

# clinical trial update

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New therapies – such as brentuximab for relapsed Hodgkin disease, romidepsin for peripheral T-cell lymphoma, and combination therapy including rituximab for elderly patients with mantle cell lymphoma – show great promise. Additional studies will identify where in therapy these agents are best utilized.

**Title:** Rituximab maintenance for two years in patients with high tumor burden follicular lymphoma responding to rituximab plus chemotherapy (PRIMA): a phase 3 randomized controlled trial.

**Authors:** Salles G, Seymour JF, Offner F, et al.

**Reference:** *Lancet*. 2011;377:42-51.

**Purpose:** Follicular lymphoma, the second most common subtype, has seen improvements in overall survival (OS), but is still incurable in most cases. The disease usually responds very well to initial first-line therapy, yet manifests with repeated relapses with the disease-free interval becoming progressively shorter. Numerous studies have established the combination of the anti-CD20 monoclonal antibody, rituximab (Rituxan), with a variety of chemotherapy combinations as the standard first-line approach for the treatment of the disease. Previous studies had suggested that rituximab maintenance therapy may be of benefit to this particular patient population. The PRIMA

(Primary Rituximab and Maintenance) study was designed to assess the benefit of two years of rituximab maintenance therapy following first-line therapy in patients with follicular lymphoma treated with rituximab and chemotherapy.

**Methods:** This was an open-label, international, multicenter, randomized study consisting of induction and maintenance therapy. Eligibility criteria included being older than age 18 with newly diagnosed disease and at least one criterion of high tumor burden – bulky disease, three separate nodes of at least 3 cm or more, symptomatic splenic enlargement, organ compression by tumor, pleural or pericardial effusion, increased serum lactic dehydrogenase or  $\beta$ 2-microglobulin, or the presence of B symptoms. Additional criteria included an Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 2 and adequate end-organ function. One reason for exclusion was use of corticosteroids at doses of > 20 mg per day within

the preceding 30 days prior to study enrollment. Patients were assigned in a 1:1 ratio to observation or rituximab maintenance therapy – 12 infusions of 375 mg/m<sup>2</sup> IV once every eight weeks starting eight weeks after the last induction therapy. Induction therapy consisted of one of three regimens combined with rituximab: CVP – cyclophosphamide (Cytosan) 750 mg/m<sup>2</sup> IV day one, vincristine (Oncovin) 1.4 mg/m<sup>2</sup> IV (2 mg max) day one, and prednisone 40 mg/m<sup>2</sup> orally days one through five with cycles repeated at every three weeks for six cycles; CHOP – cyclophosphamide and vincristine doses as above with doxorubicin (Adriamycin) 50 mg/m<sup>2</sup> IV day one and prednisone 100 mg/m<sup>2</sup> orally days one through five repeated every three weeks for six cycles; or FCM – fludarabine (Fludara) 25 mg/m<sup>2</sup> IV days one through three, cyclophosphamide 200 mg/m<sup>2</sup> orally days one through three, and mitoxantrone (Novantrone) 6 mg/m<sup>2</sup> IV day one with cycles repeating every four weeks for six cycles. Patients who obtained a complete response (CR), unconfirmed complete response, or partial response (PR) to induction therapy were eligible for randomization to the maintenance phase of the study. The primary end point of the study was progression-free survival (PFS) from the time of randomization to rituximab maintenance or observation. Secondary end points included OS, response rate, and toxicity.

**Results:** A total of 505 patients were assigned to rituximab maintenance therapy and 513 to observation. With a median follow-up of 36 months, PFS was 74.9% in the rituximab maintenance group and 57.6% in the observation group (hazard ratio [HR] 0.55, 95% CI 0.44-0.68,  $p < 0.0001$ ). The median time to progression was not reached in the rituximab group and was 48.3 months in the observation group. At the end of the maintenance phase, 71.5% of the rituximab group was in a complete or near-complete response vs. 52.3% in the observation group ( $p = 0.0001$ ). More patients who were in partial response at time of randomization converted to complete or unconfirmed complete response after two years of the rituximab maintenance therapy (71 of 139, or 52%) than those in the observation group (45 of 152, or 30%;  $p = 0.0001$ ). OS did not differ between groups. Grade 3 and 4 toxicities were reported in 24% of the rituximab maintenance group and 17% of the observation group ( $p = 0.0026$ ). The most common adverse events were infections.

**Conclusion:** Rituxan maintenance after first-line induction therapy with rituximab for the treatment of follicular lymphoma significantly improves PFS.

**Managed Care Implications:** Maintenance rituximab therapy should be considered the standard of care in patients with newly diagnosed follicular lymphoma who respond to induction therapy with the combination of rituximab and chemotherapy.

**Title:** Brentuximab vedotin (SGN-35) for relapsed CD-30-positive lymphoma.

**Authors:** Younes A, Bartlett NL, Leonard JP, et al.

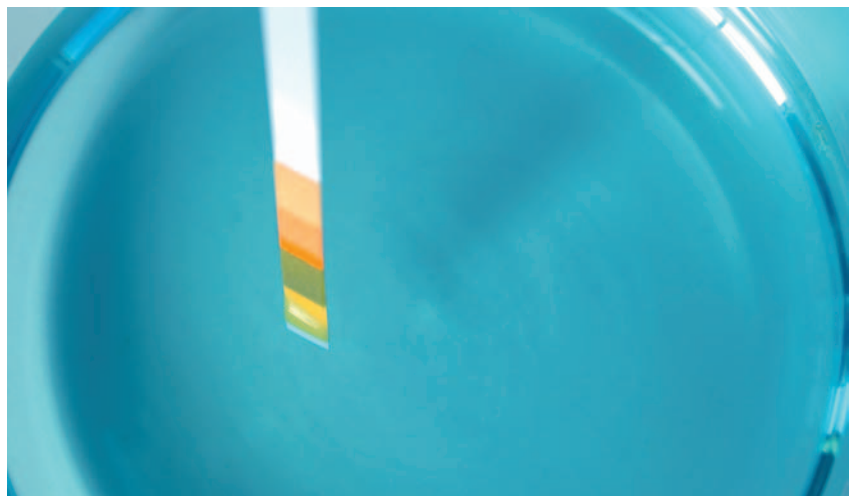
**Reference:** *N Engl J Med.* 2010;363:1812-1821.

**Purpose:** While long-term remissions are common with Hodgkin lymphoma,

15 to 30% of patients do not have that result with conventional therapy. Autologous stem cell transplant (ASCT) is potentially curative in some patients with relapsed or refractory disease, but is effective in only approximately 50% of the patients treated with this modality. The OS for patients with Hodgkin lymphoma who relapse following autologous bone marrow transplantation is only 55% and 32% at two and five years, respectively. CD-30 is expressed on the surface of Hodgkin Reed-Sternberg cells and in cells in other types of lymphoma, including anaplastic large cell, non-Hodgkin, and mature T-cell varieties. Because the normal expression of CD-30 is highly restricted to a relatively small cell population, it could represent a novel and selective treatment strategy. Brentuximab vedotin (Adcetris) is a CD-30 antibody-drug conjugate, which after binding to the CD-30 surface antigen, is rapidly internalized and transported to lysosomes, where the peptide linker is selectively cleaved. The antitubulin agent monomethyl auristatin E binds to tubulin and promotes the arrest of the cell cycle between the gap 2 phase and mitosis, causing cell apoptosis.

**Methods:** This phase 1, open-label, dose-escalation trial was initiated to assess the safety and efficacy of brentuximab vedotin in patients with relapsed or refractory CD-30-positive hematologic malignancies. Patients needed to be at least 18 years of age, have measurable disease, and have an ECOG performance status of  $\leq 2$ . Patients were excluded if they had undergone an allogeneic stem cell transplant. Brentuximab vedotin was administered intravenously at doses of 0.1 to 3.6 mg/kg every three weeks. No premedication was required. The study used a traditional dose-escalation design, followed by a cohort expansion phase. Dose-limiting toxic effects were assessed during the 21-day observation phase following the first administration of the antibody-drug conjugate. Response was assessed every six weeks with patients continuing therapy who experienced a complete remission, partial remission, or stable disease. Treatment was discontinued upon confirmed progression of disease, and patients were monitored for a minimum of 30 days after their last doses of brentuximab vedotin.

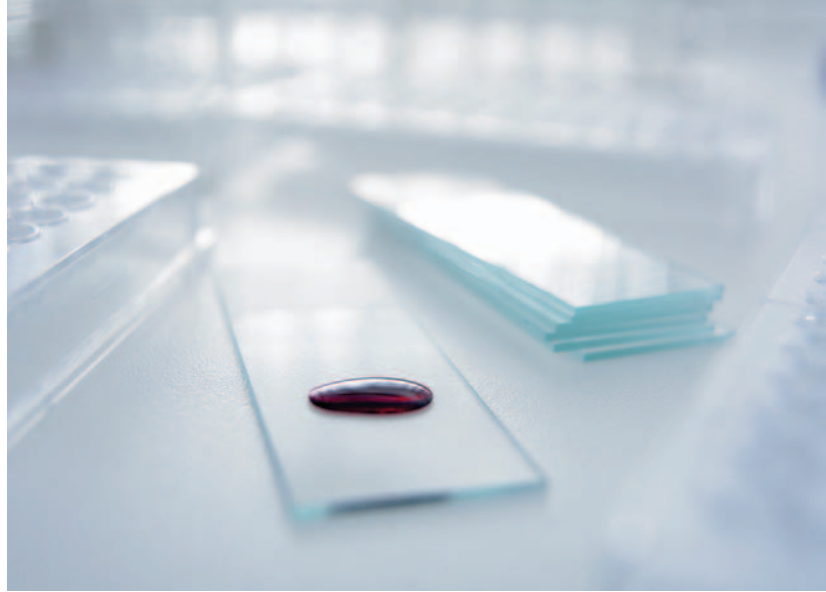
**Results:** A total of 45 patients were treated, 42 of whom had Hodgkin lymphoma. The median age of the patients was 36 years (range 20 to



87), and they had been treated with a median of three previous therapies (range 1 to 7). Seventy-three percent of the patients (33 of 45) had undergone ASCT. A dose-limiting toxicity – grade 4 thrombocytopenia – was noted in one of six patients who received a dose of 1.8 mg/kg of brentuximab vedotin. Acute renal failure was noted in one of six patients treated at the 2.7 mg/kg dose. A single patient was treated at the 3.6 mg/kg dose and developed febrile neutropenia and sepsis, contributing to the patient's death. Expanded cohorts to include 12 patients each at the 1.8 mg/kg and 2.8 mg/kg doses were investigated. Additional dose-limiting toxicities, including grade 3 hyperglycemia and grade 3 febrile neutropenia, were noted in two additional patients treated with the 2.7 mg/kg dose. The 1.8 mg/kg dose was considered the highest dose that did not cause unacceptable toxicity. The most common adverse events at this dose were usually grade 1 or 2 and consisted of fatigue, pyrexia, diarrhea, neutropenia, and peripheral neuropathy. Objective responses were noted in 17 patients, including 11 CRs. For those patients treated with the 1.8 mg/kg dose, the response rate was 50% (six of 12). The median duration of response was at least 9.7 months. Tumor regression was observed in 36 of 42 (86%) of patients who could be evaluated.

**Conclusion:** Treatment with brentuximab vedotin resulted in tumor regression for most patients treated with relapsed or refractory CD-30-positive lymphoma. Many of these responses were durable. Treatment was usually associated with mild to moderate (grade 1 or 2) adverse events.

**Managed Care Implications:** Although only a phase 1 study, durable responses were seen in patients with relapsed and/or refractory CD-30-



positive lymphomas. Positive phase 2 trials have led to the approval by the U.S. Food and Drug Administration (FDA) of brentuximab vedotin for patients with relapsed or refractory CD-30-positive Hodgkin lymphoma and systemic anaplastic large cell lymphoma. The cost of the drug is prohibitive.

**Title:** Phase 2 trial of romidepsin in patients with peripheral T-cell lymphoma.

**Authors:** Piekarcz RL, Frye R, Prince HM, et al.

**Reference:** *Blood*. 2011;117(22):5827-5834.

**Purpose:** Non-Hodgkin lymphoma arises from B cells in 85% of patients and from T cells in 10% of patients. Peripheral T-cell lymphoma (PTCL) is derived from a mature, post-thymic T-cell clone with T-cell receptor gene rearrangement and comprises the largest subclassification of T-cell lymphomas. These include patients with PTCL unspecified (NOS), angioimmunoblastic, ALK-negative anaplastic large cell, and enteropathy-associated T-cell lymphoma. PTCL is associated with a poor prognosis: a five-year survival of 32%. Effective therapy is limited with single-agent pralatrexate (Foloty) being recently approved by the FDA for treatment of the disease. Romidepsin (Istodax) is a potent

histone deacetylase (HDAC) inhibitor. In phase 1 clinical trials, a complete response was noted in a patient with PTCL. Additional patients with T-cell lymphoma were enrolled and confirmed the drug's activity. Those findings led to this phase 2 study.

**Methods:** Patients with relapsed or refractory PTCL who had failed at least two previous therapies were enrolled. Inclusion criteria included patients ages 18 and older with measurable disease, an ECOG performance status of 0 to 2, a life expectancy of greater than 12 weeks, and adequate end-organ function. Exclusion criteria included central nervous system (CNS) involvement, human immunodeficiency virus (HIV) infection, or prior therapy with an HDAC inhibitor. Romidepsin was administered as a four-hour intravenous infusion on days one, eight, and 15 of a 28-day cycle at a dose of 14 mg/m<sup>2</sup>. Doses were held for ≥ grade 3 nonhematologic toxicity, an absolute neutrophil count (ANC) of < 0.5 x 10<sup>9</sup> cells/L, or a platelet count < 50 x 10<sup>9</sup> cells/L, with scheduled dose reductions based upon a low ANC or platelet count. The primary end point of the study was to evaluate the efficacy of romidepsin in patients with T-cell lymphoma. Secondary goals included evaluation of the long-term safety of the drug.

**Results:** Forty-seven patients were



enrolled, with 45 eligible for response assessment. All patients had received prior therapy with a median of three previous treatments (range one to 11), and 18 (38%) had undergone stem cell transplantation. Thirty-four had stage IV disease, with 14 having bone marrow involvement. The majority of patients (27, or 57%) had a primary diagnosis of PTCL NOS. A CR was documented in eight of the 45 patients (18%) and a PR in an additional nine patients (20%) for an overall response rate of 38%. Responses were noted in six of 18 patients (33%) who had previously undergone a stem cell transplant. The median duration of response was 8.9 months (range two to 74) and was 29.7 months in those patients achieving a CR (range three to 74). Shorter responses, 5.2 months (range two to 23+) were noted in patients who obtained a PR. The median time

to response was 1.8 months, with the majority of responses seen within two months. Responses were noted in all PTCL classifications. The most common toxicities observed were similar to those seen in the phase 1 study and reported for other HDAC inhibitors, consisting of fatigue (40%), nausea (51%), anorexia (21%), and vomiting (19%). Hematologic toxicities included leucopenia (47%), thrombocytopenia (46%), granulocytopenia (45%), and anemia (40%). Infections occurred in 17 (36%) patients, including bacterial infections of the skin, blood, and urinary tract.

**Conclusion:** The HDAC inhibitor romidepsin has single-agent activity associated with durable responses in patients with relapsed PTCL.

**Managed Care Implications:** The FDA has recently granted approval of the use of romidepsin in patients with PTCL who have received at least one

prior therapy. Additional studies will identify where in the treatment hierarchy this drug will be used in comparison to other drugs with activity in PTCL, such as pralatrexate.

**Title:** ABVD vs. BEACOPP for Hodgkin lymphoma when high-dose salvage is planned.

**Authors:** Viviani S, Zinzani PL, Rambaldi A, et al.

**Reference:** *N Engl J Med.* 2011;365:203-212.

**Purpose:** The combination of doxorubicin (Adriamycin), bleomycin (Bleocin), vinblastine (Velban), and dacarbazine (DTIC-Dome) – or ABVD – was introduced in the mid-1970s as treatment for advanced Hodgkin lymphoma (HL). It became the standard of care after trials showed that ABVD was at least as efficacious as MOPP – mechlorethamine (Mustargen), vincristine (Oncovin), procarbazine (Matulane), and prednisone – and had fewer side effects. More recently, a third frontline regimen has been introduced, consisting of bleomycin, etoposide (Toposar), doxorubicin, cyclophosphamide (Cytoxan), vincristine, procarbazine, and prednisone – or BEACOPP. This regimen as compared with COPP-ABVD has shown an 11% increase in survival at 10 years. This study accessed the long-term clinical outcomes after initial BEACOPP as compared with ABVD in patients with advanced stage HL.

**Methods:** Eligible patients between ages 17 and 60 with a diagnosis of untreated HL in clinical stage IIB, III, or IV with an international prognostic score of 3 or higher were enrolled. Patients with clinically relevant cardiovascular or respiratory disease and/or patients who were positive for hepatitis B, hepatitis C, and/or the HIV virus were excluded. Patients were randomly assigned to receive

either ABVD for six cycles (if they had a CR after four cycles) or eight cycles, or eight cycles of BEACOPP (four courses of the escalated regimen followed by four courses of the standard regimen). Starting within one month of the end of chemotherapy, patients with a CR or very good PR ( $\geq 80\%$ ) received high-energy irradiation to nodal sites of initial bulky disease, residual disease, or both. The primary end point of the trial was the rate of freedom from first progression. Secondary end points included event-free survival, freedom from a second progression, and OS. Patients with residual or progressive disease after the initial therapy were to be treated according to a state-of-the-art high-dose salvage program. The median follow-up for patients on this trial was 61 months.

**Results:** A total of 331 patients were recruited, 168 assigned to ABVD and 163 assigned to BEACOPP. Two patients were found to be ineligible due to an incorrect diagnosis, and seven withdrew consent prior to the initiation of chemotherapy. As a result, 166 initiated therapy with

ABVD and 156 with BEACOPP. The seven-year rate of freedom from first progression was 85% in those patients treated with BEACOPP and 73% among those who had received initial treatment with ABVD ( $p = 0.004$ ). The seven-year event-free survival was 78% and 71%, respectively ( $p = 0.15$ ). The proportion of patients who had at least one episode of severe toxic effects, either hematologic or nonhematologic, in any cycle was lower in the ABVD group vs. the BEACOPP group (43% vs. 81% with hematologic toxicity,  $p < 0.001$ ; and 7% and 19% with nonhematologic toxicity,  $p = 0.001$ ). A total of 65 patients, 20 treated with BEACOPP and 45 treated with ABVD who had progressive disease or relapse after initial therapy, went on to receive the high-dose salvage regimen. Three of 20 patients treated with BEACOPP and 15 of 45 patients treated with ABVD who had progressive disease or relapse after initial therapy were alive and disease-free following high-dose salvage therapy. After the completion of all planned and salvage therapies, the seven-

year rate of freedom from a second progression was 88% in the BEACOPP group and 82% in the ABVD group ( $p = 0.12$ ), and the seven-year rate of OS was 89% and 84%, respectively ( $p = 0.39$ ).

**Conclusion:** Treatment with BEACOPP as compared with ABVD resulted in initial improved tumor control, but the long-term clinical outcome did not differ significantly between the two groups.

**Managed Care Implications:** Treatment with BEACOPP was not superior to that of ABVD and was significantly more toxic. ABVD should remain the treatment of choice for initial patients with advanced HL unless subset analysis can identify patient groups that may have improved outcomes with BEACOPP.

**Title:** Addition of rituximab to chemotherapy alone as first-line therapy improves overall survival in elderly patients with mantle cell lymphoma.

**Authors:** Griffiths R, Mikhael J, Gleeson M, et al.

**Reference:** *Blood*. 2011. doi:10.1182/blood-2011-04-348367 (Published online August 26, 2011).

**Purpose:** Mantle cell lymphoma (MCL) is characterized by initial responses, followed by relapses that result in poor long-term outcomes. Because the median age at diagnosis is older than age 65, most patients do not receive the dose-intensive regimens used to treat younger patients. Whereas the addition of rituximab (Rituxan) to first-line therapy has shown to improve OS in both aggressive and indolent subtypes of non-Hodgkin lymphoma (NHL), its benefit has not been confirmed in MCL. Although indirect evidence supports a survival benefit for rituximab in MCL, the only published randomized trial of rituximab added to chemotherapy in



previously untreated MCL showed no difference in OS. The purpose of this study was to examine the survival impact of adding rituximab to first-line chemotherapy in a group of older MCL patients treated in routine clinical practice.

**Methods:** The source of the data was the National Cancer Institute's SEER (Surveillance, Epidemiology, and End Results) cancer registry linked to Medicare enrollment and claims data. As of 2010, SEER collects and publishes cancer incidence and survival data from 18 population-based cancer registries in the U.S., covering approximately 26% of the U.S. population. Patients were included if they had a diagnosis of MCL between January 1, 1999, and December 31, 2005. The MCL had to be the first primary cancer diagnosed, and chemotherapy had to begin within 180 days of diagnosis. Both the Medicare National Claims History and the outpatient files for Healthcare Common

Procedure Coding System (HCPCS) were searched to identify patients who began chemotherapy with or without rituximab within this time period. Patients were excluded if the diagnosis of MCL occurred before the age of 65, if death occurred within the first month following diagnosis, or if Medicare enrollment occurred less than 12 months before diagnosis. Patients were stratified into four groups: 66 to 70, 71 to 75, 76 to 80, and older than age 80. Since Medicare claims do not contain laboratory tests, it was not possible to directly obtain information on elevated leukocyte count or lactate dehydrogenase levels, which are two independent prognostic factors for OS in the MCL International Prognostic Index. Medicare claims were searched to identify patients with leukocytosis via ICD-9-CM (International Classification of Diseases, 9th Edition Revision, Clinical Modification) codes 288.3 or 288.8 from 12 months before the MCL diagnosis until initiation of treatment. Another prognostic factor, ECOG performance status, is also not included in SEER-Medicare. In lieu of performance status, Medicare claims were used to identify predictors of poor performance status – use of oxygen and related respiratory therapy supplies, wheelchair and supplies, home health agency, or skilled nursing home. Patients were followed from the date of cancer diagnosis until death, the end of their claims (December 31, 2007), or the end of their Medicare Part A and/or Part B coverage, whichever came first.

**Results:** A total of 992 patients with MCL were identified between 1999 and 2005. The final cohort included 638 patients who had at least one HCPCS claim for infused chemotherapy during the study period and had the first claim within 180

days of diagnosis. The median age at diagnosis was 74 years with 58% diagnosed with stage IV disease and 64% receiving rituximab (n = 407) in addition to their chemotherapy. Patient groups were similar with respect to age, gender, race, extranodal involvement, and presence of B symptoms. The majority of patients in both treatment groups received the chemotherapy combination of cyclophosphamide (Cytoxan), doxorubicin (Adriamycin), vincristine (Oncovin), and prednisone (CHOP). The average length of first-line therapy was 21 weeks, with no difference between the two treatment groups. The median survival was 27 months for those patients treated with chemotherapy alone (n = 231) vs. 37 months for those patients treated with chemotherapy plus rituximab (p < 0.001). The proportion of patients alive at two years following the initiation of first-line therapy also favored the rituximab-treated group (63% vs. 52%; p < 0.001). For the entire cohort, 509 patients (79%) survived at least 90 days following the end of first-line therapy with no additional chemotherapy or radiation during that period. The median time to second-line therapy was 11 months and was similar in the two first-line treatment groups (p = 0.48).

**Conclusion:** First-line chemotherapy in combination with rituximab is associated with significantly improved survival in patients ages 65 and older diagnosed with MCL.

**Managed Care Implications:** These observational findings suggest that rituximab should be a part of any chemotherapy regimen for older patients with MCL. Based upon the limitations of this study, these findings should be confirmed in a prospective clinical trial.





**Title:** First-line treatment for primary testicular diffuse large B-cell lymphoma with rituximab-CHOP, CNS prophylaxis, and contralateral testis irradiation: final results of an international phase 2 trial.

**Authors:** Vitolo U, Chiappella A, Ferreri A, et al.

**Reference:** *J Clin Oncol.* 2011;29:2766-2772.

**Purpose:** Primary testicular non-Hodgkin lymphoma (PTL) is uncommon and accounts for less than 2% of all NHLs. Even though most patients present with localized disease, the outcome is poor. Two large series of PTL patients show a median OS of four to five years. Distant relapses at extranodal sites, including the CNS and contralateral testis, remain therapeutic challenges, and the best strategy to prevent CNS relapse is yet to be defined. The addition of rituximab (Rituxan) to cyclophosphamide (Cytoxan), doxorubicin (Adriamycin), vincristine (Oncovin), and prednisone – CHOP – has significantly improved OS and PFS in patients with diffuse large B-cell lymphoma (DLBCL). No specific data on this regimen in PTL are available. This prospective trial evaluates the safety and efficacy of R-CHOP21 in combination with both CNS and testicular prophylaxis.

**Methods:** Eligible patients had to be at

least 18 years of age and have previously untreated PTL with DLBCL histology with an Ann Arbor stage of I or II. Exclusion criteria included an ECOG performance status of  $\geq 2$ , major end-organ dysfunction, poor cardiac function, and CNS involvement at time of diagnosis. All patients had diagnostic orchiectomies. Treatment consisted of standard doses of R-CHOP21, and patients were restaged following three cycles. Stage I patients received six courses of R-CHOP21, and stage II patients received six to eight courses based on whether they had attained a CR or PR after three cycles of therapy. CNS prophylaxis consisted of intrathecal methotrexate (IT MTX) 12 mg weekly times four doses during the first two cycles of R-CHOP21. Following chemoimmunotherapy, prophylactic radiation to the contralateral testis was delivered to all patients. Patients with stage II disease also received involved field radiation. End points included OS, PFS, and time to progression.

**Results:** Fifty-three patients, ages 22 to 79 years old, were enrolled. All patients received R-CHOP21, 50 received CNS prophylaxis, and 47 received testicular radiation therapy. Intolerance to IT MTX and bilateral orchiectomies were the primary reasons for not completing the

prophylactic portion of the protocol. Fifty-two patients (98%) achieved a CR. At a median follow-up of 65 months, the five-year PFS and OS rates were 74% (95%; CI 59% to 84%) and 84% (95%; CI 71% to 92%), respectively. The five-year cumulative incidence of CNS relapse was 6% (95%; CI 0% to 12%). No contralateral testis relapses occurred. Ten patients died – six of progressive disease, two of acute myelogenous leukemia, one of heart failure, and one of gastric cancer. The five-year cumulative incidence of lymphoma progression or death as a result of lymphoma was 18% (95%; CI 7% to 29%).

**Conclusion:** Combined treatment with R-CHOP21, IT MTX, and testicular radiation therapy was associated with good outcomes in patients with PTL. Radiation therapy avoided contralateral testis relapse, but CNS prophylaxis deserves further investigation.

**Managed Care Implications:** The treatment of choice for patients with newly diagnosed PTL is R-CHOP21, IT MTX, and radiation therapy to the contralateral testis. Additional studies are needed to see whether the CNS prophylaxis regimen can be improved.