The 60th American Society of Hematology Annual Meeting & Exposition

Walter Alexander

The American Society of Hematology's (ASH) annual meeting, held December 1–4, 2018 in San Diego, California, hosted 29,367 medical professionals. We review various key sessions including two presentations on β-thalassemia and myelodysplastic syndromes, three presentations on chronic lymphocytic leukemia, and others on perioperative oral anticoagulation, sickle-cell anemia, diffuse large B-cell lymphoma, and multiple myeloma.

BELIEVE: Results of a Phase 3 Study of Luspatercept in Adult Patients With Beta-Thalassemia Who Require Regular Red Blood Cell Transfusions

- Maria Domenica Cappellini, MD, University of Milan, Italy

In the BELIEVE trial, a randomized, double-blind, placebo-controlled study among adults with transfusion-dependent β-thalassemia, treatment with luspatercept resulted in significant reductions in red blood cell (RBC) transfusion burden, according to lead author Dr. Maria Capellini.

Due to resultant ineffective erythropoiesis, patients with β-thalassemia may need frequent and lifelong transfusions. Many patients require transfusions every few weeks, Dr. Cappellini said. In addition to the small risk of infections or immune reactions, regular transfusions may lead eventually to iron buildup, which causes liver and/or heart problems. Currently available management for β-thalassemia is limited to transfusions and iron chelation therapy, and there are no approved, definitive curative treatments available other than bone marrow transplantation. "β-thalassemia is a very demanding disease," Dr. Cappellini commented.

Luspatercept, which reduces aberrant signaling and enhances late-stage erythropoiesis, is a first-in-class erythroid maturation agent that is under development for the treatment of adult patients with β-thalassemia- or myelodysplastic syndrome-associated anemia.

BELIEVE investigators enrolled 336 adult patients with β-thalassemia from 65 sites in 15 countries. Participants were mostly young, with a median age of 30 years, and required a median of six units of blood over a 12-week period before the trial. Patients were randomized 2:1 to subcutaneous luspatercept 1 mg/kg every three weeks or placebo. All patients received best supportive care. The primary endpoint was a ≥ 33% reduction from baseline in transfusion burden (with a reduction of ≥ 2 RBC units) during weeks 13–24.

Dr. Cappellini reported that the primary endpoint was achieved in 21.4% of patients receiving luspatercept and in 4.5% of patients receiving placebo ($P < 0.0001$). Those taking luspatercept were 5.8 times more likely to reach the primary endpoint compared with those taking placebo. Also, reductions ≥ 33% and ≥ 50% in transfusion burden were achieved in a significantly greater proportion of luspatercept-treated versus placebo-treated patients in any 12- and 24-week interval.

About 20% of patients overall had cut their number of transfusion units by one-third or more, and 10% of patients had cut their transfusion units by half or more by the trial's final quarter, said Dr. Cappellini.

Adverse event rates were similar between the luspatercept and placebo groups, and no deaths were reported among luspatercept-treated patients. Adverse events were generally mild-to-moderate and manageable, without requiring dose modifications or interruptions.

"This new approach can totally change the quality of life for the patient," Dr. Cappellini commented. "Even for those who don't become completely transfusion independent, reducing transfusions can reduce associated comorbidities."

Medalist Results: A Phase 3 Trial of Luspatercept For Anemia in Patients with Varying Risk of Myelodysplastic Syndrome with Ring Sideroblasts Who Require Red Blood Cell Transfusions

- Alan F. List, MD, Moffitt Cancer Center, Tampa, Florida

In patients with anemia due to very low-, low-, or intermediate-risk myelodysplastic syndrome-associated anemia and ring sideroblasts requiring red blood cell transfusions, treatment with luspatercept resulted in a significantly reduced transfusion burden compared with placebo. Risk categories were defined according to the Revised International Prognostic Scoring System (IPSS-R), said Dr. Alan List, MEDALIST lead investigator, at a press briefing.

Luspatercept, an investigational, first-in-class erythroid maturation agent under development for the treatment of adult patients with β-thalassemia- or myelodysplastic syndrome-associated anemia, binds to select transforming growth factor-superfamily ligands to reduce aberrant signaling and enhance late-stage erythropoiesis. Erythropoietin-stimulating agents are the first-line treatment for anemia associated with lower-risk non-del(5q) myelodysplastic syndrome. For patients who are refractory to, unresponsive to, or ineligible for erythropoietin-stimulating agents, however, there are few options, Dr. List said. Available anemia drugs only work for about one-half of patients with lower-risk myelodysplatic syndrome-related anemia and for about one-quarter of those who are dependent on RBC transfusions.

Patients included in MEDALIST, a phase 3, randomized, double-blind, placebo-controlled trial, had IPSS-R-defined, very low-, low-, or intermediate-risk, myelodysplastic syndrome-associated anemia ring sideroblasts (RBC precursors with

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iron overload) and required regular RBC transfusions every one to two months. Investigators enrolled 229 patients from 65 international sites, randomly assigning two-thirds to receive luspatercept (1.0 mg/kg) and a third to receive placebo, all via subcutaneous injections every three weeks for at least six months. The primary endpoint was RBC transfusion-independence by or after eight weeks in weeks one to 24.

A significantly larger proportion of patients treated with luspatercept achieved the primary endpoint compared with placebo (37.9% vs. 13.2%; $P < 0.0001$ during weeks 1–24). The secondary endpoint of ≥ 12-week transfusion independence also favored luspatercept over placebo (28.1% vs. 7.9%; $P = 0.0002$). Further, hematologic improvement-erythroid (HI-E) (reduction in transfusion burden ≥ 4 RBC transfusions/8 weeks or mean hemoglobin increase of ≥ 1.5 g/dL/8 weeks) was achieved significantly more often with luspatercept than with placebo (52.9% vs. 11.8%; $P < 0.0001$).

Although the most common reported adverse effects with luspatercept treatment included fatigue and muscle pain, Dr. List commented that it was difficult to determine whether these effects were related to anemia or to the drug itself. Overall, the safety profile was acceptable and luspatercept was well tolerated.

Dr. List concluded that treatment with luspatercept compared with placebo resulted in a significantly reduced transfusion burden: "Luspatercept is a potential new therapy in the treatment armamentarium for this population."

REACH: A Prospective Multi-National Trial of Hydroxyurea for Sickle Cell Anemia in Sub-Saharan Africa

- Leon Tshilolo, MD, PhD, Centre Hospitalier Monkole, Kinshasa, Democratic Republic of Congo

"Hydroxyurea is a feasible, safe, and effective treatment for African children with sickle cell anemia," Dr. Leon Tshilolo concluded, in his review of REACH (Realizing Effectiveness Across Continents with Hydroxyurea) data at a press briefing.

Data have been lacking on the drug's benefits for children living in sub-Saharan Africa, where the sickle cell anemia burden is highest, and where the rates of malaria and other infectious diseases, as well as poverty and inadequate nutrition, are extremely high. Ample data, however, support the value of hydroxyurea treatment for children with sickle cell anemia who live in high-resource countries such as the U.S. and the U.K., and in Europe.

The REACH phase 1/2 open-label trial, coordinated by Cincinnati Children's Hospital, was conducted in four countries in sub-Saharan Africa (Angola, Democratic Republic of Congo, Kenya, and Uganda) among 606 children aged 1–10 years old. Children received a fixed dose (15–20 mg/kg/day) of hydroxyurea for six months, which was then escalated to the maximum tolerated dose. The primary safety endpoint was dose-limiting laboratory toxicities (hemoglobin < 4 g/dL, neutrophils < 1000/µL, platelets < 80,000/µL, and reticulocytes < 80,000/µL). The efficacy endpoints were laboratory levels of hemoglobin and fetal hemoglobin and clinical sickle-related effects, including transfusions and survival.

Adherence was high in REACH, with no missed doses in 90% of assessments. The primary safety endpoint had occurred in only 5.1% of children when 53 participants had completed three months of treatment, and later when 133 participants had completed three months of treatment. The pretrial estimate had been that the endpoint would occur at a rate of 20% at that timepoint, Dr. Tshilolo said. Laboratory benefits increased for each parameter from baseline to month 12 (hemoglobin increased by 1.0 g/dL; fetal hemoglobin increased by 12.5%, while neutrophils, reticulocytes, and platelets decreased substantially) and were sustained at months 24 and 36.

Other clinical benefits, Dr. Tshilolo noted, included decreases of about 50% in vaso-occlusive pain, acute chest syndrome, and transfusions after a median treatment of 2.5 years. Unexpectedly, the rate and severity of malaria also decreased; malaria declined from 47.8 to 22.3 events per 100 patient-years, while clinically severe malaria (Grade 3 or above) fell from 9.9 to 2.5 events per 100 patient-years during treatment. During screening, the death rate was 3.6 per 100 patient-years. The rate decreased to 1.1 deaths per 100 patient-years on hydroxyurea. This all-cause mortality effect, Dr. Tshilolo commented, was a pronounced one.

"The current cost of treatment is beyond the daily wage of most families living in sub-Saharan Africa," Dr. Tshilolo observed. In REACH, patients received the hydroxyurea capsules, all lab tests, and transportation to clinic visits at no charge. "We hope that treatment will be made available to more patients through outside financial support, as is the case with treatment for HIV infection in several African countries."

Comparison of Efficacy and Toxicity of CD19-Specific Chimeric Antigen Receptor T-Cells Alone or in Combination with Ibrutinib For Relapsed and/or Refractory Chronic Lymphocytic Leukemia

- Jordan Gauthier, MD, Fred Hutchinson Cancer Research Center, Seattle, Washington

In patients with relapsed or refractory chronic lymphocytic leukemia (CLL), administering ibrutinib starting two weeks prior to leukapheresis and through three months after CD19-specific chimeric antigen receptor (CAR) T-cells may lead to high response rates and deep responses with decreased incidence of severe cytokine release syndrome, according to Dr. Jordan Gauthier.

When CLL patients relapse or become refractory to currently available treatments, prognosis is poor, although in most cases CLL is slow growing, Dr. Gauthier said in a press briefing. Previously, Dr. Gauthier's colleagues had studied CAR T-cells as a single therapy in 24 CLL patients who had received prior ibrutinib treatment. In most cases, ibrutinib had been discontinued before CAR T-cell treatment because of worsening CLL symptoms. Other research, however, has suggested that continuing ibrutinib before, during, or after immunotherapy with CAR T-cells may prevent tumor flare, boost efficacy, and help prevent cytokine release syndrome.

Dr. Gauthier and colleagues maintained ibrutinib treatment

before, during, and for at least three months after post-CAR T-cell therapy in a second matching group of 19 chronic lymphocytic leukemia patients who were beyond first-line treatment. The patients either had failed or were ineligible for combination chemotherapy and anti-CD20 antibody or had persistent disease after treatment with ibrutinib.

In most patients, concurrent ibrutinib was well tolerated and let to high response rates. Comparing the two groups (41 evaluable), Dr. Gauthier noted that 83% responded in the concurrent ibrutinib group and 65% responded in the no-ibrutinib group. Response was defined by a significant decrease in chronic lymphocytic leukemia cells in the blood and in the size of the lymph nodes. Analysis of marrow disease by deep sequencing that is capable of detecting 1 chronic lymphocytic leukemia cell in 1 million identified responses in 85% of patients receiving concurrent ibrutinib and in 50% of those not receiving ibrutinib. Also, expansion of CD4+ CAR T-cells was greater in those receiving ibrutinib.

In patients receiving ibrutinib, severe cytokine release syndrome occurred less often than in those who were not receiving ibrutinib (0% vs. 25%; $P = 0.03$).

Dr. Gauthier observed that for a targeted agent with CAR T-cells, these are the most encouraging results to date. Despite their being retrospective, interest is high for the TRANSCEND-CLL study, a planned prospective investigation into the effects of ibrutinib combined with CAR T-cell immunotherapy in a larger cohort.

A Randomized Phase 3 Study of Ibrutinib-(PCI-32765) Based Therapy Versus Standard Fludarabine, Cyclophosphamide, and Rituximab Chemoimmunotherapy in Untreated Younger Patients with Chronic Lymphocytic Leukemia: An ECOG-ACRIN Cancer Research Group Trial

• Tait D. Shanafelt, MD, Stanford University School of Medicine, California

A phase 3 study of ibrutinib and rituximab in combination in patients aged 70 years or older with previously untreated chronic lymphocytic leukemia (CLL) has practice-changing implications, reported Dr. Tait Shanafelt. That conclusion was based on results presented at a press briefing showing both progression-free survival (PFS) and overall survival (OS) rates to be superior to those reported for the fludarabine, cyclophosphamide, and rituximab (FCR) combination, widely considered to be the most active chemo-immunotherapy regimen to date.

CLL accounts for 11% of all lymphoid neoplasms and is one of the most common lymphoid malignancies, Dr. Shanafelt said. "The development of chemoimmunotherapy," he observed, "has brought tremendous improvement in the efficacy of CLL treatment." Ibrutinib, a Bruton's tyrosine kinase inhibitor, has exhibited durable efficacy in CLL, but its efficacy as initial treatment for younger patients relative to the FCR combination is unknown.

Investigators enrolled 529 patients aged 70 years or older (median age 57 years, about one-third female) with previously untreated, symptomatic chronic lymphocytic leukemia. Two-thirds of patients received oral ibrutinib (420 mg/day) plus rituximab IV and one-third of patients received a six-month course of intravenous (IV) fludarabine, cyclophosphamide, and rituximab. Treatment continued until disease progression.

The primary endpoint of PFS was superior with the ibrutinib/rituximab combination, with a 65% reduction in events (hazard ratio [HR] = 0.352; 95% CI, 0.223–0.558; $P < 0.00001$) after a median of 33.4 months. The hazard ratio for OS also favored the ibrutinib arm (HR = 0.168; 95% CI, 0.053–0.538; $P = 0.0003$). Analysis showed the ibrutinib/rituximab benefit over FCR to be independent of age, sex, performance status, disease stage, or the presence/absence of del11q23.

Grade 3 and grade 4 neutropenia were more common in the FCR arm than in the ibrutinib/rituximab arm (44% vs. 23%; $P < 0.0001$), as were infectious complications (17.7% vs. 7.1%; $P < 0.0001$). Overall, grades 3 and 4 treatment-related adverse events were observed in 58% of ibrutinib/rituximab patients and in 72% of FCR-treated patients ($P = 0.0042$).

"We found ibrutinib-based therapy to be both more effective and less toxic than our previous best therapy for CLL patients," Dr. Shanafelt said. He concluded, "Ibrutinib and rituximab provides superior PFS and OS compared to FCR for patients with previously untreated CLL."

ANAIS A041202: Ibrutinib Alone or in Combination with Rituximab Produces Superior Progression-Free Survival Compared with Bendamustine Plus Rituximab, in Untreated Older Patients with CLL

• Jennifer A. Woyach, MD, The Ohio State University Comprehensive Cancer Center, Columbus, Ohio

Ibrutinib produces superior PFS to standard chemo-immunotherapy (CIT) in older patients with CLL, according to results from the Alliance North American Intergroup Study (ANAIS) A041202. The findings, said lead investigator Dr. Jennifer Woyach at a press briefing, justify ibrutinib as a standard-of-care treatment for CLL patients aged 65 years and older. Also, Dr. Woyach pointed out, adding rituximab to ibrutinib did not appear to improve outcomes compared with receiving ibrutinib alone.

Despite the fact that CLL is most common in older populations, the majority of CLL-treatment trials have been conducted in younger adults. Furthermore, while the regimen most widely used in patients older than 60 years is bendamustine and rituximab, the combination has not been tested in comparison with ibrutinib. Ibrutinib's Food and Drug Administration approval for first-line treatment of CLL in 2016 was based on comparison to chemotherapy with chlorambucil, a drug approved in 1957 that today most clinicians consider obsolete. Also, while rituximab improves survival with chemotherapy, its impact in combination with ibrutinib has not been established.

ANAIS investigators enrolled 547 older patients (65–89 years old, median age 71) with previously untreated, symptomatic CLL. One-third were randomly assigned to receive bendamustine (90 mg/m^2 on days 1 and 2 of each 28-day cycle) plus rituximab (375 mg/m^2 on day 0 cycle 1, then

500 mg/m^2 on day 1 of cycles 2–6); one-third received ibrutinib (420 mg daily until disease progression) plus rituximab (375 mg/m^2 weekly for four weeks starting on cycle 2 day 1, then on day 1 of cycles 3–6); and one-third received ibrutinib (420 mg daily until disease progression) alone. Researchers tracked patient outcomes for a median of 38 months. Patients whose disease progressed after receiving bendamustine plus rituximab crossed over to receive ibrutinib as a second-line treatment. The primary endpoint was 24-month estimates of PFS.

In patients who received ibrutinib plus rituximab, PFS 24-month estimates were significantly higher (88%; 95% CI, 81–92%). They were also higher for those who received ibrutinib alone (87%; 95% CI, 81–92%) compared with bendamustine plus rituximab (74%; 95 % CI, 66–80%). However, there was no difference in overall survival among the three groups at two years.

Rates of atrial fibrillation (9%) and hypertension (29%) were higher with ibrutinib, and warrant caution and monitoring in this older population, Dr. Woyach said.

She concluded that ibrutinib is more effective than the best available CIT regimen and should be the standard of care for older patients with CLL. She added, "The study highlights the importance of doing clinical trials for older patients, because the toxicities are likely to be different for older versus younger patients, even with the same drug."

Dr. Woyach noted that while this international phase 3 trial shows that ibrutinib represents a major therapeutic advance, toxicities and also cost justify future efforts to reduce the need for long-term continuous treatment.

MAIA Results: Daratumumab Plus Lenalidomide And Dexamethasone Versus Lenalidomide And Dexamethasone in Patients with Newly Diagnosed Multiple Myeloma Who Are Ineligible For Transplant

- Thierry Facon, MD, Hospital Claude Huriez, Lille, France

Pre-specified interim analyses from the phase 3 MAIA clinical trial support adding daratumumab to lenalidomide plus dexamethasone in patients with transplant-ineligible, newly diagnosed multiple myeloma (NDMM), said Dr. Thierry Facon at a press briefing. The comparator was lenalidomide plus dexamethasone. Earlier findings from the POLLUX study of daratumumab and lenalidomide versus lenalidomide alone showed a 63% risk of disease progression or death for the combination in patients with relapsed or refractory MM.

Since 2013, lenalidomide has been the standard of care for this population, Dr. Facon said. Daratumumab, an approved targeted drug, blocks CD38, a protein found at high levels in MM cells. The mean age in MAIA was 73 years among the 737 participants, 44% of whom were aged 75 years or older. The MAIA trial, Dr. Facon pointed out, includes a higher proportion of patients over 75 years old than other studies, and is among the first to test daratumumab with lenalidomide in this population. Patients were randomly assigned to 28-day cycles of lenalidomide alone or lenalidomide plus daratumumab until disease progression. All patients received dexamethasone. Progression-free survival (PFS) was the primary endpoint.

In the group receiving lenalidomide alone, after a median follow-up of 28 months, median PFS was 31.9 months. Median PFS had not yet been reached in the daratumumab-plus-lenalidomide group. Thirty-month PFS was 71% in the daratumumab-plus-lenalidomide group and 56% in the lenalidomide-alone group (HR, 0.56 [95% CI, 0.43–0.73]; $P < 0.0001$). Patients receiving daratumumab and lenalidomide had a 44% reduction in the risk of progression or death.

The daratumumab-plus-lenalidomide group had a significantly higher overall response rate (93% vs. 81%; $P < 0.0001$), and a higher complete plus stringent complete response rate (48% vs. 25%). Minimal residual disease negativity was achieved in 24% of daratumumab/lenalidomide patients versus 7% of patients ($P < 0.0001$) receiving lenalidomide alone.

More patients in the daratumumab/lenalidomide arm had moderate or severe pneumonia and neutropenia. Overall, however, there were no new safety signals, said Dr. Facon.

He concluded, "These results support the addition of daratumumab to lenalidomide with dexamethasone as the new standard of care for patients with transplant-ineligible NDMM."

PAUSE Study: A Perioperative Management Plan For Patients with Atrial Fibrillation Receiving a Direct Oral Anticoagulant

- James Douketis, MD, McMaster University, Hamilton, Ontario, Canada

The largest study to address perioperative direct-acting oral anticoagulation (DOAC) management in patients with atrial fibrillation found a standard DOAC strategy that forgoes heparin bridging and pre-operative coagulation testing to be associated with low rates of major bleeding and acute thromboembolism. The results, said Dr. James Douketis, lead author of the PAUSE (perioperative anticoagulant use for surgery evaluation) study in a press briefing, will likely be practice-changing.

There is ample evidence for the guidance of regimen-modifying among patients undergoing elective surgery or procedures for existing conventional blood thinners like warfarin. For the increasingly prescribed DOACs, however, evidence is lacking. Anticoagulation needs to be paused to minimize bleeding risk at the same time that risk of thromboembolic events and subsequent strokes or other complications is still adequately managed. Uncertainty persists around when to interrupt direct oral anticoagulant dosing, when to resume it, and whether there is a need for heparin bridging or preoperative coagulation-function testing, Dr. Douketis said.

PAUSE investigators enrolled 3,007 patients with atrial fibrillation, who were scheduled for elective surgery/procedure at 23 centers in Canada, the U.S., and Europe, to three arms, each receiving one of three direct oral anticoagulants (apixaban, n = 1,257; dabigatran, n = 668; rivaroxaban, n = 1,082). The mean patient age was approximately 73 years (~67% male), and about one-third of patients underwent high-bleeding risk surgery/procedures. Pre-operative anticoagulant testing showed that more than 90% of patients had minimal-to-no residual levels.

The PAUSE hypothesis was that suspending anticoagulant dosing for one or two days before and after the procedure, based

on bleeding risk, would be safe and effective. For procedures with low bleeding risk, such as a colonoscopy or hernia repair, patients were instructed to stop their anticoagulant for one day before and after surgery. For procedures with a higher bleeding risk, such as major cancer, heart, or orthopedic surgery, or any procedure involving a spinal anesthetic, patients were asked to pause their anticoagulant for two days before and after the procedure.

Rates of arterial thromboembolism (ischemic stroke, transient ischemic attack, systemic embolism) were 0.16% for apixaban, 0.60% for dabigatran, and 0.37% for rivaroxaban, all within or close to the expected outcome of 0.5%. Major bleeding rates (as defined by the International Society of Thrombosis and Hemostasis) were 1.35% for apixaban, 0.90% for dabigatran, and 1.85% for rivaroxaban, all close to the expected 1.0% rate.

Dr. Douketis concluded, "In patients with atrial fibrillation who had direct oral anticoagulant interruption for an elective surgery/procedure, a simple standardized perioperative management strategy that foregoes heparin bridging and pre-op coagulation testing was associated with low rates of major bleeding (< 2%) and arterial thromboembolism (< 1%)."

Excellent Outcome of Young Patients with Favorable-Prognosis Diffuse Large B-Cell Lymphoma Treated with 4 Cycles of CHOP Plus 6 Applications of Rituximab: Results of the 592 Patients of the FLYER Trial of the Dshnhl/GLA

• Viola Poeschel, MD, Saarland University Medical School, Homburg/Saar, Germany

FLYER trial results suggest that a chemotherapy-sparing regimen does not compromise outcomes in young patients (aged 18 to 60 years old) with favorable-prognosis diffuse large B-cell lymphoma (DLBCL). The comparison, said lead investigator Dr. Viola Poeschel, showed that a regimen of two fewer cycles (four vs. six) of R-CHOP (rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone) plus two rounds of rituximab was non-inferior to the standard six courses of R-CHOP.

A sub-group of younger DLBCL patients with no bulky disease and a favorable prognosis was defined by the MInT trial, which demonstrated a three-year event-free survival rate of 89%, progression-free survival (PFS) of 95%, and overall survival (OS) of 98% with R-CHOP, Dr. Poeschel said. FLYER's goal was to test whether reducing toxicity by lowering the number of R-CHOP cycles would still preserve efficacy.

FLYER investigators enrolled 588 subjects (18–60 years old) with aggressive DLBCL receiving front-line treatment from institutions in Germany, Denmark, Norway, Italy, and Israel. All patients had stage I/II disease with favorable prognosis (aaIPI [International Prognostic Index] = 0, and no bulky disease [maximum diameter < 7.5 cm]). They were randomized to four or six 21-day cycles of R-CHOP. Rituximab, a monoclonal antibody, has fewer side effects than the chemotherapy components, and all patients received six rituximab cycles. The primary endpoint was PFS.

At 36 months, PFS was 94% in the six-cycle group (95% CI, 91%; 97%) and 96% in the four-cycle group (95% CI, 94%; 99%). OS was 98% in the six-cycle group (95% CI, 96%; 99%) and 99% in the four-cycle group (95% CI, 98%; 100%).

The reduced number of R-CHOP cycles, Dr. Poeschel observed, led to substantially lower rates of hematological adverse events (any grade, and grade 3–4 for leukocytopenia and anemia). Grade 3–4 thrombocytopenia was lower as well. Non-hematological adverse events (paresthesia, nausea, infection, vomiting, mucositis) were reduced by about one-third overall for all grades, and for grades 3–4 with the four-cycle regimen. Altogether, 1,295 adverse events occurred in the 295 patients who underwent six cycles of chemotherapy compared with 835 adverse events in the 293 patients who received just four cycles of chemotherapy.

"In young patients with favorable-prognosis DLBCL, the outcome after four cycles of R-CHOP is non-inferior compared to the previous standard six cycles of R-CHOP. Thus, chemotherapy can be spared without compromising prognosis in this population," Dr. Poeschel concluded.

Study participants will be tracked for an additional five years. ■