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59TH AMERICAN SOCIETY OF HEMATOLOGY (ASH) ANNUAL MEETING & EXPOSITION

9–12 DECEMBER 2017 • ATLANTA, GEORGIA, USA

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Weekly Subcutaneous Emicizumab a New Standard of Care in Hemophilia Management • bb2121 Anti-BCMA CAR T-Cell Therapy Leads to Durable Clinical Responses in Heavily Pretreated Relapsed/Refractory Multiple Myeloma • CTL019 Produces High 6-Month Response Rates in Highly Pretreated Adult Relapsed/Refractory Diffuse Large B-Cell Lymphoma • BLU-285, a KIT D816V Inhibitor, Proves Promising in Advanced Systemic Mastocytosis • The HbS Polymerization Inhibitor Voxelotor GBT440 Has Demonstrated Positive Initial Results in Adolescents With Sickle Cell Disease

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FL: follicular lymphoma; CLL: chronic lymphocytic leukaemia; SLL: small lymphocytic lymphoma.

PLEASE REFER TO MINIMUM PRESCRIBING INFORMATION ON THE INSIDE BACK COVER.

References: 1. Pharmaceutical Benefits Schedule. Available at: www.pbs.gov.au. Accessed December 2017.
2. Zydelig Product Information, 26 October 2017.

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CONTENTS

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BY THE PRACTICEUPDATE EDITORIAL TEAM

Weekly Subcutaneous Emicizumab a New Standard of Care in Hemophilia Management

In the largest study of pediatric hemophilia A with inhibitors to date, emicizumab prophylaxis prevented or reduced bleeds substantially and was well tolerated, updated analysis of the multicenter, open-label, phase III HAVEN 2 trial reports.

Guy Young, MD, of the Children's Hospital of Los Angeles, and University of Southern California Keck School of Medicine, explained that emicizumab is a bispecific humanized monoclonal antibody administered subcutaneously. Emicizumab bridges factors IXa and X to restore the function of missing factor VIIIa.

Emicizumab is being developed to prevent bleeds in patients with hemophilia A with and without inhibitors.

In 2017, an interim analysis of the HAVEN 2 study (n=20) in patients age 2–12 years (data cut-off in October of 2016) showed that subcutaneous, once-weekly emicizumab prophylaxis prevented or reduced bleeds successfully, provided clinically meaningful reductions in the annualized bleed rate vs prior bypassing agent treatment, and was well tolerated.

At ASH, Dr. Young presented an updated, much larger (40 additional patients, 60 total) analysis of efficacy, safety, and pharmacokinetics of once-weekly subcutaneous emicizumab prophylaxis in pediatric hemophilia A with inhibitors.

"I chose to participate in this study," Dr. Young told Elsevier's *PracticeUpdate*, "because I felt this medication could offer a great benefit for my inhibitor patients who were continuing to suffer with repeated bleeding events and the associated pain and morbidity. In addition, our center makes every effort to bring innovative therapies to our patients as soon as possible."

The study enrolled children with hemophilia A with inhibitors age 2–12 years (or 12–17 years of age in those weighing <40 kg), and is enrolling those <2 years of age treated previously with bypassing agents to emicizumab prophylaxis for ≥52 weeks.

Efficacy analyses included annual bleed rate and bleed reduction vs annual bleed rate on prior bypassing agent treatment from a prospective non-interventional study. Health-related quality of life, aspects of caregiver burden, and safety parameters were also assessed.

> "The results of the study are truly remarkable. For such a large group of children with inhibitors to experience almost no bleeding events of clinical significance is very meaningful, since the bypassing agents we had been using could not accomplish this outcome"

The updated analysis (May 2017 cut-off) included approximately 6 additional months of data vs the first interim analysis. Sixty patients with hemophilia A with inhibitors age 1–15 (median 7) years, and 57 patients age <12 years, including two age <2 years, were included in the efficacy analyses.

A total of 3 patients age ≥12 years and weighing <40 kg were enrolled. The median duration of observation was 9 weeks (range 1.6–41.6). A total of 20 patients had been observed ≥24 weeks, and 2 patients age <2 years for approximately 5 and 2 weeks, respectively.

Overall, 54/57 (94.7%) patients experienced zero treated bleeds. Of the three treated bleeds, one occurred in a joint, one in a muscle, and one in the hip, classified as "other." All were treated safely with recombinant factor VIIa.

Only one of these three treated bleeds was spontaneous. In total, 37/57 patients (64.9%) reported no bleeds. A total of 65 bleeds were reported in 20 patients: eight occurred in a joint, two in a muscle, and 55 were classified as "other." Of the 55 "other" bleeds, 26 (40.0%) were spontaneous, 36 (55.4%) traumatic, and three (4.6%) due to a procedure or surgery.

A total of 23 patients <12 years of age were followed for ≥12 weeks and were therefore included in the calculation of the population evaluated for annual bleed rate. The annual bleed rate was 0.2 (95% CI 0.06; 0.62) for treated bleeds.

A total of 18 patients <12 years of age had previously participated in the noninterventional study. Of these, 13 had been in HAVEN 2 for ≥12 weeks and were therefore included in the intra-individual comparison. A substantial reduction in annual bleed rate of 99% with emicizumab prophylaxis vs prior bypassing agent treatment was observed in these patients.

Considerable improvements in health-related quality of life and caregiver burden were also observed.

Emicizumab was well tolerated; the most common adverse events being viral upper respiratory tract infection and injection site reactions (16.7% of patients each).

A total of 6 patients experienced 7 serious adverse events (two muscle hemorrhages, one eye pain, one catheter site infection, one device-related infection, one mouth hemorrhage, one appendicitis). None were deemed related to emicizumab. No thromboembolic or thrombotic microangiopathy events were reported. No patients tested positive for antidrug antibodies.

Mean steady state trough emicizumab concentrations of approximately 50 µg/mL were maintained with longer follow-up. Pharmacokinetic profiles were consistent across age groups and body weight.

Dr. Young concluded that HAVEN 2 was the largest study in pediatric hemophilia A with inhibitors to date. Emicizumab prophylaxis prevented or reduced bleeds substantially and was well tolerated in this patient population.

Pharmacokinetics remained consistent with those seen in adolescent/adult hemophilia A.

Weekly subcutaneous emicizumab has the potential to reduce overall treatment and disease burden, and may provide a new standard of care for management of hemophilia.

"The importance of the study," he asserted, "lies in the fact that patients with hemophilia with inhibitors suffer far worse consequences than those without inhibitors. This innovative therapy offers the promise of reducing bleeding events significantly and allowing patients with inhibitors to lead more normal lives, similar to the lives of patients with hemophilia without inhibitors.

"The results of the study are truly remarkable," he continued. "For such a large group of children with inhibitors to experience almost no bleeding events of clinical significance is very meaningful, since the bypassing agents we had been using could not accomplish this outcome."

"Future directions for this medication," he added, "will focus on two groups: children <12 years of age without inhibitors and, perhaps, more importantly, very young children (<1 year of age) who may benefit from starting prophylaxis at a younger age than we are able to do now, given the fact that emicizumab is given subcutaneously vs factor. Factor is given intravenously."

"Finally," he said, "this focus could pave the way to preventing the most devastating complication of haemophilia – bleeding in the brain – an uncommon but not rare event that tends to occur in the first year of life."

www.practiceupdate.com/c/61490

bb2121 Anti-BCMA CAR T-Cell Therapy Leads to Durable Clinical Responses in Heavily Pretreated Relapsed/Refractory Multiple Myeloma

Chimeric antigen receptor T (CAR T)-cell therapy with bb2121 holds potential as a new treatment paradigm in relapsed/refractory multiple myeloma, updated results of the multicenter phase I dose escalation CRB-401 trial show.

James N. Kochenderfer, MD, of the National Cancer Institute, National Institutes of Health Clinical Center, Bethesda, Maryland, explained that CAR T-cell therapies have demonstrated robust and sustained clinical responses in several hematologic malignancies.

Data suggest that achieving acceptable benefit-to-risk profiles depends on several factors, including specificity of the antigen target and characteristics of the CAR itself, including on-target, off-tumor activity.

To evaluate the safety and efficacy of CAR T-cells in relapsed and/or refractory multiple myeloma, Dr. Kochenderfer and colleagues designed a second-generation CAR construct targeting B cell maturation antigen to redirect T cells to multiple myeloma cells.

B cell maturation antigen is a member of the tumor necrosis factor superfamily expressed primarily by malignant myeloma cells, plasma cells, and some mature B cells. bb2121 consists of autologous T cells transduced with a lentiviral vector encoding a novel CAR incorporating an anti-B cell maturation antigen single-chain variable fragment, a 4-1BB costimulatory motif, and a CD3-zeta T cell activation domain.

CRB-401 includes patients with relapsed/refractory malignant melanoma who have received at least three prior regimens, including a proteasome inhibitor and an immunomodulatory agent, or are double-refractory, and exhibit ≥ 50% B cell maturation antigen expression on malignant cells.

Peripheral blood mononuclear cells are collected via leukapheresis and shipped to a central facility for transduction, expansion, and release testing prior to return to the site for infusion.

Patients undergo lymphodepletion with fludarabine (30 mg/m^2) and cyclophosphamide (300 mg/m^2) daily for 3 days. They then receive one infusion of bb2121.

The study follows a standard 3 + 3 design with planned dose levels of 50, 150, 450, 800, and 1200 x 10^6 CAR-positive T-cells.

The primary outcome measure is incidence of adverse events, including dose-limiting toxicities. Additional outcome measures are the quality and duration of clinical response assessed according to the International Myeloma Working Group Uniform Response Criteria for Multiple Myeloma, evaluation of minimal residual disease, overall and progression-free survival, quantification of bb2121 in blood, and quantification of circulating soluble B cell maturation antigen over time.

As of May 2017, 21 patients (median 58 [37 to 74] years of age) with a median of 5 (1 to 16) years since diagnosis of malignant melanoma, had been infused with bb2121.

Eighteen patients were evaluable for initial (1-month) clinical response. Patients had received a median of 7 (range 3 to 14) prior lines of therapy, all with prior autologous stem cell transplantation. A total of 67% exhibited high-risk cytogenetics. A total of 15 of 21 (71%) had received, and 6 of 21 (29%) were refractory to, five prior therapies (bortezomib/lenalidomide/carfilzomib/pomalidomide/daratumumab).

Median follow-up duration after bb2121 infusion was 15.4 weeks (range 1.4 to 54.4). As of data cut-off, no dose-limiting toxicities and no treatment-emergent grade 3 or higher neurotoxicities similar to those reported in other CAR T clinical studies have been observed.

Primarily grade 1 or 2 cytokine release syndrome was reported in 15 of 21 (71%) patients. Two patients had grade 3 cytokine release syndrome that resolved in 24 h and four patients received tocilizumab, one with steroids, to manage cytokine release syndrome.

The syndrome was more common in the higher dose groups but did not appear related to tumor burden. One death during the study was from cardiopulmonary arrest more than 4 months after bb2121 infusion in a patient with an extensive cardiac history. This death occurred while the patient was in stringent complete response and was assessed as unrelated to bb2121.

The objective response rate was 89% and increased to 100% for patients treated with doses of 150 x 10^6 CAR-positive T-cells or higher. No patients treated with doses of 150 x 10^6 CAR-positive T-cells or higher experienced disease progression, with duration 8–54 weeks since bb2121 administration.

Minimal residual disease-negative results were obtained in all four patients evaluable for analysis. CAR-positive T-cell expansion has been demonstrated consistently and 3 of 5 patients evaluable for CAR-positive cells at 6 months harbored detectable vector copies.

Dr. Kochenderfer concluded that bb2121 shows promising efficacy at dose levels above 50 x 106 CAR-positive T-cells, with manageable cytokine release syndrome and no dose-limiting toxicities to date.

The objective response rate was 100% at these dose levels, with 8 ongoing clinical responses at 6 months and one sustained response beyond 1 year.

CAR T therapy with bb2121 holds potential as a new treatment paradigm in relapsed/refractory multiple myeloma.

Dr. Kochenderfer stated in an ASH press release, "We are excited about the early results in a patient population with very advanced myeloma for whom previous therapies have failed.

"These findings are important," he continued, "because despite recent therapeutic advances, multiple myeloma – a cancer that begins in plasma cells – remains nearly incurable. Existing therapies require patients to stay on treatment long-term with drugs that have side effects.

"CAR T-cell therapy is completely different from other available treatments for multiple myeloma," he noted. "We have patients with a sustained response who have been able to go for over a year with no additional myeloma therapy and who live with tolerable adverse effects." ■

www.practiceupdate.com/c/61918

The CAR T Agent KTE-C19 Demonstrates Significant Clinical Benefit With Manageable Adverse Effects in Refractory Aggressive Non-Hodgkin's Lymphoma

The CAR T agent KTE-C19 (axicabtagene ciloleucel) has demonstrated significant clinical benefit with manageable adverse effects in patients with non-Hodgkin's lymphoma and no curative treatment options, reports the 1-year follow-up and exploratory biomarker analyses of the ZUMA-1 trial.

Sattva S. Neelapu, MD, of the University of Texas MD Anderson Cancer Center, Houston, explained that patients with refractory non-Hodgkin's lymphoma experience poor outcomes to available therapies.

In the retroSpeCtive non-HOdgkin LymphomA Research (SCHOLAR)-1 pooled analysis of patients with refractory aggressive non-Hodgkin's lymphoma, the objective response rate was 26% and the complete response rate, 7%. Median overall survival was 6.3 months.

The primary analysis of ZUMA-1 demonstrated positive results, with an objective response rate of 82% and complete response rate of 54% after a single infusion of KTE-C19.

The safety profile was manageable: grade ≥3 cytokine release syndrome and neurologic events were generally reversible and reported in 13% and 28%, of patients, respectively. After a median follow-up duration of 8.7 months, 44% of patients in ZUMA-1 were in ongoing response.

Patients with refractory diffuse large B cell lymphoma, transformed follicular lymphoma, or primary mediastinal large B cell lymphoma were enrolled and dosed as previously reported.

Refractory disease was defined as progressive or stable disease as best response to the last line of therapy, or relapse ≤12 months after autologous stem cell transplantation. Patients must have undergone a prior anti-CD20 antibody and an anthracycline-containing regimen.

The primary endpoint was objective response rate per 2007 International Working Group criteria. Key secondary endpoints included duration of response, overall survival, and the incidence of adverse events. A key exploratory endpoint was to investigate the mechanisms of resistance using posttreatment tumor biopsies obtained at the time of relapse or progression.

Data cut-off of the long-term follow-up analysis was in August of 2017. No patients were lost to follow-up, and all surviving patients remained in disease and survival follow-up. Baseline and post-progression biopsies were evaluable by central review from 12 patients.

Of 11 patients with CD19-positive status at baseline, 3 (27%) developed CD19-negative disease at the time of disease progression. Of 10 patients evaluable for programmed death-ligand 1 (PD-L1) assessment at the time of disease progression, 8 (80%) exhibited PD-L1-positive disease.

Of the 8 patients with CD19-positive samples at progression, 5 (63%) demonstrated PD-L1-positive tumor cells. Of the 3 patients with CD19-negative samples at progression, 2 harbored PD-L1-positive tumor cells.

In addition, post-progression biopsies from 6 separate patients were evaluable by local review, of which 3 (50%) exhibited ≤1% CD19 staining. Cumulatively, 17 patients were evaluable for CD19 expression at the time of progression by either central or local review, and six (35%) expressed ≤1% CD19.

> "Ongoing responses after 24 months suggest that late relapses are uncommon. Patients in remission after 6 months tend to stay in remission. With existing therapy, median survival for people with this disease is only 6 months. We see more than half of patients – 59% – are still alive over a year after treatment"

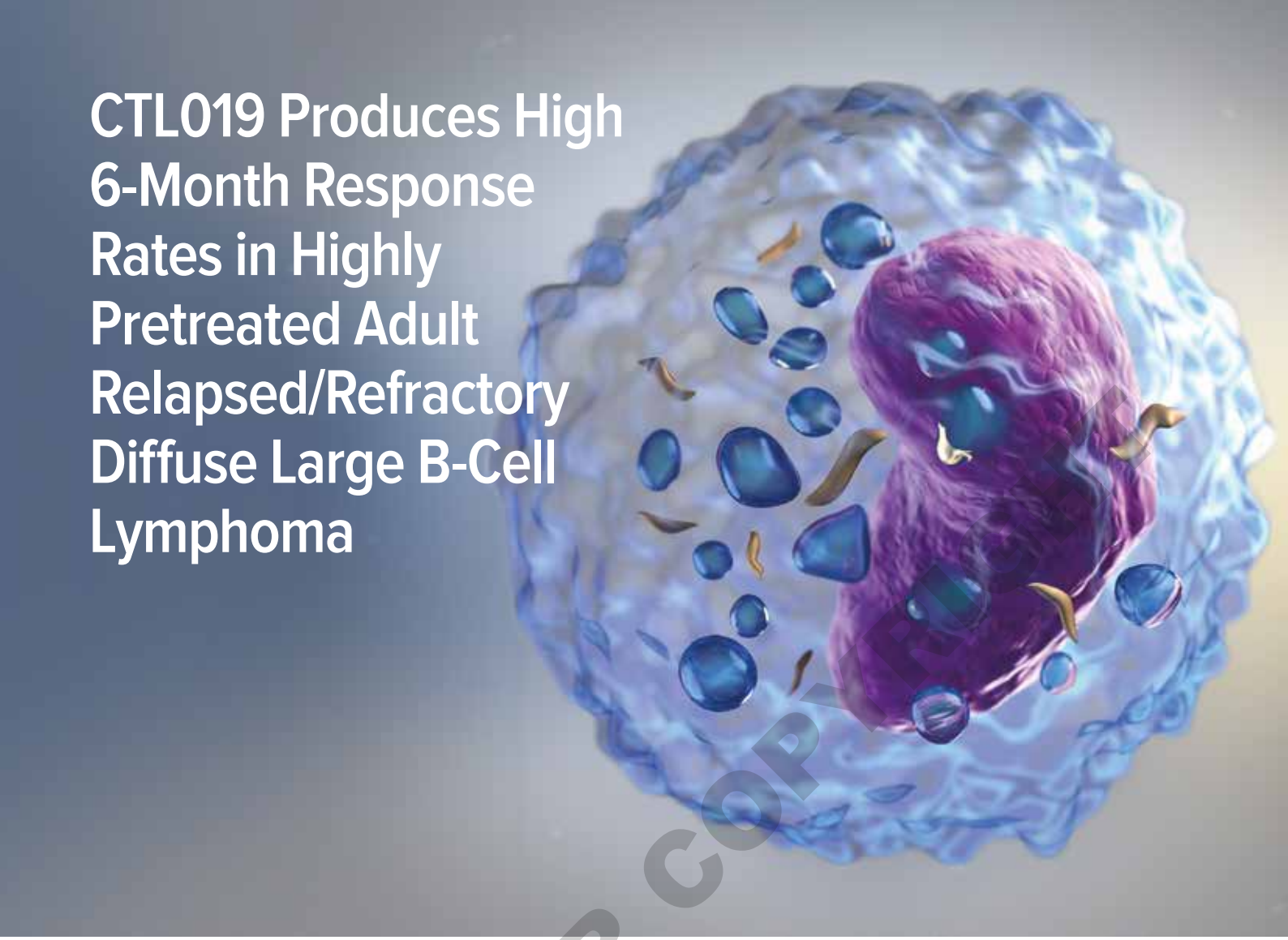
Dr. Neelapu concluded that in the ZUMA-1 study, KTE-C19 demonstrated significant clinical benefit with manageable adverse events in patients with no curative treatment options. Loss of CD19 and gain of PD-L1 expression in tumors were identified as possible mechanisms of resistance following KTE-C19 treatment.

The results provide insights into the development of novel therapeutic strategies to overcome CD19 CAR T resistance and improve outcomes further in these patients.

Dr. Neelapu stated in an ASH press release, "Long-term follow-up of ZUMA-1 confirms that responses can be durable. Ongoing responses after 24 months suggest that late relapses are uncommon. Patients in remission after 6 months tend to stay in remission. With existing therapy, median survival for people with this disease is only 6 months. We see more than half of patients – 59% – are still alive over a year after treatment." ■

www.practiceupdate.com/c/61917

CTL019 Produces High 6-Month Response Rates in Highly Pretreated Adult Relapsed/Refractory Diffuse Large B-Cell Lymphoma



The investigational CAR T-cell agent CTL019 has been shown to produce high response rates, with 95% of complete responses at 3 months sustained after 6 months, in a cohort of highly pretreated adult patients with relapsed/refractory diffuse large B-cell lymphoma. This was the outcome of the single-arm, open-label, multicenter, global, pivotal phase II JULIET trial, confirming findings of the earlier interim analysis.

Stephen J. Schuster, MD, of the Abramson Cancer Center, University of Pennsylvania, Philadelphia, explained that CTL019 (tisagenlecleucel) identifies and eliminates CD19-expressing B-cells. JULIET was performed in adults with relapsed/refractory diffuse large B-cell lymphoma.

The primary objective was met at the interim analysis, with the best overall response of 59% (complete response 43%; partial response 16%). Dr. Schuster reported results of the primary analysis of the JULIET study.

Eligible patients were 18 years and older and suffered from relapsed/refractory diffuse large B-cell lymphoma that had progressed after receiving at least two lines of chemotherapy. They were ineligible for or failed autologous stem cell transplant.

Centrally manufactured CAR T-cells were provided to patients at 27 study centers in 10 countries on four continents using cryopreserved apheresis, central production facilities, and a global supply chain. CTL019 was manufactured at two sites in the US and Germany.

Autologous T cells were transduced with a lentiviral vector encoding an anti-CD19 CAR, expanded ex vivo, cryopreserved, shipped, and infused at study centers.

The primary endpoint was best overall response rate (complete response + partial response) per independent review committee.

As of data cut-off in March of 2017, 147 patients were enrolled and 99 infused with a single dose of CTL019-transduced cells (median 3.1×10^8, range, $0.1–6.0 \times 10^8$ cells). Ninety percent of patients received bridging therapy.

Prior to infusion, patients underwent restaging, and 93% received lymphodepleting chemotherapy. Fudarabine 25 mg/m^2 and cyclophosphamide 250 mg/m^2 daily × 3 days was given to 73% of patients and 19% received bendamustine 90 mg/m^2 daily x 2 days.

The median duration from infusion to data cut-off was 5.6 months. Median patient age was 56 (range 22–76) years. At study entry, 77% of patients suffered from stage 3 or 4 disease. Patients had received a median of three (range one to six) prior lines of antineoplastic therapy. A total of 95% had received at least two and 51%, at least three prior lines. A total of 47% of patients had undergone prior autologous stem cell transplantation.

In this primary analysis of patients who received CTL019 from the US manufacturing site, among 81 infused patients with ≥3 months follow-up or earlier discontinuation, the best overall response rate was 53.1% (95% CI 42% to 64%; P < .0001) with 39.5% complete and 13.6% partial response.

At month 3, the complete response rate was 32% and the partial response rate, 6%. Among patients evaluable at 6 months (n=46), the complete response rate was 30% and the partial response rate was 7%.

Response rates were consistent across prognostic subgroups, including those who received prior autologous stem cell transplantation and those with double-hit lymphoma. The median duration of response was not reached.

The 6-month probability of being free of relapse was 73.5% (95% CI 52.0–86.6). Median overall survival was not reached. The 6-month probability of overall survival was 64.5% (95% CI 51.5–74.8).

No patient who achieved a response (complete or partial response) proceeded to allogeneic or autologous stem cell transplantation. CTL019 was detected in peripheral blood by quantitative polymerase chain reaction for up to 367 days in responders.

> "While we don't completely understand why these remissions are so durable, it's exciting and will change how this disease is treated when conventional therapies fail. We are going to be able to offer patients who don't respond to standard therapies a form of therapy that may, after a single treatment, relieve symptoms and save their lives"

Overall, 86% of patients experienced grade 3 or 4 adverse events. Cytokine release syndrome occurred in 58% of infused patients. Fifteen percent experienced grade 3 and 8%, grade 4, cytokine release syndrome using the Penn grading scale and managed by a protocol-specific algorithm.

Fifteen percent of patients received anti-interleukin 6 therapy, tocilizumab, for management of cytokine release syndrome with good response and 11% received corticosteroids.

Other grade 3 or 4 adverse events of special interest included neurologic adverse events (12% managed with supportive care), cytopenias lasting >28 days (27%), infections (20%), and febrile neutropenia (13%).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Three patients died within 30 days of infusion, all due to disease progression. No deaths were attributed to CTL019. No cytokine release syndrome- nor neurologic event-associated deaths occurred.

Dr. Schuster concluded that CTL019 produced high response rates with 95% of complete responses at 3 months sustained at 6 months in a cohort of highly pretreated adult patients with relapsed/refractory diffuse large cell B cell lymphoma. The results confirmed findings of the earlier interim analysis.

Centralized manufacturing was feasible in the first global study of CAR T-cell therapy in diffuse large B-cell lymphoma. Cytokine release syndrome and other adverse events were managed effectively and reproducibly by appropriately trained investigators without treatment-related mortality.

"Once CAR T-cells were generated," Dr. Schuster stated in an ASH press release, "we could freeze them again, allowing us to hold the product until patients were clinically ready to receive them. These are very sick patients, so this gives the treating physician some flexibility to schedule therapy when it's best for each patient."

"While we don't completely understand why these remissions are so durable," he continued, "it's exciting and will change how this disease is treated when conventional therapies fail. We are going to be able to offer patients who don't respond to standard therapies a form of therapy that may, after a single treatment, relieve symptoms and save their lives." ■

www.practiceupdate.com/c/61915

Brentuximab Vedotin + Doxorubicin, Vinblastine, Dacarbazine Proves Superior to ABVD in Previously Untreated Stage 3 or 4 Hodgkin's Lymphoma

Brentuximab vedotin + doxorubicin, vinblastine, and dacarbazine (A + AVD) has now been established as a new front-line option for patients with advanced-stage Hodgkin's lymphoma, outcome of the unblinded, open-label, randomized, multicenter, phase III ECHELON-1 study shows.

Joseph M Connors, MD, of the British Columbia Cancer Agency, Vancouver, Canada, explained that approximately 30% of patients with advanced-stage Hodgkin's lymphoma suffer from refractory disease or relapse following front-line treatment with Adriamycin, bleomycin, vinblastine, and dacarbazine (ABVD).

Brentuximab vedotin is a CD30 directed antibody–drug conjugate approved for classic Hodgkin's lymphoma after failure of autologous stem cell transplantation or at least two prior chemotherapy regimens and as consolidation post autologous stem cell transplantation for increased risk Hodgkin's lymphoma.

Dr. Connors reported data from ECHELON-1, which compared A + AVD vs ABVD as front-line therapy in previously untreated, advanced Hodgkin's lymphoma.

Patients were randomized 1:1 to A + AVD (brentuximab vedotin 1.2 mg/kg of body weight, doxorubicin 25 mg/m^2, vinblastine 6 mg/m^2, dacarbazine 375 mg/m^2) or ABVD (doxorubicin 25 mg/m^2, bleomycin 10 units per m^2, vinblastine 6 mg/m^2, dacarbazine 375 mg/m^2) IV on days 1 and 15 of up to six 28-day cycles.

Patients with a PET scan Deauville score of 5 after cycle 2 could switch to alternative therapy at the treating physician's discretion. Patients were stratified by region (Americas vs Europe vs Asia) and International Prognostic Score (0–1 vs 2–3 vs 4–7).

Toward the end of the study, the independent data monitoring committee recommended primary prophylaxis using granulocyte colony-stimulating factor for newly randomized patients receiving A + AVD based on a higher incidence of febrile neutropenia in that arm.

The primary endpoint was modified progression-free survival, defined as time to progression, death, or evidence of incomplete response followed by subsequent anticancer therapy.

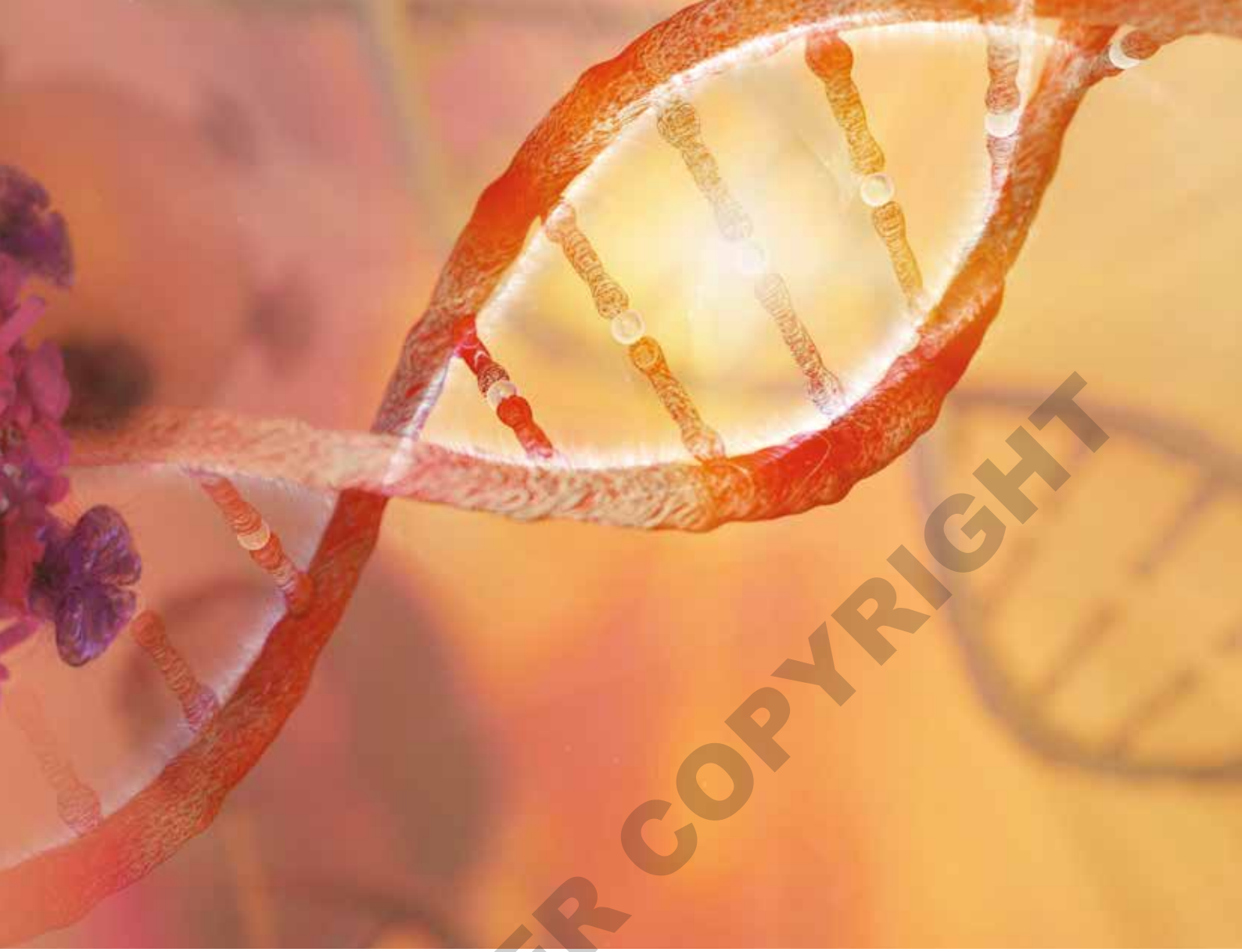
A total of 1334 patients with stage 3 (36%) or 4 (64%) Hodgkin's lymphoma were randomized (58% male; median age 36 years [range 18–83]; 34% ≥45 years of age, 14% ≥60 years of age).

The primary endpoint of modified progression-free survival was met (HR 0.770 [95% CI 0.603–0.982]; P = .035), with 117 events in the A + AVD arm and 146 events in the ABVD arm, and was consistent with investigator-reported modified progression-free survival (HR 0.725 [95% CI 0.574–0.916], P = .007).

Modified progression-free survival events were attributed to disease progression (90 vs 102), death (18 vs 22), or receipt of additional anticancer therapy for incomplete response (9 vs 22) after A + AVD or ABVD, respectively.

The 2-year modified progression-free survival was 82.1% (95% CI 78.7–85.0) with A + AVD vs 77.2% (95% CI 73.7–80.4) with ABVD and 81.0% (95% CI 77.6–83.9) with A + AVD vs 74.4% (95% CI 70.7–77.7) with ABVD.

Twenty-eight deaths occurred in the A + AVD arm and 39 in the ABVD arm (HR for interim overall



survival 0.721 [95% CI 0.443–1.173]; difference not significant).

Other secondary endpoints including complete response rate, overall response rate at the end of the randomization regimen, complete response rate at the end of front-line therapy, rate of PET negativity at the end of cycle 2, duration of response, duration of complete response, and event-free survival, also trended in favor of A + AVD.

The median treatment duration and number of completed cycles were similar across treatment arms.

Safety profiles were consistent with the known toxicities of the single agents. Neutropenia was reported in 58% of patients receiving A + AVD and 45% receiving ABVD (febrile neutropenia in 19% and 8%, respectively).

The incidence of discontinuations due to neutropenia or febrile neutropenia was ≤1% in both arms. Grade ≥3 infections were more common in the A + AVD arm (18%) than the ABVD arm (10%).

In patients receiving A + AVD, primary prophylaxis with granulocyte-colony stimulating factor (n=83) reduced febrile neutropenia from 21% to 11% and grade ≥3 infections and infestations from 18% to 11%.

Peripheral neuropathy occurred in 67% of patients receiving A + AVD and 43% of those receiving ABVD (grade ≥3: 11% A + AVD [one patient with grade 4] vs 2% ABVD). Of patients experiencing peripheral neuropathy in the A + AVD arm, 67% experienced resolution or improvement of peripheral neuropathy at last follow-up.

Pulmonary toxicity was more frequent and more severe with ABVD (grade ≥3: 3% ABVD vs <1% A + AVD). Of on-study deaths, 7 of 9 in the A + AVD arm were associated with neutropenia.

These deaths occurred in patients who had not received primary prophylaxis with granulocyte-colony stimulating factor. Of 13 on-study deaths in the ABVD arm, 11 were due to or associated with pulmonary toxicity.

Dr. Connors concluded that, compared with standard ABVD, A + AVD as frontline therapy improved outcomes for patients with advanced Hodgkin's lymphoma, including a 23% risk reduction in progression, death, or need for additional anticancer therapy.

This result establishes A + AVD as a new frontline option for patients with advanced-stage Hodgkin's lymphoma.

Dr. Connors remarked in an ASH press release, "The experimental combination with brentuximab vedotin got rid of all the disease more frequently, and this was achieved with acceptable levels of adverse effects. Treatment with brentuximab vedotin was modestly more toxic, but when we added simple measures to improve patients' blood counts, they were able to take it safely."

He continued, "We expect ABVD to cure about three-quarters of patients, which means, of course, that one-quarter will not be cured. In this study, we were able to reduce that rate of treatment failure significantly. If this new regimen is adopted widely, it will change first-line treatment of advanced Hodgkin's lymphoma." ■

www.practiceupdate.com/c/61705

The Applied Clinical Protocol for Gene Therapy for β-Thalassemia, GLOBE LV Is Shown to Be Well Tolerated and Reduces the Transfusion Requirement

The applied clinical protocol for gene therapy for β-thalassemia, GLOBE LV, has been shown to be well tolerated and to reduce the transfusion requirement. This preliminary outcome of the phase I/II Gene Therapy for Transfusion Dependent Beta-thalassemia (TIGET-BTHAL) trial of autologous hematopoietic stem cells genetically modified with GLOBE lentiviral vector was reported at ASH 2017.

Sarah Marktel, MD, of the Istituto di Ricovero e Cura a Carattere Scientifico San Raffaele Scientific Institute, Milan, Italy, explained that gene therapy for transfusion dependent β-thalassemia is based on the autologous transplantation of hematopoietic stem cells engineered by lentiviral vectors expressing a transcriptionally regulated human β-globin gene.

Gene therapy could represent an alternative to hematopoietic stem cell transplantation with the potential advantages of using autologous stem cells, tailored conditioning with no need for immune suppression post gene therapy nor risk of graft-vs-host disease or rejection.

Dr. Marktel and colleagues developed a clinical protocol of gene therapy based on the high-titer vector GLOBE, a 3rd generation self-inactivating lentiviral vector that encodes for the human β-globin gene.

Transfusion-dependent patients with β-thalassemia of any genotype undergo peripheral blood stem cell harvest following mobilization with lenograstim and plerixafor.

After transduction of immune-selected autologous CD34+ cells and successful release of the frozen drug substance, patients undergo a conditioning regimen based on myeloablative treosulfan and thiotepa favoring efficient engraftment of corrected cells with reduced extramedullary toxicity.

The route of administration of gene-modified hematopoietic stem cells is intraosseous in the posterior-superior iliac crests with the aim of enhancing engraftment and minimizing first-pass intravenous filter.

Three days after gene therapy, previously collected unstimulated autologous peripheral blood leukocytes ($1–10 \times 10^7$ CD3+ per kilogram of body weight) are reinfused intravenously to favor immune-reconstitution.

> "Our results suggest that gene therapy can correct the disease, and result in transfusion independence."

After 2 years of follow-up, patients will be followed for a further 6 years in a long-term follow-up study. On the basis of extensive efficacy and safety established in preclinical studies, the TIGET-BTHAL trial was approved and begun in 2015 at Scientific Institute San Raffaele, Milan, Italy.

The clinical study foresees treatment of 10 patients: 3 adults (group 1) followed by 3 patients age 8–17 years (group 2) and 4 patients age 3–7 years (group 3), with a staggered enrollment strategy based on evaluation of safety and preliminary efficacy in adult patients by an independent data safety monitoring board before inclusion of pediatric subjects.

In 2016 the data safety monitoring board approved enrollment of patients in group 2 and, later in 2016, those in group 3. As of 2017, seven patients (three adults age 31–35 and four pediatric patients age 6–13 years) with different genotypes (β^0/β^0, β^+/β^+, and β^0/β^+) have been treated with GLOBE-transduced CD34+ cells at a dose of 16×10^6–19.5×10^6 cells per kilogram of body weight and a vector copy number per cell ranging from 0.7 to 1.5.

Median follow-up duration is 13 (range 8–22) months. The procedure has been tolerated well by all patients, with no product-related adverse events, no evidence of replication competent lentivirus nor of abnormal clonal proliferation on regular peripheral blood and bone marrow analyses.

Grade 3–4 adverse events or serious adverse events were of principally infectious origin as expected after a myeloablative autograft.

Median duration to neutrophil engraftment was 19 (range 17–25) days and to platelet engraftment 15 (range 10–21) days. Multilineage engraftment of gene-marked cells was observed in peripheral blood and bone marrow, with a median of 0.58 (range 0.37–1.55) vector copy number per cell in GlyA+ bone marrow erythroid cells at 6 months post-gene therapy.

Polyclonal vector integration profiles have been detected in the first 3 tested patients. The 3 adult patients underwent a reduction in transfusion requirement but are still transfusion dependent at the last follow-up (22, 18, and 16 months, respectively).

Among the 4 pediatric patients, 3 have discontinued transfusion shortly after gene therapy and were transfusion-independent at last follow-up (13, 10, and 8 months, respectively).

One pediatric patient is still receiving regular blood transfusions. A correlation was observed between the level of engraftment of gene-marked cells in peripheral blood and bone marrow and the transfusion requirement.

Dr. Marktel concluded that these preliminary data suggest that the applied clinical protocol for gene therapy using GLOBE lentivirus is well tolerated and leads to a significantly reduced transfusion requirement. Follow-up analyses are ongoing.

"Our results suggest that gene therapy can correct the disease, and result in transfusion independence," Dr. Marktel said in an ASH press release. ■

www.practiceupdate.com/c/61708

Rivaroxaban Reduces Recurrence of Venous Thromboembolism Significantly More Than Dalteparin

The rate of venous thromboembolism recurrence at 6 months has been shown to be 11% for cancer patients receiving dalteparin vs 4% for those receiving rivaroxaban, outcome of the prospective, randomized, open label, multicenter pilot anticoagulation therapy in SELECTeD cancer patients at risk of recurrence of venous thromboembolism (SELECT-D) trial shows.

Annie Young, PhD, of the Warwick Medical School, University of Warwick, Coventry, UK, explained that venous thromboembolism in cancer patients is an important and increasingly frequent clinical challenge.

In the UK, dalteparin is a licensed low molecular weight heparin, administered subcutaneously, for extended treatment and prevention of recurrence of acute venous thromboembolism in cancer patients. It was considered standard treatment prior to SELECT-D.

Rivaroxaban, a direct oral anticoagulant, is a highly selective direct factor Xa inhibitor with oral bioavailability. Few comparisons of low molecular weight heparin vs direct oral anticoagulants have been performed in cancer patients with venous thromboembolism.

Dalteparin 200 IU per kilogram of body weight daily, month 1; and 150 IU per kilogram of body weight daily, months 2–6) with rivaroxaban (15 mg twice daily for 3 weeks, then 20 mg once daily for a total of 6 months) for cancer patients with venous thromboembolism (symptomatic or incidental pulmonary embolism or symptomatic lower extremity proximal deep vein thrombosis).

After 6 months of treatment in the trial, patients with deep vein thrombosis who were positive for residual vein thrombosis by compression ultrasound and those with pulmonary embolism at presentation could be randomized to placebo or rivaroxaban for a further 6 months.

The original, large sample size of 530 patients provided sufficient numbers for the second randomization (150 in each arm), which assessed the duration of anticoagulation. The trial sample size was reduced when the second randomization closed due to a high attrition rate.

The revised sample size of 200 patients in each arm provided estimates of the primary outcome (recurrence of venous thromboembolism) to within ± 4.5% (95% CI 9%), assuming recurrence rates of venous thromboembolism of 10% at 6 months.

Secondary outcomes included major bleeds and clinically relevant nonmajor bleeds (including overt bleeds resulting in unscheduled contact with a physician or interruption or discontinuation of study drug), acceptability, survival, and health economics.

Overall, 406 patients were recruited between 2013 and 2016 from 58 sites across the UK; 203 patients randomized to each arm. Patients were a median of 67 (range 22–87) years of age; 214 (53%) were males; 386 (95%) of white ethnic origin. Patients presented with either early or locally advanced disease (n=156; 38%), metastatic disease (n=240, 59%); or hematological malignancies (n=10; 3%).

Over half of the patients suffered from incidental pulmonary embolism (n=214; 53%), 47% (n=192) from symptomatic pulmonary embolism or deep vein thrombosis. A total of 280 (69%) patients were receiving anticancer treatment at the time of venous thromboembolism. The majority were receiving chemotherapy (n=232, 83%) or targeted therapy (n=41, 15%).

The rate of recurrence of venous thromboembolism at 6 months was 11% (95% CI 7–17%) for patients receiving dalteparin and 4% (95% CI 2–9%) for those receiving rivaroxaban.

The incidence of major bleeds was similar across trial arms (6 bleeds from 6 patients [3%; 95% CI 1–6%] in the dalteparin arm; 9 bleeds from 8 patients [4%; 95% CI 2–8%] in the rivaroxaban arm). More clinically relevant nonmajor bleeds occurred in the rivaroxaban arm.

Dalteparin was associated with 5 bleeds in 5 patients (2%; 95% CI 1–6%). Rivaroxaban was associated with 28 bleeds in 27 patients (13%; 95% CI 9–19%). In total, 11 patients (5%; 95% CI 3–9%) in the dalteparin arm experienced bleeds categorized as either major bleeds or clinically relevant nonmajor bleeds vs 34 patients (17%; 95% CI 12–22%) in the rivaroxaban arm.

A total of 208 (54%) patients completed 6 months of trial treatment (100 [52%] patients on dalteparin; 108 [55%] on rivaroxaban). Overall survival at 6 months was 70% (95% CI 63–76%) with dalteparin and 74% (95% CI 68–80%) with rivaroxaban.

The second randomization recruited only 92 of the required 300 patients. Of these, 82 suffered pulmonary embolisms (61 incidental and 21 symptomatic). A total of 10 were deep vein thromboses.

Patients did not continue to the second randomization due to death or withdrawal (50%), residual vein thrombosis-negative status (12%); failing eligibility criteria (24%), or declining randomization (14%).

Dr. Young concluded that SELECT-D was a large pilot, randomized trial of treatments for venous thromboembolism. SELECT-D compared a direct oral anticoagulant vs a low molecular weight heparin in patients with cancer. Treating with rivaroxaban resulted in a very low recurrence rate of venous thromboembolism at 6 months.

The number of major bleeds was similar across trial arms but more clinically relevant nonmajor bleeds were seen with rivaroxaban. A large phase III trial will be confirmed to confirm the efficacy and safety of rivaroxaban for venous thromboembolism in cancer patients.

In an ASH press release, Dr. Young stated, "Clinicians are already adopting direct oral anticoagulants into practice for these patients, and now they have data from this study to indicate that direct oral anticoagulants are potentially safe in cancer patients."

She added, "We need to be looking at different groups of people and different types of bleeds in more detail, so that we can choose the best treatment for each patient."

www.practiceupdate.com/c/61704

The Investigational mAb Mogamulizumab Proves Superior to Vorinostat in Previously Treated Cutaneous T-Cell Lymphoma

The investigational, novel CC chemokine receptor 4 (CCR4)-targeting antibody mogamulizumab has demonstrated significantly superior progression-free survival and overall response rate, and improvements in quality of life outcome measures vs vorinostat in patients with previously treated cutaneous T-cell lymphoma. This outcome of the phase III, open-label, multinational, randomized Mogamulizumab anti-CCR4 Antibody Versus ComparatOR In Ctcl (MAVORIC) study was reported at ASH 2017.

To the investigators' knowledge, MAVORIC was the largest randomized trial of systemic therapy and the first pivotal trial to use progression-free survival as a primary endpoint in cutaneous T-cell lymphoma.

Youn H. Kim, MD, of Stanford University, Stanford, California, explained to Elsevier's *PracticeUpdate*, "Cutaneous T-cell lymphoma is a rare cancer of the white blood cells, specifically T lymphocytes, that occurs primarily in the skin. It is caused when T cells begin to grow uncontrollably and accumulate in the skin. Cutaneous T-cell lymphoma can also involve the blood, lymph nodes, and internal organs."

Mogamulizumab is an investigational monoclonal antibody directed against CCR4, which is overexpressed on malignant T-cells. In a phase I-II study in cutaneous T-cell lymphoma, mogamulizumab demonstrated a tolerable safety profile with a 37% overall response rate.

Based on these results, the phase III MAVORIC trial compared mogamulizumab vs vorinostat in previously treated patients with cutaneous T-cell lymphoma.

Adult patients with histologically confirmed mycosis fungoides or Sézary syndrome who had failed at least one systemic therapy were enrolled, stratified by disease type (mycosis fungoides or Sézary syndrome) and stage (1B/2 or 3/4), and randomized 1:1 to mogamulizumab IV infusion 1.0 mg per kilogram of body weight (weekly for the first 4-week cycle and then every 2 weeks) or oral vorinostat (400 mg daily).

Patients randomized to vorinostat could cross over to mogamulizumab on progression or intolerable toxicity.

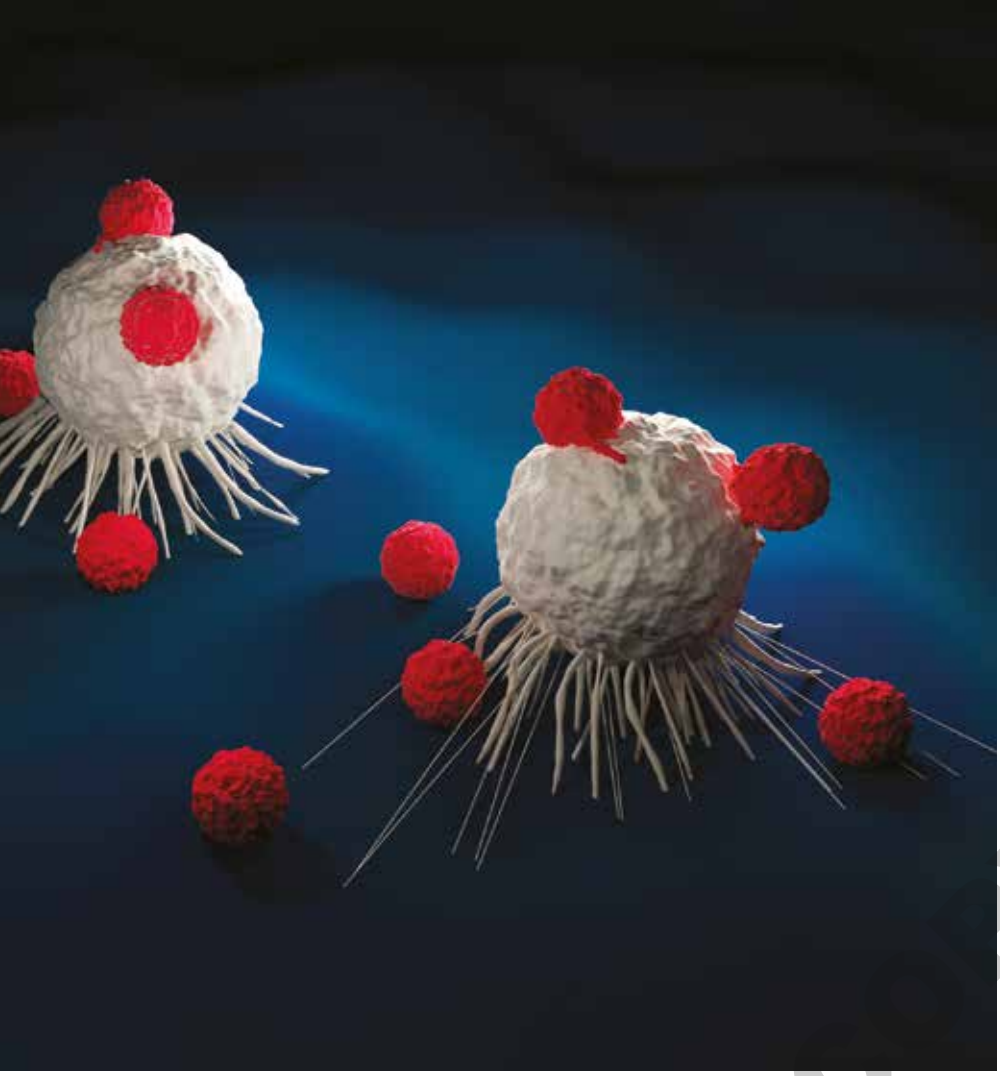
The primary endpoint was investigator-assessed progression-free survival in the randomized population using the global composite response based on skin, blood, nodes and viscera according to the International Society for Cutaneous Lymphomas/European Organisation for Research and Treatment of Cancer consensus guidelines.

Sample size was calculated to provide 90% power to detect a 50% improvement in progression-free survival. Key secondary endpoints included overall response rate, duration of response, and quality of life.

A blinded review consisted of an independent radiology evaluation of all CT scans (two-reader paradigm) and comprehensive review of all compartment data.

A total of 372 patients who exhibited the following characteristics at baseline (mogamulizumab vs vorinostat) were randomized (intent-to-treat population):

- Median age 63.5 (25–101) vs 65.0 (25–89) years
- Eastern Cooperative Oncology Group performance status 0–1, 184 (99%) vs 186 (100%)
- Eastern Cooperative Oncology Group performance status 2, 2 (1%) vs 0
- Stage 1B–2B disease, 68 (36.6%) vs 72 (38.7%)
  - Stage 1B/2A disease, 36 (19.4%) vs 49 (26.3%)
  - Stage 2B disease, 32 (17.2%) vs 23 (12.4%)
- Stage 3/4 disease, 118 (63.4%) vs 114 (61.3%)
- Mycosis fungoides, 105 (56.5%) vs 99 (53.2%)
- Sézary syndrome, 81 (43.5%) vs 87 (46.8%)



Patients in both arms had received a median of three prior systemic treatments. According to investigator assessment, treatment with mogamulizumab resulted in a significant improvement in progression-free survival vs vorinostat (HR 0.53 [95% CI 0.41, 0.69], P < .0001) with a median progression-free survival of 7.7 (95% CI 5.7, 10.3) months for mogamulizumab and 3.1 (95% CI 2.9, 4.1) months for vorinostat. Superiority of mogamulizumab was confirmed by independent review.

Mogamulizumab was associated with superior progression-free survival in predefined subgroups as well.

Global overall response rate was significantly improved in the patients randomized to mogamulizumab at 28.0% vs 4.8% for vorinostat (P < .0001). Significant improvement in the overall response rate was found with mogmulizumab vs vorinostat in patients with both mycosis fungoides (21.0% vs 7.1%, respectively; P = .0042) and Sézary syndrome (37.0% vs 2.3%, respectively; P < .0001).

The overall response rate in predefined subgroups, duration of response, and response by disease compartment all favored mogamulizumab vs vorinostat.

In addition, an overall response rate of 30.1% was observed in mogamulizumab-treated patients who crossed over from vorinostat.

Skindex-29 Symptoms Scale scores demonstrated statistically significant improvements in favor of mogamulizumab- vs vorinostat-treated patients at cycles 3, 5, and 7 (P < .05).

Median duration to meaningful deterioration on the Skindex-29 Symptoms Scale was 27.4 months for patients receiving mogamulizumab vs 6.6 months for those receiving vorinostat.

Median dose intensity for mogamulizumab was 97.5% vs 95.7% for vorinostat, supporting adequate treatment in both arms.

Treatment exposure was longer with mogamulizumab (median 170 vs 84 days for vorinostat).

The most common treatment-emergent adverse events (>20%) more frequent (>15% difference) in the mogamulizumab vs the vorinostat arm included infusion-related reactions (33.2% vs 0.5%, respectively) and drug-related skin eruptions (23.9% vs 0.5%, respectively).

The majority of treatment-emergent adverse events with mogamulizumab were mild to moderate in severity (grade 1/2, 54.9%; grade 3/4/5, 42.4%).

Dr. Kim concluded, "In this first report of a randomized phase III study evaluating progression-free survival as the primary endpoint in cutaneous T-cell lymphoma, the investigational monoclonal antibody mogamulizumab demonstrated significantly superior progression-free survival overall response rate, and quality of life vs vorinostat in patients with previously treated cutaneous T-cell lymphoma."

The safety profile was consistent with previous reports. ■

www.practiceupdate.com/c/61491

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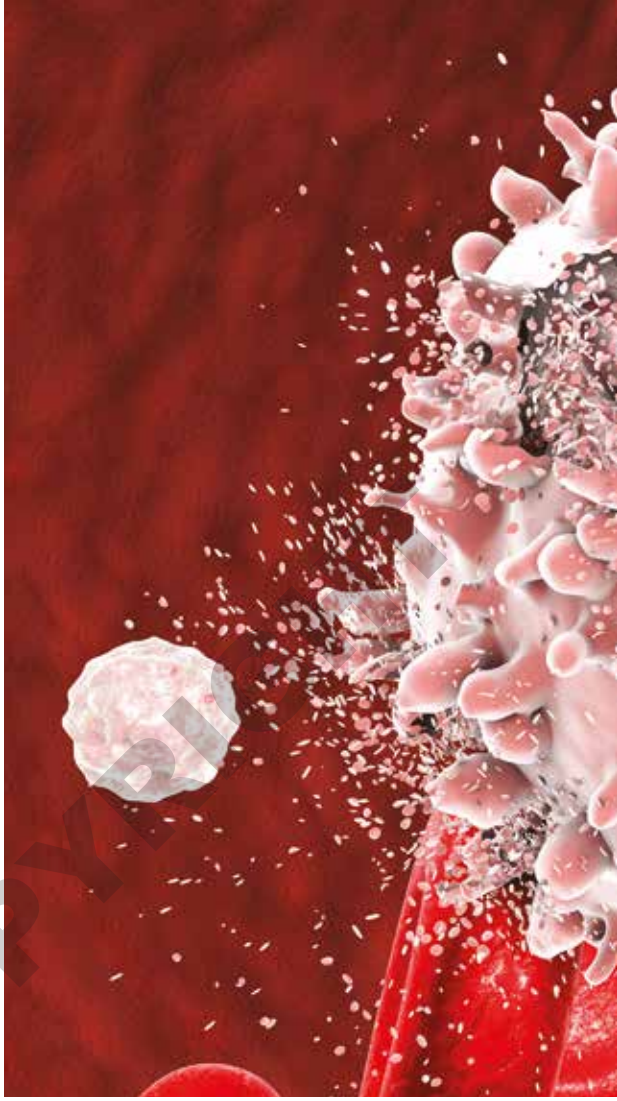
BLU-285, a KIT D816V Inhibitor, Proves Promising in Advanced Systemic Mastocytosis

BLU-285, a potent, highly selective inhibitor of KIT D816V and other activation loop mutants, has been shown to be well tolerated at the 300-mg recommended phase II dose and demonstrates considerable clinical activity in all subtypes of advanced systemic mastocytosis, outcome of a phase I dose expansion study shows.



Daniel J. DeAngelo, MD, PhD, of the Dana-Farber Cancer Institute, Boston, Massachusetts, explained that the KIT D816V mutant is a key oncogenic driver found in approximately 90% of advanced systemic mastocytosis, a group of mast cell neoplasms with poor prognosis. The group is composed aggressive systemic mastocytosis, systemic mastocytosis with an associated hematologic neoplasm, and mast cell leukemia.

The only approved agent to treat advanced systemic mastocytosis is midostaurin, a multikinase inhibitor with a broad inhibitory spectrum that includes KIT D816V (half maximal inhibitory concentration 2.8 nM).

In contrast, BLU-285 was designed as a highly potent (half maximal inhibitory concentration 0.27 nM) and highly specific oral inhibitor of KIT activation loop mutants including D816V.

Dr. DeAngelo reported results of the dose-finding segment of from an ongoing phase I study in advanced systemic mastocytosis whose goal was to define the maximum tolerated dose, recommended dose for part 2 (recommended phase II dose), and safety profile of BLU-285. Secondary objectives were to assess the pharmacokinetics and preliminary antineoplastic activity of BLU-285.

Adult patients with advanced systemic mastocytosis or refractory hematologic neoplasms per World Health Organization diagnostic criteria were eligible. BLU-285 was administered once daily on a 4-week cycle following a 3+3 escalation (Part 1)/dose expansion (Part 2) design.

Serial monitoring on therapy included adverse events per Common Terminology Criteria for Adverse Events, pharmacokinetics, biomarkers (blood/bone marrow D816V mutant allele fraction (allele-specific polymerase chain reaction); co-occurring somatic mutations (Illumina TruSight panel) and mast cell burden measures (serum tryptase, bone marrow mast cell content, splenomegaly [CT or MRI]).

At the July 2017 cut-off, 30 patients (n=15 advanced systemic mastocytosis; n=9 systemic mastocytosis with an associated hematologic neoplasm; n=3 mast cell leukemia; n=3 other D816V-mutant hematologic neoplasms) have been treated with BLU-285 in seven cohorts at doses of 30 to 400 mg daily.

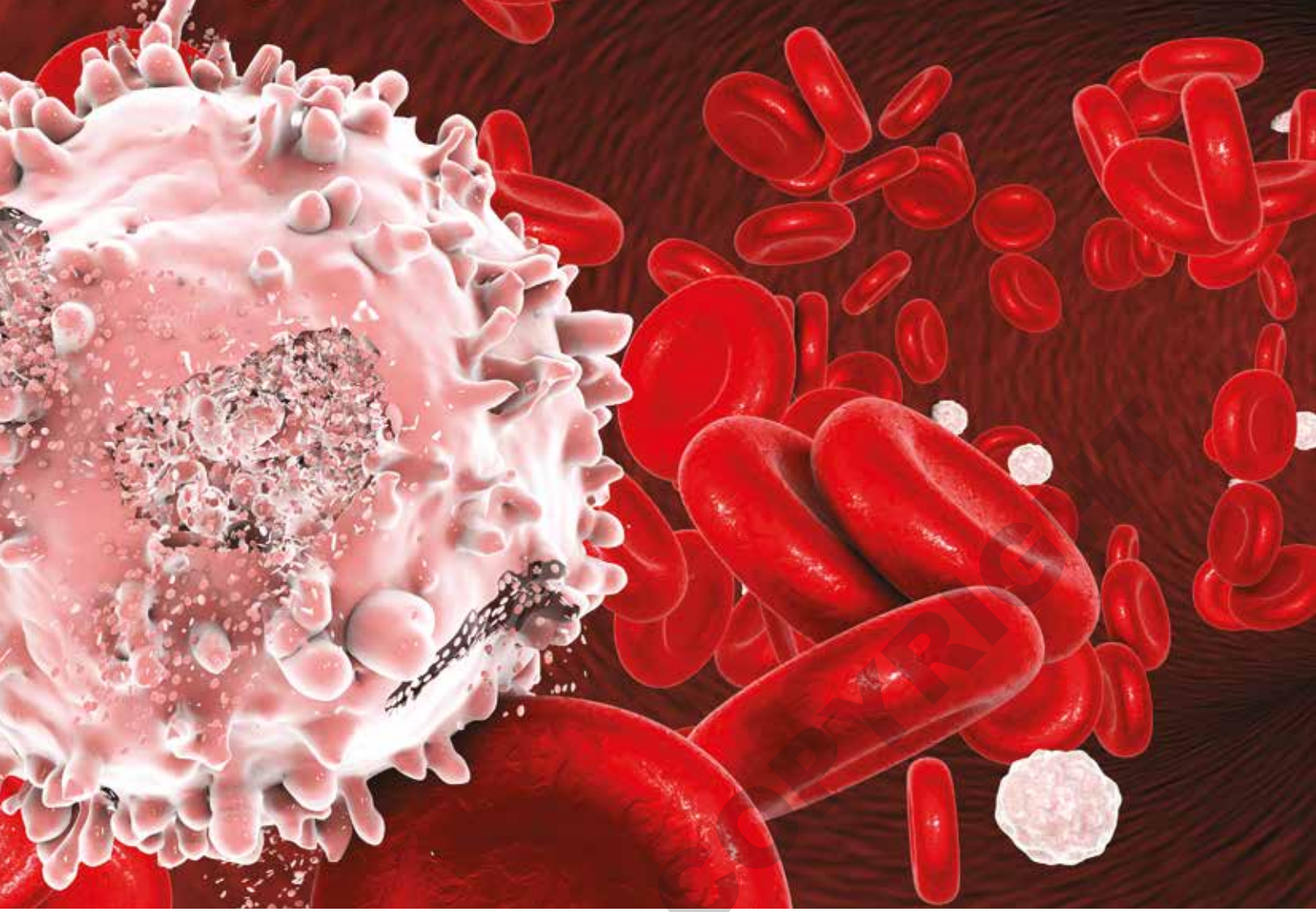
A total of 24 patients harbored the KIT D816V mutation, two patients harbored the KIT D816Y mutation, one patient harbored the KIT polymorphism M541L, and three patients harbored no detectable KIT alteration.

A total of 24 patients harbored at least one co-occurring mutation(s) in bone marrow, most frequently TET2 (n=17), DNMT3A (n=9), ASXL1 (n=7), SRSF2 (n=6), and GATA2 (n=6).

A total of 21 patients (70%) had received prior antineoplastic therapy including cladribine (n=5), imatinib (n=4), interferon-α (n= 4), midostaurin (n=4), and 5-azacitidine (n=3). All patients had received a median of one (range zero to three) prior antineoplastic therapies.

BLU-285 demonstrated significant clinical activity across all dose levels, with rapid and durable reductions in mast cell burden and D816V-mutant allele fraction relative to baseline.

Of 12 patients, 10 showed marked reductions of urticarial pigmentosa lesions. Improvements have also been observed in 30 patients with malabsorption: median weight gain 5 (–3.7 to 16.3) kg; serum albumin increase 0.5 (–0.3 to 1.7) mg/dL.



> "We are seeing a high rate of rapid and durable responses, with a very low rate of adverse side effects, in patients with an advanced or aggressive form of the disease. The rapidity of improvement is extremely dramatic"

Reductions in mast cell burden and D816V-mutant allele fraction were durable, with 28/30 patients remaining on therapy (n=7 for at least 1 year) and occurred regardless of subtype of advanced systemic mastocytosis, prior therapy, concomitant mutations, and performance status.

Importantly, marked reductions in mast cell burden were noted in two patients with mast cell leukemia that had progressed with midostaurin and two patients with advanced systemic mastocytosis who were intolerant of midostaurin. All remain on therapy at 5, 12, 7, and 14 months, respectively.

BLU-285 is rapidly absorbed (present for 2–4 h at maximum serum concentration), and half-life is approximately 25 h, supporting once-daily dosing. Mean steady state area under the curve and maximum serum concentration at 300 mg are above the maximally efficacious exposure in KIT D816-mutant xenograft models.

BLU-285 was well tolerated with most adverse events Common Terminology Criteria for Adverse Events grade 1 or 2. The most common adverse events were periorbital edema (43%), anemia, diarrhea, fatigue, peripheral edema (27% each), headache (23%), thrombocytopenia, and nausea (20% each).

Grade ≥3 treatment-related adverse events occurring in at least 2 patients included neutropenia (13%), anemia, and periorbital edema (7% each). A total of 2 patients discontinued BLU-285 (n=1) progressive acute myeloid leukemia; one with no detectable KIT mutation withdrew consent.

No patients discontinued therapy due to drug-related adverse events. One dose-limiting toxicity (grade 3 alkaline phosphatase elevation) was observed at the 60-mg dose, but maximum tolerated dose was not reached.

Based on the safety profile, pharmacokinetics, and antitumor activity, 300 mg was selected as the recommended phase II dose. Part 2 is now enrolling.

Dr. DeAngelo concluded that BLU-285, a potent, highly selective inhibitor of KIT D816V and other activation loop mutants, was well tolerated at the 300-mg recommended phase II dose.

BLU-285 demonstrated considerable clinical activity in all subtypes of advanced systemic mastocytosis, including patients who failed midostaurin and other antineoplastic therapies. These encouraging phase I data validate the selective targeting of KIT D816V and warrant further clinical testing of BLU-285 in systemic mastocytosis.

Dr. DeAngelo remarked, in an ASH press release, "We are seeing a high rate of rapid and durable responses, with a very low rate of adverse side effects, in patients with an advanced or aggressive form of the disease. The rapidity of improvement is extremely dramatic." ■

www.practiceupdate.com/c/61706

Mutations in the *SRP54* Gene Cause Severe Primary Neutropenia as Well as Shwachman-Diamond-Like Syndrome

A novel pathological pathway implicates the cotranslational process of protein targeting. This new genetic subtype represents the second cause of congenital neutropenia in the French registry, results of a study that incorporated whole exome and Sanger sequencing, as well as functional and structural assessments, show.

Christine Bellanné-Chantelot, PharmD, PhD, of the Institut National de la Santé et de la Recherche Médicale (INSERM) Gustave Roussy, Villejuif, and the Hôpital Pitié-Salpétrière, Paris, France, explained that congenital neutropenia is a heterogeneous group of diseases characterized by low neutrophil count, severe bacterial infections, increased risk of leukemic transformation and various extrahematopoietic organ dysfunctions.

Though 24 genes have been linked to the etiology of congenital neutropenia, in many patients, the genetic causes of their disease remain unknown. "In fact," Dr. Bellanné-Chantelot told Elsevier's *PracticeUpdate*, "No genetic etiology is identified in about 25% of patients with congenital neutropenia."

Whole exome sequencing was performed in a trio-based approach in 8 sporadic cases and 6 multiplex families with congenital neutropenia. Sanger sequencing was performed in a second phase on 66 additional patients from the French congenital neutropenia registry.

Structural and functional studies were performed using primary cells from patients, including fibroblasts and hematopoietic cells. In vitro granulocytic differentiation was conducted by culturing CD34+ in serum-free medium with stem cell factor, interleukin-3, and granulocyte-colony stimulating factor for 21 days.

Whole exome sequencing identified a heterozygous mutation in the *SRP54* gene, encoding the signal recognition particle (SRP) 54 GTPase protein, in 3 sporadic cases and an autosomal dominant family.

Considering these results, Dr. Bellanné-Chantelot and colleagues sequenced *SRP54* directly in the French congenital neutropenia cohort and identified 13 additional sporadic cases and 2 multiplex families. A total of 23 cases in 19 families were found to carry a *SRP54* mutation. The Thr117del in-frame deletion was found in 12 probands.

Neutropenia was profound in all patients (mean neutrophil absolute count 0.23×10^9/L). Neutropenia was diagnosed in the neonatal period or during childhood (mean age 4.2 months). Affected infants required long-term granulocyte-colony stimulating factor therapy (mean dose 9 µg per kilogram of body weight daily).

ADCT-402, A CD19-Directed mAB, Shows Encouraging Early Results in Relapsed/Refractory B-Cell Non-Hodgkin Lymphoma

In the first in-human clinical trial of ADCT-402, the drug has demonstrated encouraging single-agent antitumor activity and manageable toxicity in patients with relapsed/refractory B-cell non-Hodgkin's lymphoma, interim result of a phase I, multicenter, open-label, two-part study shows.

Brad S. Kahl, MD, of Washington University School of Medicine, Saint Louis, Missouri, explained that CD19 is expressed on the cell surface of many types of non-Hodgkin's lymphoma, including follicular and diffuse large B-cell lymphoma.

ADCT-402 (loncastuximab tesirine) is an antibody drug conjugate composed of a humanized antibody directed against human CD19 conjugated to a pyrrolobenzodiazepine dimer toxin. ADCT-402 has demonstrated potent antitumor activity against CD19-expressing B-cell malignancies in preclinical models.

Patients ≥18 years of age with relapsed/refractory B-cell non-Hodgkin's lymphoma who have failed or are intolerant to established therapies, or have no other treatment options available, are being enrolled.

The primary objectives of the dose escalation phase of the study are to evaluate the safety and tolerability of ADCT-402 and determine the maximum tolerated dose and recommended dose(s) to use in the dose expansion phase.

The primary objective of the dose expansion phase is to evaluate the safety and tolerability of the dose(s) determined in the dose escalation phase.

Efficacy (measured by overall response rate, duration of response, progression-free survival, and overall survival); pharmacokinetics; pharmacodynamics; and other exploratory endpoints are also being assessed in both parts of the study.

Patients receive 1-h intravenous infusions of ADCT-402 every 3 weeks (one cycle) according to a 3 + 3 dose escalation study design. No intrapatient dose escalation is allowed.

As of July 2017, 80 patients (55 male, 25 female; median age 65.5 [range 24–85] years, who have received a median of

Examination of bone marrow showed maturation arrest at the promyelocytic stage. In contrast to congenital neutropenia associated with *ELANE* mutations, *SRP54*-mutated patients presented a major degree of dysgranulopoiesis (abnormal localization and number of mature granules) and enlarged endoplasmic reticulum in promyelocytes as well as dystrophic neutrophils.

No evolution to acute myeloid leukemia was observed in the cohort after a median of 14.8 years despite high doses of granulocyte-colony stimulating factor. Of the 23 patients, 6 exhibited extrahematopoietic manifestations such as severe neurodevelopmental delay (n=5) and/or exocrine pancreatic insufficiency (n=3), and/or bone abnormalities (n=2).

The *SRP54* protein is a key component of the ribonucleoprotein complex signal recognition particle that mediates cotranslational targeting and insertion of secretory and membrane proteins to the endoplasmic reticulum.

Seven distinct mutations were identified that affect highly conserved residues within or interacting with G motifs involved in the GTPase activity of *SRP54*.

Of note, 17 of 18 patients with mutations located within the G1 element and predicted to affect the structure and/or stability of the NG domain presented only severe neutropenia. In contrast, the other five patients with mutations affecting either the magnesium- or guanine-binding site and/or implied in the interaction with the receptor of SRP54, were associated with features of Shwachman-Diamond-like syndrome.

During the in vitro granulocytic differentiation of both normal and mutated hematopoietic progenitors, a strong increase in *SRP54* mRNA expression levels, associated with a slight decrease in protein level, was found in patients vs controls. Moreover, *SRP54* mutations induced a major deleterious effect on proliferation and a delay in differentiation associated with increased apoptosis.

Using both in vitro-derived granulocytic cells and primary fibroblasts, *SRP54* mutations were observed to lead to stress in the endoplasmic reticulum (increased eIF2a phosphorylation, *XBP1* splicing, *ATF4*, and CHOP expression) and enhanced autophagy (higher levels of LC3-II and *ULK1* expression).

Dr. Bellanné-Chantelot concluded that the results identified a novel pathological pathway implicating the cotranslational process of protein targeting. This new genetic subtype represents the second cause of congenital neutropenia in the French registry (prevalence 6.9%).

The subtype is characterized by promyelocytic maturation arrest with dysgranulopoiesis, leading to a profound neutropenia, with poor response to granulocyte - colony stimulating factor. In few patients, the subtype is associated with severe neurodevelopmental delay and exocrine pancreatic insufficiency.

"The identification of this new entity," Dr. Bellanné-Chantelot said, "will help to (1) optimize the medical management of patients as regards this novel genetic subtype; (2) offer genetic counseling of families; and (3) better understand pathways involved in congenital neutropenia."

She added, "Future directions will be to identify proteins not targeted correctly in *SRP54*-mutated patients. Such proteins will be those essential for granulocytic differentiation, or endoplasmic reticulum/Golgi resident proteins essential for maturation of secreted or membrane-embedded proteins in granulocyte cells." ■

www.practiceupdate.com/c/61703

3 (range 1–10)] previous therapies have been recruited.

Diagnoses were: n=56, diffuse large B-cell lymphoma; n=9, mantle cell lymphoma; n=6, follicular lymphoma; n=3, marginal zone B-cell lymphoma; n=2, chronic lymphocytic leukemia; and, n=4, other.

Patients have received doses of ADCT-402 ranging from 15 to 200 µg per kilogram of body weight (a median of 2 [range 1 to 16] cycles).

Treatment-emergent adverse events have been reported in 76 (95.0%) patients, grade ≥3 treatment-emergent adverse events in 46 (57.5%) patients. The most common nonhematological all-grade treatment-emergent adverse events have been fatigue (n=35 [43.8%]), peripheral edema (n=21 [26.3%]), and nausea (n=20 [25.0%]). Grade ≥3 treatment-emergent adverse events have been:

- n=7 (8.8%), increased γ-glutamyltransferase
- n=4 (5.0%), dyspnea
- n=4 (5.0%), fatigue

Hematological all-grade and grade ≥3 treatment-emergent adverse events have included:

- n=74 of 77 (96.1%), and n=9 of 77 (11.7%), respectively, decreased hemoglobin
- n=42 of 69 (60.9%) and n=29 of 69 (42.0%), respectively, decreased neutrophil count
- n=55 of 77 (71.4%) and n=21 of 77 (27.3%), decreased platelet count, respectively

Treatment-emergent adverse events in 8 (10.0%) patients have led to treatment withdrawal (increased γ-glutamyltransferase [n=4]; increased blood alkaline phosphatase [n=1]; periorbital edema [n=1]; fatigue [n=1]; abdominal pain [n=1]; thrombocytopenia [n=1]).

Dose-limiting toxicity was reported in one patient (worsening of thrombocytopenia at 200 µg per kilogram of body weight and the maximum tolerated dose has not yet been reached.

At doses ≥120 µg per kilogram of body weight, 16 of 47 (34.0%) and 12 of 47 (25.5%) evaluable patients have achieved a complete or partial response, respectively (overall response rate 28 of 47 [59.6%]). The overall response rate for patients with diffuse large B-cell lymphoma was 20 of 35 (57.1%), with a complete response rate of 34.3% (12 of 35).

Pharmacokinetic measures for total- and pyrrolobenzodiazepine-conjugated antibody exposures were comparable, proportional to dose, and associated with modest accumulation by cycle 2. Measures for unconjugated pyrrolobenzodiazepine were predominantly below quantification levels for all doses and time points.

Dr. Kahl concluded that in this first in-human clinical trial of ADCT-402, the drug demonstrated encouraging single-agent antitumor activity and manageable toxicity in patients with relapse/refractory B-cell non-Hodgkin's lymphoma.

One dose-limiting toxicity has been reported and the maximum tolerated dose has not yet been reached. Evaluation in specific subtypes of non-Hodgkin's lymphoma is warranted, and a dose expansion in patients with diffuse large B-cell lymphoma is planned. ■

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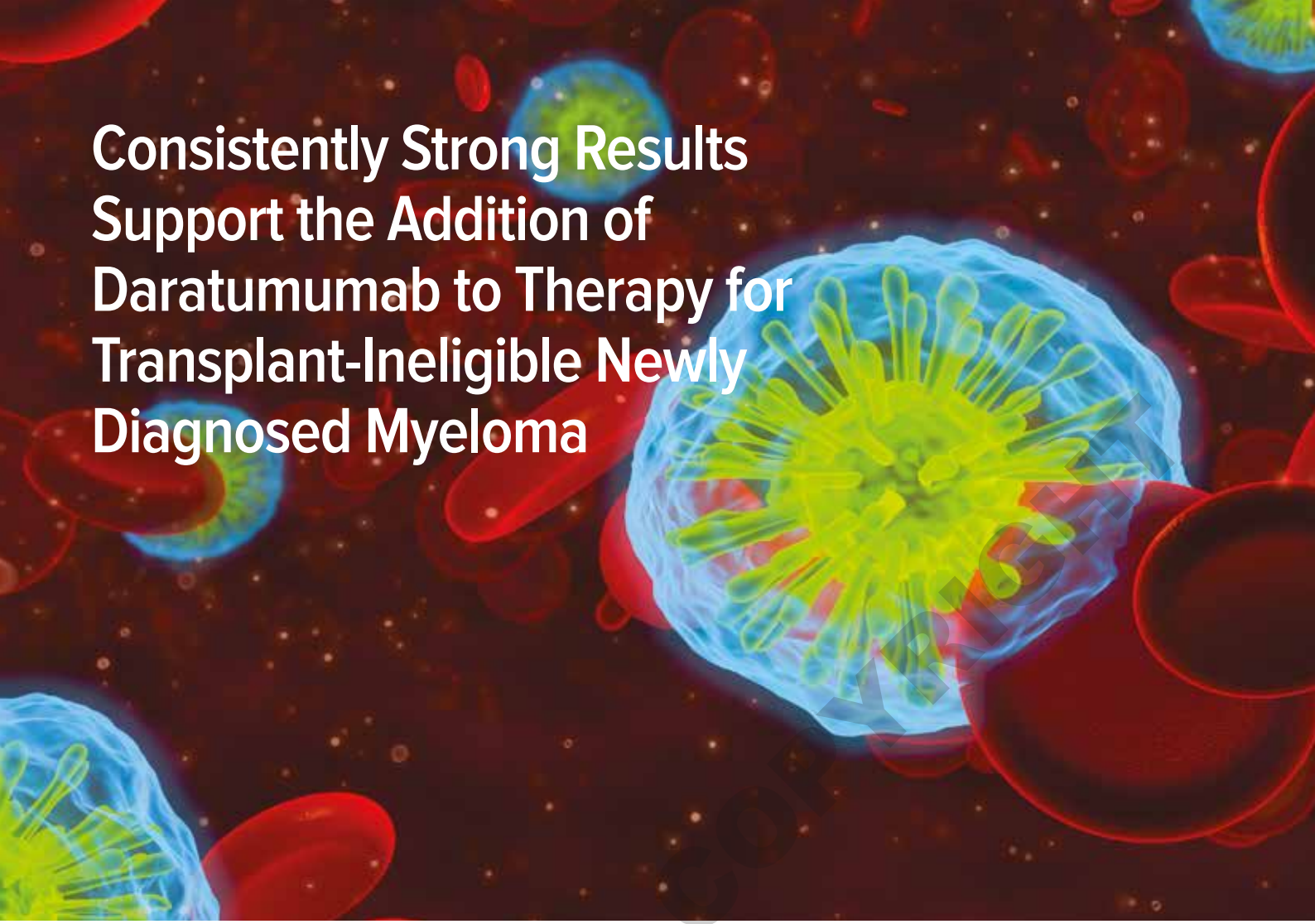

Consistently Strong Results Support the Addition of Daratumumab to Therapy for Transplant-Ineligible Newly Diagnosed Myeloma

The combination of daratumumab with bortezomib, melphalan, and prednisone (VMP) in transplant ineligible patients with newly diagnosed multiple myeloma doubled progression-free survival (HR 0.50), driven by more patients achieving deep responses, including significantly higher complete response rate and tripling of the rate of negativity for minimal residual disease, outcome of the phase III, randomized ALCYONE study shows.

Maria-Victoria Mateos, MD, of the University Hospital of Salamanca/Instituto de Investigación Biomédica de Salamanca, Spain, explained that VMP is a standard of care for transplant-ineligible newly diagnosed multiple myeloma.

"The first phase I/II study," Dr. Mateos told Elsevier's *PracticeUpdate*, "that combined bortezomib + melphalan + prednisone was in Spain in 2004. Since then, we have been working to improve on this scheme to afford maximum patient benefit."

"Initially," she continued, "bortezomib was given twice weekly, but peripheral neuropathy ensured. So, we proceeded to administer bortezomib once weekly. Weekly administration proved equally safe and effective as twice-weekly administration."

"The present study," she explained, "completes this experience of VMP + the monoclonal antibody daratumumab. It has become the first randomized phase III study of daratumumab + VMP, the standard of care, in newly diagnosed multiple myeloma."

Daratumumab, a human immunoglobulin Gκ anti-CD38 monoclonal antibody with a direct on-tumor and multifaceted immunomodulatory mechanism of action, improves progression-free survival and depth of response significantly in combination with standard of care in relapsed multiple myeloma.

Treatment-naïve patients may benefit greatly with the addition of daratumumab to standard of care regimens. Dr. Mateos reported results of the ALCYONE study, where daratumumab is added to VMP in transplant-ineligible newly diagnosed multiple myeloma.

Patients ≥65 years of age or otherwise ineligible for high-dose chemotherapy with autologous stem cell transplantation were randomized 1:1 to VMP ± daratumumab and stratified by International Staging System I, II, or III; region (Europe vs other); and age (<75 vs ≥75 years).

Patients were randomized 1:1 to either nine 6-week cycles of VMP followed by observation or the same VMP scheme + daratumumab given as continuous therapy until disease progression:

- Bortezomib: 1.3 mg/m^2 SC on days 1, 4, 8, 11, 22, 25, 29, and 32 (cycle 1) and days 1, 8, 22, and 29 (cycles 2–9)
- Melphalan: 9 mg/m^2 PO; prednisone: 60 mg/m^2 PO on days 1–4 (cycles 1–9)

In the daratumumab-VMP arm, daratumumab was given at 16 mg per kilogram of body weight IV QW for cycle 1, Q3W for cycles 2–9, and Q4W for cycles 10+ (post VMP treatment phase) until disease progression.

The primary endpoint was progression-free survival. Key secondary endpoints included overall response rate, rate of very good partial response or better, rate of complete response or better, rate of negativity for minimal residual disease (10^{-5} threshold, Adaptive clonoSEQ® Assay), overall survival, and safety.

Of 706 randomized patients (350 daratumumab-VMP; 356 VMP), median age was 71 (range 40–93) years; 29.9% were ≥75 years of age; 46.3% were male. 74.9% of patients had scored Eastern Cooperative Oncology Group ≥1, and 19.3%, 42.4%, and 38.4% were International Staging System stage I, II, and III, respectively.

Of 616 patients evaluable for fluorescent in situ hybridization/karyotyping cytogenetic analysis, 84.1% and 15.9% were at standard and high risk (positive for 17p deletion, t[14;16], t[4;14]), respectively.

At the time of prespecified analysis after 231 progression-free survival events in June of 2017, patients had received a median of 12 (range 1–24) vs nine (one to nine) treatment cycles for daratumumab-VMP vs VMP, respectively.

Of patients in the daratumumab-VMP arm, 80% had completed nine treatment cycles of VMP vs 62% of those in the VMP arm. Median cumulative bortezomib doses were 46.9 (range 1.3–55.3) mg/m^2 vs 42.2 (2.6–55.0) mg/m^2 for daratumumab-VMP vs VMP, respectively.

After a median follow-up duration of 16.5 months, the hazard ratio for progression-free survival (daratumumab-VMP vs VMP) was 0.50 (95% CI 0.38–0.65, P < .0001), representing a 50% reduction in the risk of progression or death in patients treated with daratumumab-VMP.

Median progression-free survival was not reached vs 18.1 months for daratumumab-VMP vs VMP. The treatment benefit in terms of progression-free survival of daratumumab-VMP vs VMP was consistent across all prespecified subgroups, including age ≥75 years, International Staging System stage III, and high-risk cytogenetics.

Overall response rate (90.9% vs 73.9%), at least very good partial response (71.1% vs 49.7%), at least a complete response (42.6% vs 24.4%), and the rate of negativity for minimal residual disease (22.3% vs 6.2%) were significantly higher for daratumumab-VMP vs VMP (all P < .0001). Overall survival data were immature after 93 deaths (45 vs 48 deaths for daratumumab-VMP vs VMP).

> "The future will bring new daratumumab-based combinations for newly diagnosed multiple myeloma. Our goal will be to continue improving outcomes for our patients with myeloma"

The most common (≥20%) all-grade treatment emergent adverse events (daratumumab-VMP/VMP) were neutropenia (49.7%/52.5%), thrombocytopenia (48.8%/53.7%), anemia (28.0%/37.6%), peripheral sensory neuropathy (28.3%/34.2%), upper respiratory tract infection (26.3%/13.8%), diarrhea (23.7%/24.6%), pyrexia (23.1%/20.9%), and nausea (20.8%/21.5%), respectively.

Most common (≥10%) grade 3/4 treatment-emergent adverse events (daratumumab-VMP/VMP) were neutropenia (39.9%/38.7%), thrombocytopenia (34.4%/37.6%), anemia (15.9%/19.8%), and pneumonia (11.3%/4.0%).

Only one patient in each arm discontinued treatment due to pneumonia. The rates of grade 3/4 infections were 23.1% vs 14.7%, and treatment discontinuations due to infections were 0.9% vs 1.4% for daratumumab-VMP vs VMP.

Daratumumab-associated infusion-related reactions (27.7%) were mostly grade 1/2 (grade 3/4, 4.3%/0.6%) and most (92.7%) occurred during the first infusion. Tumor lysis syndrome occurred in <1% of patients in each arm. Second primary malignancy occurred in 2.3% vs 2.5% patients in the daratumumab-VMP vs the VMP group, respectively.

Dr. Mateos concluded that the combination of daratumumab + VMP in transplant-ineligible patients with newly diagnosed multiple myeloma doubled progression-free survival (hazard ratio 0.50), driven by more patients achieving deep responses, including significantly higher rate of at least complete responses and tripling of the rate of negativity for minimal residual disease.

No new safety signals were observed when combining daratumumab + VMP.

Three phase III studies have demonstrated a consistent doubling of progression-free survival and more than threefold increase in the rate of negativity for minimal residual disease when combining daratumumab with standard of care regimens.

These results support the use of the daratumumab-based combination, daratumumab-VMP, in transplant-ineligible newly diagnosed multiple myeloma.

"The future," Dr. Mateos added, "will bring new daratumumab-based combinations for newly diagnosed multiple myeloma. Our goal will be to continue improving outcomes for our patients with myeloma." ■

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The HbS Polymerization Inhibitor Voxelotor GBT440 Has Demonstrated Positive Initial Results in Adolescents With Sickle Cell Disease

The hemoglobin S polymerization inhibitor voxelotor (GBT440) has demonstrated positive initial results in adolescents with sickle cell disease, reports a phase IIa study.

Carolyn C. Hoppe, MD, of the University of California, San Francisco, and Children's Hospital Oakland, explained that sickle cell disease is a genetic disorder in which deoxygenation induces polymerization of mutated hemoglobin S and triggers the downstream effects of red blood cell deformation (sickling), hemolysis, vaso-occlusion and inflammation.

Injury from sickle cell disease starts in infancy and accumulates over a lifetime, causing significant end-organ damage and ischemic tissue injury. These effects, in turn, lead to fatigue, pain (vaso-occlusive crisis), and other underrecognized, undertreated clinical complications associated with early death.

Voxelotor (GBT440) is an oral, once-daily therapy that modulates hemoglobin affinity for oxygen, thereby inhibiting hemoglobin polymerization. GBT440-007 is a phase IIa study designed to assess the safety, pharmacokinetics, and efficacy of voxelotor in pediatric patients with sickle cell disease (hemoglobin SS or hemoglobin S β0 thalassemia).

"This drug," Dr. Hoppe told Elsevier's *PracticeUpdate*, "was designed specifically for a primary indication of sickle cell disease. Other drugs have been repurposed for studies in sickle cell disease. The mechanism of action of voxelotor is aimed at the primary trigger, that is, hemoglobin S polymerization and red cell sickling, of the downstream cascade of events. These events, hemolysis, vaso-occlusion, and inflammation, lead to the myriad clinical complications of sickle cell disease."

Dr. Hoppe reported on the first evaluation of multiple doses of GBT440 in adolescents (12–17 years of age) with sickle cell disease. This ongoing study is being conducted in two parts.

Part A is a single dose of GBT440 at 600 mg administered to pediatric patients (6–11 years of age) and adolescents (12–17 years of age). Part B is multiple doses of GBT440 at dose levels, 900 and 1500 mg daily for 24 weeks in adolescents (approximately 12 patients at each dose).

Part A pharmacokinetic data in adolescents has been reported previously. The primary objective of Part B is to assess the effect of GBT440 on anemia.

Secondary objectives include its effect on clinical measures of hemolysis, pharmacokinetics (pharmacokinetic parameters determined using population pharmacokinetic analysis), daily sickle cell disease symptoms using a patient-reported outcome measure, and safety. Exploratory objectives include the effect on cerebral blood flow as assessed by transcranial Doppler ultrasound.

The Patient-Reported Outcome Sickle Cell Disease Severity Measure was developed as a clinical outcomes assessment following FDA guidance.

Enrollment in Part B of the 900 mg cohort is complete. As of November 2017, a total of 24 patients have received voxelotor (GBT440) and 13 patients (seven females) have received up to 16 weeks of treatment. Median age is 13 (range 12–17) years. Ninety-two percent were receiving hydroxyurea; 41% had experienced at least one painful crisis in the year prior to enrollment.

Dr. Hoppe reported data for measures of anemia and hemolysis for 11 of the 12 patients and patient-reported daily symptom scores and transcranial Doppler results for all patients who received GBT440 for 16 weeks. Safety data were reported for all 24 enrolled patients.

Of the 11 patients with evaluable efficacy data, 6 achieved hemoglobin response of >1 g/dL increase. Three patients exhibited smaller increases in hemoglobin and two patients showed no response in hemoglobin level.

Clinical measures of hemolysis improved concordantly; median reduction in percentage of reticulocytes and indirect bilirubin were 10.5% and 40%, respectively, consistent with previously reported results of GBT440 in adults with sickle cell disease.

Preliminary data following multiple doses of GBT440 suggest that pharmacokinetics in adolescents were similar to those observed in adults with sickle cell disease.

All subjects exhibited normal transcranial Doppler velocity measurements: median ranged 120 cm/s, range 89 to 143 cm/s and remained normal after 12 weeks of treatment.

Daily sickle cell disease symptom severity scores trended lower post dose vs screening.

Except for one grade 3 rash, all treatment-related adverse events were grade 1 or 2 and neither treatment-related serious adverse events nor drug discontinuations due to adverse events were observed. The most common treatment-emergent adverse events were grade 1 nausea reported in three (12.5%) patients.

Dr. Hoppe concluded that, based on preliminary results, treatment with GBT440 at 900 mg was well tolerated in all 24 adolescents. Data from 11 adolescents at 16 weeks have shown a marked improvement in hemoglobin and a reduction in clinical measures of hemolysis. Importantly, hematologic improvements have been seen in patients already managed maximally with hydroxyurea.

Though total symptom scores assessed by the Patient-Reported Outcome Sickle Cell Disease Severity Measure were low at baseline (unselected study population), a trend toward improvement was found in nine of 12 patients at 16 weeks, suggesting that the Patient-Reported Outcome Sickle Cell Disease Severity Measure is sensitive to treatment effect, supporting use in ongoing phase III study.

A treatment effect of voxelotor on transcranial Doppler velocity could not be assessed given normal measurements at baseline. This would require enrichment of patients with conditional/abnormal transcranial Doppler at baseline to assess effect.

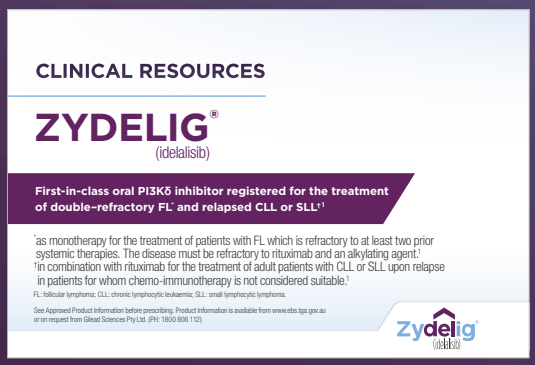
Overall, these interim results were consistent with in vivo inhibition of hemoglobin S polymerization by voxelotor (GBT440) and support the ongoing clinical evaluation of GBT440 as a potential disease-modifying therapy for sickle cell disease in an ongoing pivotal phase III study.

"These preliminary results," Dr. Hoppe noted, "together with cumulative safety data, suggest that voxelotor may translate into clinically relevant benefits." ■

www.practiceupdate.com/c/61476

ZYDELIG resources for you and your patients

Clinical resource for physicians



This clinical resource has been developed to assist healthcare professionals in the management of patients prescribed ZYDELIG. It provides an overview of recommendations for monitoring, prophylaxis, dose interruption and symptomatic management of adverse events associated with ZYDELIG. Refer to the Product Information for further information.

Navigate patient pack

This pack has been developed to help answer questions commonly asked by people being treated with ZYDELIG. It contains an information booklet covering various aspects of treatment, including an overview of the patient's condition, how ZYDELIG works and what to expect from treatment. The pack also contains a treatment diary for patients to keep record of any side effects while on treatment and a wallet card.

FL: follicular lymphoma; CLL: chronic lymphocytic leukaemia; SLL: small lymphocytic lymphoma; ANC: absolute neutrophil count; FISH: fluorescence in situ hybridisation.

PBS Information: CLL/SLL & FL. Written authority required.
Refer to PBS Schedule for full authority benefit information.

PLEASE REVIEW PRODUCT INFORMATION BEFORE PRESCRIBING. **PLEASE REFER TO THE BOXED WARNING IN THE PRODUCT INFORMATION.** TO HAVE A COPY OF THE PRODUCT INFORMATION SENT TO YOU, TELEPHONE GILEAD SCIENCES ON 1800 806 112, OR IT CAN BE ACCESSED VIA THE TGA WEBSITE (HTTPS://WWW.EBS.TGA.GOV.AU).

Minimum Product Information ZYDELIG® (idelalisib) 100 mg and 150 mg Tablets. INDICATIONS: In combination with rituximab or ofatumumab for CLL/SLL upon relapse in patients where chemo-immunotherapy is unsuitable. Monotherapy treatment of FL refractory to at least two prior systemic therapies (disease must be refractory to both rituximab and an alkylating agent). **DOSAGE AND ADMINISTRATION**: 150 mg twice daily. Dose modification may be required. **CONTRAINDICATIONS**: hypersensitivity. **PRECAUTIONS**: **Serious Infections**: treatment should not be initiated with any evidence of systemic bacterial, fungal or viral infections. Serious and fatal infections including PJP and CMV have occurred. Administer prophylaxis for PJP to all patients throughout Zydelig treatment and for 2-6 months after discontinuation, based on clinical judgement. Assess CMV status prior to initiating treatment. At least monthly monitoring for CMV is recommended in patients with positive CMV serology at baseline or other evidence of a history of CMV infection or disease. Patients with signs of infection should be promptly treated. **Hepatotoxicity**: monitoring required. **Hepatitis Infection and Reactivation**: prior screen for HBV and HCV. **Diarrhoea/Colitis**: assessment of hydration and dose interruption should be considered in severe cases. Infectious causes should be considered when assessing colitis. **Pneumonitis**: Dose interruption should be considered with any severity of symptomatic pneumonitis. Infectious causes should be considered when assessing pneumonitis. **Immunisation**: Vaccination prior to treatment of patients at substantial risk of an infection. **Neutropenia, Anaemia, Lymphopenia and Thrombocytopenia**: Grade 3 or 4 neutropenia including febrile neutropenia have occurred. Monitor bloods at least every 2 weeks for the first 6 months, weekly while absolute neutrophil count is $< 1.0x10^9$/L. Absence of neutropenia does not exclude immunosuppression and risk of serious infection. **Severe Cutaneous Reactions:** life-threatening (Grade ≥ 3) cutaneous reactions have been reported. Fatal cases of SJS-TEN have occurred when patients were treated with Zydelig when administered concomitantly with other medications associated with SJS-TEN. Treatment should be interrupted immediately if SJS or TEN is suspected and permanently discontinued where there is a case of severe cutaneous reaction. **Intestinal Perforation**: discontinue permanently. **Progressive Multifocal Leukoencephalopathy**: diagnosis should be considered with new onset of, or changes in pre-existing neurologic signs and symptoms. **Transient Lymphocytosis**. **Effects on Fertility**: highly-effective contraception during and 1 month after. **Pregnancy (Cat. D)**. **Lactation**. **Children (<18 years),** refer to full PI. **INTERACTIONS WITH OTHER MEDICINES**: **Effects of other drugs on Zydelig:** CYP3A Inducers (rifampin, phenytoin, St. John's Wort, or carbamazepine). CYP3A Inhibitors (ketoconazole). **Effects of Zydelig on other drugs:** CYP3A Substrates (alfentanil, cyclosporine, sirolimus, tacrolimus, cisapride, pimozide, fentanyl, quinidine, ergotamine, dihydroergotamine, midazolam, certain antiarrhythmics, calcium channel blockers, benzodiazepines, HMG-CoA reductase inhibitors, phosphodiesterase-5 (PDE5) inhibitors, and warfarin), refer to full PI. **ADVERSE EFFECTS**: Diarrhoea, nausea, constipation, abdominal pain, vomiting, gastroesophageal reflux disease, stomatitis, headache, lethargy, fatigue, pyrexia, peripheral oedema, chills, asthenia, rash, night sweats, pruritus, pneumonia, neutropenia, anaemia, thrombocytopenia, cough, dyspnoea, muscle spasms, sepsis, sinusitis, urinary tract infection, bronchitis, oral herpes, arthralgia, decreased appetite, weight decreased, dehydration, hypokalaemia, alanine aminotransferase increased, aspartate aminotransferase increased, insomnia. **This is not the full Product Information. Please review the full Product Information before prescribing. Product Information is available on request from Gilead Sciences Pty Ltd.**
Date of preparation 14 March 2017.

References: 1. Pharmaceutical Benefits Schedule. Available at: www.pbs.gov.au. Accessed December 2017. **2.** Zydelig Product Information, 26 October 2017.

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NOW PBS LISTED[1]

ZYDELIG – a first-in-class oral PI3Kδ inhibitor – is now PBS listed for the treatment of:

Double-refractory FL*[2]

*As monotherapy for the treatment of patients with FL which is refractory to at least two prior systemic therapies. The disease must be refractory to rituximab and an alkylating agent.[2]

Relapsed CLL or SLL†[2]

†In combination with rituximab for the treatment of adult patients with CLL or SLL upon relapse in patients for whom chemo-immunotherapy is not considered suitable.[2]

FL: follicular lymphoma; CLL: chronic lymphocytic leukaemia; SLL: small lymphocytic lymphoma.

PBS Information: CLL/SLL & FL. Written authority required.
Refer to PBS Schedule for full authority benefit information.

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