**Supplementary Materials**

**Supplementay Table 1.** 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  Female | 31.2 (14.7-59.6)  25.5 (13.0-59.1) | 0.623 |
| Age  <60 years  > 60 years | 25.3 (12.7-49.3)  30.0 (15.2-63.6) | 0.137 |
| LDH  Normal  Elevated | 23.8 (12.8-43.2)  51.0 (24.4-85.7) | <0.0001 |
| B2-MG  Normal  Elevated | 24.5 (13.3-47.6)  38.2 (21.8-72.8) | <0.0001 |
| AA stage  I-II  III-IV | 25.5 (14.5-47.1)  30.0 (14.6-63.6) | 0.020 |
| B symptoms  No  Present | 25.6 (14.4-65.8)  42.8 (18.5-81.8) | 0.001 |
| BM infiltration  No  Present | 30.4 (15.0-59.6)  23.3 (13.1-55.8) | 0.716 |

**Supplementary Table 2.** 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 3.** *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 4.** 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  Female | 55%  45% |
| ECOG PS  0-1  2-4 | 84%  16% |
| AA stage  I-II  III-IV | 47%  53% |
| B symptoms | 33% |
| LDH elevated | 59% |
| B2-MG elevated | 27% |
| BM involvement | 6% |
| IPI  Low  Low/Intermediate  Intermediate/High  High | 29%  37%  24%  10% |

**Supplementary Table 5.** 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 1.** Scattered plot showing correlations between cfDNA and LDH and beta 2-microglobulin (B2-MG) (N:249).



**Supplementary Figure 2.** PFS and OS according to PET EOT and kinetics of log hGE ctDNA.

