LymphomaHub

DLBCL

Ibrutinib plus R-CHOP for non-germinal center DLBCL: Results from a phase III trial

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On 22 March 2019, Anas Younes from Memorial Sloan Kettering Cancer Centre, New York, USA and colleagues, published in the *Journal of Clinical Oncology* results from a phase III clinical trial that investigated the efficacy of ibrutinib and rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) in patients with untreated non-germinal center B-cell (non-GCB) diffuse large B-cell lymphoma (DLBCL).

In this randomized, double-blind, placebo-controlled multicenter study (NCT01855750), the efficacy and safety of ibrutinib plus R-CHOP was compared to placebo plus R-CHOP in patients with non-GCB DLBCL. The primary endpoint was investigator-assessed event-free survival (EFS) in the intent-to-treat (ITT) population and the activated B-cell (ABC) DLBCL subgroup. Secondary endpoints included progression-free survival (PFS), overall survival (OS), and safety.

Study design & baseline characteristics

- N = 838 DLBCL patients with the non-GCB molecular subtype (ITT population)
- The ABC DLBCL subtype was confirmed in 75.9% (n = 567) of patients across the two cohorts
- Patients were randomized (1:1 ratio) for six or eight treatment 21-day cycles to either:
  - R-CHOP + placebo (n = 419):
    - R: 375 mg/m^2 intravenously
    - C: 750 mg/m^2 intravenously
    - H: 50 mg/m^2 intravenously
    - O: 1.4 mg/m^2 (maximum 2 mg) intravenously
    - P: 100 mg daily orally
  - R-CHOP + ibrutinib (n = 419):
    - Ibrutinib: 560 mg daily orally
    - R-CHOP as above
  - Median patient age: 62.0 years
  - Median time from diagnosis to treatment: 27 days
  - Baseline characteristics were well balanced between the two arms
  - Median follow-up: 34.8 months

Key findings

- EFS was not significantly increased by the addition of ibrutinib to R-CHOP (HR = 0.934; [95% CI, 0.726–200]; *P* = 0.5906), neither in the ITT population analysis nor in the ABC population analysis (HR = 0.949; [95% CI, 0.704–1.279]; *P* = 0.7311)
- PFS was not significantly increased by the addition of ibrutinib to R-CHOP (HR = 0.917; [95% CI, 0.710–1.183]; *P* = 0.5027)
- OS was not significantly increased by the addition of ibrutinib to R-CHOP (HR = 0.991; [95% CI, 0.712–1.380]; *P* = 0.9593)
- Overall response rate (ORR; ITT population):
  - R-CHOP + placebo: 93.1%
  - R-CHOP + ibrutinib: 89.3%
  - Comparison: *P* = 0.0515
- Complete response (CR; ITT population):
  - R-CHOP + placebo: 68.0%
  - R-CHOP + ibrutinib: 67.3%
  - Comparison: *P* = 0.8229
- Central nervous system relapse incidence:
  - R-CHOP + placebo: 3.8%
  - R-CHOP + ibrutinib: 2.4%
- Proportion of patients receiving at least six treatment cycles of R-CHOP:
  - R-CHOP + placebo: 90.7%
  - R-CHOP + ibrutinib: 80.8%

Subgroup analysis by age:

- Age and elevated lactate dehydrogenase levels were associated with favourable EFS outcomes
- Exploratory analysis revealed a robust linear association between age and EFS, PFS, and OS (*P* = 0.0365)
- Multivariate analysis revealed that patients < 65 years old had a more favourable outcome with R-CHOP + ibrutinib than older
- Among patients < 60 years old:
  - R-CHOP + ibrutinib improved EFS when compared to R-CHOP + placebo (HR = 0.579; [95% CI, 0.380–0.881])
  - R-CHOP + ibrutinib improved PFS when compared to R-CHOP + placebo (HR = 0.556; [95% CI, 0.359–0.860])
  - R-CHOP + ibrutinib improved OS when compared to R-CHOP + placebo (HR = 0.330; [95% CI, 0.162–0.673])
  - ORR was similar between arms in younger patients (R-CHOP + ibrutinib: 93.6% *versus* R-CHOP + placebo: 94.6%)

- CR rates were similar between arms in younger patients (R-CHOP + ibrutinib: 71.2% *versus* R-CHOP + placebo: 69.9%)
- Durable partial response longer than six months was more frequent in the R-CHOP + ibrutinib arm (57.1%), when compared to the R-CHOP + placebo arm (34.8%)

- Among patients ≥ 60 years old:
  - R-CHOP + ibrutinib reduced EFS when compared to R-CHOP + placebo (HR = 1.228; [95% CI, 0.887–1.699])
  - R-CHOP + ibrutinib decreased PFS when compared to R-CHOP + placebo (HR = 1.200; [95% CI, 0.866–1.664])
  - R-CHOP + ibrutinib decreased OS when compared to R-CHOP + placebo (HR = 1.440; [95% CI, 0.963–2.152])
  - ORR was similar between arms in younger patients (R-CHOP + ibrutinib: 86.7% *versus* R-CHOP + placebo: 91.8%)

Safety

- Any grade treatment-emergent adverse events (TEAEs) occurred in:
  - R-CHOP + placebo: 99%
  - R-CHOP + ibrutinib: 100%
- Grade ≥ 3 TEAES occurred in:
  - R-CHOP + placebo: 87.1%
  - R-CHOP + ibrutinib: 89.9%
- Serious AEs occurred in:
  - R-CHOP + placebo: 34.0%%
  - R-CHOP + ibrutinib: 53.1%
- The most commonly reported SAEs in the ibrutinib + R-CHOP *versus* the placebo + R-CHOP arm, were:
  - Febrile neutropenia: 18.8% *versus*5%
  - Pneumonia: 6.7% *versus*3%
  - Neutropenia: 4.1% *versus*1%
  - Diarrhea: 3.6% *versus*0%
  - Anemia: 3.6% *versus*2%
  - Lung infection: 3.4% *versus*7%
- More patients discontinued all treatment components in the R-CHOP + ibrutinib arm (22.4%) than the R-CHOP + placebo group (13.6%):
  - AEs were the most common reason for this discontinuation (12.2% *versus*3%)
- Rate of AEs leading to death:
  - R-CHOP + placebo: 2.9%
  - R-CHOP + ibrutinib: 4.3%

- SAEs and AEs leading to treatment discontinuation increased with older age in both arms but were more pronounced in the ibrutinib + R-CHOP *versus* the placebo + R-CHOP arm

Conclusions

- In the non-GCB population (ABC subtype) addition of ibrutinib to R-CHOP did not improve efficacy in patients with untreated DLBCL
- Age seemed to be significantly associated with treatment outcomes after ibrutinib + R-CHOP, with patients younger than 60 years having a prolonged PFS, EFS, and OS, when compared with patients receiving R-CHOP + placebo
- In older patients (≥ 60 years), ibrutinib + R-CHOP was associated with higher toxicity

References

1. Younes A. *et al*. Randomized Phase III Trial of Ibrutinib and Rituximab Plus Cyclophosphamide, Doxorubicin, Vincristine, and Prednisone in Non-Germinal Center B-Cell Diffuse Large B-Cell Lymphoma. *J Clin Oncol.* 2019 Mar 22:JCO1802403. DOI: 10.1200/JCO.18.02403 [Epub ahead of print].