

Supplementary Tables

Supplementary Table S1. Comparison of clinicopathologic features of patients with diffuse large B-cell lymphoma (DLBCL) with and without PTEN nuclear expression in the training cohort

| | in DLBCL | | <i>P</i> | in GCB-DLBCL | | <i>P</i> | in ABC-DLBCL | | <i>P</i> | in AKT ^{high} DLBCL | | <i>P</i> | in AKT ^{high} ABC | | <i>P</i> |
|------------------------------------|---------------------------|---------------------------|-------------------|---------------------------|---------------------------|-------------------|---------------------------|---------------------------|-------------------|------------------------------|---------------------------|---------------|----------------------------|---------------------------|--------------|
| | Nuclear PTEN ⁺ | Nuclear PTEN ⁻ | | Nuclear PTEN ⁺ | Nuclear PTEN ⁻ | | Nuclear PTEN ⁺ | Nuclear PTEN ⁻ | | Nuclear PTEN ⁺ | Nuclear PTEN ⁻ | | Nuclear PTEN ⁺ | Nuclear PTEN ⁻ | |
| | n=280 | n=198 | | n=136 | n=102 | | n=140 | n=94 | | n=69 | n=38 | | n=36 | n=18 | |
| GCB/ABC Subtype | | | | | | | | | | | | | | | |
| GCB | 136 | 102 | 0.58 | | | | | | | 33 | 20 | 0.69 | | | |
| ABC | 140 | 94 | | | | | | | | 36 | 18 | | | | |
| Age, years | | | | | | | | | | | | | | | |
| < 60 | 114 | 90 | 0.3 | 66 | 56 | 0.36 | 45 | 32 | 0.78 | 32 | 21 | 0.42 | 12 | 9 | 0.26 |
| ≥ 60 | 166 | 108 | | 70 | 46 | | 95 | 62 | | 37 | 17 | | 24 | 9 | |
| Sex | | | | | | | | | | | | | | | |
| Male | 174 | 108 | 0.11 | 84 | 57 | 0.42 | 88 | 51 | 0.22 | 45 | 19 | 0.15 | 21 | 9 | 0.58 |
| Female | 106 | 90 | | 52 | 45 | | 52 | 43 | | 24 | 19 | | 15 | 9 | |
| Stage | | | | | | | | | | | | | | | |
| I - II | 130 | 89 | 0.78 | 77 | 51 | 0.5 | 51 | 36 | 1 | 29 | 15 | 0.84 | 12 | 8 | 0.56 |
| III-IV | 141 | 103 | | 56 | 46 | | 83 | 57 | | 37 | 21 | | 22 | 10 | |
| B-symptoms | | | | | | | | | | | | | | | |
| No | 177 | 116 | 0.49 | 100 | 56 | 0.019 | 74 | 58 | 0.27 | 45 | 21 | 0.52 | 17 | 9 | 1 |
| Yes | 91 | 69 | | 32 | 36 | | 58 | 33 | | 22 | 14 | | 17 | 9 | |
| LDH | | | | | | | | | | | | | | | |
| Normal | 110 | 50 | <0.0001 | 58 | 25 | 0.003 | 51 | 25 | 0.045 | 28 | 6 | 0.002 | 15 | 3 | 0.06 |
| Elevated | 143 | 136 | | 66 | 68 | | 74 | 66 | | 31 | 31 | | 16 | 14 | |
| Extranodal sites | | | | | | | | | | | | | | | |
| 0 - 1 | 213 | 140 | 0.31 | 110 | 71 | 0.18 | 100 | 68 | 1 | 52 | 20 | 0.036 | 24 | 10 | 0.53 |
| ≥ 2 | 58 | 48 | | 22 | 23 | | 35 | 24 | | 14 | 15 | | 10 | 7 | |
| ECOG score | | | | | | | | | | | | | | | |
| 0 - 1 | 211 | 143 | 0.43 | 105 | 71 | 0.23 | 102 | 70 | 1 | 53 | 22 | 0.03 | 28 | 10 | 0.14 |
| ≥ 2 | 39 | 33 | | 14 | 16 | | 25 | 17 | | 8 | 11 | | 5 | 6 | |
| Tumor size | | | | | | | | | | | | | | | |
| < 5 cm | 127 | 75 | 0.66 | 64 | 38 | 0.88 | 61 | 36 | 0.75 | 31 | 6 | 0.053 | 19 | 3 | 0.11 |
| ≥ 5 cm | 88 | 58 | | 44 | 28 | | 44 | 30 | | 19 | 12 | | 8 | 6 | |
| IPI score | | | | | | | | | | | | | | | |
| 0 - 2 | 172 | 111 | 0.44 | 96 | 60 | 0.25 | 72 | 49 | 1 | 42 | 15 | 0.04 | 17 | 8 | 0.78 |
| > 2 | 102 | 77 | | 38 | 34 | | 64 | 43 | | 25 | 22 | | 17 | 10 | |
| Therapy response | | | | | | | | | | | | | | | |
| CR | 214 | 143 | 0.34 | 106 | 71 | 0.18 | 104 | 70 | 1 | 50 | 26 | 0.66 | 26 | 14 | 0.75 |
| PR | 32 | 32 | | 10 | 18 | | 22 | 14 | | 10 | 7 | | 8 | 2 | |
| SD | 8 | 14 | | 5 | 8 | | 3 | 6 | | 4 | 3 | | 1 | 2 | |
| PD | 26 | 9 | | 15 | 5 | | 11 | 4 | | 5 | 2 | | 1 | 0 | |
| Cytoplasmic PTEN expression | | | | | | | | | | | | | | | |
| Negative | 43 | 129 | <0.0001 | 29 | 72 | <0.0001 | 14 | 55 | <0.0001 | 5 | 13 | 0.0004 | 2 | 4 | 0.066 |
| Positive | 237 | 69 | | 107 | 30 | | 126 | 39 | | 64 | 25 | | 34 | 14 | |
| TP53 mutations | | | | | | | | | | | | | | | |
| No | 202 | 127 | 0.13 | 92 | 65 | 0.95 | 107 | 60 | 0.027 | 53 | 22 | 0.42 | 30 | 11 | 0.54 |
| Yes | 50 | 45 | | 32 | 23 | | 18 | 22 | | 9 | 6 | | 3 | 2 | |
| MDM2 expression | | | | | | | | | | | | | | | |
| ≤ 10% | 151 | 137 | 0.0007 | 80 | 74 | 0.018 | 70 | 63 | 0.014 | 36 | 27 | 0.058 | 18 | 12 | 0.25 |
| > 10% | 122 | 56 | | 54 | 25 | | 68 | 30 | | 33 | 11 | | 18 | 6 | |
| BCL6 expression | | | | | | | | | | | | | | | |
| ≤ 30% | 53 | 56 | 0.014 | 11 | 17 | 0.044 | 42 | 39 | 0.05 | 8 | 10 | 0.04 | 7 | 8 | 0.037 |
| > 30% | 219 | 134 | | 122 | 82 | | 97 | 52 | | 60 | 26 | | 29 | 9 | |
| IgA IHC | | | | | | | | | | | | | | | |
| 0% | 277 | 188 | 0.01 | 134 | 96 | 0.062 | 139 | 90 | 0.066 | 69 | 37 | 0.18 | 36 | 18 | 1 |
| 100% | 3 | 10 | | 2 | 6 | | 1 | 4 | | 0 | 1 | | 0 | 0 | |
| IgG IHC | | | | | | | | | | | | | | | |
| 0% | 261 | 167 | 0.002 | 127 | 87 | 0.04 | 130 | 78 | 0.032 | 66 | 33 | 0.1 | 34 | 16 | 0.46 |
| 100% | 19 | 31 | | 9 | 15 | | 10 | 16 | | 3 | 5 | | 2 | 2 | |
| IgM IHC | | | | | | | | | | | | | | | |

| | | | | | | | | | | | | | | | |
|-------|-----|-----|------|-----|----|------|----|----|------|----|----|------|----|----|------|
| < 10% | 205 | 138 | 0.41 | 117 | 86 | 0.71 | 84 | 50 | 0.35 | 49 | 29 | 0.65 | 19 | 12 | 0.33 |
| ≥ 10% | 75 | 60 | | 19 | 16 | | 56 | 44 | | 20 | 9 | | 17 | 6 | |

Abbreviations: LDH, lactate dehydrogenase; ECOG, Eastern Cooperative Oncology Group; IPI, International Prognostic Index; CR, complete remission; PR, partial response; SD, stable disease; PD, progressive disease; GCB, germinal center B-cell-like; ABC, activated B-cell-like.

Supplementary Table S2. Comparison of clinicopathologic features of patients with diffuse large B-cell lymphoma (DLBCL) with and without *PTEN* deletion in the training cohort

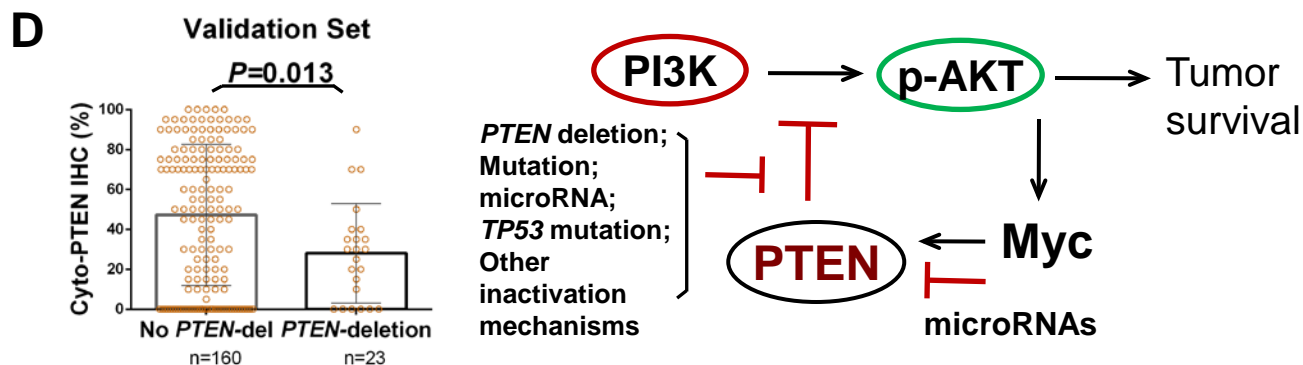
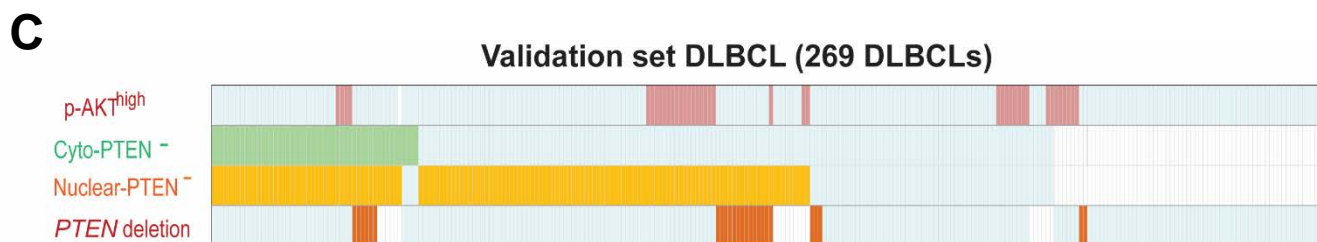
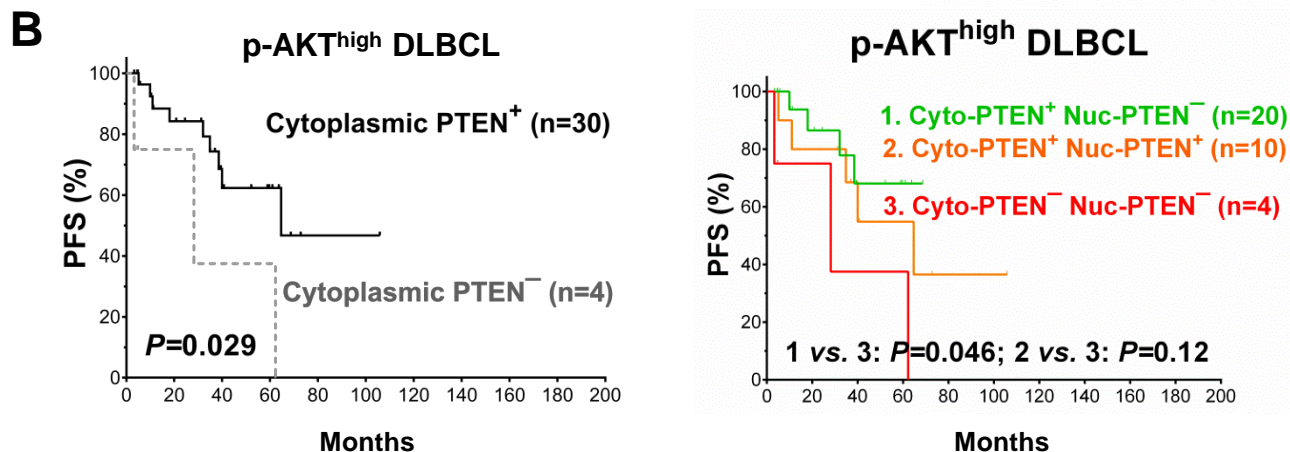
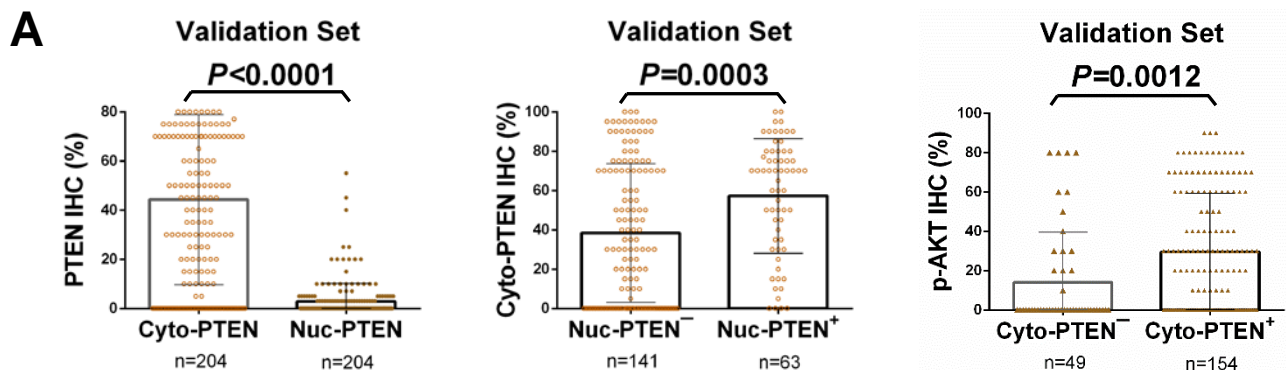
| | in DLBCL | | <i>P</i> | in GCB-DLBCL | | <i>P</i> | in ABC-DLBCL | | <i>P</i> |
|---------------------------|---------------------------------------|---|---------------|---------------------------------------|---|--------------|---------------------------------------|---|--------------|
| | <i>PTEN</i> deletion n=44 N (%) | No <i>PTEN</i> deletion n=315 N (%) | | <i>PTEN</i> deletion n=27 N (%) | No <i>PTEN</i> deletion n=157 N (%) | | <i>PTEN</i> deletion n=17 N (%) | No <i>PTEN</i> deletion n=157 N (%) | |
| Age, years | | | | | | | | | |
| < 60 | 20 (45.5) | 121 (38.4) | 0.41 | 11 (40.7) | 80 (51) | 0.41 | 9 (52.9) | 40 (25.5) | 0.024 |
| ≥ 60 | 24 (54.5) | 194 (61.6) | | 16 (59.3) | 77 (49) | | 8 (47.1) | 117 (74.5) | |
| Sex | | | | | | | | | |
| Male | 25 (56.8) | 186 (59) | 0.78 | 14 (51.9) | 89 (56.7) | 0.68 | 11 (64.7) | 97 (61.8) | 1 |
| Female | 19 (43.2) | 129 (41) | | 13 (48.1) | 68 (43.3) | | 6 (35.3) | 60 (38.2) | |
| Stage | | | | | | | | | |
| I - II | 19 (45.2) | 134 (44.2) | 0.90 | 14 (56) | 79 (52) | 0.53 | 5 (29.4) | 55 (36.7) | 0.61 |
| III-IV | 23 (54.8) | 169 (55.8) | | 11 (44) | 73 (48) | | 12 (70.6) | 95 (63.3) | |
| B-symptoms | | | | | | | | | |
| No | 30 (73.2) | 196 (65.3) | 0.32 | 21 (84) | 101 (67.8) | 0.16 | 9 (56.3) | 94 (62.7) | 0.6 |
| Yes | 11 (26.8) | 104 (34.7) | | 4 (16) | 48 (32.2) | | 7 (43.8) | 56 (37.3) | |
| LDH | | | | | | | | | |
| Normal | 20 (52.6) | 120 (42.4) | 0.23 | 15 (65.2) | 64 (45.7) | 0.11 | 5 (33.3) | 56 (39.4) | 0.78 |
| Elevated | 18 (47.4) | 163 (57.6) | | 8 (34.8) | 76 (54.3) | | 10 (66.7) | 86 (60.6) | |
| Extranodal sites | | | | | | | | | |
| 0 - 1 | 34 (81) | 229 (76.8) | 0.55 | 21 (84) | 114 (77.6) | 0.6 | 13 (76.5) | 114 (76) | 1 |
| ≥ 2 | 8 (19) | 69 (23.2) | | 4 (16) | 33 (22.4) | | 4 (23.5) | 36 (24) | |
| ECOG score | | | | | | | | | |
| 0 - 1 | 35 (92.1) | 226 (83.1) | 0.15 | 22 (95.7) | 107 (82.3) | 0.13 | 13 (86.7) | 118 (83.7) | 1 |
| ≥ 2 | 3 (7.9) | 46 (16.9) | | 1 (4.3) | 23 (17.7) | | 2 (13.3) | 23 (16.3) | |
| Tumor size | | | | | | | | | |
| < 5 cm | 18 (48.6) | 158 (59.2) | 0.22 | 11 (52.4) | 81 (61.4) | 0.48 | 7 (43.8) | 77 (57) | 0.43 |
| ≥ 5 cm | 19 (51.4) | 109 (40.8) | | 10 (47.6) | 51 (38.6) | | 9 (56.3) | 58 (43) | |
| IPI score | | | | | | | | | |
| 0 - 2 | 30 (71.4) | 183 (60.4) | 0.17 | 19 (76) | 101 (66.9) | 0.49 | 11 (64.7) | 81 (53.6) | 0.45 |
| > 2 | 12 (28.6) | 120 (39.6) | | 6 (24) | 50 (33.1) | | 6 (35.3) | 70 (46.4) | |
| Therapy response | | | | | | | | | |
| CR | 38 (86.4) | 234 (74.3) | 0.092 | 24 (88.9) | 116 (73.9) | 0.14 | 14 (82.4) | 117 (74.5) | 0.57 |
| PR | 3 | 44 | | 1 | 19 | | 2 | 25 | |
| SD | 1 | 10 | | 1 | 5 | | 0 | 5 | |
| PD | 2 | 27 | | 1 | 17 | | 1 | 10 | |
| GCB/ABC subtype | | | | | | | | | |
| GCB | 27 (61.4) | 157 (50) | 0.16 | | | | | | |
| ABC | 17 (38.6) | 157 (50) | | | | | | | |
| MDM2 expression | | | | | | | | | |
| ≤ 10% | 34 (77.3) | 173 (56) | 0.0084 | 22 (81.5) | 90 (58.4) | 0.023 | 12 (70.6) | 83 (53.5) | 0.18 |
| > 10% | 10 (22.7) | 136 (44) | | 5 (18.5) | 64 (41.6) | | 5 (29.4) | 72 (46.5) | |
| BCL6 expression | | | | | | | | | |
| ≤ 30% | 4 (9.1) | 64 (20.5) | 0.071 | 0 (0) | 20 (12.9) | 0.048 | 4 (23.5) | 44 (28) | 0.69 |
| > 30% | 40 (90.9) | 248 (79.5) | | 27 (100) | 135 (87.1) | | 13 (76.5) | 113 (72) | |
| BLIMP-1 expression | | | | | | | | | |
| < 10% | 38 (88.4) | 213 (70.8) | 0.016 | 25 (92.6) | 118 (79.2) | 0.1 | 13 (81.3) | 95 (62.5) | 0.14 |
| ≥ 10% | 5 (11.6) | 88 (29.2) | | 2 (7.4) | 31 (20.8) | | 3 (18.7) | 57 (37.5) | |

Abbreviations: LDH, lactate dehydrogenase; ECOG, Eastern Cooperative Oncology Group; IPI, International Prognostic Index; CR, complete remission; PR, partial response; SD, stable disease; PD, progressive disease; GCB, germinal center B-cell-like; ABC, activated B-cell-like.

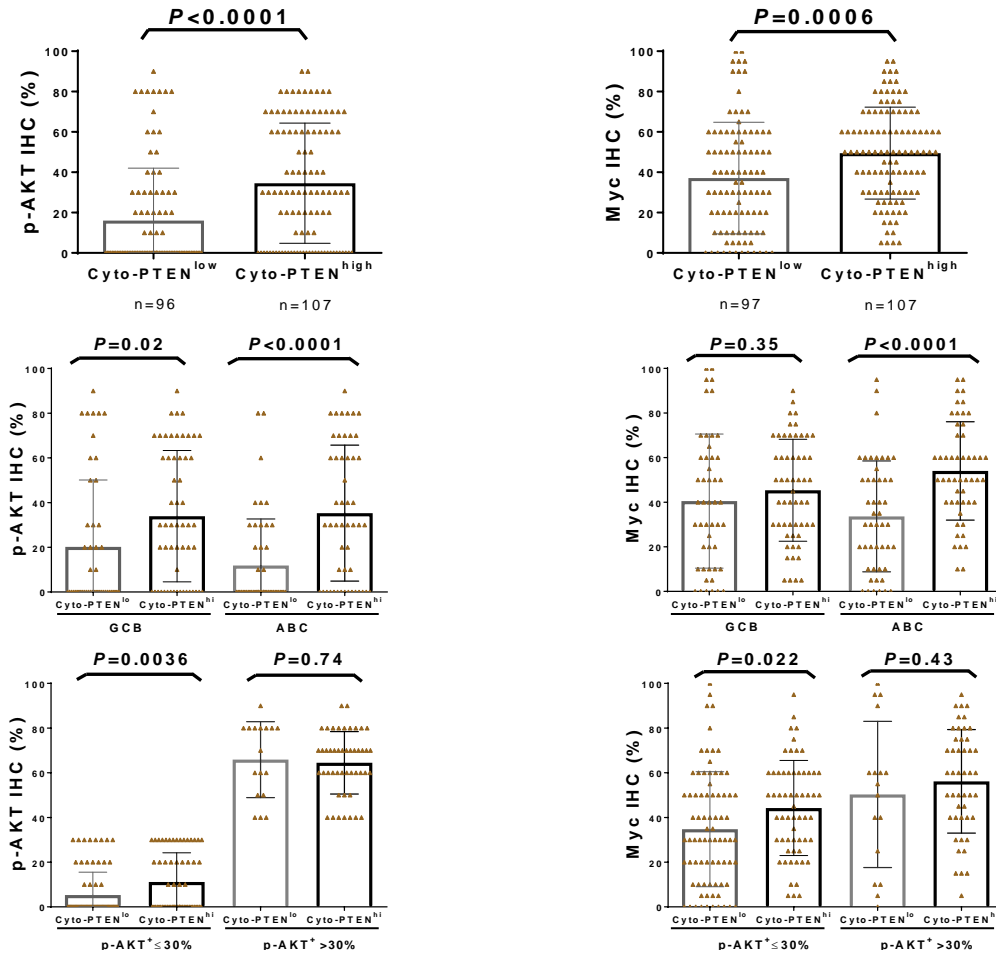
Supplementary Table S3. Comparison of clinicopathologic features of patients with diffuse large B-cell lymphoma (DLBCL) with and without *PTEN* mutation in the training cohort

| | in DLBCL | | | in GCB-DLBCL | | | in ABC-DLBCL | | |
|----------------------------|------------------|-----------------|---------------|------------------|-----------------|-------------------|------------------|-----------------|--------------|
| | MUT- <i>PTEN</i> | WT- <i>PTEN</i> | <i>P</i> | MUT- <i>PTEN</i> | WT- <i>PTEN</i> | <i>P</i> | MUT- <i>PTEN</i> | WT- <i>PTEN</i> | <i>P</i> |
| | n=39 | n=329 | | n=23 | n=166 | | n=16 | n=161 | |
| | N (%) | N (%) | | N (%) | N (%) | | N (%) | N (%) | |
| Age, years | | | | | | | | | |
| < 60 | 16 (41.0) | 140 (42.6) | 1 | 7 (30.4) | 84 (50.6) | 0.078 | 9 (56.3) | 55 (34.2) | 0.1 |
| ≥ 60 | 23 (59.0) | 189 (57.4) | | 16 (69.6) | 82 (49.4) | | 7 (43.8) | 106 (65.8) | |
| Sex | | | | | | | | | |
| Male | 23 (59.0) | 190 (57.8) | 1 | 14 (60.9) | 91 (54.8) | 0.66 | 9 (56.3) | 98 (60.9) | 0.79 |
| Female | 16 (41.0) | 139 (42.2) | | 9 (39.1) | 75 (45.2) | | 7 (43.8) | 63 (39.1) | |
| Stage | | | | | | | | | |
| I - II | 19 (51.4) | 137 (43.1) | 0.38 | 14 (60.9) | 78 (48.8) | 0.37 | 5 (35.7) | 58 (37.2) | 1 |
| III-IV | 18 (48.6) | 181 (56.9) | | 9 (39.1) | 82 (51.2) | | 9 (64.3) | 98 (62.8) | |
| B-symptoms | | | | | | | | | |
| No | 23 (65.7) | 201 (64.4) | 1 | 18 (85.7) | 106 (68.4) | 0.13 | 5 (35.7) | 93 (60) | 0.094 |
| Yes | 12 (34.3) | 111 (35.6) | | 3 (14.3) | 49 (31.6) | | 9 (64.3) | 62 (40) | |
| LDH | | | | | | | | | |
| Normal | 10 (27) | 127 (42.8) | 0.077 | 8 (36.4) | 67 (45.3) | 0.5 | 2 (13.3) | 59 (40.1) | 0.051 |
| Elevated | 27 (73) | 170 (57.2) | | 14 (63.6) | 81 (54.7) | | 13 (86.7) | 88 (59.9) | |
| Extranodal sites | | | | | | | | | |
| 0 - 1 | 28 (73.7) | 237 (76.2) | 0.69 | 16 (72.7) | 123 (79.4) | 0.58 | 12 (75) | 112 (72.7) | 1 |
| ≥ 2 | 10 (26.3) | 74 (23.8) | | 6 (27.3) | 32 (20.6) | | 4 (25) | 42 (27.3) | |
| ECOG score | | | | | | | | | |
| 0 - 1 | 30 (83.3) | 239 (82.1) | 1 | 19 (90.5) | 120 (85.1) | 0.74 | 11 (73.3) | 117 (79.1) | 0.74 |
| ≥ 2 | 6 (16.7) | 52 (17.9) | | 2 (9.5) | 21 (14.9) | | 4 (26.7) | 31 (20.9) | |
| Tumor size | | | | | | | | | |
| < 5 cm | 18 (66.7) | 149 (59.1) | 0.54 | 10 (66.7) | 76 (57.6) | 0.59 | 8 (66.7) | 72 (60.5) | 0.77 |
| ≥ 5 cm | 9 (33.3) | 103 (40.9) | | 5 (33.3) | 56 (42.4) | | 4 (33.3) | 47 (39.5) | |
| IPI score | | | | | | | | | |
| 0 - 2 | 20 (54.1) | 196 (61.8) | 0.38 | 13 (59.1) | 107 (67.3) | 0.47 | 7 (46.7) | 87 (55.8) | 0.59 |
| > 2 | 17 (45.9) | 121 (38.2) | | 9 (40.9) | 52 (32.7) | | 8 (53.3) | 69 (44.2) | |
| Therapy response | | | | | | | | | |
| CR | 28 (71.8) | 243 (73.9) | 0.85 | 17 (73.9) | 122 (73.5) | 1 | 11 (68.8) | 119 (73.9) | 0.77 |
| Non-CR | 11 (28.2) | 86 (26.1) | | 6 (26.1) | 44 (6.6) | | 5 (31.2) | 42 (26.1) | |
| GCB/ABC subtype | | | | | | | | | |
| GCB | 23 (59) | 166 (50.8) | 0.33 | | | | | | |
| ABC | 16 (41) | 161 (49.2) | | | | | | | |
| TP53 mutations | | | | | | | | | |
| No | 24 (61.5) | 251 (80.2) | 0.0079 | 12 (52.2) | 124 (77) | 0.011 | 12 (75) | 126 (83.4) | 0.4 |
| Yes | 15 (38.5) | 62 (19.8) | | 11 (47.8) | 37 (23) | | 4 (25) | 25 (16.6) | |
| MYC mutations | | | | | | | | | |
| No | 19 (48.7) | 240 (72.9) | 0.0017 | 7 (30.4) | 121 (72.5) | <0.0001 | 12 (75) | 118 (73.3) | 0.88 |
| Yes | 20 (51.3) | 89 (27.1) | | 16 (69.6) | 46 (27.5) | | 4 (25) | 43 (26.7) | |
| MYC CDS mutations | | | | | | | | | |
| No | 26 (66.7) | 291 (88.4) | 0.0002 | 11 (47.8) | 149 (89.2) | <0.0001 | 15 (93.8) | 141 (87.6) | 0.47 |
| Yes | 13 (33.3) | 38 (11.6) | | 12 (52.2) | 18 (10.8) | | 1 (6.2) | 20 (12.4) | |
| PRDM1 CDS mutations | | | | | | | | | |
| No | 20 (51.3) | 252 (77.1) | 0.0005 | 12 (52.2) | 129 (77.7) | 0.0084 | 8 (50) | 121 (76.1) | 0.024 |
| Yes | 19 (48.7) | 75 (22.9) | | 11 (47.8) | 37 (22.3) | | 8 (50) | 38 (23.9) | |
| IgG IHC | | | | | | | | | |
| 0% | 38 (97.4) | 288 (87.5) | 0.066 | 23 (100) | 151 (90.4) | 0.12 | 15 (93.8) | 136 (84.5) | 0.32 |
| 100% | 1 (2.6) | 41 (12.5) | | 0 (0) | 16 (9.6) | | 1 (6.2) | 25 (15.5) | |

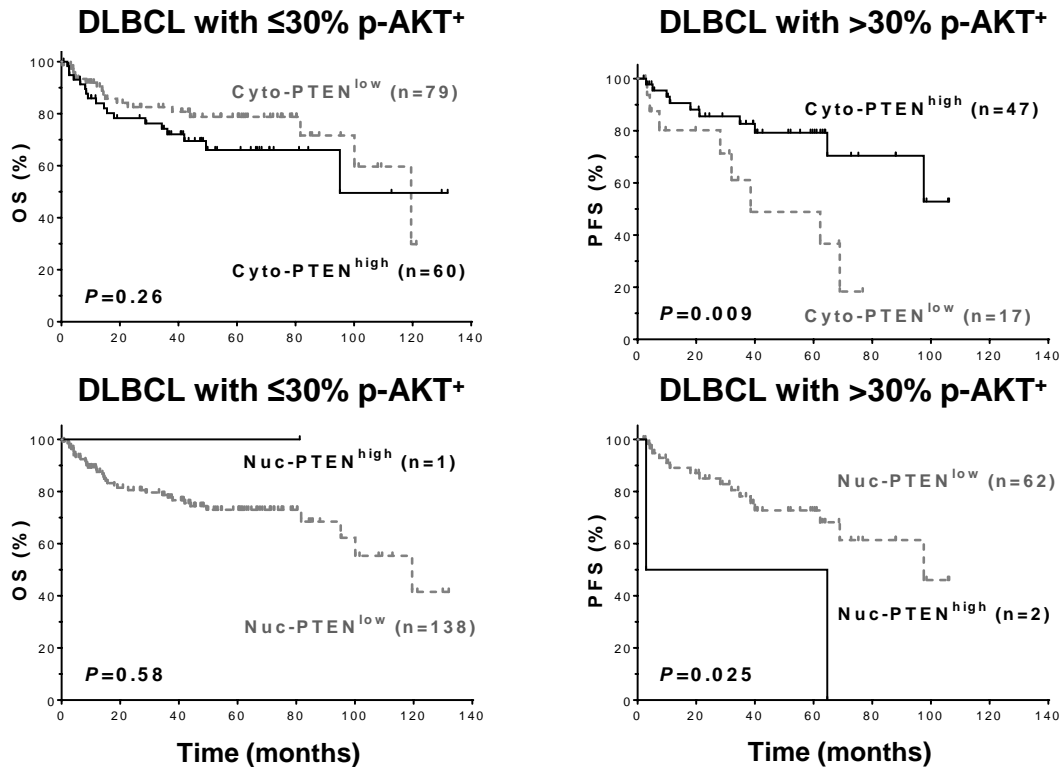
Abbreviations: LDH, lactate dehydrogenase; ECOG, Eastern Cooperative Oncology Group; IPI, International Prognostic Index; CR, complete remission; PR, partial response; SD, stable disease; PD, progressive disease; GCB, germinal center B-cell-like; ABC, activated B-cell-like; MUT, mutated; WT, wild-type.



A



B



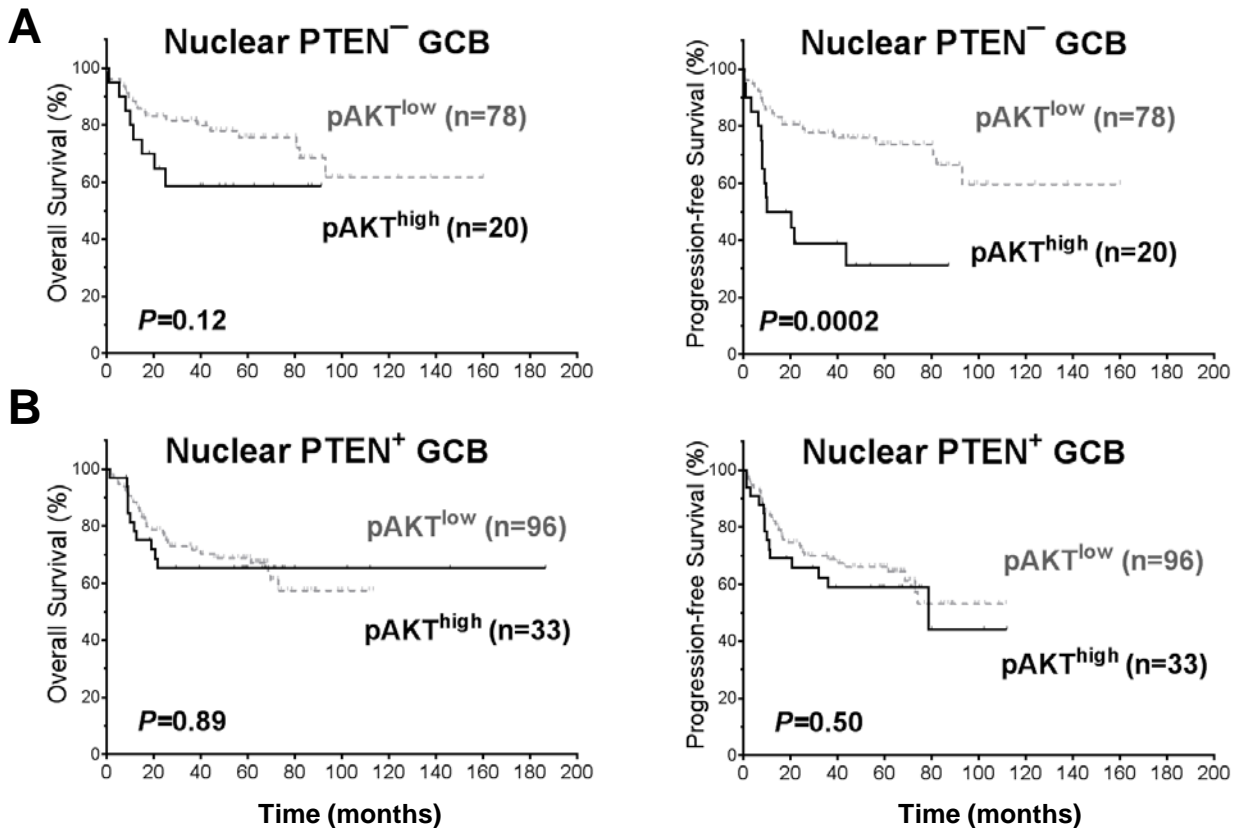


Figure Legends:

Supplementary Figure S1. PTEN/*PTEN* analysis in an independent validation cohort of patients with diffuse large B-cell lymphoma (DLBCL). **(A)** PTEN was found to be expressed mainly in the cytoplasm. Nuclear PTEN expression was positively correlated with cytoplasmic PTEN expression. Cytoplasmic PTEN expression positively correlated with p-AKT expression. **(B)** In DLBCL patients with AKT hyperactivation (high phospho-AKT expression, p-AKT^{high}), loss of cytoplasmic PTEN expression was associated with significantly shorter progression-free survival (PFS). **(C)** Distribution of *PTEN* deletion, PTEN protein loss, and p-AKT overexpression as indicated colors in the validation cohort (each column represented one patient). Cases without these abnormalities are shown in light blue or white (for negative or unknown status, respectively). **(D)** *PTEN* deletion correlated with decreased PTEN expression in the cytoplasm by unpaired *t* test. A schematic model summarizes the possible mechanisms of PTEN loss as suggested by this study.

Supplementary Figure S2. Correlative and prognostic analysis for high PTEN expression in the validation cohort. **(A)** High PTEN cytoplasmic expression was associated with higher mean levels of p-AKT and Myc expression. **(B)** Only in p-AKT⁺ cases, high PTEN cytoplasmic expression was associated with better PFS; in contrast, high PTEN nuclear expression was associated with poorer PFS.

Supplementary Figure S3. In germinal center B-cell-like (GCB) DLBCL cases of the training cohort, high phosphorylated-AKT expression (pAKT^{high}, cutoff: $\geq 70\%$) had significant adverse prognostic effects only in cases without nuclear PTEN expression (PTEN⁻, Figure A) but not in cases with nuclear PTEN expression (PTEN⁺, Figure B).