# *MYD88* L265P mutations, but not others variants, identify a subgroup of patients with activated B-cell like diffuse large B-cell lymphoma, extranodal involvement and poor outcome

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## INTRODUCTION

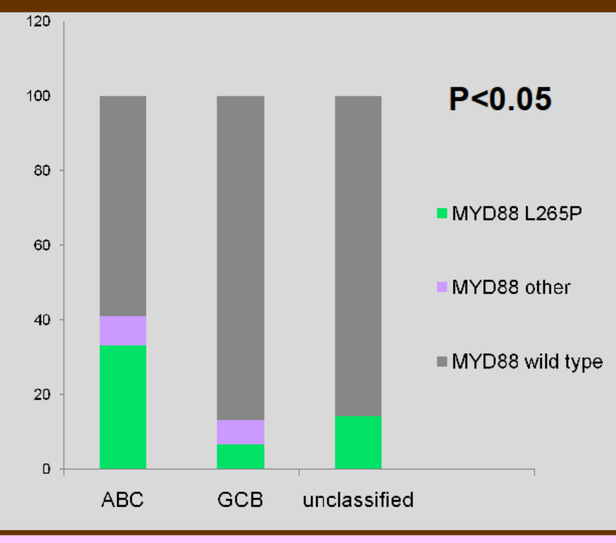
- Diffuse large B-cell lymphoma (DLBCL) is a biological and clinical heterogeneous disease.
- Most patients with unfavorable prognostic are activated B-cell (ABC) DLBCL subtype and it most likely relies on the constitutive activation of NF-κB transcription complex blocking apoptosis.
- NF-κB pathway can be simultaneously activated by B-cell receptor and Toll-like receptors (TLR).
- Somatic mutations of *MYD88* in this TLR pathway increase the NF-κB transcription capacity.

## PATIENTS AND METHODS

- 213 patients (115M / 98F; median age, 65 years), diagnosed with DLBCL *de novo* according WHO classification between 2002 and 2012.
- Screening for the most frequent *MYD88* mutations (L265P, M232T, S219C, V217F, S222R) was performed by using an allele-specific PCR assay.
- Main clinico-biological variables were recorded and analyzed according to *MYD88* mutational status.
- Median follow-up for surviving patients: 6.0 years (range 0.78-12)

## RESULTS

- *MYD88* mutation: **47 cases (22%)**
  - L265P: 39 cases
  - S219C: 4 cases
  - M232F: 4 cases
  - No V217F, S222R
- Cell of origin (N=129)
  - ABC: 54 cases
  - GCB: 61 cases
  - unclassified: 14 cases




**Biological features of 213 patients according to *MYD88* mutational status**

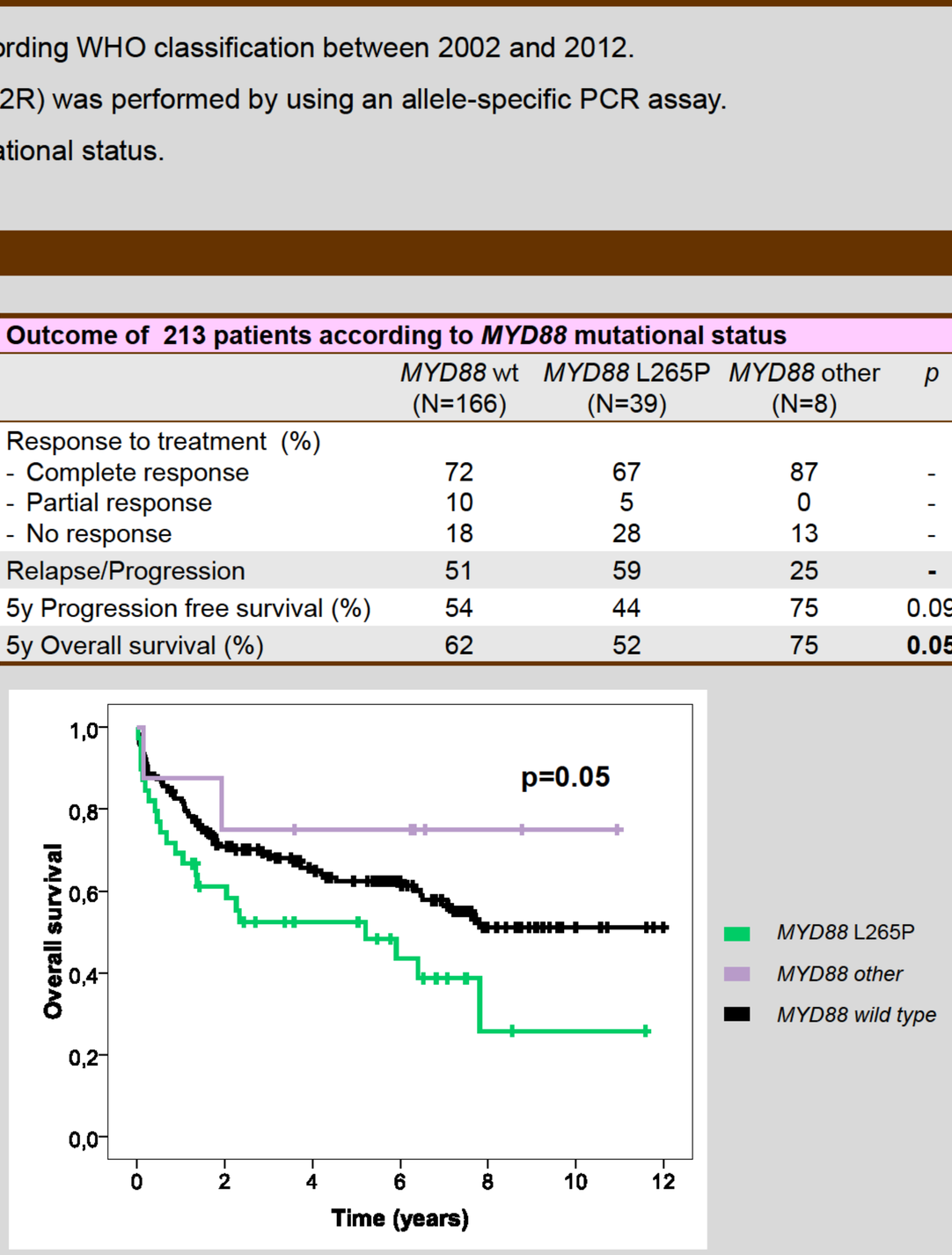
| | *MYD88* wt (N=166) | *MYD88* L265P (N=39) | *MYD88* other (N=8) | *p* |
|---|---|---|---|---|
| *MYC* rearrangement (n=129) | 11 | 4 | 0 | - |
| *BCL2* rearrangement (n=186) | 21 | 8 | 17 | **0.05** |
| *BCL6* rearrangement (n=120) | 21 | 18 | 40 | - |
| BCL2 expression (n=169) | 66 | 74 | 43 | - |
| BCL6 expression (n=191) | 68 | 71 | 87 | - |
| MYC expression (n=94) | 52 | 33 | 33 | - |
| MYC/BCL2 co-expression (n=71) | | | | |
| MYC (-) / BCL2 (-) | 26 | 6 | 0 | - |
| MYC (+/-) / BCL2 (-/+) | 33 | 75 | 100 | - |
| MYC (+) / BCL (+) | 41 | 19 | 0 | **0.03** |
| Ki67 ≥ 80% | 60 | 73 | 12.5 | **0.008** |

**Clinical features of 213 patients according to *MYD88* mutational status**

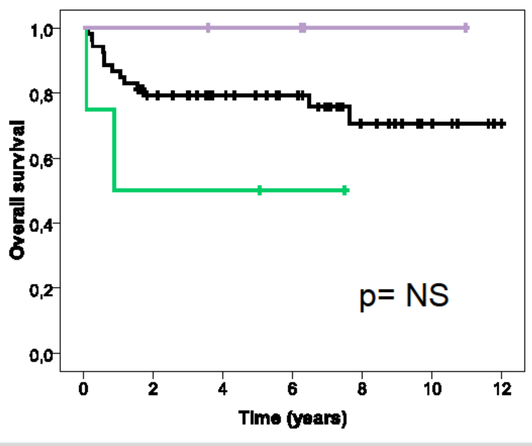
| | *MYD88* wt (N=166) | *MYD88* L265P (N=39) | *MYD88* other (N=8) | *p* |
|---|---|---|---|---|
| Male (%) | 77 | 19 | 4 | - |
| Female (%) | 79 | 17 | 4 | - |
| Median age | 63 | 69 | 69 | - |
| > 60 years(%) | 53 | 79 | 62 | **0.01** |
| B symptoms (%) | 42 | 32 | 75 | 0.07 |
| Extranodal involvement (%) | 51 | 69 | 37 | 0.08 |
| - Bone marrow | 14 | 23 | 12 | - |
| - CNS | 1.2 | 0 | 0 | - |
| - Testis | 0.6 | 10 | 0 | **0.002** |
| - Breast | 0.6 | 5 | 0 | 0.09 |
| Ann Arbor III-IV | 55 | 62 | 50 | - |
| LDH > 450 U/L | 42 | 61 | 25 | **0.05** |
| IPI | | | | |
| - Low risk | 33 | 29 | 25 | - |
| - Low/intermediate risk | 25 | 16 | 37.5 | - |
| - Intermediate/high risk | 23 | 26 | 12.5 | - |
| - High risk | 19 | 29 | 25 | - |

**Outcome of 213 patients according to *MYD88* mutational status**

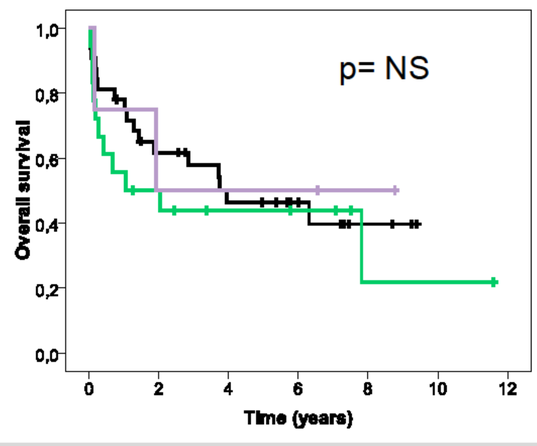
| | *MYD88* wt (N=166) | *MYD88* L265P (N=39) | *MYD88* other (N=8) | *p* |
|---|---|---|---|---|
| Response to treatment (%) | | | | |
| - Complete response | 72 | 67 | 87 | - |
| - Partial response | 10 | 5 | 0 | - |
| - No response | 18 | 28 | 13 | - |
| Relapse/Progression | 51 | 59 | 25 | - |
| 5y Progression free survival (%) | 54 | 44 | 75 | 0.09 |
| 5y Overall survival (%) | 62 | 52 | 75 | **0.05** |




GCB-DLBCL




ABC-DLBCL




| Overall survival multivariate analysis (n=110) | | |
|---|---|---|
| Variable | p | Hazard ratio |
| IPI (low, intermediate and high risk | **0.002** | 2.915 |
| Cell of origin (GCG *vs.* ABC) | **0.002** | 2.481 |

## CONCLUSIONS

- ***MYD88* L265P mutation highlights a subpopulation of older patients with activated B-cell like diffuse large B-cell lymphoma with specific extranodal involvement and unfavorable prognosis.**
- **Other *MYD88* mutations seem to appear in also old patients but with favorable outcome.**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