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DLBCL

# Bortezomib plus R-CHOP for distinct molecular DLBCL subtypes: Results from the phase III trial REMoDL-B

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On 5 April 2019, Andrew Davies from the University of Southampton, Southampton, UK, and colleagues, published in the *Lancet Oncology* results from the phase III clinical trial REMoDL-B (randomised evaluation of molecular guided therapy for diffuse large B-cell lymphoma with bortezomib; NCT01324596).

In this multicenter, randomized, open-label, adaptive, superiority, phase III trial, the efficacy of bortezomib addition to standard chemoimmunotherapy for diffuse large B-cell lymphoma (DLBCL) was investigated. Initially, all patients received one cycle of standard rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisolone (R-CHOP) treatment. Following that, gene-expression analysis was undertaken, patients were stratified by molecular DLBCL subtype (germinal center B-cell [GCB], activated B-cell [ABC], or unclassified) and further randomized to continue R-CHOP alone or with the addition of bortezomib. The primary endpoint of the study was 30-month progression-free survival (PFS) for the GCB and ABC populations. Secondary endpoints included, 30-month PFS according to cell-of-origin subgroup, overall survival (OS), disease-free survival (DFS), response rates and duration, and toxicity.

**Study design & baseline characteristics**

- N = 918 patients with previously untreated, histologically-confirmed DLBCL, with an Eastern Cooperative Oncology Group (ECOG) performance status ≤ 2, and bulky stage I or disease stage II–IV,
- Molecular DLBCL subtypes:
  - ABC: 26.6% of patients (n = 244)
  - GCB: 51.7% of patients (n = 475)
  - Unclassified: 21.7% of patients (n = 199)
- All patients initially received one 21-day R-CHOP cycle and then were randomly 1:1 assigned to R-CHOP or R-CHOP plus bortezomib (RB-CHOP) as below:
  - R-CHOP (n = 459; five additional 21-day cycles):
    - R: 375 mg/$m^2$ intravenously (IV) on Day 1
    - C: 750 mg/$m^2$ IV on Day 1
    - H: 50 mg/$m^2$ IV on Day 1
    - O: 1.4 mg/$m^2$ (maximum 2 mg) IV on Day 1
    - P: 100 mg orally once daily on Days 1–5
  - RB-CHOP (n = 459; five 21-day cycles):
    - R-CHOP as above

- Bortezomib: 1.3 mg/m$^2$ IV or 1.6 mg/m$^2$ subcutaneously on Days 1 and 8 for cycles 2–6
- Further treatment cycles were given when patient neutrophils had recovered to 1.0 × 10$^9$/L and platelets to 100 × 10$^9$/L

- Primary analysis on the modified intention-to-treat (mITT) populations comprising the GCB and ABC subgroups
- Baseline characteristics were well balanced between the R-CHOP and RB-CHOP arms:

| **DLBCL molecular subtype** | **R-CHOP arm, n (%)** | **RB-CHOP arm, n (%)** |
|---|---|---|
| Activated B cell | 121 (26·4%) | 123 (26.8%) |
| Germinal centre B cell | 240 (52·3%) | 235 (51.2%) |
| Unclassified | 98 (21.4%) | 101 (22.0%) |

**Key findings**

- The following statistically significant clinical differences between molecular DLBCL subgroups were observed:

| | **ABC subgroup (n = 244)** | **GCB subgroup (n = 475)** | **Unclassified subgroup (n = 199)** | ***P* value (ABC *vs* GCB)** |
|---|---|---|---|---|
| Age, years | 67 (22–86) | 63 (20–82) | 63 (20–84) | 0.0045 |
| Bone marrow involvement | 33/240 (13.8%) | 66/465 (14.2%) | 42/191 (22.0%) | 0.017 |
| Bulky disease >10 cm | 50/241 (20.7%) | 158/467 (33.8%) | 55/198 (27.8%) | < 0.0001 |

- Nineteen patients were identified with primary mediastinal lymphoma. Of those, 74% (n = 14) had been allocated to the GCB group and 26% (n = 5) to the unclassified group
- After a median follow-up of 30 months:

- 30-month PFS rates:
  - R-CHOP: 70.1% (95% CI, 65.0–7)
  - RB-CHOP: 74.3% (95% CI, 69.3–7)
  - Comparison: HR = 0.86; (95% CI, 0.65–1.13); *P* = 0.28
    - Adjusted HR = 0.84; (95% CI, 0.64–1.11); *P* = 0.23
  - OS events (i.e. deaths):
    - R-CHOP: 62 events
    - RB-CHOP: 54 events
  - 30-month OS rates:
    - R-CHOP: 82.7% (95% CI, 78.2–3)
    - RB-CHOP: 83.6% (95% CI, 79.0–3)
    - Comparison: HR = 0.89; (95% CI, 0.62–1.28); *P* = 0.52
      - Adjusted HR = 0.85; (95% CI, 0.59–1.23); *P* = 0.40
    - After a median follow-up of 42.3 months:
      - 30-month PFS rates:
        - R-CHOP: 70.6% (95% CI, 65.5–0)
        - RB-CHOP: 75.2% (95% CI, 70.3–4)
        - Comparison: adjusted HR = 0.82; (95% CI, 0.63–1.08); *P* = 0.16
      - Secondary analysis by DLBCL molecular subtype revealed that bortezomib did not significantly affect PFS in the ABC (adjusted HR = 0.78, [95% CI, 0.51–1.21]; *P* = 0.27), GCB (HR = 0.85, 95% CI, [0·60–1.20]; *P* = 0.35), or unclassified patient subgroup (HR = 1.29, [95% CI, 0.77–2.16]; *P* = 0.34)

**Safety**

- Bortezomib was generally well tolerated, with the most common Grade ≥ 3 adverse events (AEs) being (R-CHOP *vs* RB-CHOP):
  - Hematological toxicity (39.8% *vs* 1%)
- No significant increase in the proportion of patients with Grade ≥ 3 neutropenia, febrile neutropenia, thrombocytopenia or anemia was observed in the RB-CHOP group as compared to the R-CHOP arm
- Any grade neuropathy was more frequently observed in the RB-CHOP (56.8%) versus the R-CHOP arm (41.6%; *P*< 0.0001)
- Serious adverse events:
  - R-CHOP: 42.5% (n = 190/447)
  - RB-CHOP: 50.2% (n = 223/444)
- Deaths in the safety population:
  - R-CHOP: 16.3% (n = 73/447)

    - RB-CHOP: 15·3% (n = 68/444)
- Reason of death:
    - Progressive lymphoma:
        - R-CHOP: 68·5% (n = 50/73)
        - RB-CHOP: 79·4% (n = 54/68)
    - Treatment-related:
        - R-CHOP: 6.8% (n = 5/73)
        - RB-CHOP: 9% (n = 4/68)
    - In the ITT population, dose reductions of any treatment drug were less frequent in the R-CHOP arm (34.5%), when compared to the RB-CHOP group (42.9%)

**Conclusion**

This multicenter phase III trial with real-time DLBCL molecular characterisation showed that bortezomib addition to R-CHOP did not improve PFS in patients with DLBCL, despite their molecular subtype (ABC, GCB or unclassified)

**References**

1. Davies A. *et al*. Gene-expression profiling of bortezomib added to standard chemoimmunotherapy for diffuse large B-cell lymphoma (REMoDL-B): an open-label, randomised, phase 3 trial. *Lancet Oncol*. 2019 Apr 1. pii: S1470-2045(18)30935-5. DOI: 10.1016/S1470-2045(18)30935-5 [Epub ahead of print].