Table S1. Patient cohort and characteristics for CIRI-DLBCL, Related to Figure 1.

	Development Set	Validation Set
Number of Subjects	49	132
Median Age	61	55
Diagnosis, n (%)		
DLBCL	33 (67%)	106 (80%)
DLBCL, transformed low grade	15 (31%)	4 (3%)
PMBCL	1 (2%)	22 (17%)
Stage, n (%)		
1	7 (14%)	12 (9%)
2	6 (12%)	38 (29%)
3	8 (16%)	19 (14%)
4	28 (57%)	63 (48%)
Not available	0 (0%)	0 (0%)
IPI, n (%)		
0 to 1	15 (31%)	54 (41%)
2	13 (27%)	30 (23%)
3	9 (18%)	30 (23%)
4 to 5	12 (24%)	18 (14%)
Not available	0 (0%)	0 (0%)
Molecular Features, n (%)		
GCB	14 (29%)	49 (37%)
non-GCB	11 (22%)	48 (36%)
Not applicable	24 (49%)	35 (27%)
Early Molecular Response, n (%)		
EMR	25 (51%)	55 (42%)
No EMR	10 (20%)	15 (11%)
Not evaluated	14 (29%)	62 (47%)
Major Molecular Reponse, n (%)		
MMR	25 (51%)	60 (45%)
No MMR	7 (14%)	20 (15%)
Not evaluated	17 (35%)	52 (39%)
Interim Imaging, n (%)		
Residual Disease	26 (53%)	20 (15%)
No Residual Disease	18 (37%)	57 (43%)
Not evaluated	5 (10%)	55 (42%)
Lines of Therapy Considered		
R-CHOP	20 (41%)	77 (58%)
EPOCH-R	27 (55%)	47 (36%)
Other anthracycline-based regimen	2 (4%)	8 (6%)

This table shows the clinical characteristics for the patients used to develop and validate CIRI-DLBCL (Development Set and Validation Set). The Development Set was used to determine the parameters for pretreatment ctDNA, EMR, and MMR used in CIRI-DLBCL. The parameters for IPI, cell of origin, and interim imaging studies were obtained from the literature.

Table S2. Parameters for CIRI-DLBCL, Related to Figure 1.

Variable	Patients (n)	P(Event)	Source
Baseline Probability	1425	21.8%	Sehn, L.H. et al. *Blood*, 2007 and Ziepert, M. et al. *JCO*, 2010.

Group	Patients (n)	P(Feature I Event)	P(Feature I No Event)	Source
International Prognostic Index				Ziepert, M. et al. *JCO,* 2010.
0 to 1	553	27.3%	58.7%	
2	227	23.0%	21.0%	
3	175	30.5%	12.9%	
4 to 5	105	19.2%	7.5%	
Cell Of Origin				Scott, D.W. et al. *JCO,* 2015.
GCB	186	39.8%	63.1%	
non-GCB	143	60.2%	36.9%	
Interim Imaging				Cashen, A. et al. *J Nucl Med*, 2011; Micallef, I.N. et al. *Blood*, 2011; Nols, N. et al. *Leuk Lymphoma*, 2014; Pregno, P. et al, *Blood*, 2012; Safar, V et al. *JCO*, 2012; Yang, D.H. et al, *Eur J Cancer*, 2011; Yoo C. et al. *Ann Hematol*, 2011; Zinzani, P. et al. *Cancer*, 2011.
Interim Imaging Positive	257	58.3%	21.5%	
Interim Imaging Negative	547	41.7%	78.5%	
Pretreatment ctDNA				Current study, Development Set
ctDNA High (> 2.5 log h.G.E./mL)	27	76.5%	43.8%	
ctDNA Low (< 2.5 log h.G.E./mL)	22	23.5%	56.3%	
Early Molecular Response				Current study, Development Set
EMR	25	57.1%	81.0%	
No EMR	10	42.9%	19.0%	
Major Molecular Response				Current study, Development Set
MMR	25	50.0%	95.0%	
No MMR	7	50.0%	5.0%	

This table shows the parameters used in CIRI-DLBCL, including the baseline probability of an event for the general population, as well as the conditional probabilities of having a risk feature given an event.

Table S3. Patient cohort and characteristics for CIRI-CLL, Related to Figure 3.

	Development Set	Validation Set
Number of Subjects	699	727
Median Age	63	61
>65	288 (41%)	261 (36%)
<65	409 (59%)	465 (64%)
Sex		
Male	478 (68%)	516 (71%)
Female	221 (32%)	211 (29%)
TP53 Alterations		
Mutation or 17p deletion	41 (6%)	58 (8%)
No Mutation or 17p deletion	627 (90%)	631 (87%)
Not Evaluated	31 (4%)	38 (5%)
IGHV Status		
Mutated	229 (33%)	227 (31%)
Unmutated	427 (61%)	442 (61%)
Not Evaluated	43 (6%)	58 (8%)
Beta2 Microglobulin		
Low	435 (62%)	453 (62%)
High	244 (35%)	241 (33%)
Not Evaluated	20 (3%)	33 (5%)
Binet stage		
A	121 (17%)	124 (17%)
B	343 (49%)	350 (48%)
C	234 (33%)	253 (35%)
CLL IPI		
Low	127 (18%)	163 (22%)
Intermediate	279 (40%)	273 (38%)
High	256 (37%)	246 (34%)
Very High	37 (5%)	45 (6%)
MRD at Interim Timepoint		
Positive	484 (69%)	503 (69%)
Negative	101 (14%)	101 (14%)
Not Evaluated	114 (16%)	123 (17%)
MRD at Final Restaging		
Positive	320 (46%)	343 (47%)
Negative	217 (31%)	231 (32%)
Not Evaluated	162 (23%)	153 (21%)
Study of Enrollment		
CLL8	185 (26%)	219 (30%)
CLL10	224 (32%)	213 (29%)
CLL11	290 (41%)	295 (41%)
Therapy		
FC	91 (13%)	106 (15%)
FCR	205 (29%)	234 (32%)
BR	113 (16%)	92 (13%)
CLB	42 (6%)	44 (6%)
RCLB	126 (18%)	129 (18%)
GCLB	122 (17%)	122 (17%)

This table shows the clinical characteristics for the patients used to develop and validate CIRI-CLL (Development Set and Validation Set).

Table S4. Patient cohort and characteristics for CIRI-BRCA, Related to Figure 4.

	Development Set	Validation Set
Number of Subjects	955	417
Median Age	60.3	49
Stage		
1	344 (36%)	7 (2%)
2	530 (55%)	223 (53%)
3	81 (8%)	187 (45%)
NA	0 (0%)	0 (0%)
Grade		
1	91 (10%)	27 (6%)
2	325 (34%)	151 (36%)
3	498 (52%)	211 (51%)
NA	41 (4%)	28 (7%)
Receptor Status		
ER+/Her2-	673 (70%)	241 (58%)
ER+/Her2+	61 (6%)	1 (0%)
ER-/Her2+	60 (6%)	2 (0%)
ER-/Her2-	161 (17%)	158 (38%)
NA	0 (0%)	15 (4%)
Residual Cancer Burden		
0	0 (0%)	89 (21%)
1	0 (0%)	29 (7%)
2	0 (0%)	189 (45%)
3	0 (0%)	110 (26%)
NA	955 (100%)	0 (0%)

This table shows the clinical characteristics for the patients used to develop and validate CIRI-BRCA (Development Set and Validation Set). The Development Set was used to determine the parameters for clinical stage, grade, and receptor status used in CIRI-BRCA. The parameters for pathologic response to chemotherapy (i.e., residual cancer burden) were obtained from the literature.

Table S5. P-values for Schoenfeld residuals for CIRI, Related to STAR Methods.

DLBCL Model		CLL Model		BRCA Model	
Risk Factor	**P-Value**	**Risk Factor**	**P-Value**	**Risk Factor**	**P-Value**
IPI = 0,1	0.11	CLL-IPI = 0,1	0.26	Type = ER-/Her2-	0.57
IPI = 2	0.85	CLL-IPI = 2,3	0.09	Type = ER-/Her2+	0.98
IPI = 3	0.17	CLL-IPI = 4-6	0.19	Type = ER+/Her2-	0.80
IPI = 4,5	-	CLL-IPI = 7-10	-	Type = ER+/Her2+	1.00
COO = GCB	0.58	Treatment = FC	0.63	Grade = 1	0.22
COO = non-GCB	0.29	Treatment = FCR	0.61	Grade = 2	0.92
pretx ctDNA low	0.09	Treatment = BR	0.34	Grade = 3	0.98
pretx ctDNA high	-	Treatment = Chlorambucil	-	Stage = 1	0.18
EMR	0.08	Treatment = R-Chlorambucil	0.17	Stage = 2	0.12
No EMR	0.35	Treatment = G-Chlorambucil	-	Stage = 3	-
MMR	0.79	Interim MRD negative	0.19	RCB = 0	0.99
No MMR	0.32	Interim MRD positive	0.51	RCB = 1	0.13
PET no residual dx	0.91	Final MRD negative	0.44	RCB = 2	0.07
PET residual disease	0.0002	Final MRD positive	0.33	RCB = 3	-
Global DLBCL	**0.08**	**Global CLL**	**0.25**	**Global BRCA**	**0.40**

This table shows the individual and global P-values assessing the proportional hazard assumption by Schoenfeld residuals for each CIRI model (CIRI-DLBCL, CIRI-CLL, and CIRI-BRCA).