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MEETING REPORT

46TH ANNUAL MEETING OF THE AMERICAN SOCIETY OF CLINICAL ONCOLOGY (ASCO) 2010

LATEST DEVELOPMENTS IN CANCER CARE BY "ADVANCING QUALITY THROUGH INNOVATION"

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SUMMARY

"Advancing Quality through Innovation" was the theme of the 46th Annual Meeting of the American Society of Clinical Oncology (ASCO), held in Chicago on June 4-8, 2010. More than 30,000 members of the worldwide oncology community gathered in the windy city to discuss the most recent advances in cancer care, including novel treatments, products and services. Data from a number of first-in-human trials were disclosed at the meeting. A separate poster session on trials that are currently in progress was featured for the first time at ASCO in an effort to promote awareness and discussion among investigators regarding ongoing clinical studies and to encourage the recruitment of new investigators or the inclusion of new research sites.

INTRODUCTION

Since its foundation in 1964, the mission of the American Society of Clinical Oncology (ASCO) has been to improve cancer care and prevention by supporting the conduct of patient-oriented clinical research. The annual ASCO meeting attracts specialists within multidisciplinary approaches in the field of oncology in an attempt to facilitate the progression of cancer research at all levels of cancer care. This year's meeting was designed to promote the communication among oncology-related subspecialties by endorsing the exchange of a wide range of views regarding the latest innovations in research, quality, practice and technology in cancer therapy. Innovation-driven improvements in the quality of treatment modalities are expected to provide a novel means to combat the challenges posed by the complexity of cancer. This report will highlight the latest findings in clinical research, including the presentation of results from first-in-human trials and interim data from ongoing clinical studies. It will also present the identification of novel prognostic and diagnostic biomarkers that are expected to promote the treatment outcomes of patients with various cancer types.

FIRST-IN-HUMAN TRIALS

In the first clinical study of Centocor Ortho Biotech's **CNTO-888**, a fully human monoclonal antibody (mAb) targeting C-C motif chemokine 2 (MCP-1), patients with advanced solid tumors received 90-min infusions on days 1 and 29 and every 14 days afterwards, with 44 participants treated in ascending-dose cohorts (0.3, 1, 3, 10 and 15 mg/kg) and 23 subjects included in expanding-dose cohorts (10 and 15 mg/kg). Grade 1-2 adverse events were experienced by 15 patients, and 1 participant who had liver metastases had a grade 3 event (liver enzyme elevation). No dose-limiting toxicities (DLTs) occurred. The most common adverse events were nausea, vomiting, fatigue and headache, as well as skin and subcutaneous disorders. Pharmacokinetic data demonstrated a terminal half-life ($t_{1/2}$) of 4.4-6.9 days after the first dose, dose-proportional increases in exposure and minimum exposures associated with the doses of 10 and 15 mg/kg, which were above the concentration that exhibited activity in preclinical studies. Stable disease by Response Evaluation Criteria In Solid Tumors (RECIST) criteria was noted in four patients. In vivo tar-

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get binding was also observed. Phase II studies are planned in patients with ovarian and prostate cancer (1).

Preliminary results from 28 patients with advanced solid tumors enrolled in the first-in-human trial of **MNRP-1685A**, Genentech's mAb targeting neuropilin-1, were presented at ASCO. Escalating doses of MNRP-1685A (2-40 mg/kg) were administered i.v. on day 1 of 3-week cycles in an ascending-dose study. Nonlinear pharmacokinetics were noted across the dose range, which is consistent with the broad pattern of expression of neuropilin-1 in several tissues. Acute infusion reactions affected 17 subjects, but these were tolerable with dexamethasone premedication. A DLT of grade 3 upper gastrointestinal bleeding was seen with the dose of 20 mg/kg. Sustained elevation of placenta growth factor, a pharmacodynamic marker of antiangiogenesis, was observed with MNRP-1685A (2). A phase Ib study of MNRP-1685A in combination with bevacizumab with and without weekly paclitaxel is also being conducted in individuals with advanced solid tumors. The patients in arm A of the trial receive escalating doses of MNRP-1685A (7.5, 15, 24 and 36 mg/kg i.v.) followed by bevacizumab at 15 mg/kg i.v. on day 1 of 3-week cycles. In arm B, MNRP-1685A and bevacizumab 10 mg/kg are given on days 1 and 15 with paclitaxel 90 mg/m^2 i.v. on days 1, 8 and 15 of 4-week cycles. Administration of MNRP-1685A at doses of 12, 16 and 24 mg/kg is planned, along with one expansion cohort (3).

IMGN-388 (ImmunoGen), an immunoconjugate comprising the maytansinoid cell-killing agent DM4 attached via a covalent bond to an integrin-targeting mAb, displayed encouraging preliminary activity in a recent first-in-human study conducted in patients with solid tumors. The primary objective of this ascending-dose phase I trial was to assess the safety and pharmacokinetics of IMGN-388 administered as an i.v. infusion once every 3 weeks to 32 subjects with histologically confirmed metastatic or resectable solid tumors, including ovarian carcinoma and neuroendocrine carcinoma, as well as colorectal, prostate, breast, pancreatic and non-small cell lung cancer (NSCLC). Secondary objectives of the study included the evaluation of pharmacodynamics, immunogenicity and antitumor activity. Treatment with IMGN-388 was well tolerated up to a dose of 130 mg/m^2. The maximum tolerated dose (MTD) has not been reached and dose escalation is ongoing. Adverse events that were considered at least possibly related to IMGN-388 included grade 1-2 anorexia, nausea and vomiting. Grade 3 headache was the only DLT seen at a dose of 45 mg/m^2. Linear pharmacokinetics was observed at a dose range of 30-105 mg/m^2, with an elimination $t_{1/2}$ of approximately 28 h. Preliminary pharmacokinetic data suggest no evidence of humoral responses against the antibody or the DM4 component of IMGN-388. To date, stable disease as best response has been reported in six patients with NSCLC, uterine, breast, prostate and neuroendocrine cancer (n = 2, 1, 1, 1 and 1, respectively) following three or more treatment cycles (4, 5).

TAK-701 (Millennium Pharmaceuticals, Takeda Pharmaceutical), a humanized mAb that binds and neutralizes human hepatocyte growth factor, has demonstrated a good safety profile and promising preliminary antitumor activity in a first-in-human trial in patients with advanced nonhematological malignancies. Evaluation of the safety, including DLTs, and determination of the pharmacokinetics and MTD of TAK-701 were the primary objectives of an open-label, ascending-dose, multicenter phase I study, secondary objectives of which included the assessment of efficacy and pharmacodynamics, as well as the establishment of the recommended phase II dose. Patients (N = 22) received TAK-701 at doses of 2, 5, 10, 20 or 30 mg/kg (n = 3, 3, 3, 10 and 3, respectively) on 28-day treatment cycles (up to 12 cycles). Dose escalation was based on the incidence of DLTs during cycle 1 and followed a 3+3 design. Safety evaluation indicated that all 22 evaluable patients experienced ≥ 1 treatment-emergent adverse events (TEAEs) and 73% of subjects exhibited drug-related TEAEs, most commonly fatigue, constipation, cough, diarrhea and vomiting (41%, 27%, 27%, 23% and 23%, respectively). Grade 3-4 TEAEs included ileus, pleural effusion, dyspnea, muscular weakness, catheter-site pain, back pain, increased bilirubin, elevated γ-glutamyltransferase and urinary tract infection, among others. A biphasic pharmacokinetic profile was identified, with an initial disposition phase followed by a terminal disposition phase starting at approximately 72-168 h after infusion. The mean $t_{1/2}$ was similar across dose groups (238-297 h). Preliminary analysis of data from the cohorts receiving 2-20 mg/kg TAK-701 suggested dose-proportional pharmacokinetics. Neutralization of free serum hepatocyte growth factor was seen in pharmacodynamic assessments in five of seven evaluable subjects. Stable disease as best response was reported in 7 of 13 response-evaluable patients. The MTD has not been reached to date (6, 7).

Final data were disclosed from a first-in-human clinical study that aimed to evaluate the safety and tolerability of **TRC-093** (Micromet, TRACON Pharmaceuticals), a second-generation humanized IgG_1 mAb that targets cleaved collagen predominantly produced in the extracellular matrix of tumors, supporting further development of the product in combination with standard-of-care therapy in patients with solid tumors. TRC-093 was administered at doses of 0.5, 1.5, 5, 12 and 24 mg/kg i.v. on days 1 and 15 of each 28-day treatment cycle to 19 subjects with advanced or metastatic solid tumors refractory to standard treatment in a nonrandomized, open-label, dose-finding phase I trial. Treatment with the agent was well tolerated up to the highest dose (24 mg/kg), with no reports of DLT or treatment-related adverse events of > grade 2 in severity. Grade 2 toxicities included fatigue (n = 5) and anemia, anorexia/decreased appetite, arthralgia, joint stiffness and musculoskeletal stiffness (n = 1 subject for each). Pharmacokinetic profiling indicated linear, dose-dependent exposure, which is characteristic of an mAb. TRC-093 was not associated with the formation of human anti-human antibodies. Protein biomarker analysis revealed a reduction in the mean circulating levels of vascular endothelial growth factor (VEGF). Preliminary evidence of efficacy included stable disease for up to a period of 9 months; 26% of the participants exhibited stable disease lasting ≥ 2 months. The combination of TRC-093 with bevacizumab for the treatment of glioblastoma will be investigated in future phase Ib/II trials (8).

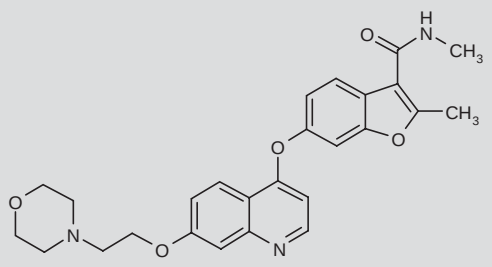
On the basis of its antiangiogenic properties and the ability to reduce tumor proliferation in preclinical studies, **CVX-060** (CovX, Pfizer), a fusion of two angiopoietin-2 (ANG-2)-binding peptides linked to CovX's proprietary humanized IgG_1 mAb, was evaluated for safety and pharmacokinetics in a first-in-human phase I trial. The ANG-2 gene (*ANGPT2*) is overexpressed in 57% of human cancers and its expression correlates with poor survival, increased microvessel density and metastasis. In stage 1 of the trial, patients with solid tumors received escalating doses of CVX-060 (0.3, 1, 3, 6, 12 or 15

mg/kg in cohorts of 3-6 subjects) given once weekly as an initial 90-min i.v. infusion, which was decreased to 30 min according to tolerability, on 4-week treatment cycles. The highest dose (15 mg/kg) was also administered to an additional 13 patients in stage 2 of the study. The primary objective of the first stage was to determine the safety and tolerability of CVX-060 in adults with advanced solid tumors and to identify/characterize treatment-related adverse events. The secondary outcome measures included serum pharmacokinetic analysis, determination of the recommended phase II dose, immunogenicity and preliminary efficacy. In stage 2, additional safety and pharmacokinetic profiling was performed, as well as investigation of biological activity. Complete data available from 30 of 34 participants suggested good tolerability for the treatment, with the most common adverse event being fatigue (23%). Proteinuria was seen in five subjects (one with grade 3 and four with grade 1-2) and grade 1 vaginal spotting was reported in two participants. The MTD was not identified. Pharmacokinetic analysis revealed dose-proportional increases in C_{max} and AUC, low volume of distribution (49.5 mL/kg) and moderate clearance (6.8 mL/kg/day). The elimination $t_{1/2}$ was estimated at approximately 5 days, which supported weekly dosing. Biological effects were observed in pharmacodynamic studies at all dose levels; these included dose-dependent increases in ANG-2 levels and significant reductions in K_{trans} in the 15 mg/kg cohort, as evaluated by dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI). Treatment response assessments performed using RECIST 1.0 criteria indicated prolonged stable disease (≥ 24 weeks) as best response in 46% of the subjects. The recommended phase II dose was established at 15 mg/kg based on safety, pharmacokinetic and pharmacodynamic data. Clinical evaluation of CVX-060 in combination with sunitinib is under way (9).

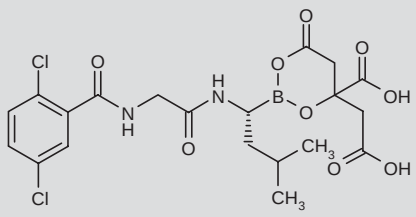
Pfizer's **PF-337210**, a highly potent and selective ATP-competitive inhibitor of vascular endothelial growth factor receptor 2 (VFGFR-2) tyrosine kinase, displayed promising dose- and schedule-related antitumor activity in a first-in-human trial in patients with advanced solid tumors. A dose-ascending phase I study was designed to assess the safety of PF-337210 (at doses of 0.67-9 mg/day, 4 mg b.i.d. and 6 mg b.i.d.) and to establish the recommended phase II dose of the agent in 46 subjects with advanced solid tumors refractory to standard therapy. The most frequently reported adverse events in all cohorts included hypertension (50%), fatigue (35%), proteinuria (20%), nausea (17%), anorexia (15%), diarrhea (13%) and bleeding (11%). None of the participants exhibited grade 4 or 5 treatment-related toxicities. The dose of 6 mg b.i.d. was described as well tolerated. Pharmacokinetic profiling revealed the occurrence of peak plasma concentrations at 1-5 h. The mean $t_{1/2}$ at all dose levels was estimated to be in the range of 4-14 h following single-dose administration. A significant reduction in tumor vascular permeability was seen in pharmacodynamic evaluation. Preliminary evidence of antitumor activity included two confirmed cases of a partial response in one subject with a neuroendocrine tumor metastatic to the liver and one patient with melanoma metastatic to the lung receiving doses of 4 and 6 mg b.i.d., respectively. Stable disease lasting four or more cycles was the best response in seven individuals receiving b.i.d. dosing. The b.i.d. schedule was associated with a greater decrease in tumor size than once-daily dosing; meaningful tumor growth control was reported in 64% and 22% of evaluable patients, respectively, in the b.i.d. and once-daily cohorts (10, 11).

Clinical data were also disclosed from the first-in-human evaluation of **MLN-9708**, a prodrug of the second-generation proteasome inhibitor MLN-2238, in patients with advanced nonhematological malignancies. MLN-9708 was administered i.v. on days 1, 4, 8 and 11 of a 21-day treatment cycle (up to a maximum of 12 cycles) to 23 patients with a diagnosis of a nonhematological malignancy (including melanoma, sarcoma, colorectal and renal cell carcinoma, as well as pancreatic, lung, thyroid and prostate cancer) for which there was no available standard treatment. Doses of 0.125, 0.25 and 0.5 mg/m^2 were given to one patient each in cycle 1; dose escalation proceeded in a standard 3+3 design based on the occurrence of DLTs in cycle 1 with doses of 1, 1.33, 1.76 and 2.34 mg/m^2 being administered to seven, four, six and three subjects, respectively. Five subjects experienced DLTs in the first treatment cycle; grade 3 rash was seen in the cohorts receiving 1 and 1.76 mg/m^2 MLN-9708 (n = 1/group), whereas grade 4 thrombocytopenia and grade 3 renal failure were reported in two and three subjects, respectively, treated with 2.34 mg/m^2 MLN-9708. The most frequent adverse events (≥ 20% of all patients at any grade) included fatigue, nausea, vomiting, diarrhea, anemia, anorexia, constipation, thrombocytopenia, abdominal pain, pyrexia and peripheral edema. The MTD was established as 1.76 mg/m^2. Preliminary pharmacokinetic/pharmacodynamic analysis revealed rapid disposition and rapid/sustained inhibition of the 20S proteasome subunit following multiple dosing. Efficacy data were not available at the time of the meeting. Subjects with NSCLC, head and neck cancer, soft tissue sarcoma and prostate cancer will be included in the expanded cohort to receive treatment with MLN-9708 at the MTD (12).

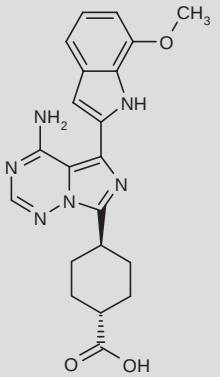
OSI-027 (OSI Pharmaceuticals) is a potent and selective inhibitor of mammalian target of rapamycin (mTOR) kinase that hinders the



PF-337210



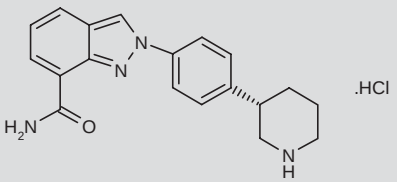
MLN-9708



OSI-027

kinase activity of both TORC-1 and TORC-2 signaling networks of mTOR. The agent was assessed in patients with advanced solid tumors or lymphoma in a first-in-human phase I trial. Escalating doses of OSI-027 on three dosing schedules (intermittent; on days 1-3 every 7 days, continuous; once daily or once weekly) have been administered to 43 patients to date. Subjects on the intermittent and once-weekly schedules received a starting dose of 10 mg/day (escalated up to 30 and 40 mg/day, respectively), whereas the starting dose on the once-daily regimen was 5 mg/day (highest dose level of 20 mg/day). The primary objective of the trial was to determine the MTD, defined as the highest dose level at which < 33% of patients experienced a DLT during the first cycle, and to establish the recommended phase II oral dose of the agent. Safety, pharmacokinetics, pharmacodynamics and preliminary antitumor activity constituted the secondary objectives of the study. Pharmacokinetic profiling of all schedules on day 1 revealed a median time to peak plasma concentration (t_{max}) of 2-6 h and a median $t_{1/2}$ of 4-17 h. The plasma concentration of the compound was found to exceed the predicted effective concentration (0.5 μM). Preliminary pharmacodynamic analysis showed marked reductions in 4E-BP1 phosphorylation in peripheral blood mononuclear cells (PBMCs) and indicated a more consistent mTOR inhibition at doses of ≥ 20 mg. However, there was no conclusive evidence of sustained inhibition of mTOR activity and additional data are required to establish a pharmacokinetic/pharmacodynamic relationship. At present, 27% of evaluable patients have remained on treatment for ≥ 12 weeks. Stable disease as best response has been reported in subjects with colorectal carcinoma, melanoma, chondrosarcoma and renal carcinoma. Good safety and tolerability were observed at up to a cumulative weekly dose of 175 mg. The most frequent adverse events were fatigue, nausea and anorexia. The MTD has not been established and dose escalation is currently ongoing (13).

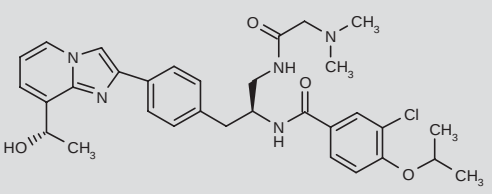
The potent and selective poly [ADP-ribose] polymerase (PARP) inhibitor **MK-4827** (Merck & Co.) was evaluated in a first-in-human clinical study in 39 patients with advanced breast cancer type 1 susceptibility protein (*BRCA*)-deficient and sporadic ovarian cancers associated with homologous recombination repair defects. Cohorts of 3-6 subjects received oral MK-4827 at escalating doses of 30, 40, 60, 80, 110, 150 and 210 mg/day on days 1-21 of a 28-day cycle, followed by continuous dosing after the first treatment cycle.



MK-4827

Antitumor activity was seen in both *BRCA*-deficient and sporadic cancers. Prolonged partial responses by RECIST, lasting for > 17, 22 and 44 weeks, were observed in 3 patients with serous ovarian cancer (1 subject with sporadic platinum-sensitive and 2 patients with *BRCA*-deficient ovarian cancers). Ongoing stable disease (> 42 weeks) was reported in one subject with heavily pretreated NSCLC. Treatment with the agent was well tolerated. Dose-limiting toxicities included grade 3 fatigue, reversible grade 3 pneumonitis and grade 3 anorexia (in the 30-, 60- and 210-mg dose groups, respectively; n = 1 subject in each group). Pharmacodynamic evaluation revealed consistent PARP inhibition in PBMCs at doses > 110 mg. Dose-proportional pharmacokinetics with a mean $t_{1/2}$ of 40 h were seen in preliminary assessments (14).

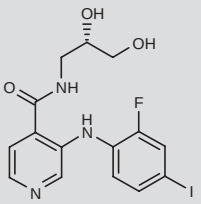
The small-molecule centromere-associated protein inhibitor **GSK-923295** (GlaxoSmithKline) has previously exhibited potent preclinical activity as an antimitotic agent, supporting its further clinical evaluation. A first-in-human phase I study was designed to investigate the safety and pharmacokinetics of GSK-923295 and to determine the MTD of the treatment in patients with advanced, relapsed or refractory solid tumors. A total of 39 subjects with pancreatic, colorectal, esophageal, hepatocellular, gastric, breast or non-small cell lung cancer (26%, 10%, 5%, 5%, 5%, 3% and 10%, respectively) received GSK-923295 by 1-h infusion at escalating doses of 10-250 mg/m^2 administered on days 1, 8 and 15 of a 28-day cycle. Therapy was continued until the occurrence of disease progression or toxicity. Dose-limiting toxicities included grade 3 aspartate aminotransferase (AST) elevation and grade 3 hypoxia seen in the 80 and 140 mg/m^2 dose groups, respectively (n = 1 of 7 subjects in each cohort), as well as grade 3 fatigue (n = 2) and grade 3 hypokalemia (n = 1) in patients receiving the 250 mg/m^2 dose. The MTD was established at 190 mg/m^2. The most commonly reported adverse event was fatigue (n = 21 of 37), which was mostly grade 1 and appeared to be related to dose. Grade 3 and 4 adverse events, each observed in one subject after the first treatment cycle, included grade 3 vomiting and total bilirubin (at doses of 105 and 250 mg/m^2, respectively) and grade 4 hyponatremia, AST and alanine aminotransferase (ALT) elevation at a dose of 140 mg/m^2. Pharmacokinetic profiling revealed dose-pro-



GSK-923295

portional increases in exposure with a $t_{1/2}$ of 9 h, and indicated no accumulation of the compound following weekly dosing. A moderate intersubject variability was reported (33%). Clinical activity was observed in one patient with urothelial cancer in the cohort receiving 250 mg/m^2 who exhibited a partial response by RECIST criteria. Stable disease lasting ≥ 3 months was reported in patients with hepatocellular (n = 1), colorectal (n = 1), pancreatic (n = 2), prostate (n = 1) and ovarian (n = 1) cancer at doses of 20, 80, 80, 140 and 190 mg/m^2, respectively (15).

Results from the first-in-human clinical evaluation of **MSC-1936369B** (AS-703026; Merck Serono), a potent and highly selective noncompetitive inhibitor of MAP kinase kinase (MEK 1/2), in patients with advanced solid tumors were also presented at this year's ASCO meeting. The primary objective of an open-label, 3+3 design phase I study conducted in patients with solid tumors was to determine the MTD of two distinct dosing schedules of MSC-1936369B administered orally once daily (schedule 1: days 1-5, 8-12 and 15-19; schedule 2: days 1-15 of 21-day cycles) following a fasting period of at least 2 h. Accelerated modified Fibonacci dose escalation was applied to each dosing schedule. Phosphorylated extracellular signal-regulated kinase (pERK) was measured in PBMCs before and after administration. Secondary outcome measures included preliminary safety, pharmacokinetics, biological activity and pharmacodynamic markers, as well as antitumor activity. Patients with solid tumors (n = 43 and 42, respectively, on schedules 1 and 2) received MSC-1936369B at dose ranges of 1-120 mg/day (schedule 1) and 1-195 mg/day (schedule 2). The most common tumor types were melanoma and colorectal carcinoma. Other types included breast, esophagus, gallbladder, head and neck, lung, mesothelioma, ovary, pancreas, renal, sarcoma, thyroid and bladder cancer. The most frequently reported grade 1-2 adverse events were skin rash, diarrhea, asthenia, nausea, visual disturbances, vomiting, peripheral edema, anemia, constipation, anorexia and pyrexia, seen in ≥ 15% of subjects with at least one dosing schedule. Dose-limiting toxicities were reported at doses of 28 and 120 mg/day (grade 3 liver function test elevation and grade 2 retinal vein occlusion, respectively) with schedule 1, but none were reported with schedule 2 up to a dose of 195 mg/day. Dose escalation is ongoing on this schedule. Preliminary pharmacokinetic analysis revealed dose-proportional increases in C_{max} and AUC. The median t_{max} and median terminal elimination $t_{1/2}$ were estimated at 1 and 5.1 h, respectively. Almost complete (≥ 80%) and sustained (> 8 h) inhibition of pERK was reported in PBMCs at 2 h after administration of MSC-1936369B at doses of ≥ 28 mg/day. Antitumor activity was observed in two previously treated melanoma subjects who exhibited confirmed partial responses at doses of 68 and 94 mg/day. The MTD has not been established (16).

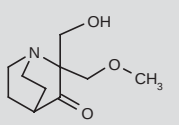


MSC-1936369B

APR-246 (Aprea, Karolinska Institutet), a member of a new class of small molecules with anticancer properties that acts by promoting the correct folding of nonfunctional cellular tumor antigen p53 and thus restoring its activity, is currently being evaluated in clinical settings as a potential new treatment strategy for patients who are resistant to conventional chemotherapy. An ongoing, open-label, noncomparative, dose-escalating, first-in-human phase I/II trial has been designed to determine the highest feasible dose of APR-246 administered on 4 consecutive days of a 21-day treatment cycle as a 2-h daily i.v. infusion in patients with refractory malignancies (including acute myeloid leukemia [AML], non-Hodgkin's lymphoma [NHL], chronic lymphocytic leukemia [CLL] and multiple myeloma) or prostate carcinoma (primary objective). The study is also aiming to evaluate the safety, pharmacokinetics and antitumor effects of the treatment. Doses of 2, 3, 10, 30, 60, 90, 110 and 130 mg/kg will be administered to three patients in each dose group. The maximum allowed plasma concentration has been established at 110 µg/mL. Following determination of the highest feasible dose, the trial will be extended to explore the pharmacokinetic profile of APR-246 in nine patients with AML (homogeneous population). A proof-of-concept phase II study has also been planned, which will assess APR-246 in combination with standard-of-care induction and up to three chemotherapy consolidation courses in elderly patients (aged ≥ 60 years) with AML and previous remission lasting ≥ 6 months. The overall response rate, defined as complete response/complete response with incomplete platelet recovery, will be the primary objective of this open-label, randomized, controlled trial (17).

PHASE I TRIALS

Encouraging interim data from an ongoing clinical trial on **PF-03446962** (Pfizer), an mAb that targets activin receptor-like kinase 1 (ALK-1), for the treatment of subjects with solid tumors were presented. The primary objective of this multicenter, multinational, dose-escalation phase I study is to determine the MTD and establish the recommended phase II dose of PF-03446962. Secondary objectives include the evaluation of safety, efficacy, pharmacokinetics and pharmacodynamics. To date, 31 evaluable patients with histologically or cytologically confirmed advanced/metastatic refractory solid tumors have been enrolled in the study and have received treatment with PF-03446962 at doses of 0.5, 1, 2, 3, 4.5 and 6.75 mg/kg (n = 5, 5, 6, 3, 4 and 8 subjects, respectively). PF-03446962 has been described as well tolerated, with fatigue, thrombocytopenia, rash/telangiectasia and nausea identified as the most frequent (> 10%) treatment-related adverse events. Pharmacokinetic profiling following a 1-h infusion of PF-03446962 revealed that the dose of 6.75 mg/kg was associated with drug concentrations that remained above the estimated therapeutic level (11 µg/mL) for a period of more than 3 weeks, with C_{max} and AUC values that were markedly below the toxicity levels calculated at the no-observable-

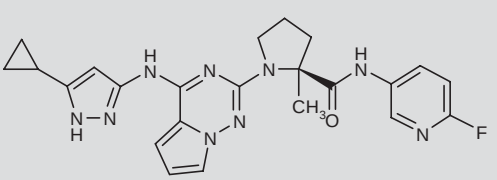


APR-246

adverse-effect-level (NOAEL) in monkeys. The mean $t_{1/2}$ was estimated at 14 and 11 days, respectively, in the 6.75 and 4.5 mg/kg dose cohorts. In clinical activity assessments, a partial response lasting for nine treatment cycles was seen in one patient with hepatocellular carcinoma, whereas stable disease (for 6 months) was observed in one subject with colorectal cancer. The study supports the development of PF-3446962 as a novel antiangiogenic strategy that may be applied in combination with agents targeting VEGF and/or VEGF tyrosine receptor kinase inhibitors or chemotherapy (18, 19).

Preliminary data from an ongoing clinical study of **BMS-754807** (Bristol-Myers Squibb), an orally bioavailable, potent and reversible dual inhibitor of human insulin-like growth factor 1 receptor (IGF-I receptor) and insulin receptor (IR) kinases, in patients with advanced or metastatic solid tumors were disclosed. The primary objective of this open-label, multiple-ascending-dose phase I trial was to determine the MTD and establish the recommended phase II dose of BMS-754807 administered orally on a once-daily schedule at doses of 4, 10, 20, 30, 50, 70 and 100 mg. A total of 23 patients have been treated to date. Assessments of safety, tolerability, pharmacokinetics, pharmacodynamics and antitumor activity were among the study's secondary objectives. The most commonly reported adverse events seen in > 10% of patients included diarrhea, constipation, nausea, vomiting, abdominal pain and fatigue. Manageable and reversible hyperglycemia and hypoglycemia were the most frequent metabolic adverse events (n = 5 and 3, respectively). There were no DLTs and dose escalation has progressed to > 100 mg. No objective tumor responses have been observed in 19 evaluable subjects. Stable disease lasting > 100 days has been reported in 8 patients. Pharmacokinetic analysis revealed dose-related increases in the exposure to BMS-754807, which exceeded the preclinical minimum effective exposures established in the Rh41 xenograft model. Pharmacodynamic evaluation showed decreased tumor glucose uptake by fluorodeoxyglucose (FDG)-positron emission tomography (PET) in patients with higher BMS-754807 exposure and higher serum insulin levels. Data obtained from fluoro-L-thymidine (FLT)-PET imaging suggest antiproliferative effects for BMS-754807 treatment. The MTD has not been reached and accrual is ongoing (20). BMS-754807 is currently under clinical evaluation as a single agent (21, 22) or in combination with carboplatin plus paclitaxel, trastuzumab and cetuximab (23-25).

Regorafenib (BAY-73-4506; Bayer Schering Pharma), an oral multikinase inhibitor of angiogenic, stromal and oncogenic receptor tyrosine kinases, was reported to be well tolerated in patients with advanced refractory NSCLC in an ongoing phase I study. This nonrandomized, single-agent study was conducted in 23 adult patients with histologically or cytologically confirmed advanced NSCLC with



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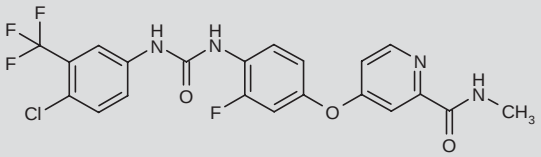


Regorafenib

documented progressive disease. Subjects received continuous oral treatment with regorafenib as 100- or 120-mg tablets (n = 22 and 1, respectively) on repeated 21-day cycles. Interim data from this trial indicated a good safety profile, with the most commonly reported adverse events being grade 1-3 hand–foot skin reaction, grade 1 extremity (limb) pain, grade 1-2 rash/desquamation and hypothyroidism, and grade 1 nausea. Efficacy analysis according to RECIST performed in 18 evaluable patients at the end of cycle 2 revealed promising clinical activity, with a disease control rate (stable disease) of 83%. The median progression-free survival was estimated to be 84 days. Pharmacokinetic profiling indicated accumulated exposure to approximately two to three times between single dose and steady state. Similar pharmacokinetics were observed between patients with NSCLC and those with other tumor types. These results support further evaluation of regorafenib in NSCLC (26).

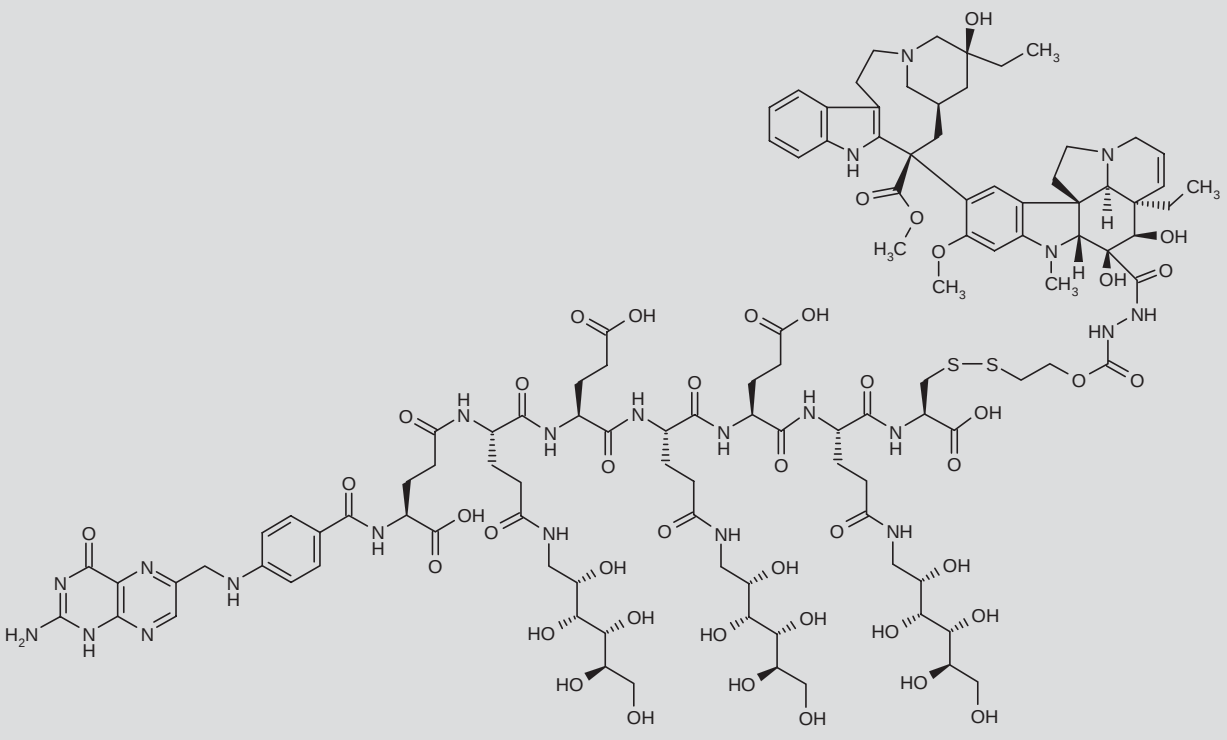
Preliminary results from a phase I trial designed to evaluate the safety and tolerability and investigate the pharmacokinetic, pharmacodynamic and antitumor activity of the histone deacetylase inhibitor **CHR-3996** (Chroma Therapeutics) in patients with advanced solid tumors were disclosed. In an open-label, dose-escalation, nonrandomized study, a total of 27 patients with advanced or metastatic solid tumors, including upper gastrointestinal tract tumors, colon, rectal, pancreas and prostate cancers, as well as melanoma, received oral CHR-3996 at doses of 5, 10, 20, 40, 80, 120 or 160 mg on 28-day treatment cycles. Safety analysis identified fatigue, nausea and vomiting as the most frequent drug-related adverse events. Pharmacokinetic data suggested dose-proportional increases in C_{max} and $AUC_{0\text{-}t}$ over the evaluated dose range (except at the 80-mg dose). The t_{max} was estimated to be in the range of 20 min to 4 h post-administration (median t_{max} = 1.5 h), with $t_{1/2}$ calculated in the range of 1-11 h (median $t_{1/2}$ = 2.6 h). Pharmacodynamic evaluation revealed significant increases in the acetylation of histone H3 lysine 9 and 14 between day 1 predose and day 1 postdose at doses of 10, 20, 40 and 160 mg. Preliminary efficacy analysis indicated no objective responses to date. Stable disease for at least 2 cycles was observed in 8 patients (31%), including 1 patient with cholangiocarcinoma who exhibited stable disease lasting for 10 months. The MTD has not yet been determined; however, it is not expected to exceed 160 mg, as two cases of DLT (grade 4 thrombocytopenia) were seen at this dose level (27, 28).

NKTR-105 (Nektar Therapeutics), a novel PEGylated sustained-release formulation of docetaxel engineered to enhance the safety, efficacy and tolerability of marketed docetaxel, is currently under evaluation for the treatment of patients with refractory solid tumors in an ongoing phase I trial. The primary objective of this open-label, ascending-dose trial is to evaluate the safety and establish the MTD of NKTR-105 in adults (aged ≥ 18 years) with histologically con-

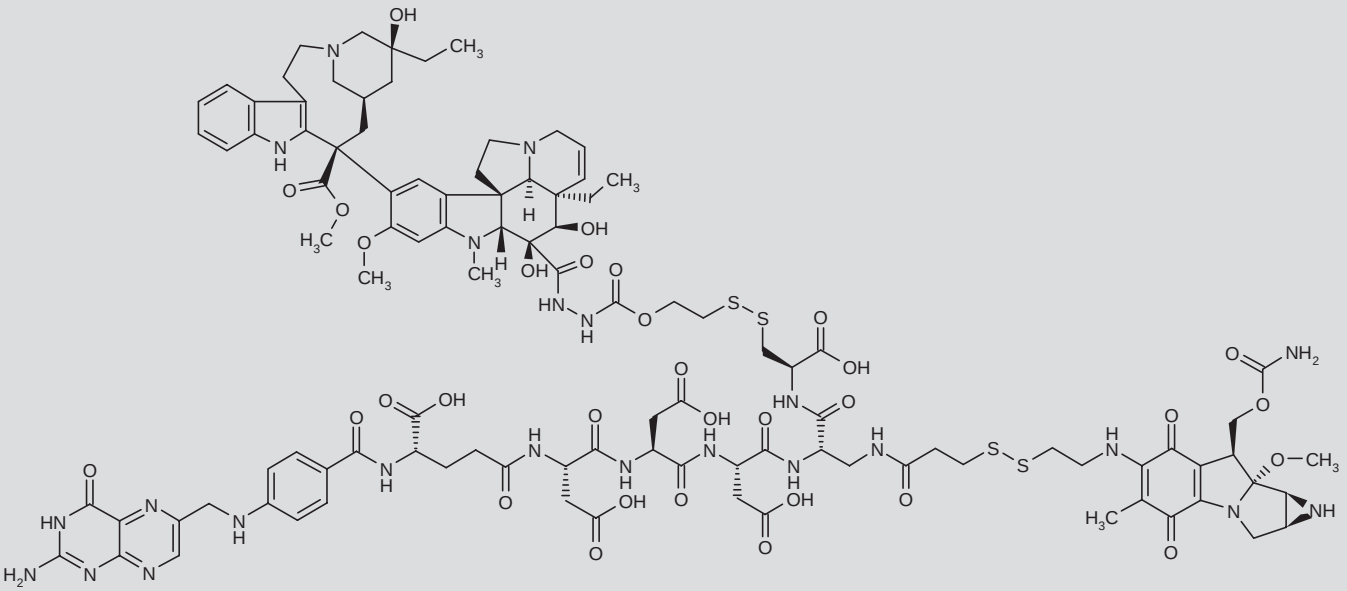
firmed, evaluable or measurable metastatic or resectable solid tumors for which there is no available standard curative or palliative therapy. The study will also investigate the plasma pharmacokinetic profile of the agent and its metabolite docetaxel (secondary objective). Cohorts of 3-6 subjects will receive a single dose of NKTR-105 given as a 1-h i.v. infusion once every 21 days. Dose escalation will proceed in a sequential 3+3 design with 15-100% escalation increments based on the severity and duration of toxicity. The study has enrolled 17 patients to date. Treatment will continue until the incidence of progressive disease and/or unacceptable toxicity (29).

In a recent phase I clinical study performed by researchers at Cornell University, **177Lu-J591**, a lutetium-177-labeled humanized mAb (J591) that targets prostate-specific membrane antigen, was described as well tolerated and exhibited reversible myelosuppression in subjects with progressive metastatic castration-resistant prostate cancer (CRPC). A total of 28 patients with CRPC who had progressed on 1-4 lines of hormonal therapy received treatment with 2 fractionated doses of 177Lu-J591 administered 2 weeks apart. Cumulative doses of 40, 50, 60, 70, 80 and 90 mCi/m^2 were given to cohorts 1-6, with each cohort comprising three to six subjects. The study's primary objective was to determine the DLT and establish the cumulative MTD. Efficacy was the secondary endpoint of the trial. Infusion reactions, all of which were transient and reversible, were seen in 36% of the participants across all groups. Thrombocytopenia and neutropenia (but not febrile neutropenia) of all grades were frequently reported (> 10%). No DLT was observed in patients receiving cumulative doses of 40-80 mCi/m^2. Asymptomatic grade 4 neutropenia lasting > 7 days was recorded in two individuals in the 90 mCi/m^2 cohort. The MTD was established at two doses of 40 mCi/m^2 (cumulative dose of 80 mCi/m^2). Efficacy data revealed reductions of 46% in prostate-specific antigen (PSA) levels in all evaluable patients; a 58% decrease in PSA was seen in combined data from cohorts 5 and 6. The estimated completion date of this study is April 2011. The combination of 177Lu-J591 with docetaxel will be assessed in a phase I trial, which is currently enrolling participants (30, 31).

Interim phase I data were recently made available from the clinical evaluation of Endocyte's folate receptor (FR)-targeted therapies **EC-0489**, a conjugate of folic acid and desacetyl vinblastine hydrazide, and the DNA-alkylating product **EC-0225**, a two-drug conjugate comprising folic acid coupled to the cytotoxic agents mitomycin C and desacetyl vinblastine hydrazide, for the treatment of solid tumors. In a multicenter, open-label, escalating-dose trial, patients with refractory or metastatic cancer for whom standard therapeutic options had been exhausted received EC-0489 as a bolus injection at doses of 1, 2.5, 4.2 or 5 mg/m^2 on days 1, 3, 5, 15, 17 and 19 of a 28-day treatment cycle in part A of the trial. Part B involved the administration of the agent on days 1, 8, 15 and 22 of a 4-week cycle. The study's primary objective was to establish the MTD, which would also be the recommended dose for phase II. Characterization of the toxicity profile and antitumor activity, as well as the collection of pilot data to identify patients with FR-expressing tumors, constituted secondary objectives. Preliminary data obtained from 14 subjects in part A indicated relatively good tolerability at doses of ≤ 2.5



EC-0489



EC-0225

mg/m^2, with 2.5 mg/m^2 identified as the MTD. Preliminary pharmacokinetic analysis revealed a biphasic elimination of the compound from circulation, with a $t_{1/2}$ of 19 min. Linear increases in C_{max} and AUC were observed and there was no free desacetyl vinblastine hydrazide in the serum. In part A of the trial, stable disease as best response was reported in patients with ovarian, peritoneal, breast, thymus and lung cancer. The feasibility of treatment with a single weekly dose of 2.5 mg/m^2 EC-0489 is currently being explored in part B of the study (32). EC-0225 was administered to 66 patients with refractory or metastatic cancer at flat doses of 0.38, 0.8, 1.1, 1.5, 2.3, 3.1 and 3.9 mg or at 2.3 and 2.88 mg/m^2 on days 1, 3, 5 (week 1) and 8, 10, 12 (week 2) of a 28-day cycle. In the final cohort, patients received EC-0225 on days 1, 3, 5, 15, 17 and 19 of a 28-day treatment schedule. EC-0225 was described as generally well tolerated. The most frequently reported adverse events included anemia, constipation, leukopenia and fatigue (29.5%, 19.7%, 16.4% and 14.8%, respectively). No pulmonary toxicities related to mitomycin C were observed in this study. The MTD was established at 2.3 mg/m^2. Long-term (> 4-month) stable disease was seen in EC-0225-treated individuals with colorectal, ovarian or prostate cancer or cholangiocarcinoma (33).

Based on promising preclinical activity in a wide range of cancer types, a phase I study is under way to evaluate **QBI-139** (Evade™; Quintessence Biosciences), a variant of human pancreatic ribonuclease 1 that is engineered to evade the native ribonuclease inhibitor. An open-label, escalating-dose phase I trial has been designed to assess the agent's safety and tolerability and determine its MTD in patients with advanced refractory solid tumors (primary outcome measures). The study's secondary endpoints include evaluation of the response rate to QBI-139 using the RECIST criteria and pharmacokinetic profiling of the agent. The trial is expected to recruit 30 participants who will receive QBI-139 (in cohorts of 3-6 patients) by i.v. infusion once weekly for 3 weeks on 21-day treatment cycles until disease progression or unacceptable toxicity is reported (34).

The Aurora B kinase-inhibitory activity of Boehringer Ingelheim's **BI-811283** has been evaluated in a phase I ascending-dose study in patients with advanced, nonresectable and/or metastatic solid tumors. The participants received treatment with 13.5-300 mg of BI-811283 as a 24-h continuous infusion once every 3 weeks. In 58 subjects, DLTs included grade 3 fatigue, neutropenia and febrile neutropenia, with the MTD being 230 mg and the recommended dose being 180 mg. The most common drug-related clinical adverse events (> 10%) were fatigue, alopecia, nausea, diarrhea and decreased appetite. Neutropenia affected 44.8% of patients, whereas leukopenia and thrombocytopenia were experienced by 39.7% and 5.2% of subjects, respectively. Pharmacokinetic analysis showed similar exposure after the first and second doses, dose-linear exposure and a $t_{1/2}$ of 10-20 h. The best overall response was stable disease lasting at least 6 weeks in 19 of 52 (36%) participants; 4 had stable disease lasting at least 6 months. Evidence of reduced histone H3 phosphorylation was seen at higher dose levels in skin biopsies (35, 36).

The CD40-targeting human mAb **CP-870893** (Pfizer), which activates antigen-presenting cells, thus triggering the release of inflammatory cytokines and enhancing antitumor cellular immunity, was recently evaluated in combination with gemcitabine in patients with pancreatic cancer. In an open-label, multiple-ascending-dose phase I trial, adults with surgically incurable pancreatic cancer (Eastern Cooperative Oncology Group [ECOG] performance status of 0-1 and adequate bone marrow, hepatic and renal function) who had not been treated with chemotherapy received gemcitabine (1000 mg/m^2 i.v.) on days 1, 8 and 15 of a 28-day treatment cycle in combination with CP-870893 (0.1-0.2 mg/kg i.v.) given on day 3 of each

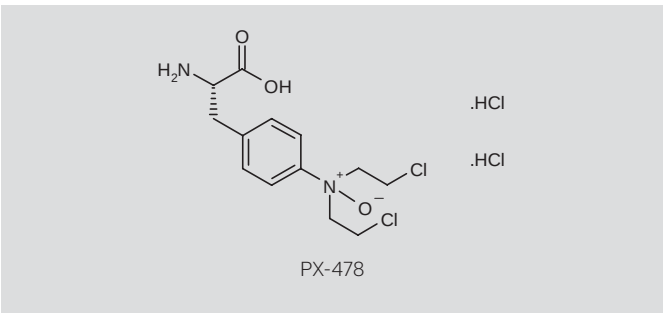
cycle. Treatment with the combination regimen was described as well tolerated. Mild to moderate cytokine release syndrome was the most frequent adverse event reported across all cohorts (20.91%) and stroke was the only DLT. The MTD of CP-870893 was established at 0.2 mg/kg, which was also selected as the recommended phase II dose. A partial response was seen in 14% of subjects, while 52% of patients exhibited stable disease as best response. At the end of the second cycle, reductions in primary pancreatic and representative metastatic lesions were observed as decreases in maximal standard uptake value in FDG-PET in seven of eight evaluable patients. Rapid increases in the levels of circulating interleukin-6 (IL-6) and interleukin-10 (IL-10) were noted in several subjects following treatment, which suggested activation of the immune response in these subjects. Based on these findings, additional evaluation of CP-870893/gemcitabine combination therapy is warranted (37, 38).

MDX-1097 (Immune System Therapeutics), a chimeric IgG mAb raised against kappa myeloma antigen, which is expressed on the surface of multiple myeloma cell lines and in malignant plasma cells isolated from patients with multiple myeloma and Waldenström's macroglobulinemia, was reported to be safe in a recent clinical study. The primary objective of the single-ascending-dose phase I trial was to evaluate the safety and efficacy and determine the MTD of MDX-1097 in subjects with multiple myeloma who had previously received at least one line of standard therapy and had achieved at least a minimal response or exhibited stable measurable disease. The study was completed by 12 participants, each treated with a single i.v. infusion of MDX-1097 (0.3, 1, 3 or 10 mg/kg; n = 3/dose group) administered over 90 min on day 1. Subjects were subsequently followed until day 45 after administration. Efficacy and pharmacodynamics were assessed by measurements of serum M-protein, serum kappa and lambda free light chain (FLC), total immunoglobulins, β_2-microglobulin, C-reactive protein, exploratory biomarkers, as well as antibodies against MDX-1097. Safety was assessed by vital signs, 12-lead ECG, ECOG performance and clinical laboratory parameters. Detectable plasma levels of MDX-1097 were reported starting after 1 h up to at least day 14 in all patients at all four dose levels; a subproportional increase in the peak level of MDX-1097 was seen with increasing doses. The terminal elimination $t_{1/2}$ was found to decrease from a mean value of 10 days at 0.3 mg/kg to 5 days at 10 mg/kg. Increases in serum kappa FLC were observed within 24 h of infusion and lasted for at least 15 days in all subjects treated with MDX-1097. There were no treatment responders based on measurements of serum M-protein. However, a favorable metabolic response was noted in 1 subject at 30 days after MDX-1097 infusion by PET scan. The patient also reported a reduction in bone pain. The dose range tested was described as safe and well tolerated, with no DLTs being evident at doses up to 10 mg/kg. The MTD was not reached in this study. A repeated-dose phase II trial of MDX-1097 (10 mg/kg) administered weekly for 8 weeks in patients with kappa-restricted multiple myeloma has been planned (39).

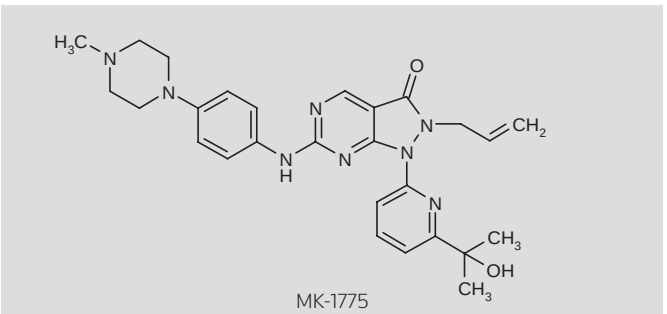
The activity of **CAT-8015** (HA-22; MedImmune), a second-generation immunotoxin comprising the Fv fragments of a CD22-directed mAb (RFB4) fused to the translocating and ADP-ribosylating domains of *Pseudomonas* exotoxin A (PE38), was assessed in a phase I clinical study performed in patients with hairy cell leukemia. Subjects with relapsed/refractory hairy cell leukemia (N = 28) who had previously received therapies including purine analogues and required treatment for cytopenia were given CAT-8015 as a 30-min i.v. infusion on days 1, 3 and 5 (daily x 3) at 28-day intervals for up to 10 treatment cycles. The agent was administered at doses of 5, 10, 20 or 30 µg/kg/day x 3 (n = 3 patients in each dose group), 40 or 50 µg/kg/day x 3 (n = 4 and 12, respectively). No DLTs were reported in the trial and the MTD has not been reached. Treatment-related toxicities, seen in 25-60% of all participants, included grade 1-2 hypoalbuminemia, edema, fever, ALT and AST elevations, as well as headache and nausea. The overall response rate was established at 82% across all dose cohorts. Based on these data, additional evaluation of the safety and efficacy of the treatment in hairy cell leukemia is warranted. Phase I evaluation of CAT-8015 at a dose range of 5-20 µg/kg/day x 3 in patients with CLL and NHL is currently under way (40, 41).

Promising clinical data on the hypoxia-inducible factor 1-α (HIF1-α) inhibitor **PX-478** (Oncothyreon), a novel agent derived from the oxidation of the nitrogen mustard moiety of melphalan, were obtained in a recent escalating-dose phase I trial conducted in individuals with advanced solid tumors. PX-478 was administered orally to 41 patients in 12 dosing cohorts at 1-88.2 mg/m^2 on days 1-5 of a 21-day treatment cycle. The agent was described as well tolerated up to a dose of 58.8 mg/m^2. The most commonly reported treatment-related adverse events included nausea, fatigue, diarrhea and vomiting (24%, 20%, 15% and 15%, respectively; all classified as grade 1-2). Pharmacokinetic profiling revealed low levels of the parent drug, with evidence of conversion to melphalan and other metabolites. Pharmacodynamic analysis suggested dose-proportional inhibition of HIF1-α. Antitumor activity was observed in 13 patients who exhibited stable disease as best response following treatment with a median of 4 cycles. The results support additional evaluation of HIF1-α inhibitors as potential antiangiogenic therapeutics (42, 43).

The safety, tolerability, pharmacokinetics and pharmacodynamics of Merck & Co.'s **MK-1775** (dose range of 25-1300 mg), administered as



PX-478



MK-1775

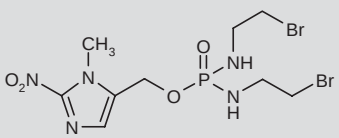
monotherapy or in combination with gemcitabine (1000 mg/m^2), cisplatin (75 mg/m^2) or carboplatin (AUC5), have been evaluated in 118 patients with advanced solid tumors in a multicenter, randomized, open-label, escalating-dose phase I trial. No DLTs were seen in the monotherapy part of the study at doses up to 1300 mg. On the combination regimen, three DLTs (grade 3 neutropenia, ALT/AST and thrombocytopenia) were observed at the 200-mg MK-1775 dose and two DLTs, namely grade 3 bilirubin and AST/ALT, were reported in the 325-mg MK-1775 dose group. Linear pharmacokinetics were observed in the MK-1775 dose range under evaluation. Preliminary pharmacodynamic analysis revealed 50% inhibition of phosphorylated cyclin-dependent kinase CDK1 following treatment with 100 mg MK-1775 for 48 h (44, 45).

Data from a phase I clinical trial on the anti-CD33 immunotoxin **HuM195/rGel** (Sloan-Kettering Institute for Cancer Research, Targa Therapeutics, The University of Texas M.D. Anderson Cancer Center) in patients with advanced myeloid malignancies were presented at ASCO. HuM195/rGel is an mAb generated by combining the humanized version of the murine M195 antibody (HuM195) with recombinant gelonin (rGel), an RNA glycosidase that inhibits protein synthesis. The target of HuM195/rGel, myeloid cell surface antigen CD33, is abundantly expressed on the surface of myeloid leukemia cells. The primary objective of the study was to assess the safety and toxicity of HuM195/rGel in subjects with refractory or relapsed advanced myeloid leukemias, refractory anemia with excess of blasts, refractory anemia with excess of blasts in transformation, chronic myelomonocytic leukemia (CMML) or chronic myeloid leukemia (CML) in accelerated phase or blast phase. Eligible patients had CD33 expression of ≥ 80%, as assessed by flow cytometry. Investigation of the pharmacokinetics and evaluation of the efficacy of the treatment were among the trial's secondary aims. A total of 28 patients with advanced myeloid leukemias, myelodysplastic syndromes and CMML (n = 23, 4 and 1, respectively) received HuM195/rGel at doses of 2.5, 3, 4.5, 7, 10 and 15 mg/m^2 administered as 1-h infusions twice weekly for 2 weeks followed by a 2-week observation period. The peak concentration of HuM195/rGel in the blood was 200-300 ng/mL, with a $t_{1/2}$ of approximately 20 h. Dose-limiting toxicity was seen in 2 of 22 evaluable subjects at a dose of 10 mg/m^2 (allergic reaction), which resulted in the identification of 7 mg/m^2 as the MTD. Antibodies against the rGel portion of the compound were developed by < 10% of the participants. Safety analysis revealed no grade 4 toxicities. The most commonly reported adverse events included fever, headache and rigors. Four participants exhibited an increased platelet count (> 100 x 10^9/L) and four individuals displayed elevated neutrophil levels (> 1 x 10^9/L). Although no complete or partial responses were reported, some patients experienced an improvement in tumor load, which supports additional evaluation of the treatment in combination with other chemotherapeutic agents (46, 47).

SCH-900105 (AV-299; AVEO Pharmaceuticals, Merck & Co.), a humanized IgG_1 mAb that targets hepatocyte growth factor, was reported to be safe and well tolerated as monotherapy or in combination with erlotinib hydrochloride in patients with advanced solid tumors. In an open-label, escalating-dose phase I trial conducted in a total of 37 subjects with relapsed or refractory solid tumors (most commonly sarcoma, ovarian carcinoma, mesothelioma and glioblastoma multiforme), SCH-900105 was administered as monotherapy at doses of 2, 5, 10 or 20 mg/kg i.v. once every 2 weeks to 24 participants, whereas 13 patients received the highest dose of the agent (20 mg/kg) in combination with erlotinib (150 mg/day). Two subjects receiving SCH-900105 monotherapy with papillary thyroid carcinoma and mixed mesodermal tumors of the ovary, respectively, achieved stable disease for > 12 months. Pharmacokinetic analysis revealed dose-proportional exposure to SCH-900105 within the dose range under evaluation and a $t_{1/2}$ of approximately 15-23 days following chronic dosing. Serum hepatocyte growth factor levels exhibited an increase after SCH-900105 administration. Treatment with SCH-900105 alone or in combination with erlotinib was well tolerated, with rash, fatigue, nausea and diarrhea being the most commonly reported (> 15%) TEAEs across all cohorts. The recommended phase II dose of SCH-900105 was established as 20 mg/kg (48, 49).

PHASE I/II TRIALS

TH-302 (Threshold Pharmaceuticals), a nitroimidazole-linked prodrug of the DNA-alkylating agent bromo-isophosphoramide mustard (Br-IPM), which is activated under severe hypoxic conditions, exhibited good safety and encouraging antitumor activity in combination with doxorubicin in patients with soft tissue sarcoma in a recent phase I/II trial. Individuals with advanced or metastatic soft tissue sarcoma (N = 37) received treatment with TH-302 in a dose escalation cohort (n = 16) or during the dose expansion part of the trial (n = 21). The study's primary objectives were to establish the MTD and DLTs of the combination regimen and to assess the efficacy of the treatment as determined by progression-free rate at 6 months. Secondary objectives included investigation of the pharmacokinetics of the combination of TH-302 with doxorubicin. TH-302 was administered i.v. over 30-60 min on days 1 and 8 of a 28-day cycle at a starting dose of 240 mg/m^2, followed by 40% dose escalations in cohorts of 3-6 subjects. Doxorubicin was given as an i.v. bolus of 75 mg/m^2 on day 1 at 2 h after the administration of TH-302 for a maximum of six cycles. Prophylactic granulocyte colony-stimulating factor (G-CSF) was added to the 240 mg/m^2 dose of TH-302 at day 8 of each cycle due to the incidence of grade 3 neutropenia. The MTD of TH-302 in combination with doxorubicin was established at 300 mg/m^2. Dose-limiting toxicities included grade 4 thrombocytopenia, grade 3 infection and grade 4 neutropenia. There was no evidence of renal or hepatic toxicity and no apparent abnormalities in other laboratory measures. Partial response and stable disease by RECIST criteria were seen in 23% and 66% of patients, respectively. The median progression-free survival was 5.4 months, with a progression-free rate at 3 and 6 months of 88% and 60%, respectively. TH-302 did not affect the pharmacokinetic profile of

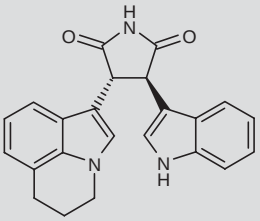


TH-302

doxorubicin. Additional clinical evaluation of the combination regimen in soft tissue sarcoma is supported by the data obtained in this trial (50, 51).

Roche's epidermal growth factor receptor (EGFR)-directed humanized IgG_1 mAb **R-7160** (RO-5083945, GA-201) was recently evaluated in subjects with metastatic solid tumors. The antibody has a glycoengineered Fc region and displays increased binding affinity for all polymorphic variants of low affinity immunoglobulin gamma Fc region receptor III-a (Fc-gamma-RIIIa), which is expressed on the surface of immune effector cells. A two-part, multicenter, open-label, nonrandomized, escalating-dose phase I/II trial was designed to evaluate the safety, tolerability and activity of R-7160 administered as monotherapy in patients with EGFR-positive solid tumors for whom no standard therapy was available. In the trial's dose escalation phase (part 1), 36 subjects received treatment once weekly across 7 dose levels (50, 100, 200, 400, 700, 1000 and 1400 mg). Doses of 700, 1000 and 1400 mg were also administered on schedules of once every 2 weeks (q2w) and once every 3 weeks (q3w) to 19 and 20 patients, respectively. In part 2 of the study, 25 individuals with mutated *KRAS* and EGFR-positive colorectal cancer in third-line therapy were given 1400 mg R-7160 on days 1 and 8 and subsequently followed a q2w regimen. Treatment with R-7160 was described as safe, with infusion-related reactions, rash and asymptomatic hypomagnesemia being the most frequently reported adverse events (experienced by 77%, 76% and 24%, respectively, of participants taking R-7160). Pharmacokinetic profiling revealed nonlinear reductions in clearance with increasing doses over the range of 50-400 mg. Linear clearance was seen at doses > 400 mg. Population pharmacokinetic methods indicated that the 1400-mg dose administered on a schedule of day 1 and 8 followed by q2w dosing was able to sustain a target concentration of 50 µg/mL for the entire dosing period in 76% of subjects. Pharmacodynamic analysis demonstrated induction of the infiltration of immune effector cells into the skin rash and the tumor site following treatment with R-7160. A partial response and stable disease were observed in 6% and 44% of patients, respectively, among the evaluable subjects treated with the highest doses of R-7160 (700-1400 mg). In 23 participants who had previously received cetuximab/panitumumab in combination with chemotherapy, 36% of R-7160-treated subjects (dose range 400-1400 mg) exhibited a better or similar progression-free survival than with the previous regimen. Based on these findings, the recommended schedule of 1400 mg on days 1 and 8 followed by q2w dosing will be further investigated in additional studies (52, 53).

Data from several phase I and II clinical studies of the c-Met inhibitor **ARQ-197** (ArQule) in patients with advanced solid tumors were presented at this year's ASCO meeting. In a 3+3 design, escalating-dose phase I trial in adult patients with advanced solid tumors (N = 14), ARQ-197 was administered orally at 360 mg b.i.d. in combination with sorafenib (at doses of 200 and 400 mg b.i.d. p.o.). To date, five subjects have received treatment at 200 mg and nine at 400 mg ARQ-197. No DLTs were reported at 200 mg ARQ-197, whereas grade 3 fatigue and dyspnea were seen in one participant receiving 400 mg ARQ-197. Based on these findings, 400 mg ARQ-197 was selected as the recommended phase II dose. Grade 3 ARQ-197-related adverse events, including fatigue, dyspnea, dry skin, musculoskeletal chest pain and hyperbilirubinemia, were observed in 29%

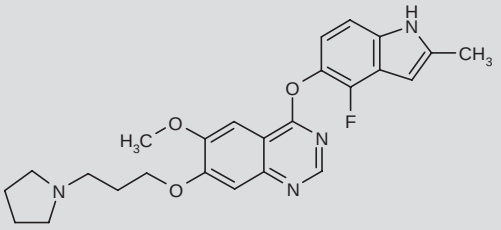


ARQ-197

of patients. Pharmacokinetic profiling revealed mean C_{max} and $AUC_{0\text{-}12}$ values of 1766 ng/mL and 14,053 h·ng/mL, respectively, on day 1 and 1986 ng/mL and 15,003 h·ng/mL, respectively, on day 29. Best response of stable disease by RECIST criteria was reported in six of nine evaluable patients; one subject with renal cell carcinoma exhibited tumor regression of 22% (54, 55). Treatment with oral ARQ-197 (360 mg b.i.d.) was described as safe and well tolerated in 20 previously treated (≤ 2 systemic chemotherapy regimens) patients with hepatocellular carcinoma and cirrhosis in a multicenter, single-cohort phase I trial. The most commonly reported adverse events (in > 10% of subjects) included fatigue, anemia, neutropenia, leukopenia, thrombocytopenia, alopecia, anorexia and diarrhea. Serious drug-related adverse events, which included grade 3 anemia and grade 3-4 leukopenia and neutropenia, were experienced by four participants (two, one and one, respectively). Stable disease by RECIST criteria, which lasted > 4 months, was seen in 5 of 15 evaluable patients, with the time to progression ranging from 3.1 to 42.3 weeks (56). Time to progression is the primary endpoint of a global, randomized, double-blind, placebo-controlled phase II trial which is currently recruiting participants and has been designed to evaluate ARQ-197 in subjects with hepatocellular carcinoma. Oral ARQ-197 (360 mg b.i.d.) or placebo will be administered to 99 participants in a 2:1 ratio. Following radiographic confirmation of disease progression, individuals in the placebo arm will be allowed to cross over to open-label ARQ-197. All patients will be assessed by computed tomography/magnetic resonance imaging performed every 6 weeks. Treatment will be continued until confirmed progression of disease, unacceptable toxicity or withdrawal of consent. Comparisons between both cohorts of median progression-free survival, overall survival, biomarker analysis, pharmacokinetics and safety constitute the study's secondary objectives. To date, 33 subjects have been enrolled and received treatment with ARQ-197 (57, 58).

PHASE II TRIALS

Cediranib (AZD-2171, Recentin™; AstraZeneca), a highly potent inhibitor of VEGFR tyrosine kinases, will be evaluated for safety and efficacy in combination with cisplatin/gemcitabine chemotherapy versus placebo plus cisplatin/gemcitabine in patients with advanced biliary tract cancers in a clinical study (59) that was expected to begin recruiting participants in June 2010. Adult subjects with histologically/cytohistologically confirmed advanced biliary tract cancer and measurable disease (ECOG performance status 0-2 and adequate hematological, hepatic and renal function) will be eligible for enrollment in this randomized phase II trial, which is expected to recruit 136 patients. The participants will be randomized to receive



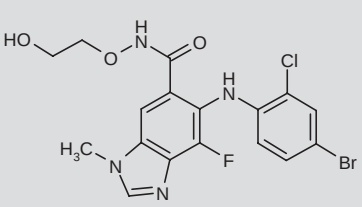
Cediranib

either oral cediranib (20 mg/day) or placebo in combination with cisplatin (25 mg/m^2) and gemcitabine (1000 mg/m^2) administered i.v. on days 1 and 8 of 28-day cycles for a total of 24 weeks or until disease progression. After 24 weeks, they will receive cediranib monotherapy or placebo until disease progression. The trial's primary endpoint is progression-free survival. Objective response rate, adverse events, quality-of-life assessments and cost–effectiveness analysis constitute the secondary endpoints. Biomarker evaluation, including circulating tumor cells, VEGF, soluble VEGFR, basic fibroblast growth factor (bFGF), lactate dehydrogenase and CA19-9, will be carried out in all subjects. A sample size of 68 participants per arm will allow a direct comparison of progression-free survival between treatments with 80% power to provide a high level of statistical significance (alpha = 0.2; 2-sided) and will permit the detection of a progression-free survival hazard ratio of 0.64 (60).

PF-00299804 (Pfizer), an irreversible and orally available, small-molecule pan-HER (erbB) inhibitor, exhibited potent antitumor activity as first-line therapy in patients with recurrent and/or metastatic squamous cell carcinoma of the head and neck (SCCHN) in an ongoing phase II trial. The study's primary objective was to evaluate the efficacy of PF-00299804, dosed continuously at 45 mg/day p.o. on 21-day cycles, in subjects with recurrent and/or metastatic SCCHN as per the objective response rate assessed every 6 weeks using the RECIST version 1.1. Dose reductions to 30 and 15 mg were allowed in cases of grade 4 hematological toxicity and grade > 3 or intolerable grade 2 nonhematological toxicities. The trial's secondary objectives included the assessment of safety and tolerability, the collection of pharmacokinetic data for meta-analysis and the exploration of predictive and pharmacodynamic biomarkers of efficacy. Partial response and stable disease were reported in 4% and 24% of subjects, respectively, as the best overall response in 38 evaluable patients, with a clinical benefit response rate (partial response and stable disease for ≥ 24 weeks) of 21.1%. The objective response rate was estimated at 10.5%. The most frequent adverse events included fatigue, gastrointestinal symptoms (diarrhea, stomatitis and nausea) and skin toxicity. No deaths due to toxicity were reported. Dose reduction and dose interruption were required in 29% and 49% of subjects, respectively, while 12% of participants discontinued due to the incidence of adverse events. Pharmacokinetic analyses are pending and accrual for stage II of the trial continues (61, 62).

The VEGFR-2 inhibitor **CT-322** (Adnexus Therapeutics, Bristol-Myers Squibb), an engineered version of a fibronectin module (PEGylated Adnectin™), was administered with and without irinotecan to patients with recurrent glioblastoma in an open-label phase II study. Patients were given CT-322 (1 or 2 mg/kg/week i.v.) in a safety lead-in and then CT-322 (1 or 2 mg/kg/week i.v.) with or without irinotecan (125 or 340 mg/m^2 i.v. every 2 weeks depending on enzyme-inducing antiepileptic drug status). A total of 51 participants received treatment, 48 of whom experienced at least 1 adverse event and 5 of whom discontinued due to related adverse events. Of four on-study deaths due to intracranial hemorrhage, one was considered possibly related to CT-322. The most common related TEAEs were fatigue, hypertension, diarrhea and nausea. The most common TEAEs of grade 3 or higher were neutropenia, increased ALT, hypertension and hypophosphatemia. The primary efficacy endpoint was progression-free survival after six cycles (5.52 months), as assessed by an independent review panel. These rates in the intent-to-treat population were 27.9%, 64.3%, 0% and 32.1%, respectively, with CT-322 1 mg/kg, CT-322 1 mg/kg plus irinotecan, CT-322 2 mg/kg and CT-322 2 mg/kg plus irinotecan. One complete and one partial response occurred in patients treated with CT-322 1 mg/kg as monotherapy. The study continues to enroll patients at the CT-322 2 mg/kg dose level (63, 64).

According to data obtained from a recent phase II study, the novel and selective non-ATP-competitive MAP kinase kinase MEK 1/2 inhibitor **selumetinib** (AZD-6244, ARRY-142886; AstraZeneca) was found to be safe and produced a clinical benefit in patients with [^{131}I]-refractory papillary thyroid carcinoma (IRPTC) and papillary thyroid carcinoma (PTC). Individuals with IRPTC and PTC (N = 32) who exhibited objective evidence of disease progression within the last 12 months received treatment with selumetinib (100 mg b.i.d.) on 28-day treatment cycles. The objective response rate was the study's primary endpoint and secondary endpoints were safety, overall survival and time to progression. Partial response and stable disease according to RECIST assessment were observed in 3% and 66% of the participants, respectively. Clinical benefit (i.e., partial response and stable disease) was reported in 31% of the subjects and had a median duration of 224.5 days. The most common treatment-related adverse events included rash (grade 1-2 and grade 3-4 reported in 9% and 18% of patients, respectively), diarrhea (grade 1-2 and grade 3-4 experienced by 44% and 5% of subjects, respectively) and fatigue (grade 1-2 and grade 3-4 observed in 41% and 8% of participants, respectively). Correlative studies evaluating the tumor *BRAF* genotype in relation to progression-free survival indicated a possible association between the mutational status and improved response to selumetinib (65, 66).



Selumetinib

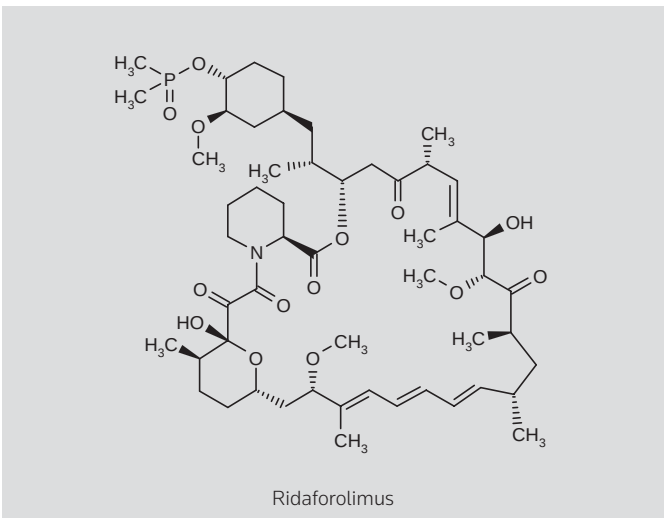
Patients with relapsed Hodgkin's lymphoma who had received at least two previous treatment regimens were included in a phase II study that evaluated the effects of the CD80-targeted primatized mAb **galiximab** (Biogen Idec), administered at a dose of 500 mg/m^2 weekly for 4 weeks, followed by 500 mg/m^2 every 4 weeks until disease progression or unacceptable toxicity. The participants were ineligible for transplant or had relapsed after receiving a stem cell transplant. The treatment was well tolerated, with grade 3-4 nonhematological toxicities observed, including three cases of hypophosphatemia, two cases of elevated liver function tests and two cases of infection. The activity of galiximab was limited, however; 1 complete and 1 partial response were observed among 29 patients receiving treatment (overall response rate = 6.9%). The complete and partial responders progressed at 7.5 and 3 months, respectively. Treatment was discontinued in 24 subjects due to progressive disease and the median time to progression was 1.6 months (67, 68).

PEDIATRIC DATA FROM PHASE I AND II CLINICAL STUDIES

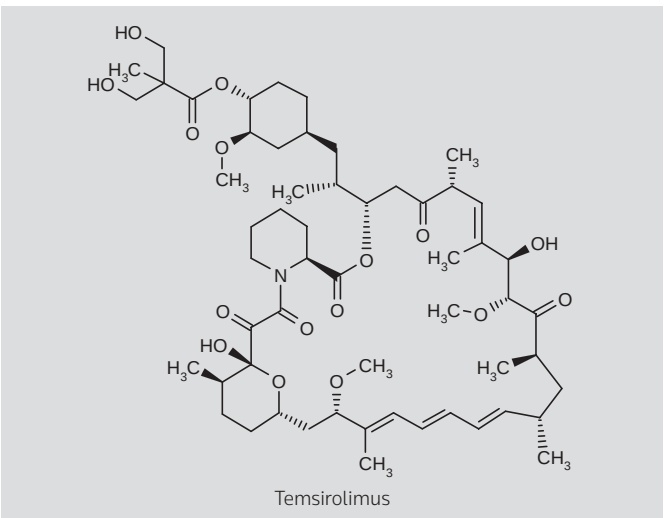
Intravenous administration of the mTOR inhibitor **ridaforolimus** (deforolimus, AP-23573, MK-8669; Ariad Pharmaceuticals, Merck & Co.) in heavily pretreated children and adolescents with refractory solid tumors was described as well tolerated in an ongoing clinical study. The multicenter, open-label, ascending-dose, sequential-group phase I trial is the first of the agent to be conducted in pediatric patients and was designed to investigate the DLT and determine the MTD of ridaforolimus (primary objectives) in children aged 2 to < 18 years with histologically proven solid malignancies, including refractory/relapsed tumors of the central nervous system (CNS). Safety, preliminary efficacy and pharmacokinetic/pharmacodynamic assessments constituted the secondary endpoints of the study. A total of 15 patients received treatment in a standard 3+3 design whereby ridaforolimus was escalated in sequential dose levels (8, 10, 13 and 16 mg/m^2/dose) administered as daily 1-h i.v. infusions for 5 days every other week on 28-day treatment cycles. No DLTs have been reported to date. The most frequently reported (> 20%) adverse events in all treatment cycles included low levels of hemoglobin, low leukocyte and platelet counts, low levels of phosphate and increased triglyceride levels. Pharmacokinetic profiling revealed dose-dependent increases in exposure to ridaforolimus, with similar C_{max}, $t_{1/2}$, AUC_{last} and clearance values across dose levels. Target inhibition of mTOR was achieved in all dose cohorts according to pharmacodynamic assessments. Stable disease as best response, determined by standard RECIST criteria, was reported in 7 of 15 patients. The median overall survival was estimated at 7.5 months. Toxicity and pharmacokinetic data support the use of ridaforolimus in combination regimens. The MTD has not yet been reached. Despite exceeding the recommended phase II dose for adults, the pediatric recommended phase II dose has not yet been determined (69, 70).

In a phase I trial conducted in pediatric patients (mean age 8.1 years) with recurrent or refractory malignancies of the CNS, the orally active γ-secretase inhibitor **MK-0752** (Merck & Co.) was evaluated at doses of 150, 200, 260, 325 and 400 mg/m^2 in order to establish the MTD of the treatment in this patient population. Two subjects with glioblastoma multiforme and posterior fossa ependymoma exhibited disease stabilization for ≥ 3 months. The most common non-dose-limiting nonhematological toxicity was grade 1-2 fatigue and the most frequent non-dose-limiting hematological toxicities included leukocyte abnormalities, lymphopenia, neutropenia and thrombocytopenia. Dose-limiting toxicities seen in the 260-mg cohort included elevated ALT and AST. The recommended phase II dose was established at 260 mg/m^2, administered on a schedule of 3 days on/4 days off (71, 72).

Temsirolimus (Pfizer), an mTOR inhibitor, was reported to be safe in pediatric patients with advanced solid tumors in a recent clinical study. An open-label, multicenter phase II trial evaluated the safety, pharmacokinetics and preliminary antitumor activity of temsirolimus (75 mg/m^2 administered once weekly as a 60-min i.v. infusion) in 52 children (aged 1-21 years) with recurrent/refractory neuroblastoma (n = 19), high-grade glioma (n = 17) or rhabdomyosarcoma (n = 16). The safety profile of temsirolimus in pediatric patients was found to be similar to that seen in adult populations. The most common drug-related clinical adverse events included asthenia (29%), fever (21%) and anorexia (15%). Thrombocytopenia, anemia, leukopenia



Ridaforolimus



Temsirolimus

and neutropenia (54%, 27%, 27% and 15%, respectively) were the most commonly reported hematological adverse events, whereas hyperlipidemia (29%), hypercholesterolemia (27%) and elevated ALT (23%) were among the most frequent biochemical adverse events. At week 12, none of the participants exhibited a complete response by RECIST criteria. A partial response was seen in one subject with neuroblastoma and one with rhabdomyosarcoma. Stable disease as best response was observed in seven, seven and three individuals, respectively, with high-grade glioma, neuroblastoma and rhabdomyosarcoma. Pharmacokinetic analysis of temsirolimus and its metabolite sirolimus revealed that the pediatric population was not at risk of excessive exposure to either compound. Despite the insufficient antitumor activity of temsirolimus seen in this study (< 2 objective responses in 12 weeks in each tumor type), disease stabilization observed in a total of 14 patients across tumor types lasting for > 3 months supports further investigation of the treatment (73).

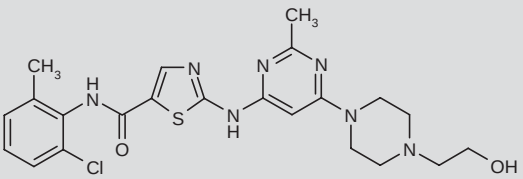
PHASE III TRIALS

Phase III studies presented at this year's ASCO meeting could signal a change in the standard first-line treatment for CML, with agents currently used in patients failing first-line imatinib treatment showing greater efficacy than imatinib mesilate. **Dasatinib** (Bristol-Myers Squibb), an inhibitor of Src kinase and breakpoint cluster region protein/tyrosine-protein kinase ABL1 (BCR-ABL), was compared to imatinib in the multicenter DASISION study, in which 519 patients with newly diagnosed Philadelphia chromosome-positive (Ph^+) CML in chronic phase were randomized to dasatinib 100 mg/day or imatinib 400 mg/day. The rate of confirmed complete cytogenetic response at 12 months was significantly greater with dasatinib (77%) than with imatinib (66%). Rates of complete cytogenetic response (83% vs. 72%) and major molecular response (46% vs. 28%) were also higher with dasatinib than with imatinib at 12 months, and major molecular response and complete cytogenetic response were obtained significantly faster with dasatinib than with imatinib. Dasatinib exhibited favorable tolerability, with similar rates of grade 3-4 anemia and neutropenia across study arms, although thrombocytopenia was more common with dasatinib. The most common nonhematological adverse events seen with dasatinib were fluid retention, nausea, vomiting, myalgia, muscle inflammation, musculoskeletal pain and rash, which were less common with dasatinib than with imatinib, in addition to diarrhea, headache and fatigue, which occurred at similar rates in both groups (74, 75).

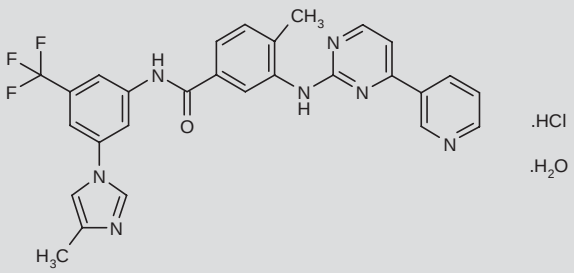
In the Evaluating Nilotinib Efficacy and Safety in Clinical Trials - Newly diagnosed Patients (ENESTnd) phase III study, 846 patients with CML in the chronic phase were randomized to the BCR-ABL inhibitor **nilotinib hydrochloride monohydrate** (Novartis Oncology) at 300 or 400 mg b.i.d., or imatinib 400 mg/day. The primary endpoint of major molecular response rate at 12 months significantly favored nilotinib (44%, 43% and 22%, respectively, for nilotinib 300 mg, nilotinib 400 mg and imatinib). At 24 months, these rates were 86%, 88% and 48%, respectively. Nilotinib was also associated with deeper responses, and suboptimal responses, treatment failure and deaths were more common with imatinib. Complete cytogenetic response rates were also higher with either nilotinib dose at 12 months and overall compared with imatinib. There were no unexpected safety events; 1% of the patients discontinued nilotinib due to hepatobiliary disorders and < 1% of nilotinib-treated participants had pleural effusions (76, 77). Among the Japanese patients included in ENESTnd (n = 79), the 12-month major molecular response rates were 57%, 50% and 24%, respectively, with nilotinib 300 mg, nilotinib 400 mg and imatinib. Median time to major molecular response was 5.8 and 8.4 months, respectively, in the nilotinib 300- and 400-mg groups and was not yet reached at the time of reporting in the imatinib cohort. The treatments were well tolerated in this subgroup (78). Pharmacokinetic profiles of nilotinib obtained from patients included in ENESTnd revealed a dose–exposure relationship that is less than proportional between the doses of nilotinib of 300 and 400 mg b.i.d., and stable exposure over 12 months with both doses. The bioavailability of nilotinib was reduced in men compared with values obtained in women. The pharmacokinetic profile of the agent was not significantly influenced by age, body weight, ethnicity or race (79). A phase II study in patients with Ph^+ CML in the early chronic phase has also been conducted to evaluate treatment with nilotinib 400 mg b.i.d. in 73 patients. All participants were followed for a median of 724 days and showed a cumulative complete cytogenetic response rate of 100% within 12 months. Major molecular response rates were 3%, 21%, 52%, 66%, 85% and 87%, respectively, at 1, 2, 3, 6, 12 and 18 months. Responses to nilotinib were stable after 2 years and no progression to advanced phase was seen in the second year. Most adverse events were grade 1-2 and manageable by dose adjustment, with the most common biochemical adverse events being increases in bilirubin, ALT, lipase and amylase (80).

BIOMARKERS

Response Genetics has launched a new test expanding its ResponseDX: Lung™ genetic test panel to detect the presence of



Dasatinib



Nilotinib hydrochloride monohydrate

EML4-ALK fusion gene variants in patients with NSCLC. These rearranged fusion genes promote tumor cell growth and predict lack of benefit from therapies that inhibit EGFR activity. ALK tyrosine kinase inhibitors have entered clinical development, where they have shown efficacy in individuals with NSCLC harboring fusion proteins of echinoderm microtubule-associated protein-like 4 (EMAP-4) and anaplastic lymphoma kinase (ALK). ResponseDX tests are PCR-based assays developed by Response Genetics to aid physicians in making therapeutic treatment decisions for patients with NSCLC, gastric cancer and colorectal cancer. The ResponseDX panels include four genes: *ERCC1* (encoding DNA excision repair protein), *TYMS* (encoding thymidylate synthase), *HER2* (encoding receptor tyrosine-protein kinase erbB-2) and *EGFR* (encoding epidermal growth factor receptor). The test panels also include the analysis of *EGFR* mutations in NSCLC and *KRAS* and *BRAF* mutations in colorectal cancer (81).

A recent study performed by Japanese scientists at Mie University School of Medicine identified the levels of serum macrophage inflammatory protein 3 alpha (MIP-3-α) as an independent prognostic factor for colorectal cancer. The study aimed to identify cytokine markers that could be related to the prognosis of patients with metastatic colorectal cancer and validate the markers' prognostic significance. In six patients with synchronous liver metastases who were receiving multidisciplinary treatments, the differences in cytokine levels in serum were assessed between the longer survival (n = 3) and the shorter survival (n = 3) subgroups. The levels of MIP-3-α in serum were estimated in all patients. Using the median level of MIP-3-α in serum that was established by an immunosorbent assay in 242 patients with colorectal cancer (28.2 pg/mL) as a cut-off point, a significantly higher level of serum MIP-3-α was identified in patients with synchronous liver metastases ($P < 0.001$). There was no correlation between MIP-3-α and other clinical/pathological variables. The overall survival of subjects with high MIP-3-α was significantly shorter than that of patients with low MIP-3-α levels ($P < 0.001$). Multivariate analysis revealed that a high level of MIP-3-α in serum was an independent prognostic factor in patients with colorectal cancer ($P < 0.001$). An association between elevated MIP-3-α in serum and poor survival was identified in 62 individuals with metastatic colorectal cancer ($P < 0.05$) (82).

Data from a randomized phase II trial conducted by researchers at Medical University Vienna and the European Institute of Oncology, Milan, in which 12 patients with CRPC received 4 treatment cycles of either docetaxel alone (75 mg/m^2 once every 21 days) or in combination with sunitinib (37.5 mg/day on days 2-15), suggested that the levels of circulating endothelial progenitor (CEP) cells may represent a novel biomarker for the response to VEGFR-targeting therapies. Treatment with sunitinib was found to correlate with a reduction in the docetaxel-induced elevation of CEP cells in CRPC (83).

The human melanoma-associated chondroitin sulfate proteoglycan 4 (encoded by *CSPG4*) and the immune regulatory protein CD276 antigen (B7-H3, encoded by *CD276*), a member of the B7 family of the Ig superfamily of proteins, were evaluated as potential prognostic biomarkers in patients with chordoma in a recent study performed by collaborating research teams from Massachusetts General Hospital and the University of Pittsburgh. The expression of the genes encoding chondroitin sulfate proteoglycan 4 and B7-H3 was assessed at the protein level by immunohistochemistry in triplicate cores taken from a tissue microarray library constructed from 70 conventional chordoma tumors. The two-tailed Fisher exact test was used to compare the expression of *CSPG4* and *CD276* with clinical and histological outcomes. Risk factors for mortality based on expression were evaluated using the Cox proportional hazard regression analysis, which controlled for other variables. Of the 70 evaluable patients, 50 and 10 developed local and distal recurrences, respectively, and 26 died. A total of 41 and 58 tumors were positive for *CSPG4* and *CD276*, respectively. *CSPG4* was expressed in 9 of 10 primary tumors that were associated with metastasis; significantly higher levels of the protein were seen in the tumors of subjects who developed metastasis than in those who did not ($P = 0.04$). The expression of *CSPG4* in primary tumors correlated with a greater risk of dying from the disease (76.9%; $P = 0.004$). After controlling for surgical margin, the association of *CSPG4* with a worse survival outcome was maintained and there was a tendency for significance between *CSPG4* expression and metastasis. The expression of *CD276* did not correlate with metastasis or survival. Furthermore, the association of *CD276* with local recurrence did not reach statistical significance (84).

Results from a recent pilot study conducted by scientists at University Hospital Zagreb and at the Institute for Medical Research and Occupational Health, Zagreb, Croatia, suggested that levels of estradiol in blood may represent a new biomarker for the diagnosis and therapeutic outcome of metastatic testicular mature teratoma. Patients (N = 20) with testicular germ cell tumors (4 with seminomas, 5 with nonseminomas and 11 with mixed germ cell tumors) who received 4 cycles of bleomycin/etoposide/cisplatin (BEP) chemotherapy and 20 age-matched control subjects were enrolled in the study. The levels of estradiol, testosterone, luteinizing hormone (LH) and follicle-stimulating hormone (FSH) were evaluated in all participants. At baseline, significantly higher estradiol levels were recorded in two patients with mature teratoma stage IIIC (950 and 12,422 pmol/L, respectively) than in other patients with testicular cancer and in control subjects. The levels of testosterone, LH and FSH were all within the normal range. Following four cycles of treatment with BEP, estrogen levels in the two patients with mature teratoma were decreased to control values (148 and 115 pmol/L, respectively), a decline which correlated with a decrease in human choriogonadotropin subunit beta and a reduction in tumor mass. In patients with higher estradiol, a significant increase in testosterone was reported (39 pmol/L) after the decrease of estradiol levels. After four cycles of BEP chemotherapy, patients received two cycles of cisplatin/etoposide/ifosfamide treatment. The levels of estradiol following six cycles of chemotherapy were within the control range and human choriogonadotropin subunit beta was undetectable in both cases. These preliminary data appear to support the estrogen dependency of testicular mature teratoma (85).

A study conducted by researchers at the University of Surrey, the Royal Surrey County Hospital and the Institute of Cancer Research, Sutton, U.K., supports the use of the transcription factor homeobox protein engrailed-2 (en-2) as a potential diagnostic biomarker for prostate cancer. Analysis of untreated, nonconcentrated urine samples (N = 258) collected under standardized conditions from patients with prostate cancer, subjects with benign prostatic hypertrophy and individuals with no prostate abnormalities after satura-

tion biopsy, revealed the presence of en-2 in the majority of men with prostate cancer (63%), but only in 3% of subjects with no prostatic abnormalities ($P < 0.001$) (86).

The measurement of cross-linked N-telopeptides of type I collagen (NTx) was described by scientists at Osaka Prefectual Medical Center for Respiratory and Allergic Diseases as a putative diagnostic biomarker of bone metastasis in patients with lung cancer. Bone metastasis represents an important factor that determines the choice of appropriate therapies for lung cancer and affects the quality of life of patients with lung cancer. Evaluation of the average serum NTx levels in 92 patients with lung cancer (including adenocarcinoma, squamous cell carcinoma, small cell carcinoma and other tumors; n = 50, 26, 15 and 1, respectively), 39 of whom also had bone metastasis, revealed a significant difference between NTx levels in subjects with and without bone metastasis (25.1 vs. 16.5, respectively; $P < 0.001$). Using the receiver operating characteristic curve, the cutoff value of serum NTx for bone metastasis in lung cancer was estimated at 19.7 (sensitivity and specificity of 71.8% and 79.2%, respectively). Multivariate analysis of the levels of calcium/inositol phosphate/alkaline phosphatase/lactate dehydrogenase in blood samples in relation to performance status and bone metastasis revealed significant differences in the levels of serum NTx ($P < 0.001$) (87).

CONCLUDING REMARKS

The latest advancements in clinical and translational research in the areas of cancer prevention, diagnosis and treatment were presented at the 46th ASCO meeting, aiming to promote the development of high-quality cancer care and to assist oncologists in their continuous efforts to overcome the challenges of the modern-day practice of clinical oncology. Several novel drug candidates, including immunotherapeutics, small-molecule inhibitors of signal transduction pathways and antimitotic agents, have entered first-in-human clinical trials, with encouraging preliminary results being reported. For the first time during an ASCO meeting, information from clinical studies currently in progress was disclosed without the inclusion of data regarding outcomes or the presentation of results, in an attempt to encourage the discussion among investigators for the conduct of successor or confirmatory trials.

DISCLOSURES

The authors state no conflicts of interest.

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