

Report from the American Society of Hematology Annual Meeting

Lymphoma

EFFICACY AND SAFETY OF OBINUTUZUMAB

Mita Manna, MD, FRCPC, Lymphoma Fellow, Department of Hematology, University of Calgary, Tom Baker Cancer Centre; **Douglas A Stewart, MD, FRCPC**, Professor, Departments of Oncology and Medicine, University of Calgary and Tom Baker Cancer Centre, Calgary

TRIAL SUMMARY: Obinutuzumab in previously untreated follicular lymphoma: assessing efficacy, safety and minimal residual disease status

Robert E, Marcus RE, Davies AJ, Ando K, et al. Obinutuzumab-based induction and maintenance prolongs progression-free survival (PFS) in patients with previously untreated follicular lymphoma: primary results of the randomized phase 3 GALLIUM study. ASH Annual Meeting, San Diego, California, December 3-6, 2016, Abstract 6.

This study reports results of a planned interim efficacy and safety analysis of GALLIUM, a global, open-label, randomized phase 3 study comparing the efficacy and safety of rituximab (R) or obinutuzumab (O) with chemotherapy followed by maintenance as first-line treatment in indolent non-Hodgkin lymphoma (iNHL). Patients (pts) were ≥ 18 years, with previously untreated, grade 1 to 3a follicular lymphoma (FL) or stage III/IV chemotherapy-naive marginal zone lymphoma (MZL). Patients were randomized 1:1 to R 375 mg/m² on day 1 of each cycle or O 1000 mg on days 1, 8 and 15 of cycle 1, and day 1 of subsequent cycles.

COMMENTARY: Chemoimmunotherapy involving rituximab (R) has resulted in PFS and overall survival (OS) advantages in patients with previously untreated advanced-stage follicular lymphoma (FL) and other iNHL. Despite the efficacy of rituximab, relapse occurs in over 30% of patients. Obinutuzumab (O) is a glycoengineered type II anti-CD20 monoclonal antibody that results in higher lev-

Responding patient then received R or O every 2 months for 2 years or until disease progression. The primary endpoint was investigator-assessed progression-free survival (PFS).

Results: The 1202 FL patients (R-chemo n=601; O-chemo n=601) included in the analysis had a median age of 59 years and 53.2% were female. Chemotherapy received was bendamustine in 57.1%, CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) in 33.1%, and CVP (cyclophosphamide, vincristine, prednisone) in 9.8%. After a median followup of 34.5 months (range, 0–54.5 months), there was a 34% reduction in the risk of progression or death (HR, 0.66; 95% CI, 0.51–0.85; p=0.001). Three-year investigator-assessed PFS rates were: O-chemo, 80.0% (95% CI, 75.9%–83.6%); R-chemo, 73.3% (95% CI, 68.8%–77.2%). The frequency of fatal adverse events (AEs) was similar (O-chemo, 4.0%; R-chemo, 3.4%). AEs led to treatment discontinuation in 16.3% of patients on O-chemo and 14.2% of patients on R-chemo in the absence of disease progression. Frequency of some AEs, e.g. infusion-related reactions, cytopenias and infections, was higher with O-chemo.

els of antibody-dependent cellular cytotoxicity and direct cell death than rituximab.

A planned interim efficacy analysis of the phase 3 GALLIUM study comparing O-based to R-based initial therapy for FL was presented at the 2016 ASH Annual Meeting.¹ O-based therapy was associated with superior 3-year investigator-assessed PFS of 80.0% relative to 73.3%

for R-based therapy (HR, 0.66, $p=0.001$). Unfortunately, due to dose and schedule differences between the arms, it is impossible to determine if this superior outcome was due to a better drug, or simply more drug. The 3-year PFS rates as assessed by the Independent Review Committee were 81.9% vs 77.9% for O- vs R-based therapy, and the 3-year OS rates were similar between the arms. Of note, O-based therapy resulted in a higher frequency of grade 3 to 5 adverse events.

Minimal residual disease (MRD) is a predictor of disease-free and overall survival in patients with iNHL. In another presentation at ASH on the GALLIUM study, Pott and colleagues assessed for MRD on blood and marrow samples at mid induction (MI) and end of induction (EOI) in 1101 FL patients enrolled in the GALLIUM study using quantitative RT-PCR for t(14:18) and clonal IghV (immunoglobulin heavy chain variable region) rearrangement.² Molecular remissions in marrow were higher in the O-chemo vs R-chemo arm (93% vs 83%; $p=0.0014$), whereas blood clearance was similarly high in both arms (96% vs 94%; $p=0.22$). Although R-bendamustine gave higher molecular response rates compared to R-CHOP and R-CVP, MRD status was similar between all three O-based chemotherapy regimens.

The authors of the GALLIUM study conclude that O-based therapy should become a new standard of care for previously untreated patients with FL. Considering that the GALLIUM study reported a minor 4% to 7% absolute improvement in PFS with obinutuzumab at less than a 3-year median followup, no suggestion of any OS improvement, and significantly higher toxicity rates, the authors' conclusion seems to be premature and overstated. Unless further followup of the GALLIUM trial demonstrates a more marked PFS benefit, or an improvement in OS, the superior strategy to treat FL patients in Canada may continue to involve R-based upfront therapy (especially using subcutaneous R), followed by O-based salvage therapy for patients who experience lack of response or early relapse following R-chemotherapy. Important evidence from the GADOLIN trial supporting this latter approach was updated at ASH 2016: rituximab-refractory iNHL patients (79% also refractory to R-CHOP or R-CVP) were randomized to O-bendamustine and O maintenance or to bendamustine alone.

With a median followup of 32 months, the O-therapy arm was associated with an 11-month improvement in median PFS (25.3 vs 14.0 months, $p<0.001$) as well as a significant improvement in OS (76% vs 63%, HR 0.58, $p=0.006$) for R-refractory FL patients.

References

1. Marcus RE, Davies AJ, Ando K, et al. Obinutuzumab-based induction and maintenance prolongs progression-free survival (PFS) in patients with previously untreated follicular lymphoma: primary results of the randomized phase 3 GALLIUM study. ASH Annual Meeting, San Diego, California, December 3-6, 2016, Abstract 6.
2. Pott C, Hoster E, Kehden B, et al. Minimal residual disease in patients with follicular lymphoma treated as first-line with obinutuzumab or rituximab-based immunochemotherapy in the phase 3 GALLIUM study. ASH Annual Meeting, San Diego, California, December 3-6, 2016, Abstract 613.
3. Cheson BD, Trněný M, Bouabdallah K, et al. Obinutuzumab plus bendamustine followed by obinutuzumab maintenance prolongs overall survival compared with bendamustine alone in patients with rituximab-refractory indolent non-Hodgkin lymphoma: updated results of the GADOLIN study. ASH Annual Meeting, San Diego, California, December 3-6, 2016, Abstract 615.

IN BRIEF

Already known

- Chemoimmunotherapy with rituximab offers a survival advantage to patients with advanced follicular lymphoma (FL), but relapse occurs in over 30% of patients.

What this trial showed

- This interim analysis of the phase 3 GALLIUM study comparing obinutuzumab (O) to rituximab as first-line treatment found a slight improvement in progression-free survival (PFS) at 3 years with obinutuzumab, but higher toxicity rates.

Next steps

- Wait to see if more marked PFS benefit of O-chemo emerges with longer followup in the GALLIUM study.
- Utilize O-chemo and O-maintenance for rituximab-refractory relapsed/refractory FL patients.