XVIII IWCLL

International Workshop on CLL
20-23 SEPTEMBER 2019 EDINBURGH

Critical Assessment and New Development of Prognostic Scoring Systems

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Disclosures

- **Advisory Boards**
  Janssen, Gilead, Roche, Abbvie, Novartis, Celgene, AstraZeneca; Arqule

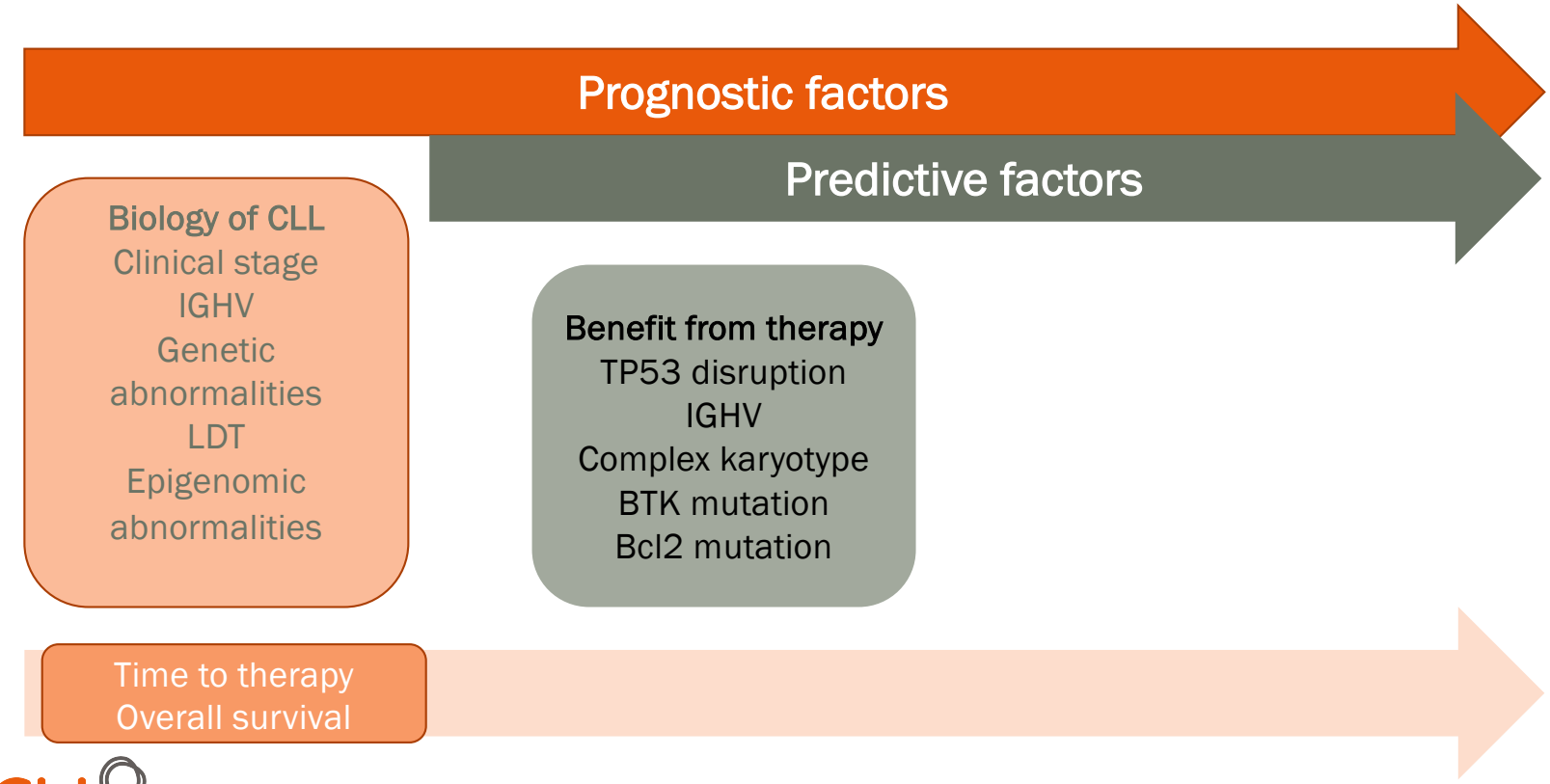
- **Honoraria/Speaker´s Bureau**
  Roche, Novartis, Gilead, Janssen, Abbvie, Celgene

- **Research support**
  Roche, Janssen, Abbvie, Gilead, BeiGene

Overview on selected scoring systems

	Stage Rai/Binet	Clinical parameter	Serum parameter	Genetic parameter	
				IGHV	*TP53*
Wierda et al. 2007	+	+	+		
Haferlach et al. 2010		+		+	+
Rossi et al. 2013					+
Pflug et al. 2014		+	+	+	+
CLL-IPI 2016	+	+	+	+	+
Delgado et al. 2017				+	+

Prognostic and predictive biomarkers



Adapted to Montserrat and Gale; Cancer 2019

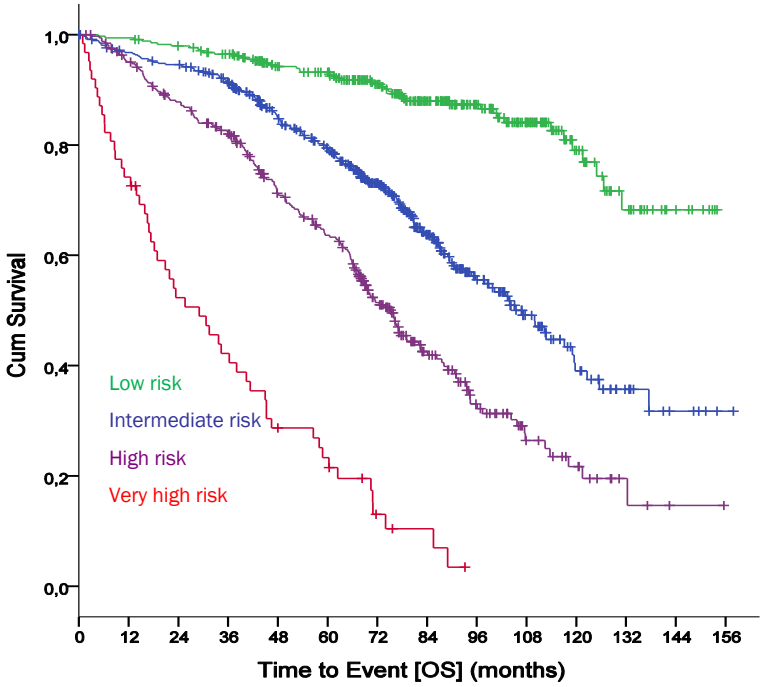
CLL International Prognostic Index - CLLIPI

Variable	Adverse factor	Coeff.	HR	Grading
TP53 (17p)	deleted and/or mutated	1.442	4.2	4
IGHV status	Unmutated	0.941	2.6	2
B2M, mg/L	> 3.5	0.665	2.0	2
Clinical stage	Binet B/C **or** Rai I-IV	0.499	1.6	1
Age	> 65 years	0.555	1.7	1
Prognostic Score				**0 – 10**

Risk group	Score	Patients N (%)	5-year OS, %	HR (95% CI)	*p* value
Low	0 – 1	340 (29)	93.2		
Intermediate	2 – 3	464 (39)	79.4	3.5 (2.5 - 4.8)	< 0.001
High	4 – 6	326 (27)	63.6	1.9 (1.5 - 2.3)	< 0.001
Very High	7 – 10	62 (5)	23.3	3.6 (2.6 - 4.8)	< 0.001

3472 patients from 5 study groups in US and Europe

1254 patients from an US and Scandinavian cohort for validation

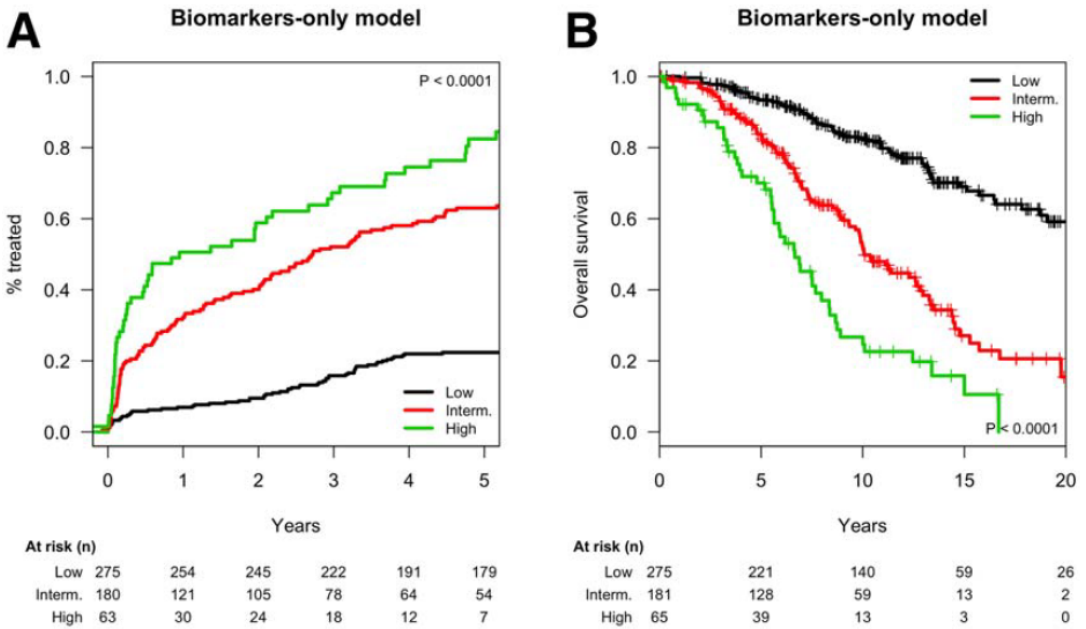


CLL-IPI Working Group , Lancet Oncol 2016

Barcelona Score

524 patients from one center in Barcelona

Risk	IGHV		Del(17p), Del(11q)
LOW	Mutated	*and*	no
INTERM.	Unmut.	*or*	yes
HIGH	Unmut.	*and*	yes



Delgado et al., Am J Hematol 2017

Scores in the era of targeted agents ?

Are the scores established in CIT era also relevant in the era of novel agents ?

Does IGHV status still play a role ?

What is the role of *TP53* mutation ?

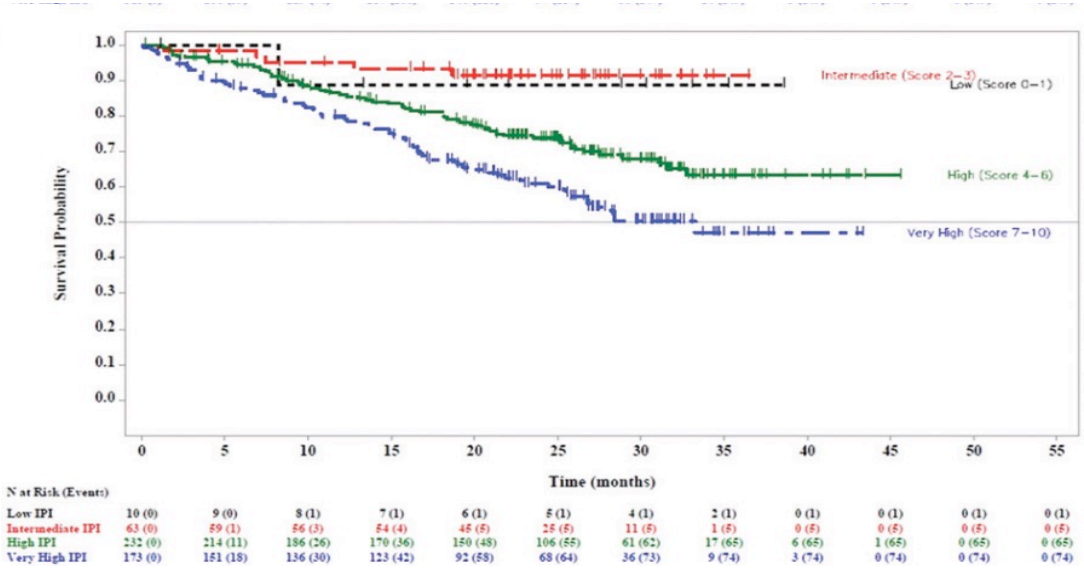
Are observation times long enough ?

Do we need scores for other endpoints ?

How can we add other parameters ?

CLLIPI with Idelalisib + Rituximab

487 patients with R/R CLL receiving idelalisib + R or + BR + Ofa



		Relapsed/Refractory CLL		Idelalisib Subgroup		Comparator Subgroup	
Variable	Adverse factor	Hazard ratio (95% CI)	*p* value	Hazard ratio (95% CI)	*p*value	Hazard ratio (95% CI)	*p* value
Age	>65 years	1.5 (1.18–1.91)	.001	1.89 (1.34–2.68)	.0003	1.14 (0.81–1.6)	.45
Stage	Rai I–VI or Binet B-C	1.29 (0.32–5.2)	.72	234475.12 (0-NR)[a]	.98	0.73 (0.18–3.04)	.67
B2M	>3.5 mg/L	2.64 (1.77–3.94)	<.0001	2.22 (1.29–3.79)	.0038	3.44 (1.87–6.32)	<.0001
IGHV	Unmutated	1.48 (1.06–2.07)	.0212	1.65 (1.02–2.68)	.0414	1.34 (0.84–2.14)	.2169
del17p/TP53M	Deleted or mutated	2.05 (1.63–2.58)	<.0001	1.86 (1.34–2.58)	.0002	2.33 (1.68–3.24)	<.0001

Soumerai et al., Leuk&Lymph 2019

Prognostic score in RR CLL

2475 patients with R/R CLL receiving CIT, Ibrutinib, Idelalisib + R or Venetoclax
Training cohort, internal and external validation cohort

Risk factor	Assigned score
Beta2-M	1
LDH	1
Hb	1
Time from last therapy	1

Risk group	Score
Low	0-1
Intermediate	2-3
High	4

No genetic biomarkers included

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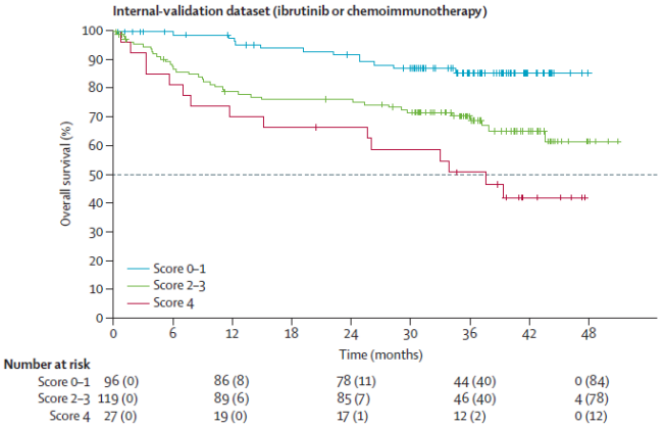
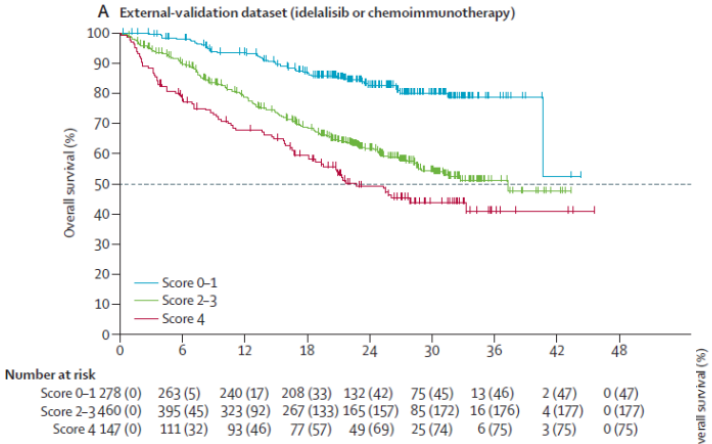
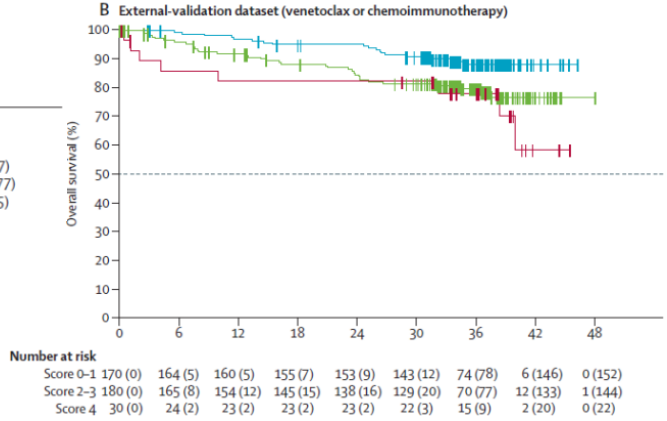
Soumerai et al., Lancet Hematol 2019

Prognostic score for relapse treatment with CIT, Ibrutinib, Idelalisib + Rituximab, Venetoclax

2475 patients with R/R CLL receiving CIT, Ibrutinib, Idelalisib + R or Venetoclax







Soumerai et al., Lancet Hematol 2019

Scores in the era of targeted agents ?

Are the scores established in CIT era also relevant in the era of novel agents ?

Not sure

Does IGHV status still play a role ? Not sure

What is the role of *TP53* mutation ? Prognostic and predictive with targeted agents

Are observation times long enough ? No. Newer scores focused on high risk patients.

Do we need scores for other endpoints ?

How can we add other parameters ?

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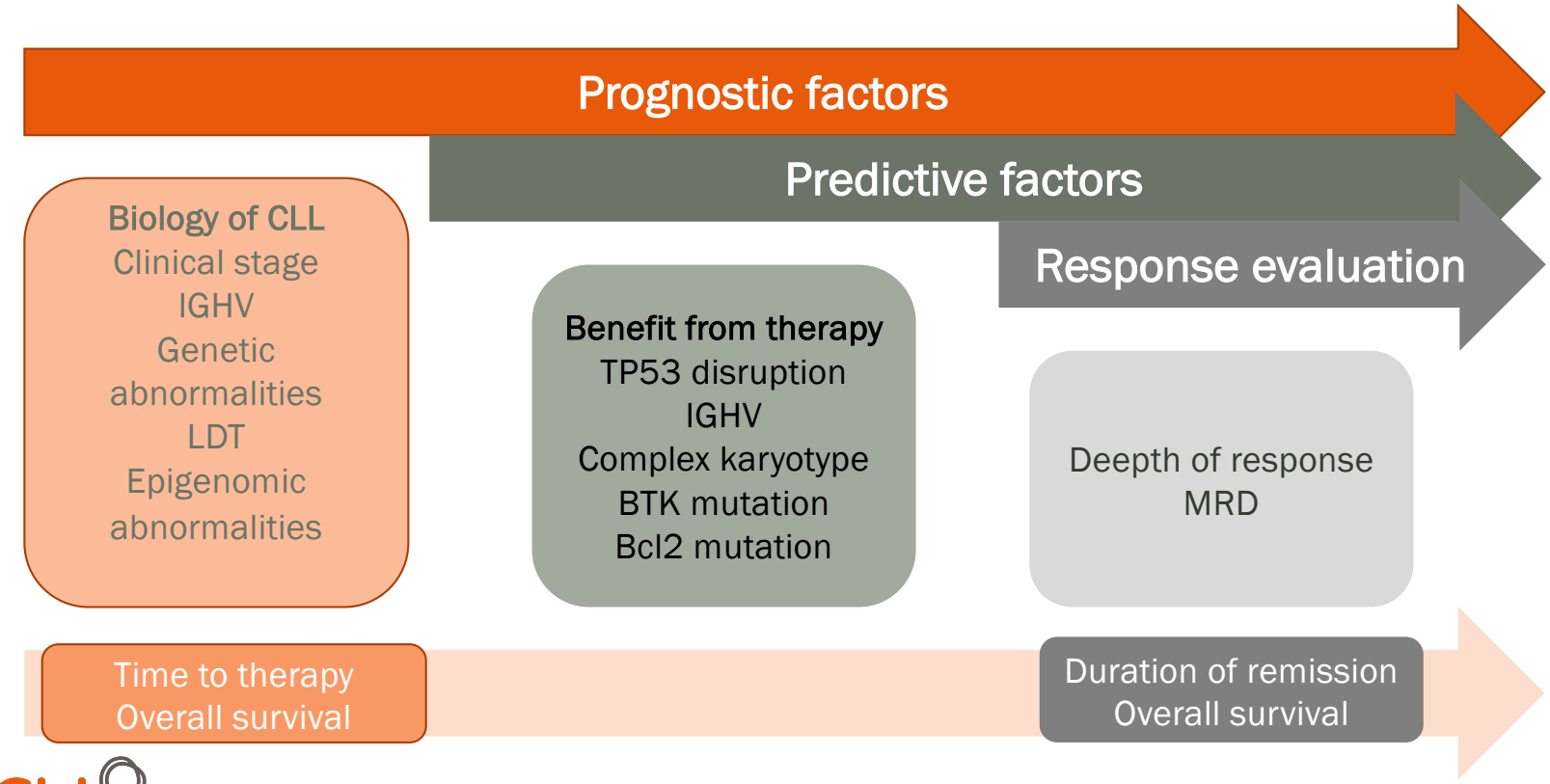
Prognostic and predictive biomarkers



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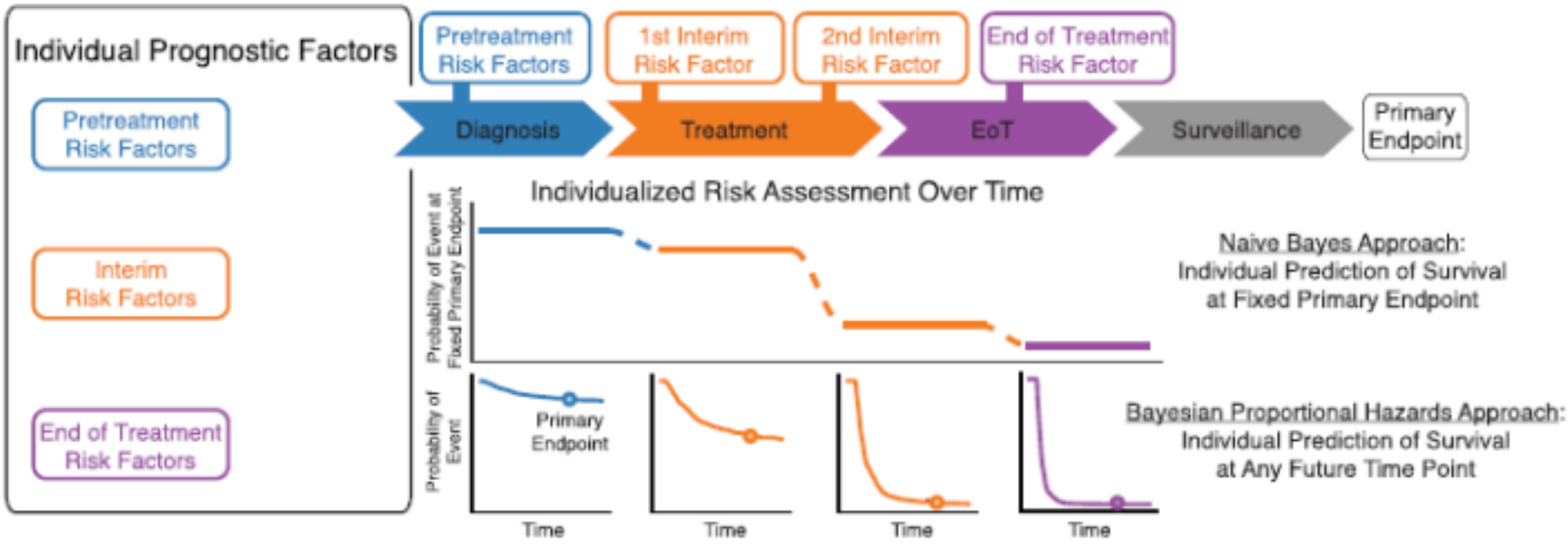
Adapted to Montserrat and Gale; Cancer 2019

Flexible risk score integrating development of risk parameters during course of the disease: continuous individualized risk index = CIRI

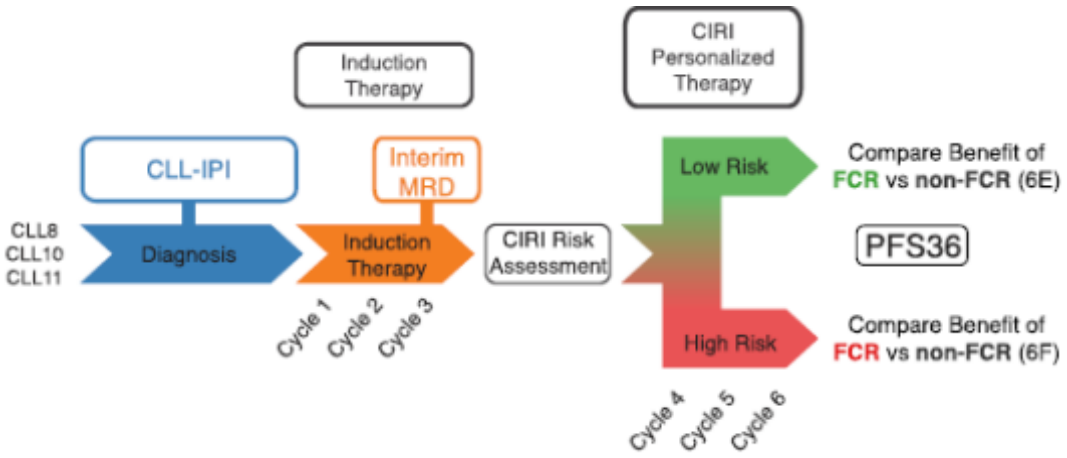
For DLBCL, CLL and BRCA

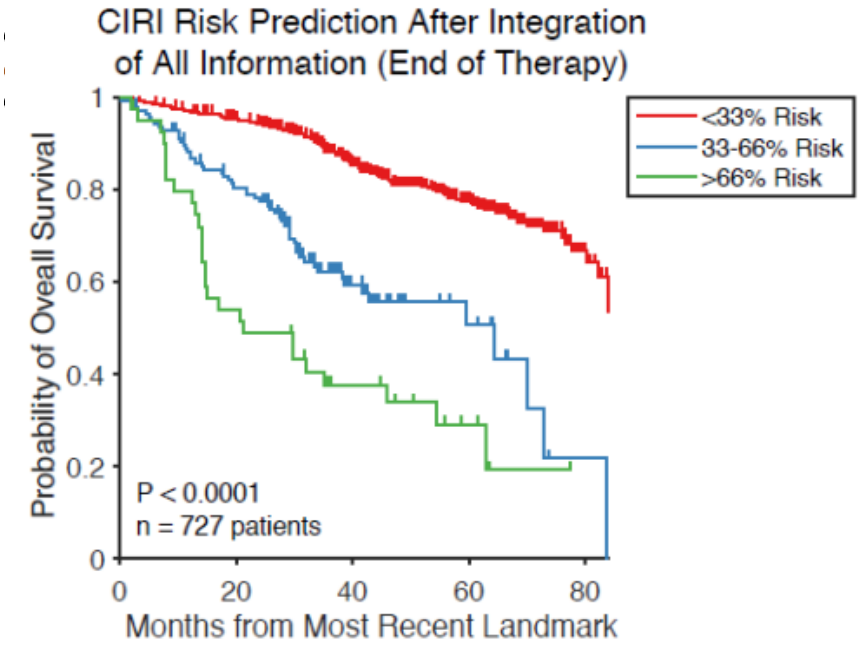


Kurtz et al., Cell 178; 2019

Integrating pretreatment and on-treatment risk factors: CIRI for CLL

Bayesian approach including 2908 predictions from 727 CLL patients





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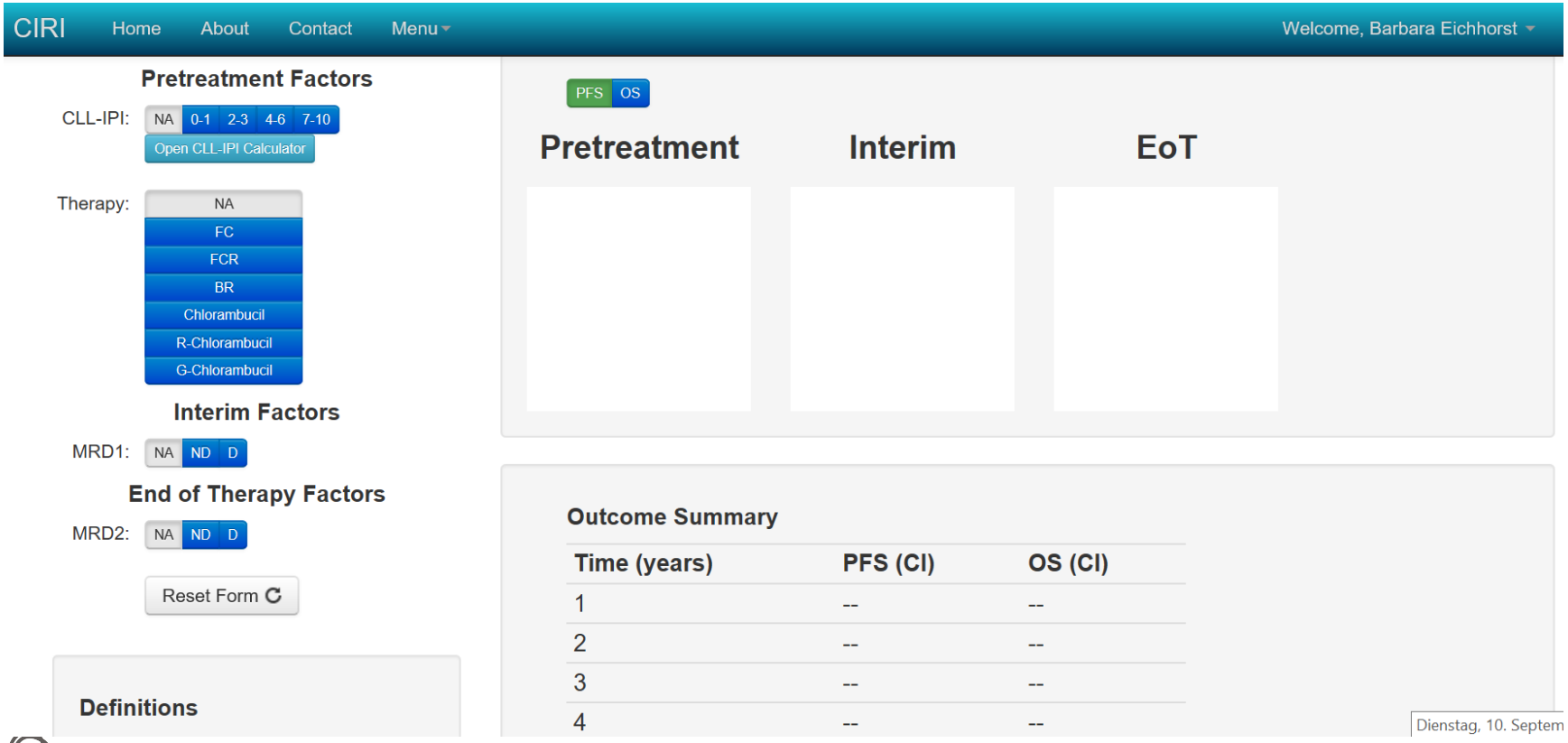
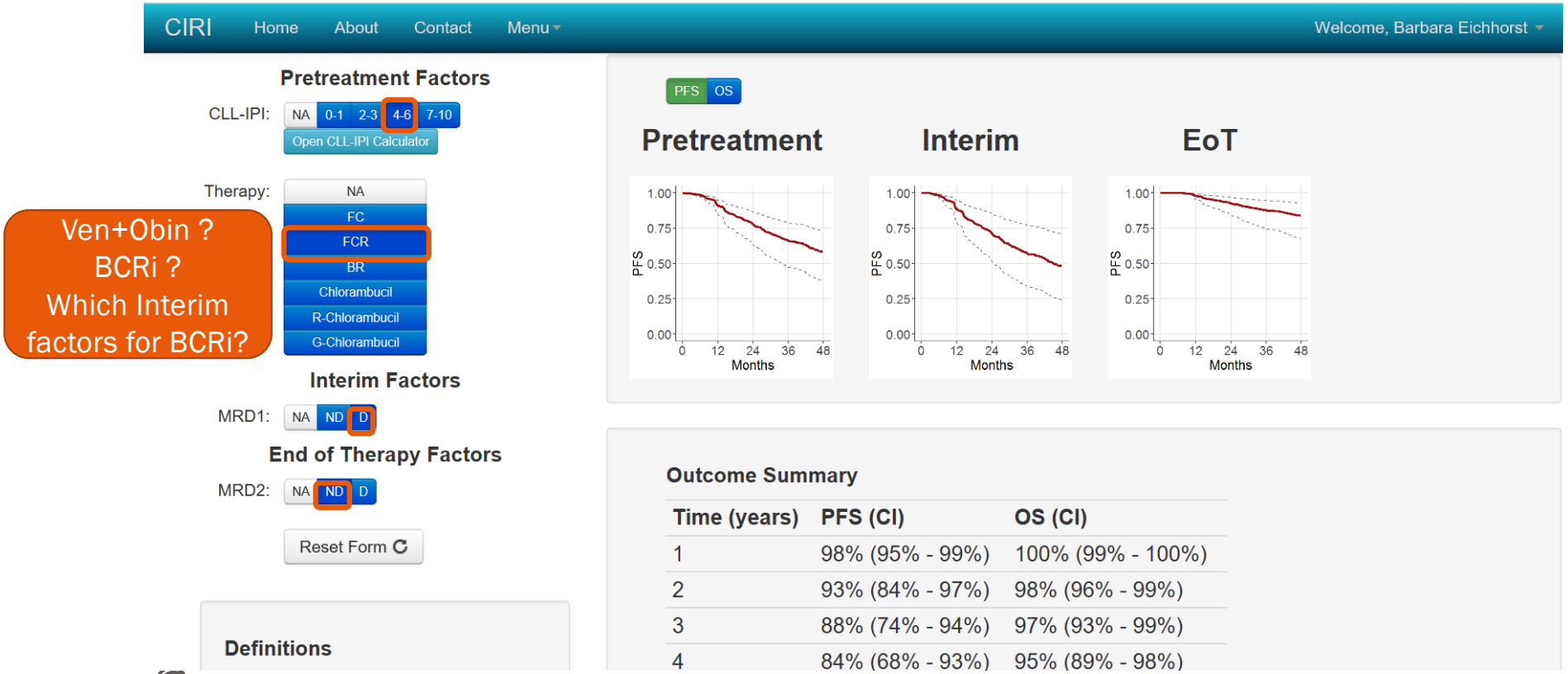
Kurtz et al., Cell 178; 2019

CIRI-CLL



https://ciri.stanford.edu/ciri_cll.php

CIRI-CLL



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Summary development of new scoring systems

- Current treatment paradigm changing

  → adapting prognostic scoring systems.

- Observation times with novel agents have to become more mature for adapted/new scores.

- More flexible scores warranted.

- Flexible scores for prediction to therapy may help guiding therapy.