LymphomaHub

FL, MZL

ASH 2018 | Results from the phase III AUGMENT trial: Lenalidome plus rituximab for R/R FL and MZL

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On Sunday 2 December 2018, during the 60th Annual Meeting of the American Society of Hematology (ASH), San Diego, CA, John Leonard from Weill Cornell Medicine and New York Presbyterian Hospital, New York, NY, USA, presented the results of the phase III trial AUGMENT (Abstract #445; Oral Session #623).

AUGMENT (NCT01938001) is a multicenter, randomized, double-blind, phase III study that investigated the efficacy and safety of lenalidomide plus rituximab in relapsed or refractory (R/R) indolent non-Hodgkin lymphoma (NHL) patients. This regimen was compared to single-agent rituximab administration, which represents the Food and Drug (FDA) approved regimen for R/R low-grade or follicular CD20-positive B-cell NHL. The primary endpoint of the study was progression-free survival (PFS) as assessed by Independent Review Committee (IRC). Secondary endpoints included, overall response rate (ORR), complete response (CR), duration of response (DoR), time-to-next anti-lymphoma treatment (TTNLT), overall survival (OS), and safety.

Study design

- N = 358 R/R follicular lymphoma Grade 1–3a (FL) or marginal zone lymphoma (MZL) patients, who were previously treated with ≥ 1 prior systemic therapy, but not refractory to rituximab
- Patients were stratified by prior rituximab treatment (yes or no), time since last anti-lymphoma therapy (≤ 2 years *vs* > 2 years, and histology (FL *vs* MZL)
- Patients were then randomized 1:1 for up to year or until disease progression (PD) or unacceptable toxicity, to either:
  - Lenalidomide + rituximab (R^2; n = 178): oral lenalidomide, 20 mg per day from D1–21 for 12 cycles (28-day cycles) + intravenous rituximab, 375 mg/m^2 weekly at D1, D8, D15 and D22 of cycle 1 and D1 of cycles 2–5
  - Placebo + rituximab (control; n = 180): placebo + intravenous rituximab, 375 mg/m^2 weekly in cycle 1 and D1 of cycles 2–5
  - Lenalidomide was reduced to 10 mg per day if creatinine clearance was between 10-59 mL/min
  - Prophylactic anticoagulation/antiplatelet Rx was recommended for at risk patients
  - Growth factor use was allowed per ASCO/ESMO guidelines
- Baseline characteristics:
  - R^2:
    - Median age (range): 64 (26–86)
    - FL histology: 83%
    - MZL histology: 17%

- Eastern Cooperative Oncology Group performance status (ECOG-PS) 1–2: 35%
- Ann Arbor stage III–IV: 69%
- Bulky disease (≥ 7 cm or ≥ 3 cm x 3): 25%
- Prior rituximab treatment: 85%
- More or two years since last anti-lymphoma therapy: 50%
- Number or prior lines:
  - One: 57%
  - Two: 17%
  - Three or more: 25%
- Control:
  - Median age (range): 62 (35–88)
  - FL histology: 82%
  - MZL histology: 18%
  - ECOG PS 1–2: 41%
  - Ann Arbor stage III–IV: 77%
  - Bulky disease (≥ 7 cm or ≥ 3 cm x 3): 27%
  - Prior rituximab treatment: 83%
  - More or two years since last anti-lymphoma therapy: 51%
  - Number or prior lines:
    - One: 54%
    - Two: 23%
    - Three or more: 23%
  - Data cut off: 22 June 2018

Results

- Median PFS (median follow-up: 28.3 months) by IRC in the intention-to-treat (ITT) population:
  - R^2: 39.4 (22.9–not reached) months
  - Control: 14.1 (12.4–17.7) months
  - Comparison: HR = 0.46; (95% CI, 0.34–62); $P < 0.0001$
- Two-year OS (median follow-up: 28.3 months) in the ITT population:
  - R^2: 93% (95% CI, 87–96%)
  - Control: 87% (95% CI, 81–92%)
  - Comparison: HR = 0.61 (95% CI, 0.33–1.13)

- OS data not mature as 16 deaths occurred in the R^2 and 26 deaths in the control arm

- Two-year OS (median follow-up: 28.3 months) in the FL subgroup:
  - R^2: 95% (95% CI, 90–98%)
  - Control: 86% (95% CI, 79–91%)
  - Comparison: HR = 0.45 (95% CI, 0.22–0.91)
  - Deaths: 11 in R^2 and 21 in the control arm
- ORR response rates by IRC assessment (ITT):
  - R^2: 78%
  - Control: 53%
  - Comparison: $P < 0.0001$
- CR rates by IRC assessment (ITT):
  - R^2: 34%
  - Control: 18%
  - Comparison: $P = 0.001$
- Partial response (PR) rates by IRC assessment (ITT):
  - R^2: 44%
  - Control: 35%
- Median DoR (ITT):
  - R^2: 36.6 months (95% CI, 22.9–not reached)
  - Control: 21.7 months (95% CI, 12.8–6)
  - Comparison: HR = 0.53; (95% CI, 0.36–79); $P = 0.0015$

Safety

- Selected all-grade treatment-emergent AEs more common in the R^2 arm (*vs* control; ≥ 10% difference) were:
  - Infections: 63% (*vs* 49%)
  - Cutaneous reactions: 32% (*vs* 12%)
  - Constipation: 26% (*vs* 14%)
  - Thrombocytopenia: 15% (*vs* 4%)
  - Tumor flare reaction: 11% (*vs* 1%)
- Grade 3–4 AEs were reported in:
  - R^2: 69%
  - Control: 32%
- Grade 3–4 AEs more common in the R^2 arm (*vs* control; ≥ 10% difference) were:

  - Neutropenia: 50% (*vs* 13%)
  - Leukopenia: 7% (*vs* 2%)
- Grade 5 AEs were reported in 2 patients in each arm
- Sixty-six percent of patients had at least one dose interruption of lenalidomide due to adverse events (AEs)
- Growth factor were administered to:
  - R^2: 36% of patients
  - Control: 12% of patients
- Patients completing all treatment cycles:
  - R^2: 71%
  - Control: 61%
- PD was more frequent in the control arm and was the most common reason for treatment discontinuation in both arms (R^2: 21 *vs* control: 54)

Conclusions

- R^2 (lenalidomide + rituximab) demonstrated superior efficacy over rituximab monotherapy plus placebo in R/R FL and MZL patients
- The greater efficacy and manageable toxicity of R^2 (lenalidomide + rituximab) allowed more patients to complete treatment when compared to the control arm (rituximab + placebo)
- AEs differed between arms with neutropenia, infections, tumor flare, and cutaneous reactions being more common in the R^2 arm; however fewer cases of SPMs and histological transformations occurred in the R^2 arm

References

1. Leonard J.P. *et al*. AUGMENT: A Phase III Randomized Study of Lenalidomide Plus Rituximab (R2) Vs Rituximab/Placebo in Patients with Relapsed/Refractory Indolent Non-Hodgkin Lymphoma. Oral Abstract #445: *ASH 60th Annual Meeting and Exposition*, December 2018, San Diego, CA