Drugs of the Future 2011, 36(10): 783-792

CCC: 0377-8282/2011
DOI: 10.1358/dof.2011.36.10.1704837



MEETING REPORT

# 47TH ANNUAL MEETING OF THE AMERICAN SOCIETY OF CLINICAL ONCOLOGY (ASCO) 2011

## FOCUS ON FIRST-IN-HUMAN AND PHASE I TRIALS

*S. Vasiliou, P. Cole and M. Gómez-Zaera*

Thomson Reuters, Barcelona, Spain

**CONTENTS**



**SUMMARY**

*"Patients. Pathways. Progress." was the collective theme of the 47th Annual Meeting of the American Society of Clinical Oncology (ASCO), held in Chicago on June 3-7, 2011. Participants at the largest oncology meeting in the world were given the opportunity to exchange a wide range of ideas related to cancer and discussed the most recent advances in cancer research and care. This year's meeting was designed to accommodate the interests of the Society's multidisciplinary membership, whereas the educational program centered on medical, surgical and radiation oncology. This report will focus on the latest developments based on findings from a number of first-in-human trials and phase I studies presented at the meeting.*

**INTRODUCTION**

The principal goal of the American Society of Clinical Oncology (ASCO) since its establishment in 1964 has been to foster communication among oncology-related subspecialities in an effort to promote the delivery of high-quality healthcare to patients with cancer. The Society aims to advance the education of physicians and other individuals involved in providing care to patients with cancer by supplying the latest and most accurate information to allow informed decisions regarding the prevention and treatment of cancer to be made. "Patients must be the primary focus and the source of inspiration for clinicians devoted to oncology" emphasized George W. Sledge, Jr., MD, the current president of ASCO, in his speech. He pointed out that understanding the pathways involved in the development of cancer and demonstrating commitment to research and clinical excellence would give rise to progress, a view summarized in the meeting's theme "Patients. Pathways. Progress.". This report will highlight the latest findings in clinical research, focusing on presentations from first-in-human trials and phase I studies.

**Correspondence:** S. Vasiliou, Thomson Reuters, Provença 398, 08025 Barcelona, Spain. E-mail: sylvia.vasiliou@thomsonreuters.com.

**FIRST-IN-HUMAN TRIALS**

**P28** (University of Illinois at Chicago), a first-in-class inhibitor of the ubiquitination of cellular tumor antigen p53, may represent a beneficial approach for the treatment of patients with p53-positive metastatic solid tumors, based on first-in-human data presented. The agent is a 28-amino-acid peptide derived from azurin, a protein secreted by *Pseudomonas aeruginosa*. It preferentially penetrates tumor cells over normal cells and suppresses their growth by a mechanism of action that involves inhibition of p53 degradation, leading to p53 accumulation and subsequent induction of cell cycle arrest at the $G_2$/M phase. A total of 15 patients with refractory solid tumors (including melanoma and sarcoma, as well as colon, pancreatic and prostate cancer; n = 7, 2, 4, 1 and 1, respectively) were enrolled in a phase I study designed to evaluate the safety, tolerability, immunogenicity, pharmacokinetics and pharmacodynamics of P28. The treatment was administered as monotherapy at doses of 0.83, 1.66, 2.5, 3.33 or 4.16 mg/kg by i.v. bolus three times weekly for a period of 4 weeks, with a 2-week interval prior to dosing at a higher level. Assessment of the treatment by Response Evaluation Criteria in Solid Tumors (RECIST) in 15 evaluable participants revealed complete regression in 1 patient with sarcoma and in 1 subject with melanoma. Partial regression was observed in one individual with prostate cancer and one participant with melanoma. Six patients exhibited stable disease (four with colon cancer and two with melanoma). Phase II evaluation of P28 is planned (1, 2).

The potent and selective hepatocyte growth factor receptor (proto-oncogene c-Met) inhibitor **INCB-028060** (Incyte) demonstrated favorable safety and antitumor activity in advanced solid tumors. The ongoing, open-label, standard 3+3 design, dose-escalating, first-in-human phase I trial was designed to investigate the safety, efficacy, pharmacokinetics and pharmacodynamics of INCB-028060 and to establish its maximum tolerated dose (MTD) in

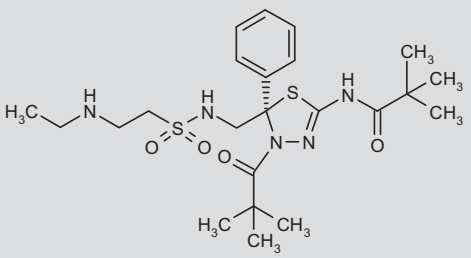
adults with advanced solid malignancies. The compound was administered at doses of 10, 20, 50, 70 or 150 mg once daily (n = 3, 4, 6, 4 and 3, respectively) or 50 mg b.i.d. (n = 3) in continuous 28-day cycles. Nausea, fatigue, tremor, headache, diarrhea and indigestion were the most frequent drug-related adverse events (AEs; all of grade 1-2 in severity). The MTD has not been reached to date and dose escalation is continuing. Stable disease lasting for 3-4 cycles has been reported in one patient with prostate cancer treated with INCB-028060 at 10 mg once daily, in one subject with hepatocellular carcinoma receiving the agent at 50 mg once daily and in two participants with colorectal carcinoma treated with 50 mg b.i.d. (3, 4).

Lilly's **litronesib** (LY-2523355), an allosteric inhibitor of kinesin-like protein KIF11 (kinesin-related motor protein Eg5) that selectively inhibits the formation of the bipolar mitotic spindle, is currently being assessed in clinical settings for the treatment of advanced and/or metastatic malignancies, including non-Hodgkin's lymphoma (NHL). The primary outcome measure of an open-label, non-randomized, parallel-assignment, dose-escalating phase I study was to determine the recommended dose of LY-2523355 and establish the appropriate schedule for the evaluation of the agent in phase II studies. Subjects with advanced cancer (N = 46) received LY-2523355 as a 1-hour i.v. infusion on days 1, 5 and 9 (schedule 1; starting dose of 2 mg/m$^2$), days 1 and 8, or days 1 and 5 (schedules 2 and 3, respectively; starting dose of 8 mg/m$^2$ for both). The patients in schedule 3 were given concomitant treatment with the neutropenia therapy pegfilgrastim (6 mg s.c.) administered on day 6 of each of the two planned 21-day treatment cycles. The most frequent AEs (≥ 10%) included neutropenia, fatigue, nausea, vomiting, rash and anorexia. Neutropenia or febrile neutropenia were described as dose-limiting toxicities (DLTs). Stable disease (SD) lasting for > 2 cycles has been attained by 16 subjects to date. Pharmacokinetic analysis revealed dose-independent clearance and a dose-dependent exposure to the compound. Negligible intra- and intercycle accumulation of LY-2523355 was observed. The MTD in schedules 1 and 2 has been established at 8 mg/m$^2$/day. This dose was associated with a response in surrogate skin biopsies on both schedules (5, 6).

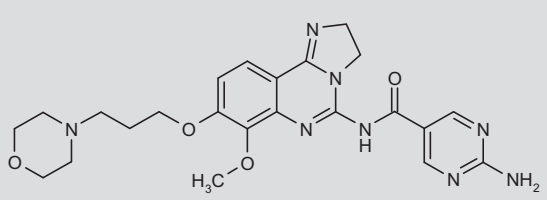
Evaluation of the safety, tolerability and pharmacodynamics, and determination of the MTD of **OTS-11101** (Otsuka Pharmaceutical/OncoTherapy Science) were the objectives of the first-in-human study of the product conducted in patients with advanced solid tumors. OTS-11101 is a peptide vaccine that acts as an inhibitor of angiogenesis by targeting vascular endothelial growth factor receptor 1 (VEGFR-1) and inducing cytotoxic T-cell lymphocytes. In a phase I trial, nine subjects with advanced solid tumors received treatment with OTS-11101 at doses of 1, 2 or 3 mg/mL (n = 3/dose level) given s.c. once weekly during a 28-day cycle. OTS-11101 was well tolerated. The most frequent AE was a reaction at the site of injection (of grade 1 in severity) seen in three subjects. The MTD was not attained. Induction of specific cytotoxic T-cell lymphocytes was observed in participants treated with OTS-11101 at 2 and 3 mg/mL. SD was reported in five patients but no objective response was seen (7).

Bayer's pan-class I phosphatidylinositol-4,5-bisphosphate 3-kinase (PI3K) inhibitor **BAY-80-6946** is currently undergoing evaluation in the first-in-human study in advanced solid tumors (8). Preliminary results were presented from the dose-escalating part of the trial, which is expected to be completed in November 2012. The primary objectives of the first-in-human, open-label, randomized, single-group assignment phase I study were to characterize the safety, tolerability and pharmacokinetics of BAY-80-6946 and to establish its MTD administered as a 1-hour i.v. infusion once weekly for 3 weeks in 4-week cycles. The product was administered to 17 subjects with advanced solid tumors (including sarcoma, pancreatic, esophageal and endometrial cancer) who did not exhibit diabetes at doses of 0.1, 0.2, 0.4, 0.8 or 1.2 mg/kg (n = 1, 3, 3, 8 and 2, respectively). Treatment with BAY-80-6946 was well tolerated. The MTD was determined to be 0.8 mg/kg. Pharmacokinetic data supported weekly administration of the agent. Generally dose-proportional exposure was observed and the mean half-life at the MTD was estimated at 38 hours. The most common drug-related AEs were fatigue, nausea, vomiting, alopecia, diarrhea, mucositis, dysgeusia (all of grade 1-2 in severity) and anemia (of grade 3 in severity). SD lasting for 6 and 8 months, respectively, was reported in patients with esophageal and endometrial cancer (9).

The orally available serine/threonine-protein kinase PLK1 inhibitor **MK-1496** (Merck & Co.) demonstrated promising preliminary antitumor activity in the first-in-human study conducted in Japanese patients with locally advanced and/or metastatic solid tumors (10). The aim of the open-label, non-randomized, dose-escalating, single-group assignment phase I trial was to establish the recommended clinical dose and to assess the safety, tolerability and pharmacokinetics of MK-1496 in individuals with locally advanced and/or metastatic solid tumors who had failed previous standard therapy. Participants (N = 27) were divided in sequential cohorts of 3-6 indi-



Litronesib



BAY-80-6946

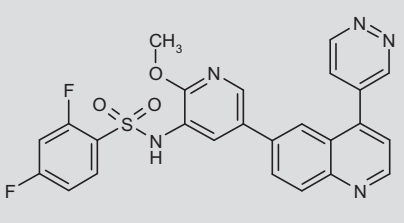
viduals to receive treatment with MK-1496 at doses of 20-120 mg p.o. administered either on day 1 of a 21-day cycle (regimen A) or on days 1, 3, 8, 10, 15 and 17 of a 28-day cycle (regimen B). A partial response by RECIST was observed in one patient with small cell lung cancer (SCLC) and one subject with head and neck cancer, with respective times to response estimated at 22 and 57 days. SD lasting > 16 weeks was seen in eight individuals. Leukopenia, neutropenia, thrombocytopenia, febrile neutropenia and anemia (35%, 35%, 29%, 18% and 18%, respectively) were the most frequent AEs of grade 3-4 in severity. The MTD was determined to be 80 mg. Pharmacokinetic analysis revealed a linear profile at the dose range under evaluation, with a half-life of 25-47 hours (11).

Based on its potent antitumor effects seen in preclinical studies, GlaxoSmithKline's **GSK-2126458** is undergoing clinical evaluation in the first-in-human trial in advanced solid tumors (12). The agent is an orally bioavailable inhibitor of PI3K-α, PI3K-β, PI3K-γ and PI3K-δ. It also suppresses the activity of serine/threonine-protein kinase mTOR complex 1 (mTORC1) and 2 (mTORC2). In the open-label, nonrandomized, parallel-assignment, dose-escalating phase I study, 129 patients with relapsed or refractory advanced solid tumors, including renal cell carcinoma, colorectal, breast, endometrial and bladder cancer, as well as melanoma (19%, 16%, 15%, 8%, 6% and 5%, respectively), received GSK-2126458 at doses of 0.1, 0.2, 0.4, 0.75, 1.5, 2, 2.5 or 3 mg/day p.o. until disease progression or unacceptable toxicity was observed. The MTD was estimated to be 2.5 mg/day in preliminary analysis of data obtained from 78 participants. Diarrhea (of grade 3 in severity) was the DLT in one and two patients in the 1.5- and 3-mg cohorts, respectively. The most frequent drug-related AEs (≥ 10%) were fatigue, nausea and diarrhea. A partial response (PR) by RECIST was seen in two patients with renal cell carcinoma treated with doses of 0.4 and 1.5 mg, respectively, and in two subjects with bladder cancer treated with doses of 2 and 2.5 mg, respectively (13). The trial is expected to be completed in December 2012.

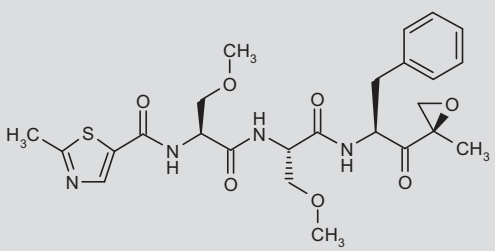
The first-in-human study of **GSK-2141795**, an inhibitor of RAC-alpha serine/threonine-protein kinase (PKB, proto-oncogene c-Akt) ($IC_{50}$ = 0.066 nM), RAC-beta serine/threonine-protein kinase (protein kinase Akt-2) ($IC_{50}$ = 1.4 nM) and RAC-gamma serine/threonine-protein kinase (protein kinase Akt-3) ($IC_{50}$ = 1.5 nM), aimed to establish the agent's MTD and recommended phase II dose in subjects with advanced solid tumors (14). The pharmacokinetics, pharmacodynamics and clinical activity of the compound were also addressed. In the dose-escalating part of the trial, 45 participants received GSK-2141795 at doses of 10, 20, 40, 75, 100 or 150 mg p.o. once daily. The MTD was estimated to be 75 mg once daily. DLTs included hypoglycemia (of grade 3-4 in severity) seen in the 75-, 100- and 150-mg dose groups, and mucositis (of grade 2 in severity) reported in patients in the 100-mg cohort. In the expansion phase of the study, a total of 31 patients with prostate and endometrial cancer received treatment with GSK-2141795 at the MTD. The most frequent (> 10%) drug-related AEs were diarrhea, nausea, fatigue, vomiting, decreased appetite, dyspepsia, hyperglycemia and rash. Pharmacokinetic analysis performed in 13 patients treated at the MTD revealed dose-proportional $AUC_{(0\text{-}24\ h)}$ and $C_{max}$ values. A PR was seen in one patient with anal cancer (15).

Findings were made available from the first-in-human evaluation of Onyx Pharmaceuticals' orally bioavailable proteasome inhibitor **ONX-0912**. The aims of the open-label, multicenter, dose-escalating, first-in-human phase I trial were to investigate the safety, tolerability and bioavailability of ONX-0912 and to establish the MTD in patients with recurrent or refractory advanced solid tumors (16). To date, a total of 25 participants have received 1-16 cycles of treatment with ONX-0912 administered at doses of 30-180 mg once daily every 14 days. Nausea, vomiting, fatigue and diarrhea (of any grade in severity) were the most frequent AEs, observed in ≥ 50% of patients. Treatment-related dehydration with vomiting and hypophosphatemia (both of grade 3 in severity) were the DLTs observed in two subjects treated with the 180-mg dose of the compound. The MTD was determined to be 150 mg/day. SD by RECIST was observed in 3 individuals who completed ≥ 15 cycles of therapy (1 with liposarcoma, 1 with prostate cancer and 1 with non-small cell lung cancer [NSCLC]), as well as in 1 participant with hepatocellular carcinoma who received 4 treatment cycles and 1 subject with chondrosarcoma who received 5 cycles of treatment. Pharmacokinetic/pharmacodynamic analysis revealed exposure to ONX-0912 in the plasma in all treated subjects, with maximum concentrations of up to 2.5 μM, thus exceeding the $IC_{50}$ for proteasome inhibition by > 50-fold. The agent correlated with inhibition of the chymotrypsin-like activity of the proteasome by > 80% at 1 hour after exposure in samples of whole blood in 50% of subjects treated at doses ≥ 90 mg. A phase Ib/II study has been planned to assess the effects of ONX-0912 in patients with hematological malignancies (17).

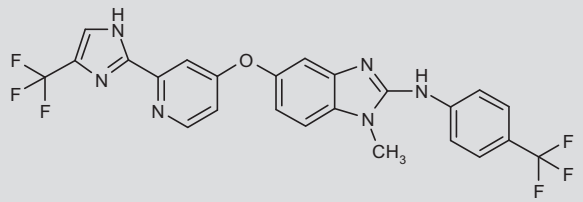
A first-in-human, dose-escalating phase I trial was conducted aiming to evaluate the effects of **RAF-265** (Novartis), a small-molecule



GSK-2126458



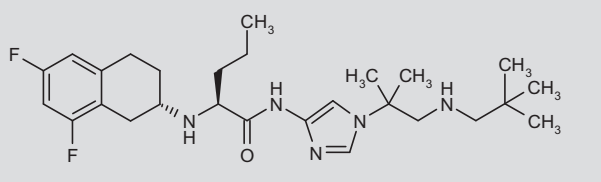
ONX-0912



RAF-265

inhibitor of V600E-mutated serine/threonine-protein kinase B-raf (*BRAF*), vascular endothelial growth factor receptor 2 (VEGFR-2), RAF proto-oncogene serine/threonine-protein kinase (proto-oncogene c-RAF), beta-type platelet-derived growth factor receptor (PDGF-R-β) and mast/stem cell growth factor receptor Kit (proto-oncogene c-Kit). Patients with locally advanced or metastatic cutaneous melanoma (N = 76) were treated at 8 oral RAF-265 dose levels, with a loading dose followed by daily doses of 2-67 mg once daily. The MTD was determined to be 48 mg once daily, with seven patients experiencing grade 3-4 thrombocytopenia after 1 cycle at 67 mg once daily. The seven DLTs recorded in six patients were hyperlipasemia, toxic retinopathy, ataxia, vision floater, diarrhea and pulmonary embolism. RAF-265 had a long half-life (11 days), and steady-state pharmacokinetics were dose-proportional at the higher doses. Best responses included six PRs across all RAF-265 doses and one complete response (CR) with 67 mg once daily. The median duration of response was 121 days and responses occurred in patients with and without *BRAF* mutations. There were also 13 partial metabolic responders according to fludeoxyglucose (FDG)-PET assessment of tumor metabolic activity. Significant changes in markers of angiogenesis were also observed over time at all dose levels. An intermittent dosing schedule is being evaluated, with the drug administered daily for 2 weeks followed by 1 week off on a 21-day cycle (18).

The first-in-patient, open-label, dose-escalating phase I trial of **PF-03084014** (PF-3084014; Pfizer) is evaluating the γ-secretase inhibitor in individuals with solid tumors. Its primary objective is the determination of the agent's MTD in subjects with advanced solid tumor malignancies and T-cell acute lymphoblastic leukemia/lymphoblastic lymphoma (19). Thirty participants with solid tumors have received escalating doses of PF-03084014 of 20, 40, 80, 100, 130 or 150 mg b.i.d. (n = 3, 3, 4, 8, 4 and 8, respectively) given continuously for 21 days. Treatment with the agent was described as safe and well



PF-03084014

tolerated. The most common treatment-related AEs were diarrhea, nausea, fatigue, decreased appetite, hypophosphatemia and rash (all of grade 1-2 in severity). The MTD has not been attained to date. Among 30 evaluable subjects, 1 with thyroid cancer receiving the 20-mg dose exhibited a CR by RECIST at cycle 19. A PR was reported in two subjects with desmoid tumors receiving the 80- and 150-mg doses. SD lasting for at least 6 weeks has been observed in 10 participants (20).

Genentech's **MEGF-0444A**, a humanized monoclonal antibody (MAb) targeting epidermal growth factor-like protein 7 (*EGFL7*), demonstrated good tolerability as a monotherapy in its first-in-human trial in patients with solid tumors (21). In the open-label, 3+3 design, dose-escalating phase Ia study, 30 individuals with advanced solid tumors received intravenous infusions of MEGF-0444A up to the highest planned dose of 15 mg/kg given every 3 weeks. Treatment with MEGF-0444A was well tolerated. The incidence of 10 serious and 8 non-serious AEs was not related to the treatment. A linear pharmacokinetic profile was observed. Dynamic contrast-enhanced MRI (DCE-MRI) measures suggested antiangiogenic activity of the antibody in selected patients (22).

A phase Ib trial was designed to investigate the safety, pharmacokinetics, pharmacodynamics and antitumor activity of MEGF-0444A in combination with the VEGF-targeted humanized MAb bevacizumab, with or without the microtubule-stabilizing agent paclitaxel, in 40 patients with advanced solid tumors (23). In arm A of the trial, MEGF-0444A was administered i.v. at doses of 2, 5 and 10 mg/kg with bevacizumab (10 mg/kg i.v.) to cohorts of 3, 3 and 6 subjects, respectively. The treatment was administered on days 1 and 15 of each 28-day cycle. Participants in arm B were also given paclitaxel (90 mg/m$^2$) on days 1, 8 and 15 of each cycle. Coadministration of MEGF-0444A with bevacizumab, with or without paclitaxel, was well tolerated. MEGF-0444A at 5 mg/kg was associated with maximal changes in DCE-MRI parameters and in the levels of circulating progenitor cells, indicative of antiangiogenic activity. The majority of AEs were rated as grade 1-2 in severity. Pharmacokinetic analysis showed a linear profile at the dose range under evaluation. The half-life of MEGF-0444A was estimated to be approximately 14 days (24).

Weekly administration of Chugai Pharmaceutical's **GC-33**, a humanized MAb targeting glypican-3 (*GPC3*), was safe in the first-in-human trial of the product in patients with advanced hepatocellular carcinoma (25). Twenty patients with incurable, locally advanced, recurrent or metastatic hepatocellular carcinoma received weekly i.v. infusions of GC-33 at doses of 2.5, 5, 10 or 20 mg/kg in the phase I trial. Fifteen participants had received prior therapy with sorafenib. Treatment with GC-33 was well tolerated at all doses, without DLTs. The most common AEs (of all grades in severity) were fatigue (50%), constipation, pyrexia and headache (35% each). Mild reactions at the site of infusion were observed in 40% of subjects only after the first infusion. Lymphopenia and hyponatremia (of grade 3-4 in severity; 10% each) were the most frequent treatment-related toxicities. The pharmacokinetic profile of the antibody was described as nonlinear. Trough concentrations in the serum reached steady state within three to six doses and the half-life was estimated at 2-7 days. SD lasting > 4 weeks was seen in four participants (26).

First-in-human data have been presented on **MORAb-004** (Ludwig Institute for Cancer Research, Morphotek), a humanized MAb

against endosialin (tumor endothelial marker 1) that recently received FDA orphan drug status in soft tissue sarcoma (27). The dose-escalating phase I trial included 33 patients with solid tumors who received MORAb-004 weekly by i.v. administration at 0.0625-16.0 mg/kg. The product was well tolerated at doses up to 12 mg/kg weekly. Seven serious AEs related to the study drug were reported in three subjects; all but one occurred with the dose of 16 mg/kg. Systemic exposure to MORAb-004 increased in a manner greater than dose-proportional across the entire dose range, and slow clearance with half-life estimates of 20-80 hours were noted. Three of 24 evaluable patients had treatment-emergent human anti-human antibody responses, which were associated with infusion toxicity. Tumor shrinkage was observed in four subjects, three of whom had prolonged disease control. The cohorts receiving MORAb-004 at 1, 2 and 4 mg/kg weekly were expanded in patients with soft tissue sarcoma and colorectal carcinoma to define an optimal dose using paired tumor biopsies and DCE-MRI (28).

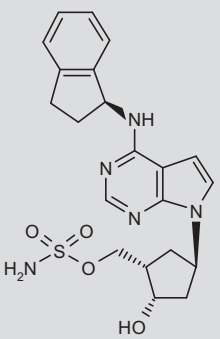
Preliminary results were recently disclosed from the ongoing first-in-human study of Pfizer's antiangiogenic CovX body **CVX-241**, a fusion protein comprising a recombinant humanized $IgG_1$ scaffold fused via a chemical linker to two engineered angiopoietin-2 (ANG-2)- and two VEGF-binding peptides (29). The multicenter, open-label, non-randomized, single-group assignment, dose-escalating phase I trial is evaluating CVX-241 administered as weekly infusions over 12 months to individuals with advanced solid tumors. Its primary endpoint is determination of the MTD of CVX-241 administered as weekly infusions over 12 months. In stage 1, cohorts of 3-6 subjects received CVX-241 at doses of 0.3, 1, 3, 6, 12, 15 or 18 mg/kg given as 90-minute i.v. infusions once weekly during 4-week treatment cycles. The MTD in stage 1 will be administered to an additional cohort of 18 patients in stage 2 of the study. Interim results obtained from 17 participants receiving CVX-241 at doses of 0.3-12 mg/kg suggest good tolerability of the product. No DLTs were reported and the most frequent AEs included fatigue (29%), decreased appetite (23%), back pain (18%) and dyspnea (18%). Escalating doses of CVX-241 (up to 3 mg/kg) correlated with increases in the levels of total ANG-2 in the serum (by 90-fold) and total VEGF in the plasma (by 2- to 3-fold). SD seen in 7 of 13 evaluable patients is the best overall response to date (30).

**EMD-640744** (Merck Serono, Merck KGaA), a vaccine comprising a mix of survivin-derived partially modified HLA class I-restricted peptides in montanide ISA-51 VG adjuvant, displayed immunological efficacy in the first-in-human study in patients with advanced solid tumors (31). The multicenter, open-label, randomized, parallel-group assignment phase I study of EMD-640744 was conducted in 53 subjects with different types of metastatic or locally advanced solid tumors (e.g., colorectal cancer [19%], ovarian cancer [17%] and melanoma [17%]) positive for at least one relevant HLA antigen (HLA class I histocompatibility antigen, A-1 alpha chain, HLA class I histocompatibility antigen, A-2 alpha chain, HLA class I histocompatibility antigen, A-3 alpha chain, HLA class I histocompatibility antigen, A-24 alpha chain, or HLA class I histocompatibility antigen, B-7 alpha chain). The trial assessed the agent's safety and tolerability, as well as its clinical and biological activity. The participants were randomized to receive EMD-640744 at doses of 30, 100 or 300 µg s.c. given once weekly during the 8-week initiation phase and once every 4 weeks in the maintenance phase of the trial. T-cell responses against the vaccine were detected by an interferon gamma (IFN-γ) Enzyme-Linked ImmunoSPOT (ELISPOT) assay and by peptide major histocompatibility complex (pMHC) class I multimer staining, respectively, in 14 of 38 and in 31 of 42 evaluable subjects. De novo responses were seen in 16 of 42 individuals. Immunostaining of intracellular cytokines demonstrated the induction of vaccine-specific T-cell surface glycoprotein $CD4^+$ T cells that could be blocked by antibodies against HLA class II histocompatibility antigens in 15 of 22 patients who also exhibited survivin-specific T-cell surface glycoprotein $CD8^+$ T-cell responses detected by pMCH class I multimer staining (32).

The first clinical study of **ATU-027** (Silence Therapeutics), an RNAi therapy targeting serine/threonine-protein kinase N3 (*PKN3*) expression in the vascular endothelium, is under way and early results are available (33). The product utilizes Silence Therapeutics' proprietary AtuPLEX™ delivery technology. ATU-027 is being administered to patients with advanced solid tumors, first as single 4-hour infusions and then, after 3 weeks, as twice-weekly infusions over 4 weeks. Doses of 0.001-0.447 mg/kg are to be administered, and at the time of reporting, 24 patients had been treated with doses of 0.001-0.180 mg/kg. There were 14 AEs in these patients, with only 1 (mood alteration) deemed related to ATU-027. Fatigue was the most common AE, occurring in eight subjects. No dose-related trends in clinical or laboratory AEs were observed and the MTD was not reached. Premedication to suppress immune responses was not required. SD was noted in nine patients assessed 1 week after the repeated treatment and six cases of SD were confirmed at the end of the study. Dose-dependent plasma exposure was noted. Three patients continued treatment after study completion, while dose escalation continued (34).

## PHASE I TRIALS

The safety, antitumor activity, pharmacokinetics and pharmacodynamics of Millennium Pharmaceuticals' small-molecule NEDD8-activating enzyme E1 regulatory subunit (*NAE*) inhibitor **MLN-4924** were assessed in a phase I trial in adults with metastatic melanoma. Determination of the agent's MTD was among its primary objectives (35). The participants (N = 20) received 1-hour i.v. infusions of MLN-4924 at doses of 50, 67, 89, 118, 157, 209 or 278 mg/m$^2$ (n = 2, 2, 2,



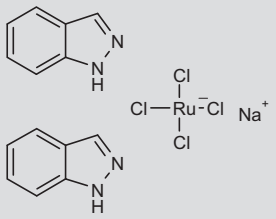

MLN-4924

4, 2, 6 and 2, respectively) on days 1, 4, 8 and 11 of 21-day treatment cycles (schedule A). MLN-4924 will also be assessed in an alternative dosing schedule (schedule B) given on days 1, 8 and 15 of each 21-day cycle. Hypophosphatemia and elevated creatinine kinase in the serum (both of grade 3 in severity) were the DLTs reported, respectively, in one patient receiving MLN-492 at 118 mg/m$^2$ and in one subject treated at the dose of 278 mg/m$^2$. The MTD was estimated at 209 mg/m$^2$. One subject with tumors expressing wild-type *BRAF* exhibiting rapidly progressive disease at entry achieved a PR by RECIST at cycle 4, and SD as best response was observed in 9 of 20 participants. The rate of disease control was estimated at 50% (36).

Patients with non-hematological solid tumors (including colorectal carcinoma, melanoma and gastric cancer) received treatment with MLN-4924 at doses of 50, 67 or 89 mg/m$^2$ on days 1, 3 and 5 of each 21-day cycle, with or without dexamethasone (8 mg; schedules B and C, respectively) given prior to MLN-4924 and on days 1, 3 and 5, in a phase I trial (37). At the time of reporting, 17 participants were treated in schedule B and 18 received treatment according to schedule C. With schedule B dosing at 50 mg/m$^2$, the DLT was elevated levels of alanine aminotransferase (ALT; grade 3 in severity). DLTs with schedule C included hyperbilirubinemia and prolonged elevation in the levels of aspartate aminotransferase (AST; both of grade 2 in severity) seen with dosing at 89 mg/m$^2$. The MTDs with schedules B and C were estimated to be 50 and 67 mg/m$^2$, respectively. SD lasting ≥ 4 cycles was the best response in seven subjects, including five patients treated in schedule B with melanoma, colorectal carcinoma and head and neck cancer (n = 3, 1 and 1, respectively) and two patients with colorectal carcinoma treated in schedule C (38).

Azaya Therapeutics is developing **ATI-1123**, a liposomal nanoparticle formulation of docetaxel, in the hope that it can provide enhanced exposure and better tolerability than standard docetaxel in patients with solid tumors. In a phase I trial, 29 individuals with advanced solid tumors whose disease was progressive following standard therapy received ATI-1123 at i.v. doses of 15, 30, 60, 75, 90 or 110 mg/m$^2$ given every 3 weeks (39). Two DLTs were noted at 110 mg/m$^2$: grade 3 febrile neutropenia and grade 3 stomatitis. The MTD was determined to be 90 mg/m$^2$, while dosing at 75 mg/m$^2$ was ongoing at the time of reporting. A PR was observed in a patient with NSCLC, while 18 other participants had SD. Pharmacokinetics appeared to be linear at most doses and $C_{max}$ and AUC values were up to fourfold higher and clearance up to fourfold lower with ATI-1123 than with standard docetaxel (40).

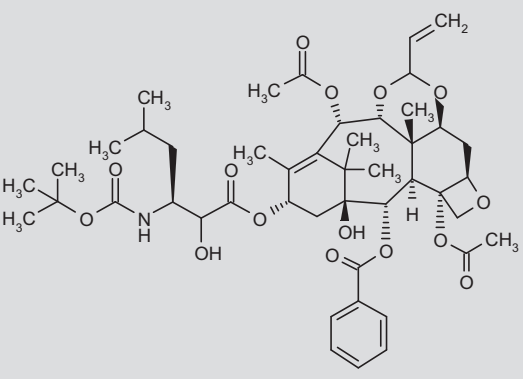
The small molecule **NKP-1339** is a first-in-class serotransferrin (transferrin)-targeted ruthenium-based proapoptotic agent that is currently undergoing clinical evaluation at Niiki Pharma. Preliminary findings from a phase I study suggest promising antitumor activity and manageable toxicity. The ongoing, open-label, dose-escalating phase I trial was designed to assess the safety, tolerability, pharmacokinetics and pharmacodynamics of NKP-1339 in patients with advanced solid tumors refractory to previous treatment. Tumor types of the participants include colon, neuroendocrine, head and neck, ovarian, cervical and pancreatic cancer, as well as NSCLC. The product was administered i.v. as a 30- to 90-minute infusion to 16 subjects at doses of 20, 40, 80, 160, 320 or 420 mg/m$^2$ on days 1, 8 and 15 of a 28-day cycle. The most frequent AEs (of grade 1-2 in severity)



NKP-1339

included nausea (n = 5), chills (n = 4), pyrexia and plasma discoloration (n = 3 each), as well as vomiting, gastroesophageal reflux disease, headache and phlebitis (n = 2 each). Six patients experienced fatigue of grade 1-3 in severity. Transient discoloration of the plasma and urine was reported in several subjects receiving NKP-1339 at 420 mg/m$^2$. The MTD has not been established to date and dose escalation is ongoing, with two additional patients receiving a dose of 500 mg/m$^2$. Interim pharmacokinetic data revealed dose-proportional $C_{max}$ and $AUC_{(0\text{-}192\ h)}$ values at doses of 20-320 mg/m$^2$ (41).

The microtubule-stabilizing agent **TPI-287** (Archer Biosciences/Tapestry Pharmaceuticals) was evaluated as monotherapy or in combination with temozolomide in pediatric and young adult patients with recurrent/refractory neuroblastoma or medulloblastoma. The aim of the open-label, multicenter, dose-escalating phase I trial was to investigate the safety, tolerability and MTD of TPI-287 administered as a single agent (42). Exploratory data on the safety and tolerability of the compound in combination with temozolomide were also collected. Assessments of the overall rate of response and progression-free survival (PFS) constituted the study's secondary objectives. The participants (N = 14) received TPI-287 as monotherapy at 90, 110, 125 or 135 mg/m$^2$ as 60-minute i.v. infusions on days 1, 8 and 15 of each 28-day cycle, or in combination with temozolomide (50 mg/m$^2$ p.o.) given on days 1-5 in cycles 3-6. Seizures in the

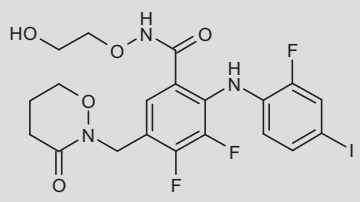


TPI-287

110 mg/m$^2$ cohort, as well as hematuria and neuropathy seen in the group receiving 135 mg/m$^2$ TPI-287 (all of grade 3 in severity), were identified as DLTs in safety analysis performed in all 14 subjects. The MTD of TPI-287 as a single agent was established at 125 mg/m$^2$. The addition of temozolomide was not associated with additional toxicities. SD lasting for ≥ 2 treatment cycles was reported in 7 of 11 evaluable patients. PFS was determined at 125 days. The mean PFS in individuals with SD was estimated at 177 days, versus 34 days in subjects with progressive disease (43).

**RO-4987655** (Roche) is a potent and highly selective non-ATP-competitive inhibitor of dual specificity mitogen-activated protein kinase kinase 1 (MKK1/MEK 1). In a phase I trial, 49 patients with advanced or metastatic solid tumors, including melanoma, colorectal carcinoma and NSCLC (n = 27, 11 and 3, respectively), received continuous once-daily doses of RO-4987655 at 1-2.5 mg p.o. followed by twice-daily administration at 3-21 mg/day p.o. in 28-day cycles (44). The aim of the study was to determine the MTD and the recommended phase II dose of the agent. Assessments of the safety and tolerability, including DLTs, were also performed, as were evaluation of the pharmacokinetics, pharmacodynamics and clinical activity of the compound. DLTs were identified as elevation in the levels of creatine kinase seen in one and two patients treated with the 17- and 21-mg dose, respectively, and blurred vision observed in the 21-mg cohort. The MTD and recommended phase II dose were established at 17 mg. The most frequently reported treatment-related AEs included skin reactions (91%), gastrointestinal disorders (57%), eye conditions (26%) and disorders associated with abnormal levels of creatine kinase (44%). Pharmacokinetic analysis revealed a linear profile in the dose range under evaluation, with a half-life of 4-6 hours and drug accumulation of approximately twofold at steady state. Two patients with melanoma exhibited a PR and five exhibited SD (lasting ≥ 4 months) by RECIST (45).

Two phase I trials were conducted in advanced solid tumors and refractory lymphomas to evaluate Roche's **RG-7112** (RO-5045337), a selective inhibitor of the interaction between cellular tumor antigen p53 and E3 ubiquitin-protein ligase Mdm2 (oncoprotein Mdm2). The first trial included 49 individuals with acute myeloid leukemia (AML), acute lymphoblastic leukemia (ALL), chronic myeloid leukemia (CML) in blast phase, refractory chronic lymphocytic leukemia (CLL) or stem cell leukemia/lymphoma, and the second study included 76 subjects with solid tumors (46, 47). The participants received treatment with an oral tablet formulation of RG-7112 administered at doses of 20-1920 mg/m$^2$/day once daily or b.i.d. for 10 days with an 18-day resting period between consecutive cycles. Pharmacokinetic profiling of the agent showed dose-proportional exposure, with no accumulation in the dose range under evaluation. The concentration of the compound in the plasma reached peak levels at approximately 4 hours after dosing at steady state on day 10 and subsequently declined with a mean half-life of approximately 1.5 days. Patients with solid tumors exhibited twofold higher exposure to RG-7112 than subjects with leukemia treated at comparable dose levels (48).



RO-4987655

In a proof-of-mechanism study, 20 adults with neoadjuvant liposarcoma (n = 11 and 9 with well- and de-differentiated liposarcoma, respectively) were treated with RG-7112 (at 1440 mg/m$^2$ p.o. once daily) for 10 days on a 28-day cycle (49). The most frequent AEs (of grade 3-4 in severity) were thrombocytopenia (n = 5), neutropenia (n = 3; including one report of febrile neutropenia) and vomiting (n = 2). Treatment with RG-7112 correlated with increases in the levels of mRNA transcripts of cellular tumor antigen p53, cyclin-dependent kinase inhibitor 1 (p21) and E3 ubiquitin-protein ligase Mdm2, with concomitant decreases in cellular proliferation. Elevated levels of growth/differentiation factor 15 (macrophage inhibitory cytokine 1, MIC-1) in the blood were seen following treatment with the agent and correlated with increased apoptosis. Early signs of clinical activity included 1 PR (seen after 1 cycle of treatment) and SD reported in 14 participants (50).

**PF-04554878** (PF-4554878; Pfizer), a second-generation reversible inhibitor of focal adhesion kinase 1 (FADK 1) and protein-tyrosine kinase 2-beta (focal adhesion kinase 2, FADK 2), is undergoing evaluation in a phase I study in patients with solid tumors, including colorectal carcinoma, as well as pancreatic, ovarian, bile duct and breast cancer (n = 15, 4, 3, 3 and 2, respectively) (51). A total of 36 participants have received continuous treatment with PF-04554878 at doses of 12.5-750 mg p.o. b.i.d. administered on a fasting schedule on 21-day cycles. Commonly reported treatment-related AEs (all of grade 1-2 in severity) included nausea (33%), vomiting (31%), unconjugated hyperbilirubinemia (31%) and fatigue (25%), as well as headache, diarrhea and decreased appetite (19% each). One patient in the 200-mg cohort exhibited headache (of grade 3 in severity) and one subject each in the 300- and 425-mg dose groups displayed unconjugated hyperbilirubinemia (of grade 3 in severity) that constituted DLTs. The recommended phase II dose on a fasting schedule has been determined at 425 mg b.i.d. Stable disease by RECIST has been observed at the end of cycle 2 in 41% of participants treated with twice-daily doses ≥ 100 mg (52).

**KW-2450**, a potent small-molecule antagonist of insulin-like growth factor 1 receptor (IGF-I receptor) and insulin receptor (IR), is undergoing clinical development at Kyowa Hakko Kirin for the treatment of solid tumors. An open-label, non-randomized, parallel-assignment, sequential, multiple-ascending-dose phase I study was designed to investigate the safety, tolerability, pharmacokinetics and pharmacodynamics of KW-2450 in patients with previously treated advanced solid tumors (53). Participants (N = 13) received treatment with the agent at 50 or 37.5 mg p.o. once daily (the starting and amended dose, respectively) for 28 days, followed by a 1-week observation period. Administration of the compound on a continuous daily schedule ensued. The mean duration of treatment was 12.6 weeks. DLTs of grade 3 in severity included non-fasting hyperglycemia and rash in two of six patients, respectively, treated at the starting dose

of 50 mg/day and in one of seven subjects in the 37.5-mg dose group. The MTD was determined to be 37.5 mg/day. Fatigue (77%), nausea (69%) and pain (46%) were the most common AEs. No CRs or PRs were reported. The half-life of KW-2450 was estimated at 10-13 hours and the $C_{max}$ was calculated to be 2.4-3 µg/mL (54).

The potent and selective small-molecule Toll-like receptor 8 agonist **VTX-2337** (VentiRx Pharmaceuticals) was evaluated in an open-label, non-randomized, single-group assignment phase I trial in patients with advanced solid tumors (55). Participants (N = 33) received escalating doses of VTX-2337 (0.1-3.9 mg/m$^2$) given s.c. to 8 cohorts of 3-8 patients on days 1, 8 and 15 of a 28-day treatment cycle. The most common types of solid tumors were colorectal and pancreatic cancer and melanoma (n = 9, 6 and 5, respectively). Safety evaluation identified reaction at the site of injection, chills, fever and flu-like symptoms as the most frequent drug-related AEs (85%, 58%, 42% and 24%, respectively; all of grade 1-2 in severity). There were no drug-related hematological or other laboratory toxicities. The MTD was established at 3.9 mg/m$^2$, with hypotension of grade 3 in severity being the DLT observed in one of six evaluable patients. Stabilization of disease at 8 weeks of treatment according to RECIST was reported in 25% of subjects. One participant displayed regression of tumors following cessation of treatment with the agent. Based on these findings, VTX-2337 is expected to enhance the efficacy of standard-of-care anticancer treatment approaches. The product will also be assessed in several tumor types, including ovarian, breast and head and neck cancer, as well as NHL, in combination with chemotherapy or radiation (56).

The safety, immunogenicity and antitumor activity of combined i.v. and intradermal (i.d.) dosing of **TriMix-DC** (Vrije Universiteit Brussel) were evaluated in patients with previously treated unresectable melanoma. The product is a vaccine comprising autologous monocyte-derived dendritic cells (DCs) electroporated with TriMix synthetic messenger RNA (smRNA), which encodes CD40 ligand, constitutively active Toll-like receptor 4 and CD70 antigen, and with smRNA encoding melanoma-associated antigen 3 (*MAGEA3*), melanoma-associated antigen C2 (*MAGEC2*), tyrosinase (*TYR*) and melanocyte protein PMEL (*PMEL*) linked to lysosome-associated membrane glycoprotein 3 (*LAMP3*). In a phase I study, patients with advanced melanoma (stage IIIC or IV) received TriMix-DC as four i.d./i.v. injections given once every 2 weeks followed by a fifth injection at week 16 (57). The vaccine was administered i.v. at doses of 4 x $10^6$, 12 x $10^6$, 20 x $10^6$ and 24 x $10^6$ DCs, respectively, in cohorts 1 (n = 3), 2 (n = 3), 3 (n = 3+3) and 4 (n = 3), and i.d. at doses of 20 x $10^6$, 12 x $10^6$, 4 x $10^6$ and 0 DCs, respectively, in cohorts 1, 2, 3 and 4. Treatment with TriMix-DC correlated with manageable AEs, including reactions at the injection site, fever and lethargy (all of grade 1 in severity), as well as chills (of grade 2 in severity). One patient has exhibited a CR by RECIST, whereas PR and SD were reported in two and six participants, respectively. Progressive disease was observed in four patients. The median PFS has been estimated at 5.2 months (58).

GlobeImmune's **GI-6207** (yeast-CEA-6D), a vaccine comprising whole heat-killed *Saccharomyces cerevisiae* that has been genetically engineered to express carcinoembryonic antigen-related cell adhesion molecule 5 (CEA), exhibited safety in patients with metastatic carcinoma expressing CEA. GI-6207 was administered s.c. to 25 patients with metastatic cancer at doses of 4, 16 or 40 yeast units (each unit = $10^7$ yeast particles) at 2-week intervals for a period of 3 months and once per month thereafter in a phase I study (59). Tumor types included colon cancer (n = 20) and rectal carcinoma (n = 2), as well as pancreatic, medullary thyroid and NSCLC (n = 1 each). Reaction at the injection site (of grade 1-2 in severity) was the most common AE. No toxicities of grade ≥ 3 in severity that could be attributable to the vaccine were reported. SD at 3 months coupled with stable or declining levels of CEA was observed in 5 of 25 subjects. No antibodies to CEA were detected in the serum of patients prior to or following vaccination with GI-6207. A phase II trial has been planned to evaluate the vaccine in subjects with medullary thyroid cancer displaying elevated levels of CEA and calcitonin (60).

## CONCLUDING REMARKS

Encouraging findings from a number of first-in-human and phase I clinical trials were disclosed at the 47th ASCO meeting. Therapeutic modalities including small molecules, MAbs, vaccines and RNAi-based approaches were evaluated in patients with cancer and may hold promise for the treatment of a wide range of malignancies.

## DISCLOSURES

The authors state no conflicts of interest.

## REFERENCES


1. Richards, J.M., Warso, M.A., Mehta, D. et al. *A first-in-class, first-in-human phase I trial of p28, a non-HDM2-mediated peptide inhibitor of p53 ubiquitination in patients with metastatic refractory solid tumors.* J Clin Oncol [47th Annu Meet Am Soc Clin Oncol (ASCO) (June 3-7, Chicago) 2011] 2011, 29(Suppl.): Abst 2511.
2. *Safety study of a cell penetrating peptide (p28) to treat solid tumors that resist standard methods of treatment (NCT00914914).* ClinicalTrials.gov Web site, June 7, 2011.
3. Donehower, R.C., Scardina, A., Hill, M. et al. *A phase I dose-escalation study of INCB028060, an inhibitor of c-MET receptor tyrosine kinase, in patients with advanced solid tumors.* J Clin Oncol [47th Annu Meet Am Soc Clin Oncol (ASCO) (June 3-7, Chicago) 2011] 2011, 29(Suppl.): Abst 3091.
4. *A dose-escalation study in subjects with advanced malignancies (NCT01072266).* ClinicalTrials.gov Web site, May 23, 2011.
5. Shih, K.C., Infante, J.R., Papadopoulos, K.P. et al. *A phase I dose-escalation study of LY2523355, an Eg5 inhibitor, administered either on days 1, 5, and 9; days 1 and 8; or days 1 and 5 with pegfilgrastim (peg) every 21 days (NCT01214642).* J Clin Oncol [47th Annu Meet Am Soc Clin Oncol (ASCO) (June 3-7, Chicago) 2011] 2011, 29(Suppl.): Abst 2600.
6. *A dose-escalation study for patients with advanced cancer (NCT01214642).* ClinicalTrials.gov Web site, August 15, 2011.
7. Hayashi, H., Kurata, T., Fujisaka, Y. et al. *First-in-human phase I study of the antiangiogenic vaccine (OTS11101) targeting VEGFR-1 in patients with solid tumors.* J Clin Oncol [47th Annu Meet Am Soc Clin Oncol (ASCO) (June 3-7, Chicago) 2011] 2011, 29(Suppl.): Abst 2568.
8. *BAY80-6946 open label, phase I study in patients with advanced cancer (NCT00962611).* ClinicalTrials.gov Web site, August 24, 2011.
9. A. Patnaik, A., Appleman, L.J., Mountz, J.M. et al. *A first-in-human phase I study of intravenous PI3K inhibitor BAY 80-6946 in patients with advanced solid tumors: Results of dose-escalation phase.* J Clin Oncol [47th Annu Meet Am Soc Clin Oncol (ASCO) (June 3-7, Chicago) 2011] 2011, 29(Suppl.): Abst 3035.

10. *Phase I study of MK-1496 in patients with advanced solid tumor (MK-1496-002 AM 4) (completed) (NCT00880568).* ClinicalTrials.gov Web site, February 11, 2011.
11. Doi, T., Murakami, H., Wan, K. et al. *A first-in-human phase I dose-escalation study of MK-1496, first-in-class orally available novel PLK1 inhibitor, in patients with advanced solid tumors*. J Clin Oncol [47th Annu Meet Am Soc Clin Oncol (ASCO) (June 3-7, Chicago) 2011] 2011, 29(Suppl.): Abst 3012.
12. *Dose-escalation study of GSK2126458 (FTIH) (NCT00972686).* ClinicalTrials.gov Web site, September 1, 2011.
13. Munster, P.N., van der Noll, R., Voest, E.E. et al. *Phase I first-in-human study of the PI3 kinase inhibitor GSK2126458 (GSK458) in patients with advanced solid tumors (study P3K112826).* J Clin Oncol [47th Annu Meet Am Soc Clin Oncol (ASCO) (June 3-7, Chicago) 2011] 2011, 29(Suppl.): Abst 3018.
14. *A phase I, open-label, first-time-in-human study of the oral AKT inhibitor GSK2141795 (NCT00920257).* ClinicalTrials.gov Web site, June 9, 2011.
15. Burris, H.A., Siu, L.L., Infante, J.R. et al. *Safety, pharmacokinetics (PK), pharmacodynamics (PD), and clinical activity of the oral AKT inhibitor GSK2141795 (GSK795) in a phase I first-in-human study.* J Clin Oncol [47th Annu Meet Am Soc Clin Oncol (ASCO) (June 3-7, Chicago) 2011] 2011, 29(Suppl.): Abst 3003.
16. *Phase 1 study of ONX 0912 administered orally in patients with advanced refractory or recurrent solid tumors (NCT01129349).* ClinicalTrials.gov Web site, May 5, 2011.
17. Papadopoulos, K.P., Mendelson, D.S., Tolcher, A.W. et al. *A phase I, open-label, dose-escalation study of the novel oral proteasome inhibitor (PI) ONX 0912 in patients with advanced refractory or recurrent solid tumors.* J Clin Oncol [47th Annu Meet Am Soc Clin Oncol (ASCO) (June 3-7, Chicago) 2011] 2011, 29(Suppl.): Abst 3075.
18. Sharfman, W.H., Hodi, F.S., Lawrence, D.P. et al. *Results from the first-in-human (FIH) phase I study of the oral RAF inhibitor RAF265 administered daily to patients with advanced cutaneous melanoma*. J Clin Oncol [47th Annu Meet Am Soc Clin Oncol (ASCO) (June 3-7, Chicago) 2011] 2011, 29(Suppl.): Abst 8508.
19. *A trial in patients with advanced cancer and leukemia (NCT00878189).* ClinicalTrials.gov Web site, August 13, 2011.
20. Messersmith, W.A., LoRusso, P., Cleary, J.M. et al. *A phase I dose-escalation study of the novel gamma secretase inhibitor PF-03084014 in patients (pts) with advanced solid tumors.* J Clin Oncol [47th Annu Meet Am Soc Clin Oncol (ASCO) (June 3-7, Chicago) 2011] 2011, 29(Suppl.): Abst 3100.
21. *A study of the safety and pharmacokinetics of MEGF0444A administered to patients with advanced solid tumors (NCT00909740).* ClinicalTrials.gov Web site, August 26, 2010.
22. Rosen, L.S., Gordon, M.S., Bai, S. et al. *A first-in-human phase Ia open-label dose-escalation study of the safety, pharmacokinetics (PK), and pharmacodynamics (PD) of the humanized monoclonal antibody (huMAb) anti-EGFL7 (MEGF0444A) administered intravenously in patients with advanced solid tumors.* J Clin Oncol [47th Annu Meet Am Soc Clin Oncol (ASCO) (June 3-7, Chicago) 2011] 2011, 29(Suppl.): Abst 2614.
23. *A study of the safety and pharmacology of MEGF0444A in combination with bevacizumab with or without paclitaxel in patients with locally advanced or metastatic solid tumors (NCT01075464).* ClinicalTrials.gov Web site, July 20, 2010.
24. Naumovski, L., Gordon, M.S., Munster, P.N. et al. *A phase Ib dose-escalation study of the safety, pharmacokinetics (PK), pharmacodynamics (PD), and antitumor activity of the humanized monoclonal antibody (huMAb) anti-EGFL7 (MEGF0444A) in combination with bevacizumab with or without paclitaxel in patients with advanced solid tumors.* J Clin Oncol [47th Annu Meet Am Soc Clin Oncol (ASCO) (June 3-7, Chicago) 2011] 2011, 29(Suppl.): Abst 2514.
25. *A phase I study of GC33 in advanced or metastatic liver cancer (hepatocellular carcinoma) (NCT00746317).* ClinicalTrials.gov Web site, August 15, 2011.
26. Zhu, A.X., Gold, P.J., El-Khoueiry, A.B., Abrams, T.A., Morikawa, H., Ohtomo, T., Philip, P.A. *A phase I study of GC33, a recombinant humanized antibody against glypican-3, in patients with advanced hepatocellular carcinoma (HCC)*. J Clin Oncol [47th Annu Meet Am Soc Clin Oncol (ASCO) (June 3-7, Chicago) 2011] 2011, 29(Suppl.): Abst 4085.
27. *A study of MORAb-004 in subjects with solid tumors (NCT00847054).* ClinicalTrials.gov Web site, August 25, 2011.
28. Carvajal, R.D., Gounder, M.M., Coughlin, C.M. et al. *A first-in-human phase I study of MORAb-004 (MOR4), a humanized monoclonal antibody recognizing TEM-1 (endosialin), in patients with solid tumors*. J Clin Oncol [47th Annu Meet Am Soc Clin Oncol (ASCO) (June 3-7, Chicago) 2011] 2011, 29(Suppl.): Abst 3086.
29. *A safety, tolerability, and pharmacokinetic trial with CVX-241 in patients with advanced solid tumors (NCT01004822).* ClinicalTrials.gov Web site, August 13, 2011.
30. Mendelson, D.S., Rosen, L.S., Gordon, M.S. et al. *First-in-human dose-escalation safety and PK trial of a novel humanized monoclonal CovX body dual inhibitor of angiopoietin 2 and vascular endothelial growth factor.* J Clin Oncol [47th Annu Meet Am Soc Clin Oncol (ASCO) (June 3-7, Chicago) 2011] 2011, 29(Suppl.): Abst 3055.
31. *EMD 640 744 in montanide ISA 51 VG administered in subjects with advanced solid tumors (NCT01012102).* ClinicalTrials.gov Web site, August 5, 2010.
32. Gross, S., Lennerz, V., Gallerani, E. et al. *First-in-human trial focusing on the immunologic effects of the survivin-derived multiepitope vaccine EMD640744*. J Clin Oncol [47th Annu Meet Am Soc Clin Oncol (ASCO) (June 3-7, Chicago) 2011] 2011, 29(Suppl.): Abst 2515.
33. *Study with Atu027 in patients with advanced solid cancer (NCT00938574).* ClinicalTrials.gov Web site, June 10, 2011.
34. Strumberg, D., Schultheis, B., Traugott, U. et al. *First-in-human phase I study of Atu027, a liposomal small interfering RNA formulation, targeting protein kinase N3 (PKN3) in patients with advanced solid tumors*. J Clin Oncol [47th Annu Meet Am Soc Clin Oncol (ASCO) (June 3-7, Chicago) 2011] 2011, 29(Suppl.): Abst 3057.
35. *Dose escalation study of MLN4924 in adults with melanoma (NCT01011530).* ClinicalTrials.gov Web site, April 26, 2011.
36. Bhatia, S., Hamid, O., Pavlick, A.C. et al. *MLN4924, an investigational NEDD8-activating enzyme (NAE) inhibitor, in patients (pts) with metastatic melanoma: Results of a phase I study.* J Clin Oncol [47th Annu Meet Am Soc Clin Oncol (ASCO) (June 3-7, Chicago) 2011] 2011, 29(Suppl.): Abst 8529.
37. *Study of MLN4924 in adult patients with nonhematologic malignancies (NCT00677170).* ClinicalTrials.gov Web site, July 13, 2011.
38. Kauh, J., S., Shapiro, G., Cohen, R.B. et al. *MLN4924, an investigational NEDD8-activating enzyme (NAE) inhibitor, in patients (pts) with advanced solid tumors: Phase I study of multiple treatment schedules*. J Clin Oncol [47th Annu Meet Am Soc Clin Oncol (ASCO) (June 3-7, Chicago) 2011] 2011, 29(Suppl.): Abst 3013.
39. *Safety study of a liposomal docetaxel formulation in patients with solid tumors who have failed previous therapies (NCT01041235).* ClinicalTrials.gov Web site, July 28, 2010.
40. Vemulapalli, S., Mita, A.C., Gallegos, N.S. et al. *Phase I study of ATI-1123, a novel human serum albumin-stabilized docetaxel liposomal formulation, in patients with advanced solid malignancies.* J Clin Oncol [47th Annu Meet Am Soc Clin Oncol (ASCO) (June 3-7, Chicago) 2011] 2011, 29(Suppl.): Abst 2609.

41. Dickson, N.R., Jones, S.F., Burris, H.A. et al. *A phase I dose-escalation study of NKP-1339 in patients with advanced solid tumors refractory to treatment*. J Clin Oncol [47th Annu Meet Am Soc Clin Oncol (ASCO) (June 3-7, Chicago) 2011] 2011, 29(Suppl.): Abst 2607.
42. *Trial of TPI 287 as a single agent and in combination with temozolomide in patients with refractory or recurrent neuroblastoma or medulloblastoma (NCT00867568).* ClinicalTrials.gov Web site, May 24, 2011.
43. Saulnier Sholler, G.L., Eslin, D., Roberts, W.D. et al. *Phase I trial of TPI 287 as a single agent and in combination with temozolomide (TMZ) in patients with refractory or recurrent neuroblastoma (NB) or medulloblastoma (MB).* J Clin Oncol [47th Annu Meet Am Soc Clin Oncol (ASCO) (June 3-7, Chicago) 2011] 2011, 29(Suppl.): Abst 9554.
44. *A dose-escalating study of RO4987655 in patients with advanced solid tumors (NCT00817518).* ClinicalTrials.gov Web site, July 19, 2011.
45. Leijen, S., Middleton, M.R., Tresca, P. et al. *Phase I (Ph) safety, pharmacodynamic (PD), and pharmacokinetic (PK) trial of a pure MEK inhibitor (i), RO4987655, in patients with advanced /metastatic solid tumor*. J Clin Oncol [47th Annu Meet Am Soc Clin Oncol (ASCO) (June 3-7, Chicago) 2011] 2011, 29(Suppl.): Abst 3017.
46. *A study of RO5045337 [RG7112] in patients with hematologic neoplasms (NCT00623870).* ClinicalTrials.gov Web site, July 19, 2011.
47. *A study of RO5045337 [RG7112] in patients with advanced solid tumors (NCT00559533).* ClinicalTrials.gov Web site, July 19, 2011.
48. Beryozkina, A., Nichols, G.L., Reckner, M. et al. *Pharmacokinetics (PK) and pharmacodynamics (PD) of RG7112, an oral murine double minute 2 (MDM2) antagonist, in patients with leukemias and solid tumors* . J Clin Oncol [47th Annu Meet Am Soc Clin Oncol (ASCO) (June 3-7, Chicago) 2011] 2011, 29(Suppl.): Abst 3039.
49. *A study of RO5045337 in patients with liposarcomas prior to debulking surgery (NCT01143740).* ClinicalTrials.gov Web site, July 19, 2011.
50. Ray-Coquard, I.L., Blay, J., Italiano, A. et al. *Neoadjuvant MDM2 antagonist RG7112 for well-differentiated and dedifferentiated liposarcomas (WD/DD LPS): A pharmacodynamic (PD) biomarker study*. J Clin Oncol [47th Annu Meet Am Soc Clin Oncol (ASCO) (June 3-7, Chicago) 2011] 2011, 29(Suppl.): Abst 10007b.
51. *A study of PF-04554878 in patients with advanced non-hematologic malignancies (B0761001) (NCT00787033).* ClinicalTrials.gov Web site, August 13, 2011.
52. Jones, S.F., Shapiro, G., Bendell, J.C. et al. *Phase I study of PF-04554878, a second-generation focal adhesion kinase (FAK) inhibitor, in patients with advanced solid tumors*. J Clin Oncol [47th Annu Meet Am Soc Clin Oncol (ASCO) (June 3-7, Chicago) 2011] 2011, 29(Suppl.): Abst 3002.
53. *Safety study to evaluate KW-2450 in subjects with advanced solid tumor (NCT00921336).* ClinicalTrials.gov Web site, September 9, 2010.
54. Dickson, M.A., LoRusso, P., Sausville, E.A. et al. *Open-label, sequential, ascending, multi-dose, phase I study of KW-2450 as monotherapy in subjects with previously treated advanced solid tumors*. J Clin Oncol [47th Annu Meet Am Soc Clin Oncol (ASCO) (June 3-7, Chicago) 2011] 2011, 29(Suppl.): Abst 3078.
55. *Safety and pharmacologic study of VTX-2337 in patients with advanced cancer (NCT00688415).* ClinicalTrials.gov Web site, December 21, 2010.
56. Cohen, P.A., Northfelt, D.W., Weiss, G.J. et al. *Phase I clinical trial of VTX-2337, a selective toll-like receptor 8 (TLR8) agonist, in patients with advanced solid tumors.* J Clin Oncol [47th Annu Meet Am Soc Clin Oncol (ASCO) (June 3-7, Chicago) 2011] 2011, 29(Suppl.): Abst 2537.
57. *A study on the safety and immunogenicity of combined intradermal and intravenous administration of an autologous mRNA electroporated dendritic cell vaccine in patients with previously treated unresectable stage III or IV melanoma (NCT01066390).* ClinicalTrials.gov Web site, February 23, 2011.
58. Neyns, B., Wilgenhof, S., Van Nuffel, A.M.T. et al. *A phase I clinical trial on the combined intravenous (IV) and intradermal (ID) administration of autologous TriMix-DC cellular therapy in patients with pretreated melanoma (TriMixIDIV).* J Clin Oncol [47th Annu Meet Am Soc Clin Oncol (ASCO) (June 3-7, Chicago) 2011] 2011, 29(Suppl.): Abst 2519.
59. *An open label phase I study to evaluate the safety and tolerability of a vaccine (GI-6207) consisting of whole, heat-killed recombinant Saccharomyces cerevisiae (yeast) genetically modified to express CEA protein in adults with metastatic CEA-expressing carcinoma (NCT00924092).* ClinicalTrials.gov Web site, August 24, 2011.
60. Madan, R.A., Bilusic, M., Hodge, J.W. et al. *A phase I trial of a yeast-based therapeutic cancer vaccine targeting CEA*. J Clin Oncol [47th Annu Meet Am Soc Clin Oncol (ASCO) (June 3-7, Chicago) 2011] 2011, 29(Suppl.): Abst 2604.