CDDF
Cancer Drug Development Forum

MEETING REPORT

CDDF Multi-Stakeholder Workshop

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

25 - 26 April 2022
Hybrid Workshop
Prepared by the CDDF

PROGRAMME COMMITTEE

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Foreword to the meeting report on MRD and ctDNA workshop

It is hard to argue that the treatment and the prognosis of cancer has not greatly improved for many entities over the last two decades. While it is important to acknowledge the contribution of earlier and better diagnosis and improved surgical technique, the main impact has been achieved by innovative therapies like small molecules, targeted therapies, immunological therapies and cellular treatments. This has translated to impressive survival benefits for many cancers, often achieved by several lines of effective treatment.

The ability to reduce tumor load by several log steps has prompted the interest to measure its residual mass beyond the limits of detection of the previous methods (mainly light microscopy and radiology). The first intention was to measure what is still there in so called "complete" remission (CR) and to better understand which of these patients may relapse. Refined fluorescence-activated cell sorting (FACS) technologies, PCR and next generation sequencing (NGS) became available and soon it was demonstrated that achieving tumour reduction beyond the limits of detection of these methods was clearly and better correlated with survival. The concept of measurable residual disease (MRD) evolved (formerly called minimal residual disease).

The longer survival of cancer patients following multiple lines of therapy also creates difficulties for the conduct of clinical trials to demonstrate an overall survival benefit within an achievable time span. Also, it may be difficult to discern the effect of an initial therapy if it is followed by several lines of salvage therapies. Therefore, additional efforts are been made to establish MRD as either an intermediary or a surrogate endpoint.

While MRD is established in haematological malignancies with significant bone marrow involvement (esp. multiple myeloma (MM), acute myeloid leukaemia (AML) and others), which thus offer relatively easy access to the tumour compartment, this was not possible for lymphomas or solid tumours. However, the discovery of circulating cell-free DNA nucleotides led to the search of nucleotides with tumour-specific mutation in circulation (circulating tumour-nucleotides, ctDNA). Again, innovative and very sensitive methods allow the assessment for each individual in the necessary time lines. While the clinical research on ctDNA as a response marker in solid tumors has started later than the evaluation of MRD in haematological malignancies it is already very likely that these markers will be as useful.

All of this highlights the need for regular assessment and discussion of scientific, methodological, clinical and regulatory aspects of these markers with all relevant stakeholders (patients, clinicians, regulators, payers, pharmaceutical industry etc.) as the implications for the advancement of cancer drug approvals are huge.

The Cancer Drug Development Forum, a non-profit association dedicated to advancing cancer drug development by facilitating constructive dialogue between all relevant stakeholders, has engaged in the discussion of the MRD concept for a long time. We held multi-stakeholder workshops in 2014 (with a focus on MM, CLL, and breast cancer), 2017 (MM), 2018 (AML, CLL) and now in 2022. The presentations and meeting reports of the previous meetings can be found on our website, www.cddf.org.

This report summarises the meeting held in Amsterdam on April 25-26, 2022. It brought together state-of-the-art presentations on the methodological aspects (see Bruno Paiva and Dominic Rothwell), their clinical application (see Marie Morfouace and Jürgen Gschwend) and regulatory assessment (see Gormley); remarkable example of non-competitive collaboration of the pharmaceutical industry (see the presentation on the MPAACT initiative, Patel) and of public-industry collaboration (see the Friends of Cancer Research presentation by Jeff Allen and the Foundation of the National Institutes of Health initiatives by Chris

Hourigan) that are likely to deliver data on the scale that is necessary to meet the statistical criteria for the evaluation of surrogate endpoints.

Nicole Gormley, from the FDA, presented the agencies guidelines on the use of MRD and a vision of how such endpoints could be used in the future with the evolution of accelerated approval pathways. It would allow new drugs to be tested in earlier lines of therapy and obtain accelerated approval on an interim readout of a response endpoint (that could be MRD or ctDNA, if sufficiently validated). The study would be continued until the assessment of a validated time-to-event endpoint (e.g. progression-free survival or overall survival) is possible. The accelerated approval would be re-assessed at this time point and, if the data allows, full approval would be granted. More details on these concepts are to be expected later this year.

This approach would address multiple difficulties in current drug development including the increasing difficulty to assess efficacy in ever later lines of therapy where tumours have evolved to be multi-resistant and patients may be too fragile due to previous therapies and disease progression. Using MRD and ctDNA as measures of response would allow faster access to innovative therapies without sacrificing the ultimate validation by well-established endpoints. Many difficulties are to be overcome on this path, not the least the methodological validation and standardisation.

Questions remain also for the payers (see Carole Longson): How to assess the economics of such endpoints? It remain essential that both sides understand the different perspectives and engage in an early and collaborative dialogue. Looking throughout Europe access to innovative therapies is not universal and often much delayed.

Without doubt the most important perspective is the one of patients. Hans Scheurer of Myeloma Patients Europe has summarised some of the key aspects in his presentation. Education about the value of studying these markers, and recognising the anxiety that is created by the detection of MRD even if the clinical significance is not always clear. Frequent bone marrow aspirations cause pain and considerable discomfort, so that methods that use peripheral blood are preferable. There is a risk that (accelerated) approvals based on responses would lead to a bias for more aggressive therapies with a disconnect of response and survival.

We would like to thank all speakers, session chairs and panel members from this workshop very much for their engagement and their excellent contribution. We hope that this meeting report will make the insights and discussions available for everybody.

The CDDF will remain engaged around these important topics and welcomes further suggestions and contributions to advance cancer drug development. Please feel free to contact us!

Axel Glasmacher and John Smyth

Program

DAY 1 - MONDAY 25 APRIL 2022

SESSION 1: STATE OF THE ART AND NEW TECHNOLOGY
Session chairs: Axel Glasmacher (CDDF, DE), John Smyth (CDDF, UK)

MRD concepts, methods and application + Q&A
Bruno Paiva (Universidad de Navarra, ES)

Established and Novel ctDNA Methodology + Q&A
Dominic Rothwell (CRUK Manchester Institute Cancer Biomarker Centre, UK)

ctDNA and MRD, an academic point of view + Q&A
Marie Morfouace (EORTC, BE)

Current Status and Clinical Application of Circulating Tumour DNA (ctDNA) and its Future Role in Clinical Practice + Q&A
Jürgen Gschwend (Technical University Munich, DE)

SESSION 2: COLLABORATION - PATHWAY TO INNOVATION
Session Chairs: Veerendra Munugalavadla (AstraZeneca, US); Pierre Démolis (ANSM, FR)

MRD: AML consortium MPAACT + Q&A
Reshma Patel (Johnson & Johnson, UK)

Exploring the use of ctDNA for Monitoring Treatment Response: The Friends of Cancer Research ctMoniTR Project + Q&A
Jeff Allen (Friends of Cancer Research, USA

The Foundation for the National Institutes of Health (FNIH) initiative on AML MRD + Q&A
Christopher Hourigan (National Institutes of Health, USA)

SESSION 3: REGULATORY PERSPECTIVES
Session Chairs: Natalie Dimier (Roche, CH) and Jaap Verweij (CDDF, NL)

Summary of Regulatory Uses of MRD and ctDNA
Nicole Gormley (FDA, USA)

DAY 2 - TUESDAY 26 APRIL 2022

SESSION 4: IMPORTANT VIEWPOINTS
Session Chairs : Hans Scheurer (MPE, NL) ; Reshma Patel (Johnson & Johnson, UK)

European In Vitro Diagnostic Regulations - Industry perspective + Q&A
Claudia Popp (Roche, CH)

Patient perspective + Q&A
Hans Scheurer (MPE, NL)

HTA perspective + Q&A
Carole Longson (NICE, UK)

MRD in Solid Cancers: perspective of industry + Q&A
Darren Hodgson (AstraZeneca, UK)

SESSION 5: HOW SHOULD WE MOVE FORWARD?
Session chairs: Axel Glasmacher (CDDF, DE), John Smyth (CDDF, UK)

Panel discussion

Learning Objectives

- to review the technology available for measuring residual disease (MRD)
- to review the technology available for measuring circulating tumour DNA (ctDNA)
- to discuss the place of MRD and ctDNA in determining the effectiveness of treatment
- to discuss the role of MRD and ctDNA in decision making for patients, physicians, regulators and HTA bodies.

Key take-home messages

- MRD is now established for haematological malignancies but less so for solid tumours.
- Circulating tumour-nucleotides (ctDNA) is increasingly proving informative for solid tumours at least in the research setting.
- The FDA is studying the use of ctDNA in relationship to the evolution of Accelerated Approval pathways.
- Patients' responses to information about their MRD or ctDNA status must be sensitively recognised in order to avoid additional anxieties.

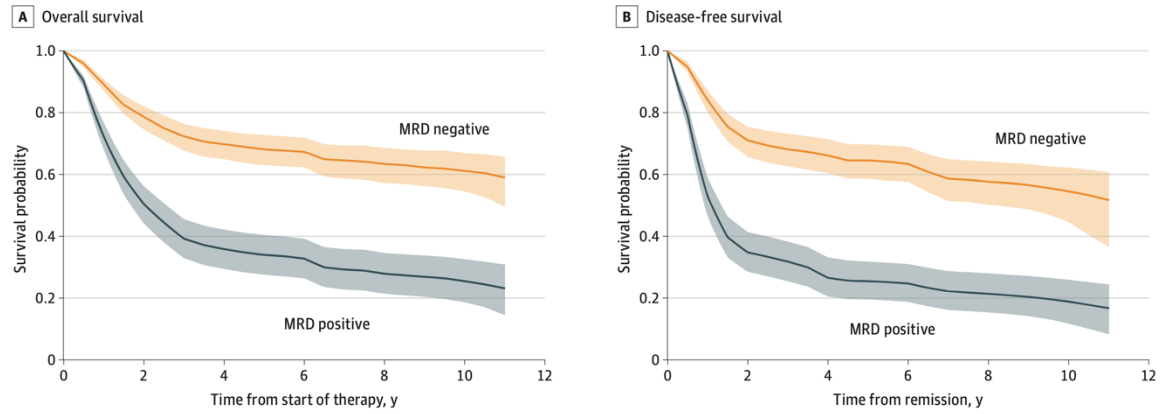
SESSION 1: STATE OF THE ART AND NEW TECHNOLOGY

MRD concepts, methods and application

Bruno Paiva (Universidad de Navarra, ES)

Dr Bruno Paiva, PharmD, PhD, is a research fellow of the Department of Haematology and Immunology at Clinica Universidad de Navarra and CIMA, Pamplona, Spain. He is also the Director of the Flow Cytometry Core of the University of Navarra. Dr Paiva's main area of expertise is the multidimensional flow cytometry analysis of haema-tological malignancies. His research focuses on immunogenomics to improve differential diagnosis, risk stratification, and monitoring of patients with monoclonal gammopathies and myeloid malignancies. He is an author or co-author of hundreds of publications in peer-reviewed journals and has been recognized with numerous awards.

New, very effective treatments have resulted in dramatic reductions of patients' tumor load in many haematological malignancies. This has made necessary the development of new measures and led to the concept of MRD (Measurable Residual Disease) which offers a direct assessment of the effect of a treatment on the amount of tumor cells. It captures the heterogeneity of tumor response among patients better than less sensitive conventional response criteria and allows to recalibrate the patient's risk after treatment. It has been shown for several haematological malignancies (namely, ALL, AML, CLL, CML and MM) that large reductions in tumor mass translate into improved survival (Fig.1). In some diseases the limit of detection has been reduced to $1{:}10^6$. Consequently, undetectable MRD is being established a new endpoint of treatment.



Overall survival (OS) (A) and disease-free survival (DFS) (B). The curves show the posterior means of survival distribution in the bayesian hierarchical analysis. The shadings of each curve show the 95% bayesian credible intervals (CrIs) for the survival proportion at the corresponding point in time of follow-up. The 5-year OS was 68% (95% CrI, 63%-73%) for the MRD-negative group and 34% (95% CrI, 28%-40%) for the MRD-positive group. The average hazard ratio for OS was 0.36 (95% CrI, 0.33-0.39), with a 5-year restricted mean survival time difference of 15.37 months (95% CrI, 13.58-17.19 months). The 5-year DFS was 64% (95% CrI, 59%-70%) for the MRD-negative group and 25% (95% CrI, 20%-32%) for the MRD-positive group. The average hazard ratio for DFS was 0.37 (95% CrI, 0.34-0.40), with a 5-year restricted mean survival time difference of 19.61 months (95% CrI, 17.33-21.92 months).

Figure 1. Association of MRD with survival outcomes in AML from a systematic review and meta-analysis of 11,151 patients (Short N. e., 2020).

However, the use of MRD is still debated as the dramatic improvements in treatment efficacy only took place in the last decade which limits the time for clinical trials that generate the evidence to establish MRD in clinical practice. There are still false expectations about the concept of MRD which is likely a pathway to cure but, in most patients, negative MRD does not guarantee a cure. A very significant problem is the lack of standardization of MRD methodology.

As an example, a recent analysis of routine care data of 1076 patients with AML by the Spanish study group PETHEMA clearly demonstrated the prognostic value of multiparameter

flow cytometry (MFC) but also the significant influence of methodological factors from sampling to the number of markers on the clinical value of the analysis (Paiva, 2021). To enable the stratification of risk and clinical decision making based on MRD the authors urged greater standardization.

	ALL	AML	CML	CLL	MM
Complexity	Intermediate	High	Low	Intermediate	Intermediate
Standardization	High	Low	High	Low	Intermediate
Clinical trials	Yes	Yes	Yes	Yes	Yes
Routine practice	Yes	Yes	Yes	Infrequent	Intermediate
Treatment decisions	Yes	Yes	Yes	Infrequent	Infrequent

Figure 2. "Overview of MRD across some haematological malignancies."

Figure 2 gives an overview of methodological complexity and standardization of MRD as well as its clinical use. For ALL and CML, which show low or intermediate disease complexity, a high level of standardization could be achieved, and this has supported the use in clinical trials, routine practice, and treatment decisions. The high complexity of AML has been an obstacle to standardization although the method is frequently used in trials and for patient management. For both, CLL and MM, MRD is a regular part of endpoints in clinical trials, but it is infrequent applied to clinical decision making. Here as well, standardization needs to be further improved.

The use of MRD in clinical trials brings up the question whether it can be used as an intermediate or surrogate endpoint for regulatory approval. Analyses in several haematological malignancies demonstrated correlation of MRD with overall survival both on the individual patient level as well as on the trial level which are necessary conditions for the establishment of new endpoint.

Interestingly and probably very relevant for the future selection of endpoints is that AML and MM MRD was not superior in predicting overall survival but several studies also demonstrated a discordance between CR and MRD rates (Moreau, 2021) (Araki, 2015).

Conclusions:

- MRD is poised to be the most relevant prognostic factor in most hematological malignancies.
- There is room for improvement, particularly if authorities enforce complete standardization (IVDR).
- Any MRD level matters in terms of risk of relapse for app. 90% of patients (exception: long-term survivors with persistent disease)
- Undetectable MRD should be defined with the highest possible sensitivity.
- Precise definition of MRD cells (e.g., differentiation from cells with CHIP mutations).
- Per the number of ongoing trials, it is plausible that by 2030 there will be guidelines on how to use MRD for treatment decisions in some hematological malignancies.
- With very few exceptions, undetectable MRD rates precede years in advance a benefit in PFS and OS.
- Methodological and treatment heterogeneity are barriers to better outcomes.

The vision for MRD in the next 5-8 years is to assess the readout of most trials app. 12 months after the last patient has been enrolled.

Established and Novel ctDNA Methodology

Dominic Rothwell (CRUK Manchester Institute Cancer Biomarker Centre, UK)

After obtaining a BSc (Hon) in Applied Genetics from the University of Liverpool Dr Dominic G. Rothwell studied for my DPhil with Professor Ian Hickson at the Weatherall Institute, University of Oxford investigating the functional role of DNA repair genes. After this, he moved into translational research, initially with Dr John Norton looking for molecular markers in multiple myeloma before joining Professor Robert Hawkins laboratory at the University of Manchester where he was responsible for developing molecular monitoring of immunotherapy trials including CAR T-cells and the establishment of a GCP compliant facility. In 2011, he joined the Nucleic Acid Biomarker (NAB) team of Professor Caroline Dive at the CRUK Manchester Institute and began his current research focus on the molecular analysis of blood borne biomarkers for use in cancer. This work focusses on utilising circulating free DNA (cfDNA) and circulating tumour cells (CTC) to enable the molecular characterisation of tumours at the genetic, epigenetic and transcriptional level from a patient blood sample. He took over as Team Leader of NAB in November 2019.

One of the main driving forces for the study of circulating DNA (ctDNA) has been the evolution of Precision Medicine. With the traditional use of chemotherapy, the targeted patient population was largely unspecified, diagnosis was dependant on histology and the "one treatment fits all" approach gave very mixed responses. The emergence of targeted therapies however is designed for sub-groups of patients with a specific driver mutation, resulting in much improved clinical response. The example of melanoma targeted for BRAF mutation is an early example of landmark clinical results. Where conventional tumour biopsies have served as the gold standard for molecular analysis, the development of so-called "liquid biopsies" (LB) can add significant value both for monitoring disease or tracking the development of emerging resistance whilst on therapy. The genetic material in LB includes circulating tumour cells, exosomes and double-stranded cell free DNA (cfDNA) released from all cells. There are higher cfDNA amounts seen in cancer patients in whom tumour derived circulating DNA (ctDNA) is produced from apoptotic cell death. Some of the advantages and disadvantages of ctDNA are summarised in Fig.1 One of the main driving forces for the study of circulating DNA (cDNA) has been the evolution of Precision Medicine. With the traditional use of chemotherapy, the targeted patient population was largely unspecified, diagnosis was dependant on histology and the "one treatment fits all" approach gave very mixed responses. The emergence of targeted therapies however is designed for sub-groups of patients with a specific driver mutation, resulting in much improved clinical response. The example of melanoma targeted for BRAF mutation is an early example of landmark clinical results. Where conventional tumour biopsies have served as the gold standard for molecular analysis, the development of so-called "liquid biopsies" (LB) can add significant value both for monitoring disease or tracking the development of emerging resistance whilst on therapy. The genetic material in LB includes circulating tumour cells, exosomes and double-stranded cell free DNA (cfDNA) released from all cells. There are higher cfDNA amounts seen in cancer patients in whom tumour derived circulating DNA (ctDNA) is produced from apoptotic cell death. Some of the advantages and disadvantages of ctDNA are summarised in Fig.3.

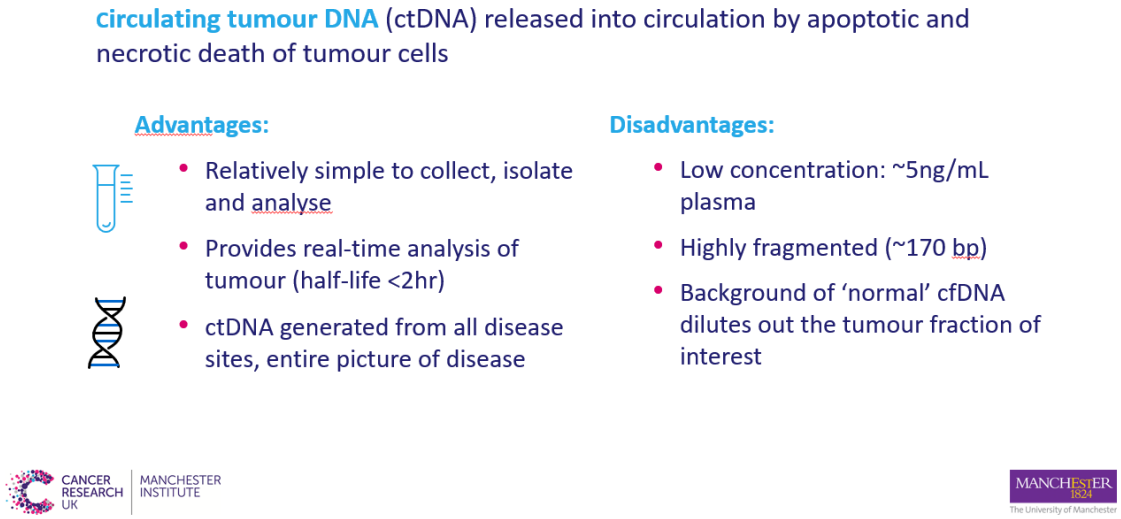


Figure 3. "Advantages and disadvantages of ct DNA"

The genetic information available from ctDNA includes somatic mutation, chromosomal aberrations and epigenetic modifications. Perhaps not surprisingly ctDNA increases with disease progression and is dependent on tumour grade, vascularity, cell death rates and therapy.

When looking at concordance between tissue and blood for genomic profiling a study of 282 patients with metastatic NSCLC showed 98% concordance for genes with FDA approved targeted therapy, which is very reassuring. In this study the results for liquid were available in 9 versus 15 days for tissue (García-Pardo, 2022) .

One of the major uses of LB is to monitor disease progression as summarised in Fig.4.

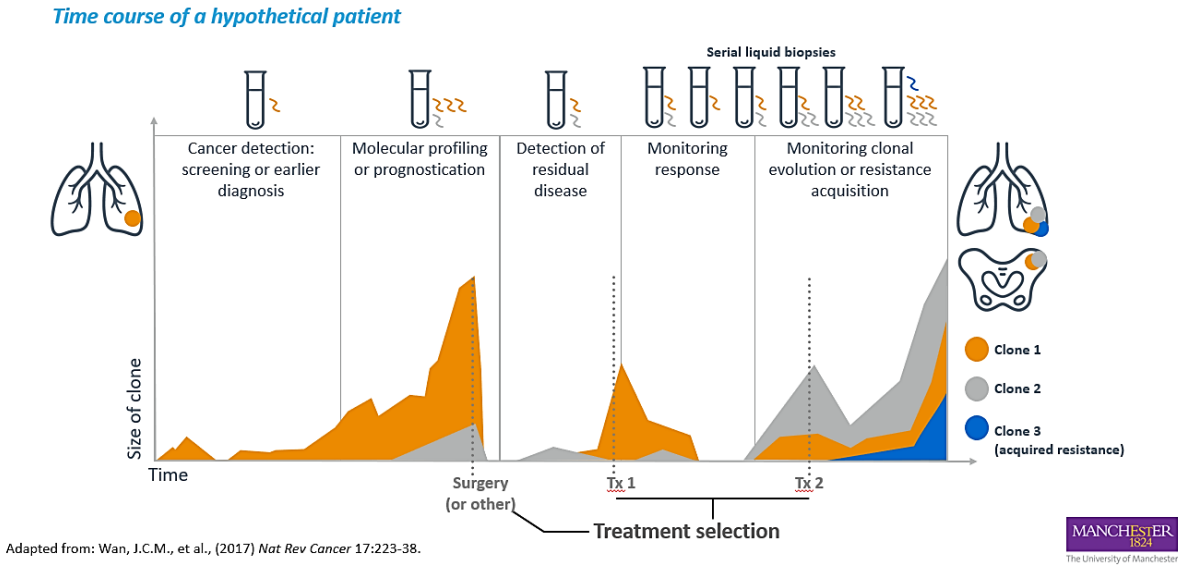


Figure 4. "Use of liquid biopsies to monitor disease progression". Adapted from (Wan, 2017)

Following treatment, the evaluation of Measurable Residual Disease (MRD) may inform decisions about further treatment, and likewise the early detection of tumour regrowth may give useful lead time for therapeutic decisions. LBs are now being studied in solid tumours and the example of lung cancer is informative. In 2020 the FDA approved the first LB test of comprehensive genomic profiling for multiple cancer related gene mutations, translocations and copy number changes.

Of the methods available for molecular analysis droplet digital PCR is useful for single mutation identification but targeted NGS gives a more comprehensive genome profile. There are now encouraging results for using these techniques in melanoma (the CAcTUS trials) and lung cancer (the TARGET trial) – (Rothwell D., 2019).Looking to the future the detection of cell free RNA may detect cancer specific RNA fusions as a sensitive marker of MRD, and methylation profiling of cfDNA may yield low cost, highly sensitive detection and monitoring of cancer.

ctDNA and MRD, an academic point of view

Marie Morfouace (EORTC, BE)

Marie Morfouace obtained her PhD in molecular biology at the University of Nantes, France in 2010. She then moved to St Jude Children's Research Hospital in Memphis, TN, for a postdoctoral fellowship focusing on identifying new therapeutics for pediatric medulloblastoma. She has been working at the EORTC since 2017, as translational research scientist, developing the EORTC SPECTA platform and as scientific lead for several pan-European research projects.

This presentation focussed on the clinical utility of circulating biomarkers as indicators of MRD, for monitoring remission and early detection of relapse.

The example of PSA monitoring in prostate cancer was compared with CA 125 monitoring in women with ovarian cancer. Measurement of PSA at the time of diagnosis allows subsequent monitoring of individual patients, both to assess the depth of response to treatment and to monitor for early progression. Since increasingly there are several options for further treatment, lead time before clinical relapse may be beneficial. In contrast measuring CA125 in the blood of patients with ovarian cancer has proved much less useful. When monitoring patients after initial treatment, short lead times detected by rising CA125 levels proved of no benefit in terms of outcome (Rutstin, 2010)

When monitoring disease with new circulating biomarker tools, considerations on best way to inform patients are crucial. Revealing a negative, or "no-change" result can be reassuring, but rising levels of a marker will almost always cause anxiety for the patient, and may not indicate a change in management, thus posing extra challenges for physicians .

How useful are ctDNA assays in detecting relapse? The results depend on which cancer is under consideration. In NSCLC, 50% of patients will relapse after initial treatment – 40% locally, 40% with distant metastases and 20% with both. In Colorectal cancer (CRC) 70% of patients relapse with distant metastases only, whereas in HNSCC, 60% will present with both local and distal recurrence. The use of ctDNA could in future be useful in indicating the presence of recurrent cancer and inform the need for investigations/re-staging to separate local from distant relapse which may inform treatment decisions. Communicating the need for such investigations must be explained sensitively to reduce rather than increase anxiety.

There may be a particular role for ctDNA in selecting patients for adjuvant therapy after treatments given with curative intent. Several studies are ongoing, particularly in CRC were detecting a positive or negative ctDNA would assign patients to adjuvant treatment or monitoring only as summarised in Fig.5.

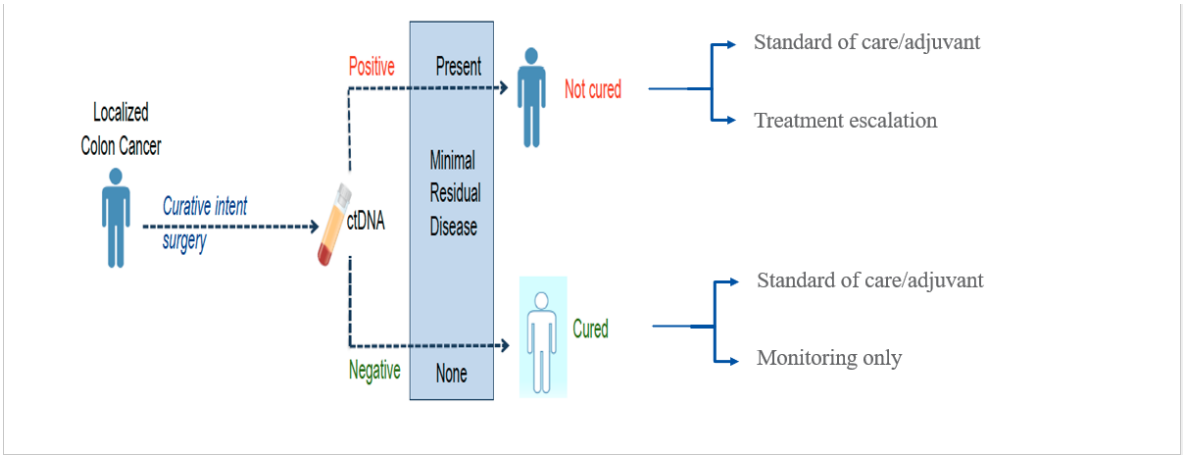


Figure 5. ctDNA positivity to select patients for adjuvant therapy?

The speed at which ctDNA is cleared may serve as an early endpoint for assessing the efficacy of a particular treatment, as illustrated in Fig.6 testing Osimertinib in NSCLC patients progressing on a TKI.

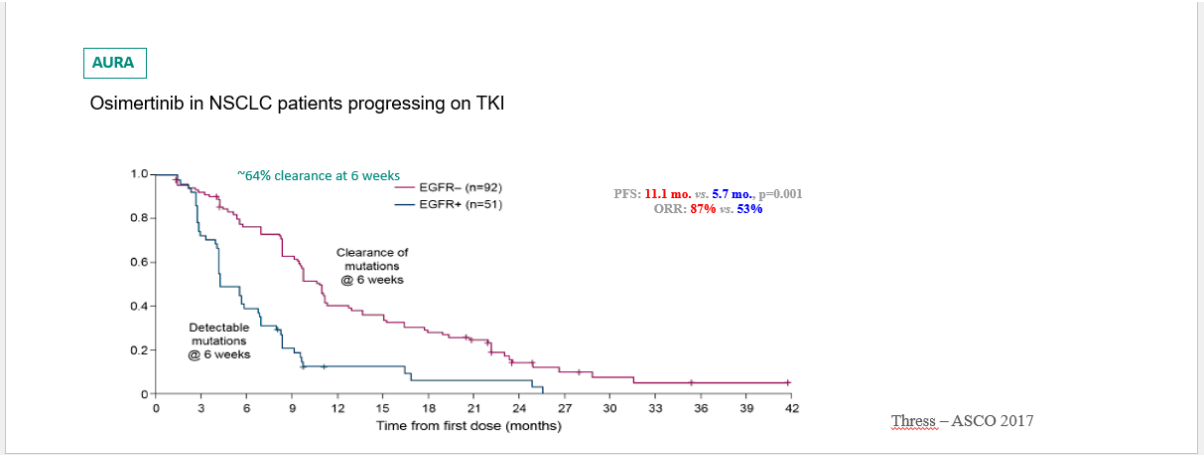


Figure 6. "ctDNA clearance as an early endpoint" (Thress, 2017)

The EORTC are in the process of planning a large data generating study in multiple tumour types to measure MRD over time as shown in Fig.7.

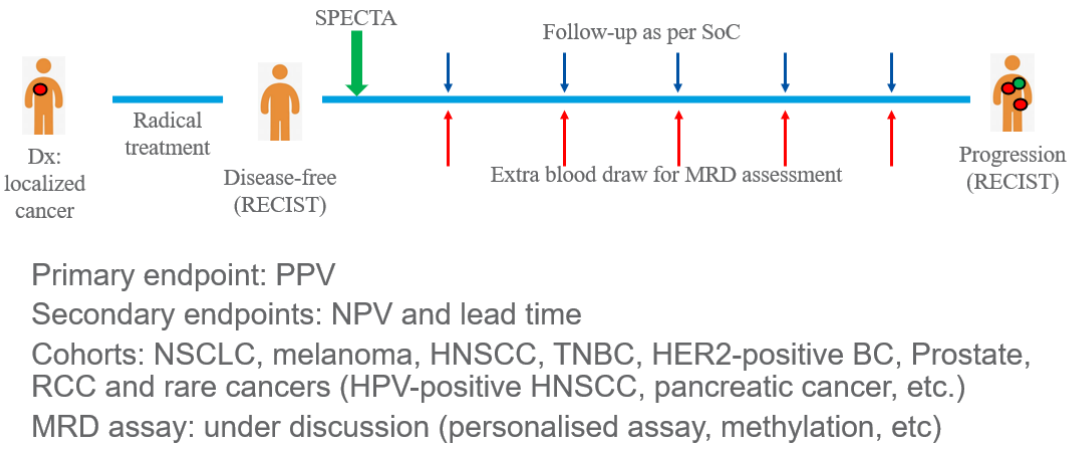


Figure 7. EORTC MRD project on data generation

In summary the questions posed in this presentation included the challenge of how to integrate ctDNA information with classic response criteria, comparing single time point

measurements with serial monitoring for recurrence, and how best to inform patients of the value of closely monitoring their disease without causing additional anxiety. The latter may be helped by increasing use of appropriate PRO data.

Current Status and Clinical Application of Circulating Tumour DNA (ctDNA) and its Future Role in Clinical Practice

Jürgen Gschwend (Technical University Munich, DE)

Prof. Dr. Jürgen Gschwend (Technical University Munich, DE) is a full Professor of Urology and the Chairman of the Department of Urology, Rechts der Isar Medical Center, since 2006. His clinical focus and research areas are uro-oncological surgery, chemotherapy and immunotherapy as well as prediction of bladder cancer response, translational research for micrometastasis in prostate and bladder cancer, and the conduction of clincial trials phase I to phase III in uro-oncology.

The detection of circulating tumour DNA (ctDNA) shows substantial potential to benefit patients' journeys in solid tumours (Fig.8). It can support patient identification during screening or at disease detection, the determination of risk for relapse after neo-adjuvant therapy or surgery. In the metastatic setting patient selection can be improved by screening for relevant mutations and in post-treatment care it can be used to monitor treatment response, detect secondary resistance or relapse.

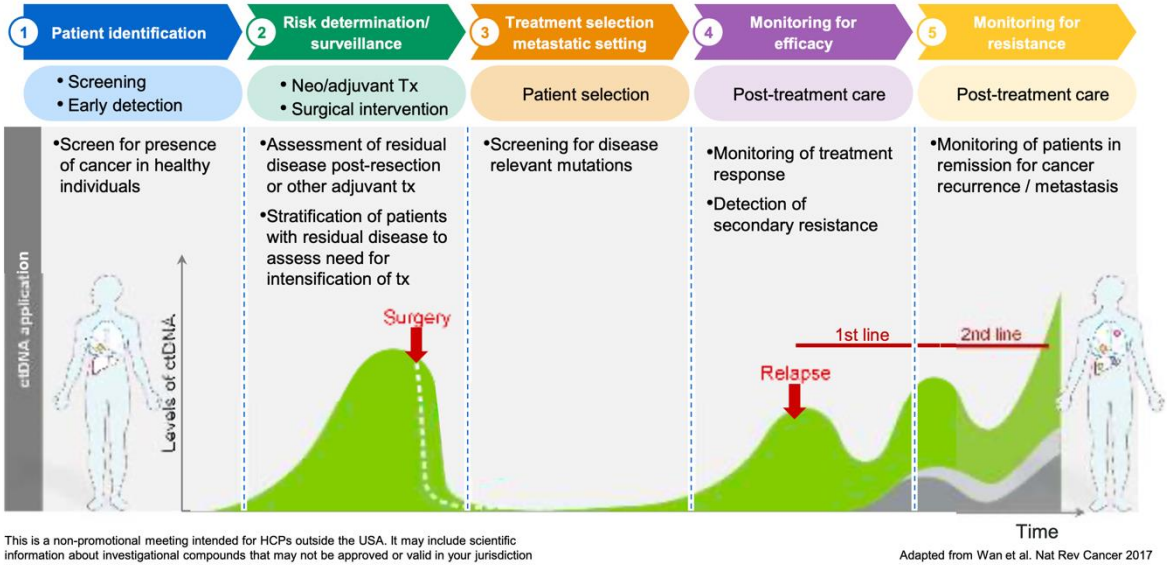


Figure 8. "ctDNA potential throughout the patient journey. Adapted from (Wan, 2017)

Early studies in three solid tumours (bladder, lung, and colon cancer) entities indicate very low relapse rates in ctDNA negative patients' post-surgery and that molecular disease progression precedes clinical relapse with a lead time between 4-7 months in all cases. This demonstrates a potential to avoid treating patients who do not require additional therapy and may shorten clinical trials and drug development timelines.

Promising data is also available from a phase II trial that include 216 patients with metastatic castration-resistant prostate-cancer (Goodall, 2020). Baseline and longitudinal positivity of ctDNA were correlated strongly with shorter rPFS. Patients with consecutive decrease in ctDNA had a better response than those with an increase. The authors concluded that these analyses could identify patients with poorer prognosis at baseline, inform on treatment response and rPFS and help to elucidate resistance mechanisms at disease progression. Similar data has been documented in metastatic urothelial cancer (Carroll, 2019) and muscle-invasive bladder cancer (Christensen, 2019).

A very important data set on the value of ctDNA comes from the IMvigor10 trial, a global phase III study in muscle-invasive urothelial cancer that tested adjuvant therapy with atezolizumab, a monoclonal antibody that targets programmed death-ligand 1 (PD-L1), against observation in 806 patients who had been treated with radical surgery (Bellmunt, 2021). While the overall analysis did not show a treatment effect on DFS (HR=0.89), differences were seen in a pre-specified analysis of the biomarker evaluable population (N=581), which was comparable to the total study population.

Fig.9 shows the outcome by ctDNA status at the start of the adjuvant treatment. While there was no difference according to adjuvant treatment in the ctDNA negative patients, a clear benefit of the intervention in overall survival could be demonstrated (HR=0.59, 95% CI: 0.41-0.86).

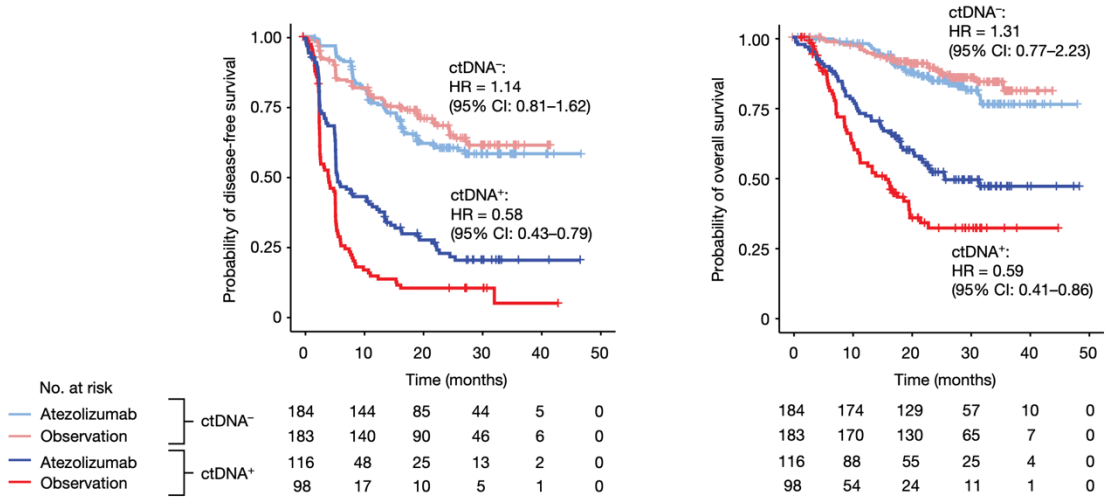


Fig. 1 | Kaplan–Meier estimates among patients evaluated for post-surgical ctDNA status. Kaplan–Meier estimates of DFS (left) comparing patients who were positive for ctDNA (ctDNA⁺ patients) treated with atezolizumab (dark blue) and ctDNA⁺ patients in the observation arm (dark red) (median: 5.9 versus 4.4 months), and comparing ctDNA⁻ patients treated with atezolizumab (light blue) and ctDNA⁻ patients in the observation arm (light red) (medians not reached). Kaplan–Meier estimates of OS (right) in patients evaluated for ctDNA status, comparing ctDNA⁺ patients treated with atezolizumab (dark blue) and ctDNA⁺ patients in the observation arm (dark red) (median: 25.8 versus 15.8 months), and comparing ctDNA⁻ patients treated with atezolizumab (light blue) and ctDNA⁻ patients in the observation arm (light red) (medians not reached).

Figure 9. "Kaplan-Meier estimates among patients evaluated for post-surgical ctDNA status". (Powles, 2021)

In conclusion: In the IMvigor010 study, post-surgical ctDNA positivity was associated with a high-risk of recurrence and death. ctDNA positivity identified patients with muscle-invasive urothelial cancer likely to derive DFS and OS improvement from adjuvant atezolizumab. This work warrants validation in the subsequent, prospective study, IMvigor011. If confirmed, the results may change our understanding of postsurgical cancer care.

In summary:

- ctDNA has many opportunities to inform our clinical management of solid tumours.
- ctDNA is of value in the early diagnosis of these diseases:
  - Track minimal residual disease
  - Monitor response and resistance
- Utility of ctDNA has been demonstrated across multiple tumour types and with many different treatment strategies including immunotherapy.
- Use of ctDNA as a biomarker may be particularly well suited to monitor early-stage disease and may help avoid over treatment of patients (help guide adjuvant therapy).
- ctDNA is being used to select patients in clinical trials.

Session 2: Collaboration - pathway to innovation

MRD: AML consortium MPAACT

Reshma Patel (Johnson & Johnson, UK)

Reshma Patel is a Senior Director of Global Regulatory Affairs at Janssen. Reshma's global experience spans across all phases of drug development, small molecules and biologics. Her in-depth knowledge and diverse experience of the global regulatory environment accumulated by leading multiple global submissions through to approval for key compounds. Currently, Reshma leads the global regulatory strategy for principal Janssen Haematology assets in Early Development. Reshma also co-leads the MRD Partnership and Alliance in AML Clinical Treatment (MPAACT). She is also the Regulatory lead for Janssen strategic goal to establish MRD as a surrogate endpoint in multiple myeloma for PFS.

The history of the MPAACT (MRD Partnership and Alliance in AML Clinical Treatment; Fig.10) consortium goes back to 2016 when Janssen explored the evaluation of MRD as an endpoint in AML. It was quickly realized that this cannot be done by one company and others were invited to join the initiative. In the same year the FDA held a public meeting on MRD with Duke-Margolis Center for Health Policy[1].

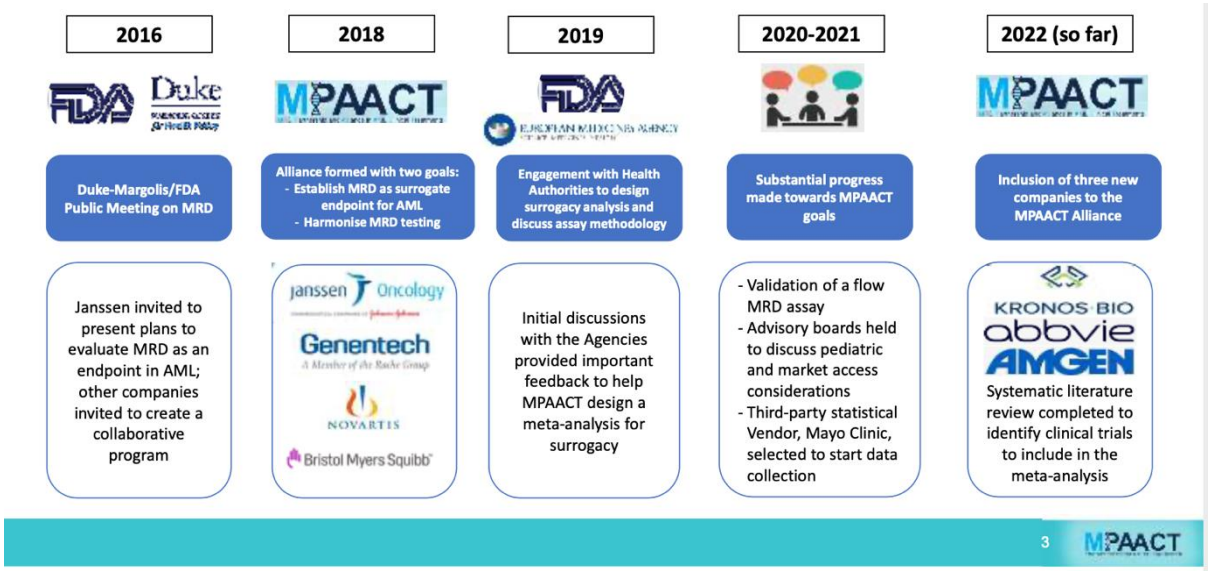


Figure 10. "MPAACT key milestone 2016-2022"

Three additional companies (Celgene (now Bristol Myers Squibb), Genentech, and Novartis) joined Janssen to form the alliance with the mission to

> *Accelerate the development and delivery of novel life-extending therapies to patients with AML, using MRD as a surrogate endpoint for OS*

The alliance formulated the following goals to achieve this mission:

Overall goals of MPAACT

- Establish MRD as a surrogate endpoint for overall survival in clinical trials of treatment for patients with AML
- Validate MRD assays to support a primary endpoint, which can be easily incorporated into clinical trials and clinical practice
- Proactively engage with regulators and HTAs to shape HA & HTA policies

[1] https://healthpolicy.duke.edu/sites/default/files/2020-03/9.7.16_agenda.pdf

Engagement the regulatory agencies was the cornerstone of the alliance and in 2019 the first FDA meeting took place (Fig. 11). It was recommended to perform an analysis of ten randomized clinical trials in the first line setting with patient-level overall survival and MRD data. A collaboration on statistical methodology was agreed. A similar positive outcome was achieved a year later in a meeting with the EMA (Fig. 11).

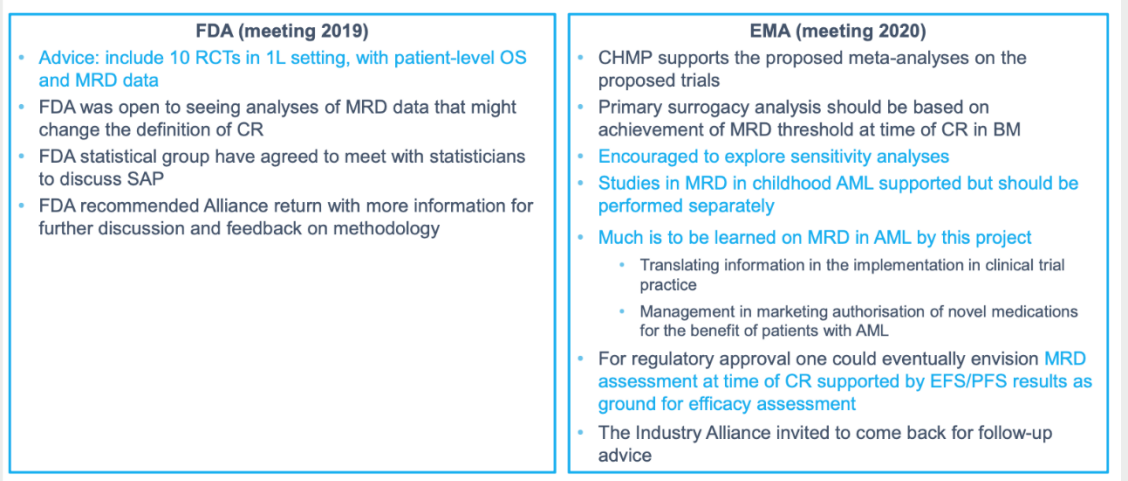


Figure 11. "FDA and EMA Meetings, 2019 and 2020"

Following these interactions, the strategic intent of MPAACT was formulated: MPAACT strives to define an MRD-based endpoint that:

- Is clinically meaningful for all intended applications in future clinical trials
- Can be measured objectively and consistently,
- Incorporates data that is already routinely collected from patients, and
- Can provide an estimate of treatment effect much earlier than OS.

MPAACT acknowledges that there is heterogeneity in how MRD is currently evaluated in AML and intends to consolidate all available data to define a single MRD-based endpoint to evaluate as a potential surrogate in parallel, new assays are validated to support consistency of testing in future clinical trials. A stepwise approach to realize these objectives was agreed.

Surrogacy: Conduct an initial retrospective meta-analysis to evaluate how well treatment effect on MRD can predict treatment effect on OS, using patient-level data. Continue to collect additional patient-level data from ongoing clinical trials to update the initial retrospective meta-analysis and reflect the most recent treatment practice. The Mayo Clinic Statistics and Data Management Center, an independent statistical partner led by Dr Qian Shi, was selected to collect the data and perform the meta-analysis to assess association of MRD with OS. The use of a third party allowed to maintain data confidentiality among the partners.

MRD Testing: Harmonize and validate assay methodology for the assessment of MRD using multiparameter flow cytometry (MFC) and next-generation sequencing (NGS), to be used in prospective AML clinical trials conducted within clinical drug development programs retrospectively collected samples, if available. Collect prospective MRD datasets using harmonized and validated assays, which may be added to a potential subsequent meta-analysis.

Regulatory Pathway: Engaging with regulators and HTAs is planned for the second half of 2022. The statistical analysis plan will be reviewed with Health Authorities prior to any surrogacy analysis.

The years 2020-2021 were used to establish the complex legal framework of the alliance, to validate a flow MRD assay. Advisory boards held to discuss paediatric and market access considerations. Data collection was begun. In 2022, so far, three new companies have been included (Abbvie, Amgen, Kronos Bio) and a systematic literature review was completed to identify further clinical trials to include in the meta-analysis.

MPAACT operating principles centre around a joint steering committee that oversees eight work streams (MRD methods, Statistics, Clinical, Regulatory, Market Access, Paediatric, Legal, Finance; Fig.12). Collaborative efforts with academic groups and key opinion leaders are critical to drive the development of MRD and achieve the Alliance's goals.

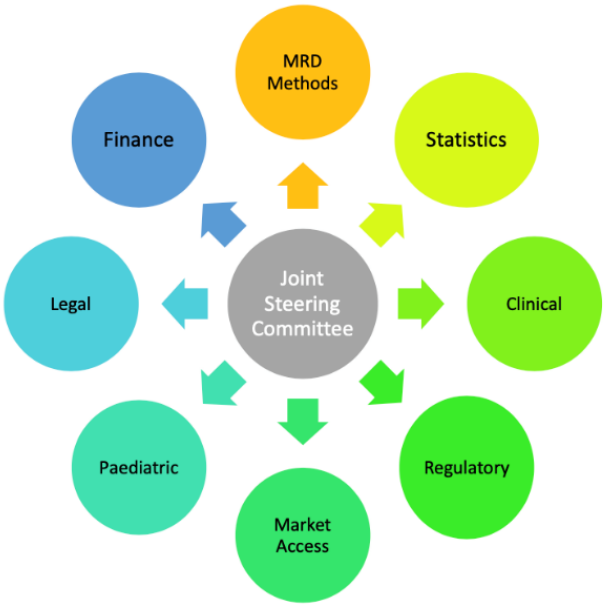


Figure 12. "MPAACT operating principles"

A widely accepted meta-analytic approach will be utilized for the retrospective meta-analysis of randomised clinical trials in patients with first-line AML therapy.

- Data from multiple randomised trials will be pooled together to assess two levels of surrogacy:
  - **Individual-level surrogacy**: Prognostic value of achieving MRD negativity for a particular patient
  - **Trial-level surrogacy**: Ability of the treatment effect on MRD to predict treatment effect on OS.

Major challenges are expected due to the data heterogeneity across trials, including:

- Patient population (newly diagnosed, maintenance, relapsed/refractory)
- Treatment mechanism of action
- Timing of MRD assessments per protocol
- MRD testing methodology and threshold for negativity

Single-arm studies will also be used to help identify the optimal MRD threshold to be used to test surrogacy. Paediatric studies are also being considered for inclusion in the analysis.

The **heterogeneity of MRD** testing methods is a considerable obstacle and to be useful, MRD methods (MFC, PCR, NGS, etc.) should be standardized and validated. Validation should encompass an end-to-end process from sample collection to results reporting. All methods need to have a clearly defined clinical threshold, be robust and reproducible and be correlated with clinically meaningful outcomes (CR, EFS, OS).

The current status of the **MPAACT methods evaluation** includes:

- MFC assay fully validated for investigational use (protocol & report available).
- A second flow assay validation is nearing completion at a vendor with multiple sites globally with an anticipated completion date in Q4 2022.
- Collaboration with Invitae to develop a targeted NGS panel for AML MRD. Feasibility has already been demonstrated; work is on-going to assess mechanisms to further optimize NGS sensitivity with a targeting ability to track ≥ 90% of trial participants.
- Continuous exploration and assessment of new technologies for suitability in supporting MRD testing in AML.
- Development of mechanisms for standardisation and identifying additional providers.

In summary,

- Many key academic investigators and industry collaborators in the AML field have been able to come together to pool data, resources, creativity, and intellectual strength to investigate the role of MRD as a surrogate endpoint.
- The robustness of the statistical analysis and resulting evaluation of MRD as a potential surrogate endpoint will be drastically improved through inclusion of all relevant randomised clinical trials.
- MPAACT aim to address heterogeneity and improve consistency in MRD testing by developing harmonised assays for use in future clinical trials with partners in the field.
- Engagement with regulatory authorities and HTAs is critical for the project's success and for implementation of MRD as a future endpoint in clinical trials of new treatments for patients with AML.
- MPAACT was founded to establish surrogacy of MRD in AML which cannot be done without collaboration and data

Exploring the use of ctDNA for Monitoring Treatment Response: The Friends of Cancer Research ctMoniTR Project

Jeff Allen (Friends of Cancer Research, USA

> Jeff Allen, Ph.D. serves as the President and CEO of Friends of Cancer Research (Friends). For over 25 years, Friends has created unique scientific partnerships, accelerated policy change, and supported groundbreaking research to deliver new therapies to patients quickly and safely. As a key thought leader on issues related to the U.S. Food and Drug Administration, healthcare, and regulatory policy, he is regularly published in prestigious medical journals and policy publications and has contributed his expertise to the legislative process on multiple occasions.

Whilst recognising that ctDNA assays may have potential application in many different stages of a patient's cancer this presentation focussed on the assessment of response, following levels of ctDNA over time to compare with conventional measurements of progressive disease and its potential to correlate with long term outcomes.

Friends of Cancer Research, USA hypothesise that the rapid turnaround time and less invasiveness of ctDNA measurement may be helpful, and its potential value for earlier identification of response will be useful both for "go – no-go" decisions and potentially regulatory approval as a surrogate marker. They recognise the challenges posed by variability of collection methods and reporting strategies when comparing different studies. They are posing the question "do changes in ctDNA levels accurately reflect the therapeutic effects of cancer therapies?" As an example, their ctMoniTR project is designed in 2 steps. The objectives of step 1 are shown in Fig.13.

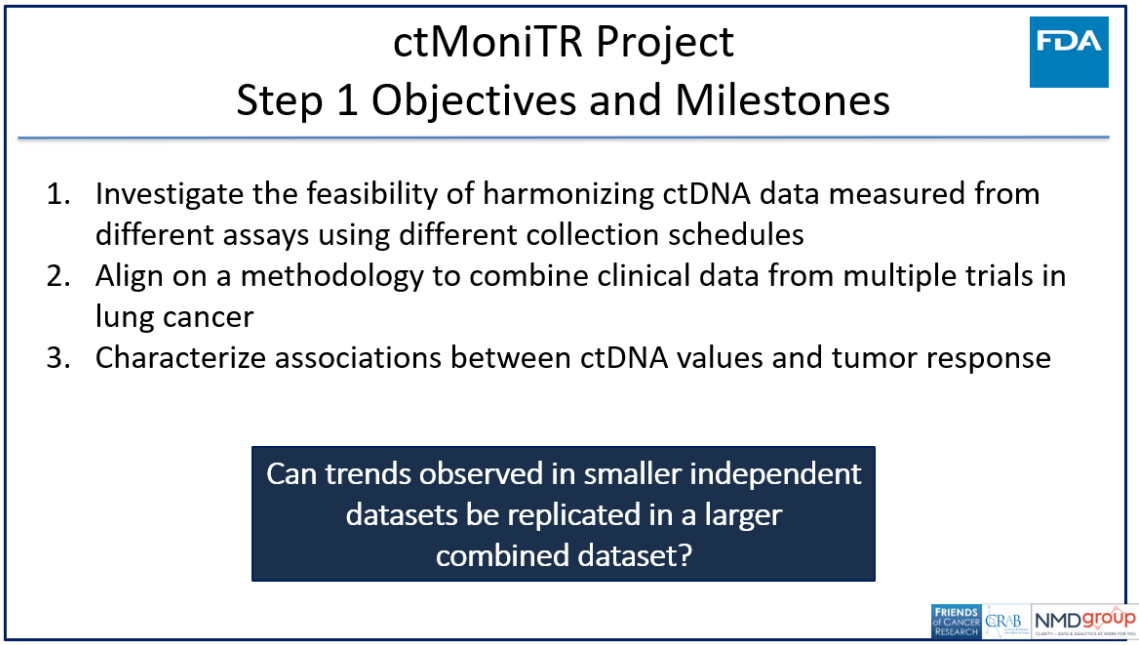


Figure 13. "ctMoniTR Project: Step 1"

The goal is to align methodology to combine data from multiple trials in lung cancer, harmonise ctDNA data measured with different assays and collection schedules and to publish the results. Their approach has been to focus on advanced NSCLC treatment with check point inhibitors using only trials where the data is already published, where there is tumour response, OS and PFS data, and ctDNA measured at baseline plus 1 or more follow up samples. They have gathered an impressive cohort of collaborators as shown in Fig.14

Figure 14. "ctMoniTr Step 1: Project Participants"

In their analysis they find robust association between ctDNA decrease and patient survival as shown in Fig.15.

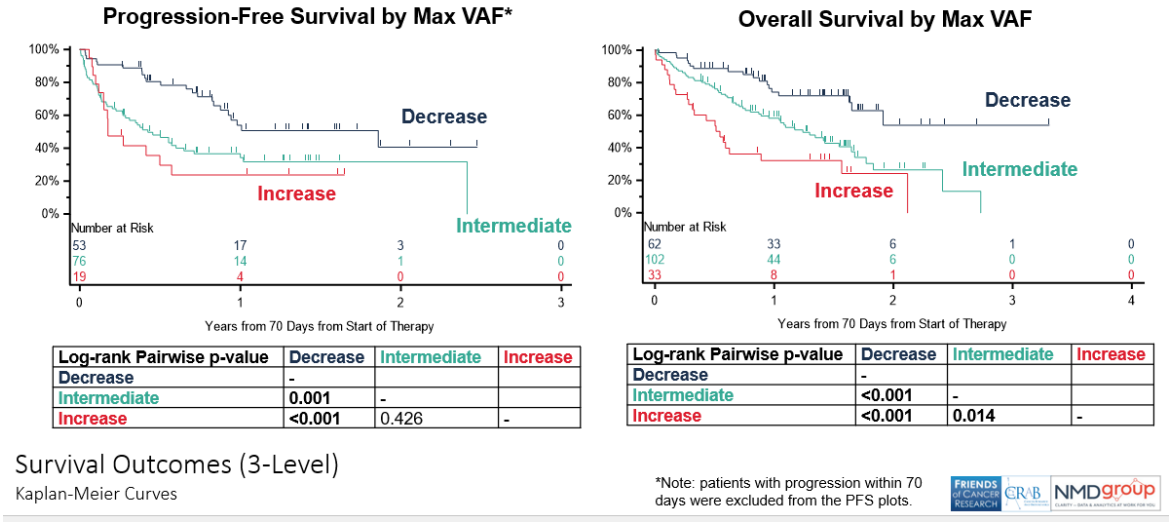


Figure 15. "Robust association between strong decreases in ct DNA and patient survival"

With step 1 almost complete they are initiating step 2 which aims to extend this with a module of NSCLC patients treated with TKI inhibitors, and a second module of lung cancer patients treated with PDL1 inhibitors to determine how long after treatment initiation is there any association between changes in ctDNA levels and clinical response. There will also be a 3rd module to look at other solid tumour types treated with check point inhibitors or TKIs. They are aiming to examine 22 clinical trials involving 3000 patients from 8 different tumour types. Beyond this they plan a project to examine ctDNA measurements in early-stage disease with an emphasis on detection of the depth of tumour response in correlation with conventional assessments.

The Foundation for the National Institutes of Health (FNIH) initiative on AML MRD

Christopher Hourigan (National Institutes of Health, USA)

Dr. Christopher Hourigan, DM DPhil FACP FRCP, is Chief of the Laboratory of Myeloid Malignancies at the National Heart, Lung, and Blood Institute of the National Institutes of Health (NIH). He is Co-director of the trans-NIH Myeloid Malignancies Program, part-time Associate Professor of Oncology at Johns Hopkins School of Medicine, and a member of the Leukemia program of Johns Hopkins Hospital. He is Co-PI of the upcoming fNIH Industry-FDA-Academic-NIH biomarkers consortium on AML MRD, co-lead of genomics for the European Leukemia Network (ELN) and a member of the American Society of Hematology (ASH) Clinical Guidelines Committee for AML.

This presentation will give an overview of MRD in AML and of work of the recently established FNIH MRD Consortium.

The criteria for complete remission in AML have changed little in the last 60 years, it mainly relies on the microscopic determination of the proportion of blasts in the bone marrow with a 5% cut-off to differentiate from healthy bone marrows. This, however, does not give an accurate impression of the remaining leukaemia cell burden (Fig. 16) below the 5% threshold that determines the risk of relapse. Different measures have the potential to identify residual leukaemia cells down to $1:10^6$.

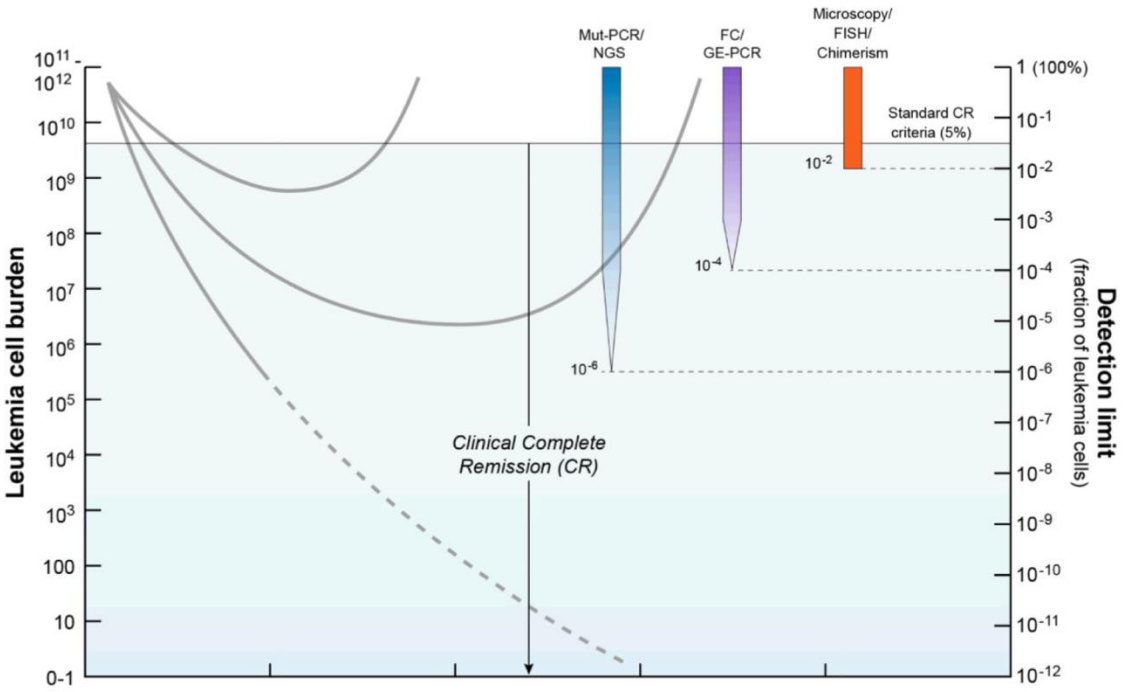


Figure 16. Detection thresholds of various MRD modalities compared to traditional clinical complete remission Axis scales solely for illustrative purposes (Hourigan, 2013).

A significant problem for the determination of MRD in AML is the considerable heterogeneity of the disease driven by the diverse underlying genetic and molecular mutations and the clonal heterogeneity and evolution.

In a first direct comparison of patient-specific single-cell DNA probes based on whole-genome sequencing with concurrent multiparameter flow cytometry the complexity of the situation was demonstrated (Dillon, 2021). In brief, none of the current state-of-the-art techniques could provide a full assessment. Not all clones with molecular mutations identified by DNA sequencing are, however, driving the leukaemia, some are benign haematopoiesis. Flow cytometry on the other side would miss more differentiated cells of leukaemic origin.

Based on the technical experiences in the determination of MRD and the clear demonstration of its prognostic value the European Leukemia Network (ELN) MRD Working Party has published guidelines for the technical aspects flow- and molecular-MRD analysis as well as for the reporting of results (Heuser, 2021).

Regardless of the methodology but with the appropriate standardizations a very clear prognostic influence of undetectable MRD could be demonstrated in several studies (Hourigan, 2016) (Araki, 2016) and a large meta-analysis (Short N. e., 2020). Remarkably, patients in complete remission according to cytomorphology but still MRD-positive did not fare better than patients with active disease. In a next step a randomised trial has demonstrated that the patients who were MRD-positive before an allogeneic stem cell transplant have worse outcomes when randomised to reduced-intensity condition (as opposed to myeloablative conditioning) (Hourigan, 2020).

Therefore, three main clinical uses of MRD can be the objectives of clinical research:

- Patient selection
- Early relapse detection
- Anti-leukemic efficacy quantification

However, the current status of MRD in AML is "good for papers but it is yet not good for patients". The next step must be the harmonization of expertise, resources, and efforts to allow MRD in AML to unfold its value for patients and drug development. To achieve this the FNIH AML MRD Consortium has been founded as a new project within the Biomarkers Consortium of the Foundation for the National Institutes of Health[2]. In addition to Chris Hourigan, Coleman Lindsley (Dana-Farber Cancer Institute), and Jerry Radich (Fred Hutchinson Cancer Research Center) are co-principal investigators. The public-sector partners are the NCI, NHLBI and the FDA (CDER and CDRH). The growing list of private sector partners include AbbVie, Amgen, AstraZeneca, Bio-Rad, Genentech, GlaxoSmithKline, Jazz Pharmaceuticals, Novartis, NuProbe, Sysmex Inostics, 10x Genomics, Thermo Fisher Scientific, and TwinStrand Biosciences. Fig. 17 gives an overview of the workflow in the consortium.

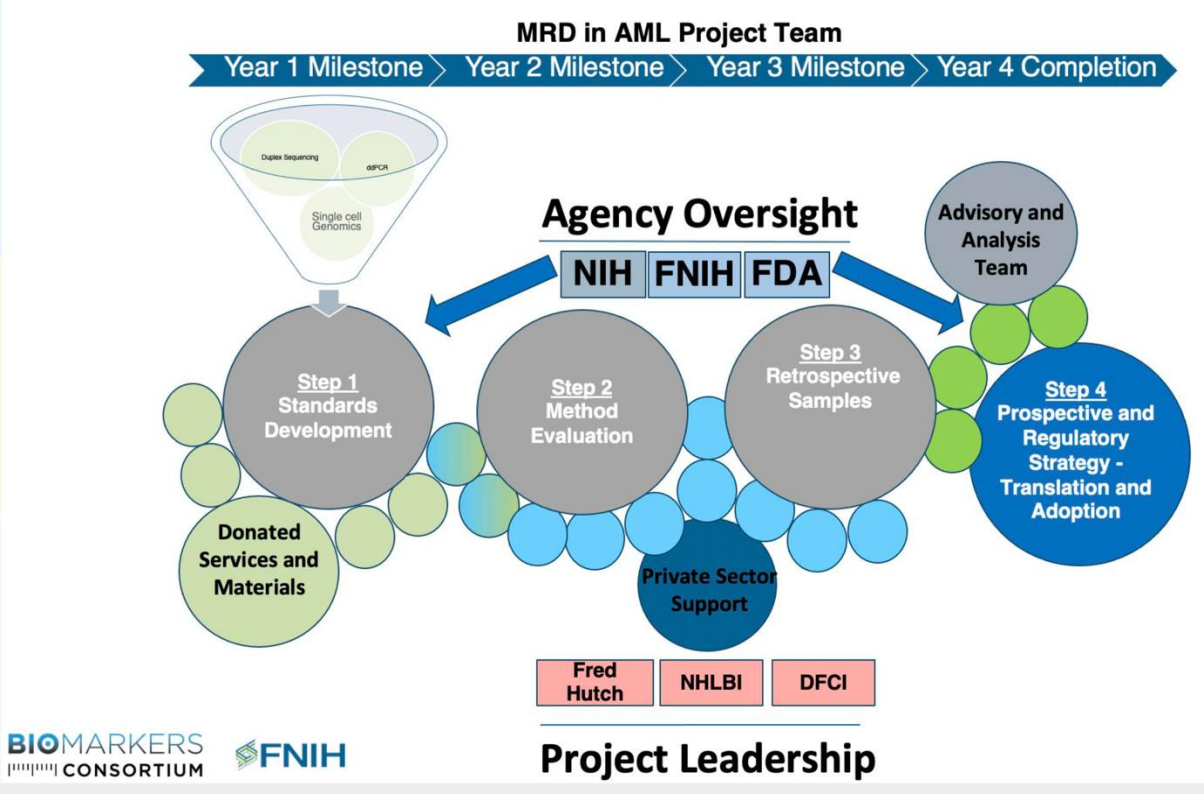


Figure 17. FNIH AML MRD Consortium project workflow

The **Standards Subgroup** focusses on determining the types of samples (cell lines, artificial cell-like material, DNA mixes, etc.), procurement, and deciding the complexity and the range of mutation levels in the mixes. It enables methods comparisons and multi-site testing.

The **Methods Subgroup** centers on molecular methodologies with parallel workstreams focusing on ultra-deep DNA variant detection and novel single cell technologies and on finding new methods, testing, developing analytic plans to compare new methods.

The **Retrospective Subgroup** obtains samples and clinical outcome data from past clinical studies that can used to test new methods. It has a focus on three treatment scenarios: Intensive cytotoxic therapy, less intensive hypomethylating agent-based therapy, allogeneic transplantation.

[2] https://fnih.org/news/announcements/fnih-biomarkers-consortium-project-will-establish-new-methods-detecting-disease

The **Prospective and Regulatory Subgroup** reaches out to U.S. Intergroup, the bone marrow transplant community and the biopharmaceutical industry to translate findings and best practices from the FNIH consortium work into the prospective generation of new evidence for AML MRD. **MyeloMATCH** is an umbrella trial supported by U.S. Intergroup (ECOG, SWOG, Alliance, Canadian Study Groups) to test treatments for AML and myelodysplastic syndromes (MDS) and to evaluate early endpoint efficacy signals in specific molecular and clinical risk groups (incl. MFC and NGS MRD protocols). **MEASURE** (Molecular Evaluation of AML Patients After Stem Cell Transplant to Understand Relapse Events) is sponsored by CIBMTR/NMDP and is a resource for Clinical Investigation in Blood and Marrow Transplantation.

Overall, the consortium works to provide evidence to unknown but answerable questions in AML MRD:

- Do serial MRD measurements allow for better prognostication in individual patients than at a single key clinical landmark?
- In what circumstances does MRD testing add information beyond baseline characterization?
- Does MRD status have the same prognostic significance if achieved after intensive vs. non-intensive therapy?
- Can blood substitute for marrow for in AML MRD assessments?
- Are all/any detected non-DTA mutations appropriate for AML MRD tracking in remission or are some more pathognomonic than others?
- How often are subclones responsible for relapse found in remission and/or in the original diagnostic sample when using highly sensitive MRD-depth NGS measurements?

The project timelines for the consortium are shown in Fig. 18.

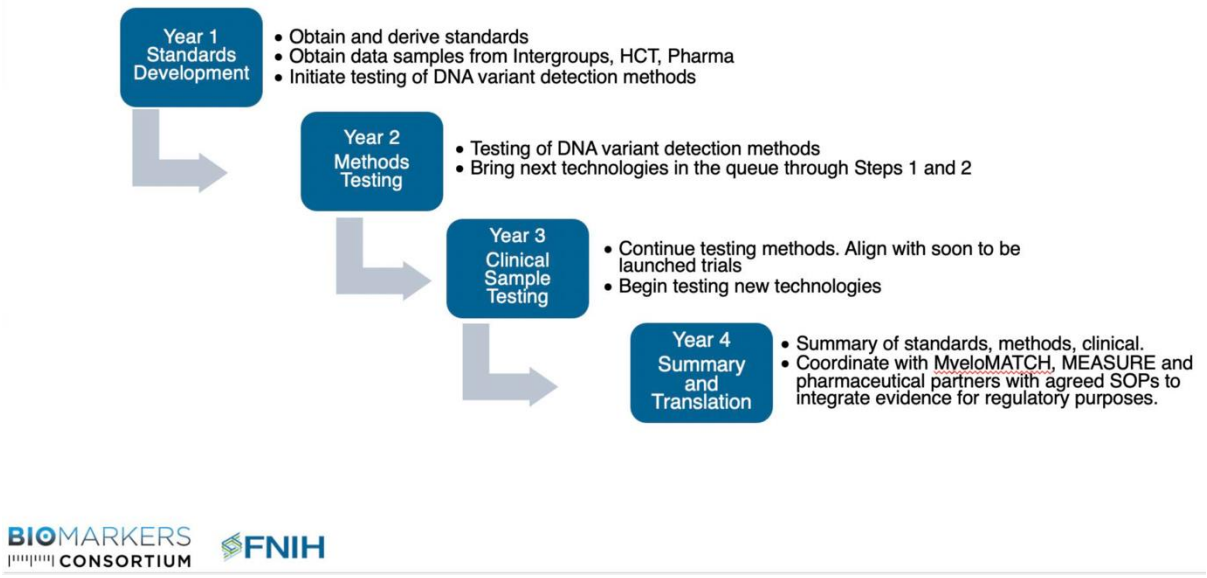


Figure 18. FNIH AML MRD Consortium project timelines

In summary,

- Nothing is complete about a complete remission in AML, but higher sensitivity measurements can better risk stratify cohorts of AML patients.
- Currently, AML MRD is good for papers, not yet for patients. Incentives and resources have traditionally not been aligned to move the field forward towards generation of

robust evidence of clinical utility using harmonized validated assays. The FNIH biomarkers consortium represents an opportunity to bridge the canyon.

- Collaboration offers a pathway to success between research and diagnostic assay companies, academic physician-scientists, regulatory agencies, the pharmaceutical industry and ultimately patients.

Session 3: Regulatory Perspectives

Summary of Regulatory Uses of MRD and ctDNA

Nicole Gormley (FDA, USA)

Nicole Gormley, MD, is the Division Director for the Division of Hematologic Malignancies II at the U.S. Food and Drug Administration. Dr. Gormley joined the FDA in 2011 and previously served as a clinical reviewer and the Multiple Myeloma Clinical Team Lead. While in these roles, Dr. Gormley has actively engaged with the multiple myeloma community on the development of novel endpoints, including minimal residual disease, and methods to address racial disparities. Dr. Gormley completed fellowship training in hematology and critical care at the National Institutes of Health and served as the Deputy Clinical Director at the National Heart, Lung and Blood Institute prior to joining the Food and Drug Administration.

MRD and ctDNA have potential as prognostic biomarkers, for screening and early detection, monitoring for relapse and increasingly to guide therapeutic decisions. From the regulatory perspective these data may be used for patient stratification, selection or enrichment of populations in clinical trials, for risk-based assignment and as an intermediate or surrogate endpoint. Enrichment based on biomarkers should be used when there is convincing data that treatment benefit is limited to the biomarker positive subpopulation. Stratification is useful when treatment is more likely to be effective in the biomarker positive patients, but where benefit cannot be ruled out in negative patients. The current criteria for Regular and Accelerated approval are listed in Fig.19.

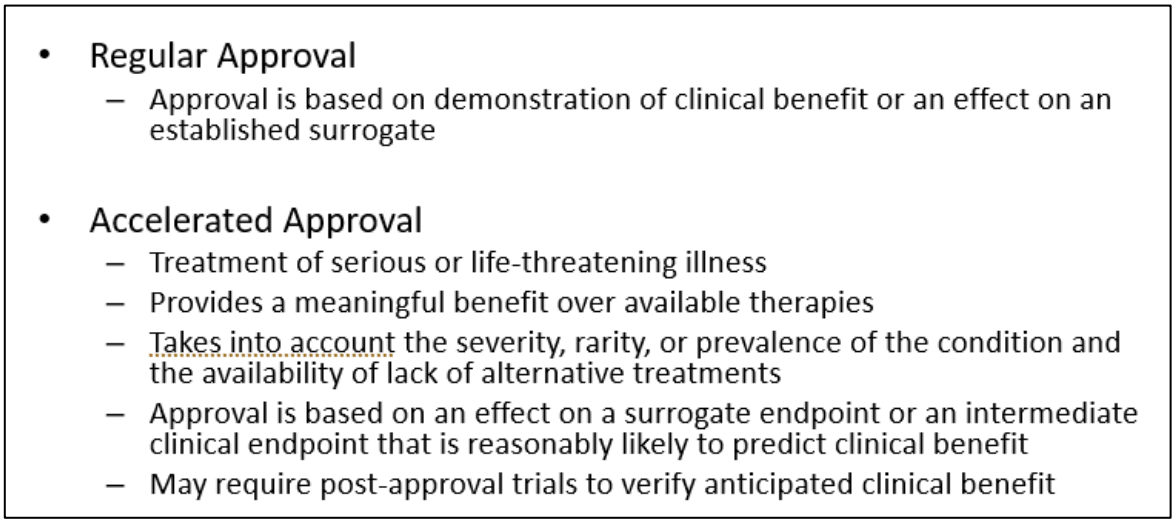


Figure 19. "Endpoint: Regulatory considerations"

For validation as a surrogate historically the Prentice Criteria have been used, where the surrogate must be a correlate of the true clinical endpoint, and the treatment effect on the surrogate should capture the full effect of treatment on the clinical endpoint. Discussions as to whether these criteria are too stringent have led to looking at newer approaches such as the use of meta-analytical methods. The latter requires patient level data, must allow for assessment of both individual and trial level surrogacy to assess the surrogate threshold effect i.e., the minimum effect on the surrogate necessary to predict an effect on the true clinical endpoint. 2 important points when designing a meta-analysis are to consider the

timing of MRD assessment and the problem of how to handle missing data. In January 2020 the FDA finalised their guidance on MRD, the scope of which is listed in Fig. 20.

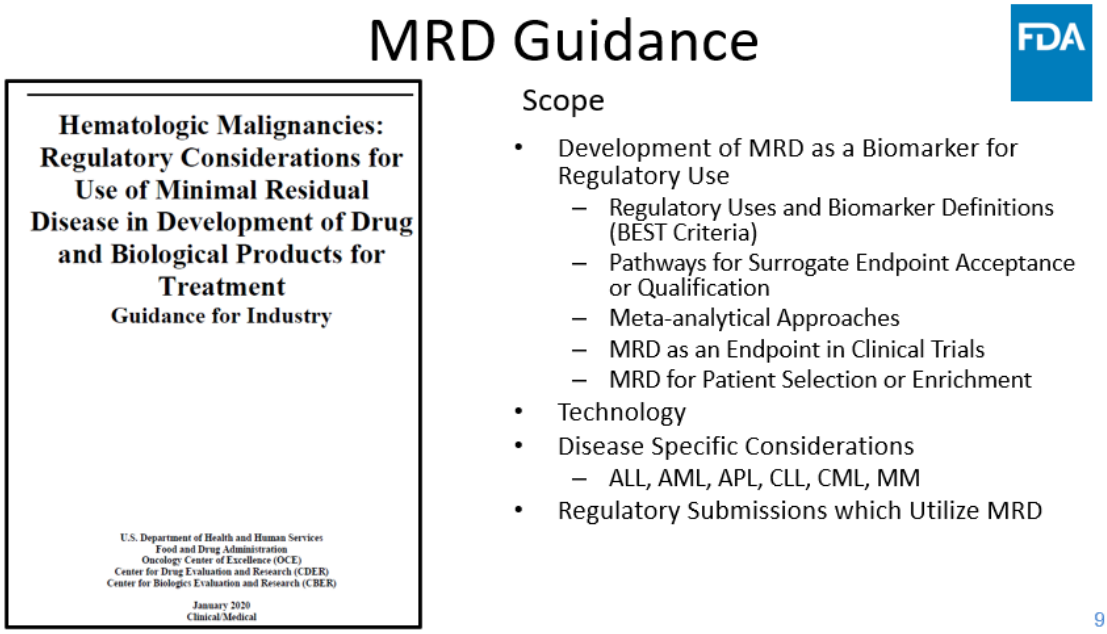


Figure 20. "FDA guidance on MRD"

In this presentation the point was made that the use of surrogates such as MRD may not be appropriate for treatments that have substantially different mechanisms of action, for example cytotoxics versus immunotherapies. So where are we today and what lies ahead? MRD results have been used in ALL for accelerated approval of Blinatumumab in MRD positive B cell Precursor ALL. MRD results are included in the prescribing information for Venetoclax and Obinutuzumab for CLL and Daratumumab and Abecma for multiple myeloma. The FDA warmly encourage early discussion with the Agency when considering MRD in clinical trials and emphasise their commitment to working with the community on these developments in the role of surrogate endpoints.

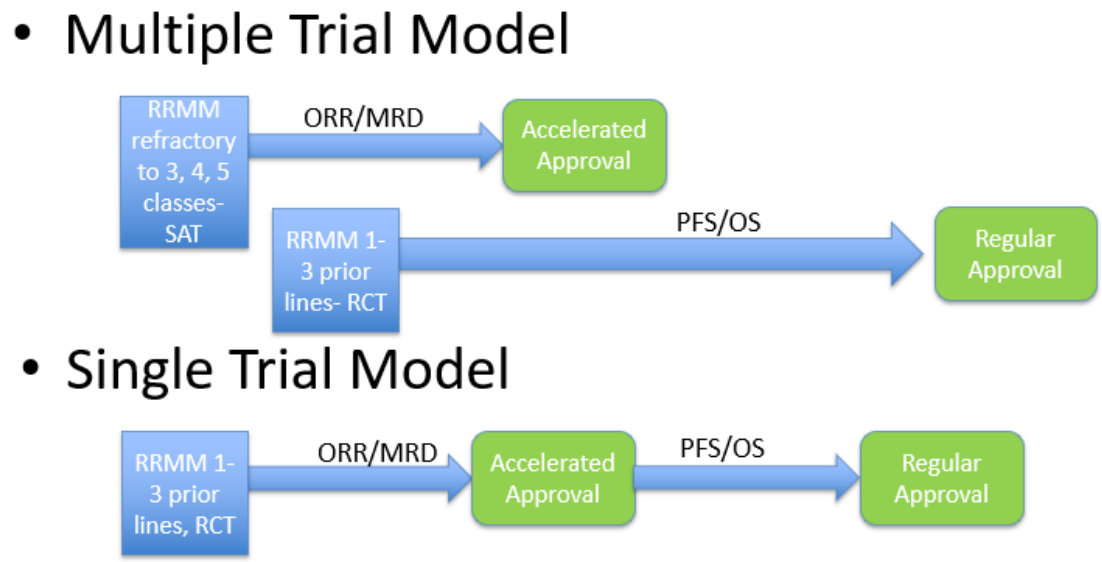


Figure 21. Drug Development Approach

Session 4: Important Viewpoints

European In Vitro Diagnostic Regulations - Industry perspective

Claudia Popp (Roche, CH)

Claudia Popp is the Head EU Regulatory Science & EMA Liaison at Roche. As a senior leader, Claudia Popp has worked for the pharmaceutical industry for more than 20 years and joined Hoffmann La Roche in 2008. She has substantial experience in global regulatory affairs and has held multiple roles within regulatory product development across molecules and therapeutic areas. She combines substantial experience of EMA and FDA processes with a deep knowledge of Health Authority interactions at national level, having held the role of Head Drug Regulatory Affairs at the Roche German Affiliate. The scope of her work there included complex drug/device interfaces.
The session was prepared in collaboration with Linda Bowen, Seagen Inc., Stephen Hall, Novartis, Hemal Morjaria, Johnson & Johnson, and Lubna Syed, Johnson & Johnson.

The Regulation (EU) 2017/746 establishes a new regulatory framework for in vitro diagnostic medical devices. The In Vitro Diagnostic Regulation ("IVDR") replaces the current In Vitro Diagnostic Directive 98/79/EC (IVDD) on 26 May 2022 and introduce substantial changes to the sector.

Research & development of innovative solutions to meet patient needs is evolving at a fast pace. The ctDNA field, and the huge progress in research & development over the past years, nicely illustrates this. The use of in vitro diagnostics and companion diagnostics is increasing significantly and provides the foundation for innovative personalized healthcare and precision medicine.

New requirements introduced by the IVDR:
The regulations introduced new requirements with regards to clinical trials using IVDs; in house developed tests; and the marketing authorisation approval procedure of drugs and biologics requiring companion diagnostics. The presentation intended to raise awareness about the new IVDR requirements:

- New risk-based classification system
- Definition of Companion Diagnostics introduced
- Performance Evaluation/ interventional clinical performance study introduced
- In house tests in scope
- Consultation procedure EMA-Notified bodies
- EUDAMED: More transparency for patients and caregivers

In view of the rapidly increasing use of IVDs, it is to be welcomed that the EU IVDR introduces high quality and safety standards. This represents an important step towards significantly improving patient safety in the EU and transparency on the use of IVDs.

All stakeholders need to urgently prepare for the implementation of the IVDR; the regulation has a critical impact on drug development including use in clinical trials and the use of IVDs in common clinical practice.

ctDNA tests are in vitro diagnostics and the IVDR will be applicable by May 26th, 2022.

However, in October 2021 the European Commission amended the timelines for IVDs with a CE marking approved under the former In Vitro Diagnostic Directive. The timelines were amended based on the risk class with the intent to avoid an overload of the Notified Bodies (see section role of Notified Bodies below).

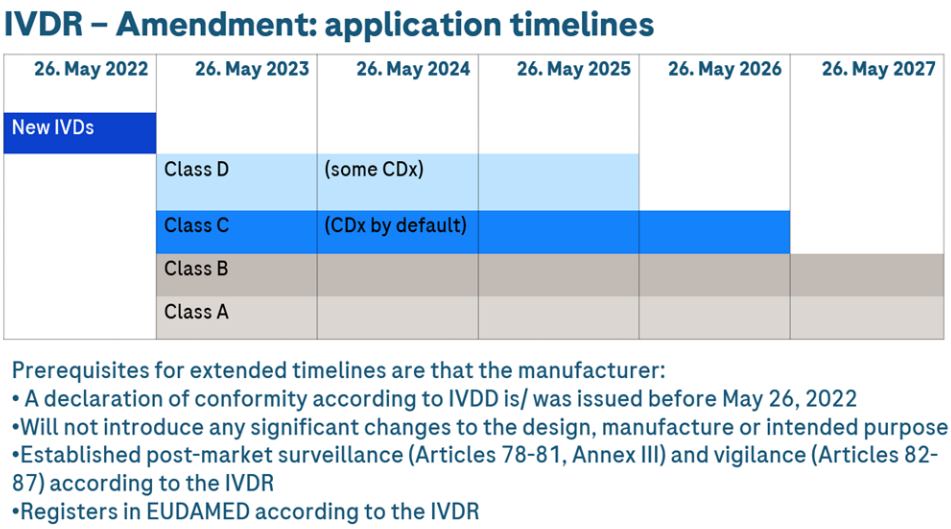


Figure 22. IVDR - Amendment: application timelines

ctDNA tests are used at various stages in the clinical setting: from screening to therapy selection, therapy response, and monitoring.

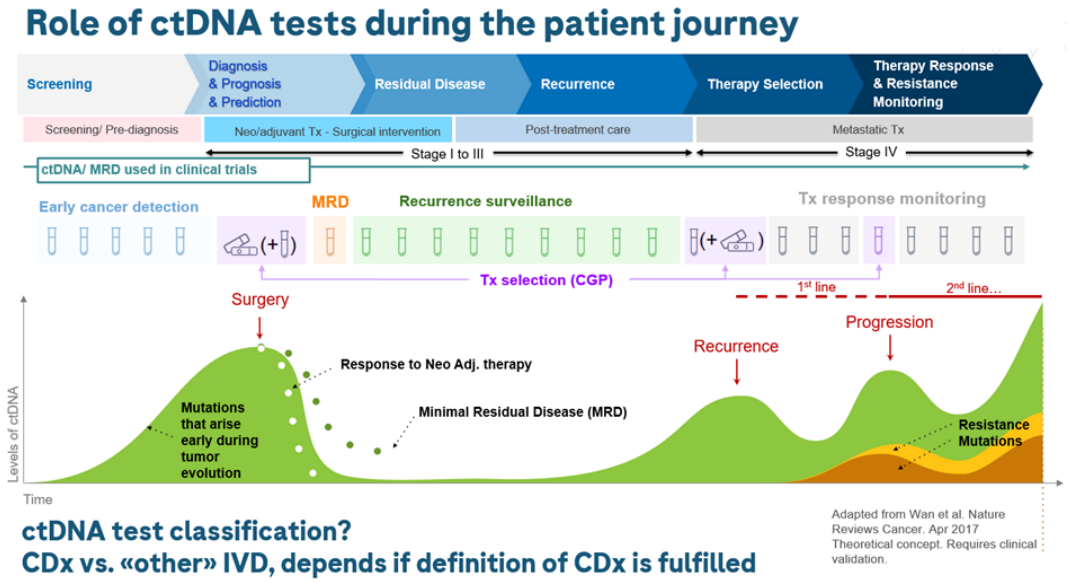


Figure 23. Adapted from Wan et al. Nature Reviews Cancer. Apr 2017 Theoretical concept. Requires clinical validation.

The intended purpose of the ctDNA test needs to be defined carefully and based on the use it needs to be assessed which requirements of the IVDR are applicable. For non-CE-marked tests used in a clinical trial, an evaluation is needed on whether a submission of an interventional clinical performance study to Health Authorities (HA) and Ethic Committees (EC) is mandatory. This is the case if a treatment decision is based on a ctDNA test.

Unfortunately, the approval process for studies using IVDs for treatment decisions is quite complex; besides the application for the drug clinical trial (CTA), an interventional clinical performance study application for the test to be used in the study needs to be submitted to the HAs and ECs in EUDAMED (European Database on Medical Devices). However, the database is not yet available for submission of performance study applications to Member States (expected to be available at the earliest at the end of 2022). Currently there is no clear

guidance on how to submit performance study device applications nor a streamlined process for obtaining consistent feedback in a simultaneous way from all Member States. **There is a high risk that the complexity and the uncertainties will delay innovative studies from being conducted in Europe;** further guidance from HA's / EC is required, preferably with anticipated timelines for review of the device information so that 'first patient in' planned for a protocol can be appropriately anticipated for site readiness activities.

Manufacturers of ctDNA/ IVD tests need to think early about the new performance evaluation requirements which are the basis for the CE marking by the Notified Bodies.

The **scientific validity**, the **analytical performance** and the **clinical performance** need to be sufficiently demonstrated and the data to be submitted to the Notified Bodies for CE assessment for the Notified Body recommendation to be provided in a timely manner to EMA.

It is essential to clarify early in the process if the IVD should be used as a companion diagnostic:

Companion diagnostic (CDx)

New definition is introduced with the IVDR:

CDx means a device which is essential for the safe and effective use of a corresponding medicinal product to:

- identify, before and/or during treatment, patients who are **most likely to benefit** from the corresponding medicinal product; or
- identify, before and/or during treatment, patients likely to be at **increased risk of serious adverse reactions** as a result of treatment with the corresponding medicinal product

The former IVDD did not contain a definition of a CDx: They were categorized as "other IVD" and defined as a low-risk class.

According to the IVDR CDx will be mainly classified as class C devices (second highest risk class).

Additional requirements are set out for performance studies using CDx in Art 58 to 77 and Annex XIV of the IVDR ("Interventional clinical performance studies").

New Consultation procedure EMA/ Notified Body introduced:

Notified Bodies and the EMA must collaborate and agree on the suitability of the CDx during the drug approval process. It is unclear if this will lead to a delay of drug approval timelines in the EU.

If the sponsor plans to use **non-CE certified ctDNA test as an in-house lab test,** they need to consider Art 5 (5) of the regulation and the post-market surveillance (Articles 78-81, Annex III) and vigilance (Articles 82-87) requirements of the IVDR.

Role of Notified bodies:

Due to the change in the classification system, the IVDR created a situation where there is a shift in the number of organisations requiring Notified Body (NB) review. Approximately 20% of IVD manufacturers went through a NB review under the IVDD whereas 90% of IVD manufacturers will require NB review under the IVDR. Adding to the complexity of the situation is that the number of NBs able to provide CE-marking for IVD products has been reduced significantly and to date only seven NBs are accredited under the IVDR. Industry has

huge concerns that Notified Bodies will not be able to authorize products and issue CE certificates in time, thus encountering long delays.

Summary and conclusion

The previous sections clearly show that the IVDR is a very complex set of regulations and there are still some open questions and urgently needed guidance from the European Commission.

The IVDR sets high standards of quality, safety and reliability to safeguard patients and enhance innovation, which is highly welcomed.

However, the complexity could lead to:

- Delays of initiation of clinical trials within the European Union for oncology products requiring a companion diagnostic due to uncertainties and the complex process of performance evaluation submissions.
- An increased risk that sponsors decide to conduct innovative trials outside the EU to avoid delays of the development program.
- Potential delays in patient treatments due to the complex situation related to in-house tests.
- Potential delays within the European Union in the approval of new medicines which require a companion diagnostic

Patient perspective

Hans Scheurer (MPE, NL)

Hans Scheurer is president of the pan-European organisation Myeloma Patients Europe (MPE) since 2016. He is a myeloma patient since 2005, and active as a patient advocate for the myeloma community since 2008. Being an educationalist, he started writing for patients about medical developments and all innovation in the myeloma field, with a passion for understandable language for patients. In his current role he focusses on good governance of the patient community of MPE, and mentoring/coaching new patient groups across the EU, with the goal of shaping meaningful patient involvement and, and in general the profession development of patient advocacy. He is active in many consortia representing the patient perspective, like EMA procedures and committees, the WECAN consortium of Cancer patient umbrella organisations, the HOVON Myeloma workgroup in the Netherlands, SISAQOL-IMI.

In this presentation Hans Scheurer discussed MRD from the patient's perspective and the advice available from advocacy groups. For the individual patient understanding the concept of measuring MRD as part of a clinical trial may be very different to its use in routine clinical practise. Trial protocols should explain why MRD is being collected and patients helped to understand that the results on a given day may or may not lead to a change in treatment. Conversely the use of MRD in routine care will usually lead to a conversation between patient and physician as to whether a change is recommended. A negative result may reduce chronic anxiety, but a positive may understandably lead to new levels of concern. The actual techniques used for determining MRD are important to the patient as well as the investigator. For example, in myeloma advances in using blood samples for ctDNA are much preferred to the more invasive (painful) use of bone marrow, but the latter remains the gold standard for genetic analysis.

Throughout the modern drug development process patient input is being increasingly recognised as invaluable. Advocacy groups can play an important role in expediting approval pathways since regulators benefit from the information provided by such groups concerning unmet need and quality of life issues. Differences exist between the EMA and FDA in the specifics of expedited approvals, but the issues are common to all regulators. Difficult decisions require sufficient robust evidence of a positive benefit versus and safety signals.

Expedited approval processes give opportunities particularly where rare disease is concerned, and especially for the early detection of possible efficacy in small trials. This can result in faster access to novel treatments. However early approval can cause controversial expectations following media announcements and can explain the gap between regulatory approval and access from a national HTA. Regulators do not consider the costs of new treatments and it is frustrating for patients that individual HTA's repeat the whole assessment that has been done by EMA/FDA, largely for cost considerations. It is encouraging that expedited approvals have increased considerably in the past decade, from 34% in 2000 to 60% in 2019.

For a long time, regulators have challenged the use of PFS for its uncertain timeline, but consecutive measurements of MRD can give evidence of sustained remission as a prelude to improved OS. The development of improved methods for patient reported outcomes (PRO) is important in this regard since some patients find repeat monitoring creates extra anxiety. Whilst reassurance following stable measurements is a good thing, some patients and regulators have raised the concern that an adverse change in MRD might lead to an unwanted increase in dose of a drug (thereby adding toxicity), or automatically lead to change to a different regime which may or may not be beneficial.

These considerations emphasise the need for clear statements in clinical trial protocols, especially concerning informed consent about the reasons for measuring MRD, and sensitive communication between physician and patient to manage very understandable anxiety. All these factors contribute to the goal of establishing Value Based Access to novel therapies.

Surrogate endpoints in Health Technology Assessment: Exploration of the HTA Perspective[3]

Carole Longson (Life Science Adviser, UK)

> Carole Longson was an Executive Director at NICE from 2000-2018 and Chief Scientific Officer at the Association of the British Pharmaceutical Industry from 2018-2020. She was formerly President of Health Technology Assessment International and now has advisory roles including Life Science Advisor at NICE. Carole is vice chair of the Medicines Discovery Catapult in the UK, was previously on Scientific Advisory Committee for Innovative Medicines Initiative and holds non-Executive Director and advisory roles in scientific endeavours in the UK and abroad.

In general, biomarkers can be assessed in the following categories[4]. A correct designation of the purpose is necessary for the development and the assessment of a biomarker.

- **Susceptibility/risk biomarker**
  - Indicates the potential for developing a disease or medical condition in an individual who does not currently have clinically apparent disease or the medical condition.
- **Diagnostic biomarker**
  - Used to detect or confirm presence of a disease or condition of interest or to identify individuals with a subtype of the disease.
- **Monitoring biomarker**
  - Measured serially for assessing status of a disease or medical condition or for evidence of exposure to (or effect of) a medical product or an environmental agent.

[3] Please see also D. Longson, Endpoints in expedited regulatory approval pathways: A HTA Perspective. Meeting Report, CDDF Multi-Stakeholder Workshop: Endpoints in Cancer Drug Development, 26-28 April 2021. https://cddf.org/wp-content/uploads/2021/09/MSW_Endpoints-in-Cancer-Drug-Development_Meeting-report_final.pdf

[4] FDA-NIH Biomarker Working Group. BEST (Biomarkers, EndpointS, and other Tools) Resource [Internet]. Silver Spring (MD): Food and Drug Administration (US); 2016-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK326791/

- **Pharmacodynamic/response (surrogate) biomarker**
  - Used to show that a biological response has occurred in an individual who has been exposed to a medical product or an environmental agent.
- **Prognostic biomarker**
  - A biomarker used to identify likelihood of a clinical event, disease recurrence or progression in patients who have the disease or medical condition of interest.
- **Predictive biomarker**
  - A biomarker used to identify individuals who are more likely than similar individuals without the biomarker to experience an effect from exposure to a medical product or an environmental agent.

Measurable Residual Disease (MRD) and Circulated Tumour Nucleotides (ctDNA) are proposed as new surrogate (predictive) biomarkers in the development of anti-cancer agents.

MRD in Solid Cancers: perspective of industry

Darren Hodgson (AstraZeneca, UK)

Darren Hodgson is Executive Director, Translational Medicine Strategy, Oncology, AstraZeneca. He had previously had positions in global drug development, academia, biotechnology, and diagnostics. Darren has over 15 years' experience as lead or core member of multi-functional global product teams and has been responsible for strategy, internal and external assay development, clinical deployment, and regulatory representation for biomarkers used as for clinical studies in all stages of drug development. Darren currently heads up an initiative to deploy circulating tumour DNA measures to identify patients with early cancers in need of treatment options and accelerate development programs. Darren was previously the translational lead for Lynparza, AstraZeneca's first in class PARP inhibitor, and is author of numerous reviews, original patents, and papers.

ctDNA Biology and Potential Utility in Drug Development

Circulating tumour DNA (ctDNA) can provide critical information about a tumour through non-invasive techniques as it carries the genetic and epigenetic markers characteristic of the disease. ctDNA often is only a small fraction of the total circulating free DNA (cfDNA) and has a short (app. two hours) half-life. Its quantity is influenced by the tumour volume, its location and its aggressiveness.

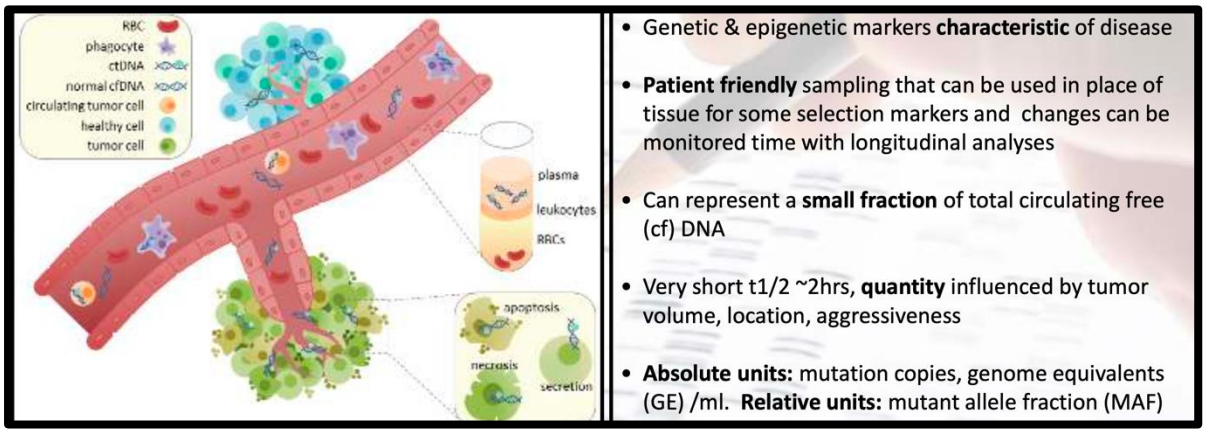


Figure 24. Biological aspects of ctDNA

Current concepts to improve the cure rates for cancer (Vasan, 2019) can be summarized as "Hit cancer earlier, harder and smarter". ctDNA can be used to improve management of cancer in the following situations (Cheng, 2021):

- Improve the diagnosis with tissue of origin and possible change in stage distributions

- Improve the assessment of prognosis with possible upstaging
- Landmark MRD assessment: E.g., after surgery or adjuvant therapy
- Surveillance with MRD: The detection of recurrence with ctDNA (with the possibility of early treatment of relapse based on ctDNA alone)
- Treatment selection: At initial diagnosis or relapse according to detected molecular markers
- Treatment switch on resistance mechanisms by ctDNA

In several clinical trials ctDNA was able to identify patients whose cancer will recur (e.g. NSCLC (Chabon, 2020) and breast cancer (Coombes, 2019) with very high hazard ratios that discriminate the prognosis of ctDNA-negative patients from those who have a positive assessment.

MRD as a Tool for Patient Selection

MRD biomarker can overcome challenges associated with conventional adjuvant drug trials and may enable early-escalation trials in high-risk patient populations while its use may spare patients who are already cured by the initial treatment the toxicity of unnecessary escalated therapy. New trials using ctDNA in such indication would have the advantage of lower overall patient numbers and shorter duration while preserving the power through higher event rates in this population. Screening numbers, however, would remain high.

Studies in lung cancer have allowed to quantify the relation of tumour volume to ctDNA detection threshold: On average a sensitivity of 1:10.000 is needed to detect a tumour of a size of one cubic cm (Abbosh, 2018). This high sensitivity and resulting risk of sampling errors ("your needle is in another haystack") makes a reliable detection of MRD negativity only possible if multiple markers per genome are employed. (Chaudhuri, 2017) (Reinert, 2019).

Sensitivity and specificity are enabled by only assessing markers known to be present in an individual's tumour (avoiding CHIP and minimising multiple testing errors) as well as using error suppression techniques.

These personalised assays are a complex two-step process where in the first step the patient's tumour is sequenced (Whole Exome Sequencing, WES) and multiple clonal mutations in tumour are identified resulting in the design of a personalized panel. In the second step the respective mutations are tracked in the patient's plasma (ctDNA analysis).

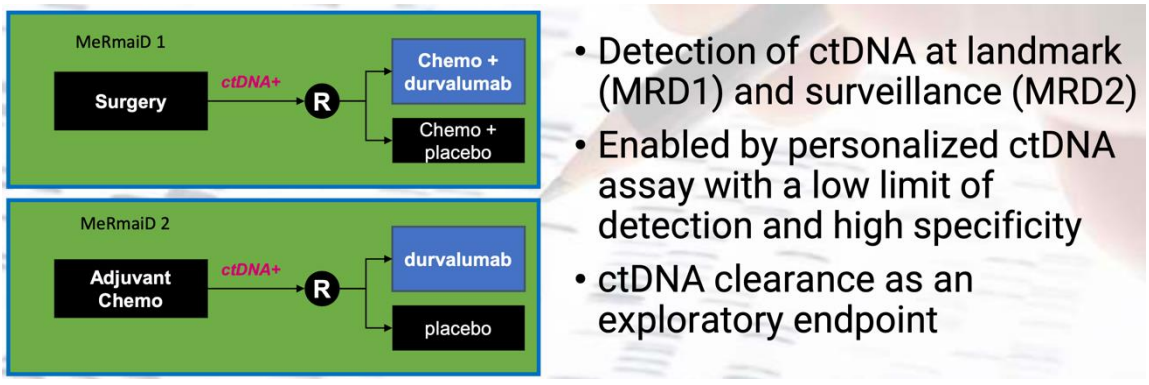


Figure 25. AstraZeneca's phase III trials using ctDNA positivity to select patients for escalated therapeutic interventions in NSCLC (MERMAID-1, NCT04385368; MERMAID-2, NCT04642469)

AstraZeneca has begun two phase III trials in NSCLC to evaluate escalated treatment interventions based on the positive finding in a personalized ctDNA assay at a landmark (after surgery) or during surveillance (Fig. 25).

Another very interesting clinical trials is the IMvigor010 adjuvant study of Atezolizumab v observation in muscle-invasive bladder cancer (MIUC) (Bellmunt, Adjuvant atezolizumab versus observation in muscle-invasive urothelial carcinoma (IMvigor010): a multicentre, open-label, randomised, phase 3 trial, 2021). While the 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 patients were evaluable and of whom 37% were baseline ctDNA-positive. The study authors' conclusions were that ctDNA-positive patients with high-risk MIUC likely to derive DFS and OS improvement from adjuvant atezolizumab. ctDNA-negative 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, ctDNA guiding adjuvant immunotherapy in urothelial carcinoma, 2021).

MRD as an Endpoint for Clinical Trials
Studies in later and advanced disease states have shown that early decreases of ctDNA levels are associated with longer PFS in patients treated with targeted agents and immune-checkpoint inhibitors. A meta-analysis of single arm studies by Zhang et al. of 1149 patients with solid tumours treated with immune-checkpoint inhibitors demonstrated the ctDNA levels are prognostic and on-treatment dynamics predictive of outcome, even in patients with stable disease according to RESIST criteria (Zhang, 2020).

The project by the Friends of Cancer Research on ctDNA focusses on the necessary standardization of the methodology[5]. Remarkably, in this project the association of reduced ctDNA levels with improved outcome could be shown[6] across studies with quite different ctDNA assays as the allelic fractions were reproducible across assay formats.

In 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 limit of detection could improve sensitivity
  - Detection of second primary malignancies
  - 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.

Session 5: How Should We Move Forward?

Panel discussion

In summary of a well-received and lively workshop the panellists and contributors emphasised 5 major points:

[5] [CDDF: Please also see the contribution of Jeff Allen on the FoCR project in this report.]
[6] https://friendsofcancerresearch.org/blog/ctmonitr-step-1-results-do-changes-in-ctdna-reflect-response-to-treatment/

1. There is a need for standardisation and quality assurance regarding the different methods for assessing MRD and ctDNA.
2. There is a need for genuine cooperation amongst stakeholders – difficult to achieve but possible, as exampled by the Friends of Cancer Research USA and the MPAACT collaboration.
3. Both above points need to be accelerated. The regulators are genuinely interested but need robust, statistically sound data.
4. HTAs likewise need 3 above but have the additional challenge of opportunity costs where funding one drug may mean that another is left behind, therefore they are even more cautious.
5. As a specific point proving MRD negativity may allow maintenance programmes to be stopped, and similarly with adjuvant therapy programmes MRD measurement may indicate the need to continue or stop early.

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