CDDF Annual Conference

# CDDF Multi-stakeholder Workshop

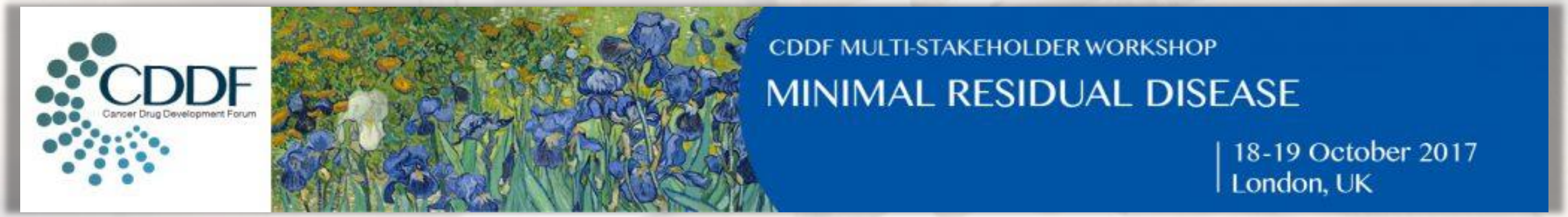
# Measurable Residual Disease (MRD) and Circulating Tumour Nucleotides (ctDNA)

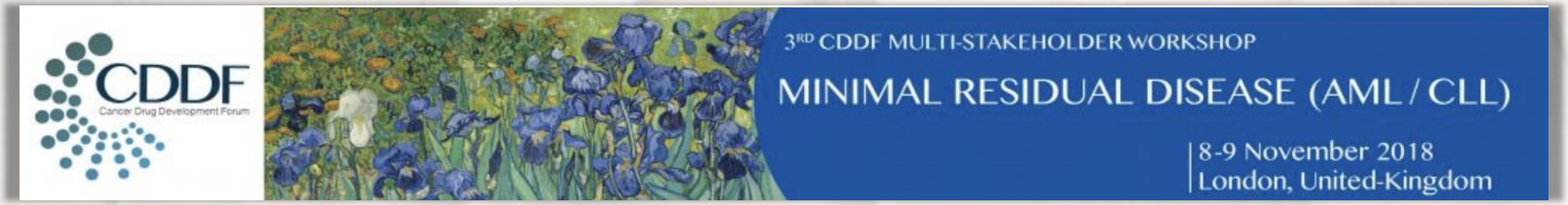
Axel Glasmacher
(CDDF, DE)

# Disclaimer

- I am a board member and the treasurer of the CDDF
- I have no financial conflicts related to the workshop's topics

# CDDF Multi-Stakeholder-Workshops on MRD


CDDF
ANNUAL CONFERENCE

Challenges in clinical trial performance

6 - 8 February 2023

CDDF Annual Conference 2023

CDDF WORKSHOP

25 - 26 April 2022

HYBRID WORKSHOP

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

# Scientific Programme Committee

**Axel Glasmacher**
CDDF, DE

**John Smyth**
CDDF, UK

**Veerendra Munugalavadla**
AstraZeneca, US

**Hans Scheurer**
Myeloma Patient Europe, NL

**Natalie Dimier**
Roche, UK

**Reshma Patel**
Johnson & Johnson, UK

# Speakers, Moderators and Panelists

## In Order of Appearance

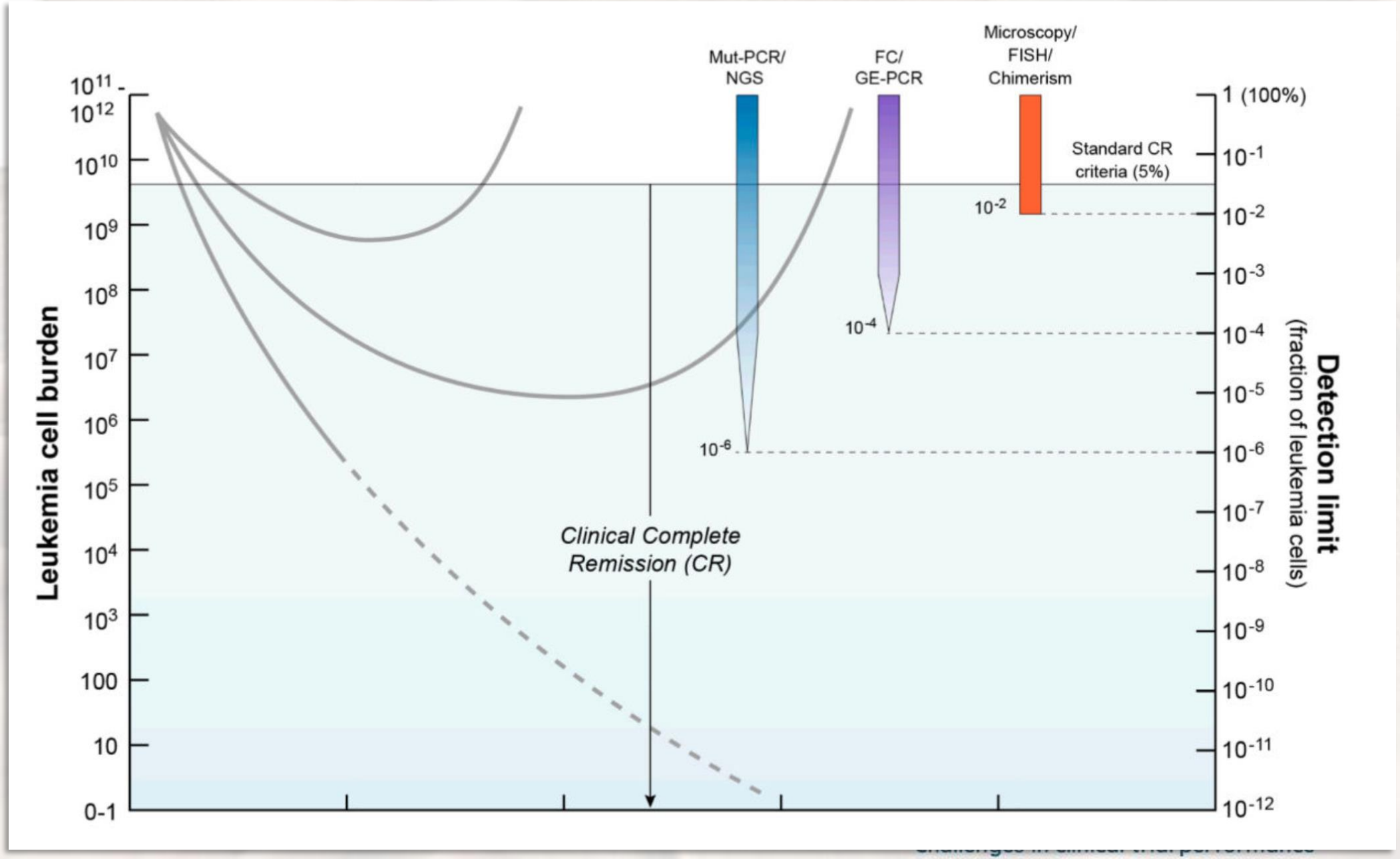
Bruno Paiva (Univ. de Navarra, ES)
Dominic Rothwell (Manchester, UK)
Jürgen Gschwend (TU Munich, DE)
Marie Morfouace (EORTC, BE)
Veerendra Munugalavadla (AstraZeneca, US)
Pierre Demolis (ANSM, FR)
Natalie Dimier (Roche, CH)
Reshma Patel (Johnson & Johnson, UK)
Christopher Hourigan (NIH, USA)
Jeff Allen (Friends of Cancer Research, USA)

Nicole Gormley (FDA, USA)
Natalie Dimier (Roche);
Paula van Hennik (MEB, NL)
Shirley Hopper (MHRA, UK)
Donna Roscoe (FDA, USA)
Claudia Popp (Roche, CH)
Hans Scheurer (MPE, NL)
Carole Longson (NICE, UK)
Darren Hodgson (AstraZeneca, UK)

# Definitions

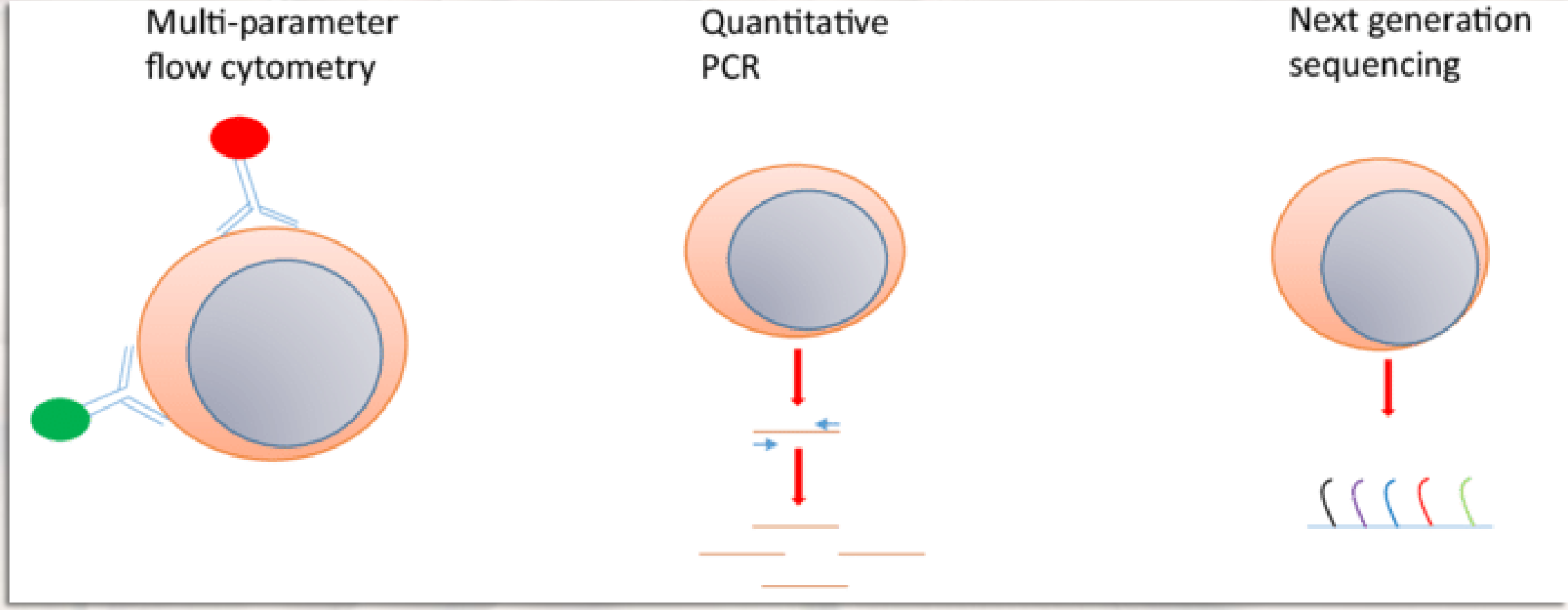
- **MRD**
  - Measurable (previously termed minimal) residual disease
  - Usually analysed in bone marrow samples
  - Detection of malignant cells down to levels of $1:10^4$ to $1:10^6$ white blood cells, compared with 1:20 in morphology-based assessments

- **ctDNA**
  - Circulating (cell-free) tumour DNA (nucleotides)
  - Usually analysed in peripheral blood samples
  - Allows to detect/track tumour-specific nucleotides (‘liquid biopsy’) to determine e.g. response or relapse of a tumour




C. Hourigan: Presentation at CDDF Workshop 2022
Hourigan et al., Nat Rev Clin Oncol. 2013; 10: 460–471.

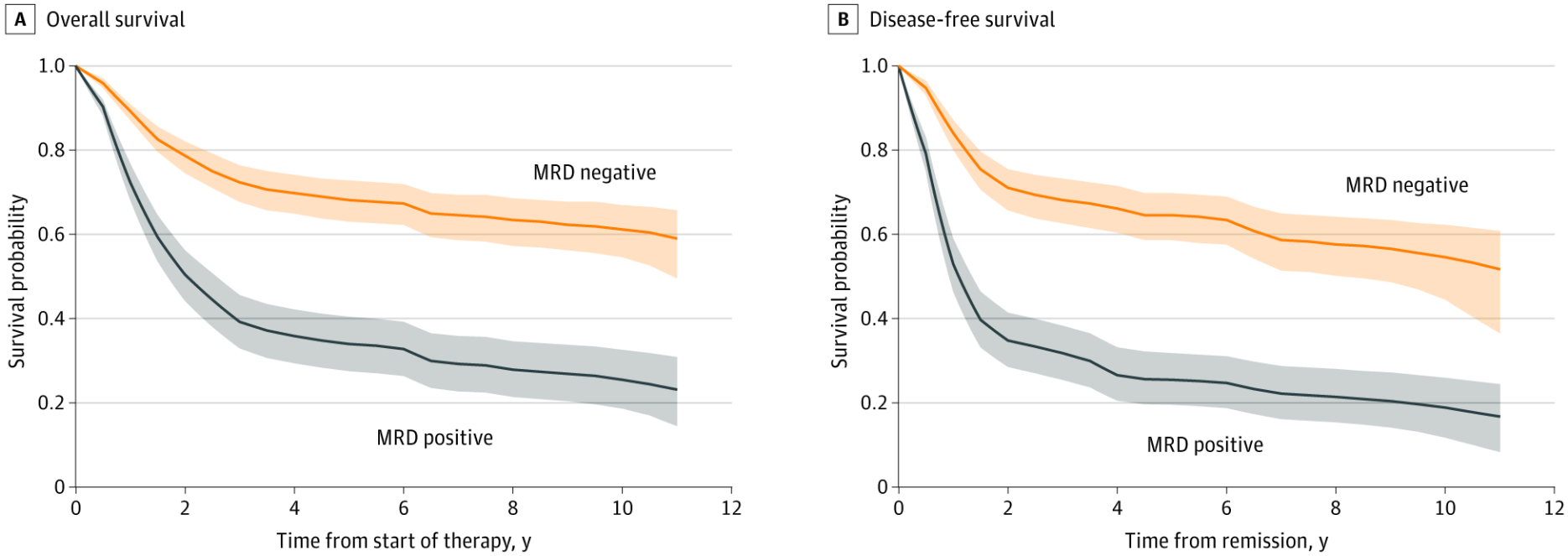
# MRD Modalities




Loke J et al., BJH 2019. doi: 10.1111/bjh.16355

# Association of MRD with survival outcomes in AML

## A Systematic Review and Meta-analysis in 11,151 patients




Short NJ, et al. JAMA Oncol. 2020;6(12):1890-1899.

# MRD assessment across some hematological malignancies

## Application depending on clinical need and methodological robustness

| | 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 |

B. Paiva: Presentation at CDDF Workshop 2022

# Definitions

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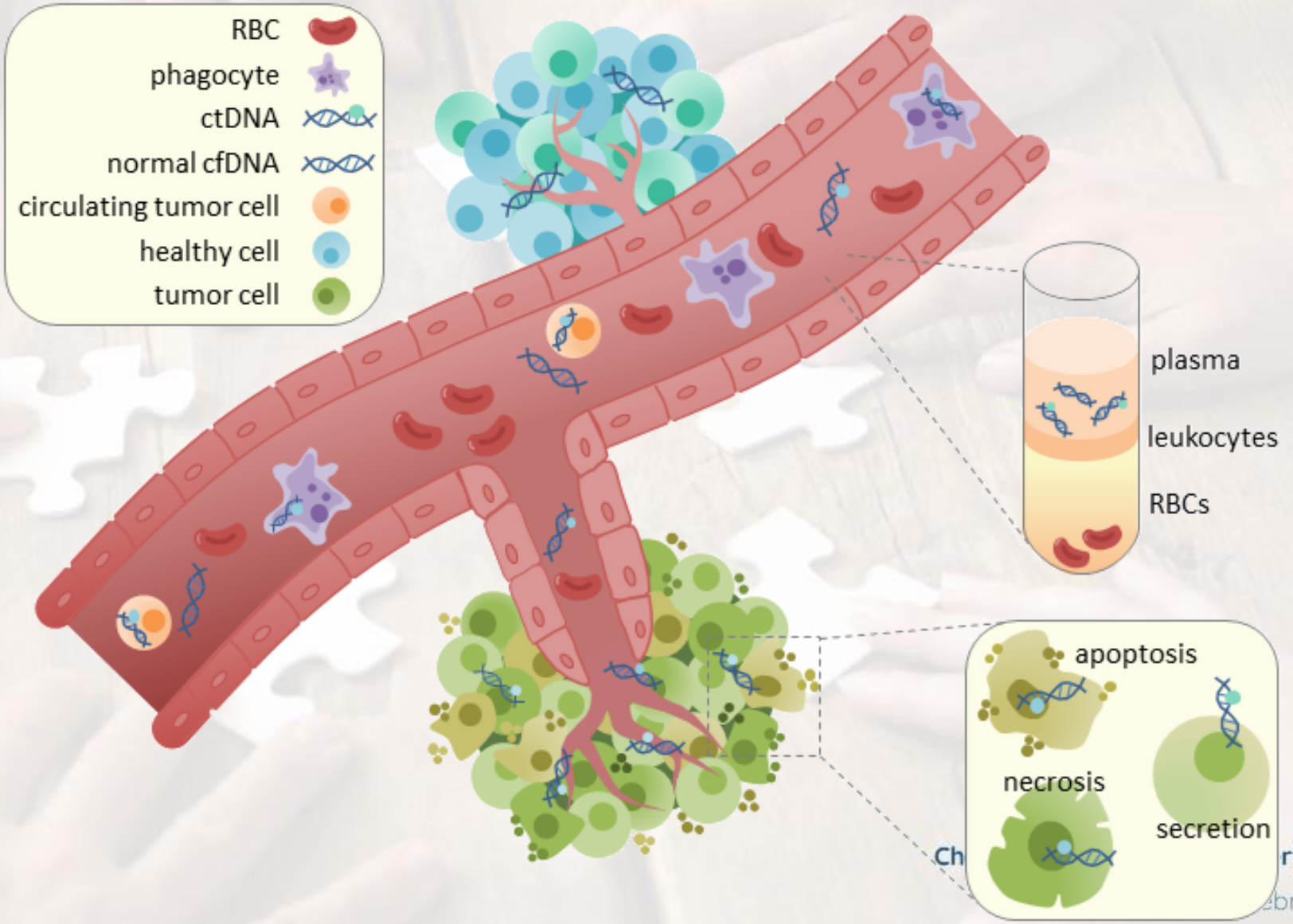
# circulating tumor DNA (ctDNA)



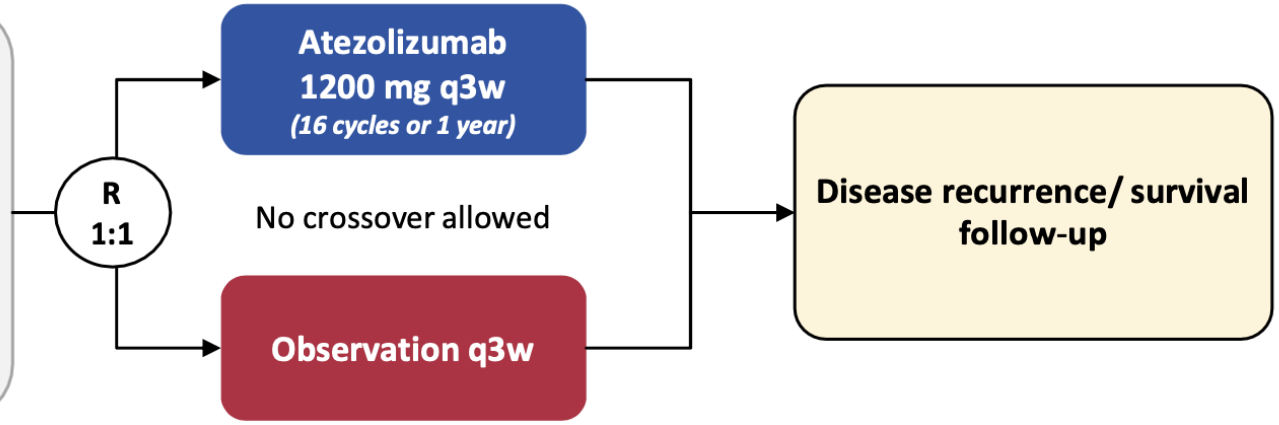



Wikipedia: Racheljunewong; 27 February 2017; accessed: 03.02.2023

# Phase 3 IMvigor010 adjuvant study in MIUC

**Key eligibility**

- High-risk MIUC (bladder, renal pelvis, ureter)
- Radical surgery with lymph node dissection within ≤ 14 weeks[a]
- No postsurgical radiation or AC
- ECOG PS 0-2
- Tissue sample for PD-L1 testing

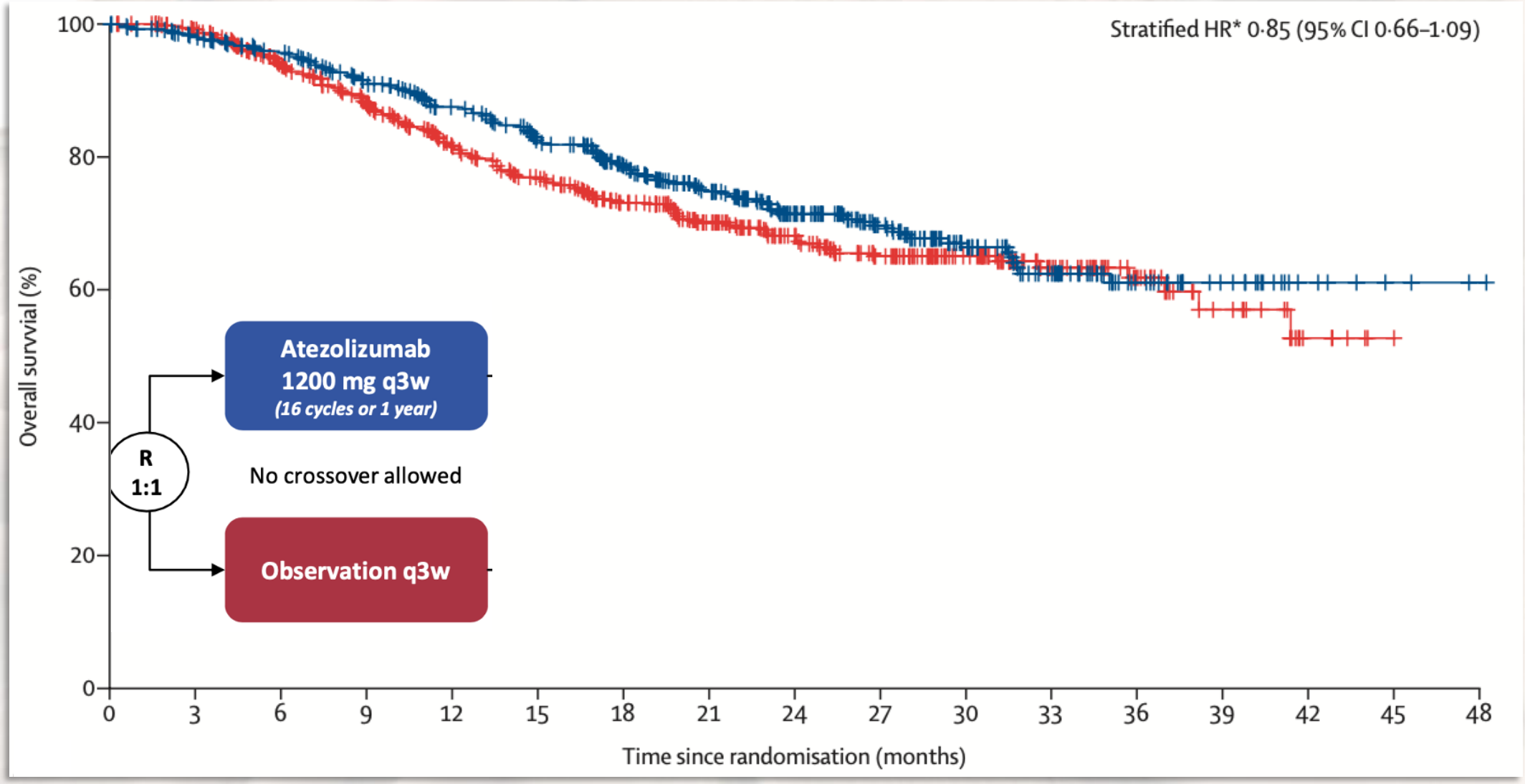



**Stratification factors**

- PD-L1 status[b]
- Nodal status
- Tumor stage
- # of lymph nodes resected
- Prior neoadjuvant chemotherapy

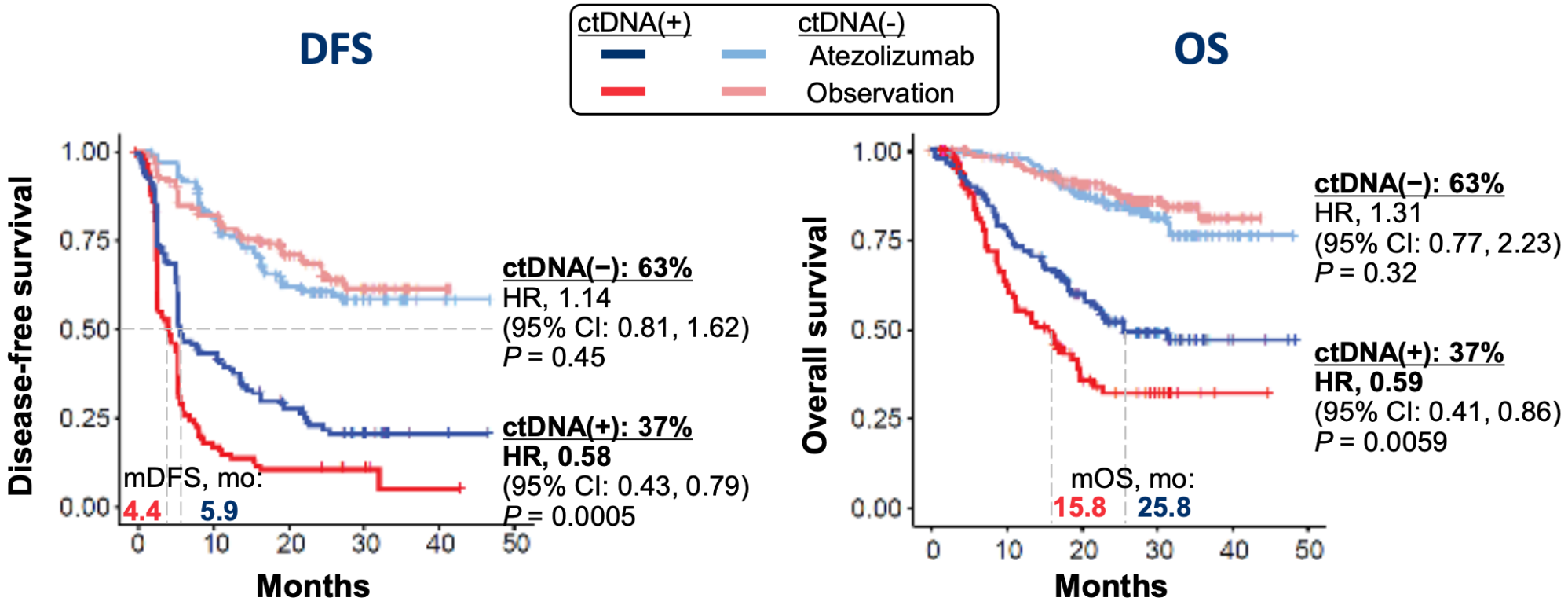
- **Primary endpoint:** DFS (ITT population)
- **Key secondary endpoint:** OS (ITT population)
- **Safety**
- **Exploratory analyses:** Predictive, prognostic and pharmaco-dynamic biomarkers in tumor tissue and blood and their association with disease recurrence[c]

J. Geschwend: Presentation at CDDF Workshop, 2022
Bellmunt J et al., Lancet Oncology 2021; 22: 525




J. Geschwend: Presentation at CDDF Workshop, 2022
Bellmunt J et al., Lancet Oncology 2021; 22: 525

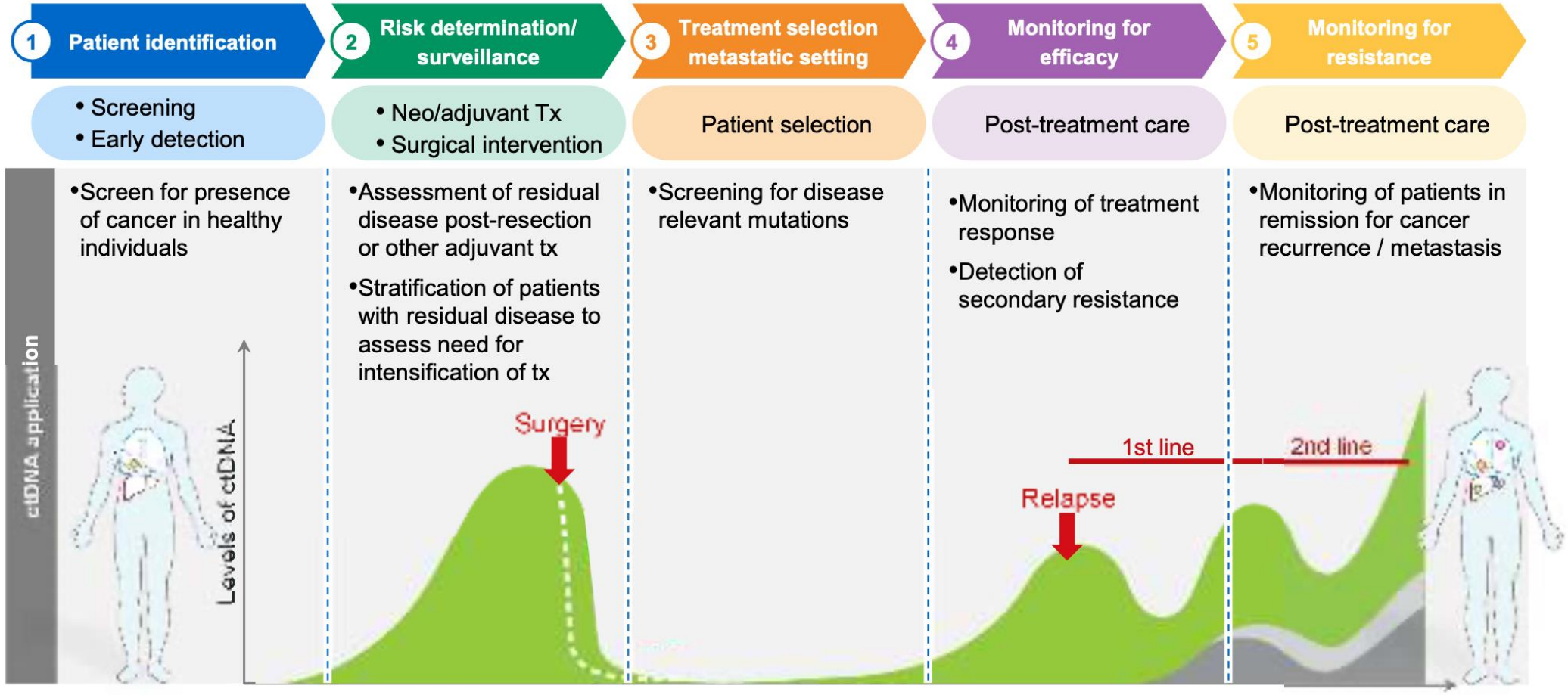
# ctDNA(+) patients had improved DFS and OS with atezolizumab vs observation




- IMvigor010 confirmed the prognostic value of ctDNA status

J. Geschwend: Presentation at CDDF Workshop, 2022
Powles T et al., Nature 2021; 595: 432

# ctDNA has substantial potential to be used throughout the patient journey




This is a non-promotional meeting intended for HCPs outside the USA. It may include scientific information about investigational compounds that may not be approved or valid in your jurisdiction

Adapted from Wan et al. Nat Rev Cancer 2017

J. Geschwend: Presentation at CDDF Workshop, 2022

# FDA: Potential uses of MRD and ctDNA

- Prognostic Biomarker
- **Clinical Uses**
  - Screening/Early Detection
  - Monitor for relapse
  - Guide therapeutic decisions
- **Regulatory Uses**
  - Patient Stratification
  - Patient Selection/Enrichment
  - Risk-based treatment assignment (Escalation / De-Escalation)
  - Intermediate Endpoint or Surrogate Endpoint

N. Gormley: Presentation at CDDF Workshop, 2022

# FDA: Potential uses of MRD and ctDNA

- Accelerated Approval
  - is based on an effect on a surrogate endpoint or an intermediate clinical endpoint that is reasonably likely to predict clinical benefit
- **Meta-analytical methods - Patient-level data**
  - Individual Level Surrogacy
    - Correlation between candidate surrogate and true clinical endpoint on an individual level
  - Trial Level Surrogacy
    - Correlation between effect of treatment on the candidate surrogate and the effect of treatment on the true clinical endpoint
  - Surrogate Threshold Effect
    - Minimum treatment effect on the surrogate necessary to predict an effect on the true clinical endpoint

N. Gormley: Presentation at CDDF Workshop, 2022

# FDA: Potential uses of MRD and cDNA

- **Meta-analysis Considerations**
  - Inclusion of more trials increases the statistical rigor of the analysis and may allow for more interrogation of the data to address uncertainties.
  - Inclusion of trials with a range of treatment effects (positive and negative trials) increases the accuracy and precision of trial level surrogacy assessment.
- **Caveats regarding use of surrogate endpoint**
  - Use of surrogate may not be appropriate for subpopulations or future trial populations if there are significant differences between the population in the meta-analysis and the trial population.
  - Use of surrogate may not be appropriate for therapeutic modalities that have substantially different MOA (e.g., cytotoxic vs. immunotherapies).

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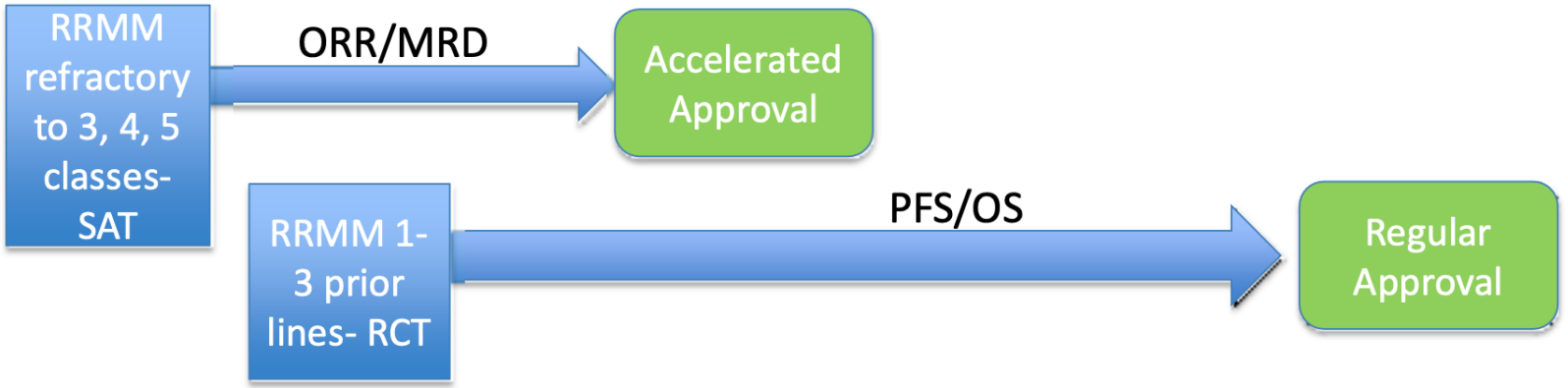
# Drug Development Approach

- Multiple Trial Model




- Single Trial Model


N. Gormley: Presentation at CDDF Workshop, 2022

# Conclusions

- ctDNA and MRD are prognostic biomarkers, but not validated surrogate endpoints
- Existing uncertainty and remaining questions regarding these endpoints for regulatory purposes
- MRD assessments in clinical trials should be discussed with the Agency
- FDA is committed to working with the community on the development of MRD and ctDNA.

**FDA Guidances for Industry**
**MRD (January 2020)**
**ctDNA (May 2022)**

N. Gormley: Presentation at CDDF Workshop, 2022

# Key Milestones to Date

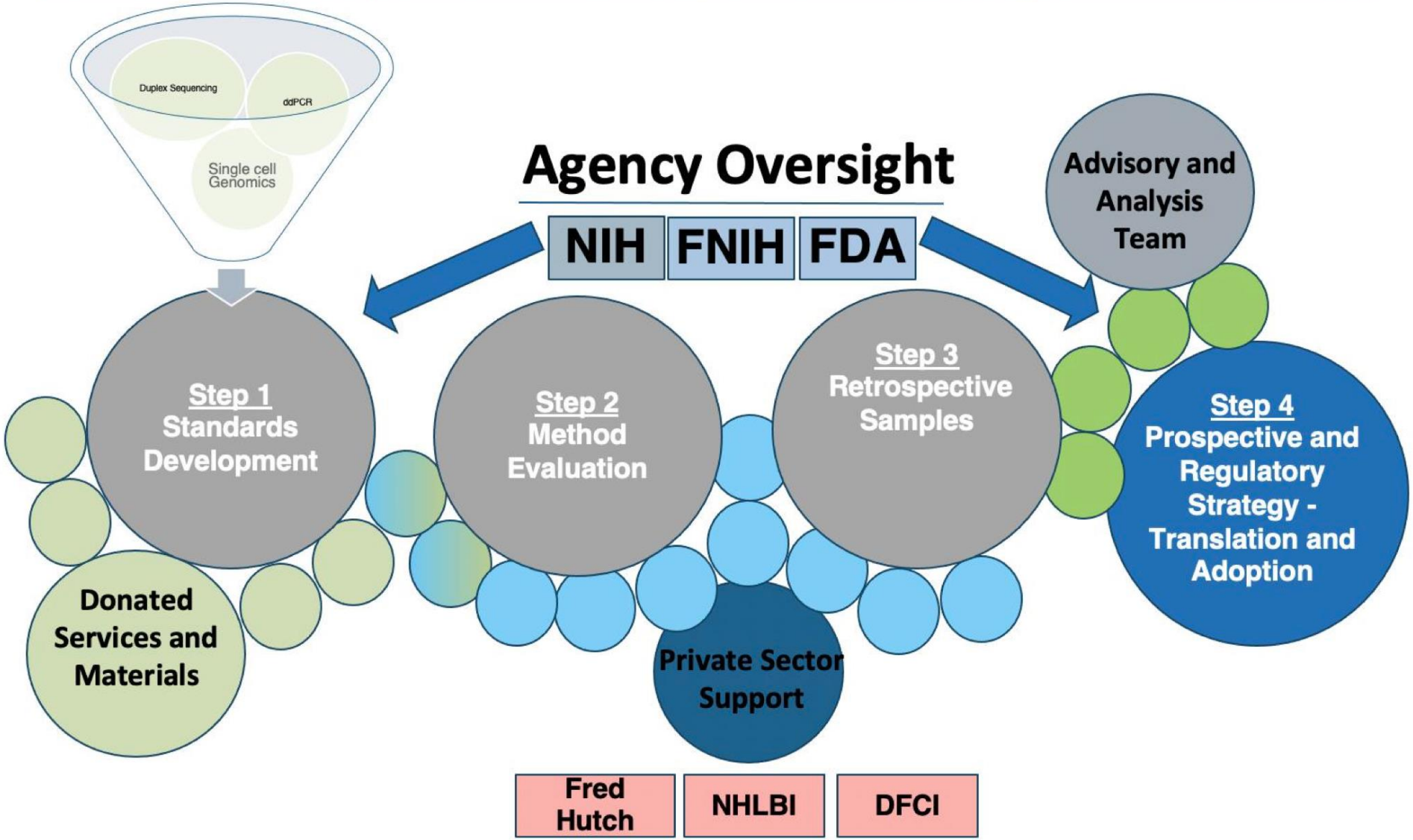
MPAACT
MRD Partnership and Alliance in AML Clinical Treatments

**MPAACT Consortium to Establish Measurable Residual Disease as a Surrogate Endpoint in Acute Myeloid Leukemia Drug Development**

| 2016 | 2018 | 2019 | 2020-2021 | 2022 (so far) |
|---|---|---|---|---|
| Duke-Margolis/FDA Public Meeting on MRD | Alliance formed with two goals:<br>- Establish MRD as surrogate endpoint for AML<br>- Harmonise MRD testing | Engagement with Health Authorities to design surrogacy analysis and discuss assay methodology | Substantial progress made towards MPAACT goals | Inclusion of three new companies to the MPAACT Alliance |
| Janssen invited to present plans to evaluate MRD as an endpoint in AML; other companies invited to create a collaborative program | janssen Oncology, Genentech, NOVARTIS, Bristol Myers Squibb | Initial discussions with the Agencies provided important feedback to help MPAACT design a meta-analysis for surrogacy | - Validation of a flow MRD assay<br>- Advisory boards held to discuss pediatric and market access considerations<br>- Third-party statistical Vendor, Mayo Clinic, selected to start data collection | KRONOS BIO, abbvie, AMGEN<br>Systematic literature review completed to identify clinical trials to include in the meta-analysis |

# MRD in AML Project Team

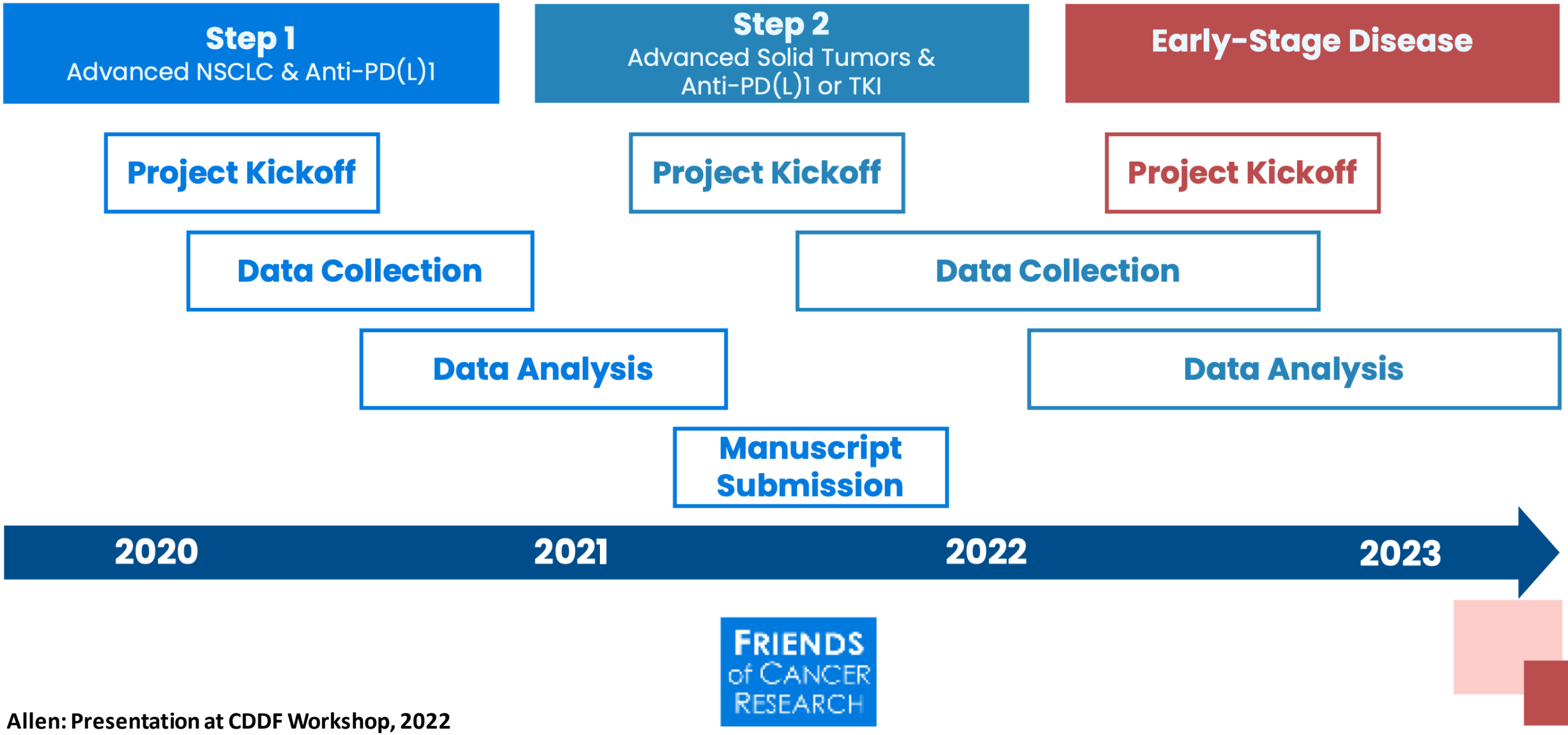
Year 1 Milestone > Year 2 Milestone > Year 3 Milestone > Year 4 Completion




BIOMARKERS CONSORTIUM FNIH

C. Hourigan: Presentation at CDDF Workshop, 2022

# ctMoniTR Project Timeline

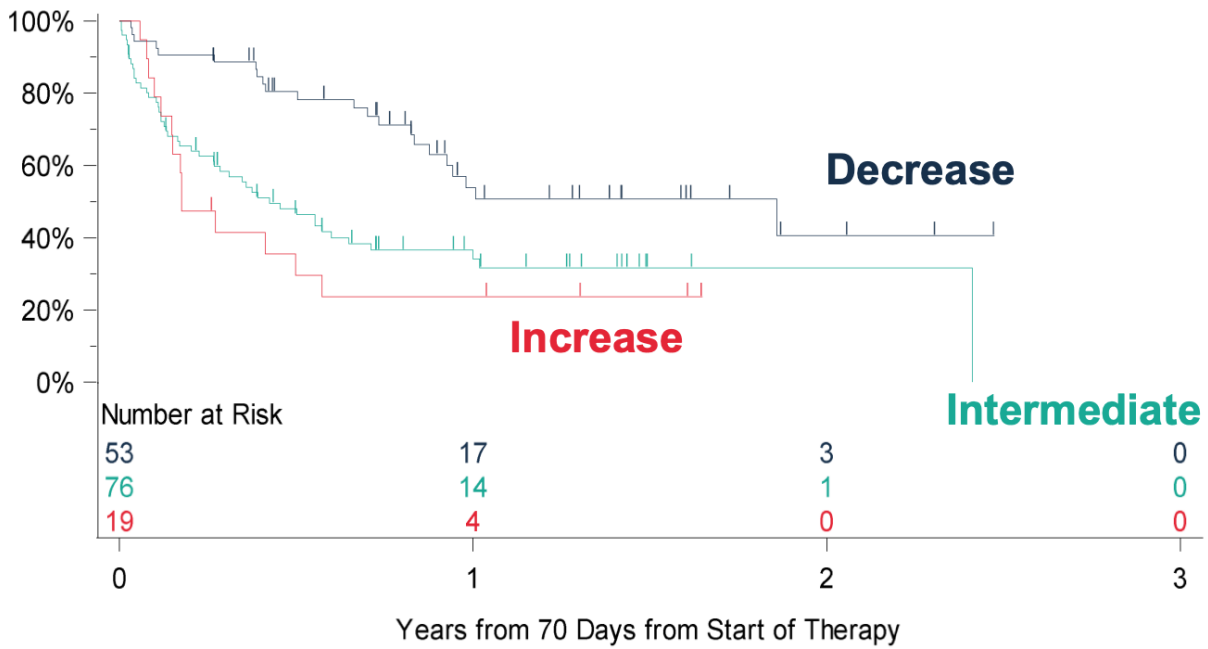



FRIENDS of CANCER RESEARCH

J. Allen: Presentation at CDDF Workshop, 2022

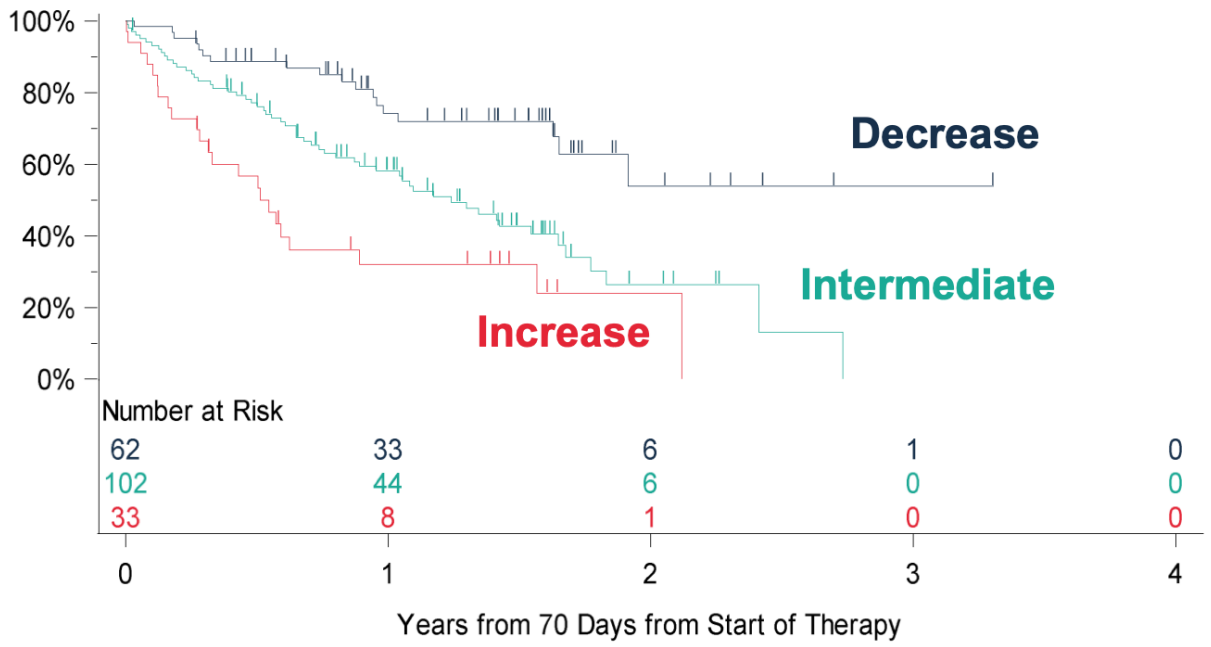
# Robust Association Observed Between Strong Decreases in ctDNA and Patient Survival

**Progression-Free Survival by Max VAF***




| Log-rank Pairwise p-value | Decrease | Intermediate | Increase |
|---|---|---|---|
| Decrease | - | | |
| Intermediate | **0.001** | - | |
| Increase | **<0.001** | 0.426 | - |

**Overall Survival by Max VAF**




| Log-rank Pairwise p-value | Decrease | Intermediate | Increase |
|---|---|---|---|
| Decrease | - | | |
| Intermediate | **<0.001** | - | |
| Increase | **<0.001** | **0.014** | - |

## Survival Outcomes (3-Level)

Kaplan-Meier Curves

**J. Allen: Presentation at CDDF Workshop, 2022**

*Note: patients with progression within 70 days were excluded from the PFS plots.

# Important Perspectives

- **Patient Perspective (Hans Scheuer, MPE)**
  - Understand the impact of MRD results in research on patients
  - Preference of peripheral blood versus bone marrow samples
  - Consider the influence of accelerated approval on patient expectations
  - Consider patient input sufficiently early in the development path
- **Health Technology Assessment (Carole Longson, UK)**
  - Limited evidence is presented supporting the validity of the relationship between the biomarker surrogate endpoint and endpoints/outcomes of most interest to HTA decision-making: HRQoL and survival
  - Whilst expression of the biomarker may be associated with efficacy/survival, it is not usually related to HRQL
  - This creates high levels of uncertainty around the real incremental impact of innovative cancer drugs

# Conclusions and Next Steps

- **Methods for MRD and ctDNA:**
  - Further standardisation and quality control
- **Validation for regulatory use:**
  - Endpoint: Demonstration of patient- and trial-level surrogacy
  - Patient selection: Diagnostic or prognostic biomarker (enrichment/stratification)
  - Treatment modification: Escalation or de-escalation of therapy
- **Important next steps:**
  - Continued collaboration towards standardisation and validation (MPAACT, FoCR, NIH)
  - Early inclusion of patient input
  - Models that allow HTA assessment after approval based on surrogate endpoint
  - Improve response assessment and definition by including MRD and ctDNA