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MEETING REPORT

16TH EUROPEAN HEMATOLOGY ASSOCIATION CONGRESS

JUNE 9-12, 2011, LONDON, UK

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SUMMARY

The 16th Annual Congress of the European Hematology Association (EHA) program included sessions on clinical, laboratory and oncological hematology, and covered a wide range of subjects, including leukemia, lymphoma, red blood cells, white blood cells and platelet disorders, hemophilia, myeloma, thrombosis, bleeding disorders, transfusion and stem cell transplant. The congress began with a satellite symposium day, supported by the pharmaceutical industry and various nonprofit organizations.

CHRONIC MYELOGENOUS LEUKEMIA (CML): IS THERE A NEED FOR FURTHER IMPROVEMENTS IN THERAPY?

At a symposium on evolving and new therapeutic treatments in hematological malignancies sponsored by MSD Oncology, Moshe Talpaz (University of Michigan) chaired a "Landmark Talk on CML", focusing on whether therapeutic improvements in CML are needed, realistic and achievable with newer treatment options. The use of **imatinib mesylate** (Glivec®, Gleevec®) and, more recently, second-generation BCR/ABL tyrosine kinase inhibitors such as **nilotinib hydrochloride monohydrate** (Tasigna®) and **dasatinib** (Sprycel®), has led to a dramatic improvement in CML survival. A third-generation, pan-BCR/ABL inhibitor, **ponatinib** (ARIAD Pharmaceuticals), with activity against a range of BCR/ABL mutants, including T3151, is currently in development. Despite the high survival rates achieved with BCR/ABL inhibitors, leukemia stem cells are resistant to these drugs, and hence the therapy is not curative. If a cure for CML is to be found, further research is required, raising the question of whether this would be the best use of resources.

Andreas Burchert (Philipps-Universität Marburg) presented the case for further research to solve the problem of persistence of stem cell-based residual disease in CML patients treated with BCR/ABL inhibitors. Possible strategies for targeting persistence mechanisms include the use of a histone deacetylase inhibitor to target stem cells, the use of a hedgehog signaling (smoothened homolog [SMO]) inhibitor such as cyclopamine, autocrine/paracrine stimulation with a tyrosine-protein kinase JAK2 inhibitor, chemokine receptor CXCR4 inhibition, or the use of pegylated interferon. In conclusion, Dr. Burchert argued that a cure is the safest and cheapest long-term treatment option for CML.

As an alternative to research for new therapies for CML, Bengt Simonsson (University of Uppsala) outlined a number of ways in which improvements could be made by optimization of existing treatments, with particular reference to the use of population-based registries. The EUTOS (EUropean Treatment Outcome Study) CML registry, established in 2007 by ELN (European Leukemia Net) in collaboration with Novartis Oncology, collects treatment and outcome data across Europe. Since 2009, data have been collected for all patients newly diagnosed with CML, irrespective of frontline treatment. Dr. Simonsson drew attention to the need for reliable criteria for stopping tyrosine kinase inhibitor treatment, relevant and uniform definitions for analyses in CML, and clarification of treatment effects on stem cells and immunology.

NOVEL TREATMENTS FOR HEMATOLOGICAL MALIGNANCIES

A symposium on novel approaches in hematological malignancies, supported by the Development Therapeutics Consortium, included a presentation by Ronan Swords (University of Texas Health Science Center) on NEDD8-activating enzyme inhibition as a potential approach to treating acute myeloid leukemia (AML) in the elderly. The small-molecule NEDD8-activating enzyme inhibitor **MLN-4924**

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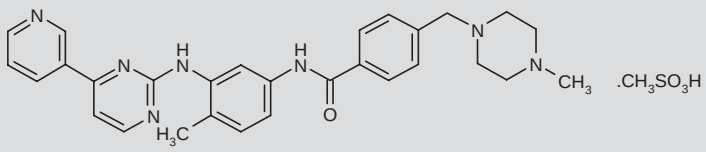
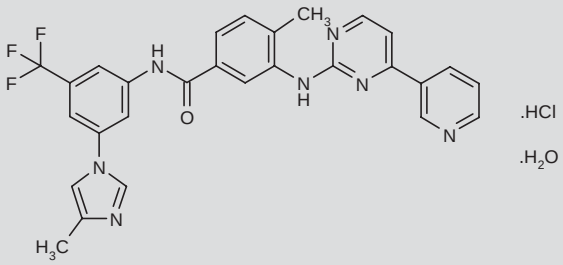


Imatinib mesylate



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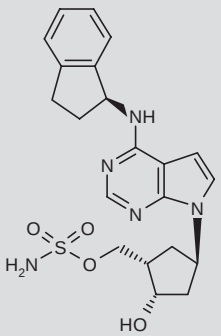
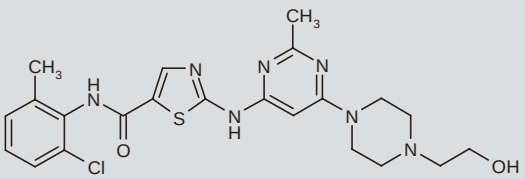
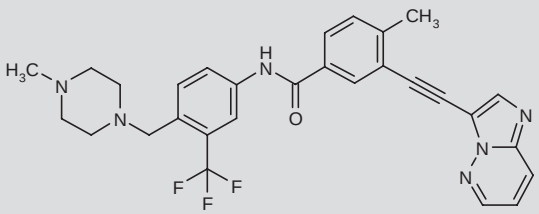


MLN-4924



Dasatinib



Ponatinib

(Millennium Pharmaceuticals), which forms a covalent complex with NEDD8, showed IC_{50} values of 150-200 nM in cell viability studies, and drug sensitivity was not affected by FL cytokine receptor (Fms-like tyrosine kinase 3, FLT-3) expression or stromal-mediated signaling. The compound was further shown to induce a threefold increase in reactive oxygen species generation, which leads to DNA damage and apoptosis.

The NEDD8-activating enzyme inhibitor MLN-4924 is currently being evaluated in a multicenter phase I safety and tolerability study in patients with AML or high-grade myelodysplastic syndrome (MDS). Updated results from this trial were disclosed in a poster presentation by Harry Erba of the University of Michigan Comprehensive Cancer Center. Accrual has been completed, and at this time 29 patients (28 AML, 1 MDS) aged 20-84 years (median of 57.7 years) have been treated at dose levels of 25-78 mg/m^2. The maximum tolerated dose (MTD) has been established as 59 mg/m^2. The most frequent treatment-emergent adverse events (AEs) of grade 3 or more were febrile neutropenia (n = 9), elevated ALT/AST (n = 5), thrombocytopenia (n = 4) and pneumonia (n = 3). Further dosing regimens are under investigation to allow higher doses with increased MLN-4924 exposure. Details were provided for four patients who achieved a complete response (CR).

Kevin Kelly (University of Texas Health Science Center) described preclinical findings on oncolytic reoviruses that demonstrate potential in the treatment of multiple myeloma (MM). The reovirus therapy Reolysin (Reosyn; Oncolytics Biotech) has undergone clinical tri-

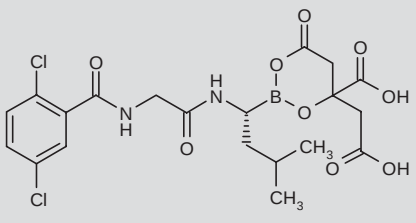
als in various cancers, but has not yet been evaluated in hematological malignancies. Reolysin selectively replicates in cells with an activated Ras pathway, which is often found in MM patients, up to 50% of whom have Ras mutations. Preclinical studies have shown that Reolysin selectively accumulates in MM cells, induces endoplasmic reticular swelling and causes an increase in intracellular Ca^{2+}. The reovirus has also been found to induce phorbol-12-myristate-13-acetate-induced protein 1 (protein Noxa; *PMAIP1*) expression in a concentration-dependent manner and to induce caspase-3. In addition, Reolysin was shown to increase the activity of bortezomib (Velcade®) in xenograft (RPMI 8226) and syngeneic (5TGM1) mouse models of MM; in each case, the combination was more effective than either agent alone. Phase I studies of Reolysin in MM, alone and in combination with bortezomib, are planned.

The validity of proteasome inhibition as a therapy for cancer has been demonstrated with the first-in-class drug bortezomib. The specific 20S proteasome inhibitor **MLN-9708** (Millennium Pharmaceuticals) is the first orally available proteasome inhibitor to be investigated in the clinic. In a poster presentation, Ruben Niesvizky of Weill Medical College of Cornell University and collaborators reported data from two ongoing phase I trials of oral MLN-9708 in patients with relapsed and/or refractory MM. Primary objectives of the trials were to evaluate safety and tolerability, and to determine the MTD using twice-weekly or weekly dosing, and the recommended phase II dose for twice-weekly dosing. The MTD was established as 2.0 mg/m^2 on the twice-weekly dosing schedule (days 1, 4, 8 and 11 of 21-day cycles). The MTD for the weekly dosing schedule (days 1, 8 and 15 of a 28-day cycle) has yet to be reached, with dose escalation progressing to 3.95 mg/m^2, suggesting that the weekly schedule permits higher oral dosing. MLN-9708 was generally well tolerated, without any observations of grade 3 or 4 peripheral neuropathy to date. Preliminary response data from the trials were also presented. By March 2011, 2 patients in the twice-weekly trial had achieved a partial response (PR) and a further 17 patients (71%) had achieved stable disease (SD) with a mean duration of 4.25 months; in the weekly trial, 1 patient had achieved a PR and a further 6 patients had achieved SD. Recruitment is continuing in four expansion cohorts in the twice-weekly trial, and dose escalation is continuing in the weekly trial.

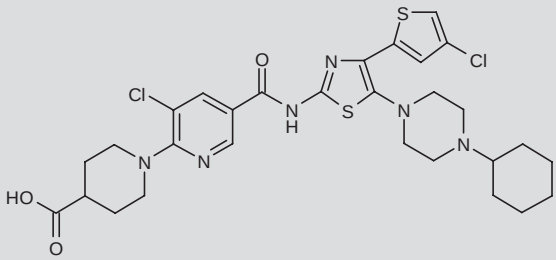
Results from a phase II 6-month extension trial of the oral thrombopoietin receptor agonist **E-5501** (Eisai) were presented in a poster by James Bussel and colleagues from Weill Medical College of Cornell University. The multicenter, parallel-group trial (ClinicalTrials.gov Identifier NCT00625443; 501-CL-004) assessed the efficacy, safety and tolerability of E-5501 in 53 patients with chronic idiopathic thrombocytopenic purpura (ITP) who had completed 28 days of treatment with E-5501 (2.5, 5, 10 or 20 mg) or placebo in a previous multicenter, randomized, double-blind, placebo-controlled phase II trial (501-CL-003). A durable platelet response was achieved in 52.8% of all subjects and an overall platelet response was seen in 75.5% of subjects; for previous responders (in 501-CL-003), the durable and overall response rates were 72% and 88.0%, respectively. Treatment with E-5501 allowed concomitant steroid medication to be reduced; of 24 patients receiving steroids, 54.2% decreased their use by at least 50% and 33.3% discontinued their use completely. A favorable safety profile was observed in both the 28-day trial and the extension study. Serious treatment-emergent adverse effects (TEAEs) were reported in 12 of 64 patients (18.8%) who participated in 1 or both trials; of these TEAEs, 4 (6.3%) were considered treatment-related.

Preliminary phase II results from a phase I/IIa trial of single-agent **navitoclax** (ABT-263, RG-7433; Abbott/Genentech) in patients with relapsed or refractory lymphoid malignancies were presented by Sven de Vos of the David Geffen School of Medicine at the University of California Los Angeles and collaborators. The objectives of the international study were to evaluate the safety, efficacy and pharmacokinetics. Patients (N = 26) were enrolled in two study arms: patients with relapsed/refractory follicular lymphoma (n = 11) and patients with other indolent B-cell lymphoid malignancies. The drug was reasonably well tolerated, with most AEs due to on-target effects. As previously reported for the phase I study, patients with chronic lymphoid leukemia (CLL; n = 6) and small lymphocytic leukemia (n = 2) showed the best tumor responses and median progression-free survival with the monotherapy. Of these eight patients, seven had a reduction in absolute lymphocyte count of more than 50%. It was recommended that in other tumor types navitoclax should be tested in combination with other agents.

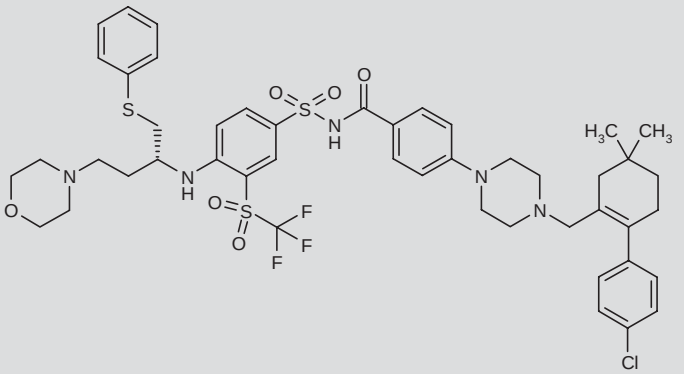
First phase II results for the anti-RhD recombinant antibody mixture rozrolimupab (SYM-001, Symphoglobulin-D; Symphogen) in primary ITP were presented by Tadeusz Robak of the Medical University of Lodz. The multicenter, dose-escalation trial aimed to assess the safety and efficacy of a single intravenous dose of rozrolimupab in RhD-positive, non-splenectomized patients with ITP. Four groups of patients received doses of 75 μg/kg (n = 11), 100 μg/kg (n = 10), 125 μg/kg (n = 10) or 150 μg/kg (n = 5). Up to 70% of patients in the individual dose groups responded. Reported adverse drug reactions included pyrexia, decreased hemoglobin and headache, and were



MLN-9708



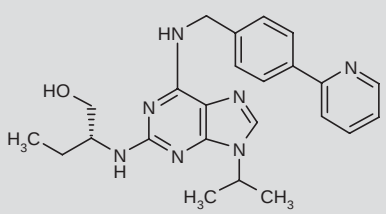
E-5501



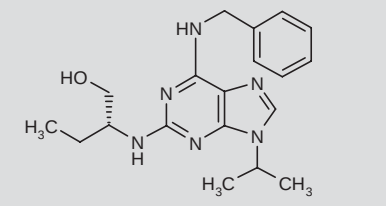
Navitoclax

generally of mild to moderate intensity, with the exception of severe headache in one patient in the 100 μg/kg dose group. Preliminary signs of clinical activity were observed, as shown by decreased hemoglobin values in all patients, although values reverted towards baseline levels during the study. Further evaluation in ITP was recommended.

Alison Michie of Glasgow University presented preclinical findings for the cyclin-dependent kinase (CDK) inhibitor **CR-8**, a novel derivative of roscovitine, showing the compound to be 100-fold more potent than **seliciclib** (*R*-roscovitine, CYC-202) in inducing apoptosis in isolated cultures of primary CLL cells. The team at Glasgow University is collaborating with Laurent Meijer of CNRS, where CR-8 originated. The compound was derived from roscovitine by an optimal substitution of pyridyl at the N^6 position. CR-8 also induced apoptosis in co-culture systems that mimic the in vivo microenvironment of CLL proliferation centers, targeting actively proliferating CLL cells. The compound was further shown to inhibit CLL cell proliferation, blocking the G_1 phase of the cell cycle. The studies revealed a nondividing population of CLL cells resistant to CR-8 in a proproliferative culture environment; this chemoresistant cell population may be responsible for minimal residual disease in CLL.



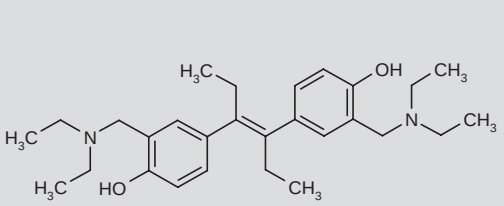
CR-8



Seliciclib

A NOVEL JAK2 INHIBITOR FOR MYELOPROLIFERATIVE NEOPLASMS (MPNs)

A new small-molecule JAK2 inhibitor, **G-6** (University of Florida/TeraDiscoveries), with efficacy in a mouse model of JAK2-Val617Phe-mediated MPN, including significant efficacy in the bone marrow, was described by Peter Sayeski (University of Florida). Preliminary biological data for G-6, a stilbenoid compound, were reported recently from the University of Florida, and the drug is now being investigated by TeraDiscoveries, which formed a strategic alliance with the University of Florida for cancer drug discovery in March 2010. A problem with most existing JAK2 inhibitors is that they have limited efficacy in the bone marrow, resulting in only palliative effects in MPN. In contrast, G-6 has demonstrated therapeutic efficacy in the bone marrow, as well as in peripheral blood, liver and spleen, in a transgenic mouse model of JAK2-Val617Phe-mediated MPN. In the bone marrow, G-6 reduced the levels of phospho-JAK2 and phospho-STAT5, completely normalized the myeloid:erythroid ratio, and significantly reduced the number of megakaryocytes. The compound also resulted in a significant reduction in the allelic burden of JAK2-Val617Phe mutant transcripts in the bone marrow by an average of 67%, with virtual elimination in one-third of treated mice.

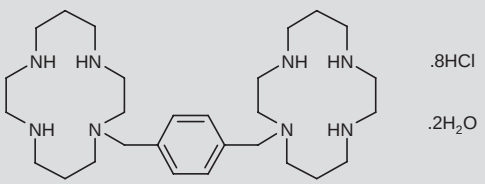


G-6

CXCR4 ANTAGONISTS FOR WHIM SYNDROME AND MULTIPLE MYELOMA

David Dale from the University of Washington presented data from a small clinical trial (ClinicalTrials.gov Identifier NCT01058993) showing that the selective CXCR4 antagonist **plerixafor hydrochloride** (AMD-3100, Mozobil®) may have potential as a targeted therapy for myelokathexis, also known as WHIM syndrome (warts, hypogammaglobulinemia, immunodeficiency and myelokathexis), which is a rare autosomal dominant disorder attributed to *CXCR4* gene mutations. The trial was conducted in six patients, five with the Arg334ter mutation and one with a novel mutation (Ser324fs365ter). Single doses of plerixafor (0.02-0.24 mg/kg s.c.) were administered at 2- to 4-day intervals, and the results were compared with those from five similarly studied healthy individuals. All six patients showed prompt increases in leukocytes to reach levels comparable with those observed in healthy subjects. Maximum levels of blood neutrophils and lymphocytes occurred at 6-12 hours, and then declined towards baseline by 24 hours. In patients, the lymphocyte responses were quantitatively and proportionally greater than the neutrophil response, with the greatest increase shown in B cells ($CD20^+$ cells), with a 60-fold increase at the 0.08 mg/kg dose. A 6.8-fold increase in $CD34^+$ stem cells was also observed with the 0.08 mg/kg dose. Furthermore, patients showed a greater proportion of B- and T-cell responses than healthy subjects. No significant AEs were observed. It was concluded that plerixafor can correct neutropenia and lymphocytopenia in patients with myelokathexis, and may correct the underlying deficiency. A therapeutic trial is being planned.

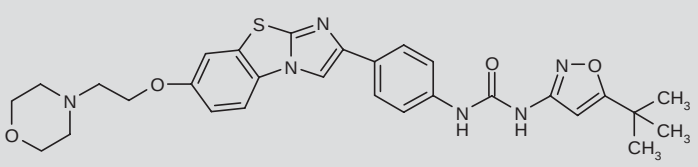
Preclinical and clinical data for the CXCR4 antagonist BKT-140 (Biokine Therapeutics) were presented by Professor Amnon Peled of the Goldyne Savad Institute of Gene Therapy. BKT-140 has potent stem cell mobilization capacity, which is of potential use for mobilizing normal hematopoietic stem cells in the treatment of MM. BKT-140 differs in its CXCR4 binding site and function from the CXCR4 antagonist plerixafor. In preclinical investigations, BKT-140, but not plerixafor, showed CXCR4-dependent cytotoxicity in MM cells. In a mouse xenograft model, BKT-140 resulted in a significant, dose-dependent reduction in the growth of MM xenografts. Data were presented from the first phase I/IIa trial (ClinicalTrials.gov Identifier NCT01010880) of BKT-140 in MM patients (N = 16). A single injection of BKT-140 (30, 100, 300 or 900 μg/kg s.c.) was administered following high-dose cyclophosphamide and granulocyte colony-stimulating factor. Toxicity and side effects were minimal; there were no grade II-IV toxicities, and AEs were mostly mild and transient. Pharmacokinetic data indicated rapid absorption with no lag time. Treatment with BKT-140 resulted in a dose-dependent increase in peripheral blood $CD34^+$ cells, as well as neutrophils, monocytes and lymphocytes. In addition, the number of days of apheresis was reduced. High doses of BKT-140 (300-900 μg/kg) induced apoptosis of MM tumor cells ($CD138^+$), while low doses (30-100 μg/kg) released MM cells from the bone marrow into the circulation. It was concluded that further investigation is warranted to assess the effect of BKT-140 in MM.



Plerixafor hydrochloride

INTERIM DATA ON QUIZARTINIB

Treatment of AML with FLT3-internal tandem duplication (*FLT3/ITD*) mutations using standard chemotherapy has been associated with poor survival and high relapse rates. During phase I studies, the potent and selective FLT-3 inhibitor **quizartinib** (AC-220; Ambit Biosciences/Astellas Pharma) has previously been shown to exhibit activity in *FLT3/ITD*$^+$ patients. A phase II trial to determine the efficacy of quizartinib monotherapy in patients with relapsed/refractory *FLT3/ITD*$^+$ AML began dosing in November 2009. Jorge Cortes of the University of Texas MD Anderson Cancer Center presented interim data from this trial for the first 62 patients, comprising 25 individuals from cohort 1 (aged 60 years or more, who were relapsed/refractory to first-line chemotherapy) and 37 individuals from cohort 2 (aged 18 years or more, who were relapsed/refractory to second-line chemotherapy or hematopoietic stem cell transplant). The most common drug-related serious AEs were febrile neutropenia and asymptomatic grade 3 QT_c prolongation. QT_c prolongation occurred in 21 patients (grade 3 in 12 patients); however, the incidence was decreased by reducing the dose from 200 mg/day, to 135 mg/day in males and 90 mg/day in females. Efficacy was evaluable for 53 patients (85%) and the overall composite complete response (cCR) was > 40%; however, a higher cCR response rate, exceeding 60%, was observed in patients refractory to chemotherapy. Median survival for all 62 patients was 24.6 weeks. The confirmatory stage of the trial is ongoing, and planning for a phase III study is under way.



Quizartinib

ACE-536 FOR THE TREATMENT OF ANEMIA

Rajasekhar Suragani (Acceleron Pharma) presented data on ACE-536, a soluble receptor fusion protein comprising a modified form of activin receptor type-2B (activin receptor type IIB) extracellular domain linked to a human Fc region, which has previously been shown to increase red blood cell (RBC) levels in several animal models. Studies were conducted to investigate which erythrocyte precursors are affected by ACE-536 and to assess the efficacy of RAP-536 (a murine analogue of ACE-536) in treating anemia in the NUP98-HOXD13 mouse model of myelodysplastic syndrome. Administration of ACE-536 (10 mg/kg s.c.) to C57BL/6 mice resulted in significant increases in hematocrit, hemoglobin and RBC levels within 4 days. These early increases were observed in the presence of an erythropoietin (EPO)-neutralizing antibody, suggesting that the effects were independent of EPO. Fluorescence-activated cell sorting analysis of bone marrow and splenic erythroblasts 72 hours after treatment with ACE-536 revealed a decrease in basophilic erythroblasts and an increase in late-stage erythroblasts and reticulocytes, suggesting that ACE-536 exhibits a novel mechanism that promotes maturation of erythroid precursors, in contrast with EPO. Treatment of 4-month-old NUP98-HOXD13 transgenic mice with RAP-536 (10 mg/kg s.c. biweekly) for 7 months resulted in a significant increase in RBC counts (+13.8%), hemoglobin (+19.8%) and hematocrit (+14.8%) compared with vehicle-treated controls.

CLINICAL DATA FOR BRENTUXIMAB VEDOTIN

The anti-CD30 antibody–drug conjugate brentuximab vedotin (SGN-35, Adcetris™; Seattle Genetics/Millennium Pharmaceuticals) has been evaluated in a population of patients with relapsed or refractory Hodgkin's lymphoma, who refused or were ineligible for autologous stem cell transplant (ASCT) (pre-ASCT patients). Results from two phase I studies in a total of 20 pre-ASCT patients were presented by Ranjana Advani of Stanford University Medical Center. Objective responses (according to Cheson, 2007) were observed in six patients (30%), with two complete and four partial responses. The safety profile was comparable to that observed in post-ASCT patients. In a poster presentation, Dr. Advani also provided results from a phase II trial of brentuximab vedotin in relapsed or refractory systemic anaplastic large cell lymphoma (sALCL). Of 15 patients with malignant cutaneous lesions at baseline, 93% had complete resolution of lesions and 100% had objective responses. AEs were generally grade 1 or 2 in severity, with the most common AEs being diarrhea and pyrexia in 60% and 47% of patients, respectively. A frontline phase I combination trial in sALCL (ClinicalTrials.gov Identifier NCT01309789) is ongoing and a randomized phase III trial in patients with $CD30^+$ cutaneous T-cell lymphoma is planned.

DISCLOSURES

The author states no conflicts of interest.