Measurable Residual Disease (MRD) in Chronic Lymphocytic Leukaemia (CLL)

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A Giant Leap Forward, Sideways or Backward?

Survival is always the optimal endpoint of cancer trials. However, in CLL this takes too long so we need a surrogate(s) endpoint

Proposed Surrogate Endpoints in CLL

Complete response rate

Overall response rate

Progression-free survival (PFS)

Time-to-progression (TTP)

Time-to-next therapy

Relapse-free survival (RFS)

Cumulative incidence of relapse (CIR)

Quality-of-life (QoL)

Studies with Better PFS but Similar or Worse Survival

FCR

BTKis

Venetoclax

Umbralisib/ublituximab

Leukemia

Early treatment with FCR versus watch and wait in patients with stage Binet A high-risk chronic lymphocytic leukemia (CLL): a randomized phase 3 trial

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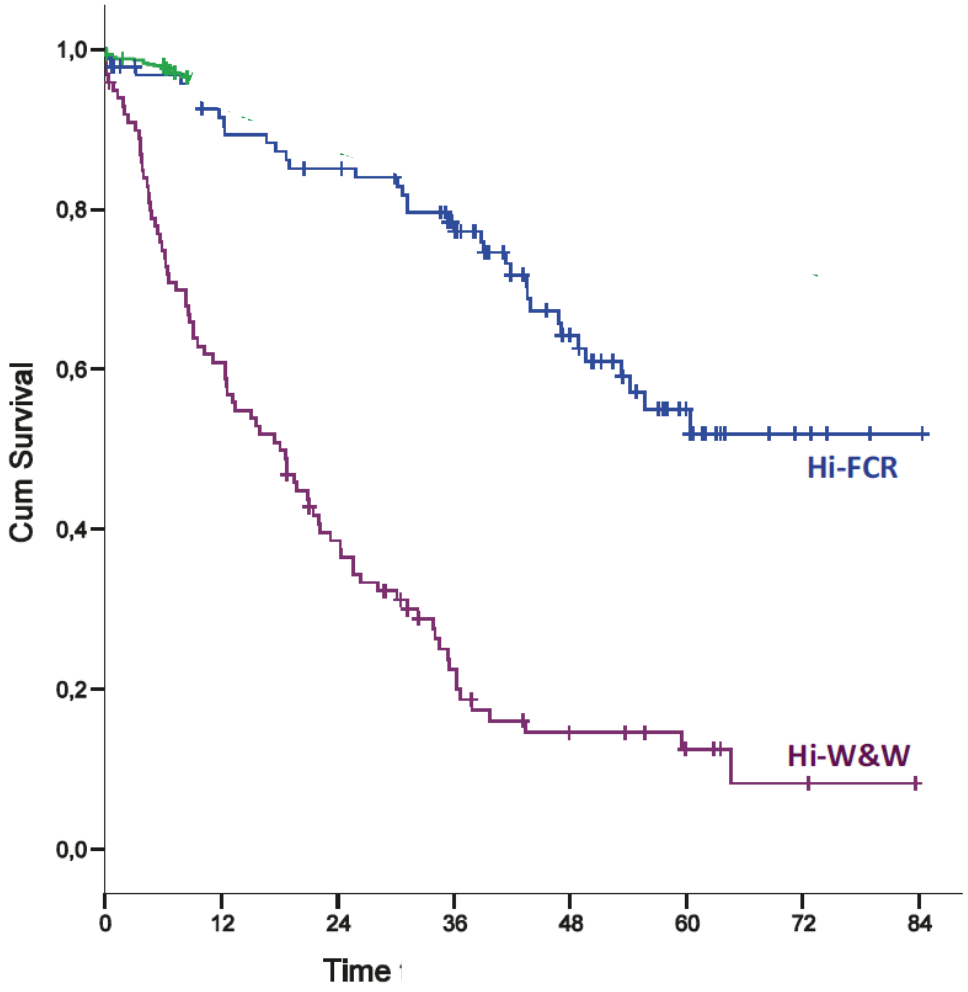
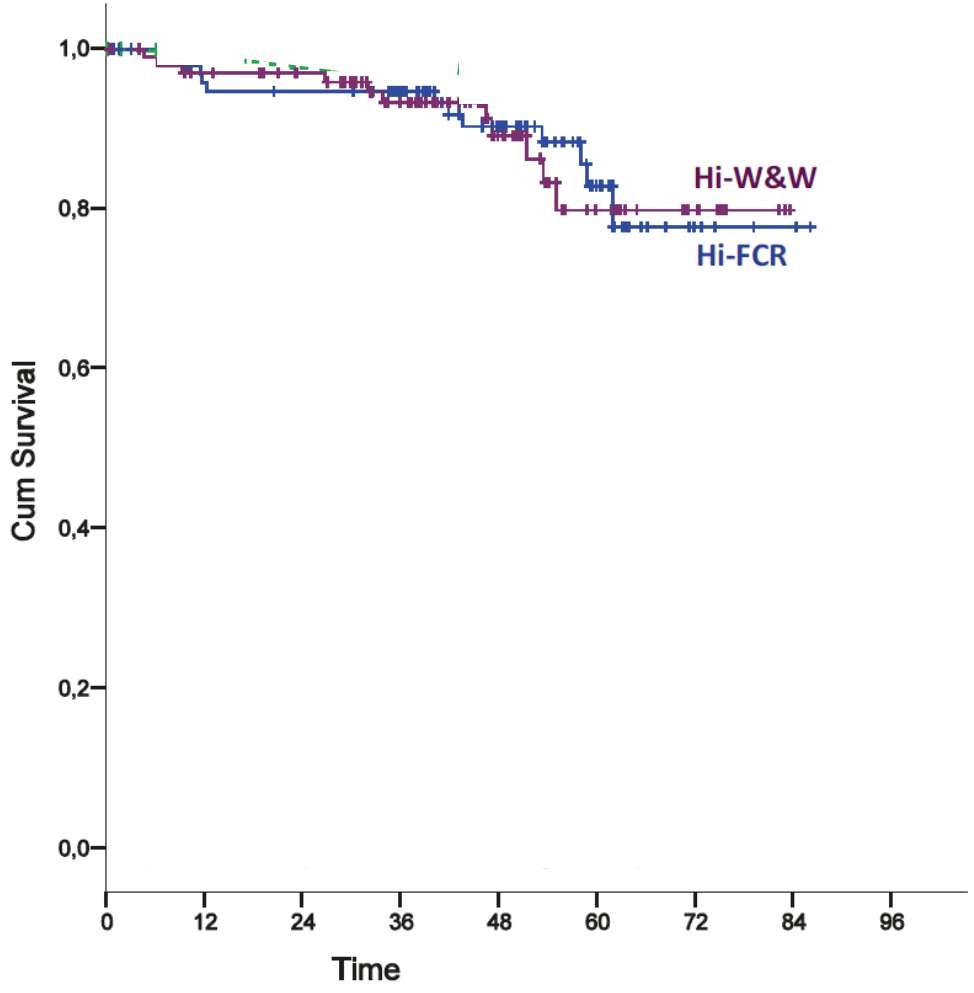
PFS



Survival



The Problems with PFS

Relatively brief follow-up interval

Informative censoring

Uncontrolled subsequent off-study therapy(ies)

Unrecorded subsequent off-study therapy(ies)

Loss to follow-up

Proposed Surrogate Endpoints in CLL

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Time-to-next therapy

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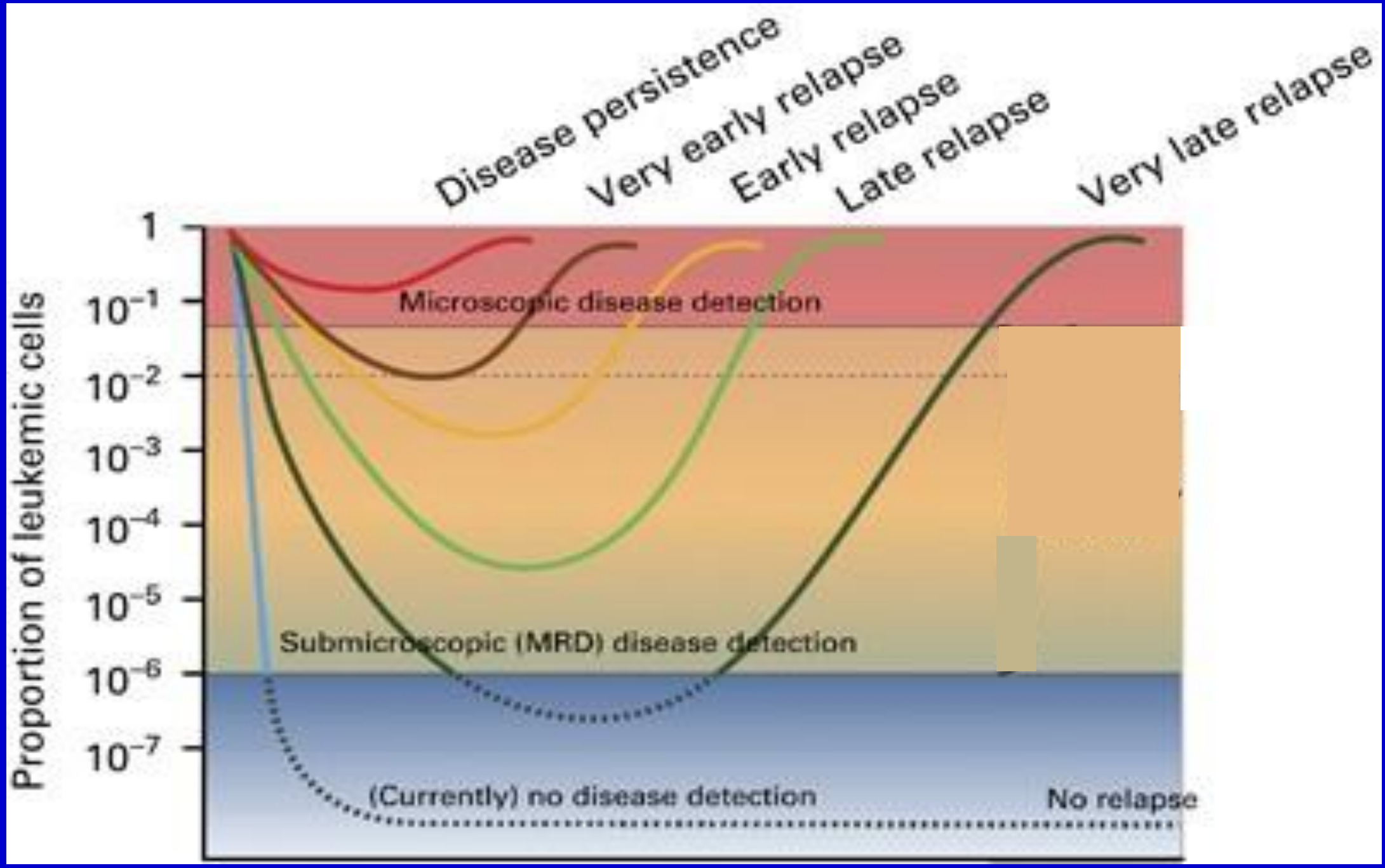
Cumulative incidence of relapse (CIR)

Quality-of-life (QoL)

Measurable residual disease (MRD)


Disease persistence
Very early relapse
Early relapse
Late relapse
Very late relapse
Proportion of leukemic cells
1
10^{-1}
10^{-2}
10^{-3}
10^{-4}
10^{-5}
10^{-6}
10^{-7}
Microscopic disease detection
Submicroscopic (MRD) disease detection
(Currently) no disease detection
No relapse


You're Fighting a Losing Battle!!!

Is it better to be MRD- or MRD+?

Is it better to be young, beautiful and rich or old, ugly and poor?

Can MRD-testing solve the survival surrogate problem?

Possibly, but there are limitations to using MRD-testing

Problems

Accuracy

Precision

Sensitivity

Specificity

Reproducibility

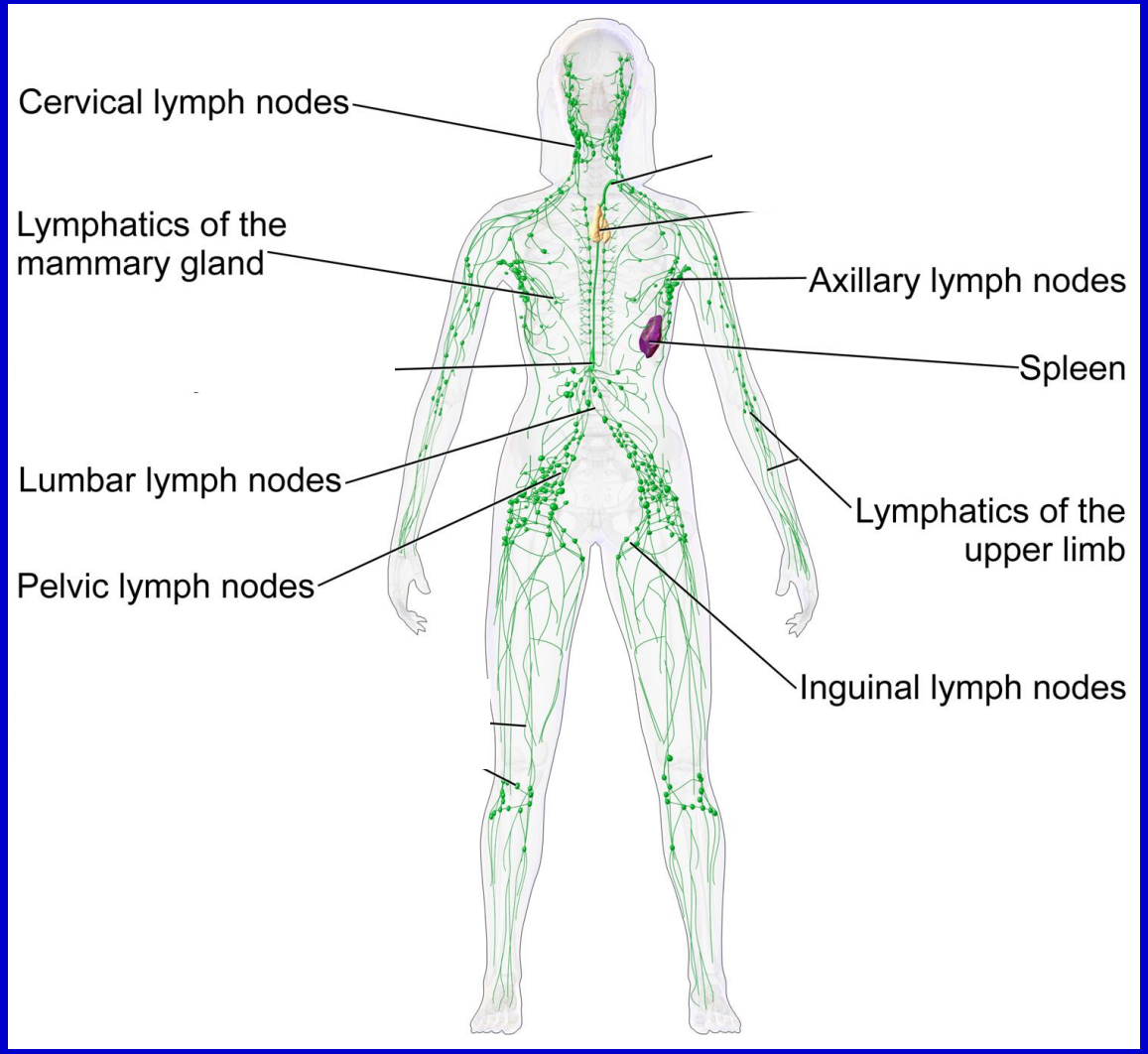
Replicability

Numbers of tests

inter-observer variability

Intra- and inter-laboratory variability


THIS IS WHERE YOU LOST YOUR WALLET?
NO, I LOST IT IN THE PARK. BUT THIS IS WHERE THE LIGHT IS.



CLL cells proliferate in the lymph nodes and spleen,
NOT the blood or bone marrow

Issues with Using MRD to Define Response

iwCLL response criteria Blood, bone marrow, lymph nodes, spleen

MRD-testing Blood, bone marrow

Someone can be MRD-negative with enlarged lymph node and/or splenomegaly

Discordance between iwCLL and MRD response criteria

Limitations of MRD-Testing

Only samples blood and/or bone marrow

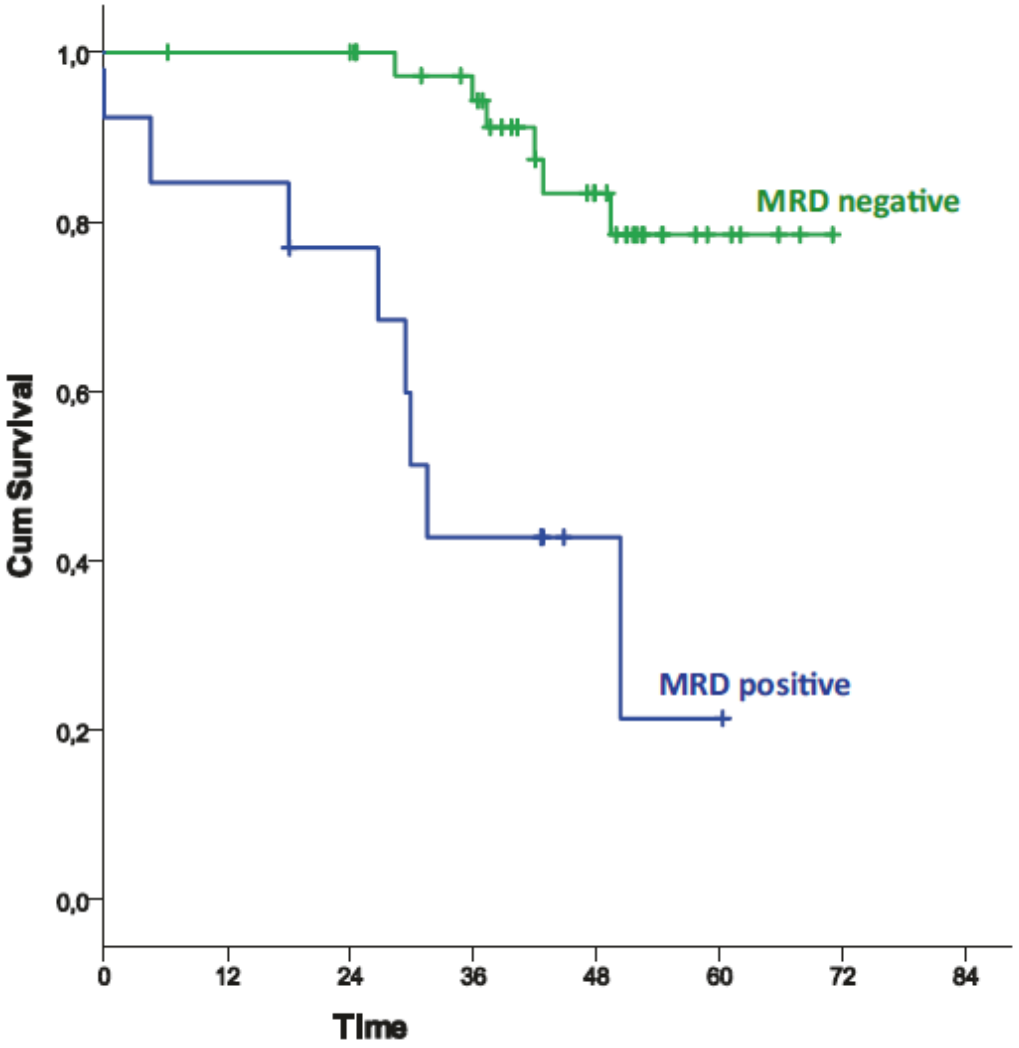
Often a single determination; no dynamics

Blood and bone marrow may have discordant results

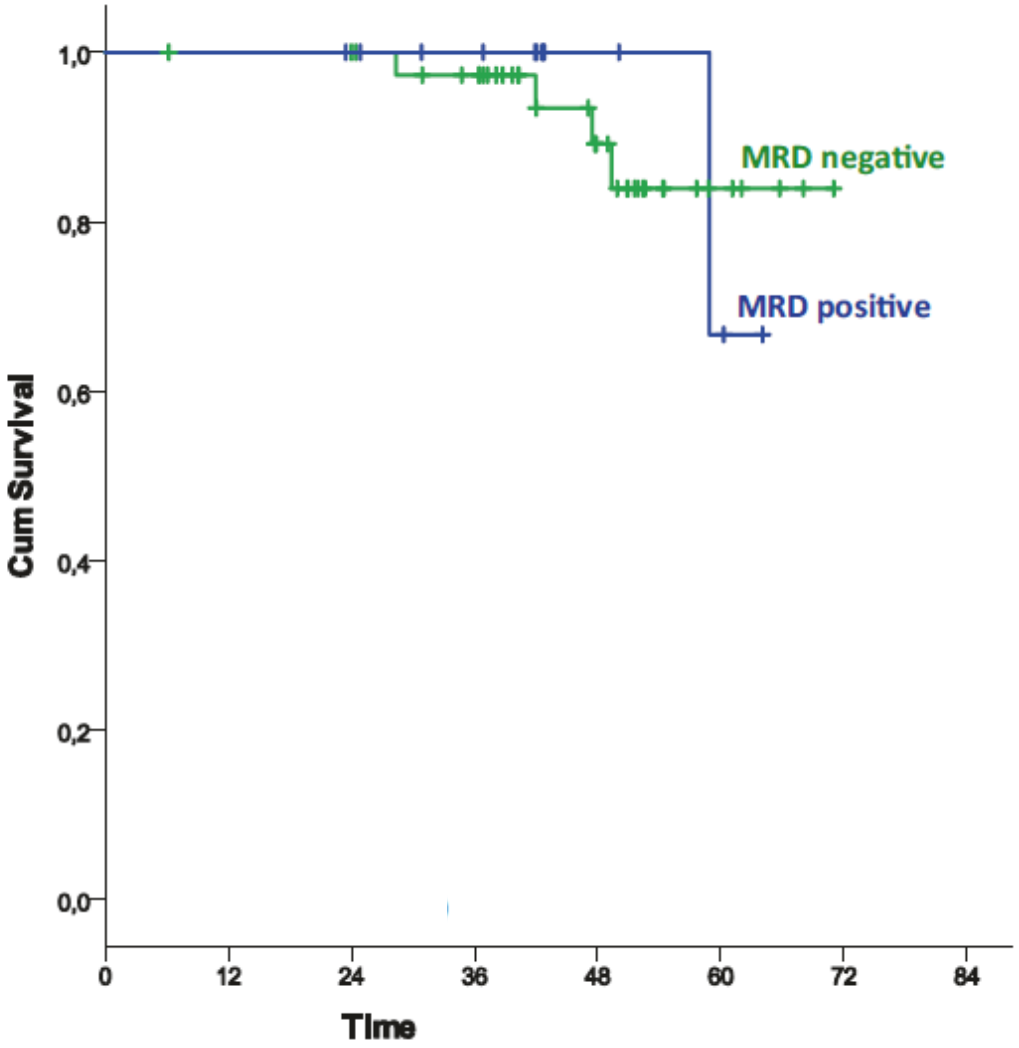
Site of CLL proliferation is lymph node, not blood or bone marrow

Not done with samples containing circulating tumor DNA (ctDNA) which might indicate residual leukaemia cells in lymph nodes and spleen where CLL proliferate

PFS



Survival



Biological Features of Residual Leukaemia Cells

Rate of loss of uMRD depends on the type of therapy

In persons with uMRD the rate of proliferation of residual leukaemia cells may be more important than the depth of MRD < 10E-4

Not every residual leukaemia cell has the same biological potential or probability to cause leukaemia recurrence

Different therapies likely have different efficacies against CLL sub-clones able to cause leukaemia recurrence

Conclusions

There is no reliable surrogate endpoint for survival in CLL including PFS or MRD-test results

MRD-testing can distinguish cohorts of subjects with different probabilities of PFS but with substantial false-positives and negatives

Prediction accuracy of MRD-testing depends on the type of therapy

Below a certain level of MRD detection site and biological features of the residual leukaemia cells may be more important than numbers

CLL MRD-testing CLL is accepted for approval by EMA but not US FDA

MRD-testing should not be used for clinical decision-making

Merci

Correlates Between MRD-Testing and PFS

Subjects < 10E-4 have better PFS compared with > 10E-4

Subjects < 10E-2 have better PFS compared with > 10E-2

Subjects < 10E-4 have better survival compared with > 10E-2

But subjects < 10E-4 have similar survival compared with > 10E-4 but < 10E-2