Minimal Residual Disease in CLL

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Acknowledgments

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- German CLL Study Group

Outline

- Background
  - Chronic Lymphocytic Leukemia (CLL)
  - Why do we need surrogate endpoints in CLL?
  - Concept and Definition of Minimal Residual Disease (MRD)
- Case studies
  - CLL8, CLL10, CLL11
- Results
  - Prentice, meta-regression modelling, meta-analytic approach
- Summary and Conclusions

Chronic Lymphocytic Leukemia

- CLL is one of the most common types of adult leukemia
  - Median age at diagnosis is around 70 years
- Slow growing, starts in the bone marrow and spreads into the bloodstream
  - Frequently diagnosed from routine blood tests when patients are asymptomatic
- Symptoms can include tiredness, swelling of the lymph nodes, fever, infection and weight loss
- Heterogeneous disease
  - For many it is indolent and may not require treatment for a number of years, others may progress and die within 1-2 years
  - Prognosis depends on disease stage and the presence of specific biomarkers at diagnosis
  - For newly diagnosed patients requiring treatment, therapy is dependent on level of co-morbidities

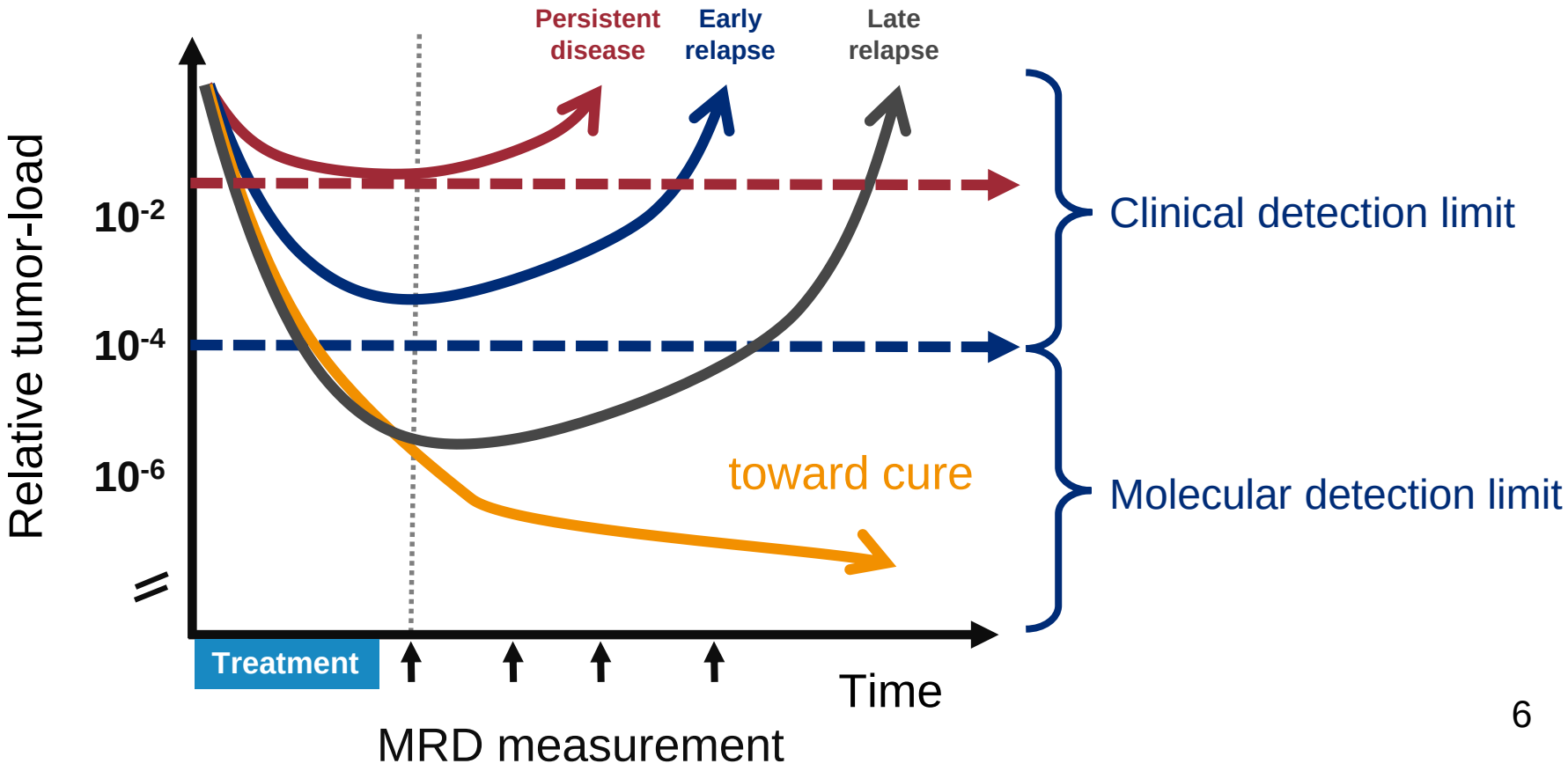
Why do we need surrogate endpoints?

- Progression-free survival (PFS) is the standard primary endpoint used in clinical trials of CLL
  - Median PFS approaching 5 years in first line treatment[1]
  - Long follow-up required to observe meaningful PFS results
  - Potential clinical trial durations of >8 years
- Surrogate endpoints are required to:
  - Provide earlier information of treatment effects and earlier access to novel treatment options
  - Reduce number of patients exposed to unproven experimental agents
  - Retain the practicability of conducting clinical studies (duration, costs)

1. Fischer K, et al. *Blood*. 2015; 06-651125 [epub ahead of print].

Concept of Minimal Residual Disease (MRD)

- MRD is a quantitative measure of remaining tumor burden at very high sensitivity
  - The lower the level of residual disease after therapy, the longer the time to progression



Definition of MRD

- MRD negativity defined as < 1 CLL cell per 10,000 leukocytes (10^{-4})[1]
  - Measured in peripheral blood and/or bone marrow samples
- **MRD response rate**: the proportion of patients in whom MRD-negative status is observed
  - Measured at the end of treatment in line with iwCLL[1] recommendation
- For the evaluation of surrogacy, patients with a valid MRD status at the end of treatment, and those with early disease progression or death are included in analysis (MRD evaluable population)
- Bone marrow measurements have greatest sensitivity, but samples are not routinely available for all patients due to the invasive procedure
  - Measures in **peripheral blood** used for surrogacy evaluation

1. International workshop on Chronic Lymphocytic Leukemia, Hallek M, et al. *Blood*. 2008;111:5446–5456.

Case Studies

- CLL8[1]
  - Two-arm, randomised phase III study of rituximab in combination with fludarabine and cyclophosphamide (FCR) versus FC chemotherapy alone in patients with previously untreated CLL
  - Median follow-up 48 months
- CLL10[2]
  - Two-arm, randomised, non-inferiority phase III study of FCR versus bendamustine combined with rituximab (BR) in patients with previously untreated CLL
  - Median follow-up 30 months
- CLL11[3]
  - Three-arm, randomised, phase III study of obinutuzumab combined with Clb (GClb) versus rituximab combined with Clb (RClb) versus Clb alone in patients with previously untreated CLL with coexisting medical conditions
  - Median follow-up 39 months

1. Böttcher S, et al. *J Clin Oncol.* 2012;30; 980–988.
2. Eichhorst B, et al. Blood. 2014;124:Abstract 19.
3. Goede V, et al. *N Engl J Med*. 2014;370:1101–1110.

Available Data from Case Studies

	CLL8		CLL10		CLL11	
	FC (N=184)	FCR (N=209)	BR (N=158)	FCR[a] (N=178)	R-Clb (N=245)	G-Clb (N=229)
PFS events, n (%)	119 (65)	107 (51)	54 (34)	43 (24)	220 (90)	163 (71)
PFS Hazard Ratio (95% Confidence Interval)	0.63 (0.48–0.82)		0.66 (0.44-0.98)		0.44 (0.36–0.54)	
MRD negativity, n (%)	57 (31)	143 (68)	99 (63)	128 (72)	8 (3)	82 (36)
MRD absolute difference	37%		9%		33%	
MRD relative risk[b]	2.20		1.15		10.38	

[a] For purpose of the surrogacy assessment, FCR was considered experimental arm
[b] Relative risk = MRD negative rate on experimental arm / MRD negative rate on control arm

For all studies, PFS results are shown for the MRD evaluable population
Data as of July 2010 (CLL8), May 2015 (CLL11), interim analysis (CLL10)

Statistical Methods used for investigating surrogacy of MRD

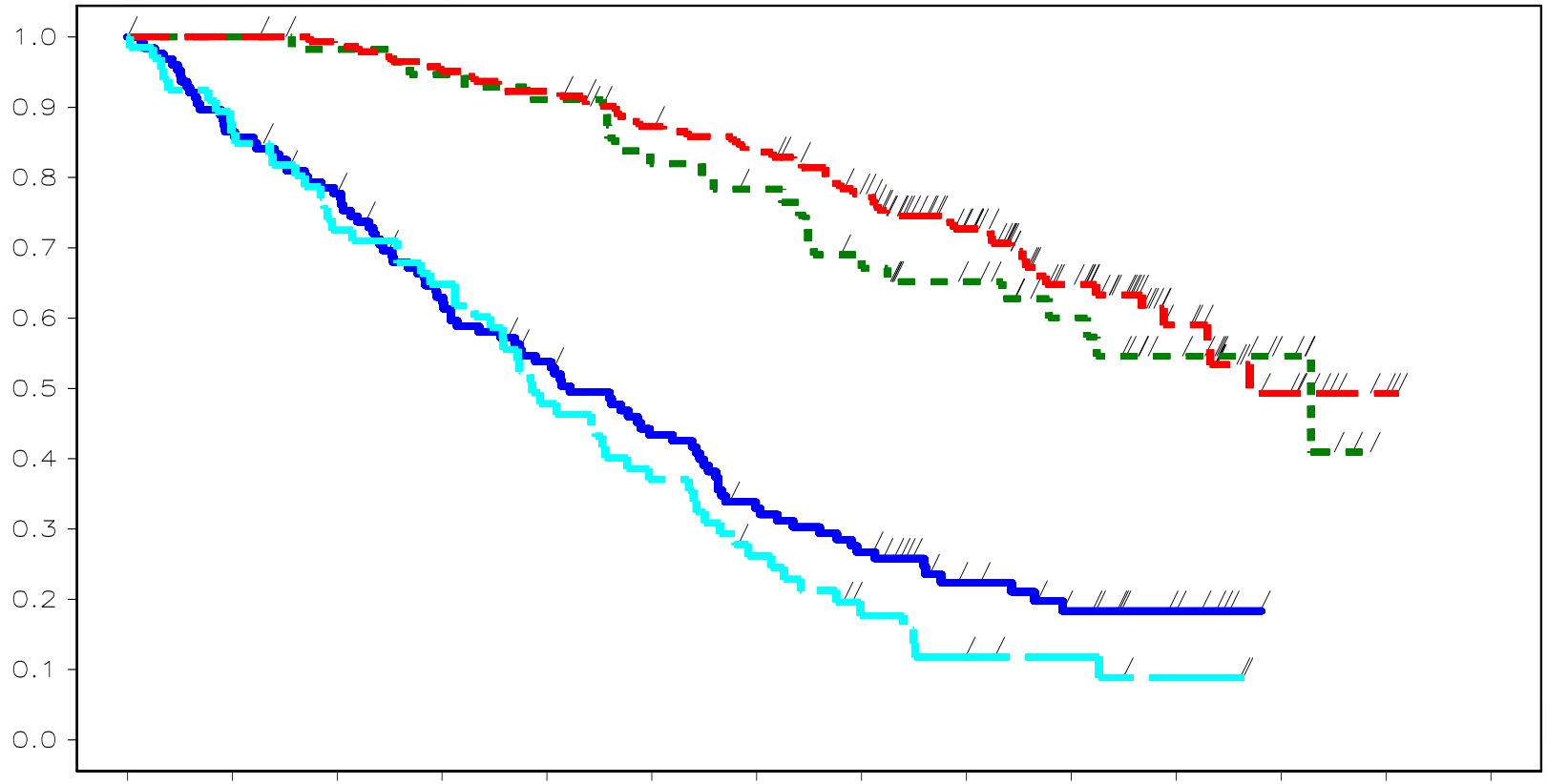
- For individual studies, the Prentice principles[1] were considered:
  1. Treatment has significant impact on surrogate
  2. Treatment has significant impact on true endpoint
  3. Surrogate has significant impact on true endpoint
  4. Full effect of treatment upon true endpoint is captured by surrogate

- Weighted linear meta-regression analysis including all available data

- Meta-analytic approach using a bivariate copula function[2]
  - Constant odds ratio of surviving beyond time *t* for MRD negative versus MRD positive patients

1. Prentice RL. *Stat Med*. 1989; 8(4): 431-40
2. Burzykowski, Molenberghs, Buyse, *J. R. Statist. Soc. A* (2004) 167,103–12

Kaplan-Meier Analysis of PFS by MRD Status CLL8



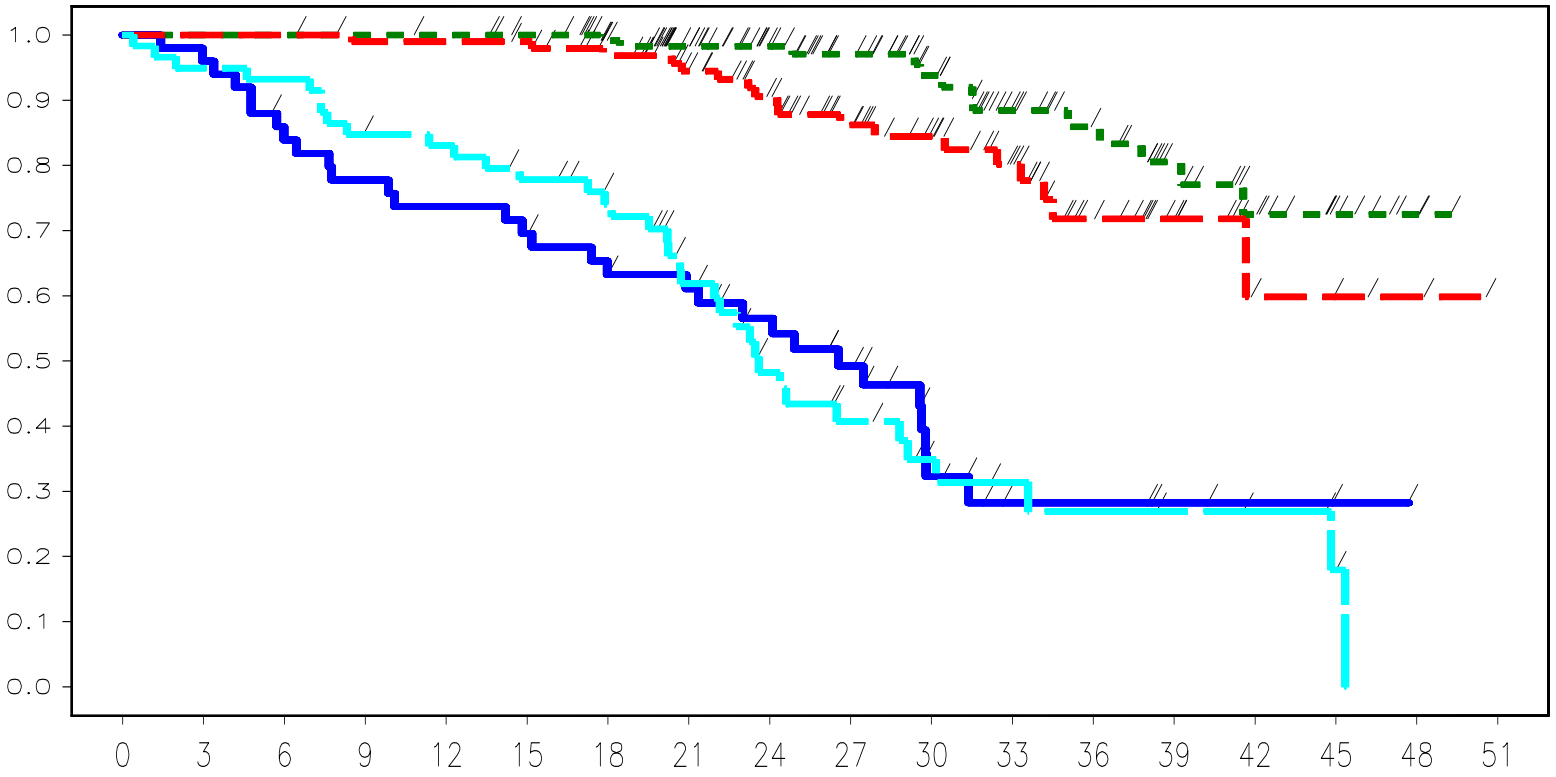
No. left	0	6	12	18	24	30	36	42	48	54	60	66	72	78
FC−NEG	57	57	55	53	51	45	42	35	29	22	15	7	0	0
FC−POS	126	109	96	76	63	50	37	30	18	12	5	0	0	0
FCR−NEG	143	143	140	135	131	121	115	102	76	50	24	11	2	0
FCR−POS	66	57	47	42	31	24	16	9	5	4	2	0	0	0

MONTHS

randomized treatment

FC−NEG
FCR−NEG
FC−POS
FCR−POS

Kaplan-Meier Analysis of PFS by MRD Status CLL10



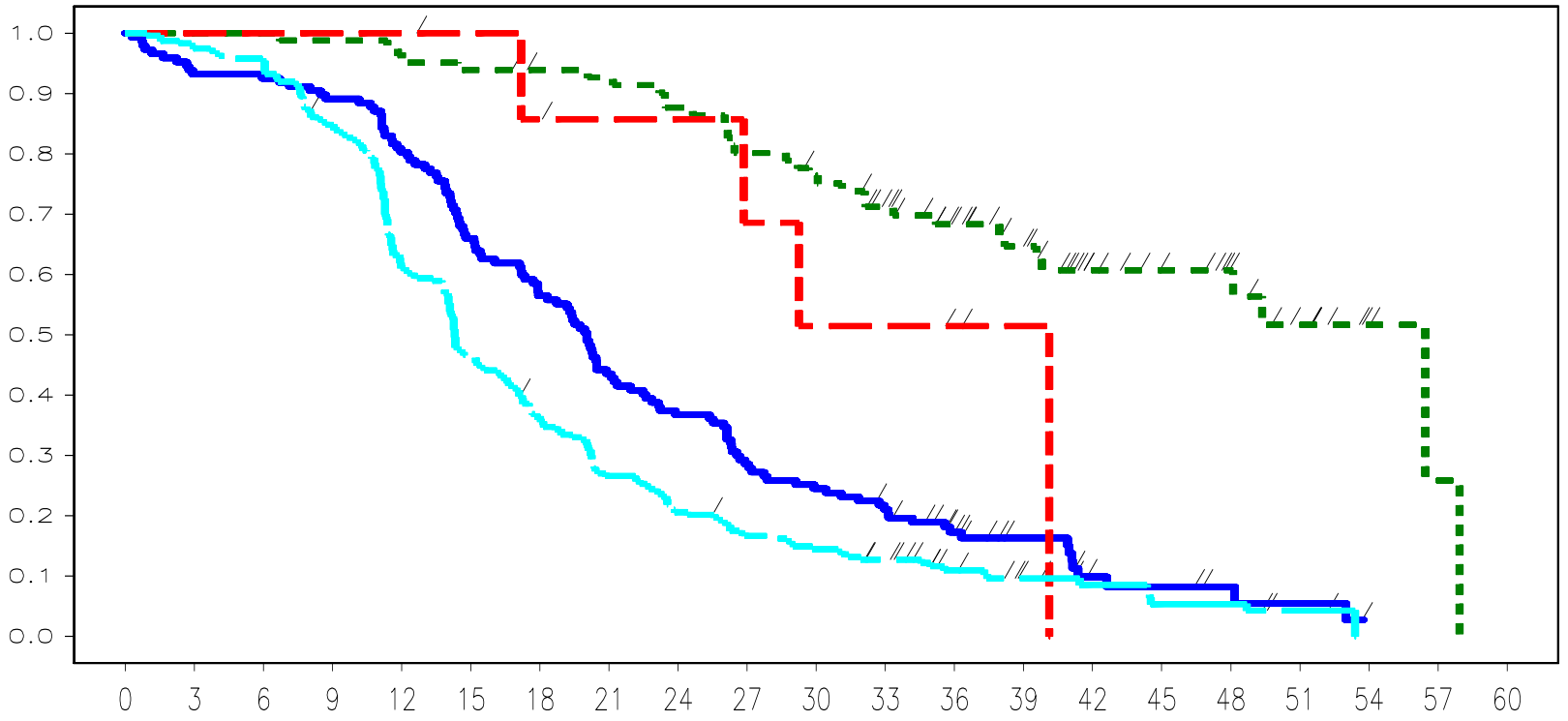
n at risk

FCR–NEG	128	128	128	128	127	124	113	99	83	71	56	41	33	23	16	8	3	0
FCR–POS	50	48	41	38	36	34	30	28	24	19	9	5	5	3	2	1	0	0
BR–NEG	99	99	99	96	96	95	88	77	67	54	44	34	20	11	4	3	2	0
BR–POS	59	56	55	49	48	44	39	29	20	15	10	7	6	5	4	2	0	0

Treatment by MRD status

FCR–NEG
BR–NEG
FCR–POS
BR–POS

Kaplan-Meier Analysis of PFS by MRD Status CLL11



n at risk																				
GClb–NEG	82	82	82	81	79	77	75	74	70	64	60	52	42	34	23	19	14	9	3	1	0
GClb–POS	147	137	136	131	118	97	83	64	54	42	36	30	20	13	6	5	3	2	0	0	0
RClb–NEG	8	8	8	8	8	7	6	5	5	4	3	3	2	1	0	0	0	0	0	0	0
RClb–POS	237	231	226	200	144	110	85	62	48	38	33	27	17	11	8	5	5	2	0	0	0

Treatment by MRD status

GClb–NEG
RClb–NEG
GClb–POS
RClb–POS

Prentice Criteria

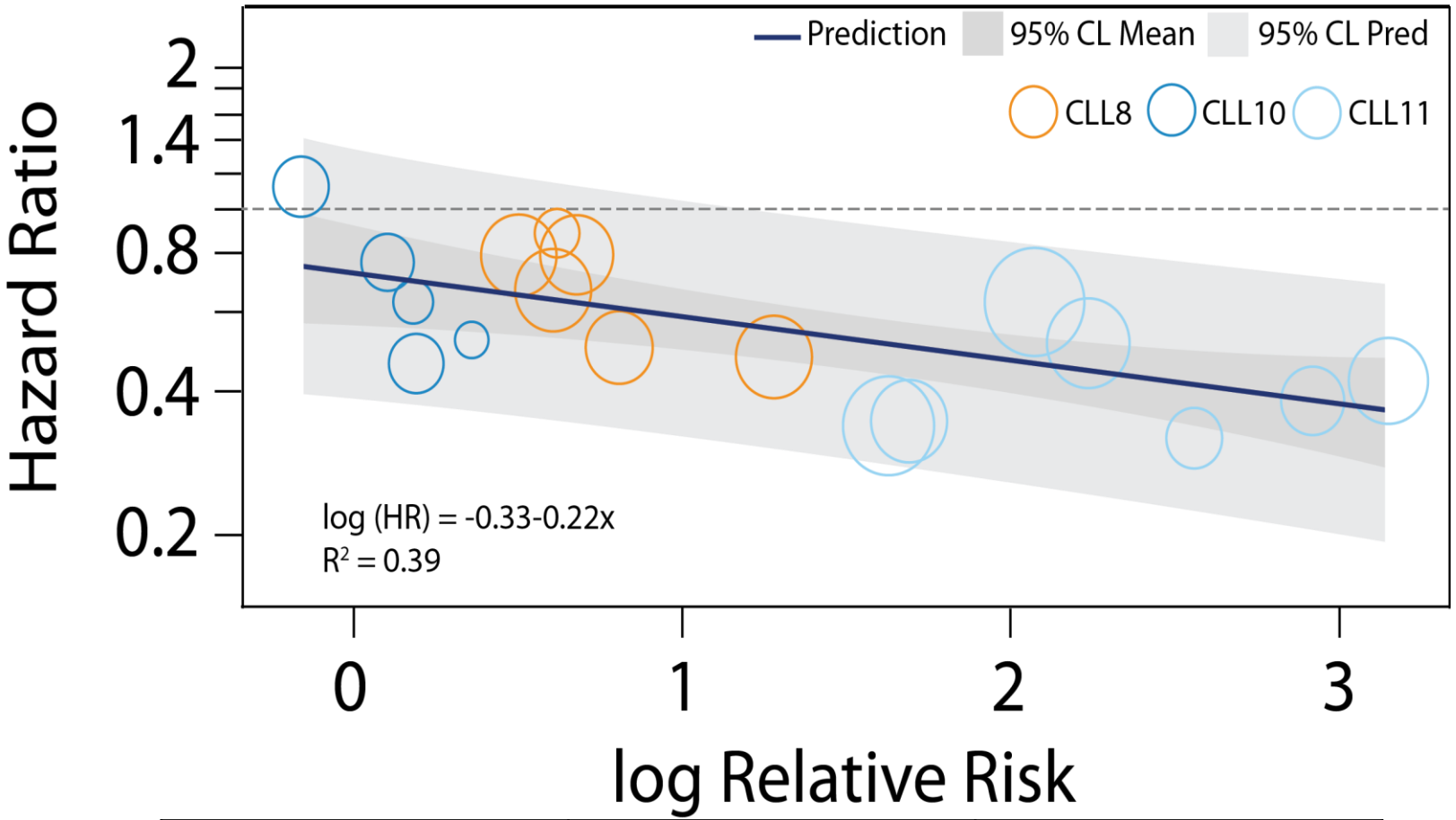
	CLL8		CLL10		CLL11	
	FC (N=184)	FCR (N=209)	BR (N=158)	FCR (N=178)	R-Clb (N=245)	G-Clb (N=229)
PFS Hazard Ratio for treatment (95% CI) P-value[a]	0.63 (0.48–0.82) 0.0005		0.66 (0.44-0.98) 0.0383		0.44 (0.36–0.54) <0.0001	
Proportion of MRD responders, n (%)	57 (31)	143 (68)	99 (63)	128 (72)	8 (3)	82 (36)
P-value[b]	0.		0.0706		<0.0001	
PFS Hazard Ratio for MRD status (- v +) (95% CI) P-value[c]	0.22 (0.17;0.30) <0.0001		0.14 (0.09;0.22) <0.0001		0.19 (0.13;0.27) <0.0001	
MRD-adjusted PFS HR for treatment (95% CI) P-value[d]	1.12 (0.84;1.48) **0.4457**		0.79 (0.52;1.18) **0.2402**		0.68 (0.55;0.85) **0.0006**	

[a]Log-rank test, [b]Chi-squared test, [c]Cox regression (univariate), [d]Cox regression (multivariate)

Meta-Regression Model

- Aim is to use observed treatment difference in MRD response rates to predict future unobserved treatment difference in PFS
- Available data used to construct a weighted meta-regression model to predict the (log) hazard ratio using the (log) relative risk
- Since data from only three studies were available, analysis was conducted using subgroups of each study:
  - CLL8: Geographical region within one country (6 groups)
  - CLL10: By subject number since no geographical data available (5 groups)
  - CLL11: By country and region (7 groups)
  - Subgroups weighted by the inverse of the square of the standard error of the logHR of PFS

Meta-Regression Model



Parameter	Estimate [95% CI]	p value
Intercept	-0.33 [-0.58;-0.08]	0.012
Slope	-0.22 [-0.36;-0.07]	0.005

Circle size reflects weighting of each subgroup to overall model; least variability in PFS HR have largest circle.
Clustering of circles by study reflects overall treatment effect (for both MRD and PFS) in the studies.
CL = Confidence limit

MRD Model Predictions

Ratio of MRD negative rates (relative risk*)	Log of relative risk	Predicted PFS HR	95% CI on individual prediction**
1.2	0.18	0.69	(0.37,1.29)
1.5	0.41	0.66	(0.36,1.22)
1.76	0.56	0.63	(0.35,1.17)
2	0.69	0.62	(0.34,1.13)

*MRD-negative rate in experimental arm / MRD-negative rate in control arm
**Prediction for observation of HR in a single study

- Validation case study
  - REACH[1] (R-FC vs FC in patients with rituximab-refractory CLL)
  - MRD negative rates: 29% FC vs 51% R-FC
  - Relative Risk = 1.76
    - Predicted PFS HR = 0.63
    - Observed PFS HR = 0.59

1. Robak T et al. . *J Clin Oncol.* 2010;28:1756-65.

Meta-Analytic Approach

- Two-stage approach to evaluating surrogacy at individual and trial levels
  - R^2_{indiv}: Association between endpoints after accounting for trial and treatment effects
  - R^2_{trial}: Quality of prediction of treatment effect on the long-term endpoint using the treatment effect on the surrogate endpoint
- Plackett copula model used to assess (binary) MRD response rate as a potential surrogate for PFS[1]
  - Stage One: Fit the copula model and determine parameter estimates, including R^2_{indiv} and treatment effects on both endpoints
  - Stage Two: Use estimates of treatment effects from Stage One to estimate the coefficient of determination as R^2_{trial}

1. Burzykowski, Molenberghs, Buyse, *J. R. Statist. Soc. A* (2004) 167,103–

Meta-Analytic Approach

- Individual-level association estimated as the constant odds ratio of remaining alive and progression-free beyond a given time for MRD responders relative to MRD non-responders
  - Odds ratio > 1 suggests longer PFS for MRD responders versus non-responders
- For the combined data from studies CLL8, CLL10 and CLL11:
  - Odds ratio=11.6 (95% CI: 8.2 – 15.0)
  - R^2_{trial}=0.41 (95% CI: 0.07 – 0.76)
- Sensitivity analysis excluding patients who did not reach end of treatment:
  - Odds ratio=8.8 (95% CI: 6.2 – 11.4)
  - R^2_{trial}=0.32 (95% CI: 0.00 – 0.67)

Summary and Conclusions

- Prentice criteria were met for two of the three studies (CLL8 and CLL10)
  - In CLL11, low numbers of MRD responders limits conclusions
- At the individual (patient) level, a strong prognostic effect of MRD was observed in Cox regression and the two-stage bivariate copula analysis
  - MRD responders have significantly better long-term outcome than non-responders
- Based on the meta-regression model, treatment effect on PFS can be predicted based on treatment effect on MRD response, but confidence intervals around individual predictions remain wide
  - MRD meta-regression model supports use of MRD as a primary endpoint in clinical studies of CLL
- Further data are required to establish a more precise quantitative relationship between treatment effects on MRD and PFS

Doing now what patients need next