Supplementary Materials

Supplementay Table S1. Plasma cfDNA concentration (ng/mL) according to clinical features. N: 249. AA: Ann Arbor; LDH: lactate dehydrogenase; B2-MG: beta-2 microglobulin; BM: bone marrow. U-Mann-Whitney test, with exact Fisher correction when applicable.

	Median (IQR)	p
Gender		
Male	31.2 (14.7-59.6)	0.623
Female	25.5 (13.0-59.1)	
Age		
<60 years	25.3 (12.7-49.3)	0.137
> 60 years	30.0 (15.2-63.6)	
LDH		
Normal	23.8 (12.8-43.2)	<0.0001
Elevated	51.0 (24.4-85.7)	
B2-MG		
Normal	24.5 (13.3-47.6)	<0.0001
Elevated	38.2 (21.8-72.8)	
AA stage		
I-II	25.5 (14.5-47.1)	0.020
III-IV	30.0 (14.6-63.6)	
B symptoms		
No	25.6 (14.4-65.8)	0.001
Present	42.8 (18.5-81.8)	
BM infiltration		
No	30.4 (15.0-59.6)	0.716
Present	23.3 (13.1-55.8)	

Supplementary Table S2. Comparison of cfDNA according to lymphoma subtype vs controls. LBCL: large B-cell lymphoma; FL: follicular lymphoma; MZL: marginal zone lymphoma; MCL: mantle cell lymphoma; small lymphocytic lymphoma/chronic lymphocytic leukemia; LpL/W: lymphoplasmacytic lymphoma/Waldenstöm macroglobulinemia; LPS-NOS: circulating low-grade unclassifiable B-cell lymphoma; cHL: classic Hodgkin lymphoma; AITL: angioimmunoblastic T-cell lymphoma; TCL: T-cell lymphoma. *1 localized BL patient was not considered.

Type of lymphoma	N	p
LBCL	88	<0.001
FL	47	<0.001
MZL	30	<0.001
MCL	13	<0.001
SLL/CLL	7	<0.001
LpL/WM	5	0.012
LPS-NOS	6	<0.001
cHL	30	<0.001
AITL	9	<0.001
Other TCL	6	<0.001
Others	6	0.002
All cases	248*	<0.001

Supplementary Table S3. *P* values for associations of cfDNA levels with characteristics at presentation according to the main lymphoma subtypes. AA: Ann Arbor; LDH: lactate dehydrogenase; B2-MG: beta-2 microglobulin; BM: bone marrow; IPI: international prognostic index; FLIPI: follicular international prognostic index. Spearman test for age, LDH, B2-MG; U-Mann-Whitney test or Kruskal Wallis test for gender, stage, B-symptoms, BM involvement, IPI and FLIPI.

	LBCL (N=88)	FL (N=47)	MZL (N=30)	MCL (N=14)	cHL (N=30)
Age	0.300 (r=0.111)	**0.017** (r=0.348)	0.054 (r=0.777)	0.462 (r=0.214)	**<0.0001** (r=0.611)
LDH	**0.003** (r=0.316)	0.271 (r=0.168)	**0.016** (r=0.443)	0.516 (r=0.190)	0.949 (r=0.012)
B2-MG	**0.002** (r=0.329)	0.200 (r=0.199)	0.066 (r=0.419)	0.852 (r=0.055)	0.056 (r=0.359)
Gender	0.232	0.203	0.595	0.791	0.154
AA stage	0.090	0.601	0.072	NA	0.179
B-symptoms	**0.001**	0.230	0.901	1	0.790
BM involvement	0.134	0.515	0.094	0.264	0.705
IPI	**0.0006**	**0.012**	**0.044**	0.066	NA
FLIPI	-	0.156	-	-	-

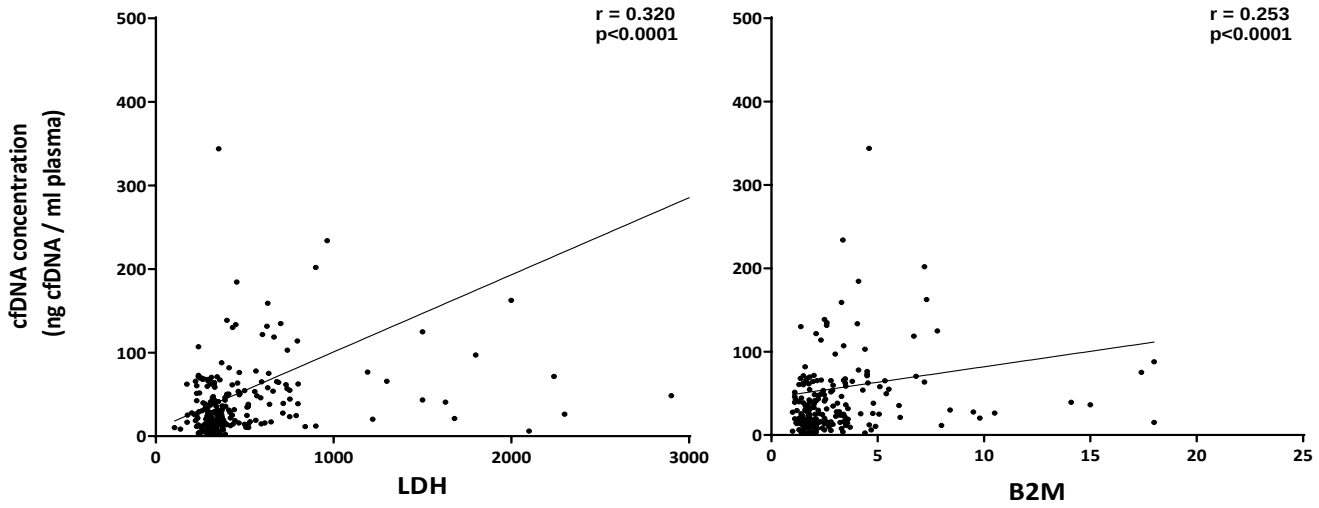
Supplementary Table S4. Clinical features of LBCL patients at diagnosis. AA: Ann Arbor; LDH: lactate dehydrogenase; B2-MG: beta-2 microglobulin; BM: bone marrow; IPI: international prognostic index.

	LBCL (N=49)
Age, years (range)	62 (20-86)
Gender	
Male	55%
Female	45%
ECOG PS	
0-1	84%
2-4	16%
AA stage	
I-II	47%
III-IV	53%
B symptoms	33%
LDH elevated	59%
B2-MG elevated	27%
BM involvement	6%
IPI	
Low	29%
Low/Intermediate	37%
Intermediate/High	24%
High	10%

Supplementary Table S5. Associations of cfDNA with clinical characteristics at diagnosis in de LBCL cohort. *1 patient without available cfDNA. AA: Ann Arbor; LDH: lactate dehydrogenase; B2-MG: beta-2 microglobulin; BM: bone marrow; IPI: international prognostic index.

	LBCL (N=48*) p
Age	0.241 (r=0.173)
LDH	0.138 (r=0.349)
B2-MG	0.194 (r=0.191)
Gender	0.582
AA stage	0.858
B-symptoms	0.498
ECOG	0.710
BM involvement	0.134
IPI	**0.015**

Supplementary Figure S1. Scattered plot showing correlations between cfDNA and LDH and beta 2-microglobulin (B2-MG) (N:249).



Supplementary Figure S2. PFS and OS based on the ctDNA kinetics (reduction of >2.5 log hGE/mL or < 2.5 log hGE/mL from diagnosis to the end of treatment).