

Highlights in Lymphoma From the 2010 American Society of Hematology Meeting

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114 Final Results From a Pivotal, Multicenter, International, Open-Label, Phase 2 Study of Romidepsin In Progressive or Relapsed Peripheral T-Cell Lymphoma (PTCL) Following Prior Systemic Therapy

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In this phase II, single-arm, open-label registration study, Coiffier and colleagues evaluated the activity of the potent histone deacetylase inhibitor romidepsin in a large number of patients with progressive or relapsed peripheral T-cell lymphoma (PTCL) following prior systemic therapy. The primary endpoint was rate of complete response (CR). Eligible patients were those with histopathologically confirmed PTCL who had measurable disease and Eastern Cooperative Oncology Group (ECOG) performance status of 0–2, and had failed or were refractory to at least 1 prior systemic therapy. The mean age of all 131 patients was 59.4 years (range, 20–83 years), and the median time since diagnosis was 1.25 years (range, 0–17 years). Patients received 14 mg/m² of romidepsin as a 4-hour infusion on days 1, 8, and 15 of a 28-day cycle for up to 6 cycles. Treatment could be extended for response or stable disease. Of the 130 patients with histopathologically confirmed PTCL, the overall response rate (ORR) was 26%, as assessed by an independent review committee using the International Workshop Criteria. A CR was observed in 13% of patients, with another 13% achieving partial response (PR). There was a 12-month median duration of response (range, 1–801+ days), although the median duration of response for patients who achieved a CR has not been reached (median duration of follow-up, 8.2 months). As of March 31, 2010, 82% of patients with a CR had not progressed. Adverse events (AEs) were reported in 126 of 131 patients (96%). AEs of grade 3 or higher were reported in 86 patients (66%), with the most common being pneumonia (5%), pyrexia (5%), sepsis (5%), and vomiting (5%). At least 1 serious AE occurred in 60 patients (46%), 22 (17%) withdrew due to AEs, 8 patients (6%) died within 30 days of the final romidepsin dose, and 1 death due to sepsis was considered possibly treatment-related.

3962 Phase II Trial of Lenalidomide - Dexamethasone - Rituximab In Relapsed or Refractory Indolent B-Cell or Mantle Cell Lymphomas Resistant to Rituximab

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In order to assess the efficacy of lenalidomide combined with rituximab, Ahmadi and coworkers conducted a single-center, open label phase II clinical trial in patients with indolent B-cell or mantle cell lymphomas (MCL) who showed resistance to previous treatment with rituximab. In part I of the study, patients received two 28-day treatment cycles of lenalidomide 10 mg every day and dexamethasone 8 mg once weekly. Upon assessment of response to part I, patients then received a single course of rituximab 375 mg/m², consisting of 4 weekly doses. Patients continued to receive lenalidomide plus dexamethasone during and after treatment with rituximab. The regimen was discontinued in patients who experienced unacceptable toxicities or disease progression. Patients were assessed 3 months after the first dose of rituximab. As of May 16, 2010, therapy had been initiated in 27 lymphoma patients (follicular, 18; MCL, 5; small lymphocytic, 3; marginal zone, 1), who had received a median of 3 prior therapies. Lactate dehydrogenase levels increased in 22% of patients, 2 deaths occurred during protocol therapy, and 1 patient was removed from the study during part I due to thrombocytopenia attributed to myelodysplasia. Part II response assessment has not been completed in 1 patient. The median follow-up is 12 months for the 23 patients who have completed both parts, with a PFS of 78% (95% confidence interval [CI], 50–91). Overall response rates (ORRs) were 22% after Part 1 (3 CR; 2 PR; 16 stable disease [SD]; 2 progressive disease [PD]) and 57% after part II (7 CR; 6 PR; 8 SD; 2 PD). Histologic ORRs after part 2 were as follows: follicular lymphoma, 60% (9 of 15 pts); mantle cell lymphoma, 50% (2 of 4 pts); small lymphocytic lymphoma, 67% (2 of 3 pts); and marginal zone lymphoma, 0% (0 of 1 pt). Nonhematologic grade 3/4 AEs possibly related to lenalidomide included hypokalemia (n=4), hypophosphatemia (n=3), pneumonia (n=3), fatigue (n=1), elevated ALT (n=1), elevated AST (n=1), tumor flare (n=1), pulmonary embolism (n=1), and hyperuricemia (n=1).

856 Bendamustine Plus Rituximab Versus Fludarabine Plus Rituximab In Patients with Relapsed Follicular, Indolent and Mantle Cell Lymphomas – Final Results of the Randomized Phase III Study NHL 2-2003 on Behalf of the StIL (Study Group Indolent Lymphomas, Germany)

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In 2003, Rummel and coworkers initiated a multicenter, randomized phase III study comparing the efficacy and safety of bendamustine plus rituximab versus fludarabine plus rituximab in 219 patients with relapsed follicular lymphoma (FL), indolent lymphoma, or MCL. Patients were randomized to receive rituximab 375 mg/m² plus either bendamustine 90 mg/m² (on days 1 and 2) or fludarabine 25 mg/m² (on days 1–3) every 28 days for up to 6 cycles. Progression-free survival (PFS) was the primary endpoint. Rituximab maintenance therapy (rituximab 375 mg/m² every 3 months for up to 2 years) was allowed in both arms. The final analysis involved 208 patients (109 bendamustine plus rituximab; 99 fludarabine plus rituximab) with a median age of 68 years and a median of 1 prior therapy. Due to protocol violations, 11 patients were not evaluable and thus not included in the analysis. The majority of patients had stage IV disease (71.6% bendamustine plus rituximab; 60.6% fludarabine plus rituximab) or stage III disease (21.1% bendamustine plus rituximab and 25.3% FR, respectively). A total of 75.2% of bendamustine plus rituximab patients and 53.4% of fludarabine plus rituximab patients received 6 cycles. At a median observation time of 33 months, the median PFS of bendamustine plus rituximab patients was significantly prolonged, compared with that of fludarabine plus rituximab patients (30 vs 11 months; hazard ratio [HR] 0.51, 95% CI, 0.34–0.67; $P < .0001$), and bendamustine plus rituximab patients also possessed a much higher ORR than fludarabine plus rituximab subjects (83.5% vs 52.5%, respectively; $P < .0001$). Although the CR rate was significantly higher in the bendamustine plus rituximab treatment arm (38.5% vs 16.2% with fludarabine plus rituximab; $P = .0004$), there was no significant difference in overall survival (OS) between arms, with death occurring in 42 bendamustine plus rituximab patients and 46 fludarabine plus rituximab patients. Rates of alopecia, stomatitis, erythema, allergic reactions, peripheral neuropathy and infectious episodes did not significantly differ between groups, nor were there major disparities in grade 3/4 hematologic toxicities (neutropenia: 8.9% with bendamustine plus rituximab vs 9.1% with fludarabine plus rituximab; leukocytopenia: 11.8% with bendamustine plus rituximab vs 12.4% with fludarabine plus rituximab). There were similar overall rates of serious AEs

(17.4% with bendamustine plus rituximab vs 22.2% with fludarabine plus rituximab).

2806 Bendamustine + Rituximab as Treatment for Elderly Patients with Relapsed or Refractory Diffuse Large B-Cell Lymphoma

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Vacirca and associates are conducting an ongoing study of combination bendamustine and rituximab treatment in relapsed or refractory diffuse large B-cell lymphoma (DLBCL) patients who have failed prior therapy and possess at least 1 measurable lesion. Bendamustine (120 mg/m²) was administered on days 1 and 2, and rituximab (375 mg/m²) on day 1 for up to six 28-day cycles. At least 8 of the first 15 patients enrolled achieved a CR or PR, allowing the study to continue until 43 patients in the modified intent-to-treat (MITT) population can be evaluated. Inclusion criteria for this cohort are enrolled patients who have received at least 1 response evaluation. Safety assessments are conducted weekly, and the Revised Response Criteria for Malignant Lymphoma is being utilized to measure disease status upon completion of every 2 cycles, with the first assessment occurring near 8 weeks postenrollment. Currently, 43 subjects with a median age of 74 years (range, 54–90 years) are enrolled. At baseline ECOG status was 0 in 42% (n=18), 1 in 53% (n=23), and 2 in 5% (n=2); and revised International Prognostic Index score was very good/good in 30% (n=13) and poor in 70% (n=30); Patients received a median of 3 cycles. To date, efficacy data from the 33 patients in the MITT cohort demonstrates an ORR of 51.6% (CR, n=5, 15.2%; PR, n=12, 36.4%), with SD in 21.2% (n=7 21.2%) and PD in 27.2% (n=9, 27.2%). A total of 8 patients withdrew or have not yet completed their first efficacy evaluations. Grade 1/2 AEs have been consistent with treatment and expected comorbidities of the DLBCL patient population. Grade 3/4 AEs included neutropenia (n=10), anemia (n=4), thrombocytopenia (n=4), and leukopenia (n=3). Among grade 3/4 AEs occurring in 1 patient (per event) were hepatic failure, disseminated herpes zoster, diarrhea, elevated liver functions, mucositis, dehydration, anorexia, and weight loss.

857 A Phase 3 Trial Comparing Bortezomib Plus Rituximab with Rituximab Alone In Patients with Relapsed, Rituximab-Naive or -Sensitive, Follicular Lymphoma

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In this randomized, open-label, multicenter, international, phase III clinical trial (LYM3001), Coiffier and

coworkers compared the efficacy of bortezomib plus rituximab combined versus rituximab (R) alone in relapsed or refractory, rituximab-naïve or rituximab-sensitive follicular lymphoma (FL) patients. Inclusion criteria were as follows: grade 1/2 measurable FL who had relapsed or progressed following prior therapy (time to progression [TTP] ≥ 6 months if prior rituximab-containing therapy), with an ECOG performance status of 2 or lower, and no peripheral neuropathy of grade 2 or higher. Patients were randomized (1:1) to either 5-week cycles of bortezomib plus rituximab (bortezomib 1.6 mg/m²; days 1, 8, 15, 22; cycles 1–5; plus rituximab 375 mg/m²; days 1, 8, 15, 22 in cycle 1 and day 1 only in cycles 2–5) or rituximab alone (same schedule as bortezomib plus rituximab arm). PFS was the primary endpoint, with ORR, CR rate, TTP, and safety as secondary endpoints. Between April 2006 and August 2008, 676 patients with similar baseline characteristics between the 2 arms and a median age of 57 years (range, 21–84) were enrolled. Most patients (93%) had an ECOG performance status of 1 or less; 51% and 48% had grade 1 and 2 FL, respectively; 83% had Ann Arbor Stage III or IV, and 38% had bone marrow involvement at baseline. Prior therapy had been administered in 3 or more lines in 33% of patients, with 44% receiving prior rituximab therapy. A total of 440 PFS events occurred at a median follow-up of 33.9 months (212 in the bortezomib plus rituximab arm, 228 in the rituximab arm). The median PFS was increased from 334 days (95% CI, 278–365) with rituximab alone to 389 days (95% CI, 351–456) with bortezomib plus rituximab (HR, 0.822; 95% CI, 0.681–0.991). The improvement provided a statistically significant 2-sided *P* value of .039. The ORR was 63% with bortezomib plus rituximab versus 49% with rituximab (*P*<.001). Verified CR rates were 25% and 18%, respectively (*P*=.035). The bortezomib plus rituximab arm had a durable response rate (>6 months) of 50% versus 38% in the rituximab arm (*P*=.002). The bortezomib plus rituximab arm experienced a significant improvement in the median time to subsequent treatment over the rituximab arm (700 vs 537 days; *P*=.027). Neither group achieved median OS. There were AEs reported for 95% of bortezomib plus rituximab and 78% of rituximab patients, mostly of grade 1 or 2. Grade 3 or higher AEs were reported in 46% of bortezomib plus rituximab and 21% of rituximab patients, with the most common being neutropenia (11% vs 4%) and diarrhea (7% vs 0%). Death during treatment occurred in 9 bortezomib plus rituximab patients and 4 rituximab patients.

594 ⁹⁰Y-Ibritumomab Tiuxetan (Zevalin®) Consolidation of First Remission In Advanced-Stage Follicular Non-Hodgkin's Lymphoma: Updated Results After a Median Follow-up of 66.2 Months From the International, Randomized, Phase III First-Line Indolent Trial (FIT) In 414 Patients

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The multinational, randomized, open-label phase III First-Line Indolent Trial (FIT) was conducted to evaluate the clinical benefit and safety of a single infusion of ⁹⁰Y-ibritumomab tiuxetan (0.4 mCi/kg; maximum dose 32 mCi) in 414 patients with CD20-positive follicular non-Hodgkin lymphoma (NHL) who had achieved a PR or CR after receiving one of the standard first-line chemotherapy regimens. Patients were randomly assigned to receive ⁹⁰Y-ibritumomab tiuxetan treatment (n=207) or observation (n=202) within 3 months of completing induction chemotherapy (chemotherapy only: 86%; combination rituximab plus chemotherapy: 14%). At the 66.2-month analysis, 5-year PFS was 47% in the ⁹⁰Y-ibritumomab tiuxetan group and 29% in the control group (HR=0.51, 95% CI, –0.39–0.65; *P*<.0001). The ⁹⁰Y-ibritumomab tiuxetan group had a median PFS of 49 months compared with 14 months in the control group. The time to next treatment for all patients, calculated from the date of randomization, largely differed between the 2 groups; the median was not reached at 99 months in the ⁹⁰Y-ibritumomab tiuxetan group versus 35 months in the control group (*P*<.0001). The ⁹⁰Y-ibritumomab group exhibited a 79% ORR to second-line treatment (57% CR/unconfirmed complete response [Cru] and 22% PR) versus 78% in the control group (59% CR/CRu, 19% PR). Similar 5-year OS rates were observed, with the ⁹⁰Y-ibritumomab group at 93% versus 89% in the control arm (*P*=.561). There have been 40 patient deaths to date, with 18 in the ⁹⁰Y-ibritumomab group and 22 in the control group. No major difference in incidence of secondary malignancies has been observed, with 16 malignancies reported in the ⁹⁰Y-ibritumomab tiuxetan group versus 9 in the control group (*P*=.19). There were 6 cases of myelodysplastic syndrome/acute myelogenous leukemia noted in the ⁹⁰Y-ibritumomab tiuxetan group and 1 case in the control group (*P*=.063).