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Meeting Report

Highlights of the 2008 Annual Meeting of the American Society of Clinical Oncology (ASCO)

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Abstract

The 2008 Annual Meeting of the American Society of Clinical Oncology (ASCO), held on May 30-June 3 in Chicago, provided a window on the hive of activity that is current cancer therapy research. Presentations covered clinical studies of newer compounds; known compounds progressing to more advanced phases; known compounds under study for new indications; first-line treatments; treatments for refractory disease; agents under development as monotherapy, combination therapy or both; products for newly developed and recurrent disease; treatments for various cancer types, both metastatic and localized; in sum, research into practically every area of cancer treatment. An idea of the reach of the congress is provided by the selection of studies detailed below.

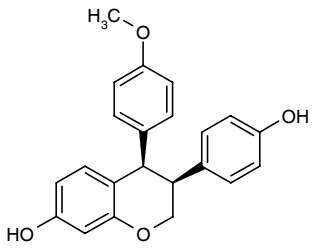
Introduction

As always, the presentations given at the Annual Meeting of the American Society of Clinical Oncology (ASCO) introduced a large number of new compounds to the scientific community and provided further data on the development of a great many other potential therapeutic agents. The large number of presentations reflects the pressing need for new treatments, as well as the encouraging progress in the recent evolution of cancer therapy, with known mechanisms of action explored in depth and new mechanisms coming to light. Taken as a whole, it seems clear that while the activity of many new compounds is limited, in the future patients will have more treatment options for new and recurrent disease. Below we provide a selection of notable clinical studies presented at the meeting, broken down by cancer type. Most deal with studies in patients with various solid tumor types, but a large variety of studies in specific cancers are also covered.

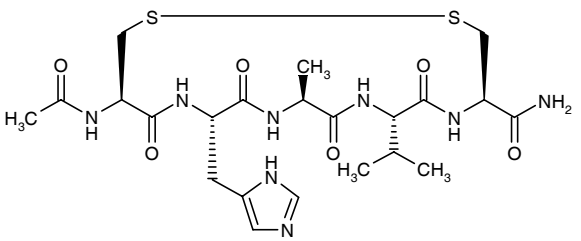
Solid tumors

Administration of Marshall Edwards' apoptosis inducer **triphendiol** (NV-196, **1**) three times daily was safe and resulted in elevated plasma concentrations of NV-196 and its metabolite NV-143 in their conjugated forms in a phase Ia study in patients with stable solid malignancies. Patients (N = 13) were given a single dose of NV-196 100 mg p.o. on day 1, with repeat dosing begun on day 3 with a 100-mg dose administered every 8 h for 5 days until the morning of the eighth day. With repeated dosing, steady-state concentrations of conjugated NV-196 and NV-143 were reached within 3 days. NV-196 was excreted primarily in a conjugated state, and the recovery of NV-196 and its metabolites was low in the urine, suggesting incomplete NV-196 absorption and/or some level of excretion via the bile duct. Toxicity included 1 case of grade 4 anemia and 2 unrelated serious adverse events (abdominal pain, bowel obstruction) (1). Triphendiol has orphan drug status in the U.S. for the treatment of pancreatic cancer, cholangiocarcinoma and stage IIB-IV malignant melanoma.

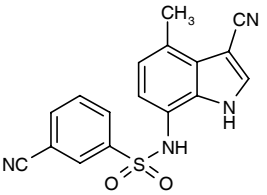
Toxicity has been manageable and activity has been seen in an ongoing phase I trial of Nektar Therapeutics' **NKTR-102** (PEG-irinotecan). Patients with a variety of refractory solid tumors have been treated in the study with doses of 58-230 mg/m^2 by 90-min infusion given weekly for 3 weeks every 4 weeks. Grade 3 diarrhea was the dose-limiting toxicity (DLT) at doses of 173 and 230 mg/m^2, and the maximum tolerated dose (MTD) is likely



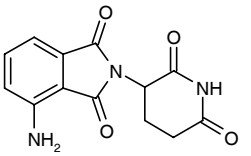
Triphendiol (**1**)



ADH-1 (**2**)



E-7820 (**3**)



Pomalidomide (**4**)

to be 144 mg/m^2. Grade 3 transient neutropenia was also seen in 2 patients and transient infusion-related visual disturbances were noted in 6 patients. Pharmacokinetic data from 12 patients showed that cumulative SN-38 exposures were 1.2-6.5-fold higher than those predicted for irinotecan at equivalent doses and treatment schedules; increased SN-38 has been linked to tumor inhibition in preclinical studies. Two partial responses were obtained in patients with advanced cervical and small cell lung cancer and there was evidence of antitumor activity in patients with ovarian cancer, Hodgkin's disease, adrenocortical cancer and esophageal cancer (2). NKTR-102 is in phase II investigation for the treatment of colorectal cancer and solid tumors.

Data from a first-in-human phase I study evaluating **EZN-2208**, Enzon's PEGylated form of SN-38, demonstrated its safety and tolerability in patients with advanced solid tumors. Twenty-three patients with different types of solid tumors were enrolled in this phase I study and received 1-h i.v. infusions of EZN-2208 at doses ranging from 1.25 to 16.5 mg/m^2. Thirteen of these patients had previously received irinotecan treatment. No DLTs were observed except for febrile neutropenia in 2 of 6 patients receiving the highest dose. The most commonly reported adverse events (AEs) were grade 1 or 2 fatigue, nausea, anorexia, diarrhea, alopecia, constipation, vomiting, anemia and neutropenia. Stable disease was observed in 7 patients. Pharmacokinetics for the three highest doses (5, 10 and 16.5 mg/m^2) were linear to dose and similar half-life values were obtained (3).

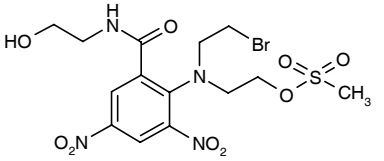
Adherex reported new phase I and initial phase II data on **ADH-1** (**2**) in combination with chemotherapy in patients with N-cadherin-expressing solid tumors at the ASCO meeting. Thirty-five patients with N-cadherin-positive advanced solid tumors received escalating systemic doses of ADH-1 (1, 2 and 4 g) and were assigned to receive either carboplatin, docetaxel or capecitabine. Whereas the MTD for ADH-1 in combination with docetaxel was found to be 2.0 g, MTD values for the carboplatin and capecitabine arms have not yet been reached. Preliminary efficacy data have shown 2 partial responses on the capecitabine arm and 4 cases of stable disease (3 on the docetaxel and 1 on the capecitabine arm). DLTs were grade 3 mucositis, thrombocytopenia, hand-and-foot syndrome, nausea/vomiting and grade 4 febrile neutropenia (4).

The MTD of **E-7820** (**3**; Eisai) of 100 mg/day p.o. was safe when given with standard doses of cetuximab (Merck KGaA) begun on day 8 of the first cycle and continued weekly in a phase I study in patients with advanced solid tumors. The study included 17 patients who received E-7820 40, 70 or 100 mg/day and a total of 46 cycles were administered. The only DLT was grade 3 transaminitis seen at the dose of 70 mg/day. Other grade 3 toxicities included acneiform rash, pruritus and elevated aspartate aminotransferase (AST), while grade 1-2 toxicities were rash, pruritus, anorexia and fatigue. Peak concentrations of E-7820 were achieved at approximately 4 h and a half-life of 3.6-4.9 h was measured. Exposure increased dose-dependently up to 100 mg/day. This dose was associated with a decline of 72% in α_2 integrin levels over the first month and an increase in vascular endothelial growth factor (VEGF) levels of 163% at the end of cycle 1. There was 1 unconfirmed partial response and 5 patients had stable disease. The treatment combination is currently under evaluation in a phase II study in patients with colorectal cancer (5). E-7820 is in phase I/II investigation at Eisai for solid tumors and in phase II for colorectal cancer.

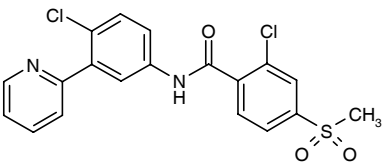
Data from a preclinical study of **pomalidomide** (CC-4047, Actimid™, **4**; Celgene) and lenalidomide (Revlimid®) investigating the effects of the agents on natural killer (NK) cell-mediated antibody-dependent cellular cytotoxicity (ADCC) and from a phase I study of pomalidomide in solid tumor patients were presented at the

meeting. In an *in vitro* ADCC system, pretreatment of NK cells with pomalidomide or lenalidomide, but not thalidomide, enhanced ADCC of HER2/neu-overexpressing breast cancer cells precoated with trastuzumab and epidermal growth factor receptor (EGFR)-positive colorectal cancer cells precoated with cetuximab. NK cell- and monocyte-mediated killing of antibody-coated tumor cells was concentration-dependent and tumor cell killing was minimal with antibody alone or either drug alone or in the presence of panitumumab. NK cell-mediated killing was associated with changes in intracellular signaling and increased granzyme B and FasL expression, while monocyte-mediated ADCC was associated with increased granzyme B and FasL expression and was blocked by an anti-interleukin-12 monoclonal antibody. In addition, ADCC was completely prevented by an inhibitor of granzyme B activity and partially inhibited by an antibody blocking the FasL–Fas interaction. Future clinical studies will evaluate the combination of pomalidomide and lenalidomide with antibodies to tumor-specific surface antigens (6). In the phase I study the recommended phase II oral dose of pomalidomide was set at 7 mg once daily when given for 21 consecutive days followed by 7 days off. After 3 patients received a 5-mg dose without DLTs, the dose was increased to 10 mg in the next 2 patients, both of whom experienced dyspnea as a DLT. When the dose was decreased to 7 mg, only 1 of 6 patients had DLT of dyspnea. Grade 3 neutropenia was also observed in 5 patients. A significant decline in prostate-specific antigen (PSA) was seen in a patient with advanced, taxane-refractory prostate cancer (7). Pomalidomide is a thalidomide analogue under development at Celgene for a variety of oncolytic indications.

Pharmacokinetic and toxicity data from three phase I studies of Proacta's **PR-104** (**5**), a prodrug that is converted to the DNA-damaging agent PR-104A in hypoxic tumor cells, were made available at the meeting. In the first clinical evaluation of the drug, 27 patients with advanced solid tumors refractory to standard therapy received a 1-h i.v. infusion every 3 weeks, with 7 dose levels evaluated. The MTD recommended for phase II was 1100 mg/m^2. Dose-dependent myelosuppression was the primary toxicity, and fatigue, nausea, anemia and dysgeusia the most common AEs. Minor tumor regressions and symptomatic improvement were seen, and the exposure achieved with the MTD has been associated with antitumor activity in tumor xenograft models. Linear plasma pharmacokinetics were observed with both PR-104 and the metabolite PR-104A (8). Patients with solid tumors (N = 10) were also enrolled in a second study and received 1-h i.v. infusions of PR-104 135, 270 or 540 mg/m^2 on days 1, 8 and 15 every 28 days. Toxicities were generally manageable and dose-dependent myelosuppression was again the primary toxicity. The MTD was at least 270 mg/m^2, with DLTs seen at this dose (grade 3 anemia) and at the 540 mg/m^2 dose (grade 4 thrombocytopenia/cerebral hemorrhage). Pharmacokinetics on this schedule appeared to be similar to those seen when PR-104 was given once every 3 weeks. Two patients had stable disease (9). A third study is evaluating the use of PR-104 in combination with gemcitabine (800 mg/m^2) or docetaxel (60 mg/m^2) in patients with advanced cancer, 30 of whom had been treated at the time of reporting. PR-104 was administered i.v. in escalating or de-escalating doses once every 3 weeks. When PR-104 was combined with gemcitabine, dose-limiting thrombocytopenia was seen and the MTD was 140 mg/m^2. With docetaxel, dose-limiting neutropenia was seen and the MTD was < 200 mg/m^2. When granulocyte colony-stimulating factor (G-CSF) was given with PR-104 and docetaxel, higher doses of PR-104A were achievable. Plasma pharmacokinetics of PR-104A did not appear to be altered by gemcitabine or docetaxel, and PR-104 did not appear to alter the plasma pharmacokinetics of gemcitabine or docetaxel. Tumor hypoxia was detected in 9 of 12 patients (10).



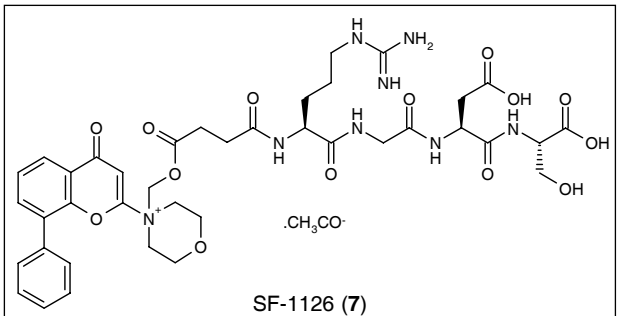
PR-104 (**5**)



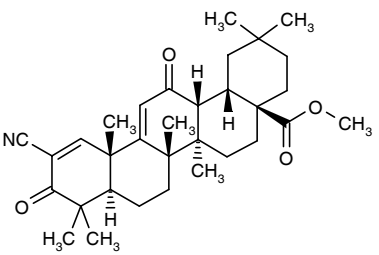
GDC-0449 (**6**)

Researchers at TGen Research Institute and Nerviano Medical Sciences presented phase I results for the oral multi-CDK (cyclin-dependent kinase) inhibitor **PHA-848125** in patients with advanced or metastatic solid tumors. PHA-848125 inhibits CDK1, CDK2 and CDK4 and neurotrophic tyrosine kinase receptor type 1 (NTRK1, Trk-A). In this phase I dose-escalation study, PHA-848125 was administered at oral doses ranging from 50 to 300 mg once daily for 7 days on a 2-week cycle. Overall, PHA-848125 was well tolerated, nausea, vomiting, diarrhea, tremor and ataxia being the most commonly reported AEs. Grade 3 and 4 ataxia occurred at 200 and 300 mg/day, respectively, began around days 4-7 of a cycle and was reversible. Mild hematological toxicity was also observed. The recommended dose for phase II studies was established at 150 mg/day, which was associated with mild to moderate and reversible toxicity. Pharmacokinetic studies showed dose-proportionality, with a predictable day 7/day 1 $AUC_{(0\text{-}24h)}$ ratio of approximately 3 (11).

First-in-human results for Genentech's **GDC-0449** (**6**) indicated good safety, activity and a unique pharmacokinetic profile. GDC-0449 is an inhibitor of the hedgehog



SF-1126 (**7**)



RTA-402 (**8**)

signaling pathway, aberrant activation of which has been associated with a variety of cancers. Nineteen patients with refractory solid tumors received a single oral dose of GDC-0449 given on day 1, followed by a 1-week break and then once-daily dosing for a 35-day cycle at 150, 270 and 540 mg/day. No DLTs were observed. Treatment resulted in 1 partial response in a patient with basal cell carcinoma (BCC) and 2 cases of stable disease in patients with BCC and adenocystic carcinoma. Pharmacokinetic studies showed a prolonged terminal half-life and drug accumulation, resulting in similar mean steady-state plasma concentrations across all dose levels. Downregulation by more than 2-fold of glioma-associated oncogene 1 (GLI1), a transcription factor involved in hedgehog signaling, was observed in skin biopsies of 11 of 14 analyzed patients (12). GDC-0449, discovered under a collaboration with Curis, is currently undergoing phase I/II studies at Genentech for the treatment of colorectal cancer, BCC and ovarian cancer.

BiPar Sciences reported on its novel poly(ADP-ribose)polymerase (PARP) inhibitor **BSI-201**, which had a good safety profile in phase I studies. The first-in-human phase I study of BSI-201 was conducted in 23 patients with advanced solid tumors who were treated at 7 different dose levels ranging from 0.5 to 8.0 mg/kg i.v. Good tolerability was observed across all doses tested and the MTD was not reached. Gastrointestinal disorders were the most commonly reported AEs. Following a dose of 1.4 mg/kg i.v., the C_{max} value was 400 ng/ml, which exceeded concentrations associated with efficacy in preclinical studies. BSI-201 was rapidly eliminated ($t_{1/2}$ = 4 min), but longer lived metabolites were detected. Stable disease lasting for 2 months was observed in 6 of 23 treated patients. Moreover, PARP inhibition in peripheral blood mononuclear cells (PBMCs) was > 50% after a single dose and reached 80% or more following multiple dosing (13).

Further phase Ib results demonstrated that BSI-201 in combination with chemotherapy holds promise for the treatment of advanced solid tumors. Fifty-five patients received BSI-201 at doses ranging from 1.1 to 8.0 mg/kg i.v. in combination with topotecan, gemcitabine, temozolomide or carboplatin/paclitaxel. BSI-201 did not increase the frequency of known toxicity associated with chemotherapy. Moreover, complete and partial responses were achieved in 1 and 5 patients, respectively, and 19 patients showed stable disease for 2 or more months (14). BSI-201 is currently undergoing phase I/II clinical trials for the treatment of metastatic breast cancer, BRCA-negative ovarian cancer, uterine cancer and glioblastoma multiforme at BiPar Sciences.

Semafore Pharmaceuticals reported positive interim results from a multicenter, dose-escalating phase I study of **SF-1126** (**7**), a targeted pan-phosphatidylinositol 3-kinase (PI3K) inhibitor, in patients with advanced solid tumors. Doses of 90, 140 and 180 mg/m^2 by i.v. infusion have been evaluated, with 1 DLT seen at 180 mg/m^2 (hypersensitivity reaction). Overall the drug has been generally well tolerated (15).

The second-generation antisense oligonucleotide survivin inhibitor **LY-2181308** (Lilly, Isis Pharmaceuticals) is a candidate for antitumor therapy that demonstrated a good toxicity and safety profile in a phase I trial. Patients (N = 31) with colon cancer, ductal breast cancer, sarcoma, stomach tumors or melanoma were treated with LY-2181308 at escalating doses from 100 to 1000 mg i.v., with an MTD of 900 mg and a biological effective dose (BED) of 750 mg, which will be used in phase II studies. The compound was generally well tolerated up to the BED dose, with flu-like symptoms and partial thromboplastin time prolongation (no bleeding) being the most frequently reported toxicities. LY-2181308 was rapidly distributed into tissues, with 90% plasma exposure cleared after 24 h. The compound is currently under study with other cytotoxic agents (16).

RTA-402 (**8**; Reata Pharmaceuticals) is an antioxidant inflammation modulator with potent anticancer and antiinflammatory activity through its suppression of NF-κB and STAT3 (signal transducer and activator of transcription 3) and induction of Nrf2. The compound has been studied in a phase I trial in patients with solid tumors and lymphoid malignancies at escalating oral doses of 5-1300 mg/day for 21 days every 28 days and was associated with minimal drug-related events in 91% of patients. Transient asymptomatic transaminase elevation was identified as a DLT. The recommended MTD for phase II studies was 900 mg/day. In pharmacokinetic studies, RTA-402's exposure in humans at the MTD was 7-fold greater than in rodents and the drug had a mean half-life of 39 h. Complete or partial responses were achieved with study treatment in mantle cell lymphoma and anaplastic thyroid carcinoma. The drug was also associated with prolonged

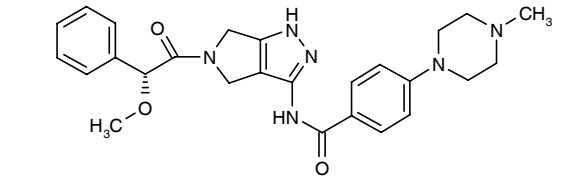
stable disease in melanoma, renal cell carcinoma and medullary thyroid carcinoma patients (17).

Results of phase I studies, presented by Nerviano Medical Sciences researchers, with the Aurora kinase inhibitor **PHA-739358** (danusertib, **9**) (see monograph, this issue) have shown that it is a well-tolerated agent for the treatment of advanced solid tumors. Forty patients received PHA-739358 on days 1, 8 and 15 every 4 weeks by a 6-h i.v. infusion at dose levels ranging from 45 to 400 mg/m^2. The recommended dose for phase II studies (RPIID) was established as 330 mg/m^2. At this dose level, DLTs were febrile neutropenia and grade 3 fatigue. Grade 4 neutropenia occurred at 400 mg/m^2. The most frequently reported drug-related AEs were grade 1/2 anorexia, nausea, fatigue and diarrhea. Stable disease was obtained in 7 patients. Inhibition of histone H3 phosphorylation, a marker of biological activity, could be seen at the RPIID and already at the 190 mg/m^2 level. Pharmacokinetics were linear, with moderate plasma clearance and a terminal half-life of 24 h (18).

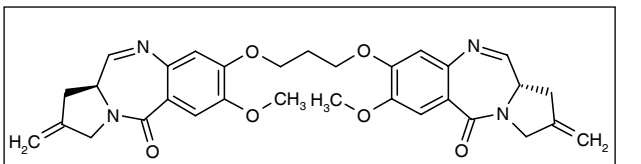
Further studies investigated PHA-739358 administered as a 24-h infusion with or without G-CSF on a 14-day cycle in patients with advanced solid tumors. Forty patients were treated at 7 dose levels ranging from 45 to 650 mg/m^2 and without concomitant G-CSF. In this arm, 500 mg/m^2 was established as the RPIID. The most frequently reported drug-related hematological toxicities were grade 3/4 neutropenia and lymphocytopenia. In parallel, 16 patients received three dose levels of PHA-739358 (580, 750 and 1000 mg/m^2) in combination with G-CSF. While the incidence and severity of drug-related hematological toxicities were reduced, the incidence of nonhematological AEs was similar. The 750 mg/m^2 group has been expanded in order to confirm the RPIID (19).

SJG-136 (SG-2000, **10**; Spirogen, Ipsen), a DNA minor groove-binding pyrrolobenzodiazepine (PBD) dimer with a broad antitumor profile *in vitro*, showed an adequate safety profile and pharmacokinetics in phase I studies in patients with advanced solid tumors. Fourteen patients received SJG-136 i.v. daily x 3 over a 21-day cycle at doses ranging from 20 to 35 μg/m^2/day. Dexamethasone pretreatment and diuretic support with spironolactone were also administered. Grade 3 soft tissue edema, dyspnea, fatigue and grade 3 transaminase elevation were DLTs at 35 μg/m^2/day. The MTD was established at 30 μg/m^2/day. According to response evaluation criteria in solid tumors (RECIST), 2 patients had a partial response and 3 patients stable disease. These results correlated with the finding of DNA crosslinks in PBMCs (20).

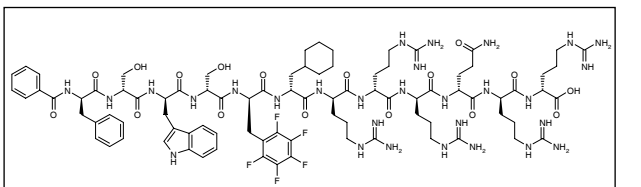
The effects of a single SJG-136 injection every 21 days were evaluated in a further phase I study that included 16 cancer patients. The MTD in this study was 45 μg/m^2, but an RPIID was not identified. Delayed vascular leak syndrome occurred in 4 of 5 patients receiving doses between 30 and 240 μg/m^2. Dose reduction to 60 μg/m^2 was then associated with liver toxicity. SJG-136 demonstrated dose-linear pharmacokinetics and biphasic clearance across all tested doses. Alternative dosing schedules are currently being investigated (21).



PHA-739358 (**9**)



SJG-136 (**10**)



CBP-501 (**11**)

The cell cycle G2 checkpoint abrogator **CBP-501** (**11**; CanBas, Takeda) has been investigated as monotherapy and in combination with cisplatin in two phase I dose-escalation studies in patients with advanced solid tumors. In the first study (N = 30), patients received CBP-501 via central catheter on days 1, 8 and 15 every 4 weeks, with a starting dose of 0.9 mg/m^2. All patients discontinued due to progressive disease. One case of DLT of transient asymptomatic G3 troponin elevation was noted at 22.5 mg/m^2. Grade 1-2 allergy was seen in 18 patients. In the combination study, patients (N = 33) received CBP-501/cisplatin at starting doses of 3.6/50 mg/m^2 with treatments given every 3 weeks. Two DLTs of grade 3 allergic reaction occurred at CBP-501/cisplatin doses of 36.4/75 mg/m^2, and the MTD was defined as 25/75 mg/m^2. The most common AE was allergic reaction (n = 16), which could be alleviated by implementation of a prophylactic regimen. Stable disease lasting over 4 months was observed in 5 patients and a partial response was obtained in a patient with endometrial adenocarcinoma. In both studies, exposure was dose-proportional over a 40-fold dose range. A phase I/II study of CBP-501 with cisplatin/pemetrexed in mesothelioma patients is under way (22).

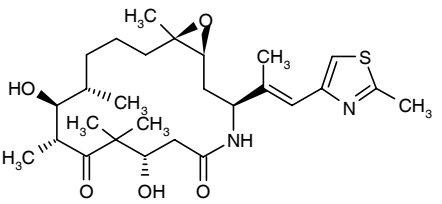
Two phase I studies of Merck & Co.'s anti-insulin-like growth factor 1 receptor (IGF1R) monoclonal antibody **MK-0646** have provided pharmacokinetic, pharmacodynamic, tolerability and safety data on the antibody in patients with advanced solid tumors. In the first-in-human study of MK-0646, 53 patients received escalating i.v. doses (1.25-20 mg/kg) weekly. The MTD was not

reached and these doses were well tolerated. The most common AE was hyperglycemia, which could be controlled with antihyperglycemic therapy. Dose-proportional pharmacokinetics were seen with doses above 2.5 mg/kg, and inhibition of pharmacodynamic endpoints, such as downregulation of IGF1R expression in tumors, was observed. The recommended weekly dose for further evaluation was 10 mg/kg, but pharmacokinetic results pointed towards dosing every 2 or 3 weeks, which is currently being evaluated (23). Dosing every 2 weeks was evaluated in a study of loading doses of 2.5-20 mg/kg followed by maintenance doses of 2.5-15 mg/kg. MK-0646 was well tolerated and the MTD was not reached. At the loading/maintenance dose of 15/5 mg/kg, grade 4 thrombocytopenia and grade 3 gastrointestinal bleeding were seen, while grade 3 pneumonitis and grade 3 increases in liver function tests were seen at 20/5 mg/kg. Pharmacokinetics appeared to be dose-proportional at doses above 5.0 mg/kg, and evidence of IGF1R signaling modulation was noted. Five patients had stable disease lasting over 4 months (24). Phase II studies are under way in various tumor types.

Vaxon Biotech's **VX-001** was associated with immunological and clinical responses in patients with advanced solid tumors enrolled in a phase I/II study. The vaccine contains $hTERT_{572Y}$, a single optimized cryptic peptide that targets tumors expressing the telomerase antigen, and has received orphan drug status in the E.U. for the treatment of telomerase catalytic subunit (TERT)-positive non-small cell lung cancer (NSCLC) in HLA-A2-positive patients. In the present study, 71 patients who had previously received standard chemotherapy were given two subcutaneous injections of 2 mg of the optimized $TERT_{572Y}$ peptide followed by four injections of 2 mg of the native $TERT_{572}$ peptide administered every 3 weeks. An early (before the third vaccination) and late (after the sixth vaccination) immunological response was seen in 51.8% and 83% of evaluable patients, respectively. Three objective clinical responses were seen along with 22 disease stabilizations, all of the latter occurring in patients with early immunological responses. Early and late responses were associated with increased survival in patients with progressive disease before vaccination. The primary toxicity consisted of grade 1 local skin reactions (25).

Ixabepilone (**12**) 8 mg/m^2/day i.v. for 5 days every 21 days was not significantly active in pediatric patients with refractory solid tumors, although results using a pediatric xenograft model had predicted activity for the agent. There were no partial or complete responses (RECIST) in the 61 patients enrolled, although 2 had prolonged stable disease. DLTs were seen in 10 patients in the first cycle and in 6 patients in subsequent cycles (26). Ixabepilone (Ixempra™) is currently marketed by Bristol-Myers Squibb in the U.S. for the treatment of metastatic breast cancer, and the company continues to evaluate ixabepilone for a wide variety of cancer indications.

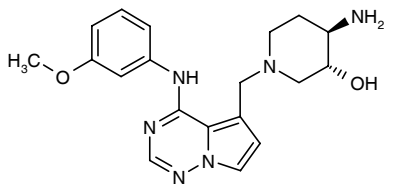
Results reported to date show **XL-765** to be generally well tolerated up to doses of 60 mg b.i.d. p.o. on 28-day cycles in patients with advanced solid tumors enrolled in a phase I dose-escalation study. The PI3K and mTOR (mammalian target of rapamycin) inhibitor is being developed by Exelixis. Data from 13 patients show no DLTs, with 1 case of grade 4 transaminitis seen at a dose of 120 mg b.i.d. Evidence of activity has been noted. Pharmacokinetic analysis revealed less than dose-proportional increases in exposure with increasing doses, with a mean $t_{1/2}$ of 3-9 h at steady state. Drug accumulation ranged from none to moderate. XL-765 also appeared to increase food-induced changes in plasma insulin in an exposure-dependent fashion. Pharmacodynamic modulation of PI3K and mTOR was noted in patient hair bulbs. Dose escalation continues (27).



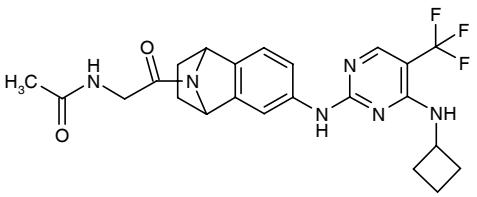
Ixabepilone (**12**)

Exelixis' **XL-184**, an orally available VEGFR, RET and c-Met kinase inhibitor, was generally well tolerated in a phase I dose-escalation study in patients with advanced malignancies (N = 69). Doses assessed were 0.08-11.52 mg/kg given for 5 of 14 days, 175 and 265 mg given daily, and in cohorts where the formulation was switched from suspension to capsules 175 and 250 mg/day. DLTs were seen at 11.52 mg/kg (grade 3 palmar/plantar erythema, grade 3 ALT [alanine aminotransferase], AST and lipase elevations), at 265 mg/day (grade 2 and 3 mucositis) and 250 mg (grade 3 AST elevation). Diarrhea and hypopigmentation of the hair were other notable toxicities. Pharmacokinetics appeared to be linear, with a $t_{1/2}$ of 59-136 h. Stable disease lasting at least 3 months was observed in 25 patients and partial responses were noted in 10 patients, 9 with medullary thyroid cancer and 1 with neuroendocrine carcinoma. The MTD was 175 mg p.o. once daily. Phase II studies of XL-184 in NSCLC and glioblastoma are ongoing, and a phase III study is planned for medullary thyroid cancer (28). Exelixis and the FDA recently agreed on a Special Protocol Assessment (SPA) for the phase III registration trial of XL-184 in medullary thyroid cancer, which began in July.

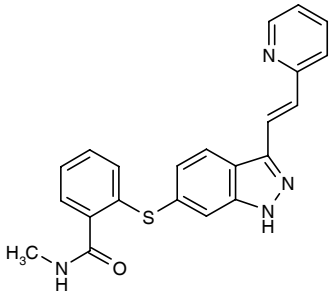
In the first part of an ongoing multicenter study, patients with advanced solid tumors were treated with escalating doses of the pan-HER and VEGFR-2 inhibitor **BMS-690514** (**13**) of 40-300 mg/day p.o. and doses up to 200 mg were generally well tolerated. Higher doses were associated with DLTs (grade 3-4 diarrhea, grade 3 reversible acute renal insufficiency). In the ongoing second part of the study, patients with NSCLC are being treated with BMS-690514 200 mg. Most AEs reported at interim analysis were mild to moderate and mechanism-based. Evidence for antitumor activity and disease control



BMS-690514 (**13**)



PF-03814735 (**14**)



Axitinib (**15**)

has been seen in both parts of the study, as well as dose-proportional exposure and linear pharmacokinetics, with a mean half-life of 11 h (29).

A study of **BMS-663513**, a fully human anti-CD137 agonist monoclonal antibody, included a dose-ascending phase (0.3-15 mg/kg i.v. once every 3 weeks every 4 weeks) in advanced solid tumor patients (n = 24) and a randomized phase (1, 3 or 10 mg/kg) in patients with advanced melanoma, renal cell carcinoma or ovarian cancer (n = 90). In part 1, doses up to 15 mg/kg were tolerated. BMS-663513 was also tolerable in part 2, with no dose–toxicity relationship. Antitumor activity was seen in part 2 in patients with melanoma, with an objective response rate of 6.4% in that group and activity seen at all doses. Linear pharmacokinetics, with a $t_{1/2}$ of 8-12 days, were observed. A phase II study of different doses and schedules in patients with advanced melanoma is under way (30).

An ongoing phase I study is evaluating dosing with **PF-03814735** (**14**), an Aurora kinase A and B inhibitor from Pfizer, over 5 or 10 consecutive days on 3-week cycles in patients with advanced solid tumors. On the 5-day schedule, oral doses of 5-100 mg/day have been investigated in 25 patients, with the MTD determined to be 80 mg/day. Febrile neutropenia was the DLT seen at 100 mg/day, while the most common treatment-related AEs at 80 mg/day were anorexia, diarrhea and vomiting. Serum exposure was dose-proportional. Enrollment at the MTD has been expanded to provide proof-of-mechanism data. At the time of reporting, no objective responses had been seen on this schedule. The 10-day schedule of escalating oral doses is being evaluated, with 3 patients treated at the time of reporting (31).

The anti-IGF1R monoclonal antibody **AVE-1642**, which is also being developed by sanofi-aventis for multiple myeloma, has been well tolerated in a phase I study in advanced solid tumor patients. AVE-1642 is first administered every 3 weeks as a single agent in cycle 1 and then in combination with docetaxel 75 mg/m^2 in cycle 2. In 14 patients treated with AVE-1642 doses of 3, 6, 12 and 18 mg/kg, there were no DLTs or serious AEs. AVE-1642 concentrations increased dose-proportionally, with no pharmacokinetic interaction observed. All AVE-1642 doses were associated with increases in mean IGF-1 levels. Four patients had stable disease while on treatment, and a breast cancer patient had a reduction in skin nodules. Further study is needed to determine the MTD of AVE-1642 alone and in combination with docetaxel (32).

Three studies of Pfizer's **axitinib** (**15**), a VEGFR and platelet-derived growth factor receptor (PDGFR) inhibitor, were presented at ASCO. In a phase I study in patients with metastatic solid tumors, the treatment regimen included bevacizumab 1 mg/kg (escalated to 2 and 5 mg/kg in the second and third cohorts, respectively), oxaliplatin/5-fluorouracil/leucovorin (FOLFOX) and axitinib started at 5 mg p.o. b.i.d. There appeared to be no interaction between axitinib and bevacizumab/FOLFOX, and data available to date indicated that the combination was well tolerated. Of a total of 15 patients, 2 had a partial response and 9 had stable disease. A phase II study comparing axitinib/FOLFOX, bevacizumab/FOLFOX and axitinib/bevacizumab/FOLFOX in metastatic colorectal cancer patients has started (33). Axitinib is being evaluated in a number of other phase II trials and a phase III trial in pancreatic cancer is under way.

Reseachers at AstraZeneca reported results from two studies investigating **AZD-4877**, a novel specific, potent inhibitor of kinesin-like protein (KIF11, Eg5; IC_{50} = 10 nM or less), in patients with advanced solid tumors. The first study included 29 patients with histologically confirmed solid tumors who received AZD-4877 at weekly doses ranging from 5 to 45 mg for 3 weeks (followed by a 1-week rest). The MTD was identified as 30 mg, but 25 mg was the dose selected for expansion and phase II studies. Neutropenia was the DLT, which was also dose-related, rapidly reversible and correlated with drug exposure. AZD-4877 showed linear pharmacokinetics, with a half-life ranging from 15 to 27 h across different dose groups. Free plasma levels at 24 h at doses of 20 mg or more exceeded preclinical IC_{50} values. Monoastral mitotic spindles were identified in PBMCs, providing proof of mechanism (34). A further study conducted in 18 patients with advanced solid tumors identified the MTD of AZD-4877 as 11 mg given as a 1-h i.v. infusion on a twice-

weekly schedule on days 1, 4, 8 and 11 of a 21-day cycle. At this dose level, the mean half-life was 16 h. DLT was dose-related neutropenia. One patient with diffuse large B cell non-Hodgkin's lymphoma (NHL) had a partial response lasting for more than 12 weeks after 2 cycles of AZD-4877 11 mg (35).

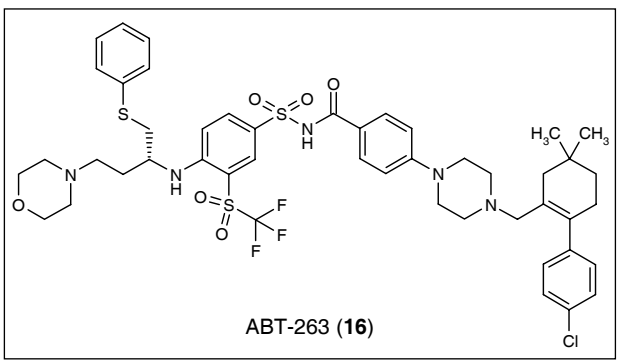
Lymphoma

Phase I results for **ABT-263** (**16**), a novel inhibitor of the antiapoptotic Bcl-2 protein family, in lymphoid malignancies were presented at ASCO. To date, 30 patients with refractory or relapsed lymphoma have been enrolled in this study that is evaluating the safety and pharmacokinetics of oral ABT-263 at escalating doses ranging from 10 to 315 mg (once daily for 14 days, followed by 7 days off drug). In the 40-mg cohort, 2 patients with bulky chronic lymphocytic leukemia (CLL) experienced 99% and 36% reductions in tumor growth at cycle 4. Researchers also observed a 75% reduction at cycle 4 in 1 patient with bulky CLL/small lymphocytic lymphoma (SLL) in the 60-mg cohort and a 20% reduction after cycle 7 in another patient in the 80-mg cohort. Finally, 1 patient with NK/T cell lymphoma receiving 315 mg ABT-263 had a 75% reduction in tumor measurement at cycle 2. ABT-263 was generally well tolerated, with 1 case of grade 3 DLT occurring in each of the 160- and 315-mg cohorts. In addition, ABT-263 showed linear pharmacokinetics, with a mean half-life of 14-20 h (36).

Furthermore, data from three ongoing phase I studies revealed that reduction in platelet counts may be a pharmacodynamic biomarker of Bcl-2 inhibition. ABT-263 treatment dose-dependently reduced platelet levels due to apoptosis, with a mean reduction of 69% compared to baseline at 315 mg. Typically, the lowest platelet counts were observed on days 3-5, with recovery during continued dosing, which is consistent with accelerated platelet senescence and compensatory increased production (37). ABT-263 is being codeveloped by Abbott and Genentech, with phase I trials under way for CLL, lymphoid malignancies and small cell lung cancer.

Multiple myeloma

Phase I data were presented for **EZN-2232** (Enzon), a recombinant human mannose-binding lectin (rhMBL) for the prevention and treatment of severe infections in patients with multiple myeloma with low levels of MBL undergoing high-dose chemotherapy. In this phase Ib study, patients (N = 18) were randomized to receive 0.5 or 1 mg/kg or no drug. No serious drug-related or grade 4 or 5 AEs were reported. Neutropenia, bacteremia and increased C-reactive protein were among the most frequently reported grade 3 AEs. Weekly administration of EZN-2232 resulted in normalization of *in vitro* C4b complement activity (38).

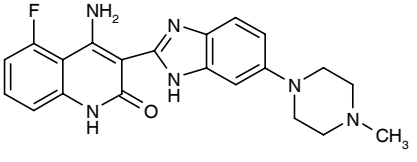


ABT-263 (**16**)

Melanoma

Phase I/II results evaluating **ADH-1** (see above) in combination with isolated limb infusion with melphalan (ILI-M) in patients with advanced in-transit melanoma of the extremity were released at the meeting. ADH-1 was escalated at 1, 2 and 4 g in cohorts of 3 patients each and given before and after ILI-M treatment. So far, 11 patients have been treated with no DLTs observed. Of 7 patients followed for 3 months posttreatment, 4 achieved a complete response and 1 stable disease, while disease progressed in 2 patients who were negative for N-cadherin. These results demonstrate that this treatment approach may be useful in regionally advanced N-cadherin-positive melanoma (39). Adherex has been granted orphan drug designation for the use of ADH-1 together with melphalan for the treatment of stage IIB/C-IV malignant melanoma.

Novartis's angiogenesis inhibitor TKI-258 (**dovitinib**, **17**) is being evaluated in phase I trials in patients with solid tumors, acute myeloid leukemia (AML), melanoma and multiple myeloma. In support of these and future studies, a population pharmacokinetic/pharmacodynamic model was developed to characterize systemic exposure and effects on biomarkers. Plasma concentrations from 87 patients were used. The model-predicted TKI-258 concentration for optimal effect on VEGF and placenta growth factor (PlGF) was approximately 200 ng/ml, which was expected to be safe. Intermittent dosing schedules for controlling drug exposure within the active range were devised: 700 mg on a 5-days-on/2-days-off schedule, or 1200 mg given every Monday, Wednesday and Friday (40). In a phase I study in patients with advanced melanoma, TKI-258 doses up to 400 mg/day were safe and well tolerated with daily oral treatment on 28-day cycles. Data from 27 patients treated at 200, 300, 400 and 500 mg were assessed. The DLTs seen at the 500-mg dose were grade 3 and 4 fatigue and grade 3 diarrhea despite therapy. Grade 3 nausea despite therapy and grade 3 fatigue were DLTs seen with the 400-mg dose.



Dovitinib (**17**)

Among 22 patients evaluated for efficacy, 9 had stable disease lasting 3.5-9 months. Evidence of biological activity (VEGF induction) seen at doses of 400-500 mg tended to correlate with vascular responses and tumor stabilization (41). Angiogenesis biomarkers were also analyzed in plasma samples from 19 AML patients enrolled in a phase I trial (doses of 200-600 mg/day; an initial 14-day cycle followed by continuous daily dosing) and in another phase I trial in 16 melanoma patients (doses of 200-500 mg/day once daily on 28-day cycles). In the AML study, dose-dependent VEGF induction (3-11-fold) and PlGF induction (3-8-fold) were seen at doses of 400 and 600 mg at cycle 1 days 3 and 7, with a return to near baseline levels at the end of cycle 1 at day 14 and after 1 week off treatment. Approximately 3-fold VEGF induction and 2-9-fold PlGF induction and a 30-50% decrease in sVEGFR-2 were noted in the melanoma study with doses of 400 and 500 mg at the end of cycle 1. Induction of basic fibroblast growth factor (bFGF; 6-fold) was also observed at 500 mg in melanoma patients at the end of cycle 1 (42).

CuraGen reported positive results from the ongoing first-in-man phase I/II study of **CR011-vcMMAE**, an antibody–drug conjugate consisting of the fully human monoclonal antibody CR-011 linked to monomethyl-auristatin E (MMAE), for the treatment of unresectable stage III or IV melanoma. During phase I, doses of the drug between 0.03 and 2.63 mg/kg were evaluated and generally well tolerated, with rash and neutropenia emerging at higher doses. A total of 130 treatment cycles were administered (range: 2 to 19+ cycles per patient). Rash and desquamation were reported at the highest dose evaluated, and the MTD was determined to be < 2.63 mg/kg i.v. once every 3 weeks. The activity of CR011-vcMMAE was dose-dependent. The MTD will be investigated in the phase II stage of the study (43).

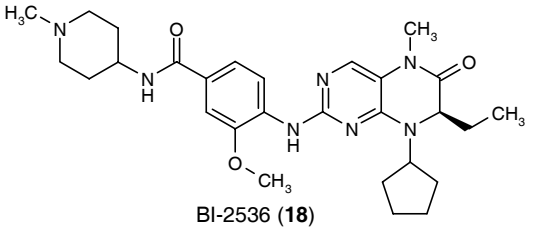
In a phase II study in patients with metastatic melanoma, 32 patients were given **axitinib** (see above) at a starting dose of 5 mg b.i.d. The overall response rate was 15.6%, with responses lasting from 2.3 to over 10 months and a median progression-free survival of 2.3 months. Survival was longer in patients with diastolic blood pressure above 90 mmHg. The most common treatment-related AEs were fatigue, hypertension, hoarseness and diarrhea, and 1 patient had grade 5 bowel perforation. Pharmacodynamic activity against targeted VEGFRs was noted. A phase III trial in patients with refractory metastatic renal cell carcinoma is planned (44).

Lung cancer

Of 63 metastatic NSCLC patients receiving at least one dose of the CTL (cytotoxic lymphocyte) vaccine **IDM-2101** (IDM Pharma) in a phase II study, 1 had a complete response, 1 had a partial response and 54 had stable disease lasting 3 months or more. The product is a 10-peptide vaccine designed to induce multispecific responses against MHC class I epitopes of carcinoembryonic antigen (CEA), p53, HER2/neu and MAGE-2/3, and includes 7 modified epitopes, 2 wild-type sequences and the class II helper epitope PADRE. In the study, HLA-A2$^+$ patients with stage IIIB/IV or recurrent disease were given six induction doses at 0.5 mg/epitope every 3 weeks and then maintenance treatment at 2-3-month intervals. Of 33 patients monitored for CTL, 30 had positive responses to 1 or more epitopes and 21 responded to at least 3 epitopes; all 9 epitopes were immunogenic in at least 1 patient. CTL responses were seen in 3 of 4 patients evaluated after 12 months. T helper (Th) cell responses against PADRE were detected in 18 of 33 patients tested. Survival at 1 year was 60% and median survival was 17.3 months; the respective figures in an HLA-A2-negative control group were 49% and 12.0 months. Fourteen patients completed 2 years of treatment without evidence of progression. There was also a trend towards increased survival in patients who responded to more epitopes. Vaccine-related toxicity was mostly mild (45).

BI-2536 (**18**) is a Polo-like kinase 1 (PLK-1) inhibitor currently undergoing phase II clinical trials at Boehringer Ingelheim for the treatment of solid tumors and refractory or relapsed advanced NHL. A recent phase I trial established the safety of BI-2536 in combination with pemetrexed in previously treated advanced or metastatic NSCLC. Thirty-three patients were recruited in this open-label, multicenter, dose-escalating phase I study and received BI-2536 at doses ranging from 100 to 325 mg i.v. in combination with pemetrexed 500 mg/m^2. The MTD for BI-2536 was identified as 300 mg. However, DLTs in expanded patient cohorts (200 and 300 mg) established an MTD for BI-2536 in combination with pemetrexed of 200 mg i.v. every 21 days. Mild to moderate nausea, rash, anorexia, stomatitis and pruritus were the most commonly reported AEs. No pharmacokinetic interaction between the two compounds was observed. Regarding efficacy, a mean progression-free survival of 3 months and stable disease rate of 56% were observed (46).

Further results from a phase II trial evaluating two dosing schedules of BI-2536 demonstrated moderate efficacy and acceptable safety of this drug as monotherapy in relapsed NSCLC. Patients (N = 95) were randomized to receive BI-2536 on day 1 (200 mg) or on days 1-3 (3 x 50 mg/3 x 60 mg). Partial responses were observed in 4.2% of patients and almost 50% showed stable disease 16 weeks after treatment initiation. Median overall survival and progression-free survival were 201 and 58 days, respectively. Grade 4 neutropenia occurred in 37% of patients, while fatigue and nausea were the most common nonhematological AEs (47).

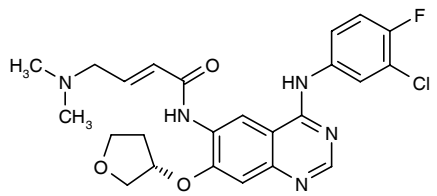


BI-2536 (**18**)

Patients with advanced, heavily pretreated NSCLC were enrolled in a dose-escalating phase I trial of Pfizer's **PF-00299804**, an orally bioavailable, small-molecule pan-HER (erbB) inhibitor. Patients received either continuous once-daily dosing or once-daily dosing for 2 weeks every 21 days with PF-00299804 doses of 16, 30, 45 or 69 mg. Durable partial responses were seen in 4 of 42 evaluable patients, and half of the patients had disease control. Evidence of efficacy was seen in patients known to be resistant to reversible EGFR tyrosine kinase inhibitors. Safety was consistent with reversible, small-molecule EGFR tyrosine kinase inhibitors and anti-EGFR monoclonal antibodies. A number of trials of PF-00299804 in NSCLC are planned or ongoing, including a study in patients with refractory, advanced disease after failure of EGFR tyrosine kinase inhibitor therapy, a study in patients with second-line/third-line advanced disease after failure of chemotherapy, a study in patients with frontline advanced disease and trials evaluating combination with targeted agents (48).

Data on 24 patients with adenocarcinoma of the lung and *EGFR* mutations treated with Boehringer Ingelheim's **BIBW-2992** (Tovok™, **19**) (see monograph, this issue) 50 mg orally once daily in an ongoing phase II study were also presented at the meeting. The agent is an inhibitor of EGFR and HER2. A partial response was seen in 12 patients and 9 had stable disease. Diarrhea and skin toxicity were the major drug-related toxicities, and no grade 4 events were seen. There were dose reductions in 7 patients and 7 stopped treatment primarily due to progressive disease. A phase II/III trial in patients with NSCLC failing reversible EGFR inhibitors and selected for the presence of T790M mutations is under way (49).

Data on the activity of the orally bioavailable multiple receptor tyrosine kinase inhibitor **XL-647** (Exelixis) in patients with NSCLC were also presented. In addition to these studies, a phase I dose-escalating study was conducted in 31 patients with advanced solid malignancies who received daily doses of 75-350 mg. The MTD was determined to be 300 mg/day in this study, with DLTs of pneumonitis seen in 1 patient at that dose and Q-T_c prolongation seen in 2 of 4 patients given 350 mg. The most common AEs were rash, diarrhea, fatigue and dry skin. Stable disease lasting over 3 months was seen in 16 patients (50). The 300-mg dose is also being investigated in a randomized phase II trial in NSCLC patients with acquired resistance to erlotinib or gefitinib or a documented T790M mutation in *EGFR*. Of 39 evaluable patients treated at the time of reporting, 1 had a partial response and 19 had stable disease. The treatment was well tolerated, with the most common toxicities being diarrhea, rash and fatigue. Three subjects with *EGFR* T790M mutations had stable disease (51). XL-647 was also evaluated in a randomized phase II study in patients with NSCLC with *EGFR* mutations. Patients received 350 mg on days 1-5 of 14-day cycles (n = 41) or daily dosing at 300 mg (n = 9). XL-647 was generally well tolerated, with few dose reductions required. With intermittent dosing, there were 10 partial responses and 17 patients with stable disease. Among the 10 patients with EGFR-activating mutations, there were 8 partial responses and 2 patients with stable disease. Planned studies include a phase I evaluation of XL-647 with the PI3K inhibitor XL-147 and a phase II study of XL-647 *versus* doublet chemotherapy in patients with newly diagnosed EGFR $FISH^+$ NSCLC (52).



BIBW-2992 (**19**)

Renal cell carcinoma

A phase I study demonstrated the feasibility and benefit of **FolateImmune** therapy combined with interferon alfa and interleukin-1 (IL-1) in previously treated patients with metastatic renal cell carcinoma. FolateImmune consists of EC90 (keyhole limpet hemocyanin–fluorescein isothiocyanate conjugate) vaccination plus GPI-0100 adjuvant followed by treatment with EC17 (folate–fluorescein isothiocyanate conjugate). Of 10 patients receiving treatment and evaluable for response, 5 had stable disease lasting at least 3 months. Median progression-free survival was 3.2 months and median overall survival was 10.4 months. In the overall patient group (N = 11), the therapy was well tolerated and toxicities were reversible, with grade 1-2 AEs including rash, pruritus, fatigue and flu-like symptoms. A phase II study is enrolling patients (53). FolateImmune was developed by Endocyte in collaboration with Purdue University.

Data on the *in vivo* efficacy of **AGS-16M18**, a fully human monoclonal antibody with high affinity for AGS-16, were presented at the meeting. AGS-16, a human cell-surface protein expressed in most renal cancers, was identified by investigators at Agensys, now part of Astellas Pharma. *In vitro,* AGS-16M18 concentration-dependently inhibited the proliferation and survival of RXF-393 and Hep G2 tumor cell lines, concentration-dependently inhibited AGS-16-induced human umbilical vein endothelial cell (HUVEC) tube formation and inhibited Hep G2 cell migration and invasion. Antitumor activity was seen *in vivo* in patient-derived clear cell kidney cancer xenografts and hepatocellular carcinomas. Tumor treatment was associated with effects on the ERK (extracellular signal-regulated kinase), Akt and PARP pathways. The efficacy of AGS-16M18 was also maintained after monoclonal antibody deglycosylation. In addition, synergistic activity was seen with the combination of AGS-16M18 and bevacizumab, sunitinib and rapamycin (54).

Results from three phase II trials of **ixabepilone** (see above) were reported. In one trial, 87 patients with

metastatic renal cell carcinoma received ixabepilone 6 mg/m^2/day i.v. for 5 days. There were 1 complete and 10 partial responses, with a median shrinkage of 12% in the 37% of patients with measurable shrinkage. The median response duration was 5.5 months. Most treatment-related toxicity was grade 1-2. Analysis of rates of tumor regression and tumor growth and data from other patients indicated that the treatment reduced the growth rate constant of metastatic renal cell carcinoma 2-fold (55).

Twenty-five patients with papillary renal cancer were treated orally with **XL-880** (1363089), a small-molecule c-Met and VEGFR-2 kinase inhibitor, at a dose of 240 mg/day on days 1-5 every 14 days in a phase II study. There were 2 confirmed and 2 unconfirmed partial responses, and stable disease was achieved by 20 patients. Tumor shrinkage was seen in 19 of 25 patients, and median progression-free survival was 13 months. The treatment was generally well tolerated, with 21 serious AEs seen in 11 patients, although most events were grade 1-2 in severity. In most patients, treatment was associated with changes in biomarkers which are known to be modulated by treatment with antiangiogenic agents, and these biomarkers may be useful in monitoring the effects of XL-880 treatment (56). The compound was licensed to GlaxoSmithKline by Exelixis last year and phase II trials are under way in papillary renal cell and head and neck squamous cell carcinoma, as well as gastric cancer.

A phase II study of **axitinib** (see above) included patients with refractory metastatic renal cell cancer who received 5 mg p.o. b.i.d. titrated to 7 and then 10 mg b.i.d. depending on tolerability. The overall response rate in patients refractory to sorafenib and sunitinib (n = 14) was 7%, in patients refractory to cytokines and sorafenib (n = 29) it was 28% and in patients refractory to sorafenib alone (n = 15) it was 27%. Grade 3-4 treatment-related AEs included fatigue, hypertension, hand-and-foot syndrome, diarrhea and dyspnea, and doses were reduced in 9 patients (57).

Prostate cancer

In patients with metastatic hormone-refractory prostate cancer (HRPC), **BI-2536** (see above) was well tolerated and showed preliminary antitumor activity, evidenced by a 25% reduction in PSA levels over baseline in 1 patient and radiologically stable disease in 6 of 20 treated patients. Grade 3-4 neutropenia was observed in 20% and 73% of patients at 200 and 250 mg, respectively. Further evaluation of BI-2536 as monotherapy will not be continued due to the lack of PSA responders. Optimal combination therapy is being investigated in preclinical studies (58).

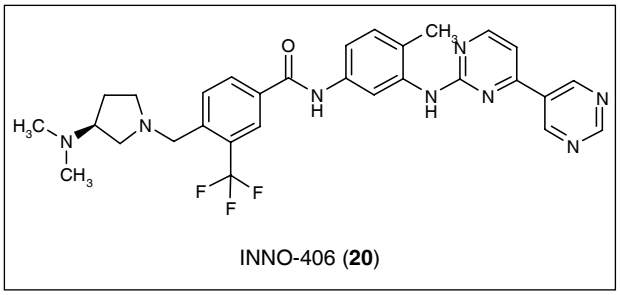
Patients with castration-refractory prostate cancer received **ixabepilone** (see above) 20 mg/m^2 i.v. weekly for 3 weeks on 4-week cycles. Patients (N = 92) were divided into groups: chemonaïve, prior taxane only and two prior cytotoxic chemotherapy treatments. In the first two groups, PSA responses were seen in 10 (32.3%) and 8 (22.2%) patients, respectively. When additional patients with measurable disease were added to these groups, partial objective responses were seen in 20.8% and 7.1%, respectively. The responses in patients receiving second-line treatment were notable, although overall responses did not meet predefined levels of activity. Toxicity was acceptable. Grade 3-4 neutropenia was seen in 6 (15.4%), 7 (14.6%) and 6 (23.1%) patients, respectively, and grade 3-4 sensory neuropathy developed in 8 (20.5%), 13 (27.1%) and 7 (26.9%) patients, respectively, of the chemonaïve group, those having received taxanes only and those having received two prior cytotoxic chemotherapy treatments (59).

Ovarian cancer

The novel humanized monoclonal antibody MORAb-003 (**farletuzumab**; Morphotek) has shown tumor cell proliferation- and tumor growth-inhibitory activity by targeting the folate receptor alpha which is highly expressed in epithelial ovarian cancers. The compound at 10 mg/ml induced complement-dependent cytotoxicity in IGROV-1 ovarian adenocarcinoma cells and ADCC in SK-OV-3 and OVCAR-3 ovarian cancer cell lines. In nude mice bearing SK-OV-3 tumor xenografts, LK-26 (precursor of MORAb-003) 0.1 mg decreased cancer growth. A dose-escalating clinical study with MORAb-003 at 12.5-400 mg/m^2 (4-week cycles) demonstrated that the compound was generally safe and well tolerated, with no reported drug-related serious or severe AEs. After 1 cycle, 7 subjects demonstrated stable disease by RECIST and 4 showed decreased levels of the tumor marker CA-125. One patient received 2 additional cycles and had a 48% decrease in CA-125. Radioactive MORAb-003 showed significant uptake in metastatic tumors, with an adequate half-life (60). Based on phase I results, MORAb-003 was further studied in subjects with epithelial ovarian cancer experiencing first platinum-sensitive relapse. In 28 patients with asymptomatic relapse, a weekly dose of MORAb-003 100 mg/m^2 resulted in 1 subject with a > 75% reduction in CA-125, another patient with a > 25% reduction, 8 subjects with unchanged CA-125 and 15 with increased values. In symptomatic relapse, combined therapy of MORAb-003 (100 mg/m^2/week) plus carboplatin and taxanes normalized CA-125 in 90% of the 41 evaluable patients. The compound increased overall response rate and duration of second remission (61).

Leukemia

The oral dual ABL/Lyn kinase inhibitor **INNO-406** (**20**; Innovive) has shown good tolerability and preliminary efficacy in a phase I study in patients with advanced Philadelphia chromosome-positive (Ph$^+$) leukemia resistant or intolerant to imatinib and who failed previous treatment with second-generation tyrosine kinase inhibitors. INNO-406 was administered orally to 56 patients with chronic myeloid leukemia (CML) in chronic, accelerated



INNO-406 (**20**)

or blast phase, or Ph^+ acute lymphocytic leukemia (ALL) at doses ranging from 30 mg once daily to 480 mg twice daily. Cytogenetic responses were seen in 8 patients, including 1 with CML who had failed both imatinib and dasatinib. INNO-406 treatment was associated with grade 3/4 AEs such as reversible transaminase and bilirubin elevations, thrombocytopenia and acute renal failure. No evidence of peripheral edema or drug-related serious neutropenia was observed. The recommended dose for phase II studies was established at 240 mg b.i.d. Further phase II studies are planned for 2008 (62).

Breast cancer

Researchers at Immutep reported positive phase I results for **IMP-321**, a soluble recombinant form of the human lymphocyte activation gene 3 protein (LAG-3) that binds with high affinity to MHC class II molecules expressed by antigen-presenting cells (APCs), thereby indirectly activating T cell responses. In this open-label, fixed-dose-escalating study, ambulatory patients with metastatic breast cancer received first-line chemotherapy with paclitaxel in combination with IMP-321 at 0.25 or 1.25 mg s.c. IMP-321 was well tolerated, with no grade 3 or 4 drug-related AEs reported. Two weeks after the last injection, a 3-fold increase in MHC class II-positive monocyte counts was detected. Cytotoxic T cell responses also increased after treatment, as circulating activated CTLs increased by 2-fold (63).

Colorectal cancer

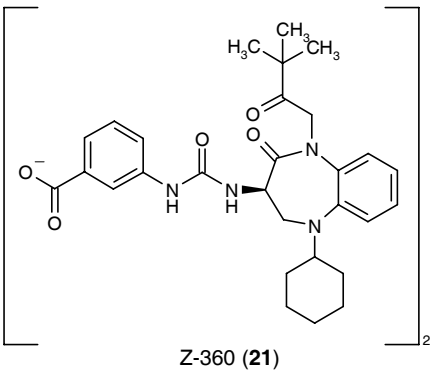
The novel liposomal formulation of irinotecan and floxuridine, **CPX-1** (Celator Pharmaceuticals), showed good tolerability and clinical benefit in a phase II study carried out in patients with advanced colorectal cancer. Twenty-six irinotecan-naïve and 33 irinotecan-refractory patients were recruited. CPX-1 by 90-min infusion (210 U/m^2 [210 mg irinotecan and 75.6 mg/m^2 floxuridine]) was given on days 1 and 15 every 28 days. In the first group, the response rate according to RECIST was 7.7% and the disease control rate was 65%, with a median progression-free survival of 3.9 months; 6 patients had progression-free survival lasting > 6 months. In the second group, median progression-free survival was 2.3 months, that of 3 patients exceeding 6 months. No objective responses were observed and disease control rate was 45%. Grade 3/4 drug-related toxicities occurred in 79.7% of patients and comprised diarrhea, neutropenia, fatigue, nausea and hypokalemia (64).

Results of two studies of **BIBW-2992** (see above) in colorectal cancer were reported at the meeting. A single radiolabeled dose of BIBW-2992 15 mg was administered to 8 healthy male subjects in a phase I pharmacokinetic study in which the agent was well tolerated. Only mild AEs of short duration were observed. The major route of BIBW-2992 elimination was via the feces. Peak plasma concentrations were reached approximately 6 h after dosing, the mean $t_{1/2}$ was 33.9 h and a relatively high apparent total body clearance was measured. Data on plasma and whole-blood radioactivity indicated the presence of one or more metabolites in plasma and whole blood with a longer $t_{1/2}$ than BIBW-2992 (65). Patients with advanced colorectal cancer received BIBW-2992 50 mg once daily on days 8-14 and the angiogenesis inhibitor BIBF-1120 (Vargatef™; Boehringer Ingelheim, Cancer Research UK) 250 mg b.i.d. was given on days 1-7. Of 46 patients treated, 20 had stable disease and the median progression-free survival was 1.8 months; median overall survival was 5.1 months. Safety was acceptable with the combination, with the most common adverse events being diarrhea (80.4%), nausea (43.5%), vomiting (32.6%), rash (41.3%) and asthenia (47.8%) (66).

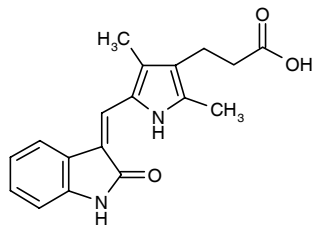
Preliminary results from a phase II study in patients with unresectable, locally advanced or metastatic colorectal cancer indicate that the combination of the EGFR-targeted IgG_1 monoclonal antibody **IMC-11F8** (ImClone) and mFOLFOX-6 is well tolerated. The treatment regimen under study consists of IMC-11F8 800 mg on day 1 followed by mFOLFOX-6 (oxaliplatin 85 mg/m^2, folinic acid 400 mg/m^2, 5-fluorouracil 400 mg/m^2 bolus followed by 2400 mg/m^2 in a continuous 46-h infusion). Cycles are repeated every 2 weeks. A partial response was seen in 15 of 23 patients with a response evaluation, and the remaining 8 patients had stable disease. Skin and nail toxicity was the most common type of IMC-11F8-related AE and was mostly grade 1-2. Pharmacokinetic data indicated that IMC-11F8 concentrations were maintained above levels associated with preclinical antitumor activity. Of 38 patients enrolled in the study, 35 had been treated and 29 remained on study at the time of reporting (67).

Pancreatic cancer

Following on the results of a phase Ib/IIa study of the combination of the cholecystokinin CCK_2 receptor antagonist **Z-360** (**21**; Zeria) with gemcitabine in patients with unresectable, advanced pancreatic cancer, a phase III trial has been planned to compare the efficacy of the combination to gemcitabine alone in advanced pancreatic cancer patients. In the phase Ib/IIa study, the safety of the combination was assessed in 33 patients randomized in double-blind fashion to oral Z-360 120 or 240 mg or placebo, with a single dose of Z-360 or placebo given on day –3 and gemcitabine 1000 mg/m^2 begun on day 1 followed by Z-360 on day 2; Z-360 or placebo was then



Z-360 (**21**)



TSU-68 (**22**)

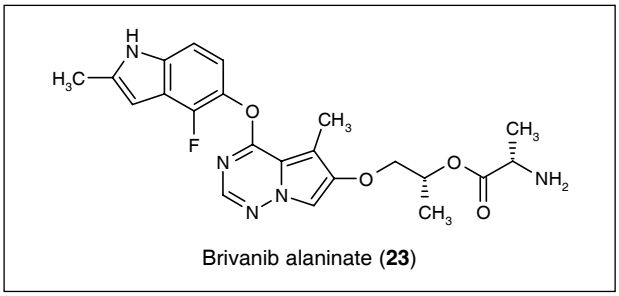
given b.i.d. and gemcitabine weekly for 3 of 4 weeks for a total of 12 weeks. The combination of Z-360 and gemcitabine was safe and well tolerated, with no dose-related AEs and nausea, abdominal pain, vomiting and fatigue being the most common events. There were no objective tumor responses but more Z-360-treated patients had improvements in pain and Karnofski performance status at the end of the study (68).

Myelofibrosis

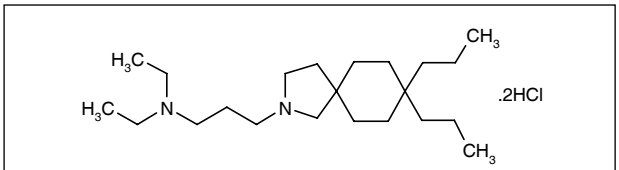
Results of a 28-day phase I/II trial of **INCB-18424** (INCB-018424; Incyte) in patients with primary myelofibrosis and post-polycythemia vera/essential thrombocythemia myelofibrosis have shown activity without significant toxicity in this group of patients. The MTD was established as 25 mg p.o. b.i.d. INCB-18424 treatment was associated with a rapid and profound reduction in spleen size, which lasted for up to 3 months. Improvement of constitutional symptoms such as fatigue, night sweats, pruritus and reduced mobility was also observed. Moreover, INCB-18424 treatment led to reduced inflammatory cytokines, angiogenic growth factors and a reduced ratio of mutated (V617F) *versus* wild-type JAK2 (69). Oral INCB-18424 is also being tested in phase II for multiple myeloma, prostate cancer and rheumatoid arthritis, and a topical formulation is undergoing phase II trials for psoriasis.

Liver cancer

A study evaluating clinical responses and plasma angiogenic markers in patients with advanced hepatocellular carcinoma produced results suggesting that **TSU-68** (**22**) is effective and safe in this patient population. The agent, a multiple kinase inhibitor (VEGFR-2, PDGFR and fibroblast growth factor receptor [FGFR]), is being developed by Taiho. The study included 35 previously treated patients who received TSU-68 800 mg p.o. daily. The safety profile of TSU-68 was favorable, with most AEs of grade 1 or 2, the most common being hypoalbuminuria, diarrhea, abdominal pain, fever and AST/ALT elevation. There was 1 withdrawal due to toxicity. There were 1 complete response, 2 partial responses and 15 cases of stable disease, with disease control lasting over 6 months in 6 patients and tumor necrosis observed in 9 patients. In plasma obtained from 30 patients, PDGF levels tended to increase from baseline to day 28 in patients with progressive disease compared to patients with some form of disease control, and VEGF levels also increased in patients with, but not in those without, progressive disease. Angiogenic factors may therefore serve as markers of efficacy (70). Phase II trials are also being conducted in patients with breast cancer.



Brivanib alaninate (**23**)



Atiprimod hydrochloride (**24**)

Gastric cancer

Results from a phase II study of **1363089** (formerly XL-880; see above) in *MET*-amplified, poorly differentiated gastric cancer and from another in patients with papillary renal cell carcinoma were presented. The study in gastric cancer patients evaluated a regimen of 1363089 240 mg/day p.o. given for 5 days followed by 9 days of rest. Interim results in 18 patients showed no partial responses and stable disease in 4 patients, no response in 2 patients with high-level *MET* gene amplification and tumor shrinkage in 2 patients with low-level chromosome 7 aneuploidy which was followed by progression. The regimen was generally well tolerated, with manageable toxicities, but the study is being extended to evaluate daily dosing with the idea of optimizing drug exposure (71).

Patients with advanced gastrointestinal malignancies who had failed prior therapy were enrolled in a two-part study, the first part evaluating treatment with Bristol-Myers Squibb's BMS-582664 (**brivanib alaninate**, **23**) 320, 600 or 800 mg/day with cetuximab 400 mg/m^2 i.v. on day 8 followed by 250 mg/m^2 weekly. BMS-582664 doses up to 800 mg/day were well tolerated and cetuximab did not appear to affect the pharmacokinetics of BMS-582664. In part 2, patients received BMS-582664 800 mg/day and the same regimen of cetuximab. Clinical activity was seen in patients with colorectal cancer treated with BMS-582664 800 mg, with 6 partial responses and 4 patients with stable disease lasting over 6 months. The best responses in colorectal cancer patients were seen in those with no prior EGFR or VEGF therapy (72).

Neuroendocrine carcinoma

Atiprimod hydrochloride (**24**; Callisto Pharmaceuticals) was well tolerated in a phase II study in patients with low- to intermediate-grade neuroendocrine carcinoma, with disease stabilization seen in those with previously progressive disease. The multicenter study evaluated atiprimod dosing based on a predefined dose de-escalation scheme and liver function tests. Of 25 evaluable patients, 23 had stable disease with a median duration of 6 cycles (approximately 6 months). The percentage of patients who were progression-free after 6 and 12 cycles (approximately 6 and 12 months, respectively) was 76.4% and 50%, respectively. Of patients with carcinoid symptoms, 82% had a decrease of at least 20% in the average daily frequency of at least one symptom. Reversible and manageable AST/ALT increases were the most important AEs, comprising all 6 possibly drug-related serious AEs. Seven patients were enrolled in an extension trial after having stable disease for over 12 months. Further evaluation of atiprimod in this indication appears to be warranted (73).

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