SYNOPSIS

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Name of Sponsor/Company	Johnson & Johnson Pharmaceutical Research & Development/Millennium Pharmaceuticals, Inc.
Name of Finished Product	VELCADE® for Injection
Name of Active Ingredient	bortezomib

Protocol No.: 26866138-LYM-3001

Title of Study: A Randomized, Open-Label, Multicenter Study of VELCADE With Rituximab or Rituximab Alone in Subjects With Relapsed or Refractory, Rituximab-Naïve or -Sensitive Follicular B-Cell Non-Hodgkin Lymphoma

EudraCT Number: 2005-005777-30

NCT No.: NCT00312845

Clinical Registry No.: 26866138-LYM-3001

Coordinating Investigator: Professeur Bertrand Coiffier, Service Hématologie, Centre, Hospitalier Lyon Sud, 69310 Pierre Bénite, France

Study Center(s): Six hundred seventy-six subjects were enrolled in the study by 164 investigators in 29 countries.

Publication (*in-process*): A Phase 3 Trial Comparing Bortezomib Plus Rituximab with Rituximab Alone in Patients with Relapsed, Rituximab-Naïve or -Sensitive, Follicular Lymphoma

Study Period: First subject consented 22 March 2006; clinical data cutoff date 15 June 2010

Phase of Development: Phase 3

Objectives: The primary objective of this study was to determine whether VELCADE with rituximab provides benefit to subjects with relapsed or refractory, rituximab-naïve or -sensitive, follicular B-cell non-Hodgkin lymphoma (NHL) relative to treatment with rituximab alone, as assessed by prolongation of progression-free survival (PFS).

Secondary objectives were to determine the following for treatment with VELCADE with rituximab relative to treatment with rituximab alone: overall response rate (ORR: complete response [CR]+ complete response unconfirmed [CRu]+ partial response [PR]); overall CR (CR+CRu) rate; duration of response; time to progression (TTP); overall survival (OS) and 1-year survival rate; and rate of durable response. Key exploratory objectives were to assess patient-reported outcomes (PROs) for both treatment groups using the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30) the EuroQoL-5Dimension (EQ-5D); time to next anti-lymphoma treatment; duration of treatment-free interval; and time to response. The safety objective was to evaluate the safety and tolerability of VELCADE in combination with rituximab.

Methodology: This was a randomized, open-label, active-controlled, multicenter, multinational, prospective study to compare the efficacy and safety of the combination of VELCADE and rituximab to single-agent rituximab in subjects who have relapsed or refractory, rituximab-naive, or -sensitive follicular B-cell NHL. Planned enrollment in the study was 670 subjects. The study comprised 3 phases: a pretreatment (screening) phase of approximately 28 days, an open-label treatment phase of up to 5 cycles

of treatment (5 weeks duration per cycle, up to 25 weeks total treatment duration), and a posttreatment phase. Subjects were centrally randomized in a 1:1 ratio to Treatment Group A or B taking into account the following stratification factors: Follicular Lymphoma International Prognostic Index (FLIPI) score (low [0 or 1 factor], intermediate [2 factors], high [≥3 factors]); prior rituximab therapy (yes, no); time since last dose of anti-lymphoma therapy (≤1 year, >1 year); and region (US/Canada, EU, Rest of World). Subjects in Treatment Group A (Vc-R group) received VELCADE for Injection 1.6 mg/m^2 administered weekly on Days 1, 8, 15, and 22 of a 35-day cycle in combination with 4 doses of 375 mg/m^2 rituximab once weekly on Days 1, 8, 15, and 22 of Cycle 1 and a single dose of 375 mg/m^2 rituximab on Day 1 of Cycles 2 through 5. Subjects in Treatment Group B (rituximab group) received 375 mg/m^2 rituximab once weekly on Days 1, 8, 15, and 22 of Cycle 1, and as a single dose of 375 mg/m^2 on Day 1 of Cycles 2 through 5. Both groups received a total of 8 doses of rituximab. Dose modifications and delays for VELCADE were permitted for possible drug toxicities as outlined in the study protocol. Rituximab dose modifications were performed according to package insert instructions and guidelines.

Throughout the open-label treatment phase, disease assessments were performed every 10 weeks. Clearly measurable sites of disease were defined as lymph node masses, splenic nodules, hepatic nodules, and other extranodal sites of lymphoma >1.0 cm in 2 perpendicular dimensions. Other sites of disease were considered assessable, but not measurable, and included objective evidence of disease identified by computed tomography (CT) scan, magnetic resonance imaging (MRI), or other procedures as necessary. Tumor assessments were evaluated in a blinded fashion by an Independent Review Committee (IRC) to confirm disease response for the purpose of the efficacy analyses. As this was an open-label study and the potential for bias existed with the investigator assessment, the IRC assessment was prospectively defined as the primary dataset for the analyses performed; the Sponsor remained blinded to subject and treatment information throughout the study. A local radiologist also assessed the CT scans or other radiographic evaluations during the conduct of the study for the purpose of treatment decision-making.

Analysis of PROs was performed through the administration of the EORTC QLQ-C30 and the EQ-5D questionnaires. The EORTC QLQ-C30 is a 30-item questionnaire incorporating 5 functional scales, 1 global health and QoL scale, 3 symptom scales, and 6 single items. The EQ-5D was administered to perform preference based utility analysis. The EQ-5D is a 5-item questionnaire used to quantify subject preferences or utilities that was administered at the same intervals as the EORTC QLQ-C30.

Comparisons of safety between the 2 study treatments were performed using laboratory test results, vital signs measurements, physical examination findings, and the incidence and severity of adverse events.

Number of Subjects (planned and analyzed): Planned enrollment in the study was 670 subjects. The analysis populations were composed of the following: the intent-to-treat (ITT) population consisted of all 676 randomized subjects (rituximab: 340; Vc-R: 336); the safety population consisted of 673 subjects (rituximab: 339; Vc-R: 334); the per-protocol (PP) population consisted of 641 subjects (rituximab: 325; Vc-R: 316); and the response-evaluable population, which consisted of 639 subjects (rituximab: 324; Vc-R: 315).

Diagnosis and Main Criteria for Inclusion: Men and women, ≥18 years of age, were eligible for this clinical study if they had follicular lymphoma (FL) (Grades 1 and 2) according to the WHO classification. Subjects must have documented relapsed or refractory, rituximab-naïve or -sensitive follicular B-NHL or progression following at least 1 prior lymphoma therapy. If any prior regimen included rituximab, the subject must have responded (CR, CRu, PR), and the TTP from the first dose of rituximab must have been 6 months or more. Additional inclusion criteria included: at least 1 measurable tumor mass (>1.5 cm in the longest dimension and >1.0 cm in the short axis) that was not previously irradiated, or had grown since previous irradiation; no active central nervous system lymphoma; Eastern Cooperative Oncology Group (ECOG) performance status ≤2; and baseline laboratory values as defined in the protocol. Primary exclusion criteria included: diagnosis or treatment of malignancy other than NHL within 1 year of randomization; previous diagnosis of a malignancy other than NHL and any radiographic or biochemical marker evidence of malignancy; evidence of a transformation from indolent NHL to a more aggressive

form of NHL; history of disallowed therapies specified in the protocol; previous therapy or surgery with residual toxic effects of Grade 3 or worse; peripheral neuropathy or neuropathic pain of Grade 2 or worse; pregnancy or lactation.

Test Product, Dose and Mode of Administration, Batch No.:
VELCADE batch numbers: V06PB9529, V06PC9585, V06PB9523, V06PC9582, V06PB9526, V06PC9586, V06PH9799, V06PC9579, V06PJ9821, V06PE9692, V06PJ9811, V06PH9800, V06PL9891, V06PL9892
Rituximab batch numbers: V06PB9524, V06PB9527, V06PH9794, V06PC9580, V06PC9617, V06PC9583, V06PH9794, V06PH9790, V06PB9525, V06PB9528, V06PC9581, V06PC9584, V06PE9693, V06PH9791, V07PA9936, V06PK9843, V06PK9844, V07PA9937, R13940, R13939, R13941, R13942

Reference Therapy, Dose and Mode of Administration, Batch No.: None

Duration of Treatment: Subjects in both treatment groups received up to 5 cycles of treatment (5 weeks duration per cycle, up to 25 weeks total treatment duration). Subjects who discontinued study drug before disease progression and before completion of the 25 weeks of treatment underwent posttreatment assessments every 10 weeks. After disease progression, only subsequent treatment and survival information were collected every 12 weeks (at minimum).

Criteria for Evaluation:
Efficacy: The criteria for each disease response category (CR, CRu, PR, stable disease [SD], relapsed disease, and progressive disease [PD]) were based on modified International Workshop to Standardize Response Criteria (IWRC) for NHL guidelines. Relapsed disease was considered to be the same as PD. An IRC performed the collection, qualification, and independent assessment of the radiographic images obtained during this study based on a prospectively designed and planned image acquisition and analysis charter. The goals were to ensure quality of imaging evaluations, completeness of evaluation studies, independence of the IRC assessments from investigator judgment, and to minimize time-to-assessment bias in either group of the study. This process also ensured that the investigators prospectively collected imaging evaluations in a standard fashion and that the imaging studies were sent to the IRC for a real time quality assessment review.

Safety: Safety and tolerability were evaluated based on adverse events; clinical laboratory test results; vital signs measurements; electrocardiograms; physical examination findings; and ECOG performance status.

Statistical Methods:
The sample size calculation for the overall population was based on the hypothesis that there would be an improvement in the median PFS by 33% (i.e., from 10 months to 13.33 months) by the addition of VELCADE to rituximab. A total of 514 events would provide 90% power (α=0.05, 2-sided) to detect such an effect. Assuming 20 months for accrual, 20 months for follow-up, and an approximate 5% dropout rate, a total of 670 subjects would be needed for the study (335 subjects per treatment group). Analysis populations were the following:

- The primary efficacy analysis set: the ITT population, which included all randomized subjects;
- The secondary analysis set: the PP population, defined as all subjects who were randomized to treatment, had no major violations of the inclusion/exclusion criteria, and underwent at least 1 post-baseline tumor assessment by the IRC. The analyses using data for the PP population were considered secondary and sensitivity analyses;
- The response-evaluable population: all subjects in the ITT population who received at least 1 dose of VELCADE or rituximab, had at least 1 measurable tumor mass at baseline, and had at least 1 post-baseline disease assessment by the IRC; and
- The safety population: all subjects who received at least 1 dose of study medication.

There were 2 planned interim analyses for this study. The clinical cut-off date for the first interim analysis was 11 April 2007. At that time the first 100 enrolled subjects had completed a minimum of 2 disease assessments. All safety data and tumor response data generated by the IRC was submitted blindly to an Independent Data Monitoring Committee (IDMC). The IDMC reviewed the unblinded data according to the pre-specified IDMC charter, and recommended that the study continue until the full enrollment of 670 subjects was reached. The IDMC met on 05 February 2009 to review the data from the second interim analysis and concluded that there were no safety issues, but requested a follow-up meeting to monitor the aggregate blinded PFS events rate. At this meeting on 18 December 2009, the blinded aggregate PFS events were reviewed and the IDMC concluded that the protocol-specified number of 514 PFS events for the main objective was likely to be unachievable within a reasonable time frame. The IDMC recommended that the study be stopped and the final analysis be conducted. After consultations with regulatory agencies in the US and the EU, the study was closed on 15 June 2010 and unblinded on 27 July 2010. This clinical cutoff was 22 months after the last subject was randomized, and 2 months beyond the 20 months expected in the protocol.

The primary efficacy endpoint was PFS, defined as the interval between the date of randomization and the date of PD or death, whichever occurred first, using the ITT population for this analysis. The primary analysis for PFS was based on the IRC assessment of PD. The PFS derived from the investigator data was evaluated and used as supportive evidence. The analysis of PFS based on the PP population was performed as a sensitivity analysis. The Kaplan-Meier method was used to estimate the distribution of overall PFS for each treatment group. The primary treatment comparison was based on an unstratified log-rank test. The HR and its 95% CI were estimated based on a Cox's regression model. A stratified log-rank test and Cox's regression model with covariates were performed as exploratory analyses. The factors FLIPI score, region, time since last anti-lymphoma therapy, and prior rituximab therapy were included in the Cox's regression model. The analysis for TTP, a secondary efficacy variable, was also considered a sensitivity analysis for PFS and was analyzed similarly.

Secondary efficacy endpoints were ORR (CR+CRu+PR); CR (CR/CRu) rate; duration of response and duration of CR; and rate of durable response (at least 6 months) based on the response-evaluable population. Overall response rate and CR rate were summarized for each treatment group. An unstratified Cochran-Mantel-Haenszel (CMH) test was used to test treatment difference. A logistic regression model was used to estimate the treatment effect measured in terms of odds ratios. The odds ratio and its 95% CI were presented. The Kaplan-Meier method was used to descriptively summarize duration of response and duration of CR. No inferential statistics were performed. Overall survival and 1-year survival rates were calculated for the ITT population based on the Kaplan-Meier method.

The median time to subsequent anti-lymphoma therapy, the most commonly reported first line of subsequent anti-lymphoma treatment, and time to next treatment in comparison with the subjects' immediate prior line of treatment were also evaluated. The Kaplan-Meier method was used to estimate the distribution of time to next anti-lymphoma treatment for each treatment group. The primary treatment comparison was based on an unstratified log-rank test. The HR and its 95% CI were estimated based on Cox's regression model. The duration of the treatment-free interval was summarized descriptively using the Kaplan-Meier method. Time to response was analyzed using the Kaplan-Meier method to estimate the cumulative distribution over time for the response-evaluable population. The unstratified log-rank test was used to compare the treatment groups. Descriptive summaries were provided for time to response for responders (CR/CRu/PR).

RESULTS:

STUDY POPULATION:

The overall population in this study was reflective of the global relapsed FL patient population. The median age of the ITT population was 57.0 years in both groups (range: 21 to 84), with 25% of all subjects >65 years of age. The ITT population consisted of 46% male and 54% female subjects (Rituximab group: 40% male/60% female; Vc-R group: 51% male/49% female). The racial composition of the ITT population was 75% White, 21% Asian, and the remainder of Black/African-American, native Hawaiian, other Pacific Islander and other racial backgrounds.

Follicular lymphoma was diagnosed in all but 1 subject, with the median time since diagnosis of 40.7 months. At baseline, 51% of all subjects had Grade 1 and 48% had Grade 2 FL. The majority of all subjects had a follicular dominant pattern of lymphoma growth (68%), as opposed to a follicular and diffuse growth pattern (31%). Fifty-four percent of all subjects had a high tumor burden, and 83% were Ann Arbor Stage III or IV. The number of nodal sites involved at baseline was 1 to 5 for 65% of subjects, and >5 for 35%. Serum LDH value was elevated for 32% of subjects. Bone marrow involvement at baseline was reported for 36% and 39% of subjects, respectively, in the rituximab and Vc-R groups. All subjects received at least 1 prior line of systemic anti-lymphoma therapy, most received 1 (41%) or 2 (26%) prior lines; 33% of all subjects received 3 or more prior lines of therapy.

The median number of cycles received was 5 cycles for VELCADE and for rituximab across both treatment groups. In the rituximab group, 74% of subjects received 5 cycles of treatment. In the Vc-R group 69% and 73% of subjects, respectively, received 5 cycles of treatment with VELCADE and rituximab. The mean dose intensity of rituximab was 131.1 mg/m^2/week for subjects in the rituximab group. For subjects in the Vc-R group, the mean dose intensity was 131.6 mg/m^2/week for rituximab and 1.16 mg/m^2/week VELCADE. The mean relative dose intensity was 0.97 for the rituximab group, and 0.88 for VELCADE and 0.96 for rituximab in the Vc-R group.

In the safety population, 72% of all subjects completed the protocol-specified 5 cycles of treatment (rituximab: 72%; Vc-R: 71%). Twenty-eight percent of subjects in the rituximab group and 29% in the Vc-R group discontinued prior to completing 5 cycles of treatment, most frequently due to disease progression (23% rituximab; 17% Vc-R). Discontinuation due to adverse events was low in both groups (1% rituximab; 6% Vc-R). Other reasons for discontinuation before completing 5 cycles of treatment were subject choice (2% rituximab; 4% Vc-R); death (1% each group), and other (1% each group). At the study end date (15 June 2010), 64% of subjects in each treatment group were discontinued due to the study closure, and 24% of subjects in each group died.

EFFICACY RESULTS:

For the primary endpoint, the median PFS for the ITT population per the IRC was 11.0 months in the rituximab group and 12.8 months in the Vc-R group. The difference was statistically significant, favoring the Vc-R group (p=0.039), and the HR of 0.822 corresponds to a 22% improvement in PFS versus rituximab alone. There was a consistent treatment effect (HR ≤0.850) in favor of the Vc-R group in all sensitivity analyses with the exception of PFS based on the investigator assessment. PFS results for most subgroups analyzed, (age ≤65, sex, race, prior rituximab therapy, FLIPI score [low, high], region, time since last anti-lymphoma therapy, Ann Arbor Stage [I, III], high tumor burden, and number of prior lines of therapy) were consistent with the primary PFS results for the ITT population.

Consistent evidence of the overall clinical benefit of the Vc-R combination was demonstrated by positive outcomes from secondary efficacy endpoints and additional endpoints of clinical benefit. The ORR per the IRC was 49% for the rituximab group and 63% for the Vc-R group (odds ratio: 0.569; p<0.001), and the overall durable (≥6 months) response rate per the IRC was 38% in the rituximab group and 50% in the Vc-R group (odds ratio: 0.608; p=0.002). The median duration of overall response was 13.8 months in the rituximab group and 16.0 months in the Vc-R group. The overall CR rate per the IRC was 18% for the rituximab group and 25% for the Vc-R group (odds ratio: 0.665; p=0.035). In both treatment groups, responses to treatment were durable; the median duration of overall response was >1 year for all

responders, and >2 years for complete responders. The median TTP as determined by the IRC was 11.3 months for the rituximab group compared with 13.3 months for the Vc-R group (HR: 0.808; p=0.027). After a median duration of follow-up of 33.9 months, the median OS was not reached in either group. The 1-year survival rates were similar (rituximab: 90.5%; Vc-R: 90.1%).At the end of the study, 80 (24%) subjects in the rituximab group and 79 (24%) subjects in the Vc-R group had died.

The median time to subsequent anti-lymphoma therapy was significantly longer (23.0 months) for subjects in the Vc-R group compared with the rituximab group (17.6 months; HR: 0.799; p=0.024), indicating a median 5.4-month prolongation in need for subsequent anti-lymphoma therapy with the addition of VELCADE to rituximab. In addition, there was no difference in the intensity of subsequent anti-lymphoma treatment following treatment with Vc-R or rituximab alone. The median duration of treatment-free interval was 4.7 months longer for subjects in the Vc-R group (17.7 months) compared with the rituximab group (13.0 months). Furthermore, the median duration of the treatment-free interval following Vc-R treatment was 2.2 months longer compared with each subject's immediate prior line of therapy. The median time to response per the IRC for the response-evaluable population was 4.7 months for the rituximab group and 4.4 months for the Vc-R group (HR: 1.509; p<0.001).

The subpopulation of subjects with poor prognostic factors (FLIPI score of ≥3 and high tumor burden) at baseline demonstrated a consistent and more pronounced treatment effect in the Vc-R group for both the primary and secondary efficacy endpoints compared with the total ITT population. The PFS was 6.7 months for the rituximab group and 9.5 months for the Vc-R group (HR: 0.667). This difference was associated with a trend in the estimated 1-year survival rate (rituximab: 76.6%; Vc-R: 83.1%; OS HR: 0.907). These positive effects were also observed in subjects who received 1 or 2 prior lines of therapy.

PATIENT-REPORTED OUTCOMES: For the key exploratory endpoint, PRO, both treatment groups showed improvements in Global Health Status compared to baseline. The rituximab group showed statistically significant improvements in Global Health Status from baseline beginning at Week 5 continuing through Week 120. The Vc-R group showed statistically significant improvements from baseline beginning at the end of treatment (Week 30) continuing through Week 120. Statistically significant differences between the groups were observed only at 3 timepoints during treatment. These transient differences favored rituximab but were small and do not appear to be clinically meaningful.

SAFETY RESULTS:
The addition of VELCADE to a standard rituximab dosing regimen did not require a change in dose or schedule of rituximab as the mean dose intensities for rituximab were similar in the rituximab (131.1 mg/m^2/week) and Vc-R (131.6 mg/m^2/week) groups. The mean relative rituximab dose intensity was 0.97 for the rituximab group, and 0.96 for rituximab in the Vc-R group. The mean dose intensity of VELCADE in the Vc-R group was 1.16 mg/m^2/week, (mean relative dose intensity of 0.88).

A higher incidence of treatment-emergent adverse events was observed in the Vc-R group compared with the rituximab group (95% versus 78%). The most commonly reported adverse events in the rituximab group were pyrexia (10%), cough (9%), fatigue (8%), and diarrhea (8%). In the Vc-R group, the most commonly reported adverse events were diarrhea (52%), nausea (29%), and pyrexia (25%), vomiting (24%), fatigue (22%), constipation (18%), neutropenia (17%), peripheral sensory neuropathy (16%), and cough (15%). The majority (67%) of reported adverse events were of toxicity Grade 1 or Grade 2. Grade 3 or higher adverse events were reported at a higher incidence in the Vc-R group compared with the rituximab group (rituximab: 21%; Vc-R: 46%). The incidence of Grade 4 events was low: 4% in the rituximab group and 9% in the Vc-R group. The incidence of Grade 5 treatment-emergent adverse events (fatal outcome) was similar between the Vc-R and rituximab groups (2% and 1%, respectively). The incidence of serious adverse events was 11% in the rituximab group and 18% in the Vc-R group. Four percent of subjects discontinued from treatment due to an adverse event (rituximab: 1%; Vc-R: 6%).

The incidence of hematologic adverse events was higher in the Vc-R group (27%) compared with the rituximab group (15%). Grade 3 or higher neutropenia was reported in 11% of subjects in the Vc-R group and 3% of subjects in the rituximab group. Grade 3 or higher febrile neutropenia and thrombocytopenia, respectively, were uncommon in both groups (rituximab: 1% and 0%; Vc-R: 1% and 3%).

Most deaths during the study were due to disease progression. By the end of the study, 23% of subjects had died (24% rituximab; 23% Vc-R), most frequently due to progressive disease (rituximab: 17%; Vc-R: 15%). Most deaths (94%) occurred at least 61 days after the first dose of study drug. Three subjects in the Vc-R treatment group died due to adverse events considered by the investigator to be treatment-related (febrile neutropenia; septic shock; bilateral pneumonia).

The incidence of peripheral neuropathy not elsewhere classified (NEC) was 1% in the rituximab group and 17% in the Vc-R group; 9 (3%) subjects in the Vc-R group experienced a Grade 3 or higher event of peripheral neuropathy NEC. In the Vc-R group, 78% of events resolved or improved and 71% of events resolved completely. The median time to resolution or improvement was 58 days and the median time to resolution was 109 days (range: 1 to 1,104 days). The incidence of peripheral neuropathy in the Vc-R and rituximab groups was not increased in subjects with prior exposure to vincristine or other neurotoxic agents.

Herpes zoster events were experienced by 1% of subjects in the rituximab group and 13% of subjects in the Vc-R group. Twelve (4%) subjects in the Vc-R group experienced Grade 3 adverse events, 1 of which led to discontinuation. Four (1%) events of herpes zoster in the Vc-R group were reported as serious (2 Grade 2, 2 Grade 3). There were no Grade 4 events of herpes zoster. Heart failure events were reported at a low incidence in both treatment groups (rituximab: 1%; Vc-R: 2%). The addition of VELCADE to rituximab did not increase the incidence of hypersensitivity and hepatitis disorders, adverse events known to be associated with rituximab treatment.

For clinical laboratory test results, there were no relevant increases from baseline due to the addition of VELCADE to rituximab treatment, with the exception of lymphocyte count. Neutrophil and platelet counts were reduced temporarily after VELCADE dosing in the Vc-R group, which recovered by end-of-treatment.

STUDY LIMITATIONS: No notable study limitations were identified by the Sponsor.

CONCLUSIONS:

- The treatment regimen of weekly VELCADE in combination with rituximab was effective in patients with relapsed or refractory, rituximab-naïve or -sensitive FL as evidenced by a statistically significant increase in PFS, and an overall clinically relevant improvement in secondary (ORR, CR rates, durable response rate, duration of response, TTP) and additional (time to subsequent anti-lymphoma treatment, treatment-free interval) efficacy endpoints compared with rituximab alone. A more pronounced treatment effect was observed in subjects with 1 or 2 prior lines of therapy and in subjects with poor prognosis high-risk factors.
- The Vc-R combination was associated with a higher incidence of treatment-emergent adverse events compared with rituximab alone. The safety of the Vc-R combination was consistent with the known safety profiles of VELCADE and rituximab. The adverse events experienced with the addition of weekly VELCADE to rituximab were predictable and manageable by dose modification or with the addition of supportive therapies if needed. No new toxicities were observed.
- The overall benefit/risk profile was positive, in that the benefits (increased PFS, ORR, CR rate, durable responses, TTP, median time to subsequent anti-lymphoma therapy, and median treatment-free interval) outweigh the risks (additional toxicity) associated with the use of the combination of weekly VELCADE with rituximab. The incidence and severity of the adverse events seen with the combination were lower than in prior experience with the twice-weekly VELCADE schedule in patients with multiple myeloma and mantle cell lymphoma.

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