CDDF
Cancer Drug Development Forum

2022

CDDF

EXECUTIVE SUMMARY

Measurable Residual Disease (MRD) & Circulating Tumour Nucleotides (ct DNA) in Cancer Drug Development

25-26 April 2022
Amsterdam, NL

Prepared by the Cancer Drug Development Forum (CDDF)

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MULTI-STAKEHOLDER WORKSHOP

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Background & Current Development

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.

CDDF Multi-Stakeholder Workshop

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**.

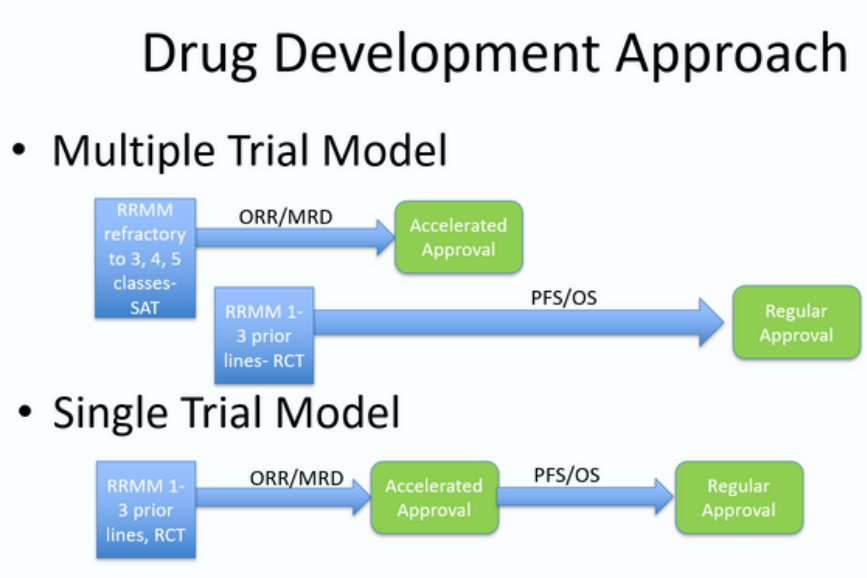
The full meeting report summarises the meeting held in Amsterdam on April 25-26, 2022 with expert presenters from academia, regulatory agencies, HTA and patient advocacy. It brought together state-of-the-art presentations on the methodological aspects, their clinical application and regulatory assessment; remarkable example of non-competitive collaboration of the pharmaceutical industry and of public-industry collaboration that are likely to deliver data on the scale that is necessary to meet the statistical criteria for the evaluation of surrogate endpoints.

This Executive Summary gives a short overview of some of the key topics discussed at the meeting. For a full account please refer to the Meeting Report.

Regulatory Perspective

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 t**he 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.

Cancer Drug Development Forum (CDDF)



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.

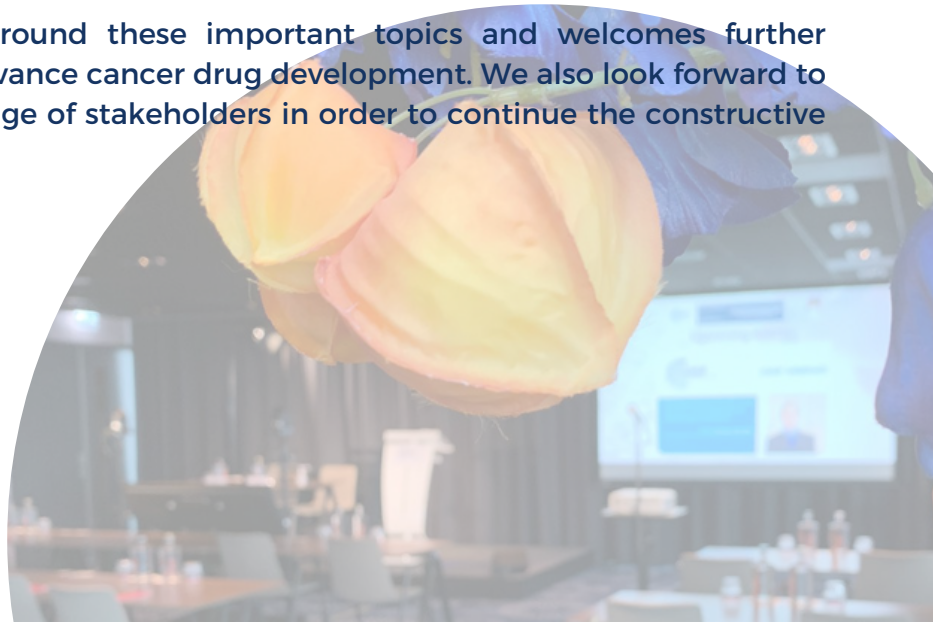
Payer's Perspective

Questions remain also for the payers: 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.

Patient's Perspective

Without doubt the most important perspective is the one of patients. Hans Scheurer of Myeloma Patients Europe has summarised some of the key aspects at the workshop. 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.

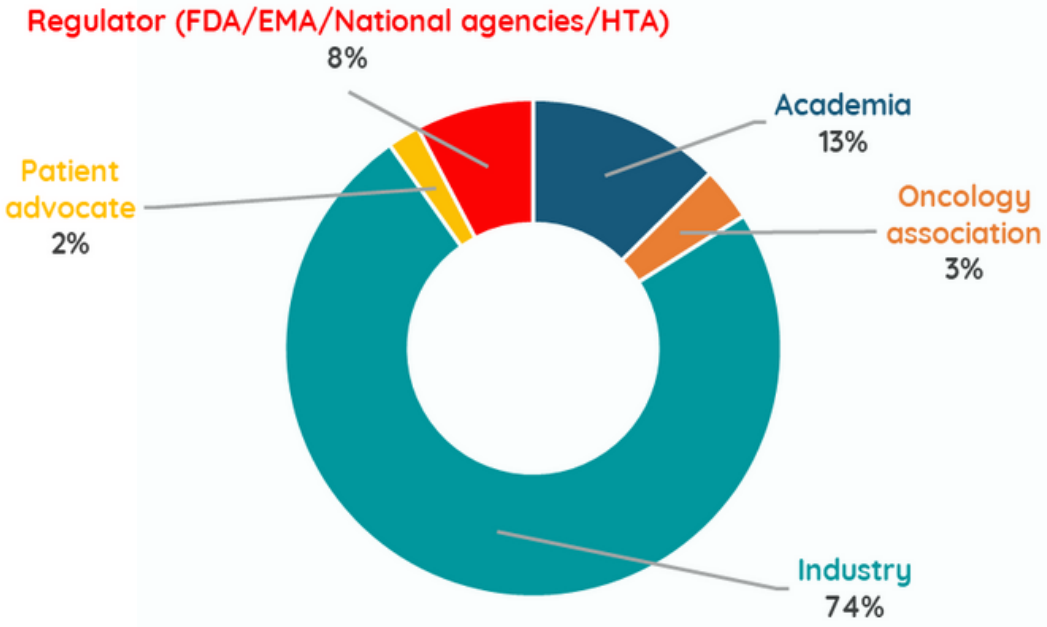
The CDDF will remain engaged around these important topics and welcomes further suggestions and contributions to advance cancer drug development. We also look forward to future collaboration with a wide range of stakeholders in order to continue the constructive dialogue in the area.



CDDF'S MULTI-STAKEHOLDER AUDIENCE & SPEAKERS

CDDF's meetings present a wide range of prespectives from **various stakeholders** who are involved in the development of oncology drugs. Our **multi-stakeholder, collaborative approach** facilitates a productive dialogue in a neutral, non-competitive space in order to **accelerate effective cancer drug development.**

CDDF Workshop: MRD & ct DNA in Oncology Drug Development



Categories of Speakers and Participants (online & on-site)

TOTAL NUMBER OF PARTICIPANTS 149

PARTICIPANTS' OVERALL SATISFACTOR 4.7/5

CDDF'S MEETINGS IN 2023

CDDF Annual Conference (Hybrid)
Challenges in Clinical Trial Performance

6 – 8 February 2023, Noordwijk aan Zee (NL)

Multi-Stakeholder Workshop (Hybrid)
Dose Optimization in Oncology Drug Development

3 – 4 April 2023, Amsterdam (NL)

Multi-Stakeholder Workshop (Hybrid)
Innovative Oncology Trial Designs

18 – 19 September 2023, Amsterdam (NL)

Multi-Stakeholder Workshop (Hybrid)
Biomarkers in Oncology Drug Development

13 -14 November 2023, Amsterdam (NL)

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