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THE 50TH ANNUAL MEETING OF THE AMERICAN SOCIETY OF HEMATOLOGY: FOCUS ON NEW ONCOLYTIC AGENTS IN DEVELOPMENT

P. Cole, I. Izco-Basurko, M. Gómez-Zaera, Z. Gajdosik

Prous Science, Provenza 388, 08025 Barcelona, Spain

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ABSTRACT

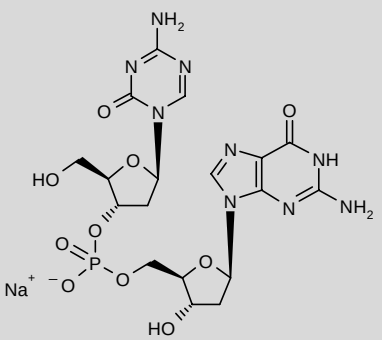
The 50th Annual Meeting of the American Society of Hematology, held in December 2008 in San Francisco, provided an extensive array of oral and poster sessions, training and educational meetings, and opportunities to meet experts and hear from pioneers in the field. Four days of talks and exhibits covered the latest investigations in blood diseases, but there was also a focus on milestones in the history of hematology in celebration of the fiftieth meeting of the society. With hundreds of oral sessions and thousands of posters, any overview of the congress is necessarily limited. A summary focused on oncolytic diseases dealing with selected treatments in the early stages of development is therefore provided here, covering preclinical studies and phase I-II clinical studies.

INTRODUCTION

Anyone interested in the latest investigations in treatments for hematological disorders would have found themselves fairly overwhelmed if they attended the most recent Annual Meeting of the American Society of Hematology, the fiftieth such meeting held. Attended by over 20,000 people, the meeting was held in the sufficiently large Moscone Center in San Francisco on December 6-9, 2008. Attendance at each session of interest and viewing of each poster was impossible for any one individual. Likewise, it is not possible to summarize all of the relevant studies reported at the congress. We therefore provide here a summary of presentations dealing with new therapeutic agents in the early stages of development for oncolytic indications, having selected some of the most compelling studies and compounds. The report is divided into sections on preclinical and clinical investigations, with the latter divided by study phase. Compounds are also grouped by type.

PRECLINICAL STUDIES

New agents for hematological cancers are aimed at an extensive variety of targets. Researchers from SuperGen, in collaboration with other entities, presented preclinical advances on a panel of novel anticancer drugs. These included **SGI-1776**, a Pim-1 serine/threonine protein kinase inhibitor that was found to inhibit the proliferation of a variety of human and murine acute lymphoblastic leukemia (ALL) cells at a concentration of 5 μM. In addition, synergistic activity in inhibiting the proliferation of ALL cells was observed in combination with rapamycin, interfering in the IL-7-induced activation of the mTOR pathway. In murine models of human primary ALL, SGI-1776 (200 mg/kg), alone or in combination with rapamycin (5 mg/kg) administered by daily gavage 5 times a week, decreased tumor burden but showed significant toxicities; therefore, further studies at lower doses are currently ongoing (1). Two novel DNA (cytosine-5)-methyltransferase 1 (Dnmt1) inhibitors, **SGI-110** and **SGI-1036**, are also in preclinical development. In vitro, both compounds induced Jun-B-, ERα- and p15-silenced gene expression, which was associated with colony growth inhibition and apoptosis in human acute myelogenous leukemia (AML) and chronic myelogenous leukemia in blast crisis (CML-BC). SGI-110 and SGI-1036 depleted histone-lysine *N*-methyltransferase EZH2 levels commonly associated with prostate, breast or bladder cancer, which was more potently decreased when SGI-1036 therapy was combined with panobinostat (2).



SGI-110

Results from several preclinical assays with Calistoga Pharmaceuticals' **CAL-101** support ongoing phase I development in patients with hematological malignancies. The novel phosphatidylinositol 3-kinase delta (PI3Kδ) inhibitor (IC_{50} = 1-10 nM) was found to suppress p110δ, which is essential for PI3Kδ signaling and expressed in more than 90% of hematological cancer cell lines. A panel of in vitro assays showed that CAL-101 decreased p-AKT levels and inhibited p-p70S6K, p-GSK-3beta and p-BAD downstream effectors, which may indicate activity against myeloid leukemia, ALL and diffuse large B-cell lymphoma. In T-cell ALL and B-cell ALL cell lines CAL-101 reduced AKT and GSK-3beta phosphorylation and cell proliferation, as well as inducing cell death (3). In samples from patients with multiple myeloma (MM), the compound induced ex vivo cytotoxicity without affecting the survival of peripheral blood mononuclear cells (PBMCs) at concentrations of 0.625-20 μM. In addition, CAL-101 induced autophagy, as observed by a significant increase in the expression of the autophagic marker LC3-II and autophagosome formation in murine T-cell lymphoma LB cells and human plasma INA-6 cells. In mice bearing LB cancer xenografts, an analogue of CAL-101 at 10 or 30 mg/kg p.o. b.i.d. inhibited tumor growth and prolonged survival compared to controls (4). Further preclinical studies demonstrated that CAL-101 was able to induce selective cytotoxicity in cells from patients with chronic lymphocytic leukemia (CLL) at high or low risk (fludarabine refractory or not, respectively), but not in normal natural killer (NK) or T cells from healthy volunteers. A pharmacokinetic analysis in a phase I trial in healthy volunteers showed that relevant plasma levels can be achieved for inhibiting the PI3K-p110δ isoform (5).

Bayer HealthCare's multikinase inhibitor **BAY-73-4506** is undergoing phase I studies for the treatment of solid tumors and phase II studies in renal cell carcinoma. Preclinical investigations now suggest that clinical evaluation in MM is also warranted. In an array of MM cell lines, including those resistant to conventional chemotherapeutics, BAY-73-4506 induced apoptosis via activation of caspase-9 and caspase-3 at low micromolar concentrations. BAY-73-4506 was active in bone marrow stromal cell–MM and endothelial cell–MM coculture systems, and antiangiogenic activity and inhibition of osteoclastogenesis were also noted in vitro. Orally administered compound significantly delayed tumor growth and prevented blood vessel formation in a nude mouse xenograft model of human MM (6).

Deciphera Pharmaceuticals' **DCC-2036** and **DCC-2157** are members of a novel class of BCR/ABL kinase inhibitors targeting kinase switch control pockets. Both have demonstrated potent (IC_{50} = 0.8-4.0 nM) inhibition of purified ABL in the switch-off (unphosphorylated) and switch-on (phosphorylated) states via a non-ATP-competitive mechanism. Both were also found to reduce proliferation and induce apoptosis in Ba/F3 cells expressing a variety of BCR/ABL tyrosine kinase inhibitor-resistant mutants. DCC-2036 was highly selective for ABL and a small subset of other tyrosine kinases. Oral treatment at 100 mg/kg/day also significantly prolonged survival in mice with CML-like leukemia induced by BCR/ABL T315I and in mice with B-ALL induced by BCR/ABL T315I. DCC-2157 was selective for ABL, SCFR (c-kit) and PDGF A/B kinases and demonstrated prolonged inhibition of p-STAT5 in BCR/ABL^+ leukemic cells after a single oral dose of 100 mg/kg in BALB/c mice. Long-term suppression of CML-like leukemia induced by BCR/ABL T315I and increased survival were seen with DCC-2157 50 mg/kg given every other day (7).

Targeting Bruton tyrosine kinase (BTK) with inhibitors such as Avila Therapeutics' **AVL-101** may be a means of effectively treating B-cell-related hematological cancers, as indicated by preclinical experiments. These studies showed inhibition of BTK but selective disruption of BCR signaling with AVL-101, which was further found to covalently modify BTK specifically at Cys-481. Irreversible binding was associated with prolonged inhibition of BTK kinase activity. Inhibition of BTK activity persisted for over 8 h after removal of AVL-101 in cultured B-cell lymphoma cells, and this inhibition was correlated with the half-life of the BTK protein. AVL-101 inhibited BCR ligand-induced calcium flux and the proliferation of several B-cell lymphoma cell lines and primary human naïve B cells, and demonstrated oral bioavailability and inhibited BTK-dependent B-cell function in vivo. Avila hopes to select an IND candidate from this class of drugs in 2009 (8, 9).

Preclinical investigations of agents targeting Janus kinase 2 (JAK2) were presented at the congress by researchers from Rigel, Exelixis and SuperGen. Rigel's **R-723** was found to be a potent (IC_{50} = 2 nM) and selective JAK2 inhibitor with strong antiproliferative activity (IC_{50} = 130-200 nM) against mouse Ba/F3 cells and human UKE1 and SET2 cell lines with the same $JAK2^{V617F}$ mutant. In a mouse stress-induced erythropoiesis model a significant delay in erythropoietin (EPO)-dependent hematocrit recovery from phenylhydrazine-induced anemia was seen with doses of 75 and 100 mg b.i.d. The agent was also effective in a murine V617F Ba/F3 leukemia model and displayed a reasonable safety profile in rodents at doses relevant for efficacy (10).

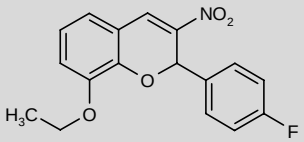
Exelixis reported results from studies on **XL-019** and **EXEL-8232**. EXEL-8232 demonstrated selectivity for JAK2, with an IC_{50} of 2 nM, inhibited the phosphorylation of JAK2 and STAT5, and inhibited the cytokine-independent growth of Ba/F3 cells. The compound was administered for 28 days every 12 h at 30 or 100 mg/kg by oral gavage in a murine bone marrow model of essential thrombocytosis, a $JAK2^{V617F}$-negative myeloproliferative disease (MPD), and the higher dose was associated with normalized platelet counts and normalized leukocytosis. EXEL-8232 treatment also eliminated extramedullary hematopoiesis in the spleen and bone marrow fibrosis. The treatment did not affect erythrocytosis in the diseased animals or wild-type controls. The study provides proof of principle for the treatment of thrombocytosis in vivo and for the treatment of $JAK2^{V617F}$-negative MPD (11). Preclinical evaluation showed that XL-019 inhibited JAK2 signaling and potently inhibited STAT1, STAT3 and STAT5 in HEL 92.1.7 cells and phosphorylation of STAT1, STAT3 and STAT5 in HEL 92.1.7 xenografts. Repeated dosing in this model resulted in maximum tumor growth inhibition of 70% at 300 mg/kg b.i.d., and effects on tumor growth were accompanied by increases in tumor cell apoptosis. A phase I study in patients with polycythemia vera is under way (12). A phase I study in patients with primary myelofibrosis, post-polycythemia vera or post-essential thrombocythemia myelofibrosis is also ongoing. Regimens of 100-300 mg/day for 21 days, 25-50 mg/day and 25 mg three times weekly are being investigated. No drug-related hematological adverse events were seen at doses below 50 mg. Of 16 patients treated with 25 mg of XL-019, 1 had grade 1 peripheral neuropathy. At this dose, signs of clinical activity were seen, including a durable reduction in blasts, improvement in anemia, a reduction in leukocytosis, reductions in splenomegaly and relief of constitutional symptoms (13).

Characterization of SuperGen's novel JAK2 inhibitor **SGI-1252** was reported in a poster. The compound inhibited the phosphorylation of STAT5 and the expression of the antiapoptotic protein Bcl-XL in HEL cells and increased STAT3 and caspase-3 activity in UKE1 cells. Further in vitro experiments showed that SGI-1252 inhibited the proliferation of native human erythroid progenitor cells from patients with Philadelphia chromosome-negative myeloproliferative disorders (14).

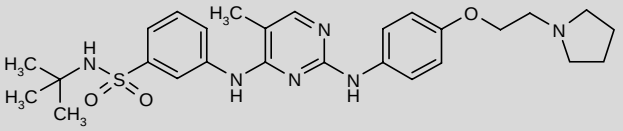
Efforts at ImmunoGen and sanofi-aventis to target CD38 for hematological malignancies have led to the identification of the humanized anti-CD38 monoclonal antibody **SAR-650984**. Subnanomolar binding affinity was demonstrated with SAR-650984, with a K_D value of 0.2 nM in Ramos (Burkitt's) lymphoma cells. In vitro, SAR-650984 increased the percentage of apoptotic Ramos lymphoma cells, SUDHL8 diffuse large B-cell lymphoma cells, DND-41 T-cell ALL cells and MOLP-8 MM cells to 30%, 95%, 70% and 50%, respectively. Assessments of complement-dependent cytotoxicity (CDC) showed that SAR-650984 reduced the viability of DND-41 and MOLP-8 cells to 10% and 33%, respectively. In an assay of antibody-dependent cellular cytotoxicity (ADCC) using human NK cells, SAR-650984 treatment was associated with a maximum percentage of specific lysis of approximately 65% compared to the nonbinding hulgG1 control. Similar in vitro CDC and ADCC activities were seen against Raji and Daudi lymphoma cells with SAR-650984 and rituximab, but greater proapoptotic activity was observed with SAR-650984. In vivo, potent antitumor activity was seen with SAR-650984 in Daudi lymphoma and NCI-H929 MM models; rituximab is not active in the latter model (15).

Activity against MM cells and antitumor activity in mice led to the clinical investigation of **BIW-8962**, an antiganglioside (GM2) monoclonal antibody designed using BioWa's Potelligent™ technology. GM2 expression was detected in 15 human MM cell lines and in 12 of 15 samples obtained from MM patients. In vitro, BIW-8962 displayed potent ADCC and less potent CDC activity. In SCID mice with KMS-11 MM cells introduced into the flank, biweekly i.v. administration of BIW-8962 for 3 weeks displayed antitumor effects at doses as low as 0.1 mg/kg. When mice were inoculated with a GM2-positive MM cell line and had tumor growth within the bone marrow microenvironment, BIW-8962 10 mg/kg i.v. biweekly for 4 weeks reduced cell growth and serum M-protein elevation. BIW-8962 is being evaluated in a phase I study in MM patients (16).

Agents other than kinase inhibitors and antibodies were discussed at the meeting. Experiments conducted with a nuclear factor NF-kappa-B inhibitor from 4SC, **V-1810**, have provided further evidence that NF-kappa-B is a valid target in MM. The IC_{50} values against the MM cell lines OPM-2, U266, NCI-H929, RPMI 8226 and primary MM cells from patients were 5-10 μM. Evidence of apoptosis was seen, which was accompanied by cell cycle arrest in OPM-2, U266 and RPMI 8226 cells. Downregulation of antiapoptotic proteins such as Mcl-1 was also seen, and downregulation of cyclin D1 or cyclin D2 – NF-kappa-B target genes – was detected in these cells, and retinoblastoma protein was found to be hypophosphorylated. NF-kappa-B activity was inhibited by V-1810, which also blocked NF-kappa-B activation induced by genotoxic drugs such as melphalan and doxorubicin. A synergistic decrease in MM cell viability was observed with V-1810 and melphalan. It was also shown that relevant concentrations of V-1810 were safely achievable in vivo (17).



Pichromene



TG-101348

From a screen of 50,000 novel chemical inhibitors of cyclin D transactivation, **pichromene**, a chromene-based compound, was identified by Canadian researchers. This compound decreased expression of cyclin D1, D2 and D3 in myeloma and leukemia cells, induced cell cycle arrest at the G0/G1 phase and reduced phosphorylated AKT. Cell-free enzymatic assays demonstrated that pichromene inhibited PI3 kinase isoforms α, β, δ and γ, but not unrelated kinases, such as PKB, Akt-2 or Akt-3, PDK1 or 2, GSK-3beta or alpha. In vitro, it induced apoptosis and cell death in 9 of 10 leukemia and 9 of 10 myeloma cell lines (IC_{50} < 10 μM), whereas pichromene was less cytotoxic in primary normal hematopoietic cells from volunteer donors of stem cells for allotransplant. Exceptionally, U266 myeloma cells were found to be resistant to the compound. When pichromene was administered at 50 mg/kg/day by oral gavage to mice bearing K-562 CML xenografts, tumor weight and volume were decreased by more than 35% after 8 days. At doses up to 500 mg/kg/day by oral gavage or i.p., no weight loss or gross organ toxicities were observed (18).

Finally, Daiichi Sankyo is developing **D-11-5908**, an oral small-molecule inhibitor of integrin $\alpha_4\beta_1$ (VLA-4), which is commonly expressed in human AML blasts. In studies presented at the congress, AML blasts isolated from 8 patients were preincubated with D-11-5908 and then treated with cytarabine (Ara-C) or Ara-C and daunorubicin. Decreases in cell viability were greater with D-11-5908 plus chemotherapy than with an isotype control antibody (27.8% vs. 10.4%). D-11-5908 also enhanced apoptosis when added to Ara-C. The ability of D-11-5908 to mobilize normal and AML cells in vivo from the marrow into the blood was observed in normal mice and in a human AML xenograft model. D-11-5908 also did not impair normal blood cell recovery after Ara-C treatment in BALB/c mice treated simultaneously with D-11-5908 and Ara-C compared to treatment with Ara-C alone (19).

CLINICAL STUDIES

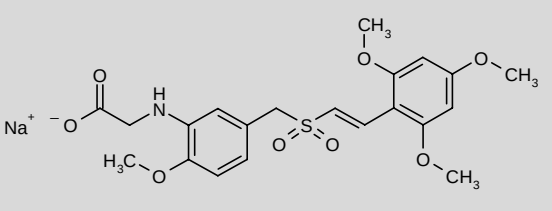
Phase I

Among presentations dealing with kinase inhibitors, preliminary results of a phase I study of the JAK2 inhibitor **TG-101348** (TargeGen) were reported at the meeting. The trial includes patients with

myelofibrosis, with 30 planned for the dose-escalation phase and 20 planned for an expanded cohort to evaluate the maximum tolerated/biologically effective dose. Oral TG-101348 is taken once daily in 28-day cycles, with doses of 30-800 to be evaluated. Pharmacokinetics were dose-proportional following single and multiple doses up to 520 mg/day, with a half-life supporting once-daily administration. The treatment was considered to be well tolerated, with the most common treatment-emergent adverse events (AEs) being nausea or vomiting, diarrhea and abdominal pain. Decreases in spleen size and control of leukocytosis were also seen and were dose-related (20). Further in vitro findings with TG-101348 were also reported at the congress. TG-101348 inhibited the growth of *FIP1L1-PDGFRA*-positive EoL-1 cells derived from chronic eosinophilic leukemia cells (IC_{50} = 900 nM), an effect associated with inhibition of JAK2 phosphorylation. TG-101348 inhibited the proliferation of mast cell leukemia HMC-1.2 cells more than HMC-1.1 cells; JAK2 and STAT5 were constitutively phosphorylated in HMC-1.2 cells but not in HMC-1.1 cells. The agent did not affect SCFR phosphorylation at concentrations up to 2 μM in HMC-1.2 cells (21).

ON-1910Na is a Polo-like kinase 1 (PLK-1) pathway modulator from Onconova Therapeutics. After the compound was found to be toxic to trisomy 8 cells in vitro, its potential in treating trisomy 8 myelodysplastic syndrome (MDS) was investigated in a pilot study. At the time of reporting, 5 patients had been treated for 4-16 weeks with regimens of 800 mg/m^2/day for 3 or 5 days. Both regimens were well tolerated, and a half-life of 1.3 h was measured, without signs of drug accumulation. Four patients had a rapid decline in the number of peripheral blasts and aneuploid cells after 4 weeks of therapy and 4 had increases in platelet and/or neutrophil counts. Patients displaying a biological response had trisomy 8 in their aneuploid clone before therapy, while a patient with monosomy 7 who was previously refractory to EPO became responsive to darbepoetin and a trisomy 8 patient became platelet transfusion-independent. The study is ongoing, with other regimens (1500 mg/m^2/day for 5 days and 1800 mg/m^2/day for 5 days every 2 weeks) to be evaluated (22). Phase I investigations of ON-1910Na in solid tumors and leukemia have also been conducted.

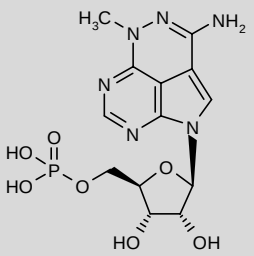
Preliminary findings from a phase I dose-escalation trial of VioQuest's **triciribine phosphate** (VQD-002) in patients with hematological malignancies supported further development and investigation of its combination with other agents. The agent is an inhibitor of protein kinase B (PKB, or AKT). Patients with relapsed or refractory leukemia received 1-h i.v. infusions on days 1, 8 and 15 of each 21-day cycle; 39 patients received doses of 15-65 mg/m^2. Concerns related to hepatic and metabolic toxicity led to assignation of 55 mg/m^2 as the maximum tolerated dose (MTD). Pharmacokinetic analyses showed dose-related accumulation of triciribine within leukemia blasts. Evidence of pharmacodynamic activity included decreased p-AKT levels within leukemic blasts. Reductions in peripheral blasts and improvements in platelet and neutrophil counts were also seen in some patients, although no complete or partial responses were observed. Accrual at the MTD is ongoing (23).



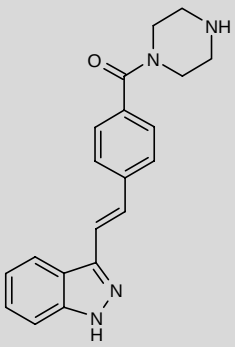
ON-1910Na

AC-220, a novel class III receptor tyrosine kinase inhibitor targeting FLT3, SCFR, CSF-1-R, ret and PDGF-R kinases, is being evaluated in an ongoing phase I clinical trial in patients with relapsed or refractory AML. In a dose-escalation 3+3 schedule, AC-220 was administered orally at 12-450 mg/day for 14 days, followed by 14 days of rest, on 28-day cycles. The primary endpoint of the study was safety and a preliminary analysis of 54 patients showed nausea and pyrexia as the most commonly reported treatment-emergent AEs (33%), following by fatigue (30%), diarrhea (28%) and peripheral edema (26%). One patient reported a grade 5 cardiac drug-related AE, three grade 3 anorexia, two grade 3 fatigue and one grade 3 vomiting and headache. Efficacy was measured according to RECIST criteria, showing 5 complete responses (CR), CR without full platelet (CRp) or neutrophil (CRi) recovery, and 11 partial responses for up to more than 41 weeks overall (median of 14 weeks) (24). AC-220 was found to be orally bioavailable, with long half-life and dose-proportional plasma levels. Furthermore, **AC-886**, a pharmacologically active metabolite of AC-220, was identified in patient plasma and urine. AC-220 and AC-886 presented similar potency and selectivity for inhibition of the phosphorylation of the FLT3-ITD mutant and the wild-type receptor (25).

Kyowa Hakko Kirin's multikinase inhibitor **KW-2449** has entered clinical development as an antileukemia agent, and presentations



Triciribine phosphate



KW-2449

detailed phase I clinical findings and the agent's potential for treating imatinib-resistant CML and Philadelphia-positive (Ph^+) ALL. A reduction in the activity of imatinib against TCC-Y/sr (Ph^+ ALL with *BCR/ABL* T315I) was not seen with KW-2449, which also showed potent growth-inhibitory activity (GI_{50} < 0.5 µmol/L) against IL-3-dependent cells transfected with *BCR/ABL* and *BCR/ABL* T315I, while imatinib did not inhibit the growth of *BCR/ABL* T315I cells. The effects of KW-2449 appeared to be due to modulation of the BCR/ABL signaling pathway at lower concentrations and inhibition of Aurora kinase at higher concentrations. In vivo, oral KW-2449 prolonged the survival of SCID mice inoculated with TCC-Y/sr leukemia, while imatinib had no effect. In another model, blast cells from CML-BC patients with the *BCR/ABL* T315I mutation were injected into NOG mice. Oral KW-2449 treatment decreased the peripheral copy number of *BCR/ABL* mRNA and $CD45^+$ blast cells in the bone marrow, while imatinib had limited activity (26). A phase I study was also undertaken in 37 patients with refractory/relapsed AML, ALL and MDS or resistant/intolerant CML. KW-2449 was well tolerated and safe at dose levels of 25-500 mg/day p.o., and although no responses were seen, transient decreases in peripheral blood and bone marrow blasts were observed. The study was terminated after sustained inhibition of p-STAT and p-FLT3 was not achieved at trough at the highest b.i.d. dose, and a phase I/II study of t.i.d. and q.i.d. dosing is planned (27).

Clinical studies of monoclonal antibodies reported at the meeting included the first-in-human study of the anti-CD23 monoclonal antibody **CSL-360** (CSL), which was administered in escalating doses to patients with AML who relapsed after at least 1 cycle of conventional chemotherapy. Doses of 0.1, 0.3, 1.0, 3.0 and 10 mg/kg were examined. At the time of reporting, 28 patients had received 200 i.v. infusions. CSL-360 was well tolerated and the MTD had not been identified; three serious AEs were possibly related to drug. Clinical observations included decreased marrow blasts in 6 of 20 patients with evaluable BMAT samples and decreased peripheral blasts in 5 of 26 patients. An allograft recipient with advanced, refractory disease achieved a sustained complete response. Pharmacokinetic analysis showed a linear clearance pattern, a long plasma half-life and a low volume of distribution. Biological effects included specific binding of CSL-360 to CD123 on AML blasts and leukemic stem cells. Sustained binding of CSL-360 was seen 1 week after the fourth dose in the two highest dose cohorts. Higher doses were also associated with prevention of IL-3-induced proliferation of blast cells ex vivo. Recruitment to the 10 mg/kg cohort was ongoing at the time of reporting, with a goal of 20 evaluable patients (28).

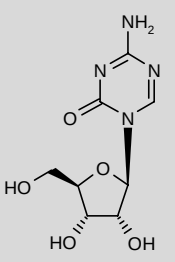
Early data from a phase I study of the anti-CS1 antibody **elotuzumab** (HuLuc6) in patients with relapsed/refractory MM were reported. Bristol-Myers Squibb recently entered into an agreement with PDL BioPharma for the development and commercialization of the agent, and phase I and I/II studies of elotuzumab in combination with other agents have been initiated. The data reported were for doses of 0.5-20 mg/kg administered every 2 weeks for four doses, with an additional four doses available to patients with at least stable disease during the initial course of therapy. Of 23 patients, 4 elotuzumab-related serious AEs occurred in 2 patients, but the MTD was not reached up to 10 mg/kg. Grade 1 and 2 AEs included chills, flushing, pyrexia, rigors, dyspnea and fatigue. The treatment also had an effect on a number of cytokines and chemokines in serum. Pharmacokinetic analyses revealed significant increases in C_{max} (to 291-384 µg/mL) and half-life (to 10-11 days) with higher doses compared to lower doses. After four doses, six patients had stable disease, four at doses of 5 mg/kg or greater. The 20 mg/kg dose cohort was still under evaluation at the time of reporting (29).

HA-22 is a high-affinity recombinant anti-CD22 immunotoxin being developed at MedImmune that has been evaluated in hairy cell leukemia (HCL) patients. Responses were seen at all HA-22 doses investigated: 5, 10, 20, 30 and 40 µg/kg given every other day for three doses. The study also includes patients with CLL, but investigation in these patients is at an earlier stage. Of 16 evaluable HCL patients, 6 had a CR and 6 had a partial response (PR). HA-22 peak plasma levels were inversely related to tumor burden and increased with repeated doses as patients responded. No dose-limiting toxicities were encountered in any cycle, although one patient had grade 2 hemolytic uremic syndrome (HUS); no grade 3 HUS occurred. In CLL patients, decreases in circulating CLL cells were seen. High levels of neutralizing antibodies were noted in 4 of 14 evaluable patients who received a total of 45 cycles, although the significance of the antibodies was not known. A phase I trial of HA-22 in pediatric ALL and non-Hodgkin's lymphoma (NHL) is ongoing, and phase I studies in adult NHL and CLL are to resume in 2009 (30).

Lastly, a dose of the DNA (cytosine-5)-methyltransferase inhibitor **azacitidine** (Vidaza®; Celgene, Pharmion) of 32 mg/m^2 was found to be safe in patients with AML or high-risk MDS who underwent allogeneic hematopoietic stem cell transplantation. Study subjects were not eligible for ablative regimens due to age or comorbidities. Azacitidine doses of 8, 16, 24 and 32 mg/m^2 were investigated, with administration for 5 days starting on day +42 for 1-4 28-day cycles. Of 80 patients transplanted, 44 were eligible to receive azacitidine, and 42 did so. The dose-limiting toxicity was thrombocytopenia, which prevented escalation from 32 mg/m^2 to 40 mg/m^2. After a median follow-up of 13 months, 12 patients had died: 8 from recurrence, 2 from graft versus host disease, 1 from pneumonia and 1 from unknown cause. Actuarial 1-year event-free and overall survival were 58% and 72%, respectively. A randomized, controlled study of azacitidine given for 1 year is planned and will compare the treatment to the best standard of care in high-risk AML/MDS patients (31).

Phase I/II

Incyte's JAK2 inhibitor **INCB-018424** demonstrated clinical efficacy in patients with myelofibrosis enrolled in a phase I/II study, and an analysis of INCB-018424-treated myelofibrosis patients revealed improved nutritional status. Oral doses of 10, 15, 25 and 50 mg b.i.d.



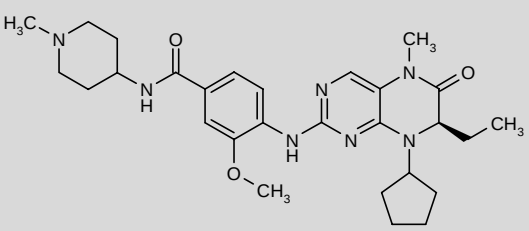
Azacitidine

and 35, 50, 100 and 200 mg once daily were evaluated in the phase I/II study, which included 134 patients with primary and post-polycythemia/essential thrombocythemia myelofibrosis. INCB-018424 was well tolerated over a median duration of therapy of approximately 7 months, with few AEs apart from mechanism-based effects on hematopoiesis. Reductions in platelet and hemoglobin counts were reversible with dose interruption and/or reduction, while clinical improvement was maintained. Clinical benefits included decreased splenomegaly, improvement in constitutional symptoms, reductions in inflammatory cytokines, improved body weight and improved overall daily activity (32). An analysis of 34 patients treated for at least 2 months with INCB-018424 25 mg b.i.d. revealed improvements in appetite, weight, hypocholesterolemia and leptin levels. Improvement in poor appetite and early satiety were noted with treatment, along with a reduction in splenomegaly. Patients progressively gained weight during treatment. Total cholesterol increased with INCB-018424 (from a median of 95 mg/dL to a median 145 mg/dL), as did plasma leptin levels (176% on average after 1 month), both of which were low at enrollment. Leptin levels were increased to the normal range (33).

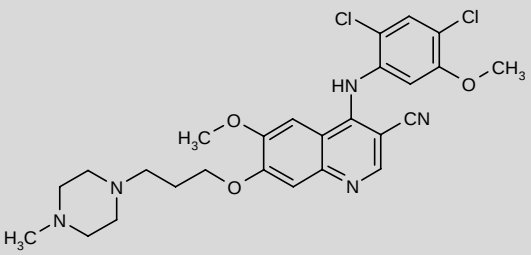
Preliminary data from two studies in which patients with CML and ALL received daily oral doses of 500 mg of the Src/ABL kinase inhibitor **bosutinib** (SKI-606; Wyeth) showed the agent to be effective in patients refractory to or intolerant of imatinib. One study included 101 patients with Ph^+ accelerated-phase and blast-phase CML and Ph^+ ALL. Among evaluable patients with no exposure to tyrosine kinase inhibitors other than imatinib, a complete hematological response was achieved by 48%, a major cytogenic response was achieved by 73% and a major molecular response was achieved by 36%. These response rates were 20%, 30% and 5%, respectively, in evaluable patients exposed to other tyrosine kinase inhibitors in addition to imatinib. Bosutinib was generally well tolerated, gastrointestinal events being the most common AEs and 11 patients permanently discontinuing treatment due to AEs (34). The phase I portion of another study identified a daily dose of 500 mg as potentially effective. Preliminary data from the phase II portion of the study in 283 patients with chronic-phase Ph^+ CML who failed imatinib therapy were presented. Among evaluable imatinib-resistant patients, 79% had a complete hematological response, while 40% had a major cytogenetic response and 33% achieved a major molecular response. Among evaluable imatinib-intolerant patients, these response rates were 76%, 59% and 28%, respectively. The treatment was generally well tolerated, gastrointestinal events again being the most common AEs and 37 patients permanently discontinued treatment due to AEs (35). Bosutinib is in phase III clinical evaluation for CML and is also being developed for breast cancer and solid tumors.

The PLK-1 inhibitor **BI-2536** (Boehringer Ingelheim) is being evaluated in a phase I/II study in patients aged 60 years or older with relapsed or refractory AML, and preliminary results were presented at the meeting. Three schedules were initially being studied, with i.v. infusions given on day 1 (schedule A), on days 1, 2 and 3 (schedule B) or on days 1 and 8 (schedule C) on 3-week cycles; schedule B was discontinued as blast reduction was only transient. Doses were escalated in the phase I portion of the study. Data from 68 patients showed the MTD to be 350 mg for schedule A and 200 mg for schedule C. Dose-limiting toxicities included neutropenic fever, sepsis, pneumonia/sepsis, intracranial bleeding/hyphema, somnolence/coma and anal thrombosis. Reductions in peripheral blood blasts were seen but were transient in most patients. There were 2 CRs and 3 PRs, and 21 patients had temporarily stable blood values. Dose-dependent pharmacodynamic activity was observed. BI-2536 pharmacokinetics were similar to those seen in other studies (36). BI-2536 is undergoing phase II evaluation in a variety of cancers, including lung, prostate and pancreatic cancer.

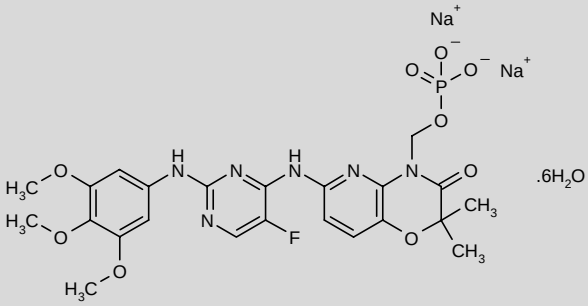
Clinical data on the oral tyrosine-protein kinase SYK inhibitor **fostamatinib disodium** (Rigel) were reported. A phase I/II study evaluated fostamatinib in patients with relapsed or refractory B-cell NHL. The phase I component included 13 patients treated with 200 or 250 mg b.i.d.; neutropenia was the dose-limiting toxicity and the 200-mg dose was chosen for phase II. Phase II included 68 patients with relapsed and heavily pretreated refractory lymphoma. Overall response rates were 22% in patients with diffuse large B-cell NHL, 10% in follicular NHL patients, 55% in CLL and 11% in patients with mantle cell lymphoma. The treatment was well tolerated overall, and more clinical trials of the agent are planned,as well as studies to



BI-2536



Bosutinib



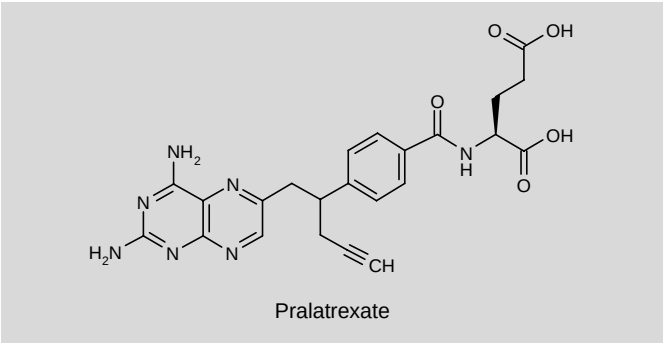
Fostamatinib disodium

identify tumors dependent on tonic B-cell receptor signaling, which is disrupted by SYK inhibition (37).

Results from an ongoing, multicenter, open-label phase I/II study of the humanized anti-CD74 monoclonal antibody **milatuzumab** (Immunomedics) in patients with MM indicated that the treatment is safe and effective. Doses of 1.5, 4.0 and 8.0 mg/kg i.v. have been administered to 21 patients; treatment is given twice weekly for 4 weeks. One case of dose-limiting toxicity occurred in the 1.5 and 4.0 mg/kg groups, along with three and two serious AEs, respectively. Neither dose-limiting toxicity nor serious AEs occurred in the highest dose group. Milatuzumab was rapidly cleared, but 4 patients had stable disease for at least 12 weeks posttreatment (with 4.0 and 8.0 mg/kg doses). No objective responses were seen, but dose escalation is continuing with recruitment to a 16.0 mg/kg dose group (38). Preclinical data indicating that milatuzumab could be used as a novel delivery antibody for targeted vaccination were also obtained from studies in which the binding efficiency, cytotoxicity and functional modulation of milatuzumab on human antigen-presenting cells (APCs) which normally express CD74 were explored. The agent bound efficiently to B cells, monocytes and different subsets of blood dendritic cells (DCs), with binding correlated with CD74 expression levels. Milatuzumab was cytotoxic against malignant B cells, but not against DCs or B cells and T cells in whole blood. Little effect on DC maturation and DC-mediated T-cell functions was noted with milatuzumab (39).

The anti-CD20 monoclonal antibody **afutuzumab** (GA-101; Biogen Idec, Genentech) was well tolerated and associated with responses in patients with CD20$^+$ NHL treated in an ongoing phase I/II study. The open-label, multicenter study evaluated dosing on days 1, 8 and 22 and then every 3 weeks for a total of 9 infusions; the first dose of 50-1600 mg was increased in the subsequent doses. Data from 21 patients showed afutuzumab to be well tolerated, with no dose-limiting toxicities and asthenia, nausea and fatigue being the most common AEs. Pharmacokinetic assessment indicated that the drug's profile was similar to that of rituximab. A half-life of approximately 7 days after the first infusion increased to 21 days with subsequent infusions. Best responses included four CRs and five PRs; stable disease was also noted in five patients (40). The activity of afutuzumab was also compared to that of rituximab in established RL human lymphoma xenografts in SCID beige mice. Afutuzumab demonstrated dose-related tumor growth inhibition, which was superior to that of rituximab. No toxic deaths or significant effects on body weight were seen with afutuzumab. The addition of cyclophosphamide increased the activity of both agents. Unlike afutuzumab, rituximab appeared to be dependent on CDC for its antitumor effect (41).

Presentations of agents with other mechanisms of action included two posters providing information on clinical trials of Allos Therapeutics' injectable dihydrofolate reductase (DHFR) inhibitor **pralatrexate** in patients with lymphoma. An open-label phase I/II study evaluated the combination of i.v. pralatrexate and gemcitabine in patients with relapsed/refractory lymphoma. A schedule wherein the agents were given every 2 weeks was found to be better tolerated than a weekly schedule. The MTD when the treatments were given every 2 weeks was pralatrexate 10 mg/m^2 with gemcitabine 300 mg/m^2 when gemcitabine was administered the day after pralatrexate. The MTD for this schedule when the agents were given

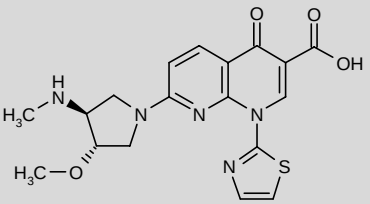


Pralatrexate

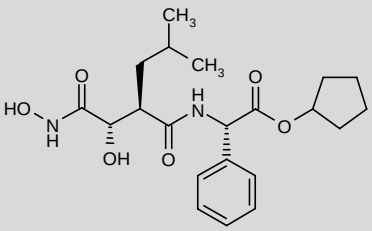
on the same day is still under investigation. There were 6 responses in 22 evaluable patients, including 4 of 6 patients with Hodgkin's lymphoma and 2 patients with diffuse large B-cell lymphoma (42). Preliminary results from a multicenter, dose-finding trial in patients with cutaneous T-cell lymphoma showed that treatment with pralatrexate plus folic acid and vitamin B_{12} supplementation was effective. Pralatrexate was administered on a 3 out of 4 week schedule or a 2 out of 3 week schedule, with doses of 10-30 mg/m^2. Of 22 evaluable patients, there were 11 PRs and 1 CR, for an overall response rate of 55%. The therapy was well tolerated. Mucosal inflammation, infection, fatigue and nausea were the most common AEs, and there was no grade 4 mucosal inflammation and no thrombocytopenia greater than grade 1. Determination of the optimal pralatrexate dose is ongoing (43).

A phase I/II study showed AEgera Therapeutics' **AEG-35156** to be effective when combined with idarubicin and cytarabine in patients with relapsed/refractory AML who had not responded to a single induction therapy or were in first relapse after a short initial CR, but not in those refractory to more than one prior induction treatment. The agent is an inhibitor of X-linked inhibitor of apoptosis protein (XIAP). In phase I, 24 patients received AEG-35156 12-250 mg/m^2 i.v. on days 1-3 followed by idarubicin 12 mg/m^2 on days 4-6 and cytarabine 1.5 g/m^2 on days 4-6 or 4-7, depending on age. In phase II, 32 patients received AEG-35156 350 mg/m^2. High levels of *XIAP* mRNA knockdown was detected in enriched AML blasts. Tolerability was good with the exception of two cases of peripheral neuropathy at the 350 mg/m^2 dose. The overall response rate in phase I was 4% and that in phase II was 47%. Only one response was seen in either phase among patients with induction failures to more than one regimen. A response was seen in 11 of 12 patients with frontline induction failures, however, and further evaluation in such patients appears warranted (44). A pharmacodynamic study in 13 patients treated at one of the centers involved in the trial also revealed a dose-dependent reduction in *XIAP* mRNA in circulating AML blasts, with the 350 mg/m^2 dose being particularly effective. Induction of apoptosis in circulating blasts was also noted, occurring preferentially in the CD34$^+$38$^-$ stem cell compartment. Of eight patients treated in the phase II portion, five achieved a CR, and all phase II patients with apoptosis induction in CD34$^+$38$^-$ cells achieved a CR (45).

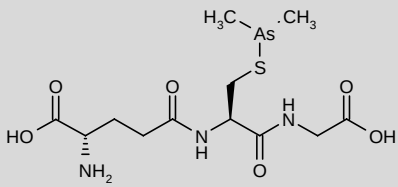
Signs of clinical activity were also seen in ongoing studies of **voreloxin** (SNS-595; Sunesis) in patients with AML. Voreloxin acts by site-specific intercalation of DNA and poisoning of topoisomerase II. In a phase I study, escalating i.v. doses of voreloxin are given on



Voreloxin



Tosedostat



Darinaparsin

days 1 and 4 with two schedules of cytarabine (schedule A: 400 mg/m^2/day by continuous i.v. infusion for 5 days; schedule B: 1 g/m^2 by daily bolus for 5 days). Starting doses of voreloxin were 10 mg/m^2 for schedule A and 70 mg/m^2 for schedule B. Data on 38 patients with relapsed/refractory disease were available. The MTD for schedule A was 80 mg/m^2, and there were nine CRs on this schedule. Treatment was generally well tolerated. Enrollment in a phase II portion of schedule A is under way. The first cohort of schedule B has been enrolled; dose expansion will depend on MTD determination (46). In the open-label phase II REVEAL-1 (Response Evaluation of Voreloxin in Elderly AML) trial in previously untreated elderly patients with AML, voreloxin 72 mg/m^2 was given weekly x 3 (schedule A) or weekly x 2 (schedule B). Remissions were achieved in 11 of 28 patients on schedule A, in which the 30-day all-cause mortality rate was 17%. Schedule B, implemented in the hope of reducing the duration of myelosuppression and improving tolerability over schedule A, had enrolled 21 patients at the time of reporting. Data on remissions were not yet available, although postinduction bone marrow ablations had been observed. Thirty-day all-cause mortality was 6%, and a decrease in morbidity and grade 3 or higher AEs were seen compared to schedule A. Patient enrollment is ongoing (47).

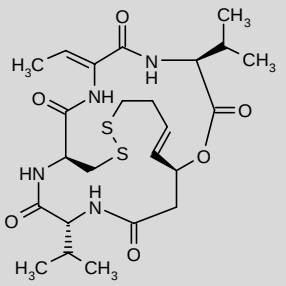
Phase II

The safety and activity of monotherapy with the chimeric humanized anti-CD40 monoclonal antibody **SGN-40** (Seattle Genetics, Genentech) seen in a phase II study in patients with diffuse large B-cell lymphoma have encouraged further evaluation of the agent in combination with other treatments in NHL. The study included 46 patients at 10 centers; 6 i.v. infusions were administered over 5 weeks, with 1 mg/kg given on day 1, 2 mg/kg given on day 4, 4 mg/kg given on day 8 and 8 mg/kg/week thereafter. Objective responses were achieved by 4 patients and lasted from 78 to > 271 days. Stable disease was noted in 10 patients. Also, approximately one-third of patients had reductions in tumor size. SGN-40 was generally well tolerated. Grade 3-4 AEs occurring in more than one patient and considered related to the study drug were fatigue (n = 2) and neutropenia (n = 2). CD40 expression, disease subtype and FcγRIIIa polymorphisms were not correlated with responses. Clinical responses are to be retrospectively correlated with a gene signature from pretreatment tumor tissue. Three trials of SGN-40-containing combination therapy are ongoing in NHL (48).

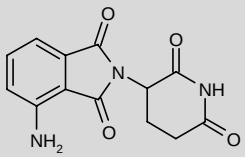
Blinatumomab (MT-103, MEDI-538; Micromet, MedImmune) is a single-chain bispecific antibody targeting the CD19 and CD3 antigens, which results in a nonrestricted cytotoxic T-cell response and activation. A preliminary analysis of a phase II clinical trial in four patients with B-cell precursor ALL has shown that minimal residual disease (MRD), a prognostic factor for drug resistance, can be eliminated after a single cycle of therapy with blinatumomab. Three patients treated with 15 mg/m^2/day i.v. for 4-week cycles and 2 weeks of rest between cycles had ongoing MRD negativity and one presented stable disease after the first cycle. In terms of safety, a grade 4 lymphopenia and grade 1/2 fever, hypokalemia, vomiting/nausea, edema and dyspnea were reported as the most commonly observed AEs (49). Another study of blinatumomab evaluated the response in patients with advanced NHL (N = 39 to date), showing 5 CR, 6 PR and 7 objective responses for up to 6 months, in contrast to 1 relapse after 14 months (50).

The inhibitor of aminopeptidases **tosedostat** (CHR-2797; Chroma Therapeutics; see monograph this issue) is expected to advance to pivotal studies in patients with AML based on encouraging phase II data. In an open-label phase II study in elderly and/or previously treated patients with AML (n = 38) or MDS (n = 3), once-daily oral treatment at the maximum acceptable dose (130 mg) was given for up to 84 days. Ten AML patients responded to treatment, 3 of whom achieved a CR and 7 a PR. Median overall survival was 130 days in the AML patients. Stable disease was maintained for over 6 months in two of the MDS patients. Tosedostat was well tolerated in elderly AML patients, with treatment interruptions for toxicity occurring only rarely. Once-daily oral dosing resulted in linear pharmacokinetics with good drug exposure. Suppression of platelets was seen with the agent and dosing interruptions may be required for patients to achieve complete remission (51). Tosedostat is also undergoing clinical evaluation in other types of cancer, including solid tumors and non-small cell lung cancer.

Preliminary data from a phase II trial indicate that the organic arsenic product **darinaparsin** (ZIO-101; Ziopharm Oncology; see monograph this issue) is a potential treatment for advanced lymphomas. The study is evaluating treatment at 300 mg/m^2 i.v. for 5 consecutive days every 28 days and 22 patients had been enrolled at the time of



Romidepsin



Pomalidomide

reporting. Efficacy evaluation included 13 patients who had received at least 2 cycles of darinaparsin. One CR and three PR were noted, all in patients who had been heavily pretreated. Two patients also achieved stable disease. Of 37 serious AEs recorded in 12 patients, 2 were considered drug-related (neutropenic fever, fall), and only 1 drug-related grade 3 AE was observed (wheezing). Patient enrollment is ongoing (52). Darinaparsin is also in phase II development for liver cancer, leukemia and MM and in phase I for solid tumors.

The results from studies of Gloucester Pharmaceuticals' histone deacetylase inhibitor **romidepsin** in peripheral T-cell lymphoma (PTCL) and cutaneous T-cell lymphoma (CTCL) were also presented at the congress. Both studies evaluated a regimen of romidepsin of 14 mg/m^2 by 4-h infusion given on days 1, 8 and 15 every 28 days. In 48 PTCL patients, the overall response rate was 31% and the mean duration of response was 9 months. Pharmacokinetic analysis revealed a half-life of 2.87 h and a C_{max} of 407.08 ng/mL. The safety profile was consistent with previous studies, with hematological effects, fatigue, nausea and anorexia being the most common drug-related AEs. A phase IIb study in patients with progressive or relapsed PTCL is ongoing at multiple centers (53). The CTCL study included 71 patients, 24 of whom responded (overall response rate = 34%). The median duration of response was 11 months. Responses were also observed at all stages of disease. An analysis of biomarkers indicated that 24-h acetylation of histone H3 correlates with response; global histone H3 acetylation at the 24-h time point was also correlated with exposure and clearance. Toxicity appeared to be manageable, with a dropout rate due to drug-related AEs of 11%. No significant effect on Q-T interval was seen with romidepsin administration (54). A registration trial of romidepsin for the treatment of PTCL is enrolling patients. The compound is also being evaluated in clinical studies for other oncological indications. The company has been granted orphan drug designation and fast track status from the FDA, as well as orphan drug status from the EMEA, for the treatment of CTCL and PTCL.

Finally, the combination of Celgene's **pomalidomide** (CC-4047; Actimid™), a TNF-α production inhibitor, and dexamethasone proved effective in the first phase II trial of the combination in patients with relapsed or refractory MM. The study included 60 patients who received pomalidomide 2 mg/day p.o. on days 1-28 of 28-day cycles, with dexamethasone 40 mg/day given on days 1, 8, 15 and 22. The treatment was associated with disease improvement or stabilization in 76% of patients, and 58% had an objective response, including one CR. The response rate among patients previously failing to respond to lenalidomide was 29%. Stable disease was noted in 18%. The treatment did not cause significant AEs in most patients; the most common major AEs were neutropenia (32%), thrombocytopenia (3%) and anemia (3%). The study is being expanded. Another phase II trial is evaluating pomalidomide with and without prednisone in 84 patients with advanced myelofibrosis with myeloid metaplasia. Results at the time of reporting included blood cell transfusion independence in 35% of patients treated with pomalidomide, and responses in 16 patients (55-57).

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