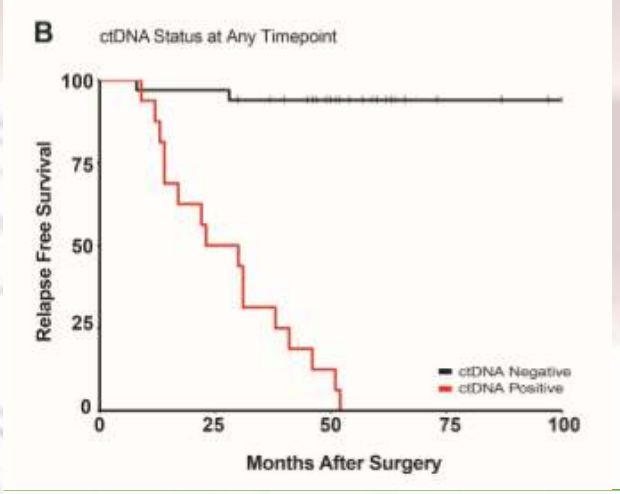
Post-Surgical Monitoring

Breast Cancer



4

NSCLC: Chabon JJ, et al. Nature. 2020;580(7802):245-251. Integrating genomic features for non-invasive early lung cancer detection

Breast Cancer - Coombes et al 2019; DOI: 10.1158/1078-0432.CCR-18-3663. Personalized detection of circulating tumor DNA antedates breast cancer metastatic recurrence

Overview

- ctDNA biology and potential utility in drug development
- **Minimal Residual Disease – patient selection**
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Measurable Residual Disease (MRD) and Circulating Tumour Nucleotides (ct DNA) in cancer drug development

MRD biomarker can overcome challenges associated with conventional adjuvant drug trials

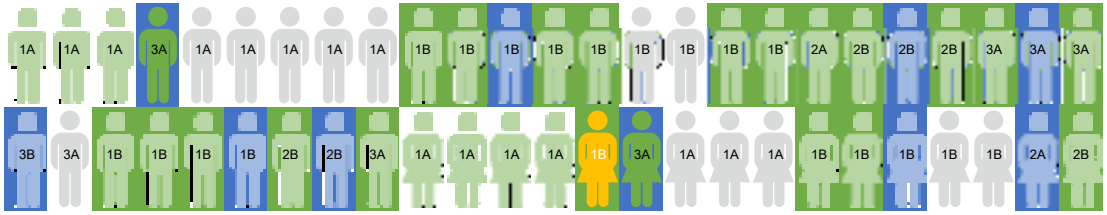
MRD is emerging as a disease space in solid tumours and may enable early-escalation trials in high-risk patient populations

Conventional adjuvant trials

Surgically cured patient

Non-surgically cured patient

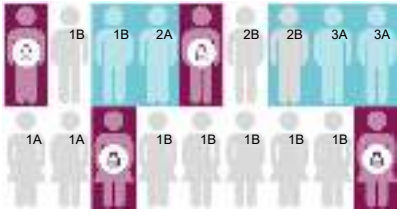
Adjuvant therapy given to Stage IB >4 cm and above



~40% of patients have residual disease post-op

- Heterogenous adjuvant trial populations with low relapse-event rates
  - High on-study recruitment numbers required to adequately power studies
  - Studies take more than a decade to read out (E1505: 2017)
- Escalation of SoC therapy presents toxicity risk in those cured by surgery

MRD-driven adjuvant trials



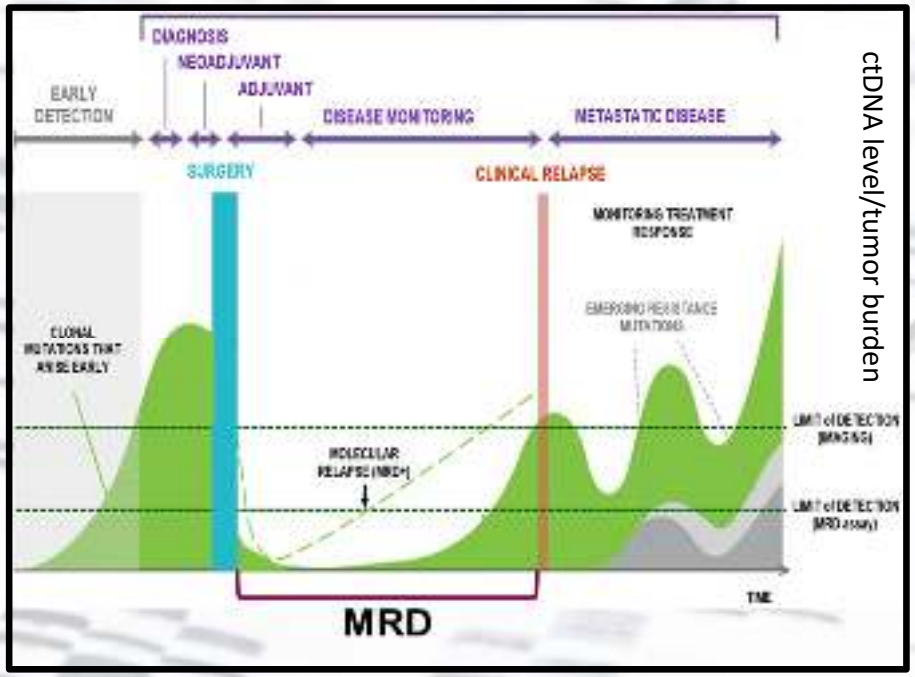
MRD+

Homogenous study population with high relapse-event rates

- Low on-study recruitment numbers
- Rapid read out of study
- Therapy escalated only in patients destined to relapse
- Opportunity to establish DFS surrogates predicated on MRD clearance

Slide courtesy of Chris Abbosh UCL, UK. Adapted from Abbosh et al AACR 2020

ctDNA Minimal Residual Disease Concept



			Estimate
T stage	T3	T1c	T1b
Nodule Diameter (cm)	5.8	2.6	1.2
Nodule Volume (cm^3)	100	10	1
MAF (%)	1.4 (0.62-3.1)	0.1 (0.06-0.18)	0.008 (0.002-0.03)

Estimate require **0.008% MAF** to detect 1 cm^3 of tumour[1]
IMAGING Critical size in 1 location **ctDNA** Critical number of cells, but can be small deposits in multiple locations

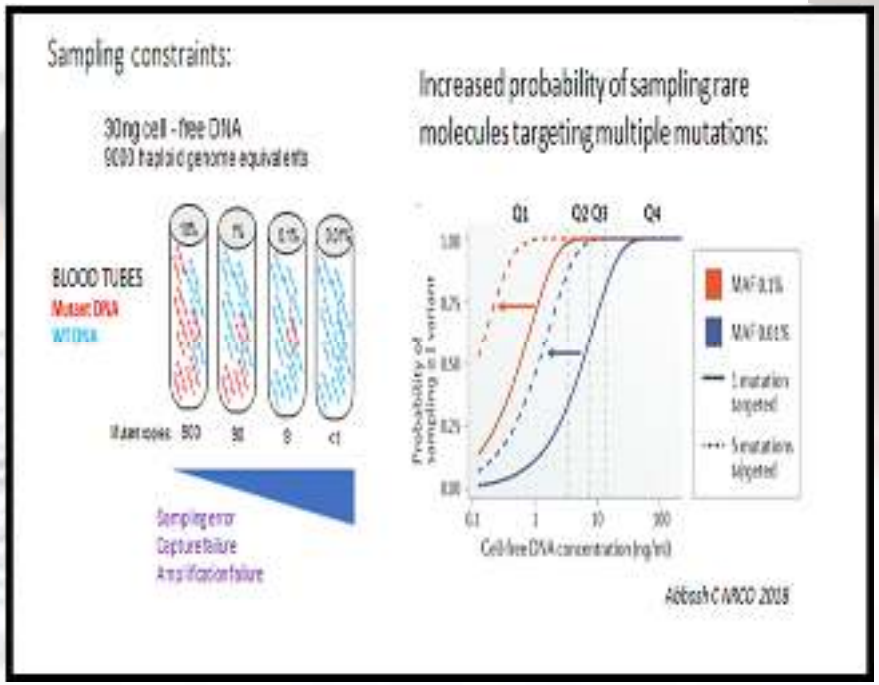
Adapted from Product brochure (Natera, https://www.natera.com/wpcontent/uploads/2020/11/Oncology-Clinical-Seeingbeyond-the-limit-Detect-residual-disease-andassess- treatment-response-SGN_AV_WP.pdf accessed on Sep 17 2021)

1. Abbosh C, et al. *Nat Rev Clin Oncol* 2018;15:577–586; MAF, mutant allele frequency

Multiple Markers Required for a ctDNA MRD Test

Something present to detect AND sufficiently sensitive/specific technology to detect it

- Independent groups calculate to detect a 1cm^3 tumor requires detecting at least 0.01% ctDNA[1]
- Around 30ng/9000 genomes of cfDNA from 10ml blood in absence of cancer/NSCLC patients after curative intent therapy[1]
- Need to detect less than 0.9 copies from 10 ml blood - sometimes your needle is in another haystack !
- This is only possible if we employ **multiple markers** per genome - concept supported by independent studies[2]
- Sensitivity enabled by only assessing markers known to be present in an individuals tumor (avoiding CHIP and minimising multiple testing) **AND** using error suppression techniques



1 Abbosh C, et al. Nat Rev Clin Oncol 2018;15:577–586
2 Aadel A. Chaudhuri et al. Cancer Discov 2017;7:1394-1403; Reinert T, JAMA Oncology. 2019;5(8):1124-31.

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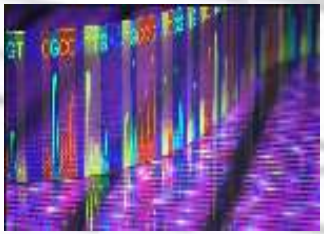
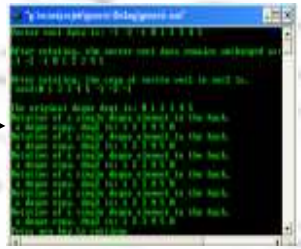
Personalised assay is a complex 2-step process

Step 1

WES + ALGORITHM IDENTIFIES MULTIPLE CLONAL MUTATIONS IN TUMOR
Prioritisation of low noise variants for subsequent tracking



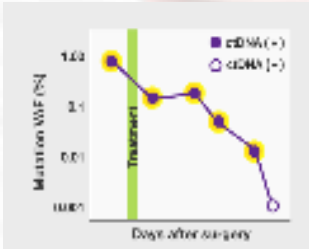
Whole Exome Sequencing



Personalized Panel design

Step 2

TRACK THE MUTATIONS IN PLASMA
Specific to original tumor, will not detect new primaries

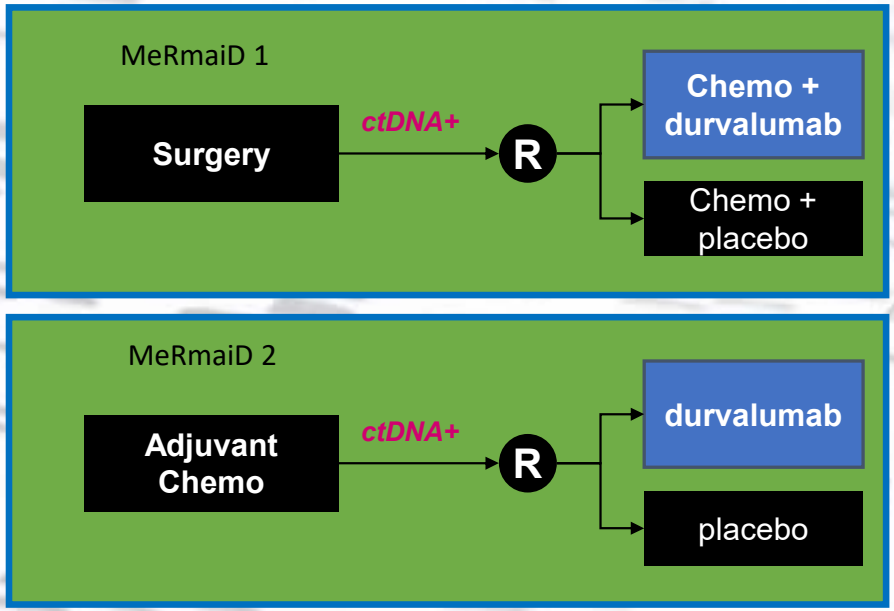


Plasma ctDNA Analysis

All completed in the window from surgery to adjuvant treatment start

*WES: Whole Exome Sequencing

MeRmaiD Studies



- Detection of ctDNA at landmark (MRD1) and surveillance (MRD2)
- Enabled by personalized ctDNA assay with a low limit of detection and high specificity
- ctDNA clearance as an exploratory endpoint

Darren Hodgson AACR Regulatory Science and Policy Track session, Liquid Biopsies in Adjuvant Solid Tumor Minimal Residual Disease, 18th May 2021

What could be the outcome of a Trial in MRD Patients ?

- IMvigor010 adjuvant study of Atezolizumab v observation in Muscle-Invasive bladder cancer
- P3 Trial did not meet its primary endpoint (DFS in the ITT population, n=809)
- Retrospective Personalised ctDNA measurements made on samples taken prior to and after 6 weeks of adjuvant treatment (72% of ITT evaluable of whom 37% were baseline ctDNA +)

Conclusions Presented by Authors

- ctDNA (+) identified patients with high-risk MIUC likely to derive DFS and OS improvement from adjuvant atezolizumab
- ctDNA(–) patients had a low risk of relapse and did not have improved outcomes with atezolizumab vs observation
- Rates of ctDNA clearance were higher in the atezolizumab vs observation arm, and clearance with atezolizumab was associated with improved DFS and OS

Powles et al ESMO Immuno-oncology Dec 2020

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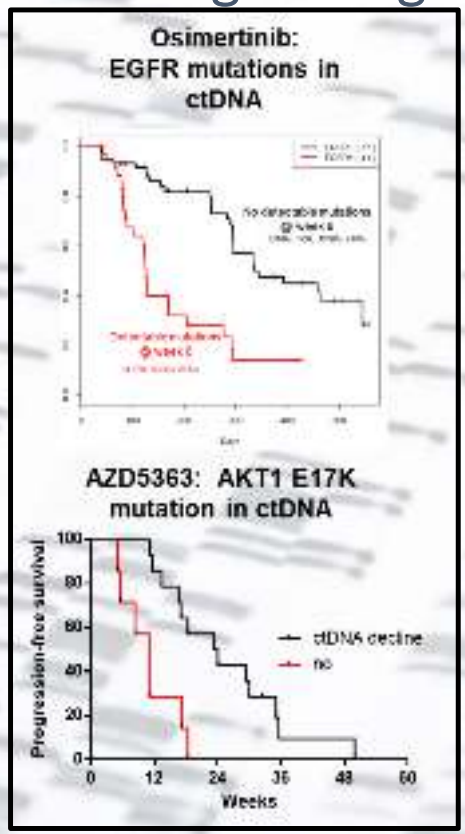
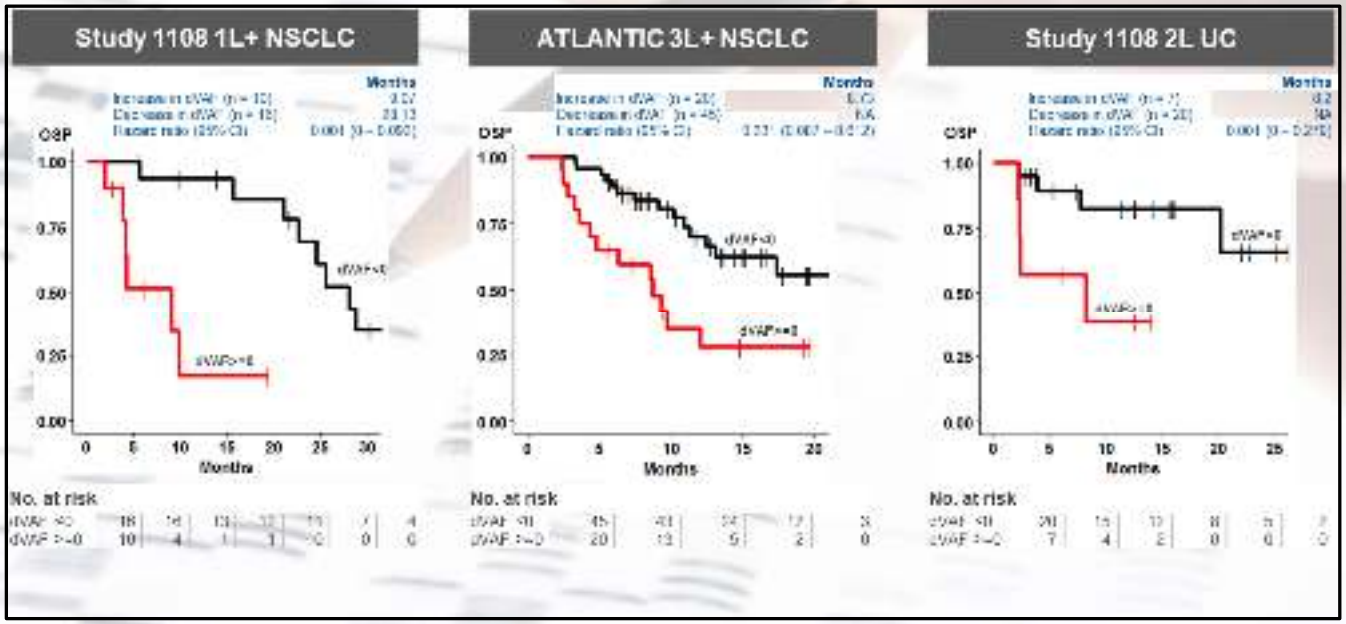
Early decreases in ctDNA levels associate with longer PFS in patients treated with targeted agents and ICI





Thress et al. *ASCO*, 2017, Hyman et al., *JCO*, 2017, Raja et al., *Clin Cancer Res, 2018)*

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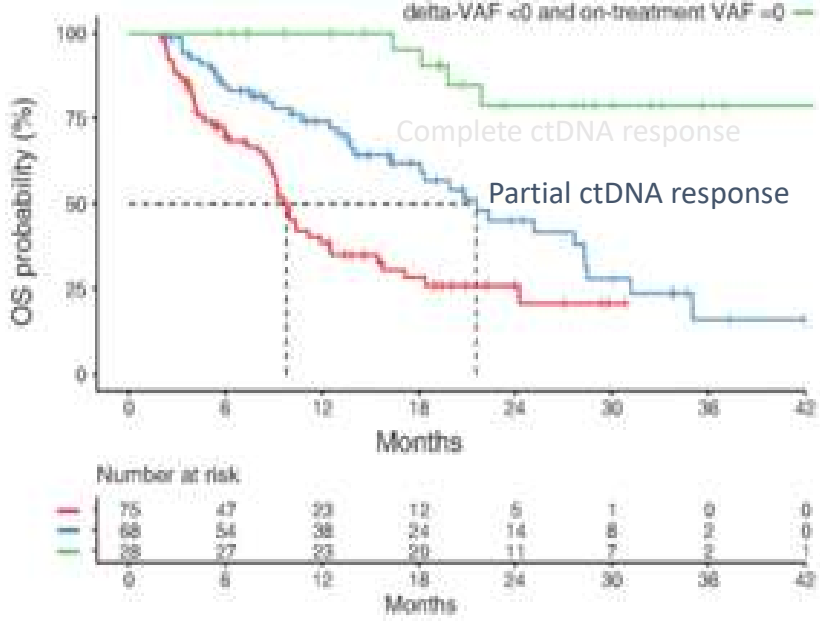
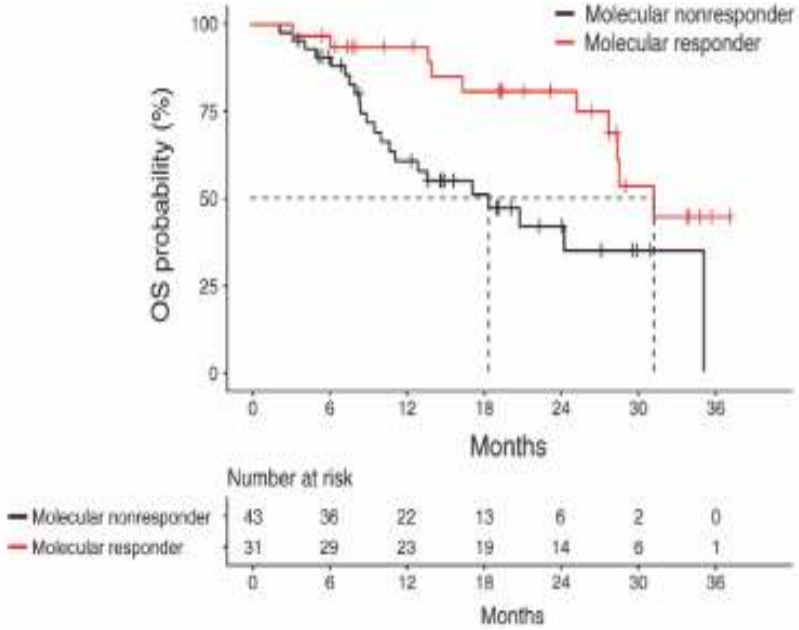
ctDNA: a new end-point ?

All patients



Amongst patients with stable disease only

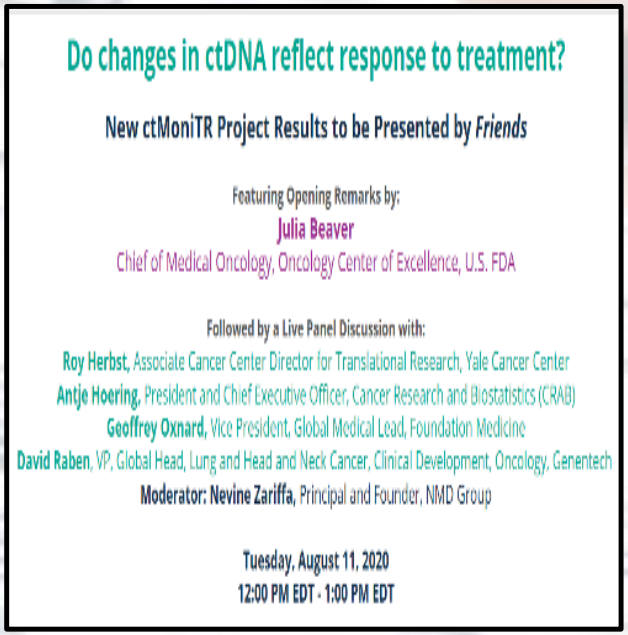


Collaboration between AZ and MSKCC
Zhang et al Cancer Discovery
https://cancerdiscovery.aacrjournals.org/content/early/2020/08/14/2159-8290.CD-20-0047

Friends of Cancer Research ctDNA for Monitoring Treatment Response

STEP 1

- Developed ctDNA metrics to harmonize across various assays in patients with advanced lung cancer treated with ICI
- Evaluated ctDNA metrics with standard clinical covariates (pooled dataset of 200 patients across 7 studies with 4 assays)
- Max (& mean) % change from first ctDNA post-baseline sample within 70 days after treatment *T1 had strongest association with outcome (< 50% decrease (yes/no))
- Decreases in the maximum Variant Allele Frequency (VAF) from Baseline to *T1 had the strongest association among all clinical covariates considered relative to
  - Tumor response (PR or Better)
  - Overall Survival (OS), and Progression-Free Survival at 6 months (PFS6)



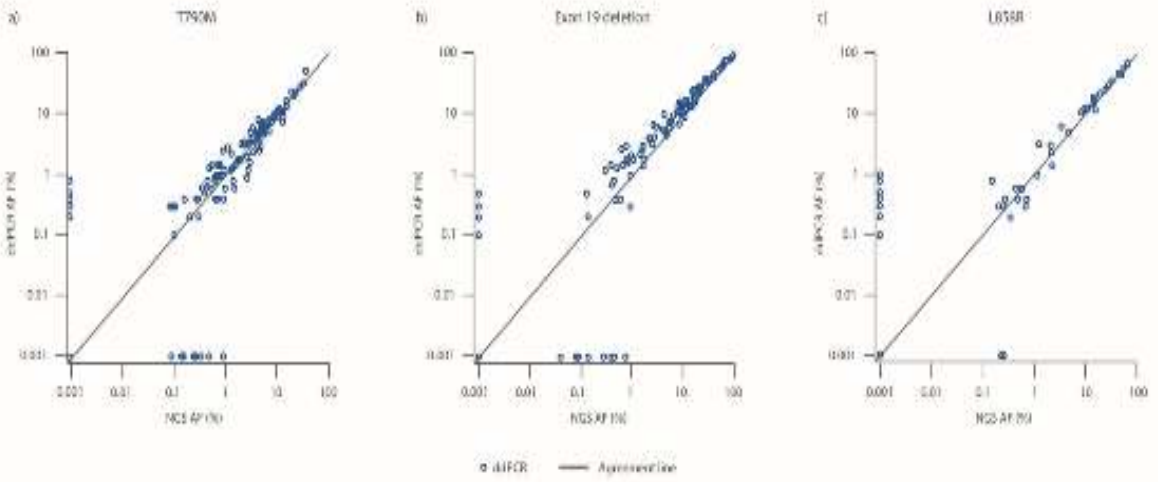
https://friendsofcancerresearch.org/blog/engaging-innovation/ctmonitr-step-1-results-do-changes-ctdna-reflect-response-treatment

STEP 2

- ctDNA to monitor treatment response in more than 25 studies representing over 3,000 cancer patients, 16 additional treatments, and several cancer types.
- Expand the study of the relationship between ctDNA and clinical outcomes across a number of clinical settings that include several drug classes and tumor types.
- FoCR is proud to partner with : AstraZeneca, Bayer, Biodesix, Boehringer Ingelheim, Bristol Myers Squibb Company, Cancer Research And Biostatistics (CRAB), EMD Serono, Inc., US Food and Drug Administration (FDA), Foundation Medicine, Inc., Genentech, Inc., Guardant Health, Inc., Illumina, Inc., Johns Hopkins University, Lilly Oncology, Merck & Co. Inc., Molecular Characterization Laboratory at Frederick National Laboratory, Memorial Sloan Kettering Cancer Center, Natera, Inc., NMD Group LLC., Novartis AG, Pfizer, Inc., Princess Margaret Cancer Centre, Regeneron Pharmaceuticals Inc., Resolution Bioscience, Inc., Takeda Pharmaceutical Company

Allelic Fraction is Reproducible Across Assay Formats

Supporting Figure 2. Allelic fraction (AF) correlation between ddPCR and NGS assays for A) T790M, B) exon deletion 19 and C) L858R in the osimertinib-treated population*



https://acsjournals.onlinelibrary.wiley.com/doi/full/10.1002/cncr.32503

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Summary

- Current ctDNA tests enable adjuvant MRD+ trials of new modalities
  - A low limit of detection is essential (<0.01% ctDNA fraction) together with high specificity, particularly if used for surveillance
  - Significance of pre-surgical ctDNA detection/levels ?
  - Value of surveillance and earlier intervention ?
- Potential improvements:
  - A lower LoD could improve sensitivity
  - Detection of second primaries
  - Logistics and delivery
- Collaboratively build our collective understanding of ctDNA recurrence as an endpoint and the relationship to relapse site
  - The field will benefit from consortia and initiatives such as ctMoniTR

Acknowledgements

Clinical collaborators and their patients

Industry collaborators through FoCR and ongoing collaborations with Guardant Health and Invitae

Clinical, Translational Medicine, Precision Medicine, Regulatory and Statistics Teams at AstraZeneca