The 23rd Congress of the European Hematology Association hosted more than 11,700 hematology medical professionals in Stockholm, Sweden from June 14 to 17. We review key sessions on multiple myeloma, chronic lymphocytic leukemia, Hodgkin lymphoma, Epstein-Barr virus positive post-transplant lymphoma, and follicular lymphoma.

**Once-Weekly Versus Twice-Weekly Carfilzomib Dosing Plus Dexamethasone in Patients With Relapsed And Refractory Multiple Myeloma: Results of the Randomized Phase 3 Arrow Study**

- Maria-Victoria Mateos, MD, PhD, Director of the Myeloma Unit, University Hospital of Salamanca-IBSAL in Salamanca, Spain

Among patients with relapsed/refractory multiple myeloma in the randomized phase 3 ARROW trial, higher-dose carfilzomib given once weekly versus twice weekly significantly improved progression-free survival (PFS) and reduced the risk of progression or death. Higher-dose carfilzomib did not affect the overall safety profile, co-lead author Dr. Mateos said in a presentation about the phase 3 ARROW study. “This provides a more convenient schedule and can improve access to an efficacious therapy for patients unable to make twice-weekly visits to the clinic.”

The selective protease inhibitor carfilzomib is approved in the United States as a single agent for patients with relapsed/refractory multiple myeloma who have received 2 or more prior therapies. The approved dose is 27 mg/m² administered intravenously on two consecutive days for 3 weeks (D1, 2, 8, 9, 15 and 16) followed by a 12-day rest period in a 28-day cycle.

Dr. Mateos pointed out that, compared with recent standard treatments in the same population, twice-weekly carfilzomib at 56 mg/m² with dexamethasone or at 27 mg/m² with lenalidomide and dexamethasone have demonstrated significant improvements in PFS and overall survival (OS).

Promising results from CHAMPION-1, a phase 1/2 study designed to test a more convenient carfilzomib regimen, led ARROW investigators to further explore once-weekly carfilzomib. CHAMPION-1 patients had relapsed/refractory multiple myeloma after 1–3 prior regimens and received once-weekly carfilzomib. The overall response rate was 77%; median PFS was 12.6 months. Analysis showed 70 mg/m² to be the maximum tolerated dose (MTD). Grade 3 or higher adverse events occurred in 62% of patients receiving the MTD.

In the ARROW study, 478 relapsed/refractory patients (median age 66 years, 56.5% of whom were age 65 years or older) with exposure to 2–3 prior lines of therapy were randomly assigned 1:1 to once-weekly or twice-weekly carfilzomib. Nearly all (99%) had received bortezomib (42% were refractory), and 84% had received lenalidomide. Patients in the once-weekly group received 20 mg/m² carfilzomib for the first cycle, and 70 mg/m² for the remaining cycles. Patients in the twice-weekly arm received 20 mg/m² for the first cycle, and 27 mg/m² for the remaining cycles.

Cumulative carfilzomib doses were 1,799 mg/m² and 1,148 mg/m² in the once-weekly and twice-weekly arms, respectively. Median duration of treatment was 38.0 weeks in the once-weekly arm and 29.1 weeks in the twice-weekly arm.

The primary endpoint was progression-free survival. Median PFS was 11.2 months in the once-weekly arm and 7.6 months in the twice-weekly arm (hazard ratio, 0.693; \( P = 0.0029 \)), with median follow-up times of 12.6 months and 12.0 months, respectively. Subgroup analysis, Dr. Mateos noted, showed benefit consistently for the once-weekly treatment across age, baseline ECOG and ISS stage, and baseline creatinine clearance groups. The benefit was also observed regardless of the number of prior lines of therapy, refractoriness to bortezomib or lenalidomide. The overall response rates were 62.9% and 40.8% for the once- and twice-weekly regimens (\( P < 0.0001 \)). Complete responses were reported in 5% and 2%, respectively, and very good partial response rates of 34% and 13% were also reported. Stringent complete responses were observed only in the once-weekly arm.

Median OS was not yet reached in either treatment group. Death rates were 24.2% and 28.6% in the once- and twice-weekly carfilzomib groups, respectively (hazard ratio, 0.80; \( P = 0.214 \)).

Serious adverse event rates were similar (43% and 41% for the once- and twice-weekly groups), as were discontinuations attributable to treatment-related adverse events (13% and 12%, respectively). Exposure-adjusted death rates for serious adverse events were also similar (2% and < 1%). “Safety findings were consistent with the known safety profile of carfilzomib, and no new risks were identified,” Dr. Mateos said.

She concluded, “Thus, in comparison with twice-weekly carfilzomib at the 27 mg/m² schedule, once-weekly carfilzomib at 70 mg/m² showed a favorable benefit–risk profile for patients with relapsed/refractory multiple myeloma.”

**Overall Survival Benefit of Obinutuzumab Over Rituximab When Combined With Chlorambucil In Patients With Chronic Lymphocytic Leukemia and Comorbidities: Final Survival Analysis Of The CLL11 Study**

- Valentin Goede, MD, Center of Integrated Oncology, University Hospital, Cologne, Germany

The use of obinutuzumab plus chlorambucil as front-line therapy in older patients with chronic lymphocytic leukemia (CLL) and comorbidities was supported by final analysis of the CLL11 study, a head-to-head comparison of chlorambucil with...
either obinutuzumab, a type 2 glycoengineered CD20-antibody, or with the type 1 antibody rituximab.

Chemotherapy alone was still standard treatment for CLL when the CLL11 study was launched in 2009, and obinutuzumab was an investigational agent. Obinutuzumab was approved in combination with chlorambucil for the treatment of CLL in November 2013. “CLL is a disease that primarily affects older people,” said Dr. Goede, study leader, “and the purpose of [CLL11] was to improve treatment for these elderly CLL patients with comorbidities by introducing immunochemo-
therapy.”

The CLL11 trial evaluated efficacy and safety in 781 patients with previously untreated CLL and comorbidities. Dr. Goede’s presentation added about 2 more years of follow-up to earlier analyses that had established the superiority of both obinutu-
zumab (1,000 mg IV on D1, D6 and D15 of C1 and D1 of C2-6) plus chlorambucil (0.5 mg/kg orally on D1 and D15 of C1-6) and rituximab (375 mg/m² IV on D1 of C1 and 500 mg/m² on D1 of C2-6) plus chlorambucil over chlorambucil alone. The primary endpoint was investigator-assessed progression-free survival. Median patient age was 73 years. An updated analy-
sis in 2015 after a median observation time of 39.0 months revealed a median PFS of 28.7 months in the obinutuzumab plus chlorambucil arm and 15.7 months in the rituximab plus chlorambucil arm (hazard ratio, 0.46 [0.38–0.55]; P < 0.0001).

The median time to next treatment (TTNT) was 51.1 months in the obinutuzumab plus chlorambucil arm and 15.7 months in the rituximab plus chlorambucil arm (hazard ratio, 0.49; 95% confidence interval, 0.41–0.58; P < 0.0001). The secondary analysis of median TTNT was 56.4 months and 34.9 months for the obinutuzumab and rituximab arms, respectively (haz-
ard ratio, 0.58, 95% confidence interval 0.4–0.73; P < 0.0001). Median overall survival (OS) had not been reached in either arm of the trial, and there were no new safety signals.

In Dr. Goede’s comparison of obinutuzumab plus chloram-
bucil versus rituximab plus chlorambucil, median observation time was 59.4 months. Median PFS was 28.9 months in the obinutuzumab plus chlorambucil arm and 15.7 months in the rituximab plus chlorambucil arm (hazard ratio, 0.49; 95% confidence interval, 0.41–0.58; P < 0.0001). The secondary analysis of median TTNT was 56.4 months and 34.9 months for the obinutuzumab and rituximab arms, respectively (hazard ratio, 0.58, 95% confidence interval 0.4–0.73; P < 0.0001). Median OS was not reached in the obinutuzumab arm and was 73.1 months in the rituximab arm (hazard ratio, 0.76; 95% confidence interval, 0.60–0.97; P = 0.0245). The overall survival advantage for obinutuzumab plus chlorambucil was generally consistent across subgroups, Dr. Goede noted.

Disease progression, the main cause of death, was reported at the rate of 16% in the obinutuzumab plus chlorambucil group and 15% in the rituximab plus chlorambucil group. The reduc-
tion in risk of progressive disease or death was 51%. Dr. Goede observed that obinutuzumab plus chlorambucil prolonged TTNT relative to rituximab plus chlorambucil by about 1.5 years while attaining an absolute treatment-free duration of about four years.

Grade 3–5 adverse events were reported in 72% of patients in the obinutuzumab plus chlorambucil group and in 60% of the rituximab plus chlorambucil group. Grade 5 (fatal) adverse event rates were 7% in the obinutuzumab arm and 10% in the rituximab arm. Secondary malignancy rates were identical at 4% for each arm, as were infection rates at < 1%. Late-onset adverse events (prolonged neutropenia, late-onset neutro-
penia, second malignancy, squamous cell carcinoma, basal cell carcinoma) were all low and similar between groups. No new safety or new late-onset toxicities were detected.

“We consider these results clinically meaningful and also remarkable in the context of the long follow-up of the trial,” Dr. Goede said. He added that the study findings suggest obinutuzumab as the preferred anti-CD20 antibody in future combination regimens for CLL.

Finally, he pointed out that the data are also reassuring regarding the choice of obinutuzumab with chlorambucil as comparators in newer trials, such as those testing ibrutinib with obinutuzumab and a triplet adding venetoclax. “We can expect these to be positive trials for progression-free survival,” he said. Toxicity profiles in these trials of chemotherapy-free regimens will be “of interest” and are characteristically differ-
ent from chemotherapy toxicity profiles.

**Moxetumomab Pasudotox in Heavily Pretreated Patients With Relapsed/Refractory Hairy Cell Leukemia: Results of a Pivotal International Study**

- Frank Giles, MD, Developmental Therapeutics Consortium, Chicago, Illinois

Intravenous moxetumomab pasudotox produced deep durable responses and eradicated minimal residual disease in a substantial portion of extensively pretreated patients with relapsed/refractory hairy cell leukemia. Findings were inde-
pendently assessed, Dr. Giles noted in an oral presentation.

Hairy cell leukemia is a rare B-cell malignancy with high CD22 expression. Relapsed/refractory hairy cell leukemia remains incurable, and there is an unmet need for new treat-
ments, Dr. Giles said. Moxetumomab pasudotox is a first-in-
class recombinant immunotoxin composed of a light chain variable domain and a heavy chain variable domain of an anti-
CD22 monoclonal antibody genetically fused to a truncated form of *Pseudomonas* exotoxin PE38.

The pivotal, single-arm, open-label study (NCT01829711) was conducted at 34 centers in 14 countries. Its primary objective was durable complete response rate (complete response with hematologic remission ≥ 181 days). Complete response was defined as hematologic remission ≥ 4 weeks, with no leukemic cells in bone marrow and no hepatomegaly, splenomegaly or lymphadenopathy. Hematologic remission was defined as neutrophils ≥ 1.5 x 10⁹/L, platelets ≥ 100 x 10⁹/L, hemoglobin ≥ 11 g/dL with no transfusion/growth factors ≥ 4 weeks.

The 80 participants (79% male, median age 60 years) had histologically confirmed hairy cell leukemia and one or more of the following: low neutrophils, platelets, hemoglobin or symptomatic splenomegaly. All patients had received two or more systemic prior therapies, including one or more purine nucleoside analogs, and had adequate hepatic and renal func-
tion. Patients received moxetumomab pasudotox 40 μg/kg intravenously on days 1, 3, and 5 of 28-day cycles, up to 6 cycles. Disease response and immunohistochemistry minimal residual disease status were determined by blinded indepen-
dent central review.

The median follow-up was 16.7 months. Durable complete
responses were observed in 48% of patients, complete responses in 51%, and complete response with minimal residual disease in 33%. The overall response rate (complete or partial response) was 79%. Dr. Giles noted that 80% of patients (64/80) achieved hematologic remission, with a median onset of 1.1 months. The median duration of complete remission, hematologic remission from complete response and progression-free survival were not reached. Although sustained B-cell depletion was observed during treatment, levels recovered by 6 months post-treatment, Giles noted.

Grade 3–4 treatment-related adverse events were reported in 30% of patients, with decreased lymphocyte count (7.5%) and hemolytic uremic syndrome (5.0%) being the most common. Although 10 patients developed hemolytic uremic syndrome or capillary leak syndrome, all events resolved with close monitoring, supportive care and/or treatment discontinuation. Dr. Giles characterized the tolerability profile as “acceptable.” In addition to achieving a high rate of independently assessed durable complete response, and eradicating minimal residual disease in the study patients, moxetumomab pasudotox showed a favorable safety profile without immunosuppression/myelosuppression. Long-term outcomes, Dr. Giles speculated, may be improved by clearing minimal residual disease in patients with advanced hairy cell leukemia.

**Brentuximab Venedotin Plus Chemotherapy in High-Risk Advanced-Stage Classical Hodgkin Lymphoma (CHL) Patients: Results of Prespecified Subgroup Analyses From The Echelon-1 Study**

- Martin Hutchings, MD, Rigshospitalet, Copenhagen, Denmark

Results from the ECHELON-1 study reveal that, compared with the overall study population, benefits for brentuximab vedotin plus chemotherapy versus chemotherapy alone were greatest in the subgroup of previously untreated classical Hodgkin lymphoma patients with high-risk features. “These subgroup analyses,” Dr. Hutchings said in an oral presentation, “are critical to the understanding of the data.”

The front-line standard of care for advanced Hodgkin lymphoma in most countries is chemotherapy with doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD). ABVD, however, is associated with myelosuppression, cardiotoxicity and pulmonary toxicity (attributed to bleomycin). Also, 25% to 30% of patients with advanced Hodgkin lymphoma will relapse or become refractory. The aim, in this population, is to achieve cure with minimal long-term toxicity, Dr. Hutchings said.

In phase 1 research in this population, the anti-CD30 antibody brentuximab vedotin in combination with doxorubicin, vinblastine, and dacarbazine demonstrated front-line efficacy. In ECHELON-1, a global open-label, multicenter, randomized phase 3 trial involving patients with previously untreated stage III or IV classic Hodgkin lymphoma, 664 were assigned to receive brentuximab vedotin, doxorubicin, vinblastine, and dacarbazine (A+AVD) and 670 were assigned to receive ABVD. Modified progression-free survival (time to progression, death, or noncomplete response and use of subsequent anticancer therapy) was the primary endpoint.

In the overall study, modified PFS was reduced in the experimental arm (A+AVD) by 23% (P = 0.035), compared with ABVD. There was a trend in the interim overall survival (OS) rate (median not reached) favoring the experimental arm (hazard ratio, 0.73; P = 0.20).

Dr. Hutchings’ subgroup analysis was prespecified and evaluated patients with stage IV disease (A+AVD, n=425; ABVD, n=421) and those with one or more extranodal sites of involvement (A+AVD, n=411; ABVD, n=416). Modified PFS was improved in the experimental arm in stage IV patients (hazard ratio, 0.77, P = 0.023), but not in stage III patients (hazard ratio, 0.92, P = 0.712). A+AVD was favored significantly among patients with more than one extranodal site (hazard ratio, 0.67; P = 0.049) and with one or more extranodal site (hazard ratio, 0.70; P = 0.18).

In addition, the experimental arm showed improved OS in these higher-risk groups. Among patients with stage IV disease, the OS hazard ratio was 0.507 (P = 0.037) for A+AVD versus ABVD. Among patients with one or more extranodal sites, the hazard ratio for OS was 0.431 (P = 0.013). Absolute reductions for both subgroups were about 4% for 2-year OS.

While peripheral neuropathy and neutropenia were more commonly reported for A+AVD, adverse event rates were generally similar across treatments and high-risk subgroups.

“In the ECHELON-1 study, patients with previously untreated classical Hodgkin lymphoma who had high-risk features such as stage IV disease or one or more extranodal sites derived greater benefit from A+AVD versus ABVD compared with the overall study population,” Dr. Hutchings concluded.

**Final Analysis of the AHL2011 Randomized Phase 3 Lyza Study Comparing an Early PET-Driven Treatment De-escalation to a Not-PET-Monitored Strategy in Patients With Advanced Stages of Hodgkin Lymphoma**

- Olivier Casanovas, MD, CHU Le Bocage and INSERM 1231, Dijon, France

Positive emission tomography (PET)-guided therapy after two cycles of escalated BEACOPP (bleomycin, etoposide, doxorubicin hydrochloride, cyclophosphamide, vincristine, procarbazine and prednisone) may allow reduced treatment-related toxicity without impairing disease control in patients with advanced Hodgkin lymphoma who are PET-negative. In an EHA press briefing, Dr. Casanovas said that interim PET positivity after two cycles of escalated BEACOPP (BEAesc) is related to a higher risk of disease progression.

LYSA investigators, Dr. Casanovas said, hypothesized that interim PET might identify a subset of patients with a better outcome suitable for de-escalation treatment after upfront BEACOPP without impairing disease control. Although 6 cycles of BEAesc provides long-term disease control in patients with advanced Hodgkin lymphoma, compared to doxorubicin, vinblastine, vincristine, and dacarbazine (ABVD), it does not improve overall survival and is associated with a higher risk of myelodysplasia/acute leukemia and infertility.

LYSA included previously untreated Hodgkin lymphoma...
patients (N=823) with stage III, IV or high-risk IIB disease to BEACOPP treatment and, after 2 cycles, randomized them 1:1 to continued treatment with standard treatment (arm A) not guided by PET (6 cycles of BEAesc) or to 4 cycles of ABVD in PET-negative patients or 4 cycles of BEAesc for PET-positive patients. The PET-driven arm (B, n = 413) was compared with standard treatment (A, n = 410). Non-inferiority in PFS in the PET-driven arm versus the standard arm was the primary endpoint.

Dr. Casanovas reported that 87% of patients were PET-negative and 13% were PET-positive after two cycles of treatment. Four cycles of subsequent ABVD were then given to 84% of patients in the experimental arm. After a median followup of 50.4 months, 4- and 5-year progression-free survival were similar: 87.1% and 85.7%, respectively, in the experimental arm and 87.4% and 86.2% in the standard arm (P = 0.68; hazard ratio, 1.08, 95% confidence interval, 0.73–1.59). Median overall survival was not reached in either arm with 4- and 5-year rates of 97.1% and 96.4%, respectively, in the experimental arm and 96.9% and 95.2% in the standard arm (P = 0.91; HR = 0.936, 95% confidence interval, 0.42–2.05).

Serious treatment-related adverse events (n = 204) were reported in 119 (26%) patients in the standard arm, and 102 were reported in 62 (17%) patients in the experimental arm. Six patients in the standard arm and 2 in the experimental arm died. The most frequent grade ≥3 adverse events were anemia (11% versus 2%), leukopenia (85% versus 74%), thrombocytopenia (44% versus 15%), and sepsis (7% versus 3%) in the standard arm and experimental arm, respectively.

Dr. Casanovas concluded, “PET performed after 2 cycles of escalated BEACOPP can be safely used to guide subsequent treatment and supports the response-adapted strategy of delivering four cycles of ABVD for patients with negative PET scans after two cycles.” He added, “We reduced the risk of serious adverse events by about 40% in the experimental arm.”

Patients who were PET-positive after 4 cycles of chemotherapy, Dr. Casanovas commented, define a poor outcome subset for whom new treatment options are needed.

### Long-Term Outcomes of Tabelecleucel (Allogeneic Third-Party Ebv-Targeted Cytotoxic T Lymphocytes) For Rituximab-Refractory Post-Transplant Ebv+ Lymphomas: A Single-Center Experience

- Susan E. Prockop, MD, Pediatric Oncologist at Memorial Sloan Kettering Cancer Center, New York, New York

When first-line rituximab therapy fails in patients with Epstein-Barr virus–associated post-transplant lymphoproliferative disorder (EBV-PTLD), treatment is extremely challenging, said Dr. Susan Prockop in an EHA poster presentation. But she reported that her study found tabelecleucel, an “off-the-shelf” allogeneic T-cell therapy, elicited high overall response rates and durable responses in patients with EBV-PTLD for whom first-line therapy failed after allogeneic hematopoietic cell transplant or solid organ transplant.

Tabelecleucel is bioengineered from donors with healthy immune function according to specific HLA restrictions and is stocked in varieties that cover most EBV-PTLD patients. Collected T-cells are exposed to specific EBV antigenic peptides, causing them to become reactive against EBV. These EBV-targeted T-cells are then introduced to the patient, after which, in contact with EBV-expressing tumors, they proliferate, initiate cytotoxicity and produce sustained responses.

Although EBV infection is generally asymptomatic, it is lifelong and implicated in a wide variety of lymphoproliferative disorders, including lymphomas. “In immunocompromised patients, including those undergoing allogeneic hematopoietic cell transplant or solid organ transplant, EBV-PTLD is really an infectious complication of immune suppression. It is a life-threatening condition,” Dr. Prockop said in an interview. Median overall survival in those who do not respond to first-line rituximab after allogeneic hematopoietic cell transplant is 16 to 56 days. Following solid organ transplant in this population after failed rituximab therapy, chemotherapy-induced treatment-related mortality is higher than for other lymphoma patients (36% at 1 year, 0% at 2 years).

Dr. Prockop presented data from study 11-130, enrolling 35 patients (median age, 28) with EBV-PTLD after hematopoietic cell transplant and study 95-024, enrolling 14 patients (median age, 18) following solid organ transplant. All had failed to respond to or had relapsed after prior rituximab.

The overall response rates (complete plus partial responses) after a median follow-up of 23.3 months were 68.8% in the hematopoietic cell transplant group and 50.0% in the solid organ transplant group, with complete responses in 57.1% and 14.3%, respectively.

Responder analyses revealed a 2-year overall survival of 83% in hematopoietic cell transplant patients and 86% in solid organ transplant patients. None of the subjects responding to tabelecleucel died of EBV-PTLD. Subjects who did not achieve complete or partial responses to tabelecleucel had short overall survival (median 1.7 months in hematopoietic cell transplant patients, 1.2 months in solid organ transplant patients). Most died of post-transplant lymphoproliferative disorder progression.

In this population of “quite ill” patients with multiple comorbidities, tabelecleucel was well tolerated, and no treatment-emergent adverse events were definitively attributed to it.

Ran Reshef, MD, Associate Professor of Medicine at Columbia University Medical Center’s Blood and Marrow Transplantation and Cell Therapy program, commented in an interview: “The treatment challenge is usually driven by the fact that these patients do not have an intact immune system because they are receiving immunosuppressive medications. Many have been through multiple medical procedures, or among children, many are on dialysis and present a huge treatment challenge.” He added, “So to have a therapy with a very good safety and tolerability profile is a major breakthrough. These are extremely strong data showing how potent this type of therapy can be.”

Dietmar Berger, MD, PhD, global head of research and development for Atara Biotherapeutics, the tabelecleucel manufacturer, noted in an interview that it can take 16 to 56 days to collect and expand a patient’s own T-cells. “Sometimes the disease can be very acute in the allogeneic hematopoietic cell
transplant setting, so you don’t have time to wait.” Dr. Berger said that Atara stores well under 100 T-cell lines, covering 90% of the population. One donor, he said, can provide enough material for hundreds of patients. “That’s a strength of this technology,” Dr. Berger said.

Further research will seek means to sensitize nonresponding tumors to T-cells. Treating patients with tabelecleucel in earlier disease states may also improve responses, according to Dr. Prockop.

Tabelecleucel is being investigated in 2 phase 3 trials of PTLD following hematopoietic cell transplant (NCT03392142) and solid organ transplant (NCT03394365). Dr. Reshef is the lead investigator in both of these trials.

**RELEVANCE: Phase 3 Efficacy and Safety Study of Lenalidomide Plus Rituximab Versus Rituximab Plus Chemotherapy, Followed by Rituximab, in Previously Untreated Follicular Lymphoma**

- Frank Morschhauser, MD, Professor of Hematology, Centre Hospitalier Universitaire Regional de Lille, Lille, France

Results of the RELEVANCE trial suggest that a novel immunomodulatory approach is a potential front-line treatment option for follicular lymphoma. RELEVANCE showed equivalent efficacy with a better toxicity profile for a chemotherapy-free regimen versus the standard of care for advanced stage, high-tumor burden, previously untreated follicular lymphoma, Dr. Morschhauser said in his presentation.

The current standard of care, rituximab plus chemotherapy followed by rituximab maintenance (R-chemo), has demonstrated 3-year progression-free survival (PFS) rates of 73% in the PRIMA study and 78% in the GALLIUM study, but is associated with repeated relapses and shorter duration of response with each line of therapy. “We know that this kind of treatment has not changed the history,” Dr. Morschhauser commented.

The novel regimen consists of immunotherapy with lenalidomide, an immunomodulatory agent that activates natural killer cells and T cells, leading to apoptosis of neoplastic B cells, plus rituximab (R2). In phase 2 studies of lenalidomide with rituximab in a similar population of follicular lymphoma patients, 3-year PFS has been around 80%. The multicenter (n = 137), international, open-label, randomized RELEVANCE trial, Dr. Morschhauser noted, is the first phase 3 trial of R2 versus R-chemo in this population of previously untreated patients (N = 1030, grade 1-3a) requiring systemic treatment (per GELF criteria).

Patients in the R2 arm (n = 513) received lenalidomide 20 mg/day on days 2–22/28 for 6 months, with responders receiving 10 mg/day for a second 6-month period, followed by a year of rituximab (375 mg/m² weekly every eight weeks). R-chemo (n = 517) was given per investigator’s choice of standard R-CHOP (rituximab with cyclophosphamide, doxorubicin, vincristine and prednisone), R-bendamustine, or R-CVP (rituximab with cyclophosphamide, vincristine and prednisone) for 6 months followed by 12 cycles of rituximab. Total treatment duration was 120 weeks. The co-primary superiority endpoints were complete response (CR)/unconfirmed complete response (CRu) at 120 weeks.

The presence of bulky disease (~40%), high-risk Follicular Lymphoma International Prognostic Index (FLIPI) scores (~48.5%) and B-symptoms (~26.5%) were similar for both groups (49% male, median age, 59).

Independent Review Committee (IRC) response evaluation at 120 weeks, Dr. Morschhauser reported, showed rates to be similar between the groups. The co-primary endpoint CR/CRu rates were 48% for R2 and 53% for R-chemo; best CR/CRu rates were 59% and 67%, respectively, and best overall response rates were 84% and 89%, respectively. Three-year duration of response was 77% for R2 and 74% for R-chemo.

Duration of complete response evaluation was also similar: 77% in the R2 group and 81% in the R-chemo group. Also, interim PFS by IRC evaluation demonstrated similarity after a median followup of 37.9 months with rates of 77% and 78% for R2 and R-chemo.

Dr. Morschhauser noted further that prespecified subgroup analyses found similarity for nearly all categories, but with some favoring of R-chemo for early stage (I/II), localized disease and low FLIPI score (0–1).

An immature analysis after a median follow-up of 37.9 months placed OS rates at 94% in both groups.

The important differences, Dr. Morschhauser said, were seen in treatment-emergent adverse events, with higher rates of grade 3–4 neutropenia (32% versus 30%), grade 4 neutropenia (8% versus 31%), febrile neutropenia (2% versus 7%), alopecia, vomiting, and peripheral neuropathy in the R-chemo group. More cutaneous reactions, rash and tumor flare reactions were reported in the R2 group. The R-chemo group also needed more growth factors (23% versus 68%). Safety discontinuation rates were similar between groups (31% for R2 and 29% for R-chemo).

Second primary malignancies were found in 7% and 10% of patients in the R2 and R-chemo groups, respectively (invasive 5% for both). Each group had 1 death related to study treatment.

“These results show that R2, a novel immunomodulatory approach, is a potential first-line option for patients with follicular lymphoma requiring treatment,” Dr. Morschhauser concluded. He added, “More importantly, it shows that this is the way to go if we want to improve results in the future.”