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"PERSONALIZING CANCER CARE": RECENT ADVANCES IN CLINICAL ONCOLOGY

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ABSTRACT

The main objective of the 45th Annual Meeting of the American Society of Clinical Oncology (ASCO), held in Orlando on May 29-June 2, 2009, was to promote the communication and exchange of ideas among a wide range of oncology-related subspecialties, aiming to support the development of scientific and clinical strategies leading to personalized cancer care. Participants were given the opportunity to review recent scientific advances and evaluate emerging clinical data in current cancer research. The meeting also encouraged the formation of domestic and international collaborations among oncology specialists.

INTRODUCTION

According to Dr. Richard L. Schilsky (2008-2009 president of the American Society of Clinical Oncology [ASCO]), "each patient with cancer is different; biologically, clinically, economically and socially and a one-size fits-all approach to treating cancer is not optimal". Addressing the attendees of the 45th Annual ASCO Meeting, held in Orlando, Florida from May 29 to June 2, 2009, Dr. Schilsky maintained that treating the patient and not the disease should be the focus of oncologists. The theme of this meeting, "Personalizing Cancer Care", was reflected in the scientific program of the congress, which included a number of sessions focusing on personalizing treatments for a range of specific cancer types. Individualized care could prove to be cost-effective by reducing the economic burden of expensive oncology care, which may ultimately be ineffective for the majority of treated patients. This review summarizes recent advances in cancer therapy and presents clinical data disclosed at ASCO, subdivided into categories based on tumor type. It will also focus on specific, individual therapies evaluated in more than one tumor type and include preliminary findings of novel therapeutics in early clinical development.

METASTATIC BREAST CANCER

In an ongoing phase I trial in patients with advanced breast cancer who were chemotherapy-naïve for metastatic disease or recurrence, the kinesin-like spindle protein inhibitor **ispinesib mesylate** (Cytokinetics) was well tolerated when administered every 14 days at 10, 12 and 14 mg/m^2. The most frequently observed toxicity was neutropenia. No dose-limiting toxicity (DLT) was observed in the 12 mg/m^2 cohort, where one and two patients showed partial responses following one and four cycles of treatment, respectively. Further exploration of the 14 mg/m^2 dose is ongoing (1).

A combination of **liposomal cisplatin** (Lipoplatin™; Regulon) with **vinorelbine** displayed promising activity as a first-line regimen for the treatment of HER2/NEU-negative metastatic breast cancer in a phase II study. Each treatment cycle, repeated every 3 weeks, comprised intravenous administration of vinorelbine (30 mg/m^2) on days 1 and 8 and liposomal cisplatin (120 mg/m^2) on days 1, 8 and 15. A total of six cycles were performed. Preliminary results from this study indicated high rates of objective response and disease

control (52% and 93%, respectively). The median times to treatment failure and progression were 5 and 8 months, respectively. The majority of treatment-related adverse events (AEs) were described as mild to moderate, with no grade 3-4 nephrotoxicity, neurotoxicity or ototoxicity (2).

A novel steroidal antiestrogen compound, **TAS-108** (Taiho), demonstrated no harmful effects on endometrial thickening (ET), bone mineral density (BMD), serum lipids and hormones in postmenopausal women with breast cancer (N = 91) in a randomized phase II study. Oral TAS-108 (40, 80 or 120 mg/day) had no effect on ET and BMD after 1 year of treatment. It caused a significant decrease in median triglyceride levels following 4 weeks of treatment, without affecting other lipid parameters. Increases in sex hormone-binding globulin and testosterone levels were observed. Further analysis in a greater number of individuals would be required to evaluate the long-term effect of the treatment (3).

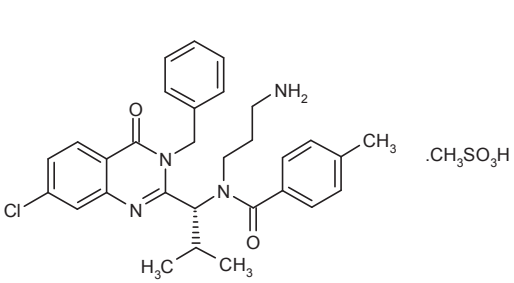
LYMPHOMA AND PLASMA CELL DISORDERS

Clinical data from phase I and II studies evaluating potential treatments for lymphoma and plasma cell disorders are summarized below. The immunomodulatory cytokine **iboctadekin** (GlaxoSmithKline) was administered at 375 mg/m^2 i.v. weekly for 4 consecutive weeks in combination with ascending i.v. doses (1-100 µg/kg) of rituximab (Chugai, Roche) to patients with CD20$^+$ B-cell non-Hodgkin's lymphoma (NHL). The combination exhibited a favorable safety profile, comparable to monotherapy with each agent, and potent biological activity. Evaluation of the dose level to be used in a future phase II trial is currently ongoing (4).

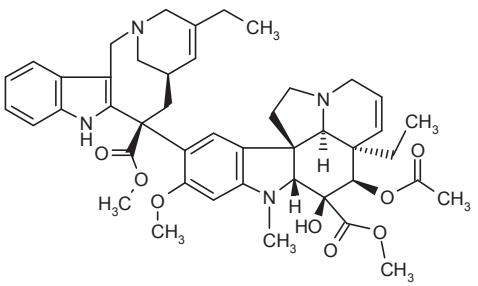
The humanized anti-CD20 antibody **veltuzumab** (Immunomedics) was well tolerated in a phase I/II study in patients (N = 19) with B-cell malignancies. Four subcutaneous injections of veltuzumab (80, 160 or 320 mg) administered 2 weeks apart resulted in evidence of therapeutic activity in initial assessments performed in 10 patients. Two and three of seven patients with NHL exhibited partial response and stable disease, respectively, 4 weeks after treatment with 80 or 160 mg veltuzumab, and three patients with chronic lymphocytic leukemia (CLL) given the 80-mg dose achieved 65-75% decreases in circulating leukemic cells (5).

Cytogenetics presented clinical data from an ongoing phase I/II study to determine the DLT and maximum tolerated dose (MTD) of the kinesin-like spindle protein inhibitor **SB-743921** with or without prophylactic granulocyte colony-stimulating factor (G-CSF) in patients with NHL or Hodgkin's lymphoma. In phase I of this trial, SB-743921 was administered on days 1 and 15 of a 28-day cycle. The study estimated the MTD of SB-743921 in the absence of G-CSF on a schedule of once every 14 days to be 6 mg/m^2. A partial response was observed in two elderly Hodgkin's lymphoma patients at doses of 6 mg/m^2 or greater. Dose escalation for the SB-743921 with G-CSF regimen is ongoing (6).

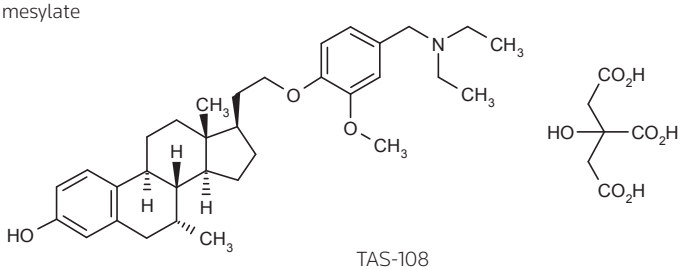
Xencor announced phase I data from the evaluation of **XmAb-2513**, an anti-CD30 Fc-engineered humanized monoclonal antibody currently under development for the treatment of relapsed Hodgkin's lymphoma and anaplastic large cell lymphoma. The dose-escalation phase of this study was designed to establish the MTD of XmAb-2513 following administration of i.v. infusions of 0.3, 1, 3, 6, 9 and 12 mg/kg. The first four doses (0.3-6 mg/kg) tested in 13 Hodgkin's



Ispinesib mesylate

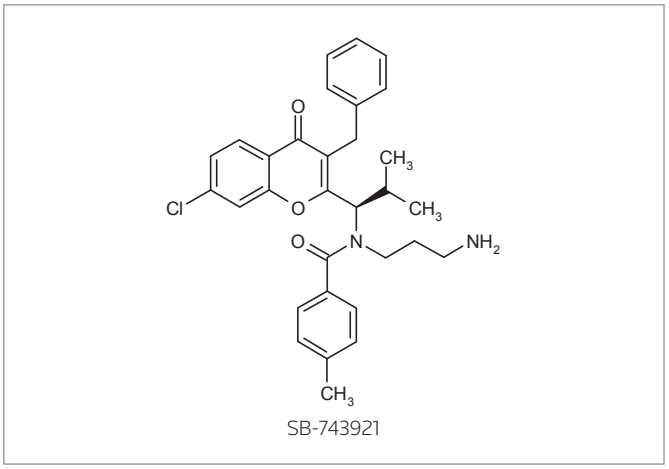


Vinorelbine



TAS-108

Metastatic breast cancer



SB-743921

Lymphoma and plasma cell disorders

lymphoma patients were well tolerated. Good tolerability and lack of immunogenicity have prevented achievement of the MTD. Encouraging biological activity and tumor reduction were observed in one and two patients with refractory Hodgkin's lymphoma in the cohorts receiving 1 and 3 mg/kg, respectively (7).

Results from a dose-escalation trial in 21 multiple myeloma patients revealed that **milatuzumab**, Immunomedics' proprietary humanized anti-CD74 antibody, may be safely administered at doses up to 8 mg/kg i.v. on a twice-weekly schedule for 4 weeks. Disease stabilization at doses of 4 and 8 mg/kg was observed in several patients for at least 12 weeks post-treatment. Further evaluation of a higher-dose cohort (16 mg/kg) is still ongoing (8).

LEUKEMIA AND MYELODYSPLASTIC SYNDROMES

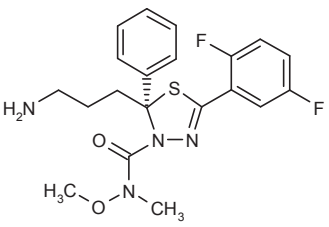
Nanomolecular **liposomal annamycin** (Callisto Pharmaceuticals) was studied in 30 patients with refractory acute lymphoblastic leukemia (ALL) in a multicenter phase I study. The MTD was 150 mg/m^2/day administered for 3 days. Of eight patients completing 3 days of treatment, five demonstrated signs of efficacy and completely cleared circulating blasts. Three patients also cleared bone marrow blasts. Two patients had tumor lysis syndromes and died. One serious AE (grade 3 mucositis) was definitely related to the drug and three other serious AEs (grade 3-4 mucositis) were probably related to the drug. No cardiac toxicity was reported. A phase I study in children and young adults with refractory ALL or acute myelogenous leukemia (AML) is ongoing (9).

To date, 15 patients with advanced leukemia have been treated with i.v. doses of Array BioPharma's kinesin-like protein inhibitor **ARRY-520** at single doses of 2.5-5.6 mg/m^2/cycle. The agent was well tolerated at doses of < 5.6 mg/m^2, and 4.5 mg/m^2 was the MTD. Signs of clinical activity were observed with doses of 3.75 mg/m^2 and above, including a complete reduction in peripheral blasts on day 5 of cycle 1. A different dose schedule is under investigation (10).

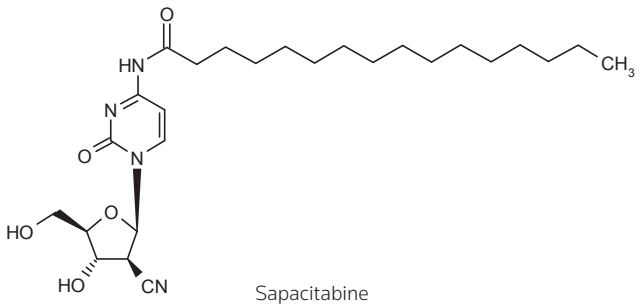
The nucleoside analogue **sapacitabine** (Cyclacel) was evaluated in a randomized phase II study in AML patients previously untreated or in first relapse, and in patients with myelodysplastic syndromes (MDS). The dosing regimens were 200 mg twice daily for 7 days every 3-4 weeks, 300 mg twice daily for 7 days every 3-5 weeks and 400 mg twice daily for 3 days per week for 2 weeks every 3-4 weeks. Among 60 AML patients, the overall response rate was 31%. The most common AEs were mostly mild to moderate. Enrollment of MDS patients is currently ongoing (11).

Antisoma's nucleolin-targeting aptamer **AS-1411** was administered along with high-dose cytarabine (HiDAC) to patients with relapsed and refractory AML in a randomized phase II study. A first cohort received AS-1411 10 mg/kg/day on days 1-7 plus cytarabine 1.5 g/m^2 twice daily on days 4-7 or cytarabine alone for 4 days. A second cohort was similarly randomized, with the AS-1411 dose increased to 40 mg/kg/day. Accrual was completed with 71 randomized patients. The main grade 3-4 toxicities were hematological and safety was similar across groups, except for an increase in grade 3 hypokalemia in the AS-1411 40 mg/kg/day group. Responses were observed in 16%, 14% and 0%, respectively, of patients administered AS-1411 10 mg/kg/day, AS-1411 40 mg/kg/day and cytarabine alone (12).

An ongoing study evaluating **TRU-016** (Trubion Pharmaceuticals), a CD37-directed small modular immunopharmaceutical (SMIP™), in patients with relapsed or refractory CLL was described. TRU-016 (0.03-10 mg/kg i.v.) administered once weekly x 4 will be evaluated in the first schedule. A second schedule will evaluate doses of 3 or 10 mg/kg on days 1, 3 and 5 (week 1) followed by three additional weekly doses. Data available from 10 patients treated on the first schedule at doses of 0.03-3 mg/kg indicated no serious AEs or DLT. Grade 1-2 infusion toxicity occurred in three patients. Of eight patients with high-risk genomic features, two had partial clearing of leukemia cutis and six had reductions in peripheral lymphocyte counts. Other signs of activity included an increase in hemoglobin and a reduction in lymph nodes in one patient and increased platelet counts in two patients (13).



ARRY-520



Sapacitabine

Leukemia and myelodysplastic syndromes

LUNG CANCER

Results from several phase II studies of potential treatments for lung cancer, including studies in patients with small and non-small cell lung cancer (SCLC and NSCLC), thymic malignancies and malignant pleural mesothelioma (MPM), were presented at ASCO.

Infinity Pharmaceuticals announced promising data on the heat shock protein HSP90 inhibitor **retaspimycin hydrochloride** (IPI-504) from a phase II trial in patients with advanced NSCLC. Intravenous administration of IPI-504 (400 mg/m^2 twice weekly for 2 of 3 weeks) was well tolerated, with evidence of antitumor activity; the best response of stable disease with 10-29% tumor reduction was observed in 7 of 24 evaluable patients (28%) (14).

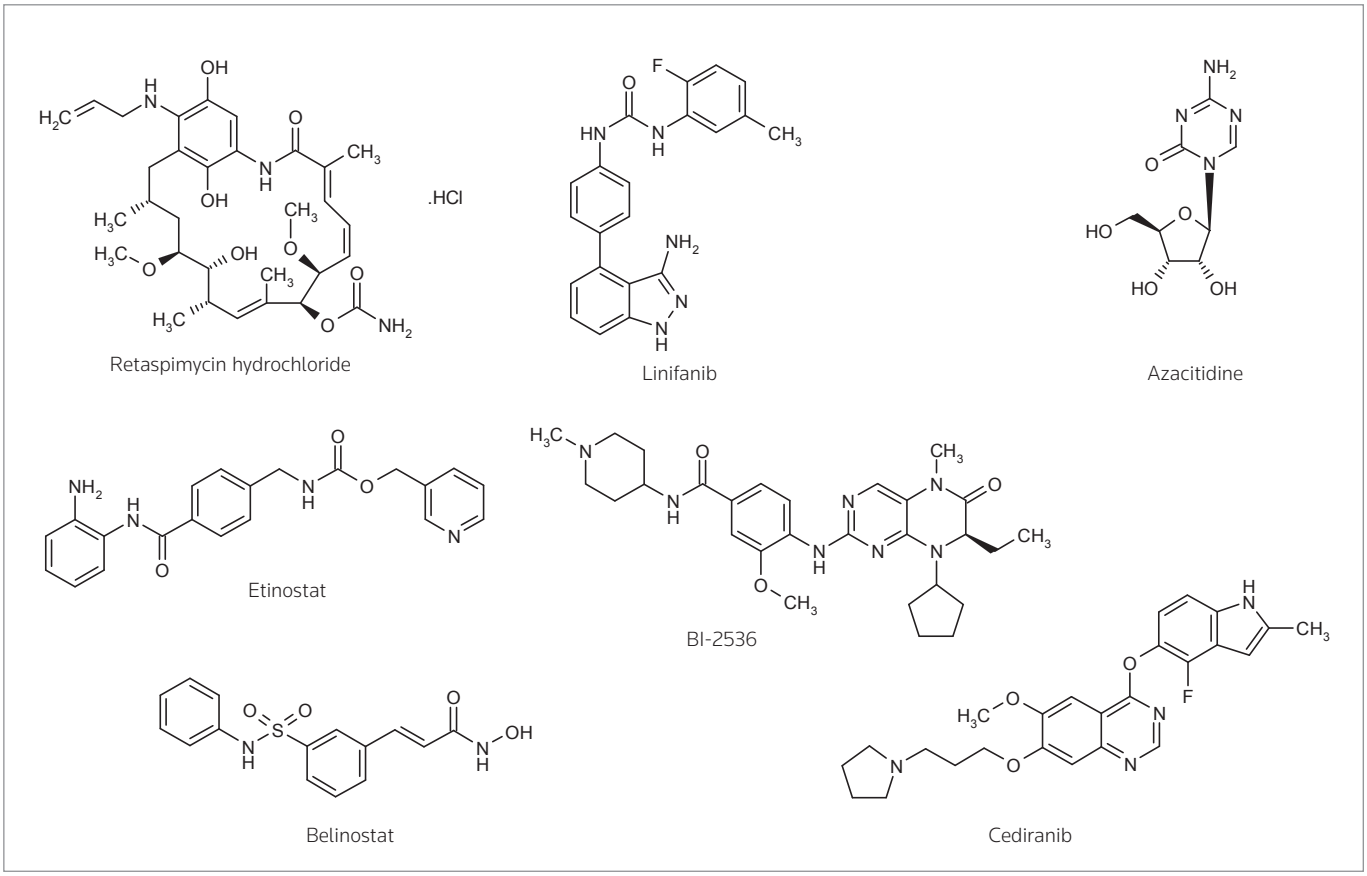
Interim results from 94 patients with locally advanced or metastatic NSCLC in an ongoing, open-label, randomized phase II trial of **linifanib** (ABT-869; Abbott) revealed acceptable safety following administration of the compound at 0.10 or 0.25 mg/kg/day. The most common mild to moderate AEs were fatigue (35%), nausea (21%) and anorexia (21%) for the low dose, and hypertension (51%), fatigue (51%) and diarrhea (43%) at the high dose (15).

The anti-CTLA4 antibody **tremelimumab** (CP-675206; Pfizer) demonstrated a good safety and tolerability profile in a randomized phase II trial in patients (N = 87) with advanced NSCLC. The treatment did not show superiority compared with best supportive care (BSC) following first-line platinum-based therapy; however, there was a 4.8% objective response rate associated with CP-675206 treatment, which may support further combination studies (16).

PF-00299804 (Pfizer) demonstrated encouraging activity in patients with advanced NSCLC who had failed prior chemotherapy and prior treatment with erlotinib. Stable disease (median duration of 11.5 weeks) was achieved in 9 of 18 response-evaluable patients with adenocarcinoma and 1 of 2 patients with nonadenocarcinoma following treatment with PF-00299804 (45 mg/day). The most common treatment-related AEs were skin and gastrointestinal disorders (17).

The combination therapy of **azacitidine** (40 mg/m^2 s.c. on days 1-6 and 8-10; Pharmion) and **entinostat** (7 mg p.o. on days 3 and 10 of a 28-day cycle; Syndax) was safe and well tolerated in patients (N = 25) with relapsed advanced NSCLC in a phase II trial. Interim results from this trial have demonstrated a durable benefit for the treatment in two patients, including a complete response (18).

In an open-label, single-arm phase II study in patients with sensitive relapsed SCLC (N = 23), treatment with the Polo-like kinase 1 (PLK1) inhibitor **BI-2536** (Boehringer Ingelheim) at 200 and 250 mg administered i.v. on day 1 every 3 weeks was well tolerated, frequent AEs including neutropenia (48%), fatigue (39%) and nausea (30%). However, it failed to demonstrate an antitumor response and will be further assessed as monotherapy in SCLC in future studies (19).



Lung cancer

A phase II study of the histone deacetylase inhibitor **belinostat** (TopoTarget) in patients with thymic malignancies revealed good tolerability for the treatment. Activity was observed in evaluable patients (n = 21) with recurrent or refractory thymoma, but not in evaluable patients (n = 8) with thymic carcinoma. Treatment responses included partial response and stable disease, respectively, in 2 and 13 thymoma patients. Further evaluation of the treatment is ongoing (20).

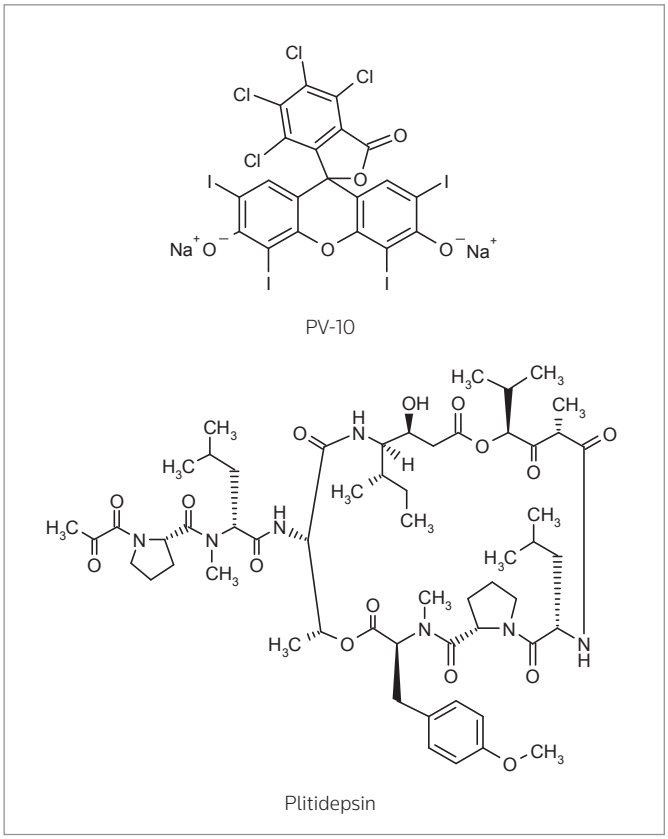
Cediranib (AZD-2171, NSC-732208; AstraZeneca) exhibited antitumor activity at a dose of 45 mg p.o. in patients with MPM following platinum-based chemotherapy in the SWOG S0509 phase II trial. There was a disease control rate of 42% according to RECIST (21).

In a phase II study conducted in previously treated MPM patients, treatment with the selective vascular targeting agent **NGR-hTNF** (MolMed) at a dose of 0.8 mg/m^2 as a 1-h i.v. infusion every 3 weeks was well tolerated. Prolonged disease control was achieved in 40% of patients (stable disease for a median duration of 4.4 months). A weekly schedule of the same dose correlated with a progression-free survival rate of 36% at 6 months and 50% of patients experienced stable disease for a median duration of 6.9 months (22).

MELANOMA

Plexxicon and Roche announced encouraging data from a phase I study of **PLX-4032**, a new, highly selective, oral treatment for patients with advanced melanoma harboring a V600E mutation in *BRAF* kinase. Dose escalation of PLX-4032 was evaluated in sequential cohorts of 3-6 patients receiving either a crystalline formulation administered continuously (doses of 100-1600 mg b.i.d.; n = 26 patients) or an optimized formulation with increased bioavailability (doses of 160-1120 mg b.i.d.; n = 28 patients). Dose-limiting toxicity was reached at 1120 mg b.i.d. The currently estimated MTD is 720 mg b.i.d., with the dose of 960 mg b.i.d. still under further exploration. PLX-4032 exhibited antitumor activity in *BRAF*^{V600E} mutant tumors; five of seven patients exhibited up to 83% tumor regression at doses of 240 mg b.i.d. or more. Tumor regression of up to 50% was observed in two of four patients with unknown *BRAF* status. All patients displaying tumor regression (n = 7) remained progression-free (4-7 months) (23). Clinical correlation of activity with pharmacokinetic (PK) and pharmacodynamic (PD) parameters in patients from this phase I trial (n = 4 receiving the crystalline formulation, n = 5 given the optimized formulation) revealed a dose-proportional increase in exposure, as measured by the $AUC_{0\text{-}24h}$ for the optimized formulation. Increased exposure also correlated with histological changes in V600E-positive *BRAF* melanomas on day 15. $AUC_{0\text{-}24h}$ values of > 400 µM*h caused a reduction in pERK pathway inhibition of > 90%, which resulted in significant decreases in F-18 fluorodeoxyglucose positron emission tomography (FDG-PET) uptake. Further analysis in additional patients is planned (24).

Provectus announced interim data from the first 40 participants in a phase II study of the radiosensitizer **PV-10** for the treatment of metastatic melanoma. Upon activation, PV-10 generates free radicals which trigger an immune response able to eliminate metastatic tumor tissue. Intralesional therapy with PV-10 was well tolerated, with transient, mild to moderate locoregional pain, vesicles or edema as the most common AEs. Interim efficacy data suggest a robust response to PV-10 in the majority of patients and locoregional disease control of 75% in 30 target lesions. Survival data are currently being collected (25).



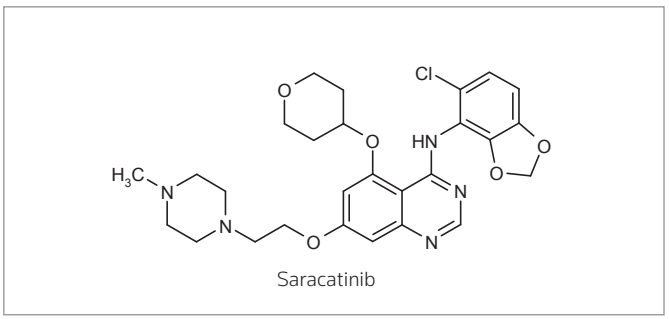
Melanoma

The human monoclonal antibody CNTO-95 (**intetumumab**; Centocor Ortho Biotech), which targets integrin α-V (vitronectin receptor subunit α), was evaluated alone or in combination with dacarbazine in a phase II trial in patients with stage IV metastatic melanoma. Treatment with CNTO-95 (5 or 10 mg/kg) alone or CNTO-95 (10 mg/kg) in combination with dacarbazine (1000 mg/m^2) every 3 weeks for eight cycles was generally well tolerated. The results at 12 months showed a trend toward improvement in progression-free survival, overall survival and disease control following the combination treatment (26).

A multicenter, phase Ib trial of **plitidepsin** (PharmaMar) administered in combination with dacarbazine as first-line treatment for advanced unresectable melanoma reported the possibility of safe administration of the combination treatment at 70% or greater of the respective single-agent recommended doses. There was a 14% partial response rate and a 19% clinically meaningful stable disease rate associated with the combination regimen. A randomized, phase II study evaluating the combination treatment compared with plitidepsin alone is currently ongoing (27).

SARCOMA

Preliminary clinical data on the evaluation of several therapeutic agents for the treatment of sarcoma were also disclosed at ASCO.



Saracatinib

Sarcoma

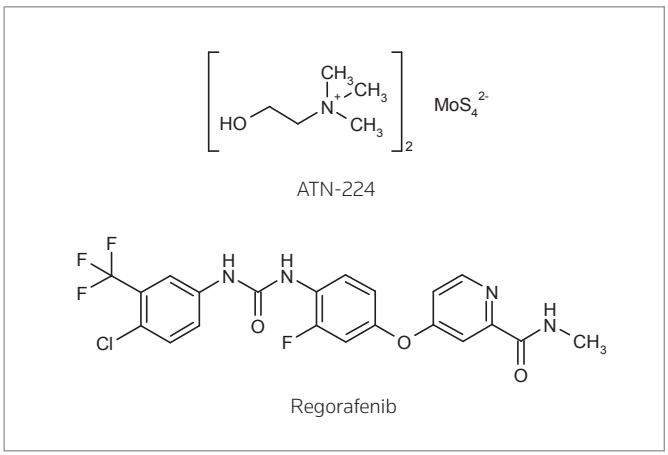
Promising preliminary activity and safety of chronic administration of the highly potent and selective vascular endothelial growth factor (VEGF) signaling inhibitor cediranib were reported in patients with alveolar soft tissue sarcoma, for which no effective treatment is currently available. Oral, once-daily administration of cediranib to seven patients (initial dose of 45 mg) was well tolerated, with the most common AEs being fatigue, diarrhea, stomatitis, headache and hypertension. Partial responses were observed in four patients, whereas two patients displayed a confirmed reduction in minimum tumor diameter of 10% or greater and < 30%. Stable disease was observed in one patient (28).

The efficacy of the highly selective, dual-specific, small-molecule Src/ABL kinase inhibitor **saracatinib** (AZD-0530; AstraZeneca) was evaluated in a phase II trial conducted by scientists at the National Cancer Institute (NCI) in 17 patients with advanced soft tissue sarcoma. The mean time to disease progression in the 13 participants was estimated at 1.7 months, with no confirmed tumor responses. Grade 3, possibly treatment-related AEs included fatigue and anemia/lymphopenia/hypokalemia. Further investigation of the treatment in combination with chemotherapy is planned (29).

R-1507 (Genmab/Roche), a recombinant human monoclonal antibody against the insulin-like growth factor 1 receptor (IGF-I receptor), exhibited clinically significant activity in patients with recurrent or refractory sarcomas, particularly Ewing's sarcoma (n = 71), osteosarcoma (n = 43), synovial sarcoma (n = 25) and rhabdomyosarcoma (n = 28), in a phase II trial. There were dramatic responses to the treatment in patients with Ewing's sarcoma and rhabdomyosarcoma. R-1507 was well tolerated and may represent a good candidate for the treatment of various types of sarcoma (30).

GENITOURINARY CANCER

Various potential treatments for genitourinary cancer were evaluated in clinical trials. In a multicenter phase II study, chemotherapy-naïve, asymptomatic patients with metastatic castration-resistant prostate cancer (CRPC) received IMC-A12 (**cixutumumab**; ImClone Systems), a monoclonal antibody against the IGF-I receptor, at a dose of 10 mg/kg i.v. every 2 weeks. The study continued until evidence of progressive disease, intolerable toxicity or other withdrawal criteria were met. Progressive disease was the cause of discontinuation in 19 of 31 patients. Nine patients exhibited disease stabilization for 6 months or longer. Most common possibly or probably treatment-related AEs included fatigue and hyperglycemia



ATN-224

Regorafenib

Genitourinary cancer

(25.8% and 19.4% of patients, respectively). Based on the modest antitumor activity observed in this trial, additional studies of IMC-A12 in CRPC have been planned (31).

The cytosolic superoxide dismutase SOD1 inhibitor **ATN-224** (Attenuon), administered as monotherapy at 30 or 300 mg/day to patients with biochemically relapsed, hormone-naïve prostate cancer (N = 52), was well tolerated, with only a few cases of reversible grade 3-4 neutropenia (4%) and grade 3 skin rash (3%). There was no progression in prostate-specific antigen (PSA) levels of patients in the low- and high-dose cohorts at 24 weeks (52% and 24%, respectively) (32).

Bayer Schering Pharma also announced results from a phase II trial of the potent, oral multikinase inhibitor **regorafenib** (BAY-73-4506). Previously untreated patients with metastatic or unresectable renal cell cancer (N = 49) received BAY-73-4506 (160 mg daily on a 3-weeks-on/1-week-off schedule). Preliminary data from this study demonstrated promising antitumor activity (27% partial response and 42% stable disease rate) and good tolerability, with the observed toxicities being typical of this drug type and manageable (33).

CENTRAL NERVOUS SYSTEM TUMORS

Preliminary results on the development of several treatments for central nervous system (CNS) tumors, in particular recurrent glioblastoma multiforme (GBM) and anaplastic astrocytoma (AA), were described in a number of presentations at ASCO.

In a phase II clinical trial conducted in patients (N = 29) with recurrent GBM, **gimatecan** (Sigma-Tau), a highly lipophilic oral camptothecin analogue, showed minimal efficacy as a single agent at 1 mg/m^2/day for 5 days on 28-day cycles. Stable disease observed in 13 patients was deemed the best response, with only 3 patients experiencing progression-free disease at 6 months. Treatment-related grade 3-4 toxicities included thrombocytopenia, leukopenia and neutropenia in 17.2%, 17.2% and 10.3% of patients, respectively (34).

ABT-510 (Abbott), a thrombospondin-1-mimetic drug, was well tolerated at s.c. doses of 20, 50, 100 and 200 mg/day with concurrent temozolomide and radiotherapy in a phase I trial in patients (N = 23)

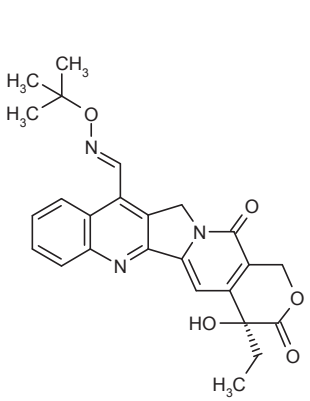
with newly diagnosed GBM. There were no grade 3-4 treatment-related toxicities associated with the treatment, even at the highest ABT-510 dose of 200 mg/day, and the MTD was not established. The median time to tumor progression and median overall survival were estimated at 220 and 422 days, respectively (35).

A phase I study evaluating the effects of **vatalanib succinate** (PTK-787; Novartis) in combination with temozolomide and standard radiation in patients with newly diagnosed GBM taking enzyme-inducing antiepileptic drugs demonstrated the treatment to be safe and well tolerated. The best response in GBM patients who completed the combination treatment (n = 13) was partial response and stable disease in 2 and 7 patients, respectively, while 2 patients experienced disease progression. The MTD was not reached and dose escalation is ongoing in this study (36).

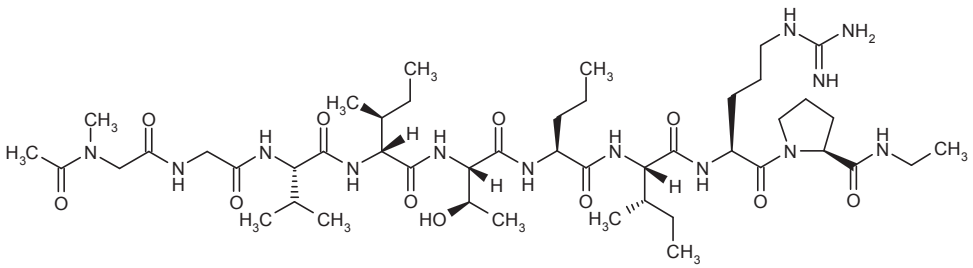
Intravenous unlabeled **TM-601** (Transmolecular), a synthetic chlorotoxin, induced measurable changes in perfusion magnetic resonance imaging (MRI) parameters in agreement with clinical response in a phase I study in patients with recurrent GBM. Patients (N = 6) received 10 mCi of ^{131}I-TM-601 prior to treatment with TM-601 (0.04 mg/kg i.v. weekly for 3 weeks on a 4-week cycle). Two of six patients demonstrated a > 25% reduction in relative cerebral blood flow and/or relative cerebral blood volume compared with baseline measurements. There was an extended response to i.v. TM-601 in both patients with improved perfusion MRI outcomes (37).

A multicenter phase II trial evaluated the antigenicity and efficacy of the epidermal growth factor receptor variant III (EGFRvIII) peptide vaccine **CDX-110** (Celldex/Pfizer) in patients with newly diagnosed EGFRvIII$^+$ GBM. The study reported EGFRvIII-specific immune responses in all patients, which were sustained or enhanced during subsequent temozolomide cycles, despite grade 2-3 lymphopenia. Promising results from this study prompted further investigation of CDX-110 with temozolomide in a larger ongoing phase II trial (38).

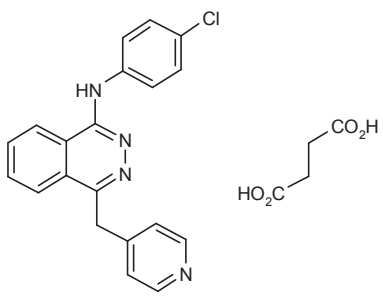
A genetically engineered herpes simplex virus type 1, **G-207** (MediGene), was evaluated as a potential treatment for recurrent malignant glioma in a recent phase I study in patients (N = 9) suffering from relapsed GBM or AA. Stereotactic intracerebral inoculation with G-207 followed by irradiation was proven feasible, safe and to induce clinically relevant responses. The median overall survival time for all patients was estimated at 229 days. The study supports further clinical development of G-207 as a therapeutic candidate for GBM and AA (39).



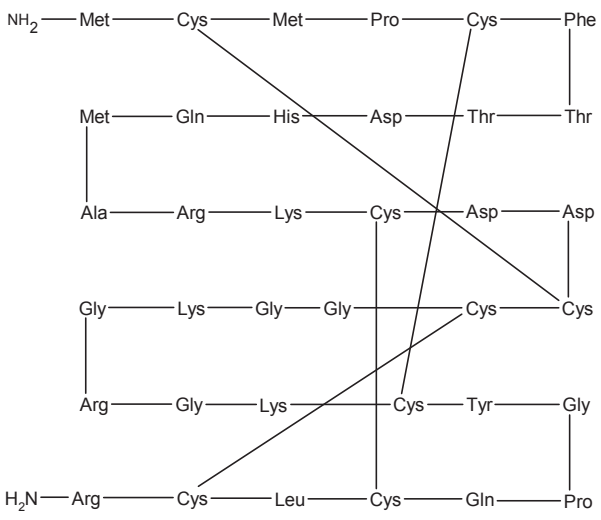
Gimatecan



ABT-510



Vatalanib succinate



TM-601

Central nervous system tumors

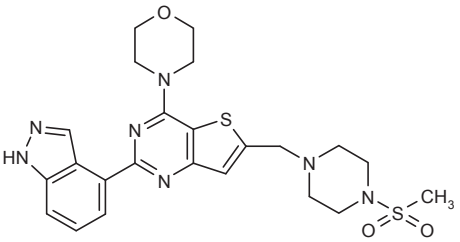
Three presentations described phase II data for the treatment of GBM patients with the c-Met, ret, Kit and VEGFR-2 inhibitor **XL-184**. A study in 46 relapsed patients evaluated daily oral treatment with XL-184 (175 mg). Objective responses were noted in 7 of 31 patients without prior antiangiogenic therapy, and measurable tumor shrinkage was observed in 3 of 9 patients with prior antiangiogenic therapy. Dose interruptions/reductions were common in this trial. A lower starting dose of 125 mg daily is currently being assessed (40). Neurovascular imaging of 38 patients in this study revealed a consistent reduction in edema at day 28 across imaging modalities. Early reduction in tumor vessel permeability and decreases in cerebral blood flow, cerebral blood volume and vessel size were observed on day 1, concomitant to a rise in the level of mobile lipids, indicating an increase in tumor necrosis (41). A biomarker analysis of patients treated in this study demonstrated significant modulation of soluble c-Met, VEGFR-2, VEGF-A, Kit and PlGF, which was apparent by day 15 of cycle 1 and correlated with XL-184 steady-state exposure. However, changes in individual plasma biomarkers were not strongly correlated with XL-184 efficacy (42).

SOLID TUMORS

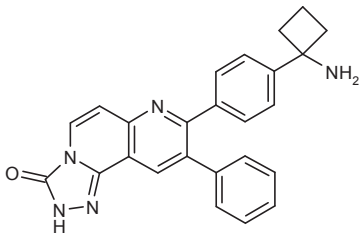
Preliminary data from an ongoing dose-escalation study of the selective ATP-competitive inhibitor of class I phosphoinositide 3-kinase (PI3K) **GDC-0941** (Genentech/Piramed) in patients with advanced solid tumors gave an indication of the agent's safety, PK profile and activity. GDC-0941 was administered on day 1 for single-dose PK/PD evaluation, and following a period of washout, the drug was administered every day for 3 of 4 weeks. Total daily dose levels up to 80 mg/day (on q.d. and b.i.d. regimens) had been administered to 19 patients on the daily treatment schedule at the time of reporting. GDC-0941 was well tolerated, with nausea, fatigue, diarrhea, peripheral edema and dysgeusia being the most common drug-related AEs, none of which were > grade 3. Dose-proportional increases in exposure were observed, together with possible signs of antitumor activity, including stable disease in a soft tissue sarcoma patient, a CA125 response in an ovarian cancer patient and a decrease in tumor FDG-PET uptake in a patient with endometrial cancer (43).

The protein kinase B (PKB/Akt) inhibitor **MK-2206** (Merck & Co.) was evaluated in a phase I trial in patients with advanced solid tumors (N = 19) at daily doses of 30, 60, 75 and 90 mg administered on 28-day cycles. At the 75-mg dose, two of three patients experienced dose-limiting rash, and 60 mg/day was determined to be the MTD. Common drug-related AEs were skin, gastrointestinal and general disorders. Exposure was dose-proportional up to the MTD. The median t_{max} was 6 h and the mean $t_{1/2}$ was 63-76 h. MK-2206 concentrations exceeded the predetermined target of approximately 50-65 nM for significant phosphorylated Akt inhibition in blood during the entire dosing interval in all patients treated at the 60-mg dose. Stable disease according to RECIST criteria was noted in one patient at 30 mg and in five patients at 60 mg. Signs of clinical activity included central tumor necrosis, decreased ascites and peripheral edema, a reduction in index lesions, normalization of liver function tests and decreased CA125 (44).

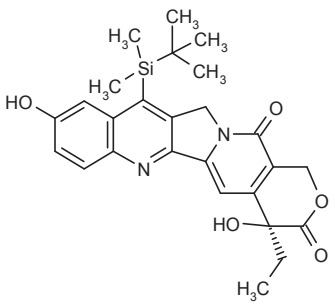
Phase I and II clinical data on the selective, non-ATP-competitive c-Met inhibitor **ARQ-197** (ArQule) in patients with advanced or



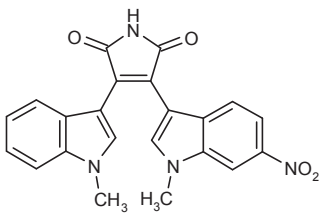
GDC-0941



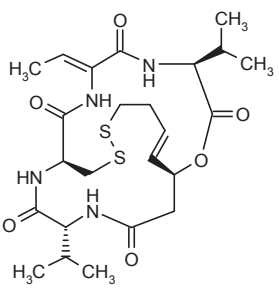
MK-2206



AR-67



MKC-1



Romidepsin

Solid tumors

metastatic solid tumors and microphthalmia-associated transcription factor (MITF) family-associated tumors were presented. Final results from a phase I PK and PD trial of ARQ-197 administered to 29 patients with advanced solid tumors suggested good tolerability, with an MTD of 300 mg b.i.d. p.o. The compound displayed linear PK and evidence of inhibition of phosphorylated c-Met and FAK. The potential antiangiogenic activity of ARQ-197 was supported by data obtained from dynamic contrast-enhanced MRI analyses (45). In a dose-escalation phase I study in patients with various metastatic solid tumors (N = 65), including colorectal, renal cell carcinoma, ovarian and lung cancer, ARQ-197 demonstrated a favorable safety profile at doses of up to 360 mg twice daily. The study reported an overall response rate of 6.3% and a disease control rate of 72.9% in 48 patients who were evaluable for efficacy (46). A combination regimen of ARQ-197 (120, 240 and 360 mg b.i.d.) and erlotinib (150 mg/day p.o.) was well tolerated, without drug–drug interactions, in a phase I dose-escalation study in 25 patients with advanced solid tumors. A linear PK profile was observed through the highest ARQ-197 dose of 360 mg b.i.d. Tumor regressions of 2.3-19.4% were observed in 4 of 10 evaluable patients and all 3 evaluable patients with SCLC had stable disease for a period of 14-32 weeks (47). Preliminary results from a phase II trial of ARQ-197 (initially administered at 120 mg b.i.d. p.o. and subsequently increased to 360 mg b.i.d.) in 28 patients with MITF-associated tumors, demonstrated an overall response rate of 5% and a disease control rate of 80% in 20 evaluable patients. Fatigue (35.7%), nausea (35.7%), vomiting (21.4%), decreased hemoglobin (10.7%) and cough (10.7%) were the most common treatment-related AEs. Based on favorable safety and preliminary anticancer activity, stage two enrollment of this study is currently ongoing (48).

The topoisomerase I inhibitor **AR-67** (Arno Therapeutics), a third-generation camptothecin analogue, was recently evaluated in a phase I study of patients with refractory solid tumors. AR-67 was infused i.v. over 1 h for 5 days of a 21-day cycle at 9 dose levels (1.2-12.4 mg/m^2/day) to 26 patients with a variety of solid tumors, including colorectal, NSCLC, SCLC, head and neck, soft tissue carcinoma and prostate cancer. It demonstrated superior lactone stability to approved analogues, antitumor activity in NSCLC patients and predictable toxicity, with no diarrhea. The MTD was estimated at 7.5 mg/m^2/day (49). PK analyses revealed a linear relationship between dose level and AUC, with 85% of the AR-67 in the active lactone form. Lactone clearance was estimated at 16.6 and 19.6 L/h/m^2 on days 1 and 5, respectively. The study suggests that the high lactone exposure coupled with low carboxylate and the apparently limited metabolism of AR-67 may account for the increased activity and reduced toxicity of the compound (50). In vitro metabolism and transport studies performed on plasma and urine samples collected from patients suggested that the absence of treatment-induced diarrhea in this trial may be due to the rapid glucuronidation processing of AR-67 by the enzyme UGT1A8, which is highly expressed in the gastrointestinal tract, thus improving the toxicity profile of the compound (51).

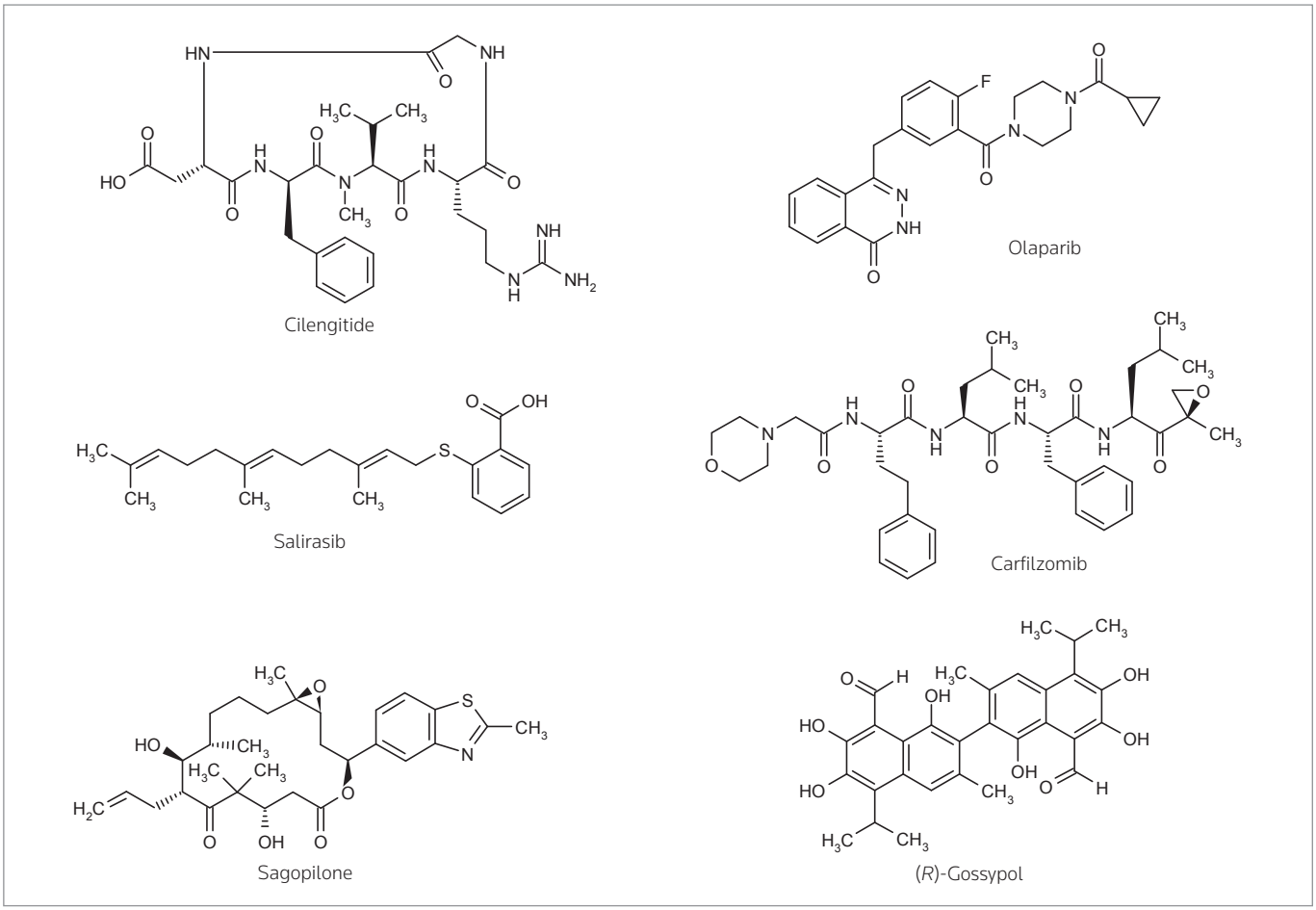
Anticancer candidate therapeutics from Exelixis were featured in several presentations at ASCO. The RAF kinase inhibitor **XL-281** was administered to 30 patients with advanced solid tumors in a phase I study assessing once-daily treatment on a 28-day cycle. The MTD was 150 mg, with the most common AEs including fatigue, diarrhea, nausea, vomiting and anorexia. One confirmed partial response was observed in a patient with ocular melanoma and 12 patients had stable disease (52). In another phase I dose-escalation study, patients with solid tumors received the PI3K inhibitor **XL-147** on days 1-21 or as a continuous daily dose. The agent was generally well tolerated and the MTD for the 21-day schedule was 600 mg. Skin rash was the most common toxicity. Dose escalation on the continuous schedule was ongoing at the time of reporting. Evidence of activity included a partial response in an NSCLC patient after 56 weeks (53). The multiple protein kinase inhibitor **XL-228** was administered to 36 patients with solid tumors or hematological malignancies in a phase I study. With weekly i.v. infusions, the maximum administered dose was 8.0 mg/kg and the drug was generally well tolerated. An unconfirmed partial response occurred in an NSCLC patient and 9 of 30 evaluable patients had stable disease lasting over 3 months (54).

EntreMed's cell cycle inhibitor **MKC-1** (125 mg/m^2 p.o. b.i.d. for 14 days on 28-day cycles) was evaluated in 19 patients with metastatic or recurrent platinum-resistant ovarian cancer in a phase II study. Following treatment, 7 participants had stable disease and 12 progressed. The median time to progression was 1.8 months. In the same study, nine patients with advanced endometrial cancer received the same treatment. Stable disease was observed in four of these patients, while five progressed. MKC-1 was well tolerated, with the most common possibly treatment-related AEs being fatigue, nausea, elevated ALT or AST, urine discoloration, anemia, anorexia, elevated alkaline phosphatase and gastrointestinal disorders (55).

Restoration of radioactive iodine (RAI) avidity was observed in 2 of 20 patients with RAI-refractory metastatic nonmedullary thyroid carcinoma in a phase II study of depsipeptide (**romidepsin**; Gloucester Pharmaceuticals); however, accrual was poor following the sudden death of a patient and the protocol was suspended. Study participants were treated with depsipeptide (13 mg/m^2 i.v.) on days 1, 8 and 15 every 28 days. In 14 evaluable patients, median overall survival was 36 months. There were no major responses in this study. Stable disease was observed in 10 patients. One patient had a grade 4 AE (pulmonary embolus) possibly related to the drug (56).

SPECIAL FOCUS ON SELECTED DRUG TARGETS FOR MULTIPLE TUMOR TYPES

Cilengitide (EMD-121974; Merck KGaA) is an angiogenesis inhibitor that targets $\alpha_v\beta_3$ integrin, a protein that promotes the proliferation of tumor-associated endothelial cells. Administration of cilengitide to patients with metastatic melanoma decreased the expression of $\alpha_v\beta_3$ integrin, which correlated with a decrease in the levels of pERK-1/2 (P = 0.03) but not pAKT or pFAK expression. The phase II study reported minimal clinical efficacy of the treatment in metastatic melanoma patients (57). Combination of cilengitide (1-h infusion twice a week at doses of 500, 1000 or 2000 mg) with temozolomide and radiation therapy was well tolerated in patients with newly diagnosed GBM. Following safety tests, 94 patients were randomly assigned to receive 500 or 2000 mg cilengitide plus chemoradiotherapy. The overall survival at 12 months for all patients was estimated at 79.5%, which suggested that the treatment may have a beneficial effect in improving the survival of newly diagnosed GBM patients (58). In an open-label, randomized phase II study, cilengi-



Special focus on selected drug targets for multiple tumor types

tide (at doses of 240, 400 or 600 mg twice a week) was better tolerated than docetaxel (75 mg/m^2 once every 3 weeks) in patients with relapsed stage IV NSCLC (N = 140). Although progression-free survival, the primary study endpoint, was greater in the docetaxel group than the cilengitide group at all doses tested, cilengitide at the highest dose of 600 mg displayed similar overall survival to docetaxel. The most common AEs reported were dyspnea (33%), nausea (30%), tumor progression (29%) and cough (23%), with dyspnea and tumor progression being more prevalent in the cilengitide- compared to the docetaxel-treated groups. However, docetaxel treatment correlated with more grade 3-4 AEs than cilengitide. Further evaluation of combination regimens with standard chemotherapy is warranted (59).

Results from two phase II studies of **olaparib** (AZD-2281), a poly(ADP-ribose) polymerase (PARP) inhibitor from AstraZeneca, in the treatment of BRCA-deficient advanced breast and ovarian cancers were presented. Both provided proof of concept for the use of olaparib in these BRCA-deficient cancers. In the breast cancer trial, continuous oral olaparib was administered on 28-day cycles at 100 or 400 mg twice daily. The overall response rate was 38% in the 400-mg group, and related toxicity was mostly mild and included fatigue, nausea, vomiting and anemia. Five patients had related grade 3 or higher fatigue, nausea or anemia. Data for the lower dose were not yet available (60). The ovarian cancer study evaluated the same doses on the same schedule. An interim analysis of 57 patients revealed an overall response rate of 33% with the 400-mg dose and 12.5% with the 100-mg dose. Additional patients had declines in CA125 of at least 50%. Toxicity included grade 1-2 nausea, fatigue and anemia, with grade 3 nausea experienced in 7% and grade 3 leukopenia in 5% of participants (61).

Preliminary results from a phase I/II study in advanced pancreatic cancer patients and a phase II study in patients with stage IIIB/IV lung adenocarcinoma enriched for *KRAS* mutations have shed light on the activity of the first-in-class Ras antagonist **salirasib**, a product being developed by Concordia Pharmaceuticals. In the phase I/II study, treatment-naïve patients received gemcitabine plus salirasib (200-800 mg b.i.d. p.o.) for 21 of 28 days. In 13 patients, the most common AEs were neutropenia, anemia, abdominal cramping, elevated liver function tests and diarrhea. At salirasib doses of 400-800 mg, progression-free survival was 4.7 months, median survival was over 10.8 months and 1-year survival was 50%. Ras inhibition was confirmed (62). The phase II study included two cohorts: patients with *KRAS* mutations previously treated with chemotherapy and previously untreated patients. Oral salirasib was administered

for 28 days on 35-day cycles. After 10 weeks of treatment, stable disease was noted in 5 of 19 patients in the previously treated group and in 3 of 8 patients in the previously untreated group. In these two groups, the median time to progression was 1 and 2 months, respectively. The most common AEs were grade 3 diarrhea and fatigue (63).

Four presentations provided phase I and II results on the proteasome inhibitor **carfilzomib** (Proteolix) in patients with MM and advanced solid tumors. In a phase I study, patients with relapsed/refractory MM received carfilzomib (15-20 mg/m^2 i.v.) on days 1, 2, 8, 9, 15 and 16 with lenalidomide (10-20 mg p.o.) on days 1-21 and low-dose dexamethasone (40 mg p.o.) on days 1, 8, 15 and 22 on 28-day cycles. Following evaluation in the first two dose cohorts in eight patients, the MTD was not reached and no drug-related serious AEs or grade 3-4 treatment-emergent AEs were observed. Four partial responses, one minor response and two cases of stable disease were noted. Dose escalation is currently ongoing (64). In the first part of an open phase II study in patients with relapsed and refractory MM, carfilzomib (20 mg/m^2 i.v.) was administered on days 1, 2, 8, 9, 15 and 16 every 28 days for up to 12 cycles. Of 39 evaluable patients, 5 patients achieved a partial or minor response. Stable disease, lasting at least 6 weeks, was observed in 16 other patients. Median time to progression was 6.2 months and toxicity was manageable. The study enrollment has been expanded and treatment has been extended to beyond 1 year (65). In a phase II study with the same carfilzomib administration schedule, but with dexamethasone (4 mg) administered prior to each dose in cycle 1, a partial response or better was noted in 57% of bortezomib-naïve patients and in 18% of bortezomib-exposed patients with relapsed MM. The median time to progression was 8.9 months in the bortezomib-exposed group (66). In a phase Ib/II study in patients with advanced metastatic solid tumors, carfilzomib was administered on the same schedule as above, with doses of 20 mg/m^2 administered on the first 2 days followed by dose escalation to 27 or 36 mg/m^2. Among 14 patients included in phase Ib and 51 in phase II, partial responses were noted in renal cancer and SCLC, while stable disease lasting over 16 weeks was noted in mesothelioma, ovarian and renal cancer and NSCLC patients. Carfilzomib (20-36 mg/m^2) was well tolerated, without severe myelosuppression, hepatotoxicity or neuropathy (67).

CNTO-328 (Centocor) is a chimeric monoclonal antibody with high affinity for human interleukin-6 (IL-6), a known facilitator of cell survival with multiple effects on proliferation, apoptosis, angiogenesis and differentiation, as well as chemoresistance. Evaluation of CNTO-328 (6 mg/kg i.v. once every 2 weeks for 12 cycles) in chemotherapy-pretreated patients (N = 54) with CRPC in a phase II trial revealed good tolerability and resulted in a PSA response rate of 3.7%. The stable disease rate was estimated at 21% by RECIST in 47 evaluable CRPC patients, while declining levels of C-reactive protein suggested biological activity (68). Combined administration of CNTO-328 (6 mg/kg i.v. once every 2 weeks) with dexamethasone (40 mg p.o.) was safe and displayed promising preliminary activity in a phase II study in patients with relapsed or refractory MM. The overall response rate for the treatment in 36 patients was 31% by EBMT (European Group for Blood and Marrow Transplantation) criteria, with an acceptable safety profile. Further evaluation of the treatment is currently ongoing (69).

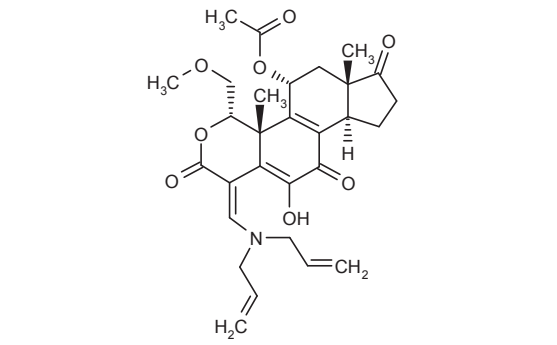
Results from two phase II studies of **sagopilone** (ZK-EPO; Bayer Schering Pharma) to treat patients with metastatic melanoma and recurrent metastatic breast cancer (MBC) were also presented. Sagopilone (16 mg/m^2 as a 3-h i.v. infusion every 21 days) demonstrated significant activity, unlike the epothilone analogues patupilone and ixabepilone, in patients (N = 34) with unresectable stage III or IV malignant lymphoma. Stable disease was observed in 10 patients for at least 12 weeks for a clinical rate benefit of 44%. The favorable safety profile of the dose used (the most common grade 1-2 side effects included sensory and motor neuropathy, anemia, neutropenia, thrombocytopenia and fatigue in 55%, 23%, 26%, 14% and 14% of patients, respectively) supports the combined use of sagopilone with other drugs for the treatment of active melanoma (70). In the second study, MBC patients previously treated with three or more anthracycline- and taxane-containing chemotherapies (N = 65) received 16 or 22 mg/m^2 sagopilone i.v. over 3 h every 21 days for up to 6 cycles. Although the compound was tolerable at both doses, it exhibited limited activity in this cohort of heavily pretreated MBC patients, with no responders according to stage 1 criteria at either dose. However, stable disease was achieved in 26% and 42% of patients, respectively, taking 16 and 22 mg/m^2 sagopilone (71).

The efficacy and safety of **(*R*)-gossypol** (AT-101; Ascenta Therapeutics), which is the most active enantiomer of the pan-Bcl-2 inhibitor and a potent inducer of proapoptotic proteins, were recently evaluated in a phase II trial in patients with recurrent GBM. Patients (N = 56) received (*R*)-gossypol (20 mg/day p.o.) for 21 days of a 28-day repeated cycle. Treatment with (*R*)-gossypol was well tolerated, without unique toxicities. The primary endpoint of overall survival is currently under evaluation. The best treatment response was deemed to be stable disease, observed in 17% of participants (72). The safety and efficacy of (*R*)-gossypol in combination with rituximab were assessed in a phase II trial in patients with grade 1-2 follicular NHL. Patients with untreated follicular NHL who did not require immediate chemotherapy (N = 23) received an induction cycle of (*R*)-gossypol (30 mg/day p.o. for 21 days) and rituximab (375 mg/m^2/week for 4 weeks), followed by a maximum of four maintenance cycles of (*R*)-gossypol and rituximab every 8 weeks in nonprogressors. The study reported the combination of (*R*)-gossypol with rituximab to be well tolerated. Reduction of the (*R*)-gossypol dose to 20 mg correlated with improved gastrointestinal tolerability. At 8 weeks the response rate did not meet statistical criteria to justify stage II enrollment. A randomized trial would be necessary to further evaluate the activity of the combination treatment (73).

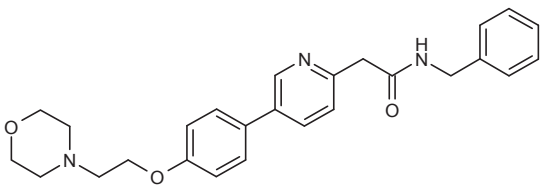
NOVEL CANCER THERAPEUTICS IN EARLY CLINICAL DEVELOPMENT

Results from various phase I and II studies evaluating potential treatments for refractory solid tumors and hematological malignancies were presented in the Developmental Therapeutics section at ASCO.

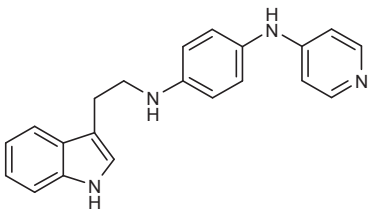
Oncothyreon released preliminary data from a phase I clinical trial of the novel PI3K inhibitor **PX-866** in patients with solid tumors. Once-daily oral administration of PX-866 (for 5 of 7 days for 2 weeks on a 28-day cycle; dose levels tested to date: 0.5, 1.0, 2.0 and 3.0 mg) demonstrated acceptable safety, with no drug-related severe AEs or DLT. Stable disease was observed in three previously progressing patients in the 0.5- and 1.0-mg cohorts, whereas two patients expe-



PX-866



KX2-391



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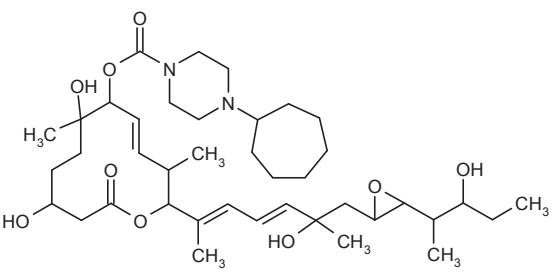

E-7107

Novel cancer therapeutics in early clinical development

rienced a decrease in pain that permitted discontinuation of analgesics (74).

The small-molecule Src kinase inhibitor **KX2-391** (Kinex) exhibited a favorable PK profile and showed evidence of biological activity in a phase I trial in patients with advanced malignancies (N = 32). PK analysis revealed dose-proportionality, a $t_{1/2}$ of 4.5 h and a t_{max} of 1 h, without any evidence of accumulation following multiple doses. The MTD was estimated to be 40 mg b.i.d. on a 3 out of 4 weeks dosing schedule. The best response of prolonged stable disease for 4 months or longer was observed in seven patients (75).

The first-in-clinic human E3 ubiquitin-protein ligase Mdm2 inhibitor **JNJ-26854165** (Johnson & Johnson) was well tolerated and displayed PD activity at doses of 150-300 mg in 37 patients with advanced refractory solid tumors in an ongoing phase I study. No objective responses have been observed so far (76).

E-7107 (Eisai), a potent, first-in-class inhibitor of the spliceosome, displayed dose-dependent PK and acceptable safety following i.v. administration to 36 patients with solid tumors. PD analysis revealed dose-dependent and reversible inhibition of target gene pre-mRNA processing. The MTD was estimated at 4 mg/m^2. No complete or partial responses were observed (77).

The novel, antibody–cytokine fusion protein **AS-1409** (Antisoma) was well tolerated at 15 μg/kg in a phase I study in 13 patients with MM or renal cell carcinoma (RCC). One patient with MM displayed a partial response and four patients experienced stable disease (78).

Santaris Pharma and Enzon announced phase I data for **EZN-2968**, a novel, hypoxia-inducible factor 1 α (HIF1 α) inhibitor in patients with advanced malignancies. EZN-2968 (daily 2-h i.v. infusion for 5 days every 4 weeks) was well tolerated in previously treated patients with advanced malignancies (N = 19). The most common grade 1-2 AEs were vomiting (32%), fatigue (26%), anemia, diarrhea, nausea and tumor pain (21% each). The best response of stable disease was achieved in 1 patient with angiosarcoma (28 weeks) and 1 patient with renal cancer (12 weeks). The dose-escalation phase of this trial is ongoing (79).

Encouraging data from a phase II trial with **MDX-1106** (ONO-4538; Medarex/Ono) in patients with refractory or selected malignancies (N = 21) were presented. Intermittent dosing of MDX-1106 (10 mg/kg by infusion) displayed clinical activity in RCC and melanoma patients without any serious toxicity. Further studies to assess the ability of MDX-1106 to enhance endogenous antitumor immunity, either as a single agent or in combination with other immunotherapies, are supported by this trial (80).

Preliminary evidence of the clinical activity of the PI3Kδ inhibitor **CAL-101** was announced by Calistoga Pharmaceuticals. Early results from an ongoing phase I dose-escalation trial of CAL-101 (50 or 100 mg p.o. b.i.d. for 28 days/cycle) in 6 patients with AML and CLL suggested good tolerability. Partial responses were observed in two patients, whereas four exhibited stable disease. A higher-dose cohort of 200 mg is currently under enrollment (81).

Innate Pharma disclosed preliminary phase I clinical data for the novel anti-KIR monoclonal antibody **IPH-2101**. Patients with non-promyelocytic AML received escalating doses of IPH-2101 (0.0003, 0.003, 0.015, 0.075 and 0.3 mg), with two more dose cohorts (1.0 and 3.0 mg/kg) to be included at a later stage. Data obtained from the first 15 patients demonstrated a good safety and tolerability profile. MTD was not reached at the dose of 0.3 mg/kg, but there were signs of natural killer cell activation (82).

In its first-in-human study, the antisense oligonucleotide against HSP27 **OGX-427** (OncoGenex Pharmaceuticals) was administered i.v. at doses of 200, 400, 600, 800 and 1000 mg on a weekly basis on 21-day cycles, after three loading doses within 9 days, to 34 patients with various types of cancer. The most common related AEs were chills, pruritus, flushing, elevated creatinine, fatigue and arthralgia, and over 80% of patients had grade 1-2 infusion reactions. At the two

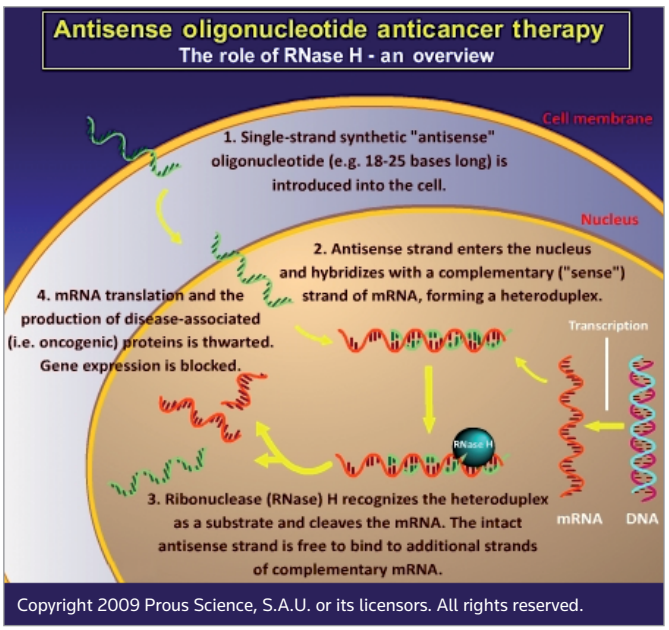

Figure 1. Gene silencing by antisense oligonucleotides; a novel approach for anticancer therapy. A synthetic, single-strand "antisense" oligonucleotide is able to recognize and bind to its complementary oncogenic mRNA molecules, thus mediating their degradation and leading to cessation of disease-associated protein production Subscribers to the online version of *Drugs of the Future* and/or Prous Science Integrity® can access the animation: Antisense oligonucleotide anticancer therapy.

highest doses, over 50% of patients had grade 3 elevations of PTT. Signs of activity included PSA declines of over 40% in three prostate cancer patients and CA125 declines of over 20% in three patients with ovarian cancer. In addition, declines in circulating tumor cells were observed at all dose levels. Stable disease lasting over 3 months was noted in five patients. PK data for doses of 200-600 mg showed a $t_{1/2}$ of 2.8-3.1 h and dose-related increases in exposure (83). A schematic diagram describing the mechanism of action of antisense oligonucleotide technology is provided in Figure 1.

ASCO RESEARCH FOUNDATION AWARD

The initiation of a pilot study, supported by the ASCO Research Foundation, to investigate the biological effects of chemotherapy plus **bavituximab** in patients with advanced NSCLC, was announced at the meeting. A 3-year US $200,000 Career Development Award was granted to the University of Texas Southwestern Medical Center to conduct this study, which is expected to supplement Peregrine's phase II clinical trial on bavituximab in combination with carboplatin and paclitaxel in patients with advanced NSCLC. In the first cohort of the Peregrine trial, 11 of the 17 evaluable NSCLC patients achieved an objective tumor response according to RECIST. Enrollment of an additional 28 NSCLC patients is currently ongoing.

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